Washington State Health Care Authority

Gene expression profile testing of cancer tissue

Draft key questions: Comment and response

November 14, 2017

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Gene Expression Profile Testing of Cancer Tissue

Draft Key Questions

Comment and Response

Provided by:

Center for Evidence-based Policy
Oregon Health & Science University

November 14, 2017

Responses to public comment on draft key questions

The Center for Evidence-based Policy is an independent vendor contracted to produce evidence assessment reports for the Washington Health Technology Assessment (HTA) program. For transparency, all comments received during the public comment periods are included in this response document. Comments related to program decisions, process, or other matters not pertaining to the evidence report are acknowledged through inclusion only.

Draft key question document comments received:

- Jeffrey Evans, MD, Washington State Urology Society
- Karen Heller, MS, CGC, Medical Policy Manager, Myriad Genetic Laboratories

Specific responses pertaining to comments are shown in **Table 1.**

Table 1. Responses to comments on Draft key questions for Gene expression profile testing of cancer tissue

Comments		Response
Commenter: Jeffrey Evans, MD, Washington State Urology Society		
	Specific comments:	
Background Section	My name is Dr. Jeff Evans and I am a urologist who is the current past president and chair of communications for the WSUS. Our organization appreciates your willingness to take public comment. Urologists periodically utilize advanced gene expression diagnostic tests when deciding treatment options for patients with adenocarcinoma of the prostate. The 2017 NCCN guidelines allow for consideration of tumor-based molecular assays in men with clinically localized disease. Retrospective case cohort studies have shown that molecular assays provide prognostic information independent of other NCCN risk groups. These include, but are not limited to, likelihood of death with conservative management and likelihood of biochemical progression after radical prostatectomy or radiation treatment. We are seeing an increasing trend toward active surveillance in low risk prostate cancer and these tests are particularly helpful in deciding if avoidance of therapy or intervention is warranted. Medicare has reviewed the literature and has made a positive coverage decision. Cell cycle progression scores as measured by the Prolaris test has been well studied and published in peer-reviewed publications.	Thank you for your comments.
Methodology	Prospective studies should not be required for approval by the HTA, as mandating this for prostate cancer is unrealistic. We agree that prospective trials are more powerful, but the long clinical course of most patients with prostate cancer make these types of studies impractical. Basing your determination on the lack of prospective studies will penalize current patients with this disease.	Thank you for your comments. The key question document states that eligible studies include randomized controlled trials as well as nonrandomized comparative studies, which could include retrospective studies. All eligible studies will be assessed for methodological quality, and the overall strength of evidence will be based on the quality assessments of the included studies.
Background Section	Urologists currently utilize this class of testing for select patients with prostate cancer and recommend they be covered. We are not recommending any particular companies assay. Medicare patients already have access to	Thank you for your comments.

	Comments	Response
Commenter: Jeffrey Evans, MD, Washington State Urology Society		
	Specific comments:	
	these tests and we feel that the Medicaid beneficiaries and state employees deserve the same coverage. We appreciate your review of our comments and addressing the issues that affect men with prostate cancer. Feel free to contact us with any questions.	

	Comments	Response
Commenter: Karen Heller, MS, CGC, Medical Policy Manager, Myriad Genetic Laboratories		
	Specific comments:	
Background Section	We commend Washington's independent Health Technology Clinical Committee for selecting this topic for a health technology assessment as these tests enable more tailored treatment for beneficiaries with certain cancers, resulting in improved clinical and financial outcomes. We focus our comments here on the tests pertaining to breast and prostate cancer.	Thank you for your comments.
Methodology	Prognostic tests are currently available and being utilized clinically because they have been shown to have substantially superior risk classification abilities compared to standard clinico-pathologic parameters. However, improvements in long term outcomes must be extrapolated, attributed to more appropriate treatment decisions based on the results of better risk classifiers. For prostate cancer, the oncologic outcome upon which treatment decisions are made is 10-year disease specific mortality. The highly variable standard of care regarding treatment, the small size of the treatment effect, and the lengthy natural history of prostate cancer results in a prohibitively large sample size requirement and a very long time period if a prospective trial were to be performed. For breast cancer, the oncologic outcome of interest for ER-positive breast cancer is 10 year distant recurrence rates. This is what treating physicians use to determine whether an early stage, ER-positive, HER2-negative breast cancer should be treated with chemotherapy (in addition to hormonal therapy). Therefore, a prospective trial to evaluate long term outcomes has similar limitations for this disease state; the trial would take so long that the technology could be outdated. We urge the Committee to consider the recommendations set out by Simon, Paik and Hayes,[1] who published an	Thank you for your comments. The key question document states that eligible studies include randomized controlled trials as well as nonrandomized comparative studies, which could include retrospective studies. All eligible studies will be assessed for methodological quality, and the overall strength of evidence will be based on the quality assessments of the included studies.

Comments		Response
Commenter: Karen Heller, MS, CGC, Medical Policy Manager, Myriad Genetic Laboratories		
	Specific comments:	
	evidentiary framework for evaluating tumor biomarkers in the absence of prospective, randomized data. This framework, adopted by ASCO,[2] describes using archived specimens in a "prospective-retrospective" manner, to not only validate the prognostic ability of a tumor marker, but also prove its medical utility. Based on these standards, breast cancer prognostics can achieve a level of evidence (LOE) IB, and prostate cancer prognostics can achieve a LOE II, which, given the current state of clinical equipoise, should be acceptable for coverage. We also urge the Committee to consider the "chain of evidence" concept as published in the Effectiveness Guidance Document from the Center for Medical Technology Policy (CMTP),[3,4] which includes several well-known experts in the field of molecular diagnostics coverage and reimbursement. According to CMTP, linking separate pieces of published evidence to prove clinical utility is an acceptable approach when a randomized controlled trial is not possible. We respectfully request that the prospective-retrospective clinical validation studies for the breast and prostate cancer prognostic tests be reviewed.[5-8] Based on the framework by Simon, if evidence supports their improved accuracy in predicting outcomes, treating physicians should be encouraged to use them to select the appropriate level of intensity of treatment, and, in fact, decision impact studies have shown that they are used to change treatment recommendations.[9-11] A "chain of evidence" can be used to infer improved outcomes based on more appropriate treatment, i.e. reduced over- and under-treatment. In particular, reductions in the amount of treatment that occurs as a result of the test can be inferred to result in less unnecessary treatment-associated morbidities for individuals confirmed as having low risk disease. We also ask that validation studies performed on registry cohorts be considered,[7,8] since they are well suited for validation of prognostic markers. While registry studies may be inappropriate for validation of predictive claims (due to potential bias in how treatment options are selected), registry studies have few, if any, patient exclusion criterion and do not specify treatment algorithms, so they enable evaluation of prognostic marker performance in a wide range of patient risk profiles and clinical settings.	

Comments		Response
Commenter: Karen Heller, MS, CGC, Medical Policy Manager, Myriad Genetic Laboratories		
	Specific comments:	
	In summary, certain outcomes that are to be the focus of this review may require a broader approach to the literature review, with the Simon framework allowing a LOE attributed to prospective-retrospective validation studies, including registry studies, and a "chain of evidence" in lieu of prospective randomized trials. Thank you again for the opportunity to provide comment on the draft.	
Citations	1. Simon RM, Paik S, and Hayes DF. Use of Archived Specimens in Evaluation of Prognostic and Predictive Biomarkers. *J Natl Cancer Inst* 2009;101: 1446 – 1452. 2. Harris LN, Ismaila N, McShane LM, et al; American Society of Clinical Oncology. Use of Biomarkers to Guide Decisions on Adjuvant Systemic Therapy for Women With Early-Stage Invasive Breast Cancer: American Society of Clinical Oncology Clinical Practice Guideline. *J Clin Oncol.* 2016 Apr 1;34(10):1134-50. 3. Center for Medical Technology Policy (CMTP) Effectiveness Guidance Document: Evaluation of Clinical Validity and Clinical Utility of Actionable Molecular Diagnostic Tests in Adult Oncology. May 1, 2013. Accessed May 10th 2017 at http://www.cmtpnet.org/docs/resources/MDX_EGD.pdf 4. Deverka P, et al. Generating and evaluating evidence of the clinical utility of molecular diagnostic tests in oncology. Genet Med. 2016 Aug;18(8):780-7. 5. Filipits M, Rudas M, Jakesz R, et al. A new molecular predictor of distant recurrence in ER-positive, HER2-negative breast cancer adds independent information to conventional clinical risk factors. Clin Cancer Res. 2011;17(18):6012–6020. 6. Buus R, Sestak I, Kronenwett R, et al. Comparison of EndoPredict and EPclin With Oncotype DX Recurrence Score for Prediction of Risk of Distant Recurrence After Endocrine Therapy. J Natl Cancer Inst. 2016 Jul 10;108(11). doi: 10.1093/jnci/djw149. Print 2016 Nov. 7. Cuzick J, Berney DM, Fisher G, et al. Transatlantic Prostate Group. Prognostic value of a cell cycle progression signature for prostate cancer death in conservatively managed needle biopsy cohort. Br J Cancer 2012 Mar 13; 106(6):1095-9. 8. Cuzick J, Stone S, Fisher G, et al. Validation of an RNA cell cycle progression score for predicting death from prostate	

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From: Jeff Evans
To: HCA ST Health Tech Assessment Prog
Cc: Jeffrey Frankel; Debi Johnson; Paul Kozlowski; Jonathon Wright; MD Ken Berger
Subject: Public Comment from Washington State Urology Society
Date: Friday, October 20, 2017 5:41:20 PM

Submitted by:

Jeffrey Evans, MD
Washington State Urology Society
jeffreylewisevans@yahoo.com
206-852-3397

Regarding:

Gene expression profile testing of cancer tissue

Dear Committee members,

My name is Dr. Jeff Evans and I am a urologist who is the current past president and chair of communications for the WSUS. Our organization appreciates your willingness to take public comment.

Urologists periodically utilize advanced gene expression diagnostic tests when deciding treatment options for patients with adenocarcinoma of the prostate. The 2017 NCCN guidelines allow for consideration of tumor-based molecular assays in men with clinically localized disease. Retrospective case cohort studies have shown that molecular assays provide prognostic information independent of other NCCN risk groups. These include, but are not limited to, likelihood of death with conservative management and likelihood of biochemical progression after radical prostatectomy or radiation treatment.

We are seeing an increasing trend toward active surveillance in low risk prostate cancer and these tests are particularly helpful in deciding if avoidance of therapy or intervention is warranted. Medicare has reviewed the literature and has made a positive coverage decision. Cell cycle progression scores as measured by the Prolaris test has been well studied and published in peer-reviewed publications. Prospective studies should not be required for approval by the HTA, as mandating this for prostate cancer is unrealistic. We agree that

prospective trials are more powerful, but the long clinical course of most patients with prostate cancer make these types of studies impractical. Basing your determination on the lack of prospective studies will penalize current patients with this disease.

Urologists currently utilize this class of testing for select patients with prostate cancer and recommend they be covered. We are not recommending any particular companies assay. Medicare patients already have access to these tests and we feel that the Medicaid beneficiaries and state employees deserve the same coverage.

We appreciate your review of our comments and addressing the issues that affect men with prostate cancer. Feel free to contact us with any questions.

Respectfully,

Jeffrey Evans, MD

Submitted by:
Karen Heller, MS, CGC
Medical Policy Manager
Myriad Genetic Laboratories
Salt Lake City, UT
kheller@myriad.com
214-789-5014

October 18th, 2017

Comment on: Draft key questions and background: Gene expression profile testing of cancer tissue

We commend Washington's independent Health Technology Clinical Committee for selecting this topic for a health technology assessment as these tests enable more tailored treatment for beneficiaries with certain cancers, resulting in improved clinical and financial outcomes. We focus our comments here on the tests pertaining to **breast** and **prostate** cancer.

Prognostic tests are currently available and being utilized clinically because they have been shown to have substantially superior risk classification abilities compared to standard clinico-pathologic parameters. However, improvements in long term outcomes must be extrapolated, attributed to more appropriate treatment decisions based on the results of better risk classifiers. For prostate cancer, the oncologic outcome upon which treatment decisions are made is 10-year disease specific mortality. The highly variable standard of care regarding treatment, the small size of the treatment effect, and the lengthy natural history of prostate cancer results in a prohibitively large sample size requirement and a very long time period if a prospective trial were to be performed. For breast cancer, the oncologic outcome of interest for ER-positive breast cancer is 10 year distant recurrence rates. This is what treating physicians use to determine whether an early stage, ER-positive, HER2-negative breast cancer should be treated with chemotherapy (in addition to hormonal therapy). Therefore, a prospective trial to evaluate long term outcomes has similar limitations for this disease state; the trial would take so long that the technology could be outdated.

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References:

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