Genomic testing can help identify patients at heightened risk for esophageal cancer

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Barrett's esophagus (BE) develops in a subset of patients with gastroesophageal reflux disease (GERD) and can increase the risk of developing cancer of the esophagus. Although periodic surveillance for cancer is recommended for BE patients, these examinations may fail to identify pre-cancerous dysplasia and early cancers. A report in the *Journal of Molecular Diagnostics* describes a test using next-generation sequencing (NGS) to detect genomic mutations in precancerous esophageal tissue, which may improve cancer surveillance and early detection in patients with BE.

"BE results from injury of the esophageal mucosa associated with gastroesophageal reflux, which leads to inflammation (esophagitis) and eventually BE," explained Antonia R. Sepulveda, MD, PhD, Professor of Pathology and Cell Biology, Vice Chair for Translational Research, and Director of the Division of Gastrointestinal Pathology at Columbia University College of Physicians and Surgeons, New York, NY. In the normal esophagus, the tissue lining is made of flat squamous cells that appear pearly white and smooth during endoscopy. In patients with BE, the cells lining the esophagus appear more like cells characteristic of the small intestine (known as specialized intestinal metaplasia). As BE progresses, cells may become more disordered and disorganized, sequentially changing to low-grade dysplasia, high-grade dysplasia (HGD), and eventually esophageal adenocarcinoma (EAC).

Pathology evaluation of biopsy samples is the gold standard for detection of dysplasia in BE. Molecular testing of BE has not entered clinical

practice in part due to limitations of molecular testing methods requiring fresh or frozen tissue samples and lack of sensitivity to detect low-level mutations in precancerous samples.

Dr. Sepulveda and colleagues tested readily-available formalin-fixed, paraffin-embedded (FFPE) tissue taken from esophageal biopsies or endoscopic mucosal resections. Using NGS methods, the researchers analyzed FFPE tissue samples from 13 "non-progressors" (patients with BE who never manifested dysplasia or EAC during at least two years of monitoring), 15 "progressors" (patients who developed HGD or EAC), and control samples showing no evidence of Barrett's intestinal metaplasia. The researchers found that progressors had mutations in 75% (6/8) of cases compared to 0% in non-progressors. The tumor suppressor TP53 was the most commonly mutated gene in the BE progressor group. Mutations were also found in the APC and CDKN2A tumor suppressor genes.

"The ability to detect mutations in non-neoplastic mucosa, quantitatively and with high detection sensitivity, makes it possible to use NGS mutational testing in the early detection and surveillance of patients who develop BE," noted Dr. Sepulveda.

BE is considered one of the most significant risk factors for EAC. Compared with the general population, patients with BE have more than an 11-fold increased risk for EAC. Although EAC is a relatively rare cancer, it is the tenth leading cause of cancer death in the United States. Between 2005 and 2011, about 18% of EAC patients survived for five years. However, because earlier cancer detection is associated with longer survival, there is a great need for detecting cancer early and finding biomarkers that can help predict patients at greatest risk.

More information: "Evaluation of Mutational Testing of Pre-neoplastic Barrett's Mucosa by Next Generation Sequencing of FFPE

Endoscopic Samples for Detection of Concurrent Dysplasia and Adenocarcinoma in Barrett's Esophagus," by Armando Del Portillo, Stephen M. Lagana, Yuan Yao, Takeshi Uehara, Nirag Jhala, Tapan Ganguly, Peter Nagy, Jorge Gutierrez, Aesis Luna, Julian Abrams, Yang Liu, Randall Brand, Jorge L. Sepulveda, Gary W. Falk, and Antonia R. Sepulveda (DOI: dx.doi.org/10.1016/j.jmoldx.2015.02.006). Published online ahead of the *Journal of Molecular Diagnostics*, Volume 17, Issue 4 (July 2015)