Published in final edited form as:

Nat Genet. 2014 August ; 46(8): 806–807. doi:10.1038/ng.3047.

From genomics to diagnostics of esophageal adenocarcinoma

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2-sentence strapline

The genetic determinants of the progression from premalignant Barrett's esophagus to esophageal adenocarcinoma are not known. A new study reports genomic sequence analyses of this progression and uses the insights to identify high-risk Barrett's esophagus in a new non-endoscopic test.

In 2012, more than 450,000 new cases of esophageal cancer are estimated to have occurred worldwide, making it the eighth most common cancer.¹ In less developed regions, squamous cell carcinoma is by far the most common histologic type. In contrast, the U.S. has seen a remarkable 500% increase in the incidence of adenocarcinoma, from a relative rarity in the 1970s, to the most common type of esophageal cancer today; similar increases have been documented in much of western Europe and Australia.² Unfortunately, the vast majority of people are not diagnosed with their esophageal cancer until a late stage, and regardless of the histologic type, most succumb within a year of diagnosis. Thus prevention and early detection must remain society's "plan A" for combatting this disease.³ The research reported by Rebecca Fitzgerald and colleagues on page 837 is a relatively rare example of a study in which both a cancer and its key precursor lesion have been sequenced, and contributes in a number of useful ways to prevention efforts as well as understanding the timing and frequency of somatic mutations in neoplastic progression in the esophagus.⁴

Ordering of genomic abnormalities

Most esophageal adenocarcinomas (EA) arise in a metaplastic epithelium, termed Barrett's esophagus (BE), usually as a consequence of chronic gastroesophageal reflux.⁵ Since persons with BE have about thirty-fold higher risk of developing esophageal adenocarcinoma, it is often recommended that they undergo periodic surveillance with endoscopy and multiple biopsies to detect the development of high-grade dysplasia or an early cancer which can be effectively treated.⁶ However, BE can remain in a relatively quiescent state for many years without becoming malignant; conversely, when it occasionally does "go bad" it can happen quite quickly.⁷ Consequently, the effectiveness of surveillance for reducing mortality is a topic of much debate, especially when costs are taken into account.^{8,9} Identifying robust biomarkers of neoplastic progression risk would be quite helpful in directing primary and secondary prevention efforts to those most likely to

benefit, while permitting the large majority of those unlikely to develop EA to avoid subsequent procedures, risks, costs and worry.

Weaver, *et al.*,⁴ address this need through a series of experiments designed to identify recurrently-mutated genes in EA and determine the stages of neoplastic progression at which they become mutated. They performed whole-genome sequencing of cancer cases in a discovery cohort (n=22), and identified 26 genes with recurrent mutations for targeted resequencing in an additional 90 cancer cases. Finally, targeted resequencing for this validated gene panel was carried out in 40 non-dysplastic BE and 39 high-grade dysplastic BE samples. Remarkably, they observed that many of the so-called driver mutations of EA were already present in non-dysplastic BE, expanding upon previous reports by Dulak *et al.*¹⁰ and Agrawal, *et al.*¹¹ In particular, 53% of the non-dysplastic BE biopsies and 91% of high-grade dysplastic BE samples harbored one or more mutations in the panel. The exceptions were *SMAD4*, which was mutated only in invasive cancers, and *TP53*, which was mutated only rarely (2.5%) in non-dysplastic BE but frequently in high-grade dysplasia (72%) and invasive cancer samples (69%). It should be noted that the relatively small size of the discovery cohort, and the observation that additional genes varied in their mutation frequency between stages, but at a level of statistical significance that did not survive correction for multiple testing, suggests that increased sample size may identify additional genes useful in discrimination.

Opportunities for Translation

While the presence of mutated *TP53* in high grade dysplasia and its predictiveness of subsequent EA has been known for a number of years,¹² a particularly exciting aspect of the research reported by Weaver, *et al.*⁴ relates to the application of this knowledge to a developing non-endoscopic clinical test – the Cytosponge.¹³ This is a dissolvable capsule which contains a compressed mesh attached to a string. After being swallowed and allowed to dissolve in the stomach, the expanded mesh is withdrawn and placed into a preservative. The authors established the ability of the Cytosponge to collect cells in which *TP53* mutations can be reliably detected, despite low and variable allele fractions of mutant DNA (ranging from <1% to 36%). They further demonstrated the ability of this approach to identify the presence of high-grade dysplasia with 86% sensitivity (19 mutations detected in 22 individuals with high-grade BE) and 100% specificity (0 mutations detected in 67 individuals with non-dysplastic BE or with no BE).

How might this approach be translated into improved clinical care? In the current paradigm, there is a substantial “risk gap” between the large number of persons in the general population who may have recurrent symptoms of gastroesophageal reflux and/or other risk factors for EA, and the much smaller number in whom significant mutations and other genomic abnormalities have already occurred, marking them as having significant absolute risk of developing the malignancy. Performing an invasive endoscopy in (potentially) all persons with recurrent reflux symptoms, who comprise about 20% of the adult population, is an expensive proposition with very low yield. A non-endoscopic test, such as the Cytosponge with *TP53* mutation assays, would provide the primary care provider with an important tool to bridge this risk gap (Figure 1). For example the office-based test could be

offered only to selected individuals, e.g., those considered at elevated risk based on a panel of known risk factors and blood-based biomarkers, and only those with evidence of TP53 mutations would be referred to secondary care providers. This would potentially result in many fewer individuals undergoing endoscopy, but those who did would be at substantially higher risk, and an appropriate population for more invasive tests and intensive prevention and treatment efforts. This technology has not matured yet, but is getting closer. Inexpensive and reliable assays available outside of a research setting are needed, in concert with prospective studies and clinical trials. The inclusion of endpoints other than high-grade dysplasia also should be considered.⁵ However, as recent simulation modeling predicts that incidence of EA will continue to increase for two more decades, with a cumulative number of cause-specific deaths of approximately 160,000 in the U.S. alone, progress in this area cannot come fast enough.¹⁴

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Figure 1.

Potential role for the Cytosponge in clinical care. Development and validation of assays based on the Cytosponge may provide primary care practitioners with a significant new tool for differentiating between persons at relatively high risk of esophageal adenocarcinoma who might benefit from more invasive diagnostic procedures, and those who can safely forego them and focus on risk reduction.