EC DECISIONDx

Fact Sheet

Talk to Your Doctor

- Hearing the words "you have esophageal cancer" is overwhelming and would leave anyone with a lot of questions. If you have been diagnosed with esophageal cancer your doctor may be considering pre-operative chemoradiation therapy (sometimes called CTRT) as part of your treatment.

- It is important to know about a new test that can tell you and your doctor whether you are likely to benefit from pre-operative chemoradiation therapy. The test, **DecisionDx-EC**, is available only through Castle Biosciences, a company that focuses on molecular diagnostic and prognostic testing for rare cancers.

- Castle Biosciences developed this guide to help you and your doctor decide whether this test is right for you.

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Background

The Challenge: Identifying Which Patients Will Respond to Pre-Operative Chemoradiation Therapy

Based upon National Cancer Comprehensive Network (NCCN) guidelines, pre-operative CTRT is recommended for tumor shrinkage and stabilization, as well as improved overall survival. Unfortunately, 20-35% of patients receiving CTRT will experience no clinical benefit despite exposure to the risks of CTRT therapy and a potentially unnecessary delay of surgery. Until today, physicians have had no way of knowing who these "refractory" or "extremely resistant" patients are.

Knowing which patients are likely to experience extreme resistance to CTRT (exCTRT) would enable physicians to personalize treatment plans for these patients by carefully considering the risk of regimens to which response is unlikely.

DecisionDx-EC: Predicting Resistance to Pre-Operative Chemoradiation Therapy

The **DecisionDx-EC** test was discovered at The University of Texas MD Anderson Cancer Center (MD Anderson) as a way to predict likelihood of response to neoadjuvant (pre-operative) chemoradiation therapy (CTRT) in individual patients with esophageal adenocarcinoma. The test assesses three protein biomarkers from diagnostic biopsy tissue, then provides validated biological information that aids the physician and patient in treatment planning.

Initial clinical validation study was completed at MD Anderson and presented at the annual meeting of the American Society of Clinical Oncology in 2011. **Castle Biosciences, Inc.** exclusively licensed this technology and recently completed a multi-center effort to technically and clinically validate the proprietary test. These multi-center clinical validation studies found that the **DecisionDx-EC** test was able to predict extreme resistance to CTRT with a high PPV (positive predicted value), meaning that when the test identified a tumor sample as exCTRT, it was accurate > 90% of the time.

Clinical Data

Potential Clinical Benefits

Knowing which patients are likely to experience extreme resistance to pre-operative chemoradiation therapy allows patients unlikely to experience benefit to avoid the potential toxicities and morbidities associated with these treatment regimens and perhaps accelerate the time to surgical intervention.

Clinical Validation

Initial Clinical Validation Study: The DecisionDx-EC test completed clinical development and validation under research laboratory conditions at MD Anderson. Data from these initial MD Anderson development and

validation studies were presented at the annual meeting of the American Society of Clinical Oncology in 2011 (Ajani, JCO 2011). Patients received CTRT followed by surgery. For these studies, researchers defined extreme resistance to chemoradiation therapy as patients having greater than 50% residual tumor upon surgical resection per the Rohatgi research tool. In the clinical validation study, biostatistical analysis of the logistic regression model used to classify extreme resistance samples yielded an uncorrected area under the receiver operating curve, or AUC, of 0.96 and corrected AUC of 0.95. This statistical measure is used to assess new tests on a scale where 0.5 means the result is similar to chance, and 1.0 means that the test perfectly predicts the known outcome.

Analytical Validation Studies: Over 250 specimen runs were employed during the development and optimization of the test under CLIA laboratory conditions. Concurrent blinded scoring was undertaken by two clinical experts, a pathologist and a doctorate-level clinical scientist. These two experts achieved 94% concordance.

Second Clinical Validation Study: A second, prospectively planned, multi-center clinical validation study was initiated and completed following finalization of the CLIA standard operating procedures. This study achieved several important objectives:

- Confirmed the concordance between the research grading tool used by MD Anderson and the College of American Pathologists (CAP) Treatment Response Grading (TRG) tool used clinically for esophageal cancer. This study employed centralized blinded pathology scoring of paired post-treatment resection tissue. Each specimen was graded according to both tools. Blinded scoring showed the following:

	CAP TRG	Rohatgi Method	Concordance
Pathologic complete response	Grade 0	0% residual tumor	100%
Partial response	Grade 1 or 2	>0%and ≤50%	100%
exCTRT	Grade 3	>50%	100%

- Maintained the high level of test scoring concordance between the two clinical scientists established in the first clinical validation study. The concordance between the two clinical scientists in the second study was 98%;

- Established the positive predictive value (PPV) of the DecisionDx-EC test under CLIA conditions. The PPV was found to be 92%, meaning that when the assay predicts likelihood of ex-CTRT, it is highly accurate.

Based on the results of the validation studies, the **DecisionDx-EC** test is able to predict extreme resistance to chemoradiation therapy (exCTRT) with a high positive predictive value.

Additional clinical use studies are underway.

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More Information

How to Order

DecisionDx-EC is now available as a CLIA-certified laboratory service, and can only be ordered by a licensed healthcare provider (physician, advanced nurse practitioner or physician's assistant).

New customers: Call customer service line (866-788-9007) to review the ordering/shipping process before placing your order. Or, email us at contact@castlebiosciences.com. All customers must fill out and fax the requisition form, which can be found at **www.MyEsophagealCancer.com.** Turnaround time is generally less than two to three weeks following receipt of the specimen from the pathology lab.

Reimbursement

Castle Biosciences works with Medicare, commercial insurers, and the physician's institution to secure coverage for **DecisionDx-EC** on the patient's behalf. The Company accepts assignment for all insurance companies, and also has a Patient Assistance Program.

Additional Information

For more information about **DecisionDx-EC** please visit **www.MyEsophagealCancer.com**.

Select References

Lassen, et al. Clinical development of a proprietary immunohistochemistry (IHC) assay to detect pathologic complete response (pathCR) in esophageal adenocarcinoma (EC). Gastrointest Endosc 2013; 77 (suppl; abstr Su1526).

National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology. Esophageal and Esophagogastric Junction Cancers Version 2.2013. 2013; National Comprehensive Cancer Network.

van Hagen, et al. Preoperative chemoradiotherapy for esophageal or junctional cancer. N Engl J Med, 2012; 366: 2074-2084.

Sims-Mourtada, et al. Sonic Hedgehog promotes multiple drug resistance by regulation of drug transport. Oncogene, 2007; 26: 5674-5679.

Izzo, et. al. Diseases of the Esophagus, 2009.

Izzo, et al. Pretherapy nuclear factor-kappaB status, chemoradiation resistance, and metastatic progression in esophageal carcinoma. Molecular Cancer Therapeutics, 2006; 5: 2844-2850

Sims-Mourtada, et al. Hedgehog: an attribute to tumor regrowth after chemoradiotherapy and a target to improve radiation response. Clinical Cancer Research 2006; 12: 6565-6572.

Ajani, et al. Validated biomarker signatures that predict pathologic response to preoperative chemoradiation therapy (CTRT) with high specificity and desirable sensitivity levels in patients with esophageal cancer (EC). J Clin Oncol 2011; 29 (suppl; abstr 4027).

Rohatgi, et al. Failure patterns correlate with the proportion of residual carcinoma after preoperative chemoradiotherapy for carcinoma of the esophagus. Cancer 2005; 104 (7): 1349-1355.

Rohatgi, et al. Characterization of pathologic complete response after preoperative chemoradiotherapy in carcinoma of the esophagus and outcome after pathologic complete response. Cancer 2005; 104 (11): 2365-2372.

Dittrick, et al. Pathologic nonresponders after neoadjuvant chemoradiation for esophageal cancer demonstrate no survival benefit compared with patients treated with primary esophagectomy. Annals of Surgical Oncology 2012; 19: 1678-1684.