

Key Question 2

What is the comparative effectiveness of imaging techniques for restaging patients with primary and recurrent colorectal cancer after initial treatment?

a. What is the test performance of the imaging techniques used (singly, in combination, or in a specific sequence) to restage colorectal cancer when compared with a reference standard?

b. What is the impact of alternative imaging techniques on intermediate outcomes, including stage reclassification and changes in therapeutic management?

c. What is the impact of alternative imaging techniques on clinical outcomes?

d. What are the adverse effects or harms associated with using imaging techniques, including harms of test-directed management?

e. How is the comparative effectiveness of imaging techniques modified by the following factors:

i. Patient-level characteristics (e.g., age, sex, body mass index)

ii. Disease characteristics (e.g., tumor grade)

iii. Imaging technique or protocol characteristics (e.g., use of different tracers or contrast agents, radiation dose of the imaging modality, slice thickness, timing of contrast)

PICOTS Criteria (Population, Intervention, Comparator, Outcomes, Timing, Setting)

Populations

- Adult patients with an established diagnosis of primary colorectal cancer
- Adult patients with an established diagnosis of recurrent colorectal cancer

Interventions

Noninvasive imaging using the following tests (alone or in combination) to assess the stage of colorectal cancer:

- CT
- PET/CT
- MRI
- Endoscopic ultrasound

Combinations of particular interest include endoscopic ultrasound to evaluate the T stage combined with PET/CT or CT to evaluate the N and M stages.

Reference Standards To Assess Test Performance

- Histopathological examination of tissue
- Intraoperative findings
- Clinical followup

Histopathology of surgically resected specimens is the reference standard for pretherapy staging. In patients undergoing surgery, the nodal (N) stage

and spread of the tumor to nearby regional structures and other organs is assessed intraoperatively, either by palpation or ultrasound. However, in patients with metastatic disease who undergo palliative care, a combination of initial biopsy results and clinical followup serves as the reference standard.

Clinicians use the results from the imaging modality or modalities to arrive at a stage determination that is compared against the stage established by the reference standard. These comparisons tell us how many people were correctly classified in the various stages of the disease and allow us to calculate the test performance metrics of sensitivity, specificity, and accuracy. The selection of the reference standard is important in evaluating the true performance of an imaging modality for staging.

Comparators

- Any direct comparisons of the imaging tests of interest
- Any direct comparisons of variations of any of the imaging tests of interest (e.g., diffusion-weighted MRI vs. T2-weighted MRI)

Comparators thought to be of particular clinical interest are listed below:

- For colon cancer: a contrast-enhanced CT of the chest, abdomen, and pelvis versus whole-body PET/CT versus a contrast-enhanced MRI of the chest, abdomen, and pelvis
- For rectal cancer: a contrast-enhanced CT of the abdomen and pelvis versus an MRI of the abdomen and pelvis
- For rectal cancer: endoscopic ultrasound versus MRI
- For suspected liver metastasis: CT scan versus MRI or PET/CT of the abdomen
- For suspected widespread metastasis, CT of the chest, abdomen, and pelvis versus whole-body PET/CT or contrast-enhanced MRI of the chest, abdomen, and pelvis

We note that this list is based on a preliminary literature search and discussions with a limited number of clinicians and the Technical Expert Panel (TEP). Thus, we do not anticipate that the listed items cover all of the comparisons of interest. We expect that additional comparisons will be identified during the literature review.

Outcomes

- Test performance outcomes
- Test performance (e.g., sensitivity, specificity, understaging, and overstaging) against a reference standard test (pathological

examination, intraoperative findings, clinical followup)

- Intermediate outcomes
- Stage reclassification
- Changes in therapeutic management
- Clinical outcomes
 - Overall mortality
 - Colorectal cancer-specific mortality
 - Quality of life and anxiety
 - Need for additional staging tests, including invasive procedures
 - Need for additional treatment, including surgery, radiotherapy, or chemotherapy
 - Resource utilization related to testing and treatment (when reported in the included studies)
- Adverse effects and harms
 - Harms of testing per se (e.g., radiation exposure)
 - Harms from test-directed treatments (e.g., overtreatment, undertreatment)

Timing

- Primary staging
- Interim restaging
- Duration of followup will vary by outcome (e.g., from no followup for test performance measurements to many years for mortality)

Setting

- Any setting will be considered

Dated: June 13, 2013.

Carolyn M. Clancy,

AHRQ, Director.

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DEPARTMENT OF HEALTH AND HUMAN SERVICES**Food and Drug Administration**

[Docket No. FDA-2013-N-0001]

Cardiovascular and Renal Drugs Advisory Committee; Notice of Meeting

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice.

This notice announces a forthcoming meeting of a public advisory committee of the Food and Drug Administration (FDA). The meeting will be open to the public.

Name of Committee: Cardiovascular and Renal Drugs Advisory Committee.

General Function of the Committee: To provide advice and recommendations to the Agency on FDA's regulatory issues.

Date and Time: The meeting will be held on August 6, 2013, from 8 a.m. to 4 p.m.

Location: FDA White Oak Campus, 10903 New Hampshire Ave., Building

31 Conference Center, the Great Room (Rm. 1503), Silver Spring, MD 20993-0002. Information regarding special accommodations due to a disability, visitor parking, and transportation may be accessed at: <http://www.fda.gov/AdvisoryCommittees/default.htm>; under the heading "Resources for You," click on "Public Meetings at the FDA White Oak Campus." Please note that visitors to the White Oak Campus must enter through Building 1.

Contact Person: Kristina Toliver, Center for Drug Evaluation and Research, Food and Drug Administration, 10903 New Hampshire Ave., Bldg. 31, Rm. 2417, Silver Spring, MD 20993-0002, 301-796-9001, FAX: 301-847-8533, email: CRDAC@fda.hhs.gov, or FDA Advisory Committee Information Line, 1-800-741-8138 (301-443-0572 in the Washington, DC area).

A notice in the **Federal Register** about last minute modifications that impact a previously announced advisory committee meeting cannot always be published quickly enough to provide timely notice. Therefore, you should always check the Agency's Web site at <http://www.fda.gov/AdvisoryCommittees/default.htm> and scroll down to the appropriate advisory committee meeting link, or call the advisory committee information line to learn about possible modifications before coming to the meeting.

Agenda: On August 6, 2013, the committee will discuss new drug application (NDA) 204819, proposed trade name ADEMPAS (riociguat coated tablet), submitted by Bayer HealthCare Pharmaceuticals Inc., for the treatment of: (1) Chronic thromboembolic pulmonary hypertension World Health Organization (WHO) Group 4 to improve exercise capacity and WHO functional class and (2) pulmonary arterial hypertension (WHO Group 1) to improve exercise capacity, improve WHO functional class, and to delay clinical worsening.

FDA intends to make background material available to the public no later than 2 business days before the meeting. If FDA is unable to post the background material on its Web site prior to the meeting, the background material will be made publicly available at the location of the advisory committee meeting, and the background material will be posted on FDA's Web site after the meeting. Background material is available at <http://www.fda.gov/AdvisoryCommittees/Calendar/default.htm>. Scroll down to the appropriate advisory committee meeting link.

Procedure: Interested persons may present data, information, or views, orally or in writing, on issues pending before the committee. Written submissions may be made to the contact person on or before July 22, 2013. Oral presentations from the public will be scheduled between approximately 12:30 p.m. to 1:30 p.m. Those individuals interested in making formal oral presentations should notify the contact person and submit a brief statement of the general nature of the evidence or arguments they wish to present, the names and addresses of proposed participants, and an indication of the approximate time requested to make their presentation on or before July 12, 2013. Time allotted for each presentation may be limited. If the number of registrants requesting to speak is greater than can be reasonably accommodated during the scheduled open public hearing session, FDA may conduct a lottery to determine the speakers for the scheduled open public hearing session. The contact person will notify interested persons regarding their request to speak by July 15, 2013.

Persons attending FDA's advisory committee meetings are advised that the Agency is not responsible for providing access to electrical outlets.

FDA welcomes the attendance of the public at its advisory committee meetings and will make every effort to accommodate persons with physical disabilities or special needs. If you require special accommodations due to a disability, please contact Kristina Toliver at least 7 days in advance of the meeting.

FDA is committed to the orderly conduct of its advisory committee meetings. Please visit our Web site at <http://www.fda.gov/AdvisoryCommittees/AboutAdvisoryCommittees/ucm111462.htm> for procedures on public conduct during advisory committee meetings.

Notice of this meeting is given under the Federal Advisory Committee Act (5 U.S.C. app. 2).

Dated: June 21, 2013.

Jill Hartzler Warner,

Acting Associate Commissioner for Special Medical Programs.

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DEPARTMENT OF HEALTH AND HUMAN SERVICES

Health Resources and Services Administration

Lists of Designated Primary Medical Care, Mental Health, and Dental Health Professional Shortage Areas

AGENCY: Health Resources and Services Administration, HHS.

ACTION: Notice.

SUMMARY: This notice advises the public of the published lists of all geographic areas, population groups, and facilities designated as primary medical care, mental health, and dental health professional shortage areas (HPSAs) as of May 11, 2013, available on the Health Resources and Services Administration (HRSA) Web site at <http://www.hrsa.gov/shortage/>. HPSAs are designated or withdrawn by the Secretary of Health and Human Services (HHS) under the authority of section 332 of the Public Health Service (PHS) Act and 42 CFR part 5.

FOR FURTHER INFORMATION CONTACT: Requests for further information on the HPSA designations listed on the HRSA Web site below and requests for additional designations, withdrawals, or reapplication for designation should be submitted to Victoria Hux, Chief, Shortage Designation Branch, Bureau of Clinician Recruitment and Service, Health Resources and Services Administration, Room 9A-55, Parklawn Building, 5600 Fishers Lane, Rockville, Maryland 20857, (301) 594-0816, <http://www.hrsa.gov/shortage/>.

SUPPLEMENTARY INFORMATION:

Background

Section 332 of the PHS Act, 42 U.S.C. 254e, provides that the Secretary of HHS shall designate HPSAs based on criteria established by regulation. HPSAs are defined in section 332 to include (1) Urban and rural geographic areas with shortages of health professionals, (2) population groups with such shortages, and (3) facilities with such shortages. Section 332 further requires that the Secretary annually publish a list of the designated geographic areas, population groups, and facilities. The lists of HPSAs are to be reviewed at least annually and revised as necessary. HRSA's Bureau of Clinician Recruitment and Service (BCRS) has the responsibility for designating and updating HPSAs.

Public or private nonprofit entities are eligible to apply for assignment of National Health Service Corps (NHSC) personnel to provide primary care,