Discovery of Methylated DNA Biomarkers for the Potential Non-Endoscopic Detection of Barrett's Esophagus

Andrew Kalra, BS [1], Ke Ma, MD [1,2], Yifan Yang, BS [1], Yulan Cheng, MD [1], Daniel G. Lunz, MBA [3], Indu Bastakoti, BS [3], Sarah Laun, PhD [3], Lisa Kann, PhD [3], Francia Pierre, MPH [3], Stephen J. Meltzer, MD [1]

[1] Johns Hopkins University School of Medicine, Baltimore, MD, USA
[2] Department of Medicine, Einstein Health Network, Philadelphia, USA
[3] Capsulomics Inc., Baltimore, MD, USA

INTRODUCTION

- Barrett's esophagus (BE) is a known precursor of esophageal adenocarcinoma (EAC), the type of esophageal cancer that accounts for over 80% of all esophageal cancer cases in the United States.
- The current gold standard for diagnosis of BE is endoscopic biopsy with histologic examination.
- Unfortunately, most individuals in the United States do not undergo endoscopy and thus BE is not diagnosed, resulting in progression toward fatal EAC in most undiagnosed BE cases.
- For this reason, minimally invasive sponge or balloon devices have been studied in conjunction with various types of biomarkers.
- However, most markers used in current BE diagnostic biomarker panels are outdated, lacking in sufficient specificity and sensitivity, and warrant substantial improvement.

OBJECTIVE

- To discover diagnostic methylation biomarkers for better detection of BE.

METHODS

- Using a novel approach, we accessed and integrated 6 Infinium HumanMethylation450 BeadChip datasets from various research groups within the Gene Expression Omnibus (GEO) database.
- Then, we selected probes that were highly methylated in Barrett's (beta ≥ 0.30) and mostly unmethylated in normal esophageal and gastric tissues (beta ≤ 0.05).
- This selection yielded 30 candidate BE-specific markers.
- All 30 candidate markers were identified from research groups who used microdissection and/or careful histopathologic review of each tissue biopsy.
- We then analyzed 248 BE, 184 normal esophageal, and 101 normal gastric tissue samples from our archives.
- After designing qMSP primers and probes, and further testing, we assayed 12 candidate markers in 21 matched normal-BE tissue pairs, 8 matched normal-BE-tumor tissue triplets, and 17 matched normal-tumor tissue pairs.

RESULTS

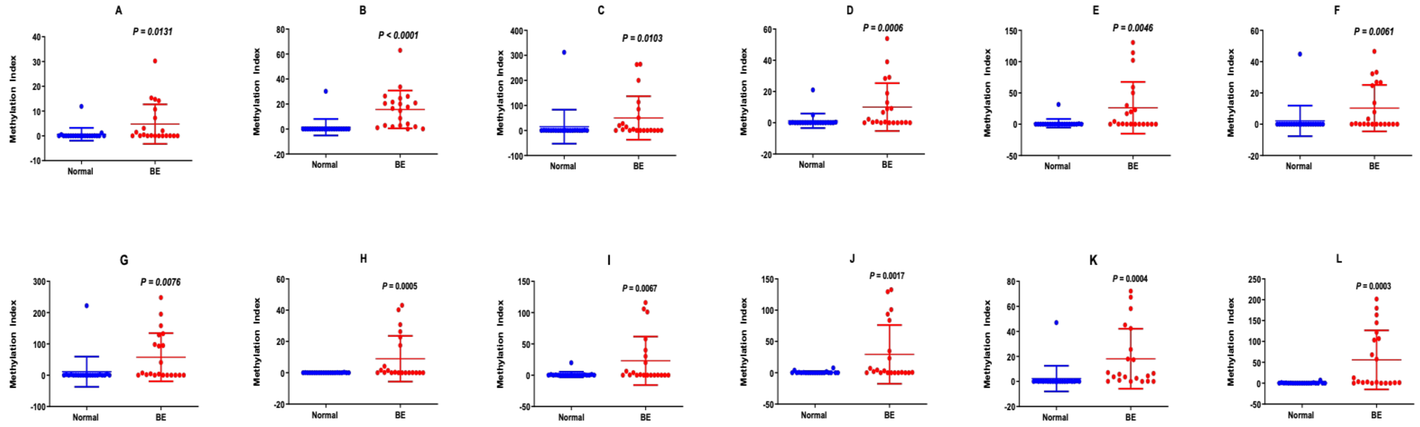

Figure 1. Comparison of methylation levels of all 12 initial candidate biomarkers between DNA in 21 matched normal *vs*. Barrett's esophagus (BE) tissue pairs. All $p < 0.01$.

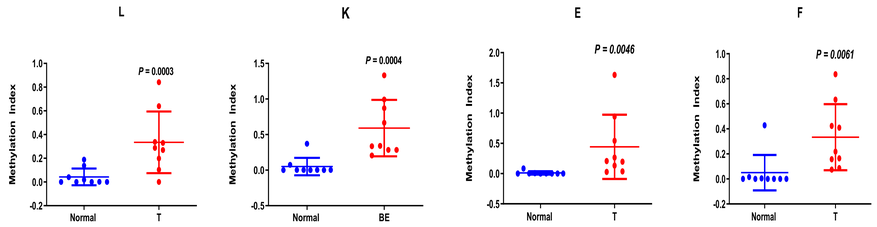

Figure 2. Comparison of methylation levels in 4 of the 12 candidate markers between DNA in 17 matched normal *vs.* tumor tissue pairs. All $p < 0.01$.

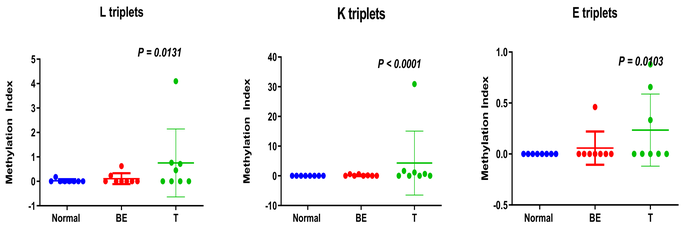

Figure 3. Comparison of methylation levels in 3 of the 12 candidate markers between DNA in 8 matched normal *vs.* Barrett's esophagus *vs.* tumor tissue triplets. All $p < 0.05$.

CONCLUSIONS

- This discriminatory biomarker panel shows potential for BE diagnosis using an inexpensive, minimally invasive sampling technique and thus merits further study in case-control sponge studies.
- Due to our systematic and rigid method of selecting these markers, these genes are expected to be extremely important for the diagnosis of BE.

***All biomarkers are patent pending and are therefore "masked" on this poster.**