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DEPARTMENT OF HEALTH AND HUMAN SERVICES

Agency for Healthcare Research and Quality

Scientific Information Request on Imaging Techniques for the Surveillance, Diagnosis, and Staging of Hepatocellular Carcinoma

AGENCY: Agency for Healthcare Research and Quality (AHRQ), HHS.

ACTION: Request for Scientific Information Submissions

SUMMARY: The Agency for Healthcare Research and Quality (AHRQ) is seeking scientific information submissions from the public on imaging techniques for the surveillance, diagnosis, and staging of hepatocellular carcinoma. Scientific information is being solicited to inform our review of *Imaging Techniques for the Surveillance, Diagnosis, and Staging of Hepatocellular Carcinoma*, which is currently being conducted by the Evidence-based Practice Centers for the AHRQ Effective Health Care Program. Access to published and unpublished pertinent scientific information on imaging techniques for the surveillance, diagnosis, and staging of hepatocellular carcinoma will improve the quality of this review. AHRQ is conducting this comparative effectiveness review pursuant to Section 1013 of the Medicare Prescription Drug, Improvement, and Modernization Act of 2003, Public Law 108-173, and Section 902(a) of the Public Health Service Act, 42 U.S.C. 299a(a).

DATES: *Submission Deadline* on or before [INSERT DATE 30 DAYS AFTER DATE OF PUBLICATION IN THE FEDERAL REGISTER].

ADDRESSES:

Online submissions: http://effectivehealthcare.AHRQ.gov/index.cfm/submit-scientific-information-packets/. Please select the study for which you are submitting information from the list to upload your documents.

E-mail submissions: SIPS@epc-src.org.

Print submissions:

Mailing Address:

Portland VA Research Foundation

Scientific Resource Center

ATTN: Scientific Information Packet Coordinator

PO Box 69539

Portland, OR 97239

Shipping Address (FedEx, UPS, etc.):

Portland VA Research Foundation

Scientific Resource Center

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3710 SW U.S. Veterans Hospital Road

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Portland, OR 97239

FOR FURTHER INFORMATION CONTACT:

Robin Paynter, Research Librarian, Telephone: 503-220-8262 ext. 58652 or Email: SIPS@epc-src.org.

SUPPLEMENTARY INFORMATION:

The Agency for Healthcare Research and Quality has commissioned the Effective Health Care (EHC) Program Evidence-based Practice Centers to complete a review of the evidence for *Imaging Techniques for the Surveillance, Diagnosis, and Staging of Hepatocellular Carcinoma*.

The EHC Program is dedicated to identifying as many studies as possible that are relevant to the questions for each of its reviews. In order to do so, we are supplementing the usual manual and electronic database searches of the literature by requesting information from the public (e.g., details of studies conducted). We are looking for studies that report on imaging techniques for the surveillance, diagnosis, and staging of hepatocellular carcinoma, including those that describe adverse events. The entire research protocol, including the key questions, is also available online at: http://www.effectivehealthcare.AHRQ.gov/search-for-guides-reviews-and-reports/?pageaction=displayproduct&productID=1600#7839

This notice is to notify the public that the EHC program would find the following information on imaging techniques for the surveillance, diagnosis, and staging of hepatocellular carcinoma helpful:

- A list of completed studies your company has sponsored for this indication. In the list, *indicate whether results are available on ClinicalTrials.gov along with the ClinicalTrials.gov trial number*.
- *For completed studies that do not have results on ClinicalTrials.gov*, a summary, including the following elements: study number, study period, design, methodology, indication and diagnosis, proper use instructions, inclusion and exclusion

criteria, primary and secondary outcomes, baseline characteristics, number of patients screened /eligible /enrolled /lost to follow-up /withdrawn /analyzed, effectiveness/efficacy, and safety results.

- *A list of ongoing studies your company has sponsored for this indication*. In the list, please provide the ClinicalTrials.gov trial number or, if the trial is not registered, the protocol for the study including a study number, the study period, design, methodology, indication and diagnosis, proper use instructions, inclusion and exclusion criteria, and primary and secondary outcomes.
- Description of whether the above studies constitute *ALL Phase II and above clinical trials* sponsored by your company for this indication and an index outlining the relevant information in each submitted file.

Your contribution is very beneficial to the Program. The contents of all submissions will be made available to the public upon request. Materials submitted must be publicly available or can be made public. Materials that are considered confidential; marketing materials; study types not included in the review; or information on indications not included in the review cannot be used by the Effective Health Care Program. This is a voluntary request for information, and all costs for complying with this request must be borne by the submitter.

The draft of this review will be posted on AHRQ's EHC program website and available for public comment for a period of 4 weeks. If you would like to be notified when the draft is posted, please sign up for the e-mail list at: http://effectivehealthcare.AHRQ.gov/index.cfm/join-the-email-list1/.

The systematic review will answer the following questions. This information is provided as background. AHRQ is not requesting that the public provide answers to these questions. The entire research protocol, is also available online at: http://www.effectivehealthcare.AHRQ.gov/search-for-guides-reviews-and-reports/?pageaction=displayproduct&productID=1600#7839

Key Question 1

What is the comparative effectiveness of available imaging-based surveillance strategies (listed below under interventions for KQ 1), used singly or in sequence for detecting hepatocellular carcinoma (HCC) among individuals undergoing surveillance for HCC (individuals at high risk for HCC and individuals who have undergone liver transplants for HCC)?

a. What is the comparative test performance of imaging-based surveillance strategies for detecting HCC?

i. How is a particular technique's test performance modified by use of various reference standards (e.g., explanted liver samples, histological diagnosis, or clinical and imaging followup)?

ii. How is the comparative effectiveness modified by patient-level characteristics (e.g., body mass index, number of lesions, tumor diameter, or cause of liver disease) or other factors (e.g., technical aspects of imaging techniques, biomarker levels, test operator or interpreter skill, setting)?

b. What is the comparative effectiveness of imaging-based surveillance strategies on intermediate outcomes like diagnostic thinking?

c. What is the comparative effectiveness of imaging-based surveillance strategies on clinical and patient-centered outcomes?

d. What are the adverse effects or harms associated with imaging-based surveillance strategies?

Key Question 2

What is the comparative effectiveness of imaging techniques (listed under the interventions for KQ 2), used singly, in combination, or in sequence in diagnosing HCC among individuals in whom an abnormal lesion has been detected while undergoing surveillance for HCC (individuals at high risk for HCC and individuals who have undergone liver transplants for HCC) or through the evolution of symptoms and abdominal imaging done for other indications?

a. What is the comparative test performance of imaging techniques for diagnosing HCC?

i. How is a particular technique's test performance modified by use of various reference standards (e.g., explanted liver samples, histological diagnosis, or clinical and imaging followup)?

ii. How is the comparative effectiveness modified by patient-level characteristics (e.g., body mass index, number of lesions, tumor diameter, or cause of liver disease) or other factors (e.g., technical aspects of imaging techniques, biomarker levels, test operator or interpreter skill, setting)?

b. What is the comparative effectiveness of the various imaging techniques on intermediate outcomes like diagnostic thinking and use of additional diagnostic procedures such as fine-needle or core biopsy?

c. What is the comparative effectiveness of the various imaging techniques on clinical and patient-centered outcomes?

d. What are the adverse effects or harms (related to testing or a test-associated diagnostic workup) associated with the various imaging techniques?

Key Question 3

What is the comparative effectiveness of imaging techniques (listed under the interventions for KQ 3), used singly, in combination, or in sequence in staging HCC among patients diagnosed with HCC?

a. What is the comparative test performance of imaging techniques to predict HCC tumor stage?

i. How is a particular technique's test performance modified by use of various reference standards (e.g., explanted liver samples, histological diagnosis, or clinical and imaging followup)?

ii. How is the comparative effectiveness modified by patient-level characteristics (e.g., body mass index, number of lesions, tumor diameter, or cause of liver disease) or other factors (e.g., technical aspects of imaging techniques, biomarker levels, test operator or interpreter skill, setting)?

b. What is the comparative test performance of imaging techniques on diagnostic thinking?

c. What is the comparative effectiveness of imaging techniques on clinical and patient-centered outcomes?

d. What are the adverse effects or harms associated with using imaging techniques related to testing or test-associated diagnostic workup?

PICOTS (Population(s), Interventions, Comparators, Outcomes, Timing, Settings) by Key Question

Population(s)

- Key Question 1
    - Patients at high risk for HCC undergoing surveillance. The population of high-risk patients is defined, as per the AASLD

clinical guidelines, as composed of the following: Asian male HBV carriers over age 40, Asian female HBV carriers over age 50, HBV carriers with a family history of HCC, African/North American black HBV carriers, all individuals with cirrhosis (including alcoholic cirrhosis), HBV or HCV carriers with cirrhosis, and patients with stage 4 primary biliary cirrhosis.6 Other definitions of high-risk patients as defined by the primary studies will be accepted.

- Patients who have undergone liver transplants for HCC, either with or without HCC detected in the explanted liver.
- Both population groups will be considered separately.

- Key Question 2
  - Patients at high risk for HCC in whom a suspicious lesion(s) has been detected by surveillance or by other means.
  - Patients who have undergone liver transplants for HCC, either with or without HCC detected in the explanted liver.
  - Both population groups will be considered separately.
- Key Question 3
  - Patients diagnosed with HCC who require staging before initial treatment.
- All Key Questions
  - Patients with cholangiocarcinoma will be excluded.

<u>Interventions</u>

- Key Question 1
  - US, spiral CT, multidetector CT (MDCT), dual energy CT, or MRI.
  - Studies that included surveillance strategies of any other imaging test with or without additional biomarkers would also be included. The strategies could include the techniques being used singly or in a specific sequence.

- Key Question 2
    - Imaging techniques, used singly, in combination, or in a specific sequence, including US, spiral CT, MDCT, dual energy CT, MRI (including contrast agents like Gd-EOB-DTPA and SPIO), or fluorodeoxyglucose positron emission tomography (FDG-PET) with different tracers (including 18F, fluorothymidine [FLT], 11C-choline, and 11C=methionine, or others).
- Key Question 3
    - Imaging techniques, used singly, in combination, or in a specific sequence, including US, spiral CT, MDCT, dual energy CT, MRI with contrast (including contrast agents such as Gd-EOB-DTPA and SPIO), FDG-PET with different tracers (including 18F, FLT, 11C-choline, and 11C-methionine, or others), or contrast CT.
    - Test performance of imaging techniques will be stratified by the different staging systems used.
- All Key Questions
    - Outdated imaging techniques (e.g., conventional, nonspiral/nonmultidetector CT, or imaging techniques used before 1995) will be excluded.
    - Imaging techniques not available or in use in the United States (e.g., hepatic portography) will be excluded.

Comparators

- For studies of diagnostic accuracy (comparative test performance), the reference standard comparators will be histopathology (based on explanted liver specimens or biopsy) or clinical and imaging followup, and the imaging comparators will be alternative imaging tests or strategies.

- For studies of comparative effectiveness, the comparators will be no imaging or alternative imaging strategies.

Outcomes for Each Key Question

Key Question 1

- Diagnostic outcomes include:
    - Detection rates of HCC lesions.
    - Types of HCC lesions detected.
    - Test performance (e.g., sensitivity and specificity, predictive values, likelihood ratios, area under the receiver operating curve, or others) for diagnosing HCC, including stage-specific accuracy.
    - For all KQs, potential modifiers of measures of test performance will be evaluated, including the reference standards used (e.g., explanted liver samples, histological diagnosis, or clinical and imaging followup), patient and tumor-level characteristics (e.g., body mass index, number of lesions, tumor diameter, or cause of liver disease), or other factors (e.g., technical aspects of the imaging techniques, biomarker levels, test operator or interpreter skill, setting).
- Intermediate outcomes include:
    - Effects on diagnostic thinking.
    - Effects on clinical decisionmaking.
- Clinical and patient-centered outcomes include:
    - Overall mortality or survival.
    - Recurrence of HCC, including rates of seeding by fine-needle aspiration.

- Quality of life as measured with scales such as the Short-Form Health Survey (SF-36) or EuroQol 5D (EQ-5™) or as defined by the primary studies.
- Psychosocial effects of diagnostic testing on patients, patients' caregivers, and other family members, as measured by self-reported questionnaire instruments.
- Resource utilization and patient burden (e.g., costs associated with the imaging procedure, access to the imaging facility, the number of imaging procedures, and other procedures conducted).

Key Question 2

- Diagnostic outcomes include:
  - Type of HCC lesions detected.
  - Test performance (e.g., sensitivity and specificity, predictive values, likelihood ratios, area under the receiver operating curve, or others) for diagnosing HCC. As in KQ 1, potential modifiers of measures of test performance will be evaluated, including the reference standards used (e.g., explanted liver samples, histological diagnosis, or clinical and imaging followup), patient and tumor-level characteristics (e.g., body mass index, number of lesions, tumor diameter, or cause of liver disease), or other factors (e.g., technical aspects of the imaging techniques, biomarker levels, test operator or interpreter skill, setting).
- Intermediate outcomes include:
  - Effects on diagnostic thinking.
  - Effects on clinical decisionmaking.
- Clinical and patient centered outcomes include:
  - Overall mortality or survival.

- Recurrence of HCC, including rates of seeding by fine-needle aspiration
- Quality of life as measured with scales such as the Short-Form Health Survey (SF-36) or EuroQol 5D (EQ-5™) or as defined by the primary studies.
- Psychosocial effects of diagnostic testing on patients, patients' caregivers, and other family members, as measured by self-reported questionnaire instruments.
- Resource utilization and patient burden (e.g., costs associated with the imaging procedure, access to the imaging facility, the number of imaging procedures and other procedures conducted).

Key Question 3

- Diagnostic outcomes include:
  - Measures for stage-specific accuracy of imaging (e.g., Obuchowski method for calculating the area under the receiver operating curve, stage reclassification rates).
- Intermediate outcomes include:
  - Effects on diagnostic thinking.
  - Effects on clinical decisionmaking.
- Clinical and patient-centered outcomes include:
  - Overall mortality or survival.
  - Recurrence of HCC, including rates of seeding by fine-needle aspiration
  - Quality of life as measured with scales such as the Short-Form Health Survey (SF-36) or EuroQol 5D (EQ-5™) or as defined in the primary studies.

- Psychosocial effects of diagnostic testing on patients, patients' caregivers, and other family members as measured by self-reported questionnaire instruments.
- Resource utilization and patient burden (e.g., costs associated with the imaging procedure, access to the imaging facility, the number of imaging procedures and additional procedures conducted).

Key Questions 1d, 2d, and 3d (Adverse Events or Harms)

- Adverse effects or harms associated with the imaging techniques (e.g., test-related anxiety, adverse events secondary to venipuncture, contrast allergy, exposure to radiation).
- Adverse effects or harms associated with test-associated diagnostic workup (e.g., harms of biopsy or harms associated with workup of other incidental tumors discovered on imaging).

Timing

- No restrictions will be placed on timing.
- For studies of comparative effectiveness, duration of followup, timing of interventions, and frequency of interventions will be recorded.

Settings

- All relevant care settings (e.g., primary and secondary care).

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