HERC Coverage Guidance – Biomarker tests of cancer tissue for prognosis and potential response to treatment
Disposition of Public Comments

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Commenters

Identification	Stakeholder
A	Oncology and Genetics Clinical Nurse Specialist, Providence Cancer Center
B	Senior Director, Health Policy & Reimbursement, Roche Diagnostics Corporation North America
C	President and CEO, ZERO - The End of Prostate Cancer
D	Genetic counselor, Myriad Genetic Laboratories (which performs the Prolaris® test)
E	Urologist, Oregon Urology Institute

Public Comments

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A	1	The National Comprehensive Cancer Network (NCCN), the American Society of Clinical Oncology (ASCO), and the European Society for Clinical Oncology (ESMO) recommend routine microsatellite instability (MSI) testing of either all colorectal (CRC) tumors, or all CRC <70 years, with MSI testing of those >70 if Bethesda guidelines are met. Universal screening for MSI identification is more sensitive than following previously established testing criteria using Bethesda and/or Amsterdam criteria (Balmana, J, et al, 2013).	NCCN guidelines are considered in the CG document. As noted in Table 6, NCCN rates evidence about MSI as category 2A, "based upon lower-level evidence, there is uniform NCCN consensus that the intervention is appropriate." Screening of colon tumor tissue may be done with either MSI or IHC testing, and IHC is considered the more cost-effective option. The AHRQ review found evidence of analytic and clinical validity for MSI testing, but did not identify evidence of improved patient outcomes. Therefore there is not yet evidence of clinical utility. There are also appropriate, perhaps more cost-effective alternatives available, therefore MSI is not recommended for coverage.
A	2	The rationale for routine MSI testing is for its potential to identify individuals with Lynch Syndrome (aka Hereditary non-polyposis colorectal cancer syndrome - HPNCC). Lynch Syndrome is inherited in autosomal dominant fashion and is estimated to be the cause of 2-4% of colorectal cancers.	This background information is correct.
A	3	MSI testing to detect Lynch Syndrome affects the care of colorectal cancer patients. The diagnosis of Lynch Syndrome is useful for determining optimal surgical management in colorectal cancer patients (Balmana, J (2013).	See comment A1. Identifying a syndrome which would affect planning and screening would be an important patient oriented outcome. However, there is an alternative available and there is currently insufficient

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			evidence of clinical utility.
A	4	Patients with Lynch Syndrome are on average, younger at diagnosis, and MSI is associated with improved prognosis. Therefore, the identification of Lynch Syndrome affects the management of colorectal cancer survivors.	AHRQ meta-analysis of 6 studies (total N = 3439) found an overall hazard ratio for cancer-specific survival for patients with MSI-H (microsatellite instability high) tumors compared with MSS (microsatellite stability) tumors of 0.63; 95% CI, (0.51 to 0.79). Risk of bias was rated as medium. MA of 12 studies (total N = 8839) rated as low or medium risk of bias found an overall hazard ratio for overall survival for patients with MSI-H compared with MSS of 0.57; 95% CI (0.43 to 0.77). Despite these numbers, AHRQ found no direct evidence that using the test was related to improved outcomes for patients, even in the cases such as this one where tests had evidence of clinical validity. In other words, there is not yet proof of clinical utility and alternatives are available. Therefore, HTAS has made a weak recommendation against coverage.
A	5	Colorectal cancer patients with Lynch Syndrome are at significantly increased risk for 2nd primary colorectal cancers. Colonoscopy every 1-2 years is recommended by the NCCN for people with Lynch Syndrome.	This NCCN recommendation is correct. See A3.
A	6	Women with Lynch Syndrome are also at substantially increased risk for endometrial and ovarian cancer, which can be prevented with surgery after childbearing is complete.	This is correct. See A3.
A	7	In 2009, the Evaluation of Genomic Applications in Practice and Prevention (EGAPP), a CDC working group, recommended routine MSI testing of all newly diagnosed colorectal cancer. The EGAPP working group concluded that	The EGAPP report from 2009 is considered in the AHRQ review that

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		there was sufficient evidence to support routine MSI testing of patients with newly diagnosed colorectal cancers in order to achieve improved health outcomes for their relatives.	provided the basis of this CG document (reference #1096). Discussion of MSI testing from the AHRQ review has been added to the CG document; AHRQ found insufficient evidence of clinical utility as discussed above.
A	8	In genetics, the standard of care is to consider relatives when choosing tests. This is commonly at odds with the structure of health care reimbursement in the United States. Individuals often have insurance benefits that are dependent on genetic test information from relatives. For individual patients and families at risk for Lynch Syndrome, testing colon tumors for MSI as a first step is usually less expensive and more efficient than initiating testing for germline Lynch Syndrome-causing mutations first, especially in unaffected relatives.	Commenter notes that testing tumors for MSI is more cost-effective than alternatives; no new sources are cited.
A	9	Thank you for your consideration of Oregon Health Plan coverage for routine MSI testing. Please contact me if I can be of assistance.	Thank you for your comments.
B	10	Dear Health Evidence Review Commission Members: On behalf of The Roche Group (“Roche”), a global leader in research-focused healthcare with combined strengths in pharmaceuticals and diagnostics, I am pleased to submit comments in response to the draft coverage guidance from the Health Evidence Review Commission (“the Commission”) entitled “Biomarker Tests of Cancer Tissue for Prognosis and Potential Response to Treatment”.	Thank you for your comments.
B	11	In the draft coverage guidance, the Commission recommends (with a strong recommendation) for coverage of BRAF gene testing for melanoma and epidermal growth factor receptor (EGFR) gene mutation testing for non-small-cell lung cancer (NSCLC). Roche applauds the strong recommendation from the Commission regarding BRAF gene mutation testing for melanoma and EGFR gene mutation testing for NSCLC.	Thank you for your comments.
B	12	BRAF Test Citing a Blue Cross Blue Shield Technology Evaluation Center report, the Commission noted that the evidence supports the clinical validity and utility of the cobas® 4800 BRAF V600 Test1 in “[U]sing the test to select patients for treatment results in improved outcomes compared to the usual standard of care.”	This is correct.
B	13	The Commission’s recommendation is also supported by the National Comprehensive Cancer Network Guidelines (NCCN).2 The Roche cobas® 4800 BRAF V600 test received FDA approval as a test to determine the tumor mutational status and as a companion diagnostic to vemurafenib (Zelboraf™). The drug’s “Indications and Usage” section of its labeling specifically notes the use of an FDA approved test: *“ZELBORAF™ is a kinase inhibitor indicated for the treatment of patients with unresectable or metastatic melanoma with BRAFV600E mutation as detected by an FDA-approved test.” (3)*	This background information from NCCN is correct.

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B	14	EGFR Test Based on its evaluation, the Commission found that there was sufficient evidence demonstrating that the test was more effective and had similar or less risk than the alternatives. While the reports referenced in the development of this guideline note the differing opinions regarding the usefulness of the test in affecting outcomes, we support the Commission's decision to give the test a strong recommendation.	Thank you for your comments.
B	15	This position is consistent with the NCCN Guidelines on NSCLC which recognize EGFR variants as critical considerations in the selection of targeted therapies for patients with NSCLC. (4)	This is correct.
B	16	The Roche cobas® EGFR Mutation Test also received FDA-approval as a companion diagnostic to erlotinib (Tarceva®) and the drug's "Indications and Usage" section of its labeling specifically notes the use of an FDA approved test: *"First-line treatment of patients with metastatic non-small cell lung cancer (NSCLC) whose tumors have epidermal growth factor receptor (EGFR) exon 19 deletions or exon 21 (L858R) substitution mutations as detected by an FDA-approved test." (5)*	Thank you for your comment. HTAS recommends coverage for EGFR in non small cell lung cancer.
B	17	The Commission's decision to support the use of BRAF and EGFR biomarker tests for the prognosis and potential response to treatment is consistent with that of numerous Medicare Administrative Contractors (MACs) including Palmetto GBA that have decided to provide coverage for these tests under the Medicare program. Palmetto administers Medicare's Molecular Diagnostics Services Program (MolDX), a program that was developed to identify and establish coverage and reimbursement for molecular diagnostic tests. Palmetto, in reviewing the clinical evidence on BRAF and EGFR, developed coverage policies specifically calling out the use of an FDA-approved companion diagnostic in order to receive coverage for the EGFR and BRAF tests.	Thank you for the information.
B	18	We appreciate the opportunity to submit comments on this draft coverage guidance and, again, strongly support the position taken by the Commission.	Thank you for your comments.
C	19	I write today on behalf of ZERO – The End of Prostate Cancer, a national nonprofit organization dedicated to ending prostate cancer. In 2015 alone, more than 228,000 men will be diagnosed with prostate cancer. More than 90 percent of these new cases will be diagnosed at an early stage when the possibility of cure is best.	Thank you for your comments.
C	20	There is a significant problem with over- and under-treatment in prostate cancer which results in some men receiving unnecessary treatments with significant side effects, and some men dying unnecessarily of prostate cancer. Risk stratification in prostate cancer is significantly improved with the addition of genomic testing tools. These tools provide valuable information about how the prostate tumor will behave and the possibility that the cancer will kill helping to shape treatment plans. The National Comprehensive Cancer Network (NCCN) guidelines suggest considering tumor based molecular testing to guide treatment, specifically Oncotype Dx for prostate and Prolaris.	The AHRQ review used as a basis for the coverage guidance found that direct evidence is insufficient to establish the analytic validity, clinical validity, or clinical utility of either test (Prolaris® or Oncotype Dx®).

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C	21	ZERO does not endorse specific products, treatments or brands but we strongly believe that patients should have access to the full array of available tools to make an informed and educated decision about their treatment. We encourage you to approve coverage for the existing molecular tests to improve and save lives of men diagnosed with prostate cancer. As President and CEO of ZERO - The End of Prostate Cancer, I encourage you to consider the thousands of men that can be negatively impacted by not covering these tests.	Thank you for your comments.
D	22	Thank you for the opportunity to comment on HERC's draft biomarker coverage guidance; our comments are particular to Prolaris®, Myriad's prostate cancer prognostic test. We are encouraged by HERC's recognition of the need for additional prognostic tests for prostate cancer. Currently available clinical and pathologic parameters are limited in their ability to distinguish between aggressive and indolent localized prostate tumors. (1-3)	References 1-2 describe PSA as a screening tool for prostate cancer, which is outside the scope of this document. Reference 3 is a validation study of CAPRA, a risk assessment tool for cancer recurrence after radical prostatectomy. This study of 2,096 men in a military database found that "Increasing CAPRA scores were significantly associated with increasing risk of adverse pathologic outcomes."
D	23	Despite a 10-year mortality risk of only 3% (4) and knowledge that many prostate cancers do not cause death when initial management is conservative, nearly 90% of men receive definitive treatment, with the potential for significant treatment-related side effects. (5-8) Under-treatment of men with more aggressive tumors also remains a significant clinical risk. (4)	SEER reports a 98.9% survival rate at 5 years; 10-year survival was not available at the link provided in reference 4. This link also did not opine on the dangers of undertreatment. Reference 5 is a case vignette. Reference 6, Wilt 2012, is an RCT (N=731) of observation vs radical prostatectomy for localized prostate cancer, which found no significant difference in all-cause or cancer-specific mortality through 12 years of follow-up. Reference 7 is a descriptive analysis of trends in cancer treatment,

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			highlighting substantial, unexplained variability in management. The 90% figure provided in the comment is not supported. Reference 8 is a retrospective cohort study (N=32,465) of men who underwent surgery or radiotherapy for prostate cancer, which found that complications of treatment are frequent.
D	24	Clinical validity studies in varied patient cohorts demonstrate Prolaris' consistent ability to better stratify patients based on meaningful oncologic endpoints.[9-14]	References 9, 10, 11, and 12 provide the basis for the analysis done by BCBS, which is the core source for the CG document. The authors conclude that "As a whole, the evidence on clinical validity … is insufficient." Bishoff 2014 (reference 13) was published after the BCBS search date. It is a cohort study (N=582) in which the CCP score (Prolaris® test) was performed on actual or simulated biopsy specimens, and records were analyzed for biochemical recurrence (BCR, defined as postoperative PSA greater than 0.2 ng/ml or secondary treatment [radiation or androgen therapy] for increasing PSA regardless of attaining the 0.2 ng/ml cutoff point) and metastatic disease. No other outcomes were reported (OS, DSS, etc). Because of small sample size and lack of reporting on critical and important

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			outcomes, HTAS does not consider this evidence sufficient to recommend coverage. Reference 14, Cuzick 2014, is not a peer-reviewed publication.
D	25	Clinical utility studies show that physicians and patients use this new information to alter medical management based on the level of risk predicted by the Prolaris score.[15-17] Prolaris' net effect is to reduce the treatment burden for localized prostate cancer.[15-17]	BCBS did not identify any published data on clinical utility. Shore 2013 (Reference 15) was published after the BCBS search dates; however it would not have been included because it relied on a retrospective questionnaire administered to 15 community urologists. HTAS does not consider this sufficient evidence to guide coverage recommendations. Reference 16 (Crawford 2014) was done similarly, but in a pre-post style survey of clinicians treating 331 patients. It concludes that CCP testing changes treatment decisions in about 65% of cases. Number of clinicians is not stated and it is unknown how patients were selected for CCP testing. Actual treatment decisions were only available for 116 cases and showed 80% concordance with the survey. This study is not of sufficient quality to alter HTAS decision. Reference 17 (Gonzalgo 2014) is not a peer-reviewed publication.
D	26	Independent studies suggest that reducing unnecessary interventions reduces morbidity without increasing mortality.[6,18,19] This shift away from unnecessary treatments yields cost-savings to the healthcare system.	Reference 18 is a guideline panel report from 1995 and is not relevant

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			in the current environment. Reference 19 is a simulation model of a hypothetical cohort demonstrating that active surveillance is a viable option under a wide range of assumptions. This does not inform the HTAS decision on coverage. The subcommittee discussed that avoidance of unnecessary aggressive treatment is an important outcome; however, there is insufficient evidence that this test reduces aggressive treatment more effectively than other existing tools.
D	28	Prolaris received a favorable technical assessment by MolDX[22] and has been incorporated into treatment guidelines[23]. Based on this new information, we request coverage for Prolaris for beneficiaries with biopsy-proven, localized prostate cancer when a clinician requires additional patient-specific information to make treatment recommendations.	It is correct that a LCD has recommended coverage under very specific clinical conditions and only when the ordering physician is certified in the Myriad Prolaris Certification and Training Registry. NCCN states certain men "could consider" biomarker testing in its 2015 guidelines for risk stratification, stating "clinical utility awaits evaluation by prospective, randomized clinical trials, which are unlikely to be done [because the tests are being marketed under the less rigorous FDA regulatory pathway for biomarkers]." The subcommittee determined that coverage should not be recommended unless the biomarker test has greater utility than

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			existing technology for patient-centered outcomes such as avoidance of surgery or cancer related mortality.
D	29	Evidence: Analytical Validation: Prolaris has well-established analytical validity published and documented in: • Cuzick (2011)[9] (selection process for cell cycle progression genes; development of Prolaris score) Technical specifications (http://www.prolaris.com/information-for-physicians/pathology/technical-specifications/).	See comment D24, this study was considered by the core source and deemed insufficient to establish clinical validity of the test. .
D	30	Clinical Validation: Prolaris was clinically validated in nine cohorts involving >2,900 patients, published in five peer-reviewed publications[9-13] and one poster presentation[14]. The HERC review accurately states that some cohorts include management approaches not representative of the population of interest; however, each study's goal was to demonstrate the Prolaris score's prognostic significance in treated patients (prostatectomy cohorts) and conservatively managed patients (TURP and biopsy cohorts). The Prolaris score was consistently predictive of meaningful oncologic outcomes (recurrence or disease-specific mortality) with similar hazard ratios around two, and multivariate analyses demonstrated the Prolaris score added significant unique, prognostic information beyond that obtained from standard clinico-pathologic variables.	See comment D24.
D	31	The validation cohorts/outcomes are listed below: • Cuzick (2011)[9] - 353 post-prostatectomy/biochemical recurrence; 337 conservatively managed/10-year mortality • Cuzick (2012)[10] - 349 conservatively managed/10-year mortality • Cooperberg (2013)[11] - 413 post-prostatectomy/biochemical recurrence • Freedland (2013)[12] - 141 post-radiation/biochemical recurrence • Bishoff[13] (2014 - published after the last BCBSA TEC review) – post-prostatectomy (biopsy samples)/biochemical recurrence (283) or metastatic disease (299) Cuzick (2014)[14] - 757 conservatively managed/disease specific mortality	See Comment D24. Cuzick 2011,Cuzick 2012, Cooperberg 2013, and Freedland 2013 are all considered in the core source and found to be insufficient to establish clinical validity of the test. Bishoff 2014 is a multicenter retrospective cohort study (N = 582) in which CCP score is associated with biochemical recurrence and metastatic disease. The study has methodologic limitations including lack of standardization of patient selection and biopsy methods across centers. While this study despite its

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			limitations may support clinical validity, there is no evidence linking the CCP score to critical outcomes such as mortality, or changes in treatment. Cuzick 2014 is not a peer-reviewed publication.
D	32	Clinical Utility: The Center for Medical Technology Policy (CMTP) recognizes that prospective randomized controlled trials of molecular diagnostics in oncology may not be necessary when evidence exists linking treatment choices to patient outcomes.[20]	The source provided is a PowerPoint presentation from the Center for Medical Technology Policy and in fact states that "Under limited, specified circumstances, longitudinal observational study designs are acceptable options for assessing clinical utility," and that there must be a "compelling rationale" for not doing RCT. This rationale does not exist in prostate cancer; prospective RCTs are feasible and ethical.
D	33	CMTP suggests prospective observational studies to demonstrate clinical utility in specified circumstances, including when "there is genuine uncertainty on the part of the expert medical community regarding the preferred clinical pathway;" as is the case for localized prostate cancer. Prolaris' clinical utility is documented in two decision impact studies[15,16]. A third, larger study is underway; preliminary results were presented in poster form[17] and a manuscript has been submitted for publication. • Shore (2013)[15] - Hypothesis-generating retrospective survey of 15 urologists participating in a clinical validation trial revealed that Prolaris would have led to a change in management for 32% of the 294 cases, with a net-effect of shifting from more aggressive to more conservative treatment. • Crawford (2013)[16] – Prospective study evaluated the impact of Prolaris for 150 physicians in 31 states ordering Prolaris on prostate cancer needle biopsy specimens from 305 patients (low, intermediate and high-risk groups). Surveyed physicians reported that Prolaris influenced their decisions 98% of the time, with a change in recommendations post-Prolaris for 65% of cases. Prostatectomies were reduced by 49.5%; radiation was	Please see above. Shore 2013 was a small retrospective survey. Crawford 2013 had a high loss to follow-up and, in those cases that were audited, an 80% concordance with actual treatment. Gonzalgo is a poster presentation that is not published in a peer-reviewed journal. It is a prospective registry of 816 patients assessing how a physician's recommended treatment

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		reduced by 29.6%. Actual treatment selections were confirmed via third-party patient chart audit. Gonzalgo[17] - PROCEDE−1000 is the largest clinically−controlled, prospective registry evaluating Prolaris' impact on prostate cancer treatment by 105 physicians from 20 states, including Oregon. In addition to physician recommendations pre- and post-Prolaris testing, physician/patient consensus treatment decisions and actual treatment administered are evaluated. Interim analysis of 816 patients shows Prolaris resulted in significant reductions in prostatectomies (27%), radiation therapy (44% primary; 56% adjuvant), brachytherapy (46% interstitial, 66% HDR) and hormonal therapy (33% neoadjuvant, 68% concurrent). For every 1-unit increase in mortality risk by Prolaris, there was an associated 3.3% rise in the odds of increase in treatment (vice-versa for decrease in treatment) (estimated OR = 1.033).	was altered by CCP testing. Treatment plans changed in 44.24% of cases, with the majority (31.86%) having less treatment than initially recommended. This is an interim analysis and does not consider critical outcomes such as mortality.
D	34	Positive Technical Assessment and Medicare coverage: MolDX performs technical assessments for Medicare contractors, evaluating clinical utility, analytical validity and clinical validity based on 'ACCE' criteria developed by CDC.[21] Prolaris received a favorable evaluation by MolDx, and an LCD (MolDX: Prolaris™ Prostate Cancer Genomic Assay L35629, effective March 2, 2015) provides coverage for Medicare beneficiaries with biopsy-proven, untreated localized prostate cancer in low and very low-risk groups.[22] Additional registry data and treatment guidelines are being reviewed to consider expanding coverage to intermediate and high-risk cohorts, since clinical validation and clinical utility studies support benefits for all risk levels.	Please see comment D28.
D	35	Societal Guidelines: National Comprehensive Cancer Network (NCCN) 2015 Prostate Cancer treatment guidelines were updated October 24, 2014 to include Prolaris.[23] Footnote 'b' on page PROS-1 suggests Prolaris be considered in the initial clinical assessment of men with clinically localized disease who are symptomatic or with a life expectancy of >5y, to better stratify risk of adverse outcome (and therefore guide treatment decisions).	NCCN states "could consider," please see Comment D28.
D	36	Cost-Benefit to Healthcare System: A system economic analysis of Prolaris demonstrated a net savings of $2,850 per patient tested over 10 years. (24) Savings result from increased use of active surveillance in low− and intermediate−risk patients, and reduced progression rates in high−risk patients with more aggressive disease who transition to multi−modality therapy. The model estimates over $1 million in savings per year for the Oregon Health Plan with the use of Prolaris for all localized prostate cancer compared with the current approach.	Reference 24 is not a peer-reviewed publication. Thank you for your comments.
E	37	I am a practicing urologist in Springfield with a large population of prostate cancer patients. I strongly urge you to consider coverage through Oregon Medicaid.	Thank you for your comments.
E	38	I have used the test for more than a year and have found it quite beneficial in the decision-making process for treatment	Thank you for your comments.

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		of prostate cancer.	
E	39	As you may know, prostate cancer is the most common malignancy in men and the second cause of cancer death.	This information is correct.
E	40	Some cancers are aggressive and need aggressive treatments. Others can be monitored without treatment. Risk stratification is key. The Prolaris test is a useful component of our decision-making process as we decide whom to treat and whom to observe. This has been recognized by the National Comprehensive Cancer Network (NCCN) in their treatment guidelines – arguably the gold standard for cancer treatment.	NCCN guidelines are discussed in the CG document under "Policy Landscape".
E	41	I appreciate your consideration in this matter	Thank you for your comments.

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