Catherine Schnabel, PhD
Vice President, Translational Science
bioTheranostics, Inc
9640 Towne Centre Drive, Suite 200, San Diego, CA 92121
858-587-5884; cathy.schnabel@biotheranostics.com
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NCCN Guidelines Panel: Occult Primary

To the NCCN panel members:

On behalf of bioTheranostics Inc., I respectfully request the NCCN Occult Primary Guideline Panel to review the enclosed information for consideration of gene expression profiling (GEP) as a complementary molecular technology in the diagnostic evaluation of patients with Occult Primary cancers.

Specific Changes: Request recommendation of the gene expression-based test, CancerTYPE ID,[1-3] as a complementary diagnostic approach in the evaluation of patients with Occult Primary tumors in situations where standard techniques have proven inconclusive for identification of primary tumor site, where limited tumor tissue is available to enable extensive IHC studies, and where differential diagnoses of likely tumor types are associated with diverse treatment options.

Regulatory Status and Certifications: CancerTYPE ID is conducted and the results are generated at the bioTheranostics clinical laboratory in San Diego, California. The bioTheranostics clinical laboratory is Clinical Laboratory Improvement Amendments (CLIA)-certified, College of American Pathologists (CAP)-accredited, and licensed in all 50 states.

Rationale: Diagnostic workup of patients with suspected Cancers of Unknown Primary (CUP) is performed with the goal to identify the primary site, to inform treatment according to the appropriate NCCN Guideline for Treatment of Cancer by Site; or, if a primary site cannot be established, to treat according to the most likely primary site. Despite its heterogeneous nature, CUP has traditionally been treated as a single entity with empiric chemotherapy with marginal response rates.[4,5] However, as site-specific and molecularly-targeted therapies improve and become more specific for solid tumor types and subtypes, the use of broad-based chemotherapy is increasingly inadequate, and an evidence-based approach to identify CUP subtypes that may experience improved response and survival is favored. As diagnostic clarity of the primary site in cases of CUP may significantly impact a patient's management and prognosis, there continues to be a clinical unmet need for molecular adjuncts to aid in determination of tumor type.

Test Description: CancerTYPE ID is 92 gene, molecular profiling assay performed on RNA extracted from formalin fixed paraffin embedded tumor tissue that provides a molecular diagnosis of tumor type and subtype through an algorithmic-based comparison of a tumor's gene expression profile to a database of >2,000 tumors of known type and subtype.[1,6,7]

Key published clinical studies, all of which were conducted at major centers of excellence, are summarized below.

Publication	Study Description	Key Results
Kerr et al, 2012 [1]	▪ Multi-institutional, prospectively-defined, blinded diagnostic validation study ▪ N=790 cases	▪ 87% (95% CI, 84-89%) overall accuracy ▪ Diagnostic accuracy stable across metastatic, high-grade, and limited tissue cases (P = 0.16, 0.58, and 0.16)
Weiss et al, 2013 [2]	▪ Prospectively-defined, blinded, diagnostic benefit (vs IHC) study in metastatic and high-grade tumors ▪ N=122	▪ Statistically superior accuracy vs IHC (79% vs 69%; p=0.019)
Hainsworth et al, 2013 [3]	▪ Prospective, single-arm study in CUP patients treated with assay-directed chemotherapy ▪ N=289	▪ Assay provided tumor type prediction in 98% of CUP cases ▪ Overall survival 3.4 months greater than historical cohort

Data Summary—Diagnostic Accuracy and Benefit: The clinical validation for CancerTYPE ID diagnostic accuracy was investigated in a prospectively-defined, multi-institutional, blinded study of 790 tumor samples led by investigators from Massachusetts General Hospital, Mayo Clinic, and UCLA.[1] This study demonstrated 87% (95% CI, 84-89%) overall accuracy, and notably, statistically similar performance in metastatic and high grade

tumors, and in samples with limited tissue (P=0.16, 0.58, and 0.16, respectively). Additional correlative studies with clinical presentation, pathology, response to treatment, disease course, and predictive biomarker testing have demonstrated concordance of GEP results in approximately 75% of CUP cases evaluated.[8,9]

The potential diagnostic benefit of CancerTYPE ID was investigated in a prospectively-defined, blinded comparative effectiveness study led by investigators from the City of Hope.[2] In a head-to-head comparison, CancerTYPE ID demonstrated statistically significant improvement in diagnostic accuracy compared to immunohistochemistry (IHC) in poorly-to-undifferentiated metastatic tumors (79% vs 69%; P=0.019). Similar results have been reported utilizing a different GEP-based assay (89% vs 83%; P=0.013).[10] Taken together, these findings support a role for GEP to enhance the diagnostic resolution of pathologic evaluations.

Data Summary—Clinical Benefit: The potential clinical benefit of CancerTYPE ID was investigated in a prospective, single-arm study, wherein treatment-naïve patients diagnosed with CUP were treated with assay-directed, site-specific chemotherapy regimens.[3] A molecular diagnosis was rendered in 98% of cases, and 48% of the predicted tumor types contained molecularly targeted therapeutic options. CancerTYPE ID-directed therapy led to a median overall survival of 12.5 months, 3.4 months longer than the pre-specified historical cohort from the same clinical trial network. Interpretation of these findings was confounded by the lack of randomization and did not account for the inherent heterogeneity and prognostic variability associated with CUP. Results were consistent with the rationale that treatment selection based on diagnostic certainty should lead to improved patient outcomes by employing a site-directed approach;[11] however, the study did not definitively demonstrate improvement in overall survival. We acknowledge and respect the Panel's previous comments that the available data supporting improved clinical outcomes need confirmation through methodologically definitive studies.

As the preeminent Clinical Practice Guidelines in Oncology, recommendations made by this NCCN Panel have wide-ranging impact, including community practitioners who recognize the NCCN Guidelines as the standard of care. We respectfully point out that the current language clearly states where evidentiary gaps exist, but does not directly guide appropriate use of GEP in Occult Primary tumors. Given that there is existing Medicare coverage for CancerTYPE ID, NCCN guidance on appropriate use would be particularly important. We put forward for consideration that appropriate use of CancerTYPE ID would be in a subset of clinical cases where standard techniques have proven inconclusive for identification of primary tumor site, where limited tissue is available to render diagnosis, and where differential diagnoses of likely tumor types are associated with diverse treatment options. In addition, payer coverage determinations at the regional and national level are strongly influenced by the NCCN Guidelines, and thus impact access to GEP-based assays in the community oncology setting. For the above mentioned reasons, we respectfully submit that a Category 2 recommendation be made for GEP in Occult Primary tumors, which would acknowledge the diagnostic value of the test in the subset of cases where standard techniques have not defined a diagnosis while also acknowledging the need for definitive data regarding clinical outcomes.

We appreciate the opportunity to provide this information for consideration by the NCCN Occult Primary Guideline Panel. Further, we share your commitment to assuring the judicious introduction of innovative new health care technologies. If you have any questions or require additional information, please do not hesitate to contact me directly (858-587-5884 or cathy.schnabel@biotheranostics.com).

Sincerely,

Catherine Schnabel, PhD
Vice President, Translational Science
bioTheranostics, Inc

Cited and Enclosed References:
1. Kerr SE, et al. Clin Cancer Res 2012;18:3952-60.
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Additional References Cited:
4. Greco FA, Hainsworth JD. Cancer: Principles and Practice of Oncology. DeVita VTJ, Hellman S, and Rosenberg SA. 2011; 2033-2051.
5. Varadhachary GR, J Natl Compr Canc Netw 2011;9:1406-1412.
6. Ma XJ, et al. Arch Pathol Lab Med 2006;130(4):465-73.
7. Erlander MG, et al. J Mol Diagn 2011;13:493-503.
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10. Handorf CR et al. Am J Surg Pathol. 2013;37(7):1067-75.
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