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. HHSA29020100006C). The findings and conclusions in this document are those of the authors, who are responsible for its content, and do not necessarily represent the views of AHRQ. No statement in this report should be construed as an official position of AHRQ or of the U.S. Department of Health and Human Services.

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

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

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Preface

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

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

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

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

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Executive Summary

Background

Horizon scanning is an activity undertaken to identify technological and system innovations that could have important impacts or bring about paradigm shifts. In the health care sector, horizon scanning pertains to 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 18,000 leads about potential topics has resulted in identification and tracking of about 2,000 topics across the 14 AHRQ priority areas and 1 cross-cutting area; about 550 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 150 experts nationwide who were invited and agreed to participate. The experts comprise a range of generalists and specialists in the health care sector whose experience reflects clinical practice, clinical research, health care delivery, health business, health technology assessment, or health facility administration perspectives. Each expert uses the structured form to also disclose any potential intellectual or financial conflicts of interest.
(COIs). Perspectives of an expert with a COI are balanced by perspectives of experts without COIs. No more than two experts with a possible COI are considered out of a total of the five to eight experts who are sought to provide comment for each topic. Experts are identified in the system by the perspective they bring (e.g., clinical, research, health systems, health business, health administration, health policy).

The topics included in this report had scores and/or supporting rationales at or above the overall average for all topics in this priority area that received comments by experts. Of key importance is that topic scores alone are not the sole criterion for inclusion—experts’ rationales are the main drivers for the designation of potentially high impact. We then associated topics that emerged as having potentially high impact with a further subcategorization of “lower,” “moderate,” or “higher” within the high-impact-potential range. As the Healthcare Horizon Scanning System grows in number of topics on which expert opinions are received and as the development status of the interventions changes, the list of topics designated as having potentially high impact is expected to change over time. This report is 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 29 topics for which (1) preliminary data from a trial intended to support regulatory approval for drugs (i.e., phase III data for most drugs and phase II data for accelerated, fast-track, or orphan drugs), phase II or III data for devices or procedures, or data from pilot programs were available; (2) information was compiled and sent for expert comment before May 15, 2014, in this priority area; and (3) we received five to eight sets of comments from experts between July 1, 2013, and May 23, 2014. (A total of 189 topics in this priority area were being tracked in the system as of May 15, 2014.) 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 15 summaries on 19 topics (indicated by an asterisk) that emerged as having higher-impact potential on the basis of expert comments and assessment of potential impact.

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**Discussion**

**Prior Potential High Impact Topics Archived**

The following two topics that had been previous high-impact-potential topics have been archived since the December 2013 report because they have timed out of the horizon scanning system, with U.S. Food and Drug Administration (FDA) approval being 2 years ago.

- **Pertuzumab (Perjeta) for treatment of advanced HER2-positive breast cancer:** In the December 2013 High-Impact Interventions report (and earlier high-impact reports), commenters thought this drug had moderate high-impact potential with significant potential to improve on existing HER2-positive metastatic breast cancer treatment. FDA approved...
pertuzumab in June 2012—two years ago. This drug has diffused and no longer meets criteria for tracking and has been archived in the horizon scanning system.

- **Vismodegib (Erivedge) for treatment of advanced basal cell carcinoma:** In the December 2013 report (and earlier high-impact reports), commenters considered vismodegib to have moderate high-impact-potential. Vismodegib is a first-in-class agent, and commenters found the response rates reported in trials to be compelling in a patient population lacking a systemic treatment option. However, commenters were cautious regarding vismodegib’s potential to improve patient health outcomes because of the lack of long-term followup data. Vismodegib received FDA approval in January 2012; the topic has been archived from the horizon scanning system because it has diffused and has been available for more than 2 years.

**Eligible Topics Not Deemed High Impact**

In this section, we briefly discuss topics in the table above that were deemed to have no high-impact potential at this time based on reviews made by expert commenters, poor outcomes in clinical trials, or no longer meeting Horizon Scanning requirements.

- **Automated breast ultrasound (somo.v automated breast ultrasound system) for breast cancer screening of patients with dense breast tissue:** This topic had been deemed as having high-impact potential in the December 2013 report, but new expert comments deemed it as having no high-impact potential unless new data demonstrate an advantage over other methods and that until then, clinicians would be reluctant to use this method. A large (20,000 patient) screening study is under way and we will track the topic in the horizon scanning system until those data are reported. Experts expressed concern, (largely from trials of manual ultrasound) that incorporating ultrasound into screening paradigms for these patients would elevate the false-positive rate and unnecessary biopsies. In contrast, commenters anticipated patients accepting automated breast ultrasound, especially if prior mammography had inconclusive results. The somo.v automated breast ultrasound system received FDA approval in September 2012.

- **Doxepin oral rinse for the treatment of radiation therapy–associated oral mucositis:** Expert commenters considered various factors when deciding doxepin has moderate potential to address an unmet need. Among them, clinical data showed only a marginal improvement in treating radiation therapy–associated oral mucositis. Additionally, in the randomized controlled trial investigating doxepin, a placebo was used as a comparator rather than a competing oral rinse, limiting commenters’ ability to assess the benefits of doxepin oral rinse.

- **Methylated Septin 9 blood test for colorectal cancer screening:** As a blood-based screening method for colorectal cancer, this topic had been designated in December 2013 as a potential high-impact intervention; but new expert comments on more recent data deemed the specificity and sensitivity of the test to be below par compared with other screening methods. Experts saw little potential at this time, although they thought the test has potential to address a need in patients who would prefer a blood test over a stool test. In recent action, an FDA panel voted that the benefits outweighed the risks, so the test may eventually be approved for marketing.

- **Obinutuzumab (Gazyva) for treatment of chronic lymphocytic leukemia:** Obinutuzumab has some potential to address an unmet need, commenters thought, but overall saw this as having small, incremental impact. They stated that other CD20-specific interventions for treating chronic lymphocytic leukemia (CLL) exist and, as another
monoclonal antibody intervention, obinutuzumab could be easily included in the clinical pathway without substantially disrupting health care infrastructure or patient management. Thus, we have archived it in the horizon scanning system. On November 2013, FDA approved obinutuzumab for treating CLL.

- **Oncolytic reovirus (Reolysin) for treatment of head and neck cancer**: Experts thought the data were few and weak regarding this indication, and thus, saw minimal potential to address an unmet need. On the other hand, patients with recurrent head and neck cancer have limited treatment options; experts thought this intervention’s unique mechanism of action could lead to physicians adopting it as an alternative treatment should additional data be forthcoming. Trials are ongoing, and we will continue tracking this topic until results have been reported.

- **Talimogene laherparepvec for treatment of advanced melanoma**: Commenters determined that talimogene laherparepvec has some potential to improve health outcomes in some patients with melanoma but cited insufficient efficacy data as a barrier hindering patient and physician acceptance. Despite talimogene laherparepvec meeting its primary endpoint of improving durable response rate, it did not demonstrate a statistically significant improvement in overall survival. It is questionable as to whether it will receive FDA approval based on current data. We will continue to track the topic in the horizon scanning system.

- **Trametinib (Mekinist) for treatment of advanced melanoma with activated BRAF mutation**: FDA approved trametinib on the basis of phase I data and it has some potential to meet a need in patients with BRAF-mutant melanoma, commenters agreed. However, they thought clinical data from two small trials were insufficient and suggested that larger trials are needed. Additionally, as selection of BRAF mutation–positive melanoma patients for potential treatment with BRAF inhibitors (dabrafenib, vemurafenib) is already well established, trametinib adoption was not seen as having potential for a dramatic impact on health care infrastructure or patient management. FDA approved trametinib for treating advanced melanoma as a monotherapy in May 2013 and approved it for treating advanced melanoma in combination with dabrafenib in January 2014. Thus we are archiving this topic in the horizon scanning system.

- **Trebananib (AMG 389) for treatment of ovarian cancer**: In clinical trials, trebananib improved progression–free survival compared with placebo in patients with recurrent ovarian cancer. The response, however, was considered marginally incremental by expert commenters. In particular, commenters cited the lack of an overall survival benefit; additional data are anticipated and we will continue to track the topic in the horizon scanning system. Because trebananib is administered as a standard intravenous (IV) infusion, commenters anticipated no barriers for acceptance and minimal disruption to health care infrastructure.

**Eligible Topics Deemed High Impact**

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 address include both solid tumors (advanced melanoma, breast cancer, colorectal cancer [CRC], gastric cancer, prostate cancer, and thyroid cancer) and hematologic malignancies (Castleman’s disease, CLL, mantle cell lymphoma, and non-Hodgkin’s 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 an antibody-drug conjugate (ADC) and two monoclonal antibodies. The ADC targets a tumor-associated antigen overexpressed by a subset of cancers and represents a personalized therapy intended for a specific patient population. The monoclonal antibodies target molecules involved in two hallmarks of cancer angiogenesis and immune tolerance. 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. Many models have been developed, and we describe one of them as an example to address this unmet need: the model pioneered by the Teenage Cancer Trust of the United Kingdom (UK) and the U.S.-based Teen Cancer America. These are two nonprofit organizations that work in partnership 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 United Kingdom, and the ongoing BRIGHTLIGHT study is assessing this care model’s impact on health outcomes. Teen Cancer America, following the UK model, recently established its first AYA unit in the United States, and plans for several additional centers are ongoing. Development of other AYA programs not affiliated with these organizations is also ongoing.
**Key Expert Comments:** Most experts commenting on AYA oncology care model programs agreed that there is an important unmet medical need for health care models focusing on AYAs. However they were concerned about the lack of clinical data demonstrating improved health outcomes in AYAs treated under such program regimens. One clinician in particular was concerned that this care model might lead to structural and administrative changes before evidence demonstrated that health outcomes were improved. If this specialized care model is implemented, clinicians and patients would widely accept its programs, experts also thought. Discrepancies existed in expert opinion on the impact this intervention would have on health disparities: some experts thought limited access would increase disparities while others thought it could decrease disparities between AYAs and non-AYAs. Cost information about these models is not readily available. Costs incurred would include medical and social work staff trained to care for AYAs, physical environments attuned to needs of AYAs, AYA-focused support groups, extended hours, and care coordination targeted at the mobile lifestyles of many AYAs (e.g., attending college).

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

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**Breast Cancer**

**Ado-Trastuzumab Emtansine (Kadcyla) Antibody-Drug Conjugate for Treatment of 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 the epidermal growth factor receptor family member HER2. This breast cancer subtype comprises about 20% of breast cancer cases and historically has been associated with more aggressive disease and poorer outcomes. Although treatment of HER2-positive breast cancer improved with the availability of HER2-targeted therapies such as trastuzumab (Herceptin®), lapatinib (Tykerb®), and pertuzumab (Perjeta®), many patients’ cancers still progress despite treatment, and additional options are needed. Ado-trastuzumab emtansine (Kadcyla™, F. Hoffmann-La Roche, Ltd., Basel, Switzerland) is a novel HER2-directed therapy recently approved by FDA. The drug is administered as an IV infusion in outpatient infusion centers. Formerly known as trastuzumab-DM1, ado-trastuzumab emtansine couples the potent chemotherapeutic agent emtansine (a microtubule assembly inhibitor) to the HER2-specific antibody trastuzumab. The toxin and antibody are coupled in such a way that emtansine is held in a stable, inactive form outside the cell, and 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 is targeted to cells expressing HER2, potentially reducing toxicity in noncancerous tissues. Ado-trastuzumab emtansine is being studied in several phase III trials for treating HER2-positive breast cancer. Verma et al. (2012) published results from one of these trials (EMILIA) that compared the drug with second-line therapy of lapatinib and capecitabine. Results indicated that ado-trastuzumab emtansine increased progression-free and overall survival and reduced severe adverse events. In February 2013, FDA approved ado-trastuzumab emtansine monotherapy as second-line treatment of HER2-positive metastatic breast cancer based on these results. The biologic is given at a dosage of 3.6 mg/kg, administered by IV 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 prescription-drug prices listed costs (as of June 2014) ranging from about $2,900 to $3,040 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. Ado-trastuzumab emtansine is typically covered for labeled indications by third-party payers as a specialty pharmaceutical that requires preauthorization for outpatient infusion therapy.

- **Key Expert Comments:** Overall, experts commenting on this intervention believe that ado-trastuzumab emtansine has significant potential to improve outcomes for patients with HER2-positive metastatic breast cancer. They thought that the shortcomings of previous therapies represented a significant unmet need. Experts also thought that the drug’s potential to displace current standard of care for HER2-positive metastatic breast cancer could have significant impacts on patient management. Because the drug is second-line therapy, it does not displace other therapy, and thus adds to costs of patient care, experts noted. They added that its cost was comparable to monthly costs of other targeted cancer therapies.

- **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 tumor growth and mTOR inhibitors’ demonstrated efficacy in treating various cancers, researchers are studying these agents in a large number of clinical trials for treating a wide variety of cancers. Baselga and colleagues (2012) 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). Results of the 724-patient trial indicated 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 when treatment has failed with letrozole or anastrozole. A May 2014 query of a U.S.-based, online aggregator of prescription-drug prices identified a retail price of about $9,700 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. Other studies are examining use of everolimus in the adjuvant setting for hormone receptor-positive disease. Additionally, studies are 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 has been shown to achieve low recurrence rates equivalent to those achieved with total mastectomy. Achieving optimal outcomes requires that the excised tumor’s tissue margins be cancer free. If subsequent pathologic analysis reveals that 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 a 596-patient trial, Schnabel et al. (2014) compared the MarginProbe System in combination with standard intraoperative assessment with standard intraoperative assessment alone. The authors reported that MarginProbe use increased the rates at which surgeons identified positive surgical margins and removed additional tissue to achieve clean surgical margins (62% for MarginProbe; 22% for standard assessment, p<0.0001). In January 2013, FDA approved the MarginProbe device 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 about $40,000. 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 bundled payment. Eleven third-party payers whose policies we searched either have no coverage policies on MarginProbe or if they have a policy, consider the system experimental or investigational at this time, and thus do not provide additional coverage for its use. The Wall Street Journal reported in July 2013 that the added per-surgery cost for use of the system during a breast resection was quoted by several hospitals as about $995 additional per surgery; other reports have stated that the procedure adds about $2,000 to the surgery cost.

- **Key Expert Comments:** Experts commenting on MarginProbe thought it has potential to improve patient quality of life and outcomes by avoiding a need for second surgeries in women undergoing breast-conservation surgery. However, more data determining accurate distinction between negative and positive margins are needed for experts to adequately evaluate the potential impact of intervention. Overall, experts thought MarginProbe would be easily adopted by patients and surgeons without causing significant disruption in health care infrastructure or patient management.

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

Stool DNA Molecular Test (Cologuard) for Colorectal Cancer Screening

- **Key Facts:** New screening methodologies are highly desired that could improve the accuracy of existing noninvasive screening tests for colorectal cancer (CRC) and increase the percentage of the population that undergoes recommended CRC screening. Research has demonstrated that cells undergo a number of genetic and epigenetic changes during malignant transformation, and detecting these changes may indicate a precancerous lesion or cancer. The Cologuard stool DNA test is a molecular diagnostic designed to detect such changes in colon-derived cells sloughed off the intestinal walls and secreted with stool. Investigators studied the test in a 10,000-patient trial in which patients underwent Cologuard screening, fecal immunohistochemical testing (FIT, a standard noninvasive test that detects blood in stool) and colonoscopy. Imperiale and collaborators (2014) reported that, using colonoscopy findings as the gold standard, the sensitivity of Cologuard was 92.3% for CRC and 42.4% for precancerous lesions. These results compared favorably to the sensitivity of FIT, which was 73.8% and 23.8% for CRC and precancerous lesions, respectively. However, the reported specificity of Cologuard was lower than that of FIT: 86.6% versus 94.9%. A premarket approval application for Cologuard is under review by FDA. In March 2014, FDA’s Molecular and Clinical Genetics Advisory Panel voted unanimously that the benefits of Cologuard for CRC screening outweighed the risks, recommending that FDA approve the test. The Cologuard test is undergoing parallel review by FDA and the U.S. Centers for Medicare & Medicaid Services, which could facilitate the development of a national coverage determination should Cologuard be approved by FDA. The test’s anticipated cost has not been released.

- **Key Expert Comments:** Overall, experts suggested that stool DNA testing has potential to improve on the accuracy of current noninvasive stool-based tests such as fecal occult blood testing and FIT. However, the biggest shifts in patient outcomes and management were envisioned in patients switching from colonoscopy to stool DNA testing or in patients who previously would not undergo screening opting to undergo stool DNA testing, noted experts. Some expert commenters questioned whether these changes were likely; therefore, our overall assessment is that Cologuard is at the lower end of the high-impact-potential range.

- **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 females with cancer, treatments can negatively and often permanently affect fertility (i.e., gonadotoxicity). As cancer survivorship continues to grow because of improved diagnosis and treatment, fertility preservation has become an increasingly important concern for women and girls who wish to conceive at some future time after undergoing gonadotoxic therapy. Cryopreserved eggs or embryos obtained before treatment for later in vitro fertilization have been the only standard options that are not considered to be experimental at this time. However, this approach is not an option for many patients (e.g., pediatric patients). A new option to preserve fertility after cancer treatment involves ovarian tissue harvesting and cryopreservation for future reimplantation after disease remission. This option is available to
both 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 is typically collected in 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 reimplemented with the intent of restoring ovarian function and fertility. Depending on the patient, the autograft may be placed near the original location of the ovary, or a location such as the forearm or abdomen. This intervention remains in early stages of development with larger studies under way to assess the safety and efficacy of ovarian tissue cryopreservation and tissue reimplantation. Eight case series (Callejo et al., 2013; Dittrich et al., 2012; Dolmans et al., 2013; Donnez et al., 2012; Donnez et al., 2011; Revelli et al, 2103; Schmidt et al., 2011; Stern et al., 2013) have reported successful restoration of ovarian function after reimplantation 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 female 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 as having significant potential for disruption of patient management. If not covered by insurance or widely available as a procedure, access could be limited and increase health disparities between fertile and infertile women.

- **Potential for High Impact:** High

**Gastric Cancer**

**Ramucirumab (Cyramza) for Treatment of Gastric Cancer**

- **Key Facts:** Even though surgical techniques, radiotherapy, and chemotherapy are available for patients with gastric cancer, outcomes remain poor because the cancer is locally advanced or metastatic in most patients at the time of diagnosis. Researchers have reported that gastric cancer progression depends heavily on vascular and epidermal growth factor pathways and have focused on developing drugs that target such pathways. Standard first-line therapy usually includes a combination of fluoropyrimidine/platinum–based chemotherapy with targeted drugs. Unfortunately the cancer progresses in most cases. Vascular endothelial growth factor receptor 2 (VEGFR2) has a pivotal role in forming most blood vessels involving VEGF pathways, and blocking this receptor could lead to improved outcomes in patients with advanced gastric cancer. In studying an antibody against VEGFR2, ramucirumab (Cyramza™, ImClone Systems, a subsidiary of Eli Lilly and Co., Indianapolis, IN), researchers have reported results from two studies using agent as monotherapy or combination therapy with paclitaxel for treating advanced gastric cancer.
The REGARD trial studied patients whose disease had progressed after chemotherapy. Results from Fuchs and co-authors (2014) for the 355-patient, placebo-controlled trial showed improved median overall survival (5.2 versus 3.8 months) and treatment (median 4 doses) was generally well tolerated; reported common adverse events were hypertension and diarrhea. The RAINBOW trial studied ramucirumab in combination with paclitaxel for treating gastric cancer. As reported by Wilke et al. (2014), overall survival increased by 2.27 months, but adverse events were twice as severe in the combination therapy as in the paclitaxel-alone group. These events included abdominal pain, anemia, asthenia, fatigue, hypertension, leukopenia, and neutropenia.

Basing its decision on the results from the REGARD trial, FDA approved ramucirumab in April 2014 for treating advanced gastric cancer or gastroesophageal junction adenocarcinoma, as monotherapy after prior fluoropyrimidine/platinum-based chemotherapy. The labeling includes a boxed warning about increased risk of hemorrhage, including severe and sometimes fatal events. Ramucirumab is administered intravenously at a dosage of 8 mg/kg every 2 weeks until disease progression or toxicity limits further treatment. Thus, an adult of about 70 kg (154 lb) would require would require about 560 mg. A June 2014 query of a U.S.-based, online aggregator of prescription-drug prices showed costs of six vials of Cyramza 100 mg/10 mL of about $6,500 to $7,000—an amount sufficient for about one treatment. A search of 11 representative, private, third-party payers that publish their coverage policies online found no policies regarding ramucirumab at this time, most likely because policies had not been updated as of the recent approval date. Drugs intended for treating patients in whom cancer has been diagnosed are usually covered for their prescribed use, and it is likely third-party payers will cover ramucirumab as a specialty pharmaceutical.

- **Key Expert Comments:** Most experts commenting on ramucirumab agreed that there is an unmet need for second-line therapy for advanced gastric cancer therapies, because no FDA-approved option had been available before this approval. Although ramucirumab showed efficacy in patients with advanced gastric cancer, experts thought it has only moderate potential to fulfill this need because survival was only marginally increased, and the benefits might not outweigh the increase in adverse events. However, because no other FDA-approved second-line treatments are available, experts thought this would be accepted as a treatment option by both patients and clinicians.

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

**Hematologic Malignancies**

**Ibrutinib (Imbruvica) and Idelalisib for Treatment of Non-Hodgkin’s Lymphomas**

- **Key Facts:** B-cell non-Hodgkin’s lymphomas (NHLs), such as CLL and mantle cell lymphoma, often respond well to first-line therapy; however, most affected patients experience recurrence. In this situation, available therapies have limited or no efficacy. Additionally, certain molecularly defined subtypes, such as CLL harboring a deletion in the short arm of chromosome 17, respond poorly to standard therapies. New agents to treat these cancers are highly desired. Recent research has identified the kinases Btk and PI3K-delta as potential targets for treating B-cell malignancies.

  Ibrutinib (Imbruvica™) is an oral, first-in-class Btk inhibitor under study for treating a wide range of B-cell malignancies. In single-arm, phase II studies reported in 2013 by
Farooqui et al. and Byrd et al., ibrutinib demonstrated substantial activity in patients with mantle cell lymphoma or CLL, with response rates between 66% and 71%. More recently, data were reported by Byrd and co-authors (2014) from a randomized controlled trial of ibrutinib versus the CD20 antibody ofatumumab for treating patients with relapsed/refractory CLL. Ibrutinib significantly improved overall survival compared with ofatumumab (hazard ratio, 0.434; 95% confidence interval, 0.238 to 0.789; p=0.0049). FDA approved ibrutinib November 2013 for treating patients with mantle cell lymphoma and in February 2014 for treating patients with CLL. The labeled dosage for mantle cell lymphoma is 560 mg once daily, and for CLL, 420 mg once daily. The retail prices for ibrutinib at the mantle cell lymphoma and CLL doses are about $11,600 and $8,700 per month, respectively.

Idelalisib is an oral, first-in-class, PI3K-delta inhibitor also under study for treating a wide range of B-cell malignancies. In results of a randomized, double-blind, placebo-controlled trial of patients with relapsed/refractory CLL, Furman and collaborators (2014) reported that adding idelalisib to standard treatment with rituximab improved both progression-free survival (85% reduction in risk of progression or death) and the overall response rate (81% rituximab plus idelalisib vs. 13% rituximab plus placebo). In results of a single-arm trial of idelalisib for treating relapsed/refractory indolent NHL reported by Gopal et al. (2014), a response rate of 57% was observed. Regulatory submissions for both CLL and indolent NHL indications have been made to FDA; decisions are expected in August 2014 and September 2014, respectively.

- **Key Expert Comments:** Overall, experts opined that a significant need exists for novel treatments of B-cell lymphomas and that the response rates observed in initial trials of ibrutinib and idelalisib indicated that the drugs have significant potential to improve patient outcomes. However, experts commenting suggested that further confirmatory studies are needed, particularly studies comparing ibrutinib and idelalisib to alternatives. Experts believed that the relatively benign side-effect profiles of ibrutinib and idelalisib and their potential to be used in treating several B-cell malignancies place these drugs at the higher end of the high-impact-potential range.

- **Potential for High Impact:** High

**Siltuximab (Sylvant) for Treatment of Multicentric Castleman's Disease**

- **Key Facts:** Multicentric Castleman’s disease is a rare lymphoproliferative disorder without effective treatment options. Siltuximab is a monoclonal antibody specific for interleukin-6 (IL-6), a cytokine whose upregulation is thought to underlie the pathogenesis of multicentric Castleman’s disease. Treatment with siltuximab purportedly neutralizes IL-6, thereby improving disease symptoms. In results of a randomized, placebo-controlled trial reported by Wong et al. (2013), patients treated with siltuximab demonstrated significantly improved tumor and symptom response (34% siltuximab vs. 0% placebo, p=0.0012). Siltuximab was generally well tolerated, with similar rates of adverse events reported in both treatment and placebo arms of the trial. In April 2014, FDA approved siltuximab as the first treatment approved for this disease. According to the prescribing information, siltuximab is indicated for treating patients “with multicentric Castleman’s disease (MCD) who are human immunodeficiency virus (HIV) negative and human herpesvirus-8 (HHV-8) negative.” The drug is administered by IV infusion every 3 weeks, until disease progression, at a dosage of 11 mg/kg given over 1 hour. A June 2014 query of a U.S.-based, online aggregator of prescription-drug prices showed costs ranging from about $900 to $940 for a 100 mg vial.

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An adult of about 70 kg (154 lb) require about 770 mg or 8 vials at a cost of about $7,500 per dose.

- **Key Expert Comments**: Overall, experts concurred that siltuximab has the potential to fill a significant unmet need of patients with multicentric Castleman’s disease, given that no other FDA-approved therapies exist for this indication and basing their opinions on the promising results regarding disease response rate from a randomized clinical trial. However, siltuximab’s overall impact was limited by the small size of the eligible patient population and the preliminary nature of the data on a therapy that could potentially be taken for extended periods of time.

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

### 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, which modestly 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. Scher et al. (2012) reported that 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 by Beer et al. (2014) 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 metastatic castration-resistant prostate cancer (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. Enzalutamide is administered at a dosage of 160 mg (4 capsules) once daily. A June 2014 inquiry of a U.S.-based, online aggregator of prescription-drug prices showed a retail cost for 1 month of treatment (120 capsules) of about $8,500. The drug is considered a specialty pharmaceutical; insurers and Medicare Part D generally require preauthorization and impose quantity limits on each prescription.

- **Key Expert Comments**: Overall, experts suggested that enzalutamide has significant potential to improve health outcomes in patients with CRPC, citing the positive results in terms of progression-free and overall survival observed in two randomized control trials. Basing their thoughts on the observed efficacy and the ease of administering enzalutamide, commenters envisioned widespread adoption. Studies will be needed to integrate enzalutamide and other recently approved prostate cancer therapies into treatment guidelines.

- **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, in which samples are collected while the patient is inside 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 target 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 (e.g., Natarajan et al, 2011; Siddiqui et al., 2013; Kuru et al., 2013) 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 cost more than 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:** Overall, commenters indicated that substantial shortcomings exist in existing prostate biopsy methods and that MRI-TRUS fusion has potential to improve the detection rate of clinically significant prostate cancer. However, the lack of data demonstrating improved health outcomes, the increased cost associated with the procedure, and a lack of clarity regarding reimbursement for the procedure were seen as limiting 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. This treatment may reduce the side-effect profile of treatment and more effectively target 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 (Parker et al., 2013) 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.

- **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 impact on health care system infrastructure and practices.

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

Pembrolizumab (MK-3475) for Treatment of Advanced Melanoma

- **Key Facts:** There is a medical need for novel treatments for advanced melanoma, because despite advances in melanoma therapies, outcomes are poor. Researchers have demonstrated that several types of cancer have developed mechanisms to evade the cellular immune response, in particular the cytotoxic response involving T cells. Under normal conditions, immune cells use these so-called immune checkpoints to prevent exacerbated immune responses, which could lead to damage of neighboring tissues and organs. A promising melanoma-treatment approach involves immune-system checkpoint inhibitors, which prolong the patient’s immune cytotoxic T-lymphocyte response, targeting and killing cancer cells. Even though ipilimumab, an antibody against CTLA-4, has shown durable immune responses in some patients with melanoma, such response is limited to a small number of patients. Additionally, researchers have also shown high expression of the programmed death-1 (PD-1) ligand in cancer cells, a biomarker also involved in suppressing the immune response in patients with melanoma. Researchers are studying pembrolizumab (MK-3475, Merck & Co., Inc., Whitehouse Station, NJ), an antibody targeting PD-1, as treatment for advanced melanoma. It also is under study for nonsmall cell lung cancer, gastric cancer, blood cancers, and cancers of the breast, head and neck, and urothelial tract. In results from a 135-patient, placebo-controlled trial, the highest response rate was observed in 52% of patients with advanced melanoma who were treated with 10 mg/kg of pembrolizumab every 2 weeks. In this trial, Hamid and colleagues (2013) found no statistical significance in the response rate between patients treated with pembrolizumab who had received prior ipilimumab treatment and those who had not. The most common adverse events associated with pembrolizumab treatment were fatigue, rash, pruritus, and diarrhea and were observed in 79% of patients. In January 2013, FDA granted pembrolizumab breakthrough therapy designation for melanoma. A year later, Merck began the submission of a biologic license application, and in May 2014, FDA granted pembrolizumab priority review with a decision expected by October 2014. Pricing information for pembrolizumab does not exist because it is not commercially available. The price for pembrolizumab could be similar to that of ipilimumab, another checkpoint inhibitor reported to cost about $120,000 per patient per year. An expanded-access program is available for select patients requiring pembrolizumab for melanoma treatment. Although there is no coverage information for pembrolizumab, it is likely that it will be covered by third-party payers if it receives FDA approval.

- **Key Expert Comments:** Pembrolizumab has moderate potential to address an unmet need, some experts thought. They attributed their reasons to scarce safety and efficacy data and a similar mechanism of action to that of approved and soon-to-be approved melanoma therapies. However, experts with a clinical perspective regarded pembrolizumab as having high potential to fulfill the unmet need because it can be used as second-line treatment in patients with very poor prognoses whose disease has relapsed after ipilimumab treatment.

- **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. A drawback of the system is the 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 treatments 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 (Narayanan et al., 2012; Martin et al., 2013), primary liver cancer (Cheung et al., 2013; Cannon et al., 2013), and liver metastases (Kingham et al., 2012). 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 potential addition to cancer treatment options. It could be particularly useful in pancreatic cancer, for which experts noted a large unmet need, and it could significantly shift the way patients are managed. On the other hand, for hepatocellular cancer, IRE does not appear to offer advantages over other options, the experts stated. They concurred that IRE could be the only option for patients with cancer localized near critical structures or organs. The available data are insufficient to prove patients have better outcomes with IRE than with other ablation techniques, experts indicated, and expressed the need for controlled trials on efficacy before wider adoption. Based on this input, our overall assessment is that this intervention is in the lower end of the high-impact-potential range.

- **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 of 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 their prognosis 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 phase III clinical trial comparing sorafenib to placebo in patients with progressive, radioactive iodine–refractory, differentiated thyroid
cancer, Brose and colleagues (2013) reported sorafenib extended progression-free survival by approximately 86% (10.8 months vs. 5.8 months for placebo). Based on these data, a new drug application was submitted to FDA for using sorafenib in treating thyroid cancer. After 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 FDA-approved therapies exist for this indication and given the promising progression-free survival results in recent data from the 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 this age group 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 UK Teenage Cancer Trust and Teen Cancer America illustrates the interventions that a comprehensive AYA-focused oncology program may entail.\(^9\)\(^,\)\(^10\) Teen Cancer America reportedly is the first program in the United States 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 creating 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. 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.\textsuperscript{5,15} Preliminary data demonstrated improved clinical trial enrollment among patients treated in an AYA oncology program.\textsuperscript{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.\textsuperscript{16} As of November 2013, the study had enrolled 523 AYA patients with recent cancer diagnoses.\textsuperscript{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)\textsuperscript{10} is a nonprofit organization established in 2011 as the U.S. extension of Teenage Cancer Trust, a UK charity organization based in London.\textsuperscript{9} These organizations form partnerships with hospitals and cancer centers to design and implement AYA cancer units.\textsuperscript{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 constructing and operating 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.\textsuperscript{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 and cost: Since 1990, the Teenage Cancer Trust has funded 26 dedicated AYA oncology units throughout the United Kingdom, with another 9 in development.\textsuperscript{19} The U.S. arm of the organization, Teen Cancer America, was launched in December 2011.\textsuperscript{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. In November 2012, this organization opened the first exclusively AYA-dedicated oncology unit in the United States.\textsuperscript{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.\textsuperscript{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 States have established AYA oncology programs that provide dedicated services, programming, and/or space for AYA patients. This care model is rapidly diffusing nationwide, with more than 30 programs in place.

Current Approach to Care

Upon diagnosis of cancer, 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 a facility’s patients. 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 geared to AYAs with cancer to address some of the needs of this patient population.\textsuperscript{8}
Most experts commenting on this program agreed that there is an unmet medical necessity for health care models focusing on AYAs. However they were concerned about the lack of clinical data demonstrating improved health outcomes in AYAs treated under such program regimens. One clinician in particular was concerned that this care model would require structural and administrative changes but not necessarily result in better health outcomes. If such specialized care is implemented, clinicians and patients would widely accept their programs, experts also thought. However there were differences of opinion on the effect this intervention would have on health disparities: some experts thought limited access would increase disparities while others, with clinical perspective, thought it could decrease disparities between AYAs and non-AYAs. 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 this intervention.\textsuperscript{21-28} We have organized the following discussion of expert comments by the parameters on which they commented.

Unmet need and health outcomes: Experts are aware of the physical and emotional needs AYAs have during cancer care, which are not addressed by standard pediatric and adult cancer health care systems. Although there is a medical need for specialized AYA care models, additional data on health improvement are necessary for experts to agree on the benefit this program will offer. In contrast, another expert thought that AYA health outcomes are influenced more by the lack of health insurance rather than not having access to AYA specialized care. The program has moderate potential to improve AYA patient outcomes, experts thought.

Acceptance and adoption: Experts anticipate most clinicians are likely to adopt this specialized program for AYAs. Although acceptance is expected to be slow at first, as more health centers adopt AYA health care programs, more physicians will accept such programs, was the opinion of one expert.\textsuperscript{27} Another expert thought additional training requirements and insufficient evidence of improved health outcomes would also hinder clinical acceptance.\textsuperscript{25} Experts agreed unanimously on the acceptance of this model by AYA patients and their families.

Health care delivery infrastructure and patient management: Most experts thought specialized AYA oncology units would have moderate impact to health care delivery infrastructure and patient management. They indicated that oncology wings could be adapted for AYA treatment with minimal renovation, although two experts anticipated hospitals dedicating new physical space and infrastructure for this purpose.\textsuperscript{23,28} Overall, experts anticipated minimal change to AYA patient treatment, but noted patients would benefit from having access to counselors and other medical resources focusing on AYA health outcomes.

Health disparities: Experts had differing opinions on the impact specialized AYA care models would have on health disparities. Three experts thought the slow diffusion of AYA health centers
could increase health disparities due to limited accessibility. However, both a clinical and a research expert commenting on this program suggested it has potential to minimize disparities between AYAs and non-AYAs, in particular for patients who lack family support.\textsuperscript{26,28}
Breast Cancer Interventions
Ado-Trastuzumab Emtansine (Kadcyla) Antibody-Drug Conjugate for Treatment of 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. Indeed, HER2+ breast cancer treatment outcomes have improved with the availability of targeted therapies such as the HER2-specific monoclonal antibody trastuzumab (Herceptin®), the HER2 kinase inhibitor lapatinib (Tykerb®), and the HER2-specific monoclonal antibody pertuzumab (Perjeta®). However, many patients’ cancers still progress during these treatments and compounds with improved efficacy are highly desired.

Intervention: Ado-trastuzumab emtansine (Kadcyla™, formerly called trastuzumab-DM1), an antibody-drug conjugate (ADC), couples the HER2-specific monoclonal antibody (trastuzumab) to a potent chemotherapeutic agent, the microtubule assembly inhibitor emtansine (DM1). 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. 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 retained 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). Ado-trastuzumab emtansine is an intravenous (IV) medication that is administered at dosage of 3.6 mg/kg once every 3 weeks, until disease progression or unacceptable toxicity.

Clinical trials: Ado-trastuzumab emtansine is being studied in a number of trials in patients with metastatic disease. In 2012, investigators published results 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. In this randomized, open-label trial, 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% confidence interval [CI], 0.55 to 0.77; p<0.001; overall survival at second interim analysis was 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). In 2014, investigators published results from the phase III TH3RESA trial, which compared ado-trastuzumab emtansine to treatment of physician’s choice in treating patients with metastatic disease who had undergone multiple therapies including trastuzumab and lapatinib. In this randomized, open-label trial, investigators reported that patients who received ado-trastuzumab emtansine exhibited increased progression-free survival (6.2 vs. 3.3 months, stratified HR, 0.528; 95% CI, 0.422 to 0.661; p<0.0001) while simultaneously reducing the overall incidence of grade 3 or higher adverse events. A third phase III trial (MARIANNE) in metastatic disease is studying a combination of trastuzumab and pertuzumab in the first-line setting. Besides these studies in patients with...
metastatic disease, ado-trastuzumab emtansine is also under study for treating nonmetastatic breast cancer as an adjuvant (postsurgery) treatment option.37,38

Manufacturer and regulatory status: Ado-trastuzumab emtansine was developed by F. Hoffmann-La Roche, Ltd., (Basel, Switzerland). In February 2013, the U.S. Food and Drug Administration (FDA) approved ado-trastuzumab emtansine for treating “patients with HER2-positive (HER2+), metastatic breast cancer (MBC) who previously received trastuzumab and a taxane, separately or in combination.”39,40 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.40

Diffusion and cost: Roche announced pricing of ado-trastuzumab emtansine at $9,800 per month of treatment.41 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. A U.S.-based, online aggregator of prescription-drug prices listed costs as of December 2013 of about $2,934–$3,041 for one 100 mg vial.42 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. Ado-trastuzumab emtansine became available shortly after approval, and Roche has reported strong uptake of the drug in 2013.43,44

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 regarding ado-trastuzumab emtansine.45-51 All payers with identified policies 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). As an IV medication administered in the health care setting, ado-trastuzumab emtansine 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 untreated 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). More recently, a three-drug regimen of trastuzumab, pertuzumab, and docetaxel has been used in the first-line setting. 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.52 The recent FDA approval of ado-trastuzumab emtansine in the second-line setting provides new treatment options for patients with metastatic breast cancer.
Overall, experts commenting on this intervention believe that ado-trastuzumab emtansine has 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 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.\textsuperscript{53-59} 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 those outcomes in patients treated with lapatinib plus capecitabine in the EMILIA trial. This suggested 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.\textsuperscript{59}

**Acceptance and adoption:** Ado-trastuzumab emtansine will be readily adopted by physicians and patients, according to expert commenters. Factors promoting adoption included its potential to increase survival and its relatively good safety profile. However, the high cost of ado-trastuzumab emtansine was one potential obstacle raised by the experts.

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

**Health disparities:** The anticipated high cost of ado-trastuzumab emtansine was one potential obstacle to alleviating disparities in cancer care raised by the experts, who noted it would be added to current regimens.
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. Multiple mechanisms of resistance to endocrine therapy have been identified, including signaling through the mammalian target of rapamycin (mTOR)/phosphatidylinositol-3 kinase (PI3K) pathway.

**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 or mutated or both in various cancers, suggesting that agents inhibiting mTOR pathway molecules could function as anticancer agents. Based on this observation, a class of drugs that inhibits mTOR via a mechanism of action similar to that of the naturally occurring macrolide antibiotic rapamycin (also known as sirolimus) has been developed. Rapamycin-like mTOR inhibitors have been approved for treating cancers, including everolimus (Afinitor®) for treating renal cell carcinoma, subependymal giant cell astrocytoma, angiomyolipoma associated with tuberous sclerosis, and pancreatic neuroendocrine tumors, and temsirolimus (Torisel®) for treating renal cell carcinoma.

Given mTOR’s central role in multiple, cancer-related cellular processes, its inhibition may represent a viable treatment 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. Everolimus is an oral medication administered at a dosage of 10 mg once daily.

**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). Results from a randomized, double-blind, placebo-controlled trial of 724 patients (BOLERO-2) were published in 2012. 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; HR, 0.43; p<0.0001).

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.

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. 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.

**Manufacturer and regulatory status:** Novartis International AG (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.
**Diffusion and cost:** A May 2014 query of a U.S.-based, online aggregator of prescription-drug prices identified a retail price of about $9,700 per month for everolimus. 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. These payers consider 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. Recent trial data suggest HER2-positive breast cancer that has progressed after treatment with trastuzumab is another potential indication for everolimus. Researchers anticipate that treating this patient population with trastuzumab plus everolimus to inhibit the mTOR pathway might restore sensitivity to trastuzumab. Subsequent to expert comment on this topic, results from a phase III randomized, double-blind, placebo-controlled 569-patient study (BOLERO-3) testing the efficacy of everolimus as add-on treatment to trastuzumab were published in 2014. Everolimus (10 mg daily) plus weekly trastuzumab (25 mg/kg) improved the progression-free survival endpoint by 1.22 months (7.00 months with everolimus plus trastuzumab vs. 5.78 months with placebo plus trastuzumab; HR, 0.78; p<0.0067).

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 and the PI3K inhibitor BKM120 in combination with the anti–estrogen agent fulvestrant for patients who have undergone prior endocrine therapy for metastatic disease.

**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. 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).
Experts commenting on this intervention suggested that results for progression-free survival in patients with 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.\textsuperscript{82-87} 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.\textsuperscript{85} 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, in which case it likely would be administered over long periods of time.\textsuperscript{86}

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.\textsuperscript{86} 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 up-front 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 costs for infusion-based chemotherapy.86

**Health care delivery infrastructure and patient management:** As an orally administered medication, everolimus use was not anticipated by experts to significantly shift health care staffing or infrastructure. They also thought it would not 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 staffs who are responsible for processing prior authorization requests.86

**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 underinsured 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%. 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. Investigators have also begun to test a version of the device for margin assessment in patients undergoing prostatectomy to treat prostate cancer.

The system uses radiofrequency (RF) spectroscopy, in which tissue is subjected to an electromagnetic field, measuring its response to stimulation. Research findings have indicated that RF spectroscopy can differentiate between normal and cancerous tissue based on their bioelectric profiles. 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. 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.

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

Clinical trials: In a multicenter randomized trial, MarginProbe was used together with standard intraoperative methods (described as visual inspection, palpation, and intraoperative imaging, but without any intraoperative pathologic assessment of the surgical specimen) to assess tumor margins from patients with nonpalpable breast malignancies. After undergoing breast-conserving surgery 596 women were randomly divided to control and device arms. In addition to intraoperative imaging, MarginProbe was used in the device arm to examine the tumor margins and determine whether additional excision of breast tissue was required. 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. Results reported in 2014 by Schnabel and collaborators showed that in the device and control arms the rates of false-negative were 24.8% and 66.1%, respectively, and the rates of false-positive were 53.6% and 16.6%, respectively. The rate of CSR of all positive margins on positive main specimens was 62% (101 of 163) and 22% (33 of 147) in the device and control arms, respectively (p<0.001). The percentage of patients who underwent reexcision procedures was 19.8% (59 of 298) in the device arm versus 25.8% (77 of 298) in the control arm (6% absolute, 23% relative reduction), and there was no significant difference in the removed tissue volume. 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). Furthermore, how the device compares to other methods for intraoperative tissue assessment (i.e., cytology, frozen section analysis of the lumpectomy specimen, etc.) is unknown.

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

**Diffusion and cost:** In March 2013, Dune Medical announced that the first MarginProbe System had been installed in the United States. The average system cost, as reported in ECRI Institute’s PricePaid database by hospitals acquiring the device during the fourth quarter of 2013, is $39,995. 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. The Wall Street Journal reported in July 2013 that the added per-surgery cost of using the system during a breast resection was quoted by several hospitals as $995 per surgery.

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. 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.

**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 too large a 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. MarginProbe can be used during lumpectomy to assess whether tumor margins are cancer free, potentially reducing the need for second surgeries.
Experts commenting on MarginProbe thought it has the potential of improving patient quality of life by avoiding a need for second surgeries in women undergoing breast-conservation surgery. However, more data determining accurate distinction between negative and positive margins are needed for experts to adequately evaluate the medical need for this intervention. Overall, experts thought MarginProbe would be easily adopted by patients and physicians without causing significant disruption in health care infrastructure or patient management. 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 this intervention. \(^{104-109}\) We have organized the following discussion of expert comments according to the parameters on which they commented.

**Unmet need and health outcomes:** Because of a high percentage of lumpectomies requiring subsequent surgeries, an unmet need exists for a device that can rapidly assess margins to ensure complete excision of malignant breast tissue, the experts concurred. Although this intervention is not expected to affect long-term health outcomes, experts agreed patients would benefit from avoiding subsequent surgeries and the associated anxiety, distress, and safety issues. One clinical expert was concerned with the device’s sensitivity and specificity to reduce reexcision rates and would like to see more data to support MarginProbe’s purported mechanism of action.\(^{104}\)

**Acceptance and adoption:** Patients and physicians would easily adopt MarginProbe, the experts thought. They did not anticipate it having a significant impact on patient management; it would eliminate the need for postsurgery histology tests and reduce the number of subsequent surgeries. One expert speculated if MarginProbe consistently decreased the number of second lumpectomies, it could become standard practice of the clinical pathway.

**Health system infrastructure and staffing:** Aside from the actual cost of the MarginProbe device, experts assume that it would have minimal impact on health care system staffing and infrastructure. Even though MarginProbe adoption will require additional training and extend time of surgery, it would benefit patients by eliminating postsurgery histology tests and reducing second surgeries, an expert thought.

**Health disparities:** Most experts believe adoption of the MarginProbe system would not have a significant impact on health disparities. One expert expressed concern that if MarginProbe was offered exclusively at health centers serving high socioeconomic classes, it could restrict MarginProbe access for underserved populations, who would continue to undergo multiple surgeries to completely remove cancer tissue from the breast.\(^{104}\) Conversely, two experts did not anticipate the system affecting health disparities any more than other diagnostic and therapeutic methods on the market.\(^{106,107}\)
Colorectal Cancer Intervention
Stool DNA Molecular Test (Cologuard) 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, the U.S. Centers for Disease Control and Prevention estimated that in 2012, 34.9% of screening-eligible individuals were not up to date with screening recommendations and 27.7% of screening-eligible individuals had never undergone screening. Therefore, new screening methods are highly desired that could increase the percentage of the population that undergoes recommended CRC screening.

Intervention: Cologuard is an in vitro diagnostic test intended to detect genetic signatures of colorectal precancers and cancers in cells shed from the intestinal walls and excreted with stool. To undergo screening, patients provide a stool sample of at least 36 g, which is analyzed for the presence of three markers associated with CRC and precancerous lesions:

- Hypermethylated DNA derived from two genes known to be methylated in CRCs and adenomas (NDRG4 and BMP3)
- Alleles of the KRAS gene known to be acquired as somatic mutations in CRCs and adenomas
- Blood using a highly sensitive fecal immunochemical test (FIT)

Integration of the methylation marker, mutation marker, and hemoglobin results generates a positive or negative result based on cutoffs established by prior analysis of known samples.

The Exact Sciences CRC screening test is designed to be integrated easily into routine laboratory schedules and automated systems.

Clinical trials: Cologuard was assessed in a multicenter trial, DEEP-C (n=12,776), comparing the stool DNA test to FIT using colonoscopy as the standard of truth. Asymptomatic patients between the ages of 50 and 84 years and considered at average risk of CRC were enrolled in the trial. All patients provided a stool specimen and underwent colonoscopy screening within 90 days of providing the sample. The trial’s primary endpoint was the ability of the DNA test to detect colorectal cancer, with a secondary endpoint of the test’s ability to detect advanced precancerous lesions. All stool samples were analyzed in a central laboratory and testers were blinded to results of FIT and clinical findings. Among recruited participants, 9,989 (78.2%) had fully interpretable results with colonoscopy identifying 65 participants with CRC and 757 participants with advanced precancerous lesions. Compared to FIT, the stool DNA test demonstrated increased sensitivity for CRC (92.3% vs. 73.8%) and precancerous lesions (42.4% vs. 23.8%). Among participants with nonadvanced or negative findings by colonoscopy, the specificity of stool DNA testing and FIT were 86.6% and 94.9%, respectively. In a patient population at average risk for CRC, the number of individuals who would needed to be screened to detect one cancer was reported as 154 for colonoscopy, 166 for stool DNA testing, and 208 for FIT.

Manufacturer and regulatory status: Exact Sciences Corp. (Madison, WI) developed the Cologuard stool DNA screening test. In June 2013, Exact Sciences completed submission to FDA of a modular premarket approval (PMA) application for Cologuard. In March 2014, FDA’s Molecular and Clinical Genetics Advisory Panel met and voted (10-0) on three separate questions that the Cologuard test was safe, effective, and that its benefits outweighed its risks. FDA’s final decision on the Cologuard PMA is pending. Proposed product labeling submitted to the FDA panel describes the Cologuard test as follows.
Cologuard is intended for use as an adjunctive screening test for the detection of colorectal neoplasia associated DNA markers and for the presence of occult hemoglobin in human stool. A positive result may indicate the presence of colorectal cancer or pre-malignant colorectal neoplasia. Cologuard is not intended as a replacement for diagnostic colonoscopy. Cologuard is intended to be used in conjunction with colonoscopy and other test methods in accordance with recognized screening guidelines. A positive result in Cologuard, as with any screening test, should be followed by colonoscopy. Cologuard is intended for patients who are typical candidates for colorectal cancer screening, adults of either sex, 50 years or older, who are at average risk for colorectal cancer.

Pricing information is not available for the Exact Sciences CRC screening test; however, it will most likely be priced higher than FIT tests (which cost about $25) but lower than optical colonoscopy (which costs between $700 and $3,000 depending on type of colonoscopy and setting). \(^\text{118}\) Cost estimates suggest that the Exact Sciences CRC screening test would be priced at a few hundred dollars per test. \(^\text{119,120}\) The overall cost to implement a screening program based on the Exact Sciences CRC test would depend on the frequency with which the test must be administered to ensure adequate screening. The company has recommended a screening interval of 3 years, and a proposed postapproval study would examine the utility of repeat screening on that time frame. \(^\text{121}\) Ultimately, the cost-effectiveness of stool DNA-based screening would depend on additional factors such as sensitivity and specificity during real-world use, screening compliance rates, and patient compliance with followup care in the event of a positive screening result.

Exact Sciences has indicated that its test will undergo a parallel review by FDA and the U.S. Centers for Medicare & Medicaid Services (CMS) with the intention of establishing a national coverage determination. \(^\text{122}\) In April 2008, CMS issued a decision memo regarding fecal DNA testing for CRC to address earlier versions of stool DNA testing. At the time, CMS did not expand its CRC screening benefit to this technology; however, it stated that upon FDA approval of a novel, commercially available fecal DNA test, CMS would reconsider this position. \(^\text{123}\)

**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 fecal occult blood test (FOBT)/FIT, sigmoidoscopy every 5 years, double-contrast barium enema every 5 years, computed tomography colonography every 5 years, or colonoscopy every 10 years. \(^\text{124}\) For noncolonoscopy tests, positive results require a subsequent colonoscopy to confirm the result and perform any required biopsy of suspicious polyps. \(^\text{124}\) Stool DNA testing would provide another CRC screening option that would most likely compete with other noninvasive testing options such as FOBT/FIT.
Overall, experts suggested that stool DNA testing has potential to improve on the accuracy of current noninvasive stool-based tests such as FOBT and FIT, which could improve screening results. However, the biggest shifts in patient outcomes and management were envisioned in patients switching from colonoscopy to stool DNA testing or patients currently unscreened now opting for stool DNA testing, and expert commenters questioned whether these changes in screening patterns were likely; therefore, our overall assessment is that Cologuard is at the lower end of the high-impact-potential range.

Results and Discussion of Comments

Six experts, with clinical, research, health devices, and health systems backgrounds, offered perspectives on this topic. 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 improvements on existing CRC cancer screening methods was considered either moderately or very important by expert commenters. Commenters cited the large number of individuals who are not adherent with CRC screening despite the clear benefits of CRC cancer screening on survival and suggested that additional testing options could lead to additional patients being screened.

The stool DNA test’s potential to improve patient health is moderate according to the majority of expert commenters. On one hand, commenters cited the potential of a new noninvasive test to improve screening compliance and suggested that it represents an improvement over existing fecal tests testing for presence of blood (i.e., FIT, FOBT). However, commenters also noted that although the test demonstrated an improved sensitivity for CRC and precancerous lesions, no trial had indicated that this increase in sensitivity led to improved patient health outcomes. Additionally, commenters questioned whether results from a trial involving a one-time test could be extrapolated to the standard screening setting in which FIT or FOBT is performed annually. Lastly, although several commenters suggested that the stool DNA test could increase screening compliance, one reviewer with a health systems perspective noted that, like FIT and FOBT, Cologuard is still a fecal-based test requiring the patient to collect and return a stool sample, which some patients may find objectionable.

Acceptance and adoption: Expert comments on acceptance and adoption varied depending on whether the commenter viewed the stool DNA test as an alternative to FIT/FOBT or as an alternative to colonoscopy. Experts who saw the stool DNA test as competing with FIT/FOBT did not foresee large barriers to adoption and suggested that stool DNA testing could supplant these other noninvasive tests. Experts who saw the stool DNA test as competing with colonoscopy suggested that clinicians would be unlikely to recommend the stool DNA test over colonoscopy and, therefore, the stool DNA test would likely be reserved for the portion of the screening population that refuses colonoscopy. One commenter with a research perspective suggested that
clinicians’ high degrees of familiarity with existing test methods could pose a barrier to adoption of a new test and that further study might be needed to identify the best position for the stool DNA test within the CRC screening test menu. A commenter with a clinical perspective suggested that some patients who are highly motivated to undergo screening might opt for both colonoscopy and stool DNA testing.

Health care delivery infrastructure and patient management: Expert comments on potential changes to health care delivery infrastructure and patient management again diverged on whether the commenter viewed the stool DNA test as an alternative to colonoscopy or an alternative to other noninvasive test methods. If the stool DNA test were to replace colonoscopy for some patients, experts suggested, it would cause moderate shifts in both infrastructure and patient management. They cited the reduction in demand for screening colonoscopy and a shift of required resources from endoscopy suites to the clinical laboratory. Whereas if the stool DNA test were to replace other noninvasive tests, the majority of commenters thought, little change would be seen in health care infrastructure or patient management outside a potential change in the frequency of testing. One reviewer with a health devices perspective suggested that the adoption of stool DNA testing among non-screening–compliant patients could lead to an increase in demand for colonoscopy services.

Health Disparities: Expert commenters did not envision that the availability of stool DNA testing would have a significant impact on health disparities. Although some commenters suggested that an improved noninvasive test option could improve screening among underserved patient populations that might not have easy access to colonoscopy-based screening, other commenters suggested that the likely increased cost of stool DNA testing relative to FIT/FOBT could further exacerbate existing health disparities if this cost difference restricted its use.
Fertility Issues Associated with Gonadotoxict 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. Prepubertal girls and reproductive-age women who require gonadotoxic cancer treatments often express a desire to preserve fertility. In vitro fertilization and embryo cryopreservation is the only standard option available to girls and women who wish to be able to have children after cancer remission. 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. 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.

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. Before gonadotoxic cancer therapies are started, clinicians retrieve a patient’s ovarian tissue and carefully cryopreserve it. 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 among 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. Tissue harvesting can coincide with oophorectomy, and an ovarian biopsy specimen may be sent for histopathological analysis to rule out the presence of malignant cells. 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.

Once the patient completes treatment, reimplantation of the cryopreserved ovarian tissue is performed with the intent of restoring her 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). 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.

As an alternative, surgeons can also place the autograft in a heterotopic location such as the abdominal wall, forearm, or rectus muscle, 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.
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. 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. Puberty was successfully initiated via reimplantation of cryopreserved ovarian tissue in a 13-year-old girl with Ewing sarcoma several years earlier. 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. A 2013 study of 11 women who underwent reimplantation of cryopreserved ovarian tissue reported 5 live births and 1 ongoing pregnancy. 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. 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.

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. 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
- Boston IVF, Boston, MA
- Hadassah Medical Center, Jerusalem, Israel
- Oregon Health & Science University, Portland
- University of Kansas Medical Center Research Institute, Kansas City
- Weill Medical College of Cornell University, New York, NY

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.

Diffusion and cost: Initial uptake of ovarian tissue cryopreservation could be limited by lack of third-party coverage. 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). No specific policies were identified for the other six payers.

Although official policies generally 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.

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.\textsuperscript{167}

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.\textsuperscript{136,137} 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.\textsuperscript{137}

Besides ovarian tissue cryopreservation, several investigational approaches exist for fertility preservation: oocyte cryopreservation, oocyte in vitro maturation, and pharmacological ovarian suppression.\textsuperscript{138} With the exception of gonadal shielding and ovarian transposition to prevent radiation exposure, these fertility preservation options are limited to reproductive-age women.

**Figure 6. 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.\textsuperscript{168-173} 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 highlighted the lack of any fertility preservation options for prepubertal 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 health devices and research backgrounds noted the potential risk of re-seeding the cancer or passing genetic predisposition for malignancy to offspring.\textsuperscript{168,173}

**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.
Gastric Cancer Intervention
Ramucirumab (Cyramza) for Treatment of Gastric Cancer

**Unmet need:** The majority of patients with gastric cancer present with locally advanced or metastatic disease.\(^ {174}\) Despite recent advancements in surgical techniques, radiotherapy, and chemotherapy, the prognosis for these patients remains poor.\(^ {175}\) Inhibiting the vascular and epidermal growth factor pathways using targeted drugs has been a focus of experimental therapies for treating gastric cancers, but to date, these therapies have had limited success.\(^ {174,176,177}\)

**Intervention:** Vascular endothelial growth factor (VEGFs) are highly expressed by many tumor types and are thought to signal to their cognate receptors (e.g., VEGF receptor 2 [VEGFR2]) on endothelial cells, promoting these cells’ proliferation, migration, and survival. These processes are essential to angiogenesis, which is thought to be required for both the growth of large tumors and the metastasis (i.e., systemic spread) of cancers. Increased VEGF expression in tumors and serum is linked with lymph node involvement, metastasis, and poor outcomes for patients with advanced gastric cancer, providing a rational for this approach.\(^ {174,178-180}\)

Existing inhibitors of angiogenesis through the VEGF/VEGFR signaling axis target either a single VEGF ligand (e.g., VEGF-A by bevacizumab) or inhibit multiple receptor tyrosine kinases (e.g., the multikinase inhibitors sorafenib and sunitinib). Because multiple VEGFs exist, targeting a single VEGF may allow residual VEGFR activation by other ligands. Conversely, because available small-molecule kinase inhibitors simultaneously modulate multiple signaling pathways, they may have less favorable efficacy or toxicity profiles compared with agents of greater specificity.

Ramucirumab is a human monoclonal antibody specific for VEGFR2. Ramucirumab binds to the extracellular domain of VEGFR2, blocking this receptor from interacting with any VEGF ligands and inhibiting the downstream signaling cascade.\(^ {181,182}\) By targeting VEGFR2 and preventing interaction with all VEGFR2 ligands, ramucirumab may exhibit enhanced target inhibition and higher specificity than available VEGF/VEGFR–targeted agents.\(^ {182}\) Among VEGFR2-specific agents, ramucirumab is furthest along in development.\(^ {181}\) FDA has approved ramucirumab for patients with advanced gastric cancer or gastroesophageal junction adenocarcinoma, as a single agent after prior fluoropyrimidine- or platinum-containing chemotherapy. Ramucirumab is administered intravenously at a dosage of 8 mg/kg every 2 weeks.\(^ {183}\)

**Clinical trials:** Ramucirumab is being tested as second-line treatment of gastric cancer as a monotherapy ( REGARD trial)\(^ {184}\) and as combination therapy together with paclitaxel (RAINBOW trial).\(^ {185,186}\)

Results from a phase III, randomized, double-blind, placebo-controlled trial of 355 patients ( REGARD) were published in 2014.\(^ {184}\) Used as a second-line monotherapy administered at a dosage of 8 mg/kg every 2 weeks, ramucirumab met its primary endpoint of improving overall survival in patients as determined by investigator assessment (5.2 months with ramucirumab vs. 3.8 months with placebo; HR, 0.776; p=0.042).\(^ {184}\)

Although overall survival of patients in the REGARD trial seem incremental, these results have similar survival benefits to that of trials comparing second-line cytotoxic chemotherapy to best supportive care, which have the potential of including ramucirumab in a clinical pathway in which no second-line treatment for gastric cancer is available. Additionally, the results from this trial also confirm the participation of VEGFR2 in advanced gastric cancer and the importance of targeting this pathway to improve outcomes in this patient population.\(^ {184}\) As monotherapy, ramucirumab treatment was tolerated by patients. Ramucirumab prescribing information lists the most common side effects observed in patients with advanced gastric cancer were hypertension and diarrhea.\(^ {183}\) In the REGARD trial, the most common grade 3 adverse events experienced by patients were
hypertension (8% ramucirumab; 3% placebo), fatigue (6% ramucirumab; 10% placebo), anemia (6% ramucirumab; 8% placebo), abdominal pain (6% ramucirumab; 3% placebo), ascites (4.2% ramucirumab; 4.3% placebo), hyponatremia (3.4% ramucirumab; 0.9% placebo), and decreased appetite (3% ramucirumab; 3% placebo).183,184

As a combination therapy, ramucirumab and paclitaxel treatment met the endpoint of increasing overall survival by 2.27 months as determined by researcher assessment (9.63 months with ramucirumab plus paclitaxel vs. 7.36 months with paclitaxel; HR, 0.807; p=0.0169).185,186 Researchers presented the results from this phase III, randomized, double-blind, placebo-controlled trial of 665 patients (RAINBOW) at the 2014 Gastrointestinal Cancers Symposium. Even though median overall survival was 1.6 times greater in the ramucirumab and paclitaxel combination than ramucirumab alone, drug-related toxicities occurred at least twice as often with the combination therapy than with paclitaxel alone. The most common grade 3 and higher adverse events reported in the RAINBOW trial were neutropenia (40.7% combination; 18.8% paclitaxel), leukopenia (17.4% combination; 6.7% paclitaxel), hypertension (14.1% combination; 2.4% paclitaxel), anemia (9.2% combination; 10.3% paclitaxel), fatigue (7.0% combination; 4.0% paclitaxel), abdominal pain (5.5% combination; 3.3% paclitaxel), and asthenia (5.5% combination; 3.3% paclitaxel).185

**Manufacturer and regulatory status:** Ramucirumab was developed by ImClone Systems, a subsidiary of Eli Lilly and Co. (Indianapolis, IN). Based on the REGARD trial results, Eli Lilly submitted a biologics license application (BLA) to FDA for use of single-agent ramucirumab in treating gastric cancer. FDA granted the BLA a priority review designation and approved ramucirumab in April 2014.

**Diffusion and cost:** According to a U.S.-based, online aggregator of prescription-drug prices performed in June 2014, the month when Cyramza became available in the market, the retail price for six vials (a single dose for a patient weighing 70kg) of Cyramza (100 mg/10mL) ranged between $6,500 and $7,000.187 No coverage, coding, or payment information regarding ramucirumab is available at this time. However, drugs intended to treat patients in whom cancer has been diagnosed are typically covered for their FDA-approved indications. For example, the VEGF inhibitor bevacizumab is considered medically necessary and is covered for its FDA-approved indications by multiple third-party payers.188-197 Therefore, because of its FDA approval, use of ramucirumab for treating patients with locally advanced or metastatic gastric cancer is likely to be reimbursed. As an IV drug administered by health care professionals, ramucirumab would be covered under health plans’ medical benefit.

**Clinical Pathway at Point of This Intervention**

Metastatic gastric cancer is typically treated with systemic chemotherapy.177,198 In cases of acute bleeding or gastrointestinal blockage, radiation therapy and/or surgical resection may be employed. First-line chemotherapy typically includes a combination of fluoropyrimidine/platinum-based chemotherapies with or without targeted molecular therapy (e.g., the monoclonal antibody trastuzumab in the case of human EGFR2–positive disease).175,177,180 Additional, targeted therapies under investigation for treating gastric cancer act on a variety of molecular signaling pathways, including EGFR, hepatocyte growth factor receptor (cMET), mTOR, and VEGF.179,180

In clinical trials, ramucirumab is administered in combination with paclitaxel or best supportive care in the second-line treatment setting. Ramucirumab is likely to be part of combination therapy for metastatic disease that includes other systemic chemotherapies or targeted therapies or both.199
Figure 7. Overall high-impact potential: ramucirumab (Cyramza) for treatment of gastric cancer

Most experts commenting on ramucirumab agreed that there is a need for alternative advanced gastric cancer therapies. Although ramucirumab showed efficacy in patients with gastric cancer, experts thought ramucirumab has moderate potential to fulfill this need because survival was marginally increased and the benefits might not outweigh the increase in adverse events. Experts agreed ramucirumab for treating gastric cancer is not sufficient as monotherapy and most likely will be part of a combination therapy. 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 ramucirumab for treating gastric cancer.\textsuperscript{200-205} We have organized the following discussion of expert comments according to the parameters on which they commented.

Unmet need and health outcomes: Because of the limited response to chemotherapy intervention and lack of alternative options for gastric cancer treatments, experts agreed that an unmet need exists and ramucirumab has the potential to address this unmet need. However, combination therapy of ramucirumab plus chemotherapy as second-line treatment was associated with severe adverse events, and experts pointed out that survival was increased by only a few months. In contrast, a clinical expert suggested that as monotherapy, ramucirumab could be an alternative for patients who cannot tolerate the side effects of doublet and triplet chemotherapy.\textsuperscript{203}

Acceptance and adoption: Experts anticipate that both physicians and patients will adopt ramucirumab for treating gastric cancer. Physicians do not have many second-line alternatives and most likely will adopt ramucirumab as a combination therapy. Patients will probably accept ramucirumab because it would be the only alternative to extend their lifespans. However, an expert remarked that for elderly patients, minimal life extension would not be worth experiencing ramucirumab-associated adverse events.

Health care delivery infrastructure and patient management: Experts do not anticipate any change in health care delivery and infrastructure. They thought ramucirumab could be easily incorporated by physicians and hospital staff who are already trained to administer IV chemotherapy. Patient management is also expected to be unaffected. An expert with a research perspective anticipates that monitoring for adverse events, particularly hypertension, will be important for patient outcomes.\textsuperscript{201}

Health disparities: Experts expect that ramucirumab will have disparities similar to other antibody-based therapies: it will be too expensive for underprivileged or uninsured patients. Being a new treatment for a cancer that has limited second-line options, ramucirumab however, will most likely have third-party payer coverage and be available to patients who have gastric cancer.
Hematologic Malignancy Interventions
Ibrutinib (Imbruvica™) and Idelalisib 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. NHLs derived from both B cells and T cells exist; however, the majority are of B-cell origin. 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 (CLL) and mantle cell lymphoma. For patients with these conditions whose disease has recurred and who exhibit resistance to rituximab, few treatment options exist. Moreover, patients with some forms of CLL, such as that harboring a deletion on the short arm of chromosome 17, have a poor prognosis.

Intervention: Ibrutinib (Imbruvica™) is a first-in-class, orally administered, small molecule that inhibits Bruton’s tyrosine kinase (Btk), a nonreceptor tyrosine kinase that plays multiple roles in the regulation of B lymphocytes.206 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, inhibiting Btk may inactivate these pathways, potentially depriving malignant B cells of signals driving proliferation and survival.206 Besides Btk’s role in regulating proliferation and survival downstream of the B-cell receptor, it 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 to be caused by the inhibition of these pathways.207,208

Idelalisib is a first-in-class, orally administered, small-molecule inhibitor of phosphoinositide 3-kinase (PI3K) delta.209,210 PI3K plays a central role in regulating fundamental processes such as cell growth, proliferation, and survival. In certain cancers, including NHLs, the PI3K pathway becomes highly active and is thought to contribute to malignant transformation. Like Btk, PI3K signals downstream of the B-cell receptor, and it has been hypothesized to play a role in malignant transformation caused by chronic B-cell receptor signaling.206 Four PI3K catalytic subunit isoforms exist: alpha, beta, gamma, and delta. The delta isoform is predominantly expressed in immune-system cells, particularly leukocytes, and is thought to play a role in regulating leukocyte proliferation. Idelalisib is selective for the PI3K delta isoform; therefore, its PI3K pathway-inhibiting activity may be limited to hematologic cells, potentially targeting malignant B cells while limiting systemic toxicity that might be associated with pan-PI3K inhibition.211,212

Clinical trials: Investigators have reported results from multiple trials of ibrutinib and idelalisib in treating patients with various NHLs.

From a single-arm, open-label trial (n=85) of ibrutinib (420 or 840 mg once daily) in patients with CLL 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.213 In a separate single-arm,
open-label trial of ibrutinib (420 mg once daily) in 53 patients with high-risk CLL (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.\textsuperscript{214} Importantly, both ibrutinib trials in patients with CLL demonstrated equivalent response rates in patients with or without a 17p deletion.\textsuperscript{213,214}

More recently, researchers presented results from the first randomized controlled trial of ibrutinib in patients with CLL, the RESONATE trial. In this open-label trial, 391 patients with relapsed/refractory CLL were randomly assigned to treatment with either ibrutinib (420 mg once daily) or ofatumumab (300 mg initial dose, 2,000 mg weekly for weeks 2–8, and 2,000 mg every 4 weeks for weeks 12–24). Compared with patients receiving ofatumumab, patients receiving ibrutinib exhibited improved progression-free survival (median not reached vs. 8.1 months; HR, 0.215; p<0.0001) and improved overall survival (median not reached in either arm; HR, 0.434; p=0.0049).\textsuperscript{215}

For patients with mantle cell lymphoma, data from a single-arm, open-label trial of ibrutinib (560 mg once daily) in 111 patients with relapsed or refractory disease, Wang and colleagues reported an overall response rate of 68% (21% complete response, 47% partial response).\textsuperscript{216}

In clinical trials, ibrutinib was reported as being well tolerated, with the majority of adverse events being of mild-to-moderate severity.\textsuperscript{213,214} According to ibrutinib’s prescribing information, common adverse events included abdominal pain, anemia, arthralgia, bruising, constipation, decreased appetite, diarrhea, dizziness, dyspnea, fatigue, musculoskeletal pain, nausea, neutropenia, peripheral edema, pyrexia, rash, sinusitis, stomatitis, thrombocytopenia, upper respiratory tract infection, and vomiting.\textsuperscript{217}

Regarding idelalisib, investigators published results in 2014 from a randomized, double-blind, placebo-controlled trial in treating relapsed/refractory CLL.\textsuperscript{218} In this trial, 220 patients with decreased renal function, previous therapy-induced myelosuppression, or major coexisting illnesses received rituximab and either idelalisib (150 mg twice daily) or matching placebo. On the primary endpoint of progression-free survival, median progression-free survival had not been reached at the time of analysis in the idelalisib group compared to a median of 5.5 months in the placebo group (HR for progression or death 0.15, p<0.001). Overall response rate also favored patients in the idelalisib arm compared with response rate in patients in the placebo arm (81% vs. 13%, odds ratio 29.92, p<0.001). Serious adverse events occurred in 40% of patients in the idelalisib arm compared with 35% of patients in the placebo arm.

Investigators also published results in 2014 from a trial of idelalisib in patients with relapsed/refractory indolent NHL (follicular lymphoma, small lymphocytic lymphoma, marginal-zone lymphoma, or lymphoplasmacytic lymphoma) who had received between 2 and 12 previous indolent NHL therapies (median 4).\textsuperscript{219} In this trial (n=125), all patients received idelalisib (150 mg twice daily). Investigators reported a 57% response rate, including a 6% complete response rate.

In clinical trials, treatment with idelalisib was reported as being well tolerated with the majority of adverse events being mild to moderate in severity.\textsuperscript{218,219} Frequent adverse events associated with idelalisib monotherapy included cough, diarrhea, dyspnea, fatigue, pneumonia, pyrexia, and rash.\textsuperscript{219} Frequent adverse events associated with idelalisib used in combination with rituximab included chills, cough, fatigue, infusion-related reactions (due to rituximab infusion), nausea, and pyrexia. Rates of chills, diarrhea, pyrexia, and rash were higher in the idelalisib-plus-rituximab arm than in the placebo-plus-rituximab arm.\textsuperscript{218}

**Manufacturer and regulatory status:** Ibrutinib was developed by Pharmacyclics, Inc. (of Sunnyvale, CA), in collaboration with the Janssen Biotech unit of Johnson & Johnson (New Brunswick, NJ). FDA has granted ibrutinib breakthrough therapy designation for three indications: (1) CLL harboring a 17p deletion, (2) relapsed/refractory mantle cell lymphoma, and (3)
Waldenström’s macroglobulinemia. 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. A second accelerated approval for use of the drug in treating patients with CLL who have received at least one prior therapy followed in February 2014. In April 2014, the developers submitted a supplemental new drug application seeking full approval for the CLL indication based on the RESONATE trial data. According to a June 2014 query of a U.S.-based, online aggregator of prescription-drug prices, the retail price for ibrutinib at the CLL and mantle cell lymphoma doses is approximately $8,700 per month and $11,600 per month, respectively. 

Idelalisib is being developed by Gilead Sciences, Inc. (Foster City, CA). FDA has granted idelalisib breakthrough therapy designation for treating patients with CLL. In September 2013, the company submitted a new drug application to FDA for using idelalisib in treating indolent NHL, and a decision deadline under the Prescription Drug User Fee Act (PDUFA) is set for September 2014. In December 2013, a second new drug application was submitted to FDA for the CLL indication. The CLL new drug application has been granted priority review by FDA, and a PDUFA decision date has been set for August 2014.

Several additional novel agents are also in late-stage clinical trials for treating B-cell NHLs, in particular CLL. FDA recently approved obinutuzumab (Gazyva™), a next-generation anti-CD20 antibody for treating CLL, and positive results have been reported for the phosphoinositide 3-kinase inhibitor idelalisib in treating CLL and indolent NHLs. Additional studies will be needed to optimize the combination 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 NHL diagnosed in the patient, the patient’s overall condition, and his or her response to any earlier lines of therapy. Treatments for CLL, indolent NHL, and mantle cell lymphoma include various combinations of cytotoxic agents typically in combination with the monoclonal antibody rituximab. Other agents used in treating relapsed/refractory NHLs include bortezomib and lenalidomide for mantle cell lymphoma and alemtuzumab, lenalidomide, obinutuzumab, and ofatumumab for CLL. Ibrutinib and idelalisib would represent additional treatment options for patients with relapsed B-cell NHL or certain high-risk patients with previously untreated NHL (e.g., patients with CLL harboring a chromosome 17 deletion).

**Figure 8. Overall high-impact potential: ibrutinib (Imbruvica) and idelalisib for treating non-Hodgkin’s lymphomas**

Overall, experts opined that a significant need exists for novel treatments of B-cell lymphomas and that the response rates observed in initial trials of ibrutinib and idelalisib indicated that the drugs have significant potential to improve patient outcomes. However, reviewers suggested that further study is needed to confirm this early promise, particularly studies comparing ibrutinib and idelalisib to alternative treatments. Experts believe that the relatively benign side-effect profile of
ibrutinib and idelalisib and their potential to be used in treating several B-cell malignancies are significant. Based on this input, our overall assessment is that this intervention is in the higher end of the high-impact-potential range.

Results and Discussion of Comments

Six experts, with clinical, research, and health systems backgrounds, offered perspectives on the topic of ibrutinib for treating CLL.230-235 and six experts, with similar backgrounds, offered perspectives on the topic of ibrutinib for treating mantle cell lymphoma.236-241 It should be noted that experts offered perspectives on these topics before the recent release of data from the phase III trial comparing ibrutinib with ofatumumab in treating patients with relapsed/refractory CLL. We have organized the following discussion of expert comments according to the parameters on which they commented.

Ibrutinib

Unmet need and health outcomes: A moderate to high unmet need for new treatments for CLL and mantle cell lymphoma was seen by the majority of expert commenters. They cited the propensity of these malignancies to recur and the lack of effective treatment options for patients with relapsed disease. However, multiple commenters also noted that the relatively small number of patients affected by the diseases (particularly mantle cell lymphoma) limited the magnitude of the unmet need.

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.234

Acceptance and adoption: Both clinicians and patients were seen by commenters as highly likely to 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. However, 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.

Health disparities: Commenters noted that disparities could be exacerbated for those unable to pay for the drug, as it is likely to be costly. This would be primarily an issue for the uninsured, as commenters thought that payers would be likely to cover the drug once it is approved.
Idelalisib

Six experts, with clinical, research, and health systems backgrounds, offered perspectives on the topic of idelalisib for treating CLL,\textsuperscript{242-247} and six experts, with similar backgrounds, offered perspectives on the topic of idelalisib for treating indolent NHL.\textsuperscript{248-253}

**Unmet need and health outcomes:** A moderate unmet need exists in the treatment of CLL and indolent NHL according to the majority of expert commenters, who cited the fact that treatments for these conditions are rarely curative and that treatment options for patients with relapsed/refractory disease are of limited efficacy. One expert with a clinical perspective suggested that patients intolerant of intensive chemotherapy treatments (e.g., elderly patients, patients with coexisting conditions) in particular had few available treatment options.\textsuperscript{245} Commenters viewing the unmet need that idelalisib purports to address as only minimal cited the range of available therapies used in treating B-cell lymphomas and noted that idelalisib was being used as an adjunctive therapy to rituximab in the largest clinical trial of the drug reported to date. One commenter with a clinical perspective suggested that the availability of ibrutinib limited the magnitude of the unmet need in treating CLL; however, this commenter also noted that differences between the drugs are likely to render them each more efficacious in certain contexts.\textsuperscript{246}

Idelalisib has a moderate potential to improve CLL and indolent NHL patient health according to the majority of expert commenters, who cited the promising data from initial trials of the drug and its logical mechanism of action. The majority of commenters also noted the preliminary nature of the data on idelalisib’s safety and efficacy. Underscoring the preliminary nature of the data, one commenter with a clinical perspective suggested that initial data indicated limited accumulating toxicity with long-term exposure to idelalisib while also suggesting that the long-term effects of PI3K inhibition by idelalisib would need to be examined in further trials.\textsuperscript{251} Commenters who suggested that idelalisib has only minimal potential to improve patient health cited the preliminary nature of the data and suggested that this left them unsure of the ultimate clinical benefit provided by the drug.

**Acceptance and adoption:** Both physicians and patients would likely widely adopt idelalisib, the experts thought, given limited treatment alternatives, ease of oral administration, and preliminary data indicating promising signs of efficacy. Expert commenters who envisioned less widespread adoption again cited the preliminary nature of the data and suggested that some physicians and patients would await further data before opting for idelalisib treatment. Additionally, experts envisioned a high cost of idelalisib, which could place a financial burden on patients and cause them to opt for treatment alternatives.

**Health system infrastructure and staffing:** As an orally administered drug, idelalisib is unlikely to cause much if any change in health care system infrastructure and staffing, according to experts. A few experts suggested that displacement of certain intravenously administered CLL and indolent NHL treatments by idelalisib could cause a shift of patient care out of infusion centers; however, this was only seen as a minor disruption to the health care system.

**Health disparities:** Commenters noted that disparities could be exacerbated for those unable to pay for the drug, as it is likely to be costly. Some commenters thought that efficacy of this drug was still uncertain enough that they were unsure about the likelihood for coverage by insurance.
Siltuximab (Sylvant) for Treatment of Multicentric Castleman's Disease

**Unmet need:** Castleman’s disease (also known as giant lymph node hyperplasia or angiofollicular lymph node hyperplasia) is a rare lymphoproliferative disorder that manifests as enlarged lymph nodes caused by accumulation of nonclonal B cells.\textsuperscript{254} Patients with multicentric Castleman’s disease experience significant morbidity. Few treatment options are available, and relapses in this patient population are common.\textsuperscript{255} Therefore, novel treatments are needed. The recent FDA approval of siltuximab (Sylvant™) makes available for the first time a medication specifically indicated for treating patients with multicentric Castleman’s disease.

**Intervention:** Overproduction of the pleiotropic cytokine interleukin-6 (IL-6) has been implicated in the pathogenesis of Castleman’s disease.\textsuperscript{255} Evidence suggesting a role for IL-6 in Castleman’s disease has come from multiple sources. Researchers have observed elevated levels of IL-6 in patients with the disease. Additionally, animal models in which IL-6 expression was experimentally elevated developed symptoms consistent with Castleman’s disease. Lastly, a link between human herpes virus-8 (HHV-8) infection and Castleman’s disease has been attributed to the production of a viral IL-6 ortholog, vIL-6 (an orthologous gene is one present in different species that evolved from a common ancestor).\textsuperscript{256} Based on these observations, researchers have hypothesized that blocking the activity of IL-6 could ameliorate the symptoms of Castleman’s disease.\textsuperscript{256,257}

Siltuximab is a chimeric monoclonal antibody for IL-6. Antibody binding to IL-6 may neutralize the cytokine, preventing it from exerting its pathogenic effects.\textsuperscript{257} In clinical trials for treating Castleman’s disease, siltuximab is being administered in a 1-hour infusion at a dose of 11 mg/kg. Infusions are given once every 3 weeks and the treatment may go on indefinitely, barring disease progression or toxicity.\textsuperscript{258,259}

**Clinical trials:** Siltuximab was studied in an 80-patient, randomized, placebo-controlled, double-blind clinical trial in which patients were assigned in a 2:1 ratio to treatment with either siltuximab or placebo.\textsuperscript{258} Although Castleman’s disease is frequently associated with HHV-8 infection in HIV-positive patients, HHV-8 and HIV-positive patients were excluded from the trial because siltuximab did not demonstrate binding to viral IL-6 in a preclinical trial.\textsuperscript{260} The primary endpoint of the trial was the number of patients who achieved a tumor response and a symptomatic response. In the trial, a higher percentage of patients in the siltuximab arm achieved a durable tumor and symptomatic response than patients in the placebo arm (34\% vs. 0\%, p=0.0012). The rate of treatment-emergent adverse events was similar in the siltuximab- and placebo-treated patients despite patients receiving siltuximab for more than twice as long as patients received placebo (median 375 days vs. 152 days). Grade 3 or above adverse events were reported in 47\% of patients receiving siltuximab versus 54\% of patients receiving placebo, and severe adverse events were reported in 23\% of patients receiving siltuximab versus 19\% of patients.\textsuperscript{258} The most common adverse events that occurred at least 10\% more often in patients receiving siltuximab than with placebo were pruritus, increased weight, rash, hyperuricemia, and upper respiratory tract infection.\textsuperscript{260}

**Manufacturer and regulatory status:** Siltuximab was developed by the Janssen Biotech unit of Johnson & Johnson (New Brunswick, NJ). In April 2014, FDA approved a BLA for siltuximab, allowing marketing of siltuximab for treating patients “with multicentric Castleman’s disease (MCD) who are human immunodeficiency virus (HIV) negative and human herpesvirus-8 (HHV-8) negative.”\textsuperscript{260,261} The siltuximab BLA was reviewed under FDA’s priority review program, and the...
agency had previously granted siltuximab orphan drug status for treating multicentric Castleman’s disease.\textsuperscript{261,262}

**Diffusion and cost:** Siltuximab has only recently become available on the U.S. market. According to a June 2014 query of a U.S.-based, online aggregator of prescription-drug prices, retail prices for 100 mg and 400 mg vials of siltuximab for infusion are about $940 and $3,600, respectively.\textsuperscript{263} A 70 kg (154 lb) adult at a dose of 11 mg/kg administered once every 3 weeks would require approximately two 400-mg vials per treatment, which would cost about $7,200 per treatment.

**Clinical Pathway at Point of This Intervention**

Before siltuximab was approved, no therapies had been approved by FDA for treating multicentric Castleman’s disease; however, multiple systemic therapies have been used off label. These have included traditional cytotoxic chemotherapy regimens as well as more recent additions, such as the anti-CD20 monoclonal antibody rituximab and the immunomodulatory drug thalidomide.\textsuperscript{254,255}

Several antibodies targeting IL-6 signaling exist besides siltuximab. Although the majority of these compounds are investigational and, therefore, are not commercially available, one anti-IL-6–receptor antibody, tocilizumab, is FDA approved for another condition, rheumatoid arthritis. Preliminary studies of tocilizumab for treating Castleman’s disease have been conducted, and the drug could be prescribed off label for this indication.\textsuperscript{256}

![Figure 9. Overall high-impact potential: siltuximab (Sylvant) for treatment of multicentric Castleman's disease](image)

Overall, experts concurred that siltuximab has potential to fill a significant unmet need of patients with multicentric Castleman’s disease, given results from a clinical trial and the fact that FDA has approved no other therapies for this indication. However, siltuximab’s overall impact is limited by the small size of the eligible patient population and the preliminary nature of the data on a therapy that could potentially be taken for extended periods. 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 this topic.\textsuperscript{264-269} 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 novel therapies for treating Castleman’s disease is moderately to very important according to expert commenters, who cited the lack of FDA-approved therapies for the condition and its significant morbidity. Although commenters universally noted the lack of effective therapies, the majority also noted that the small
number of patients affected by this condition limited the magnitude of the unmet need overall. The majority of expert commenters suggested that siltuximab has moderate potential to improve health in patients with multicentric Castleman’s disease. Although commenters suggested that the phase II trial results that led to FDA approval were promising in terms of response rate and limited toxicity, they also noted the preliminary nature of these data. Experts noted that siltuximab does not represent a cure for multicentric Castleman’s disease and, therefore, longer-term studies of the treatment’s impact on patient outcomes and quality of life are needed.

**Acceptance and adoption**: Siltuximab is likely to achieve moderate to wide adoption by clinicians and patients, according to expert commenters. These commenters noted that lack of viable alternatives, the relatively low levels of toxicity associated with treatment, and the familiar mode of IV infusion as factors promoting clinician adoption. However, several experts suggested that cost might be a barrier for some patients and the need for ongoing infusions every 3 weeks. Additionally, one expert with a clinical perspective suggested that the potential for hypersensitivity reactions, which could require hospitalization, could dissuade some patients.

**Health care delivery infrastructure and patient management**: Siltuximab would cause little to no change in health care facility staffing or infrastructure according to expert commenters. Commenters cited the familiar mode of IV infusion and the fact that patients with multicentric Castleman’s disease frequently receive off-label IV treatments for their disease. Furthermore, experts thought that the small number of patients with multicentric Castleman’s disease would limit any potential impacts in health care delivery and infrastructure.

**Health disparities**: Siltuximab cost information was not available to expert commenters at the time they commented. Even in the absence of this information, the consensus among commenters was that siltuximab would likely be expensive, based on similar drugs. The anticipated per-infusion cost, combined with the need to receive the infusions for an extended period of time, led commenters to conclude that adoption of siltuximab would increase the cost of care for this patient population. As a result, this new therapy may exacerbate disparities between the un- or underinsured and those who can either afford it or whose insurance covers it.
Prostate Cancer Interventions
Enzalutamide (Xtandi) for Treatment of 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.\(^{270}\) 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 even when castration-level androgens are being used 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.\(^{270}\) This hypothesis was affirmed by the demonstration that further inhibition of androgen synthesis with abiraterone improved outcomes in this patient population.\(^{271}\)

Enzalutamide (Xtandi\textsuperscript{®}) 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.\(^{272}\) Unlike available androgen receptor antagonists, enzalutamide purportedly exhibits no androgen-receptor agonist activity.

Enzalutamide is an oral medication given at a dose of 160 mg (4 capsules), taken once daily. Unlike the recently FDA-approved androgen-synthesis inhibitor abiraterone, enzalutamide does not require co-administration of low-dose prednisone.\(^{273,274}\)

**Clinical trials:** Enzalutamide has been studied in two phase III, randomized, double-blind, 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

Both trials were stopped early after interim analyses indicated a benefit of active treatment.\(^{275,276}\)

In the AFFIRM trial, overall survival in 800 patients randomly assigned to receive enzalutamide was 18.4 months versus 13.6 months in 399 patients assigned to receive placebo (HR, 0.63; 95% CI, 0.53 to 0.75; \(p<0.001\)).\(^{275}\) In the PREVAIL trial, enzalutamide improved progression-free survival and overall survival compared with placebo; risk of disease progression or death were decreased by 81% (HR, 0.19; 95% CI, 0.15 to 0.23; \(p<0.001\)) and 29% (HR, 0.71; 95% CI, 0.60 to 0.84; \(p<0.001\)), respectively.\(^{276}\) 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.\(^{275,276}\)

**Manufacturer and regulatory status:** Medivation, Inc. (San Francisco, CA), and Astellas Pharma, Inc. (Tokyo, Japan), jointly developed and market enzalutamide. Basing its decision on the AFFIRM trial data, FDA approved enzalutamide in August 2012 for treating mCRPC in patients who have previously received treatment with docetaxel.\(^{277}\) A supplemental new drug application for using enzalutamide in chemotherapy-naïve patients with mCRPC has been submitted to FDA. The agency has granted the new drug application a priority review designation, and a decision date under the PDUFA is set for September 18, 2014.\(^{278}\)

**Diffusion and cost:** In the U.S. market, enzalutamide has been available since September 2012. National Comprehensive Cancer Network guidelines include use of enzalutamide as a treatment
option for patients with mCRPC, both before and after chemotherapy with docetaxel.\textsuperscript{279} Ongoing phase III trials may lead to expanded indications in chemotherapy-naïve mCRPC and nonmetastatic CRPC, promoting further diffusion.\textsuperscript{280} A June 2014 query of a U.S.-based, online aggregator of prescription-drug prices identified a retail price of about $8,500 for a 1-month supply of enzalutamide, or $102,000 per patient per year.\textsuperscript{281}

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.\textsuperscript{282-285} These payers considered enzalutamide to be medically necessary when prescribed according to FDA-approved indications for mCRPC; but 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 June 2014 publication of the PREVAIL data in chemotherapy-naïve patients. Formularies of representative plans classify enzalutamide as a specialty pharmaceutical and 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 have been 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 abiraterone, the radiopharmaceutical radium-223, or the taxane cabazitaxel.\textsuperscript{279} In its FDA-approved indication, enzalutamide represents a potential treatment alternative after docetaxel has been used, and based on recently published data from chemotherapy-naïve patients, may move into this setting as well.

**Figure 10. Overall high-impact potential: enzalutamide (Xtandi) for treatment of metastatic castration-resistant prostate cancer**

Overall, experts suggested that enzalutamide has significant potential to improve health outcomes in patients with mCRPC, citing the positive results in terms of progression-free and overall survival observed in two randomized controlled trials. Basing their opinions on the observed efficacy and ease of administering enzalutamide, commenters envisioned widespread adoption. Studies are needed to integrate enzalutamide and other recently approved prostate cancer therapies
into treatment guidelines. 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, health systems, and health administration backgrounds, offered perspectives on enzalutamide for treating prostate cancer.\cite{286,291} 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 enzalutamide purportedly addresses is moderately to very important according to experts commenting. They cited the need for additional therapies for CRPC. Experts rating enzalutamide’s importance as moderate suggested that the recent availability of other treatments intended for this patient population (i.e., sipuleucel-T, abiraterone) reduced the magnitude of unmet need. However, two clinical experts suggested that even the incremental benefit of enzalutamide over existing options was significant, citing the observable prostate-specific antigen (PSA) declines during enzalutamide treatment as a benefit over sipuleucel-T, and the lack of need to monitor liver function as a benefit over abiraterone.\cite{286,290} Similarly, enzalutamide’s potential to improve patient health has moderate to high potential, according to expert commenters. They cited the two positive phase III trials of enzalutamide, which both demonstrated improved overall survival. Multiple expert commenters suggested that clinical trials were needed to assess the benefits of enzalutamide relative to the recently approved hormone therapy abiraterone.

**Acceptance and adoption:** Experts expected widespread adoption of enzalutamide by both physicians and patients. They cited the promising safety and efficacy results in clinical trials, the ease of oral, once-daily administration, and the limited patient monitoring required of clinicians as factors favoring adoption. The only barrier envisioned by expert commenters was the high cost of therapy, which even when covered by insurers could involve high co-payments, which could dissuade some patients from accessing or opting for the therapy.

**Health care delivery infrastructure and patient management:** Adopting the therapy would involve minimal changes to health care delivery infrastructure or patient management, experts thought. Some experts noted the potential for small shifts in patient management if patients who might otherwise have received the autologous vaccine sipuleucel-T—which is administered by infusion and requires multiple immune cell collections by leukapheresis—receive enzalutamide instead.

**Health disparities:** Prostate cancer is diagnosed at later stages, and survival is worse in minority populations and in those with lower socioeconomic status. The high cost of this therapy could further exacerbate disparities in treatment for those who are insured but unable to afford the co-payments and for the uninsured.
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 inconsistent results and predictive values.\(^{292,293}\) The standard of care, transrectal ultrasound (TRUS)-guided prostate biopsy, provides a convenient and cost-efficient approach, but procedural shortcomings include high false-negative rates as well as high rates of detecting microfocal cancers of little clinical significance.\(^{292,294}\) Although considered more accurate, MRI-guided targeted biopsy is more expensive than TRUS-guided prostate biopsy and requires highly specialized equipment and staff training.\(^{292,294}\) 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 magnetic resonance imaging (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.\(^{295-297}\) 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.\(^{292,294}\) MRI-TRUS fusion-guided biopsy requires coordination between the radiologist who interprets the MRI and the urologist who performs the TRUS.

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.\(^{292,294}\) 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.\(^{292,294,298,299}\)

**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 had either persistent, elevated PSA levels but an earlier 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.\(^{295}\)

Data were released from a second study using the PercuNav image fusion and navigation technology (Royal Philips Electronics, Amsterdam, the Netherlands) and performed 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 did biopsy, and fewer cases of Gleason score 3+4 or lower, “thus mitigating the detection of lower-grade disease.”\(^{300}\) In a study published in 2009 of 693 prostatectomy and 119 biopsy specimens, Stark and colleagues found that a Gleason score of 4+3 was associated with higher mortality than the Gleason 3+4 pattern.\(^{301}\)
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.\textsuperscript{302}

An ongoing clinical trial of the PercuNav image fusion and navigation technology is under way, 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.\textsuperscript{303} Another trial is comparing positive biopsy rates using the Urostation image-fusion platform, developed by Koelis (Grenoble, France) compared with standard TRUS-guided biopsy in 300 patients with suspected prostate cancer and no prior prostate biopsy history.\textsuperscript{304}

**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\textsuperscript{305}
- BioJet\textsuperscript{TM} 3D MR-TRUS Fusion Prostate Biopsy System, Geo Scan Medical, LLC (Lakewood Ranch, FL)\textsuperscript{306}
- BiopSee Advanced Image Guided Prostate Biopsy System, MedCom\textsuperscript{307}
- Hi Vision Ascendus Platform with real-time virtual sonography, Hitachi Medical Corp. (Tokyo, Japan)\textsuperscript{308}
- PercuNav image fusion and navigation technology, Philips\textsuperscript{309}
- UroNav Fusion Biopsy System, Invivo Corp., a Philips subsidiary\textsuperscript{310}
- UroStation, Koelis\textsuperscript{311,312}

These devices have received 510(k) marketing clearance from FDA.\textsuperscript{305,309,313-317}

**Diffusion and cost:** Image-fusion, prostate-biopsy software platforms are gradually diffusing throughout the United States. The 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.\textsuperscript{312,313,315} Many newly purchased systems for prostate biopsy include software with this capability.\textsuperscript{306,308}

MRI-TRUS image fusion–guided biopsies cost more to perform than standard TRUS-guided biopsy for image acquisition and processing; however, the fusion–guided biopsy is likely to be substantially less expensive than an in-bore MRI-guided biopsy. Despite the increased cost of MRI-TRUS fusion biopsy, the majority of costs associated with prostate cancer come from treating the disease. More accurately identifying those with clinically significant cancer in need of treatment might offset increased costs of diagnostic accuracy.\textsuperscript{318} An estimated 1 million prostate biopsies are performed in the United States each year;\textsuperscript{292} therefore, modifying the standard of care for prostate biopsy could have a significant impact on overall costs of prostate cancer screening, diagnosis, and treatment.

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 policies for 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 diagnosis (e.g., magnetic resonance spectroscopy, MRI, or saturation biopsy) and staging to be investigational and therefore ineligible for coverage.\textsuperscript{319-324} Ongoing trials of image fusion platforms may support diffusion.
**Clinical Pathway at Point of This Intervention**

Primary screening for prostate cancer often begins in people around the age of 50 years and may include digital rectal exams and PSA testing, although recommendations for PSA testing have recently changed. Abnormal findings on these tests or other suspicions of prostate cancer often warrant a prostate biopsy. 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. 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. Multiparametric MRI has been explored as an imaging modality with the potential to identify suspicious areas and obtain targeted biopsies. Besides the purported improvement in prostate cancer detection, MRI may enable physicians to distinguish small, indolent lesions from higher-grade, more clinically significant lesions. However, in-bore MRI-guided biopsy is expensive, cumbersome, and must be performed in a specialized setting. Image fusion–guided prostate biopsy overlays previously obtained MRIs onto real-time ultrasound imaging to enable improved lesion-targeted biopsy in the urologist’s office.

**Figure 11. Overall high-impact potential: magnetic resonance imaging–ultrasound image fusion to guide prostate biopsy**

Overall, commenters indicated that substantial shortcomings exist in prostate biopsy methods and that MRI-TRUS fusion has potential to improve the detection rate of clinically significant prostate cancer. However, the lack of data demonstrating improved health outcomes, the increased cost associated with the procedure, and a lack of clarity regarding reimbursement for the procedure were seen as limiting adoption. 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. 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 potentially addressed by MRI-TRUS fusion biopsy was viewed as moderately to very important by the majority of expert commenters. Commenters rating the unmet need highly cited the high false-positive and false-negative rates of conventional TRUS biopsy and the limited ability of conventional TRUS biopsy to target high-risk regions of interest. The availability of other biopsy methods was cited as a factor limiting the magnitude of the unmet need by multiple commenters. Two commenters speaking from health systems and research perspectives suggested that MRI-TRUS fusion biopsy addressed an unmet need of only minimal importance, questioning whether a need exists to identify more prostate...
cancers when the risk-benefit profile of treating focal prostate cancer is unclear.\textsuperscript{331,335} Conversely, multiple experts suggested that the purported ability of MRI-TRUS to more accurately differentiate high-grade from low-grade disease might allow more appropriate treatment, potentially improving patient health outcomes. Additionally, experts thought, patient outcomes could be improved by identifying clinically important cancers that would be missed by conventional TRUS-guided biopsy.

**Acceptance and adoption:** Physician adoption was seen as likely to be moderate by the majority of experts. Factors listed by commenters as promoting adoption included the potential for improved biopsy accuracy with limited additional costs to urologists. However, several commenters noted that the lack of additional reimbursement for the fusion procedure and the required training on the use of MRI-TRUS fusion could limit physician adoption. One clinical expert suggested that the level of training and increased cost associated with the technique would likely limit use to centers of excellence and that the patient population in which the technique would be used would be those patients under active surveillance and with a continuously rising PSA despite a previous negative TRUS biopsy.\textsuperscript{334} Patient adoption was generally viewed as more likely by expert commenters, who cited the tendency of patients to opt for the most advanced diagnostic methods. Factors that could limit patient adoption, according to commenters, include the potential for additional costs that might be passed on to the patient and the requirement for an additional visit to a health care facility for the required MRI.

**Health care delivery infrastructure and patient management:** Small impacts on health care system infrastructure and patient management would be expected with MRI-TRUS fusion biopsy, noted experts. Shifts they noted include scheduling pre-biopsy MRI and training radiologists and urologists in interpreting MRI images and performing targeted biopsies, respectively. Multiple commenters also noted the potential for MRI-TRUS biopsy to cause a shift in the number of patients with biopsy-diagnosed prostate cancer and, therefore, a shift in the number of patients undergoing prostate cancer treatments. However, the disruption to patient management was thought to be small by commenters.

**Health disparities:** The requirement for a pre-biopsy MRI would substantially increase the cost of an MRI-TRUS biopsy relative to a standard TRUS biopsy according to expert commenters. Besides these direct costs, commenters also noted, changes to biopsy procedures could alter treatment of some patients, potentially changing downstream costs of treating biopsy-identified prostate cancer. While some experts saw little potential for impact on disparities, others pointed out that more accurate assessment of the risk of progression of prostate cancer could spare some patients from expensive treatment and make active surveillance programs more attractive. The ultimate impact of this option for biopsy on health disparities is difficult to estimate.
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. 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]). These 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 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.

**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. This may both reduce the side effects of treatment relative to current radionuclide treatments and improve patient outcomes. 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.

**Clinical trials:** In July 2013, results were published from a double-blind, randomized controlled trial of the radiopharmaceutical versus placebo in 921 patients with CRPC and skeletal metastases who were ineligible for initial or further treatment with docetaxel. In this trial, radium-223 dichloride was reported to have increased overall survival by 3.6 months compared with survival with placebo, representing a 30% reduction in the risk of death compared with placebo (p=0.001). 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, 0.66; p<0.001).

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. Other commonly reported adverse events were similar between groups (bone pain, constipation, diarrhea, nausea, and vomiting). The relatively benign adverse-event profile of radium-223 dichloride treatment may allow its use in combination with other cancer treatments. For example, investigators have initiated a phase III clinical trial testing the combination of radium-223 and the androgen-synthesis inhibitor abiraterone in patients with bone-predominant, asymptomatic, CRPC.

**Manufacturer and regulatory status:** Algeta ASA (Oslo, Norway), and Bayer AG (Leverkusen, Germany), developed radium-223 dichloride. In March 2014, Bayer completed a takeover of Algeta.

Bayer submitted a new drug application to FDA for this indication in December 2012, and FDA granted the submission priority review status in February 2013. 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
Before the approval, FDA had granted radium-223 dichloride fast-track status for treating CRPC with bone metastases.³⁴⁶

**Diffusion and cost:** The wholesale cost of radium-223 dichloride is reportedly $11,500 per injection ($69,000 for a full course of 6 injections).³⁴⁷ The U.S. Nuclear Regulatory Commission has cleared distribution of radium-223 dichloride; individual sites must be licensed to administer the drug.³⁴⁷

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 7 payers with policies for radium-223 dichloride specifying that they cover the treatment for patients with bone metastases from CRPC.³⁴⁸⁻³⁵⁴ 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.³⁵⁵,³⁵⁶ 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.³⁵⁷

**Clinical Pathway at Point of This Intervention**

Patients with cancer that has metastasized to bone are typically treated with a combination of locoregional treatments, systemic therapies, and pain medications.³³⁶ Palliative local treatments for bone metastases include external beam radiation therapy, MR-guided focused ultrasound ablation, and surgical resection.³⁵⁸ 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.³⁵⁹ 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.³³⁶ Radium-223 dichloride represents a novel, systemic radionuclide as the first alpha particle–emitting radionuclide indicated for treating this condition.

**Figure 12. 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 pain, particularly for patients with prostate cancer bone metastases. Although experts saw significant potential for wide adoption, the similar nature of this agent to other 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, health devices, and health systems backgrounds, offered perspectives on this intervention. 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 and significant impact 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 thought, 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 improve 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 the treatment would be widely adopted. Experts cited its reported efficacy, safety, relatively benign adverse-event profile, ease of use, and routine administration as factors that would enhance adoption. One expert with a health devices 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 over 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 would 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 Intervention
**Pembrolizumab (MK-3475) for Treatment of Advanced Melanoma**

**Unmet need:** Despite recent advances in treating melanoma, patients in whom advanced melanoma has been diagnosed have a poor prognosis and new treatments are needed. Recent phase III clinical trials with the anti-CTLA-4 monoclonal antibody ipilimumab (Yervoy®) demonstrated the potential of immune system checkpoint inhibitors to produce durable responses in patients with advanced melanoma by activating the body’s immune system. However, only a small minority of patients experience such a response, and new approaches to stimulate immune responses to melanoma are highly sought. One approach targets the programmed death-1 (PD-1) receptor, a second immune checkpoint pathway that purportedly suppresses the antimelanoma immune response. Several molecules targeting PD-1 or PD-1 ligands are under study in clinical trials for treating melanoma, including the PD-1–specific monoclonal antibody pembrolizumab.

**Intervention:** Researchers have suggested that evading destruction by the body’s immune system is one of the fundamental hallmarks of cancer and have identified multiple mechanisms by which cancers induce immune tolerance. One such mechanism is the co-option by tumors of endogenous mechanisms limiting T-cell responses. These so-called immune checkpoints are thought to prevent runaway immune responses; however, by aberrantly activating these immune checkpoints, cancers purportedly can reduce the body’s anticancer immune response.

PD-1 is a central player in one of these checkpoints. PD-1 is expressed by many cells of the immune system, including high expression levels on activated T cells. Research has demonstrated that in many cases, the tumor microenvironment expresses a ligand for PD-1 (PD-L1). Binding of PD1-L to PD-1 is thought to induce T-cell anergy (diminished response to persistent antigen exposure), limiting tumor rejection by tumor-specific T cells in the effector phase of the immune response. Disrupting the immune tolerance–inducing signaling between tumor-expressed PD-L1 and immune cell–expressed PD-1 is a therapeutic target that could potentially induce an immune response to the cancer by “releasing a brake” placed on the immune response through the PD-1 signaling pathway.

Pembrolizumab is a humanized monoclonal antibody highly specific for PD-1. The Fc region of the antibody has been modified to reduce the induction of antibody-dependent cellular cytotoxicity and complement-mediated cytotoxicity, which have the potential to deplete immune cells expressing PD-1. Pembrolizumab binding to PD-1 purportedly prevents the interaction between PD-1 and its ligands, preventing activation of the immune checkpoint and leading to an increase in anticancer immune response.

Pembrolizumab is administered by IV infusion. The drug has been tested at a variety of doses in clinical trials, and recently initiated trials are testing 10 mg/kg dosing. Patients may receive pembrolizumab infusions once every 2–3 weeks, and treatment may continue for up to 2 years.

**Clinical trials:** Pembrolizumab is being tested primarily as immunotherapy for advanced melanoma and nonsmall cell lung cancer. Furthermore, investigators have initiated phase I trials of pembrolizumab for treating triple-negative breast cancer, head and neck cancer, urothelial tract cancer, gastric cancer, and blood cancers.

Results from a phase I, open-label trial of 135 patients with advanced melanoma were published in 2013. Investigators reported that 10 mg/kg pembrolizumab administered every 2 weeks had the highest response rate (52%; 95% CI, 38% to 66%) Additionally, no significant difference was observed in the response rate between patients who had previously received ipilimumab (38%; 95% CI, 23% to 55%) and those who had not (39%; 95% CI, 26% to 49%). The most common pembrolizumab-related adverse events included fatigue, rash, pruritus, and diarrhea; side effects
were reported in 79% of patients. From the total number experiencing side effects, 13% of patients experienced grade 3 or 4 adverse events.\textsuperscript{378}

**Manufacturer and regulatory status:** Pembrolizumab is being developed by Merck & Co., Inc. (Whitehouse Station, NJ). In January 2014, the company announced that it had initiated a rolling submission of a biologic license application to FDA for pembrolizumab. FDA had earlier granted the drug breakthrough therapy designation for treating advanced melanoma.\textsuperscript{379} In May 2014, FDA granted pembrolizumab priority review for metastatic melanoma treatment and a decision is expected by October 2014.\textsuperscript{380} Pembrolizumab is available to select patients through an expanded access program.

**Diffusion and cost:** Pembrolizumab is not yet commercially available, and no cost information is available. Potential pricing of pembrolizumab may be inferred from the cost of the commercially available CTLA-4 inhibitor ipilimumab, which costs $120,000 for a four-dose regimen.\textsuperscript{381}

No coverage, coding, or payment information is available at this time. However, drugs that show some tumor response, progression-free survival, and overall survival efficacy are usually covered as specialty pharmaceuticals requiring prior authorization.

**Clinical Pathway at Point of This Intervention**

For systemic treatment of advanced melanoma, three options exist: immunotherapy, targeted therapy for melanoma that harbors specific genetic changes, and cytotoxic chemotherapy. According to National Comprehensive Cancer Network guidelines for treating melanoma, preferred systemic treatment options include the following:\textsuperscript{382}

- BRAF inhibitor (i.e., dabrafenib or vemurafenib) for patients with \textit{BRAF} mutation–positive melanoma
- Dabrafenib plus the MEK inhibitor trametinib for patients with \textit{BRAF} mutation–positive melanoma
- High-dose interleukin-2
- Ipilimumab

If approved by FDA, pembrolizumab has the potential to compete with existing treatments for advanced melanoma. In clinical trials, pembrolizumab is being compared head-to-head with ipilimumab and/or chemotherapy as first- or second-line treatment for advanced melanoma. Additionally, several other manufacturers are developing agents targeting the PD-1 pathway, which could compete with pembrolizumab if the drugs in this class are approved.\textsuperscript{369}

Pembrolizumab might also be used as part of combination therapy. For example, recently reported results from a small trial of the combination of ipilimumab and another PD-1 inhibitor under study, nivolumab, demonstrated substantial activity in advanced melanoma.\textsuperscript{383} Additionally, pembrolizumab’s developer recently announced plans for trials of pembrolizumab in combination with various agents not yet approved by FDA, including in combination with the viral immunotherapy talimogene laherparepvec.\textsuperscript{384}

An additional technology that may be used in concert with anti-PD1 antibodies is a genomic test that could identify levels of PD-L1 expression by tumors. The mechanism of action of PD-1 antibodies such as pembrolizumab suggests that they may be more efficacious in patients whose tumors express high levels of PD-L1.\textsuperscript{369} However, ongoing trials of pembrolizumab in melanoma are not selecting patients on the basis of this marker.
Pembrolizumab has moderate potential to address an unmet need for melanoma patients, some experts thought. They attributed their reasons to scarce safety and efficacy data, and a similar mechanism of action to that of approved and other soon-to-be-approved melanoma therapies. However, expert clinicians regarded pembrolizumab as having high impact potential to fulfill the unmet need because it can be used as second-line treatment in patients with very poor prognosis whose disease has relapsed after ipilimumab treatment. 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 pembrolizumab for treating advanced melanoma. We have organized the following discussion of expert comments by the parameters on which they commented.

**Unmet need and health outcomes:** There is an unmet need for new drugs for patients diagnosed with advanced melanoma, the experts agreed. Despite some experts stating that pembrolizumab will not effectively address this need, most agreed that more drugs that target the PD-1 pathway are needed to close the gap for patients whose melanoma does not respond to current therapies. Additionally, this same group of experts also believes that pembrolizumab efficacy data have shown its potential to improve patient health and progression-free survival.

**Acceptance and adoption:** Although a couple of experts are concerned that pembrolizumab will be adopted only if future clinical data prove it to be better than similar treatments, most experts agreed that pembrolizumab would be readily and easily adopted by both physicians and patients on the basis of available data, its routine administration route (IV), and a safety profile suggesting its adverse events are no worse than similar anticancer agents. Experts also pointed out that advanced melanoma progresses rapidly; thus, any drug capable of slowing progression will be accepted for treating melanoma.

**Health care delivery infrastructure and patient management:** As an intravenously administered agent, pembrolizumab is not expected to affect health care delivery or infrastructure, noted experts. Additionally, they do not anticipate much impact on patient management other the fact that patients now have an option when ipilimumab treatment stops working. Experts also thought that if sufficient efficacy data accumulate, pembrolizumab might displace ipilimumab as first-line therapy.

**Health disparities:** Experts are concerned that pembrolizumab will be costly and could increase health disparities between patients with and without insurance, and even those with insurance, if the drug is more costly than existing options. On the other hand, experts also pointed out that current melanoma treatments are also very costly and speculated that as a cancer treatment, it will probably will be covered by insurance.
Solid Tumor Ablation Intervention
Irreversible Electroporation (NanoKnife) for Ablation of Solid Tumors

Unmet need: Tumor ablation using various forms of energy has become a standard approach in the armamentarium of cancer treatment modalities. Available ablation methods include radiofrequency (RF), cryotherapy, and microwaves, which all rely on thermal energy to destroy tumors by heating or cooling tissue. Thermal ablation can lead to collateral damage in adjacent tissues and adverse events during and after treatment. The inability to precisely control the impact of treatment in 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.392,395

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.394 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.394,395

An interventional radiologist or surgeon performs IRE procedures using a percutaneous, laparoscopic, or open surgical approach.395 Neuromuscular stimulation by the electric field produced during IRE treatment can cause uncontrolled movement and pain; therefore, IRE requires general anesthesia and muscle blockade.394 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.394,396 A single ablation purportedly takes only a minute, and IRE electrodes can be repositioned to allow for multiple ablations.397 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,398-401 and an FDA-approved investigational device exemption trial in prostate cancer patients is slated to commence by the end of 2014.402 In June 2013, Cheung and colleagues reported on 11 patients with 18 hepatocellular carcinoma lesions that were not amenable 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.398

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.403

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.399

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.404

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.400

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.398-401 One patient death was reported in one study’s 90-day morbidity followup.401

**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.405 While much of the recently published literature on IRE addresses its use in treating unresectable hepatic or pancreatic tumors,406 the manufacturer has recently received approval from FDA to conduct a trial using IRE for the treatment of focal prostate cancer that is anticipated to start before the end of 2014.402

**Diffusion and cost:** Several dozen cancer centers in the United States have acquired IRE systems and advertise use of the system for treating various cancers.394 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.407 Searches of 11 representative, private, third-party payers that publish their coverage policies online (i.e., Aetna, Anthem, Blue Cross/Blue Shield Alabama, Blue Cross/Blue Shield Massachusetts, CIGNA, HealthPartners, Humana, Medica, Regence, United Healthcare, Wellmark) identified 2 payers (Aetna and Anthem) with policies that denied coverage for use of IRE to ablate tissue.408,409 Other payers have no policies addressing use of NanoKnife. The U.S. Centers for Medicare & Medicaid Services has no national coverage determination for IRE to treat unresectable tumors. Coverage decisions are left to the discretion of local Medicare carriers, although because FDA has not approved the device for cancer indications, local carriers may choose to not reimburse.

The American Medical Association (AMA) has not assigned a specific Common Procedural Terminology (CPT) code to describe IRE to treat unresectable tumors. However, AMA provides general codes that facilities may use to represent unlisted procedures of the lungs, liver, pancreas, or urinary system. Using these codes to describe IRE does not guarantee reimbursement.

ECRI Institute’s analysis of capital costs of tumor ablation systems that hospitals reported to its capital equipment pricing database found that the average quoted costs for electroporation systems ($208,986) are about three to six times the costs quoted for other ablation modalities (radiofrequency: $34,722; cryoablation: $52,000; and microwave ablation systems: $71,957).410 Costs of single-use disposable probes used for each procedure are close to $2,000 each.
Clinical Pathway at Point of This Intervention

In treating focal malignancies, IRE may compete with other RF ablation, laser ablation, cryoablation, microwave ablation, and chemical ablation procedures. 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.\textsuperscript{393}

Figure 14. Overall high-impact potential: irreversible electroporation (NanoKnife) for treatment of solid tumors

As a novel, nonthermal tumor ablation technique, IRE was viewed by experts as a potential addition to cancer treatment options. It could be particularly useful in pancreatic cancer, for which experts noted a large unmet need and it could significantly shift the way patients are managed. On the other hand, experts stated IRE does not adequately address an unmet need for hepatocellular carcinoma treatment but concurred that IRE could be the only option for patients with hepatocellular carcinoma localized near critical structures and/or organs. The available data is insufficient to prove patients have better outcomes with IRE than with other ablation techniques, experts indicated, and expressed the need for controlled trials on efficacy before wider adoption. 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. Six experts, with clinical, research, and health systems backgrounds, offered perspectives on IRE for treating pancreatic cancer,\textsuperscript{411-416} and six experts with similar backgrounds, offered perspectives on IRE for treating hepatocellular carcinoma;\textsuperscript{417-422} 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: Experts commenting on IRE for treating hepatocellular carcinoma agreed that this technology addresses an unmet need, particularly when cancer is found near essential structures. Additionally, experts also thought IRE could address an unmet need for patients with unresectable advanced pancreatic cancer because of high mortality and lack of treatment options. Available data did not suggest IRE could lead to better health outcomes than current treatments for hepatocellular carcinoma, some experts pointed out. Meanwhile, other experts doubted IRE has potential to cure pancreatic cancer, but anticipated treatment might increase survival rates and improve quality of life. Experts also indicated IRE safety and efficacy should be compared with current treatment options to evaluate the long-term outcomes and determine whether IRE increases the overall survival rate. An advantage experts pointed out about IRE was that it theoretically targets malignant cells without damaging neighboring tissue, in
contrast to thermal and RF ablation, which generate heat, causing collateral damage to organs and blood vessels.

**Acceptance and adoption:** Experts foresee only a moderate chance of widespread IRE adoption due to its cost, marginal improved survival rates, and lack of data demonstrating benefits thus far. On the other hand, current off-label use of IRE could increase adoption thought one research expert. Overall, experts agreed that physicians would favor adopting IRE if additional data proving safety and efficacy became available. Patients might be willing to accept it as an option if they had no other treatment options, even if efficacy data are limited. However, patient adoption could be limited by availability, high cost for the procedure, and no third-party payer coverage.

**Health care delivery infrastructure and patient management:** IRE implementation will require capital outlay to acquire the device, consumables needed for each procedure, ongoing maintenance costs, and substantial training of hospital staff to use the equipment safely and consistently, some experts thought. On the other hand, experts noted that health care infrastructure will not be affected dramatically in hospitals where other types of ablation procedures are performed regularly. Patient management could change if IRE supplements or replaces chemotherapies and biologic therapies.

**Health disparities:** The initial high price of the IRE system as well as the maintenance cost would limit access to this form of therapy. One expert believes that this would be more noticeable in smaller regional hospitals where implementing IRE would not be possible. Some experts commented that Medicare and third-party payers do not cover IRE because it has not been cleared by FDA for cancer treatment. Experts also foresee health disparities in lower-income patients and those without health insurance who could not afford off-label IRE costs. On the other hand, if IRE demonstrates efficacy in treating cancer and receives FDA approval, experts think, IRE cost would be reimbursed by third-party payers and would reduce health disparities.
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.\(^{423}\) Although most patients with differentiated thyroid cancer are cured by treatment with radioactive iodine, surgery, and thyroid-stimulating hormone suppression, about 15% develop recurrent disease. Recurrent disease, particularly metastatic disease, is frequently less responsive to radioactive iodine, and patients have a poor prognosis and limited treatment options.\(^{423,424}\)

**Intervention:** Sorafenib (Nexavar\(^{®}\)) is an oral, small-molecule tyrosine kinase inhibitor with activity against multiple kinases, including vascular endothelial growth factor receptor (VEGFR) 2, VEGFR3, RET, and BRAF.\(^{425}\) 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 BRAF 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 disease.\(^{423}\)

**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 (RR-DTC); however, data from randomized controlled trials have been lacking.\(^{423}\) Therefore, researchers undertook the phase III DECISION trial to assess the efficacy of sorafenib compared with placebo in patients with progressive, radioactive iodine–refractory, differentiated thyroid cancer. In this trial (n=417), patients were randomly assigned to receive sorafenib (400 mg, twice daily) or placebo.\(^{426}\)

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; HR 0.58; p<0.0001).\(^{427}\) 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.\(^{427,428}\) Two deaths during the trial, one in each study arm, were attributed to the study drug.\(^{427}\)

**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.”\(^{428,429}\)

**Diffusion and cost:** Although sorafenib has only recently been approved by FDA for treating radioactive iodine-refractory thyroid cancer, the drug has been FDA approved for treating renal cell carcinoma since 2005 and for treating hepatocellular carcinoma since 2007.\(^{428}\) 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.\(^{71,431-433}\) 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. 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 $11,500.\textsuperscript{430}

**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 RR-DTC.\textsuperscript{423,434} Additionally, safety and efficacy of lenvatinib is also being tested in this patient population and positive results have been reported.\textsuperscript{435}

**Figure 15. 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 as the first FDA approved therapy for this indication and given the promising, recent phase III results regarding progression-free survival. The magnitude of sorafenib’s impact was lessened by the relatively small patient population affected and fact that it is easily adopted as an oral therapy and thus does not impose any health care staffing or infrastructure burden. 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 sorafenib for treating differentiated thyroid cancer.\textsuperscript{436–441} 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 by experts commenting as having moderate importance. Experts noted the relative absence of therapeutic options for radioactive iodine–refractory disease, but also noted that the relatively small patient population with radioactive iodine–refractory thyroid cancer limits the importance of the unmet need. Experts suggested that sorafenib has 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, stated experts, who noted that many oncologists are familiar with this drug even before its approval for this indication. Experts noted that some third-party payers had policies in place that reimbursed
for using sorafenib in this patient population. Most experts predicted patient acceptance of this new treatment option, with adverse effects and cost being potential barriers to acceptance by some patients. However, in the absence of other therapeutic alternatives, experts suggested, 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 adoption of sorafenib. Experts cited the oral route of administration and the familiarity of medical oncologists with using the drug as factors mitigating any impact on health care staffing and infrastructure. Among the small shifts to staffing and infrastructure that experts suggested may occur included potential changes to address drug-related toxicity or a potential shift from infusion-based cytotoxic chemotherapy to self-administered therapy. An expert with a clinical perspective suggested that the health care provider could change if some endocrinologists (rather than medical oncologists) were to prescribe sorafenib.436 Several experts anticipated that treatment paradigms would be modified to include the use of this agent following its approval.

Health disparities: Commenters expect cost to be the primary concern in terms of impact on health disparities.
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