Comparative Effectiveness Review Disposition of Comments Report

Research Review Title: *Imaging Tests for the Diagnosis and Staging of Pancreatic Adenocarcinoma*

Draft review available for public comment from November 26, 2013 to January 14, 2014

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Comments to Research Review

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The tables below include the responses by the authors of the review to each comment that was submitted for this draft review. The responses to comments in this disposition report are those of the authors, who are responsible for its contents, and do not necessarily represent the views of the Agency for Healthcare Research and Quality.

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Commentator & Affiliation	Section	Comment	Response
Peer Reviewer 2	Introduction	b. Introduction: Please modify the introduction with the above in mind. Let me give you a common (routine actually) clinical example that you are welcome to use...how does your study help in this real-life scenario...A 76 y.o. patient with abdominal pain but without weight loss or jaundice or new onset diabetes gets a non-contrast CT scan due to renal insufficiency that shows a fullness in the head of the pancreas that is clearly resectable. Serum CEA and Ca19-19 are normal. They have some other medical problems that make them a moderate risk for surgery and are suspicious of physicians from prior experiences. They want proof that this is pancreatic cancer before they will consider surgery. How does your study apply here?	Providing specific guidance on management (i.e., recommendations) is the purview of a clinical practice guideline rather than an EPC Comparative Effectiveness Review such as this. We did revise the report to be clearer about the clinical implications.
Peer Reviewer 2	Introduction	You need to set the stage regarding how these modes of imaging are complementary, and that there are significant differences in quality of these studies based upon local expertise. The reader needs to understand how your analysis puts them head-to-head on specific questions, but does not lend itself well to clinical algorithms. In present form, this context is lost...	We agree that centers differ in their expertise and experience, and one of our Key Questions addressed whether there is any evidence for how comparative accuracy differs based on this factor (see questions 1d and 2d on page 6 of the main report). Unfortunately, studies have not tackled this issue directly. We did find inconsistent effects for several comparisons, but studies did not report enough information to determine whether this was due to differential experience.
Peer Reviewer 3	Introduction	b. Introduction: See above	No response necessary
Peer Reviewer 4	Introduction	b. Introduction: Looks appropriate	No response necessary
TEP Reviewer 1	Introduction	b. Introduction: well done	No response necessary
TEP Reviewer 2	Introduction	b. Introduction: Well organized and generally accurate.	No response necessary
TEP Reviewer 2	Introduction	In the ‘structured abstract’, under ‘objectives’, remove ‘cancer’ after pancreatic adenocarcinoma. The word ‘cancer’ is redundant here.	We have reworded the objective: : “Our objectives were to synthesize the available information on the diagnostic accuracy and clinical utility of commonly used imaging tests for the diagnosis and staging of pancreatic adenocarcinoma, as well as screening for pancreatic adenocarcinoma in high risk individuals.”
TEP Reviewer 3	Introduction	b. Introduction: satisfactory and good overview	No response necessary

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer 2	Methods	c. Methods: The criteria are standard and a priori make sense, however, the exclusion has led to a significant loss of context and unfortunately, thus clinical relevance.	Our inclusion criteria were developed using consultation with experts in the field, and we applied them according to the accepted methods of systematic review. These were designed with an orientation to producing optimal answers to important clinical questions about how different imaging tests compare. Similarly, the Key Questions themselves were developed to be clinically relevant based substantial input from experts in the field as well as our preliminary literature searches. We discussed some limitations of our inclusion criteria in the Discussion section.
Peer Reviewer 3	Methods	c. Methods: I do believe the search strategies are reasonable and well presented.	No response necessary
Peer Reviewer 4	Methods	c. Methods: They seem appropriate. However the way the studies have been included or excluded, though appears rational, excludes most of the highly regarded and cited studies on pancreatic cancer. Some of the inferences are therefore based on studies that might appear scientifically sound on the face of it, but are obscure and not considered high quality by the experts in the field.	It is unclear which excluded studies are considered highly regarded by the reviewer. Regarding the included studies, we agree that many had high risk of bias, and most were rated either high or moderate risk of bias
TEP Reviewer 1	Methods	c. Methods: yes	No response necessary
TEP Reviewer 2	Methods	c. Methods: Generally yes, with no specific comments to add.	No response necessary
TEP Reviewer 3	Methods	c. Methods: the methods used were reasonable and there was no sense of bias or any mistakes in assumptions	No response necessary
Peer Reviewer 2	Results	d. Results: The data regarding PET/CT for pancreatic cancer are limited, but I am aware of 2 studies nearing publication that are absolutely in conflict with one another. At best, the use of this modality for pancreatic cancer is controversial. I recommend removing this concept, or at a minimum, not drawing any conclusions given the limited data you have to consider. Importantly, you should make a strong note that most PET/CT studies are without dynamic IV contrast, yet that is not the case of the included studies, so any conclusions that do not specifically mandate dynamic IV contrast are not appropriate as this will be misinterpreted by the reader. i.e. lines 42/43 in the executive discussion as PET/CT being more accurate that MDCT. Not true in the real world....Page 20, line 23 PET/CT 100% specific: Also not true, and there is emerging data that it may have up to a 50% false positive rate in assessment of potential metastases!	Once the studies nearing publication are published, they can be assessed and included by future systematic reviews. Regarding dynamic IV contrast, we re-examined the two PET-CT vs CT studies on which our conclusion was based, and actually neither study's PET-CT used dynamic IV contrast, so they are not atypical in the way you suggest. Thus it seems that our conclusion is worded appropriately. The revised report contains the mention that neither study used dynamic IV contrast (page 44 of the main report).

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Peer Reviewer 3	Results	d. Results: The methods of presenting the data are somewhat tedious, and monotonous. It might be helpful to present some more detail on individual high quality studies from each section.	Because many studies were considered Low risk of bias, and some were Moderate risk of bias, we did not want to cherry pick some studies for detailed discussion, given the possibility of introducing bias into the synthesis.
Peer Reviewer 4	Results	d. Results: The detail seems appropriate and the characteristics of the studies included are defined. I however have a major concern with the studies included and those excluded as I had mentioned in the methods section.	It is unclear which excluded studies are considered highly regarded by the reviewer. Regarding the included studies, we agree that many had high risk of bias, and most were rated either high or moderate risk of bias
TEP Reviewer 1	Results	d. Results: yes, it is staged so that the reader can access more details	No response necessary
TEP Reviewer 2	Results	d. Results: The amount of information presented is extensive. However, the summary sections provide the key data in readable format.	No response necessary
TEP Reviewer 3	Results	d. Results: they did a fine job . However there is a new study just published in radiology and gastroenterology which addresses this exact topic and will need to be either incorporated or at least mentioned. it is Radiology 2014; 270:248–260 http://dx.doi.org/10.1053/j.gastro.2013.11.004	We added a paragraph about this 2014 position statement on what the radiologist should be reporting about the images taken to determine the stage of pancreatic adenocarcinoma ((in the Introduction section at the end of the Resectability subsection)
Peer Reviewer 2	Discussion	e. Discussion/ Conclusion: Page 22, line 7 you conclude MDCT = EUS-FNA in determination of resectability. This is out of clinical context. One cannot operate on EUS-FNA alone. To perform an operation without assessment of liver or lung metastases is malpractice. I don't want to seem petty, but such a conclusion is dangerous out of context and you do not provide the context. Furthermore, there are extensive data regarding the short-comings of EUS in assessment of the uncinate process and potential involvement of the superior mesenteric artery and vein. Thus, the conclusion at a minimum needs to be confined to lesions in the cephalad aspect of the head of the gland. MDCT and EUS are complementary in this regard.	We had not suggested that one would operate based on EUS-FNA results alone; planning the resection would clearly require more information. We added a clarification to this point in the Discussion section in the subsection "Key Findings and Strength of Evidence": "We note that surgical planning clearly requires more than just EUS-FNA, and so surgery would not be performed based on EUS-FNA alone."
Peer Reviewer 2	Discussion	EUS is clearly superior in T stage assessment. This is probably important in the context of neoadjuvant therapy, and I would encourage you to discuss this.	We added a mention in the Discussion of how a more accurate T staging would improve the planning of neoadjuvant therapy.
Peer Reviewer 2	Discussion	For question 2a - staging accuracy. You chose not to comment on Lymph node staging accuracy, but I would encourage you to draw a conclusion. None of the modes of imaging are any better than the perverbial coin toss, and this is very important as LN involvement by imaging is routinely discussed as gospel in tumor boards! Please emphasize that no imaging modality provides clinically meaningful data regarding LN status.	We did not draw a conclusion for lymph node staging accuracy due to insufficient evidence. There was only one included study addressing this outcome. It compared MDCT and MRI with respect to N staging, and the data were inconclusive as to which is more accurate.
Peer Reviewer 3	Discussion	e. Discussion/ Conclusion: See part a	No response necessary

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer 4	Discussion	About Key Question 1. I agree overall. Comparisons from published studies from different specialities using EUS-FNA, CT, MRI, PET/PET-CT scan and DWI are difficult, as the size distribution of tumors included in different studies are often very different with resultant differences in sensitivity and specificity. Early diagnosis is the key element in management of pancreatic cancer. The various diagnostic modalities should be compared only using patients with similar size profiles. Little data is available with modalities other than EUS-FNA for accuracy based on tumor size, especially in early stage small tumors. From the limited data available so far on this, EUS-FNA has high sensitivity and specificity for diagnosing for pancreatic tumors less than 25 mm in size.	The point about comparing the tests in patients with similar size profiles is well taken; it is one of the benefits of the study designs of the included studies in that they performed their tests on a single group of patients. We added mention of this advantage, see the beginning of the evidence for Key Question 1b.
TEP Reviewer 1	Discussion	e. Discussion/ Conclusion: yes	No response necessary
TEP Reviewer 2	Discussion	e. Discussion/ Conclusion: Generally yes.	No response necessary
TEP Reviewer 3	Discussion	e. Discussion/ Conclusion: i think that the authors do make a case for new studies to address the issues with State of the art technology	No response necessary
Peer Reviewer 1	1. General Comment:	In the title and throughout the entire manuscript, please clarify whether you are referring to EUS imaging alone or EUS FNA (with cytologic interpretation). Certainly the performance characteristics and applicability of the data of differ for EUS versus EUS FNA.	Studies that never mentioned the possibility of taking an FNA were excluded because our prior discussions with Technical Experts indicated that the key unique contribution of EUS is to permit biopsy. However, we did not require that all patients in a given study actually *receive* an FNA, because during EUS the endoscopist may see no clear target for biopsy. There were some systematic reviews that included some studies of EUS alone, and sometimes these could not clearly be separated from studies of EUS-FNA, and we still included those reviews. We have clarified these points in the revision.
Peer Reviewer 1	10. Page 28 of 260 (line 49):	"For EUS-FNA, a specialized ultrasound probe is introduced orally and advanced via endoscope through the upper gastrointestinal tract toward the pancreas. The probe's proximity to the pancreas allows the ultrasound to access and image the entire pancreas, the related vasculature, and associated lymph nodes. Consider rewording – something to the effect of: "For EUS-FNA, the ultrasound transducer, which is positioned at the endoscope tip, is directly applied against the duodenal or gastric wall. This minimizes intervening adipose tissue and air that must be traversed by the ultrasound, therefore enhancing the image quality. This allows EUS to access and image the entire pancreas, the related vasculature, lymph nodes, and portions of the liver."	We have made this edit

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Peer Reviewer 1	1a. General Comment:	Also, there is much debate as to whether FNA should be performed for patients with potentially resectable lesions. As written, this manuscript seems to advocate that EUS should always be accompanied by FNA. The role of FNA should be discussed.	The revision states that there is current debate about whether an endoscopist should actually take an FNA of a resectable lesion. For our report, we defined EUS-FNA as the procedural ability to take FNA, not the requirement that all lesions must have been sampled by FNA.
Peer Reviewer 1	2. General Comment:	It would be ideal to provide the reader some guidelines as to the role of EUS and EUS FNA for different patient cohorts based on initial CT or MRI results. For instance if initial CT/MRI finds a pancreatic mass that is: 1.) Clearly resectable, 2.) Clearly unresectable, or 3.) Indeterminate (in terms of whether a mass is present or the resectability).	Providing specific guidance on management (i.e., recommendations) is the purview of a clinical practice guideline rather than an EPC Comparative Effectiveness Review such as this. We did revise the report to be clearer about the clinical implications. The revised Executive Summary (page ES-20) acknowledges that several of the tests may be appropriate for a given patient, and that evidence does not point to an optimal sequence of tests for all patients. None of our included studies compared patients who did vs. did not receive EUS-FNA after already undergoing CT or MRI.
Peer Reviewer 1	3. General Comment:	In terms of the performance characteristics of each imaging modality for vascular involvement, you speak globally about the vessels, but there are some data (although not much or high quality data) based on specific vessels.	Our evidence tables provide information on specific vessels, but there was never enough accuracy data on a given vessel. Consequently we combined the data on vessel involvement.
Peer Reviewer 1	4. General Comment:	While you have an excellent group of authors, I believe the content, acceptance of this material and impact on clinical medicine may be aided by inclusion of other well recognized and respected surgeons, radiologists, and endosonographers.	Our Key Informants as well as our Technical Expert Panel included those with such expertise.
Peer Reviewer 1	5. Page 9 of 260 (line 11):	"In 2013 in the United States, about 45,000 people will receive a diagnosis of pancreatic cancer and 38,000 will die of the disease." Please update with a reference for estimates for 2014.	We have updated the numbers and the reference.
Peer Reviewer 1	6. Page 9 of 260 (line 52):	"The major blood vessels of focus are the superior mesenteric vein (SMV), portal vein, celiac artery, common hepatic artery, and superior mesenteric artery." Consider listing the arteries before the veins given that arterial involvement always (except in few centers as part of research trials) confer unresectability, while a much larger group of patients with PV and/or SMV involvement are considered resectable.	We have made this edit.
Peer Reviewer 1	7. Page 10 of 260 (line 9):	"A concern about MDCT is that the procedure exposes the patient to radiation and, therefore, may increase cancer risk." While this is a concern when using CT as part of a screening program (e.g. high risk kindreds), it is an irrelevant issue for the vast majority of patients used in this setting; to diagnose sporadic pancreatic cancer.	We have added that this is more of a concern with screening.

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Peer Reviewer 1	8. Page 20 of 260 (line 46):	"Key Question 3: What are the rates of harms of imaging techniques…" Most do not use the term "rates of harms" and instead consider "adverse events." You may want to briefly mention that there is harm for failed or delayed diagnosis, the rate of which varies among imaging modalities.	The word "harm" is standard in EPC reports.
Peer Reviewer 1	9. Page 20 of 260 (line 46):	"One included study found that about 10 percent of patients state that EUS-FNA is very uncomfortable, and 11 percent of patients state that MRI is very uncomfortable." Given current sedation use, patients are very seldom aware of any EUS intra-procedural events and rarely report any discomfort, in particular report being "very uncomfortable." Certainly post procedure pain or pancreatitis may develop, but to report that 10% of patients state that EUS FNA is very uncomfortable does not reflect current practice.	This was the only study we identified that reported the rate.
Peer Reviewer 2	General Comments	a. General Comments: This manuscript aims to provide an assessment of comparative effectiveness between 4 modes of imaging in the assessment of pancreatic cancer. Specifically, the question is whether surgical therapy appropriate. This is a very important component of this review because as written, the manuscript does not provide value to experienced pancreatic surgeons, and may be inappropriately interpreted by other readers. The problem is that the modes of imaging each have their own strengths and weaknesses, and as such are typically complementary in clinical decision making. Unfortunately, comparative effectiveness examines them head-to-head on specific questions, and critical thinking and algorithms are lost. With significant modifications to the introduction and conclusions, the manuscript may be valuable to non-surgeons and surgical trainees.	We agree that there is heterogeneity in how these four imaging modalities are used by clinicians and by institutions. The purpose of this review was to provide information to patients, providers and policymakers which it accomplishes within the limits of the available data on this subject. The Effective Health Care Program's Eisenberg Center creates derivative products from systematic reviews performed by EPCs that are tailored to different audiences. Guideline developers use systematic reviews of the evidence along with other inputs when creating recommendations for clinical practice.
Peer Reviewer 2	General Comments	f. Clarity and Usability: PET/CT is not funded for inpatients. Pt is admitted with a resectable lesion by CT and has a bilirubin of 5 and a questionable liver lesion.....can't get the study and operate if indicated during that admission thus avoiding stenting (data we should do this if possible) If PET/CT is of value in pancreatic cancer patients, many of them would benefit from having this study as an inpatient....P.S. this reality impacts the value of the studies you have to evaluate.	We have added information about insurance coverage of various tests. Payers typically try to weigh benefits and harms as well as other considerations when determining whether to cover tests and procedures.
Peer Reviewer 2	General Comments	This was an enormous amount of work. The authors should be complemented on many very positive aspects of the manuscript and it is very well written. In that context and my desire for this to significantly contribute as is clearly possible, please understand that as a high-volume pancreatic surgeon (it is all I do), I was very frustrated by the manuscript in its current form. I would strongly suggest the authors consider including a pancreatic surgeon as a co-author, as such an individual would dramatically improve the impact of the work by providing additional clinical perspective.	Our Key Informants as well as our Technical Expert Panel included those with such expertise

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer 3	General Comments	a. General Comments: My biggest concern regarding this effort is that I do not feel it is presented in a clinically relevant manner. From a clinical standpoint patients are approached very differently depending on how they present to the clinic. The vast majority of patients present with metastatic disease. This is almost always quite clearly defined on ct imaging (which is the first test performed in almost every patient). No other testing is therefore necessary in this group, and patients will typically undergo a ct guided biopsy for diagnosis. In patients who present with resectable disease, tissue diagnosis is not warranted, and again, CT imaging is typically all that is necessary. Trying to define T stage is useless. For these reasons, I feel that it would be helpful to present these data in a format that breaks these into metastatic, locally unresectable, borderline resectable, and resectable. This would give the reader a better feeling for when eus should be considered, when mri should be considered, etc.	The report acknowledges that CT is usually the first test. However, the reality is that some studies have compared diagnosis with CT alone versus diagnosis with some other imaging tests, and it is important to know whether the tests are differentially accurate. We did not want to assume that the typical test is also the best test. About T stage, we included it only because it was one facet of clinical stage, even though its importance for pancreatic cancer is low. In fact, few studies even reported T staging accuracy. We agree that it would be useful to be able to categorize the results as you suggest, but the studies did not provide sufficient information for doing so. It would be a valuable way for future studies to present their findings.
Peer Reviewer 3	General Comments	f. Clarity and Usability: Yes, the report is well organized.	No response necessary
Peer Reviewer 3	General Comments	The overall quality of the data/studies is quite poor, with most studies having significant bias. Because of this, it will be difficult to make definitive recommendations, or truly inform the reader of which test is most accurate for any given situation	No response necessary
Peer Reviewer 4	General Comments	a. General Comments: The report looks meaningful and addresses the key points in clinical practice	No response necessary
Peer Reviewer 4	General Comments	f. Clarity and Usability: The data are clearly presented and seem reasonably usable. I am not sure about some of the conclusions drawn in the study.	No response necessary. We respond below to specific comments about the conclusions of the report.

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Peer Reviewer 4	General Comments	About Key Question 2 Most of data for staging of pancreatic cancers has focused on determining vascular involvement (particularly arterial involvement) and presence of distant metastasis. However studies reporting outcomes in pancreatic cancer patients report that tumor size and locoregional lymph node involvement by tumor are key determinants of post-operative survival following surgical resection. (1-15) Besides, the arterial involvement with tumor is more important than venous involvement, since vascular reconstruction can now be performed in patients with venous involvement. (16) Most experts recognize that EUS-FNA is not superior to CT with angiogram for assessing arterial involvement of celiac trunk or superior mesenteric artery, though there is only one study documenting this (17). CT with angiogram is far superior to EUS for determining the infiltration of arteries (celiac artery, superior mesenteric artery), whose involvement cannot be clearly evaluated by EUS especially in larger tumors. EUS-FNA is however more accurate in lymph node staging of the pancreatic cancer, with high sensitivity and with high positive predictive value for tumor involvement of lymph nodes from FNA cytologic evaluation. Once again, the size of tumor is key in making such comparisons. EUS is valuable in determining resectability of small tumors or tumors that are not visualized on CT/MRI scans. MDCT is however superior to EUS-FNA for determining resectability of larger tumors.	We appreciate your comments on the staging question. We examined the 17 references you sent; 15 were not included in our report because they did not involve imaging, one was not included in our report because it was a narrative review, a one was not included in our report because the imaging test was EUS without the possibility of performing FNA.
Peer Reviewer 4	General Comments	Reveiwer agrees with our conclusions on Key Question 3: What are the rates of harms of imaging techniques (e.g., MDCT angiography with or without 3D reconstruction, other MDCT, EUS-FNA, PET/CT, MRI) when used to diagnose and/or stage pancreatic adenocarcinoma?	No response necessary
Peer Reviewer 4	General Comments	Reviewer agrees with our conclusions on Key Question 4: What is the screening accuracy of imaging techniques (e.g., MDCT angiography with or without 3D reconstruction, other MDCT, EUS-FNA, PET/CT, MRI) for detecting precursor lesion(s) of pancreatic cancer or pancreatic adenocarcinoma in high-risk asymptomatic adults (i.e., those at genetic or familial risk of pancreatic adenocarcinoma)?	No response necessary
TEP Reviewer 1	General Comments	a. General Comments: yes. Well done.	No response necessary
TEP Reviewer 1	General Comments	f. Clarity and Usability: yes	No response necessary
TEP Reviewer 2	General Comments	a. General Comments: Yes, the report is clinically meaningful. The conclusions drawn for the extent of the literature reviewed, are relatively modest. Also, the rate of change of technology with regard to MDCT, MRI and PET/CT, also limit the conclusions that can be drawn as do the fact that no outcome data are correlated.	No response necessary

Commentator & Affiliation	Section	Comment	Response
TEP Reviewer 2	General Comments	f. Clarity and Usability: As the dataset reviewed is very extensive and can not be fully summarized in the structured abstract. An additional 2guidelin-3 page high level summary following the abstract would be very helpful to enhance clarity and explicitly itemize the key conclusions drawn along with the major limitations, the latter in particular with regard to screening.	The executive summary serves this purpose as a brief overview of the main points of the report
TEP Reviewer 2	General Comments	The questions are mostly clearly states.	No response necessary
TEP Reviewer 2	General Comments	The structured abstract is balanced and fair and represents a fairly accurate summary of the data. Would recommend adding that EUS-FNA small advantage for staging over MDCT, may be outweighed by the operator dependency of the procedure.	When we looked at all the staging evidence directly comparing EUS-FNA and MDCT, the only clear conclusion we could draw was that EUS-FNA is more accurate for T staging (based on one study). Given the small quantity of evidence we graded this as Low strength. We also considered a study on vessel involvement, but its results were less clear on the comparison, so we drew no conclusion. In terms of a general statement about staging (and all its facets), we believe there is not enough clarity in the literature to support a general claim of superiority. In the introduction, we mentioned the fact that EUS-FNA accuracy may be operator dependent.
TEP Reviewer 3	General Comments	a. General Comments: the key questions are asked and the questions were not very surprising and are the typical questions asked when looking at technology for disease detection and accuracy	No response necessary
TEP Reviewer 3	General Comments	f. Clarity and Usability: i think the conclusions are that there is no strong conclusion based on data but that current practice is still what will be used going forward	No response necessary

Commentator & Affiliation	Section	Comment	Response
Public Reviewer 1 (Medical Imaging and Technology Alliance)	General Comments	1) Imaging modalities have varied functions and uses in a clinical setting. As such, comparative analyses of modalities are of limited value, especially when removed from the particular clinical setting and circumstances of the individual patient. Medical imaging includes multiple modalities and each modality provides unique and many times complementary value in better understanding the clinical situation. In fact, outside the context of a particular episode of clinical care, comparisons of modalities do not appropriately value the contribution of each modality to healthcare. Rather imaging modalities should be considered in the context of the information they add to the clinical situation and how they add value in establishing appropriate care for the individual patient. AHRQ acknowledges this in the Draft Report as "different imaging tests are believed to have utility in different circumstances (e.g., when suspicious of metastatic disease vs. localized disease) and a clear delineation of the relevant evidence would help guide clinicians and patients in choosing the most appropriate imaging test."4	The current reality is that different imaging tests are being used for overlapping purposes. Thus, the question emerges: when used for the same purpose (e.g., assessment of vessel involvement) in the same patients, which test is more accurate? Answering this was a key purpose of our report. Regarding how multiple tests should be used together, we also looked for pertinent evidence, and unfortunately the issue has not been studied with direct comparisons. We have added this clarification in the revision.
Public Reviewer 1 (Medical Imaging and Technology Alliance)	General Comments	Access to appropriate imaging is necessary to inform clinical decisions related to the proper diagnosis and treatment of disease. In order to better direct the optimal use of imaging, physician societies and other provider groups have developed appropriate use criteria and practice guidelines specific to individual clinical indications. These clinical decision-support tools are based on research and evidence, and aid physicians to determine the appropriate scans to be used for specific clinical indications.	We are aware of the existence of clinical practice guidelines, and that they are helpful in defining appropriate use. This report is a summary of evidence that may inform such guidance, rather than the guidance itself.
Public Reviewer 1 (Medical Imaging and Technology Alliance)	General Comments	The National Comprehensive Cancer Network (NCCN) has clinical practice guidelines on pancreatic adenocarcinoma.5 The guidelines outline considerations and approaches to care. For each stage of care, appropriate testing and treatment are outlined. In addition, imaging modalities are discussed. For example, triphasic CT provides "clear distinction between a hypodense lesion in the pancreas and the rest of the organ" but in some staging, endoscopic ultrasound can provide additional information "for patients whose CT scans show no lesion or who have questionable involvement of blood vessels or lymph node."6 These guidelines appropriately acknowledge that clinical value of each imaging modality is determined by how it informs specific clinical care, not how it ranks in comparison to other modalities.	We are aware of the existence of clinical practice guidelines, and that they are helpful in defining appropriate use. This report is a summary of evidence that may inform such guidance. Regarding the NCCN guideline, we made our evidence review as transparent as possible so that users could examine the extent to which the evidence and our conclusions are consistent with existing or planned guidelines.

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Public Reviewer 1 (Medical Imaging and Technology Alliance)	General Comments	MITA advocates the development and use of physician-developed appropriateness criteria to guide treatment decisions and training of hospital and imaging facility personnel who perform medical imaging exams. In order to provide optimal care and prevent medical errors, physicians and technologists must account for the patient's individual needs. By providing proper training and adhering to these standards and initiatives, physicians can ensure that patients receive the life-saving benefits of medical imaging technology.	We agree that there is value in the development of appropriateness criteria as well as accounting for individual patient needs. The purpose of this report was to compare the performance of different imaging tests to determine whether clear patterns emerge that can guide patient care.
Public Reviewer 1 (Medical Imaging and Technology Alliance)	General Comments	2) Outcomes related to the use of imaging must be defined to reflect the unique contribution of imaging to clinical decisions. The Draft Report points to lack of studies on "patient-oriented outcomes".7 In particular, the AHRQ states, "No included studies compared these tests for their subsequent impacts on patient management, survival, or quality of life."8 This is cited as a gap in evidence. However, we offer that this is not a gap, but rather includes some endpoints which are inappropriate to evaluate diagnostic imaging in the context of patient care.	We believe that the outcomes of patient management, survival, and quality of life are among the set of appropriate outcomes. The outcomes for this report were determined with input from Key Informants (including experts in pancreatic cancer), and they thought the outcomes were important to include.
Public Reviewer 1 (Medical Imaging and Technology Alliance)	General Comments	One consideration is that it is difficult to isolate the contribution of diagnostic imaging from the larger care paradigm, and in fact, due to the incremental value of diagnostic imaging within the delivery of healthcare, diagnostic imaging's value outside the care paradigm would be of limited meaning. Models that attempt to extract diagnostic imaging from the care that it informs neglect to reflect the reality of healthcare delivery. In fact, in clinical practice, a patient may have multiple diagnostic tests, with additional value from each test used to inform the complex clinical decision process in unique and inimitable ways. In addition, some diagnostics tests are synergistic. For example, a PET scan may be ordered in follow up to a CT scan that shows small indeterminate lesions. Additionally, as the science of cancer staging progresses, diagnostic imaging may inform decision-making in concert with other tests including biomarker identification, genomic studies, and other assays.	Our goal was to uncover evidence to support clinical actions such as the ones you listed. Rather than assuming that each additional ordered test provides unique value, we comprehensively searched the literature to support test strategies. Unfortunately, different multiple-test strategies have not been compared systematically (our Key Questions 1c and 2c involve comparisons of different test strategies and we noted the lack of such direct evidence on pages 34 and 46 of the main report), thus we could draw no relevant conclusions on this issue.
Public Reviewer 1 (Medical Imaging and Technology Alliance)	General Comments	A more appropriate endpoint for diagnostic imaging would be similar to that which AHRQ considers as "how patients were managed differently after different tests."9 That is, changes in therapeutic management or stage reclassification are appropriate terminal points when considering the impact of diagnostic imaging on healthcare. A recent article on the topic suggests, "The outcomes, or endpoints, appropriate to assessing whether diagnostic interventions are reasonable and necessary are best characterized as "change in clinical management." This is distinct from the outcomes, or endpoints, classically applied in assessing whether therapeutic interventions are reasonable and necessary."10	No included studies reported comparative data on patient management

Commentator & Affiliation	Section	Comment	Response
Public Reviewer 1 (Medical Imaging and Technology Alliance)	General Comments	3) Innovative, dose-lowering imaging technologies support quality care. The Draft Report also points to radiation dose as a potential harm of CT and PET/CT.11 In recent years, innovative, dose-lowering technologies have limited dose while maintaining imaging quality. Due to lower dose and high clinical efficacy, the CT and PET/CT benefit-to-risk profiles have improved.	Low dose CT may be appropriate for some indications (e.g., renal calculi). It can be used for lung cancer where a nodule is easy to detect against a background of air. However, for pancreatic cancer there is no existing data to show this is viable for routine MDCT. Low dose CT is already used in PET CT. However, the majority of radiation dose in PET CT comes from the radiotracer (i.e., for the PET component) not from the CT. Therefore low dose CT would not influence the dose in that modality. Harms of CT, such as those that may be influenced by dose, were discussed in Key Question 3 on harms (starting on page 49 of the main report)
Public Reviewer 1 (Medical Imaging and Technology Alliance)	General Comments	Dose efficiency and dose reduction have been important design considerations for CT for many years. The focus on these design considerations has grown and intensified in more recent years, and has yielded a variety of new and innovative hardware and software features that directly help physicians both reduce and monitor dose for CT exams. The CT industry has developed new features that enable both the dose to be displayed prior to scanning, and to alert operators to potentially higher than expected doses, as well as enabling electronic recording of the CT dose in the patient record. These features are important for both the patient as well as facilities, since they provide facilities with the ability to compare the dose of their CT protocols and establish optimized reference values.	We appreciate the efforts of CT manufacturers and others to control and reduce radiation dose while preserving image quality. We also note that the majority of radiation dose in PET CT comes from the radiotracer for the PET component.

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Public Reviewer 1 (Medical Imaging and Technology Alliance)	General Comments	The dose monitoring/reduction features described below play a significant role in helping to reduce the dose for CT exams, while maintaining diagnostic quality and the capability to report and record dose. For example: • Automatic Exposure Control helps optimize dose for each patient for the given diagnostic task. This feature adjusts the exposure to use only what is needed to maintain a constant image quality. This feature is now standard on CT systems. • Wider coverage detectors minimize the amount of x-ray that falls outside of the active detector region, thereby reducing dose to the patient without impacting image quality. Systems are now available in a range of wide coverage designs. • "Shutter" modes block unused x-ray at the beginning and end of helical scans and therefore do not degrade image quality. This feature is now standard on many CT systems and is "built in" to each helical acquisition. • Advanced electronics in data acquisition systems result in better imaging performance and less noise, thereby enabling equal performance at a lower dose. • First generation CT iterative reconstruction results in a significant dose reduction potential, while maintaining diagnostic image quality, and is well suited to CTC studies. Iterative reconstruction is available on new systems and also as an upgrade to many installed base systems. • More advanced second generation CT iterative reconstruction provides even further dose reduction potential, where some expert users are able to achieve some exams approaching 1 mSv levels for combined supine and prone CTC scans, while still maintaining diagnostic image quality. This feature is becoming widely available on new systems. • The DICOM Dose Structured Report allows the exam dose to be electronically captured with the patient record. This feature is now standard on all new CT systems and has also been implemented on newer installed base systems.	We appreciate the efforts of CT manufacturers and others to control and reduce radiation dose while preserving image quality. We also note that the majority of radiation dose in PET CT comes from the radiotracer for the PET component.

Commentator & Affiliation	Section	Comment	Response
Public Reviewer 1 (Medical Imaging and Technology Alliance)		MITA leads industry efforts to coordinate and establish standards to mitigate radiation dose. Adoption of these standards benefits patient dose. MITA's approach builds upon existing manufacturer safety measures – including equipment safety standards, protocol development, quality and safety checks, provider education programs and physician-developed medical guidelines – to minimize radiation dose as much as possible, and to provide even greater degrees of coordination, transparency and reporting in the delivery of medical radiation. Recent examples of MITA standards which have addressed dose include: • NEMA XR 25-2010, Computed Tomography Dose Check. This standard introduced two novel features to assist the imaging team in providing better patient care: dose notifications and dose alerts. Dose notifications are designed to provide a clear indication to health care providers when the parameters for a CT scan will result in a dose higher than the facility's pre-determined dose threshold for routine use. Dose alerts are designed to prevent dose levels for a complete exam from exceeding pre-determined thresholds that are deemed excessive by the facility. This feature can be configured to prevent equipment operation. These protections help the operator and ultimately the physician to better understand dose implications of protocol choices, and should significantly reduce exposure due to inappropriate scan parameter settings. • NEMA standard XR 26 - 2012, Access Controls for Computed Tomography: Identification, Interlocks, and Logs. This standard requires software features that ensure only an authorized operator can alter the controls of CT equipment. This industry-wide standard requires the institutionalization of administrative privileges, access levels, and the recording of clinical protocols to ensure safe and appropriate use. • NEMA standard XR 27 - 2012, X-ray Equipment for Interventional Procedures User Quality Control Mode. This standard helps imaging facilities conduct quality testing and monitoring of X-ray equipment used for interventional procedures. • NEMA standard XR 29 - 2013, Standard Attributes on Computed Tomography (CT) Equipment Related to Dose Optimization and Management. This standard, known also as MITA "Smart Dose", is the fourth dose-related standard to be released by MITA since 2010. This standard includes four components: 1. DICOM Dose Structured Reporting – This enables the recording of post-exam dose information in a standardized electronic format. This information can be included in the patient record, promoting the establishment of diagnostic reference levels, as well as facility dose management and quality assurance. 2. Pediatric and adult reference protocols – These are a set of pre-loaded protocols on a CT system that serve as a baseline for a variety of clinical tests.	We appreciate the efforts of CT manufacturers and others to control and reduce radiation dose while preserving image quality. We also note that the majority of radiation dose in PET CT comes from the radiotracer for the PET component.

Commentator & Affiliation	Section	Comment	Response
Public Reviewer 1 (Medical Imaging and Technology Alliance)	General Comments	(continued) 3. CT Dose Check – CT Dose Check incorporates two features—dose notifications and dose alerts that can inform operators and physicians when dose exceeds established thresholds. 4. Automatic Exposure Control (AEC) – AEC automatically adjusts the amount of radiation used based on the size, shape and composition of the patient, in order to achieve a specified level of image quality.	We appreciate the efforts of CT manufacturers and others to control and reduce radiation dose while preserving image quality. We also note that the majority of radiation dose in PET CT comes from the radiotracer for the PET component.
Public Reviewer 2 (Mouen Khashab)	General Comments	The conclusions from the above document pose an unfair argument against the use of EUS +/- FNA in patients with suspected pancreatic cancer and I have no doubt that some payers will (mistakenly) use this to deny coverage. The use of CT and EUS are for diagnosis, staging, and assessing resectability.	The basis for the comment is unclear. Regarding EUS-FNA, we concluded "MDCT and EUS-FNA are approximately equally accurate in the assessment of resectability of pancreatic adenocarcinoma in unstaged symptomatic adults (Strength of evidence: low)", which is not a conclusion that EUS-FNA is worse than MDCT, but rather that they are similar in this regard. We also concluded "US-FNA is more accurate than MDCT in the assessment of the T stage of pancreatic adenocarcinoma in symptomatic adults The results on accuracy, though less ideal than patient outcomes, may be used as one input into decisions by insurers, but there are also important considerations such as the balance of benefits and harms of various tests, and the option of tissue diagnosis with EUS-FNA that could influence coverage decisions.
Public Reviewer 2 (Mouen Khashab)	General Comments	Diagnosis: Any imaging modality will detect large tumors but EUS has clear advantage for small tumor and for pancreatic neuoendocrine tumors (Gastrointest Endosc. 2011 Apr;73(4):691-6. doi: 10.1016/j.gie.2010.08.030. Epub 2010 Nov 10.EUS is still superior to multidetector computerized tomography for detection of pancreatic neuroendocrine tumors. Khashab MA, Yong E, Lennon AM, Shin EJ, Amateau S, Hruban RH, Olino K, Giday S, Fishman EK, Wolfgang CL, Edil BH, Makary M, Canto MI) and Ann Intern Med. 2004 Nov 16;141(10):753-63. Comparison of endoscopic ultrasonography and multidetector computed tomography for detecting and staging pancreatic cancer. DeWitt J, Devereaux B, Chriswell M, McGreevy K, Howard T, Imperiale TF, Ciaccia D, Lane KA, Maglinte D, Kopecky K, LeBlanc J, McHenry L, Madura J, Aisen A, Cramer H, Cummings O, Sherman S.	We understand that your opinion is that EUS-FNA is superior, and our purpose was to examine the best evidence ourselves. This examination did result in a conclusion that for T staging, EUS-FNA was superior to MDCT. For resectability, we concluded they had similar accuracy. The strength of the evidence was low for both conclusions, mostly because they were each supported by only a single direct comparative study. About the two articles you cited, we included the Dewitt review in our report and noted the fact that those authors concluded that EUS is superior for diagnosis. We did not include the Khashab study; we excluded it because neuroendocrine tumors were outside our scope.

Commentator & Affiliation	Section	Comment	Response
Public Reviewer 2 (Mouen Khashab)	General Comments	Staging: I Agree that EUS is better for T staging, both equivalent for nodal staging, CT better for distant mets. But studies have also showed that both are complimentary and doing both of them improves overall accuacy (John Dewitt's study above) 3. All above focus on EUS and not FNA. At least 5% of pancreatic masses turn to be pathologies that should not have been operated on (mets, lymphoma, chronic panc, autoimmune pancreatitis). FNA saves 5% of patients from having un-needed Whipples 4. EUS detects small liver lesions that are impossible to detect by CT 5. EUS is mostly done in tertiary centers and genrally speaking quality tends to be good due to that. CT is done everywhere. We now use MDCT 128 slices. Lot of places have 4 and 16 slice MDCT. There is no way these are better than EUS. This is an important point. I admit that at Hopkins with 128 slice CT, 3D reconstruction and Elliott Fishman reading these pancreatic protocol CT scans, EUS is not better than CT. However, the accuracy of outside CT is miserable and our management frequently changes once we repeat the CT at our hospital 6. I do not think PET has any role in pancreatic cancer.. besides it is very expensive 7. In terms of EUS-FNA risk, tumor seeding is a reportable cases, transduodenal FNA of head masses is not an issues since the duodenum comes out with surgical specimen, and risk of pancreatitis is 0.2% in a study by Mohamed Eloubeidi of 4900 patients	This examination did result in a conclusion that for T staging, EUS-FNA was superior to MDCT. Regarding the Dewitt review, in comparing our conclusions to theirs, our report notes (page 66) that we reached the same conclusion about resectability i.e. approximate equivalence), but we did not conclude that EUS is more sensitive (or more accurate in general) than MDCT. In comparing EUS-FNA to MDCT for diagnosis, we performed a meta-analysis of three studies. This evidence suggested a slight advantage of EUS-FNA, but the difference was not statistically significant and was too imprecise to permit a conclusion of approximate equivalence. The difference may involve the inclusion of single-slice CT by Dewitt (which we excluded because it is an outdated technology).
Public Reviewer 3 (Pancreatic Cancer Action Network)	General Comments	While we appreciate AHRQ's efforts to examine imaging tests for pancreatic cancer through the Effective Health Care Program, as a scientific, evidence-based organization, we strongly believe there are currently not enough data on imaging tests for pancreatic cancer to allow any meaningful conclusions at this time. The draft report itself notes that "the evidence was usually too imprecise to permit conclusions" and that there was "sufficient evidence (only) for some tentative evidence-based conclusions." More than ten key sub-questions in fact could not be answered.	This is true. There were many Key Questions asked that could not be answered. Hopefully evidence will be collected in the future to better guide decisions.
Public Reviewer 3 (Pancreatic Cancer Action Network)	General Comments	Statement on the accuracy of PET/CT over MDCT (multidetector computed tomography) with metastases We question the assertion in the Results section (page v) that there is "sufficient evidence to conclude that PET/CT is more accurate than MDCT in assessing metastases." The authors acknowledge in Table 8 that the strength of evidence is only moderate. We believe the existing research allows AHRQ to say only that there is evidence to suggest that PET/CT can provide complementary information to MDCT in assessing metastases. We therefore respectfully ask that the language in the final report be modified to reflect the current uncertainty as to which test is more accurate.	We stand by our conclusion as well as its evidence grade (moderate). These were determined by a systematic process involving a careful consideration of the best evidence available. Based on two studies that directly compared the technologies (all patients received both tests), PET-CT had statistically significantly better specificity, and also had a higher sensitivity but was not statistically significantly higher.

Commentator & Affiliation	Section	Comment	Response
Public Reviewer 3 (Pancreatic Cancer Action Network)	General Comments	Statement on negative results when screening high-risk individuals We strenuously object to the statement in the Results section (page v) that "(i)n the screening of people at high risk of developing pancreatic adenocarcinoma, most people have negative results on pertinent imaging tests, and available studies do not correlate the results of a given imaging test to subsequent diagnoses." These two points are repeated in the last paragraph on page ES-14. While we agree that studies to date show that most high-risk individuals have negative results when screened, we again are deeply concerned that there is not currently enough evidence to support this statement.	We have edited the description of the screening studies. We note that the accuracy of any given imaging test could not be determined, since studies did not provide results separately for each screening test.
Public Reviewer 3 (Pancreatic Cancer Action Network)	General Comments	The authors state that "Our goal was not to determine if screening HRIs for pancreatic cancer was appropriate or effective, but rather to determine which imaging modalities might be more accurate for screening." However, we believe that the conclusion that "most people have negative results" makes an inference about screening HRIs and as a result could have a chilling effect on the ongoing research in this area. We urge AHRQ to make only the point that available studies do not allow AHRQ to correlate the results of a given imaging test to subsequent diagnoses.	We have edited the description of the screening studies to avoid giving the impression that we are arguing against screening. Unfortunately, the evidence is insufficient for determining the accuracy of any individual imaging test when used for this purpose.
Public Reviewer 3 (Pancreatic Cancer Action Network)	General Comments	We are also concerned that the studies referenced did not have standard definition of "high risk." The number of first-degree relatives with pancreatic cancer makes a tremendous difference in the level of risk, for example. Without a standard definition, it is impossible to make generalized statements about the value of screening high-risk individuals.	We agree that the studies defined high-risk differently. We mentioned the varying definitions on ES-18 and pages 58-59.
Public Reviewer 3 (Pancreatic Cancer Action Network)	General Comments	If a generalized statement about the value of screening in high-risk individuals is considered essential to the report, AHRQ must remember that the draft report also notes that some people have positive results. This fact cannot be omitted from the statement if the findings on negative results are also included. While we would prefer that the final report omit any statements on the value of screening HRIs, at the very least, we urge the authors to give the statement appropriate balance and to explicitly recognize the lack of definitive research on this question.	We agree that both false positive and false negative results have important consequences and that true positives and true negatives are valuable to patients. This value needs to be considered alongside the potential risks of repeat imaging, for example, the radiation dose. The published evidence is not sufficient for determining the best choice of screening strategies..
Public Reviewer 3 (Pancreatic Cancer Action Network)	General Comments	Statement on the usefulness of endoscopic ultrasound (EUS) in screening high-risk individuals Under "Conclusions for Key Question 4" (page 50), the authors note that two "(s)tudies reviewed have suggested the use of EUS as an adjunct to another screening modality such as CT or MR." Only six studies met the inclusion criteria for Key Question 4. We want to call your attention to several ongoing studies at academic centers that use EUS as a first-line screening tool in people at high risk for pancreatic cancer.	We summarized all available evidence on screening of HRIs for pancreatic adenocarcinoma. Perhaps you are referring to the CAPS studies, which we also included. The results of ongoing screening studies may provide useful data for future updates of this report.

Commentator & Affiliation	Section	Comment	Response
Public Reviewer 3 (Pancreatic Cancer Action Network)	General Comments	Call for future research We agree that there are many gaps in the comparative assessment of imaging tests for diagnosing and staging pancreatic adenocarcinoma as well as gaps in screening for HRIs. As the authors noted, pancreatic cancer has a 6% five-year relative survival rate, partially because there are few effective early detection tools or treatments. The Pancreatic Cancer Action Network strongly believes that our nation's research goal must be to focus on ways to improve survival, which includes research into early detection and staging tests in addition to research focused on finding treatments for disseminated disease. We look forward to the day when we can engage in meaningful comparative effectiveness research into the many different tools available for treating pancreatic cancer, as well as for early detection and staging.	We agree that we must continue to research ways to improve survival, and we look forward to future research.
Public Reviewer 3 (Pancreatic Cancer Action Network)	General Comments	Conclusion We appreciate the work that has gone into developing this report. AHRQ is a leading authority on research, reports, and other tools that examine the quality, safety, effectiveness, and efficiency of health care. These reports are generally very useful in the practice of medicine today, precisely because they are typically based on strong scientific evidence. Unfortunately, we do not believe that this report meets those same standards, given the lack of available evidence. Thank you very much for considering our comments, and if we can be of further assistance, please do not hesitate to contact us.	No response necessary