Study Number: CASE 1221

Protocol Date: 14AUG2023

Study Title: Detection of Barrett's Esophagus in Patients without GERD symptoms

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FUNDING SPONSOR: NCI BETRNet and SPORE grants

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1.0 BACKGROUND AND RATIONALE

Whereas the rate of many common cancers has declined, the incidence of esophageal adenocarcinoma (EAC) has increased greater than six-fold over the past 3 decades.(1) Furthermore, the outcome of this cancer remains poor, accounting for over 1 in 50 adult male cancer-related deaths.(2) Although Barrett's esophagus (BE), a precursor of EAC, can be easily recognized at endoscopy, current clinical strategies of endoscopic screening and surveillance based on the close association of BE with chronic Gastroesophageal Reflux Disease (GERD) in adults are woefully inadequate. Nearly 40% of patients who develop EAC have no preceding symptoms of GERD(3, 4) and less than 5% of EAC's are diagnosed in patients whose BE was recognized prior to cancer diagnosis.(5) In recognition of the burden of morbidity and mortality caused by EAC and the clinical need to develop more effective screening, surveillance, and ablative strategies for BE, EsoCheck and EsoGuard ("EC/EG") have been developed to offer an alternative to endoscopic screening, to improve the detection, prognostication, and treatment of BE, with the ultimate goal of reducing the mortality associated with EAC.

There has been a startling rise in the incidence of esophageal adenocarcinoma (EAC) in the United States during the past three decades, especially in white males where the incidence has gone up more than six fold.(1, 6-8) National statistics estimate 16,980 new cases of esophageal cancer, mainly adenocarcinomas, in 2015.(9) Although there have been advances in chemotherapy, radiotherapy, and surgical therapy, the prognosis remains poor with a dismally low five year survival of less than 20%.(9) Most EACs originate in Barrett's epithelium, a pre-malignant condition in which normal squamous epithelium is replaced by metaplastic specialized intestinal type columnar epithelium.(10-17) Despite endoscopic screening and surveillance efforts,(18) less than 5% of EAC are diagnosed in individuals with previously detected BE.(5) Gastroesophageal reflux disease (GERD) is closely associated with BE and is present in about 10% of patients who have endoscopy for GERD(16, 18-20) but even if esophago-gastro-duodenoscopy (EGD) was recommended in all adults with GERD, studies show that this strategy would only be partially effective at preventing EAC or detecting it early.(3, 4) The reason for limited effectiveness is that nearly 40% of adenocarcinomas occur in individuals without GERD symptoms.(3, 4) Other risk factors for BE and EAC include older age, male gender, white race, obesity, family history, and smoking.(17, 21, 22) We propose to use these risk factors to help detect BE in those without GERD symptoms.

Screening for BE is recommended in men with chronic GERD with two or more risk factors for BE or EAC.(21) Risk factors include age >50 years, White race, central obesity (waist circumference >102 cm or waist–hip ratio >0.9), smoking, and a family history of BE or EAC. Screening can be considered in women with multiple, four or more, risk factors for BE or EAC. Our studies of the Explorys database has shown that these risk factors are independent predictors of risk of BE and patients who do not have GERD and have three or more risk factors have a risk for BE that is similar to patients with GERD who have two risk factors. Using EC/EG we propose to expand screening to patients without GERD who have three or more risk factors for BE. This will enable the detection of BE in a group that is at risk for developing EAC but are currently not offered EGD.

Endoscopy is the gold standard for diagnosis of BE, as biopsies obtained during endoscopy are the only means by which to identify intestinal metaplasia (as well as dysplasia). A more efficient use of diagnostic endoscopy in the setting of BE screening, whereby the "hit rate" were to

increase for finding disease, and the rate of negative endoscopy were to decrease, would be advantageous. EC/EG offers a means by which to achieve this goal. Using EC/EG as a triage step to suggest who, among those at risk of BE, should have an endoscopy, may be expected both to increase positive endoscopies and to decrease negative ones, due to the known high sensitivity, specificity, negative predictive value and useful positive predictive value of EG on samples collected via EC. EC/EG would also enable the screening of patients without GERD symptoms who are currently do not undergo EGD, expanding the detection of BE and prevention of EAC. The goal of this study is to demonstrate the ability to detect BE in a non-GERD population that is at risk for BE and demonstrate an improvement to the utilization of endoscopy when it is performed on those with a positive EC/EG result.

2.0 OBJECTIVES

We study whether using EsoCheck/EsoGuard (EC/EG) can detect BE in patients at risk for BE who are currently not being detected and are not undergoing routine EGD.

AIM 1. **Assess whether EC/EG can identify BE in a population at risk for BE**
Estimate the positive predictive value of EC/EG in a non-GERD population that has three or more non-GERD risk factors for BE. Patients who are at risk will be offered EC/EG. Those who are positive will undergo subsequent EGD.

AIM 2. **Confirm that patients who are negative as assessed by EC/EG do not have BE.**
Estimate the proportion of patients negative via EC/EG who subsequently are proven negative via EGD. This would be measured by offering EGD to a proportion of patients who are EC/EG negative.

3.0 PATIENT SELECTION

3.1 Inclusion Criteria

Patients who are undergoing colonoscopy are considered a reasonable representation of the population. Signed permission will be obtained from physicians who are performing colonoscopy to contact and recruit their subjects for this research. Patients who are at risk for BE but do not have chronic GERD and have not had a prior EGD will be accrued at time of their colonoscopy (21). Those eligible will be:

1. Adults $\geq$ 50 who have no prior EGD and are able to provide informed consent
2. No known coagulopathy, no known esophageal varices.
3. No significant dysphagia or odynophagia
4. Absence of chronic GERD, defined as five or more years of heartburn or regurgitation with symptoms at least once a week when not on medications for GERD symptoms.
5. Subjects to qualify must meet criterion 4, be over age 50, and have two additional risk factors for BE (white race, central obesity defined as waist size $\geq$ 35 inches for women and $\geq$ 40

inches for men, male gender, current smoker or smoking history ≥ 10 pack years, confirmed family history in at least two members with one being a first degree relative).

3.2 Exclusion Criterion

1. History of prior EGD procedure
2. Inability to provide written informed consent
3. History of weekly of more frequent heartburn or regurgitation for five or more years
4. On anti-coagulant drug(s) that cannot be temporarily discontinued or coagulopathy with INR > 1.5
5. Known history of esophageal varices or esophageal stricture
6. Any contraindication, as deemed in Investigator's medical judgment, to undergoing the EsoCheck procedure, undergoing the EGD procedure, and/or having biopsies taken, including but not limited to due to comorbidities such as coagulopathy or a known history of esophageal diverticula, esophageal fistula and/or esophageal ulceration
7. History of difficulty swallowing (dysphagia) or painful swallowing (odynophagia), including swallowing pills
8. Oropharyngeal tumor
9. History of esophageal or gastric surgery, with exception on uncomplicated surgical fundoplication procedure
10. History of myocardial infarction or cerebrovascular accident within past 6 months

4.0 REGISTRATION PROCEDURES

Subjects will be identified through prescreening in the Electronic Medical Record (EMR) of patients scheduled for screening colonoscopy or other endoscopy procedures. All endoscopy patients will receive a Clinical Research Opportunity Flyer with their endoscopy prep instructions which allows for a potential subject to opt-out of research. After the patients report for their scheduled colonoscopy or other endoscopic visit, they will be additionally exposed to the research opportunity flyer in the endoscopy waiting room. If they do not "opt-out", and are found to be agreeable for study inclusion, the informed consent process and a signed informed consent form will be obtained by a study nurse or non-conflicted study investigator not performing said scheduled procedure.

5.0 DATA SAFETY MONITORING PLAN

This multicenter investigation employs two diagnostic assessments (EsoGuard and both EGD visualization as well as pathologic assessment of EGD biopsies), both of which make use of marketed medical devices which have obtained FDA 510(k) clearances (EsoCheck and

endoscopies). As well, the EsoGuard test is offered as an LDT at a CLIA/CAP certified facility (ResearchDx, Irvine, CA). It will perform non-endoscopic sampling of the esophagus. Endoscopy with biopsy sampling of the esophagus will be performed subsequently as needed when EsoCheck is positive or if those with a negative EsoCheck volunteer for a research endoscopy. The recruitment, non-endoscopic sampling, upper endoscopic screening protocols and collection of biospecimens pose minimal risk to participants. Because of this low risk status, the data safety monitoring (DSM) plan for this trial focuses on close monitoring by the principal investigators in conjunction with a safety officer, along with prompt reporting of any serious adverse events to the NIH and to the IRB at the respective institution.

The frequency of data review for this study is shown in the following table:

Table 2 Data Safety Monitoring Plan

Data type	Frequency of review
Subject accrual (adherence to protocol regarding demographics, inclusion/exclusion)	Quarterly
Adverse event rates (injuries) related to endoscopic procedures	Quarterly

Qualifications and responsibilities of the Safety Officer

The safety officer for this trial will be Jeffry Katz, M.D. who is independent and is not participating in this clinical trial. Dr. Katz is board certified in gastroenterology and has experience running epidemiological studies. He understands the types and severity of injuries commonly experienced as a result of upper endoscopy. As Safety Officer, Dr. Katz will review the reports sent by the study coordinator (at the frequency outlined above) and determine whether there is any corrective action, trigger of an ad hoc review, or stopping rule violation that should be communicated to the study investigators, UH Cancer Center IRB, the University Hospitals Case Medical Center IRB, and the NCI.

Measurement and reporting of subject accrual, adherence to inclusion/exclusion criteria

Review of the rate of subject accrual, adherence to inclusion/exclusion criteria occurs every 3 months during the study. Because BE and EAC predominantly affect Caucasian males we expect to see a lower recruitment of women and other ethnic groups.

Measurement and reporting of adverse events

We plan to collect injury data from the endoscopic procedures quarterly. We plan to present unblended adverse events data to the principal investigators and the safety officer throughout this trial. Any adverse event will also be reported to the Quality Assurance Committee of the institution where it occurs and the IRB. Adverse event forms that meet the goals of this data safety monitoring plan already exist and will be used by the study staff to report injuries or other adverse events caused by endoscopic procedures. The risks of routine diagnostic upper endoscopy are minimal and include a risk of bleeding, aspiration, and adverse reaction to sedative medications. The complication rate for routine sedated upper endoscopic diagnostic procedures is 0.1 to 0.5%(23). The complication rate for balloon detection study is expected to

be much lower as no complications have been noted in over 600 cases performed to date. Any adverse event rate over 0.5 % in 12 months will be reported to all institutional IRBs and the NIH.

Stopping rules

In this minimal risk trial it is unlikely that excess adverse events will occur and require stopping the trial. However, as outlined, we will monitor injury rates in all participants and the safety officer, together with the study investigators, will alert the IRB and the NIH if a larger than reasonably expected injury rate (> 0.5%) should occur.

6.0 STUDY CALENDAR

Study Team will:

- Ensure IRB approved DHI Clinical Research Opportunity Flyers are provided to endoscopy patients with their endoscopy prep instructions sent by central scheduling
- Identify a potential subject in Soarian or Provation the day before the colonoscopy.
- Complete HIPAA approved pre-screening of potential subject for inclusion/exclusion criteria in EMR
- Check that potential subject is not listed on the DHI Research "Opt Out" List.
- Obtain treating gastroenterologist permission to approach patient on day of procedure and if yes,
- Ensure DHI Clinical Research Opportunity Flyers (openly available to patients in the general waiting area of the GI suite), which contain research contact "opt out" procedures, are provided.
- Once the potential subject has completed their standard of care (SOC) admission process, and has been assigned to their pre-procedure station, the study coordinator will ask the admitting nurse the following questions:

1. *Did the patient ask to <u>not</u> be contacted for research?*
2. *Does the patient speak and understand English?*
3. *Has the patient been administered sedative medication?*

- If the subject meets the criteria listed above (answers "no" to questions #1, #3, and "yes" to question #2) the patient will be approached by the study coordinator. The study coordinator will use the Research Introduction Script *(below)* to determine if the subject is interested in participating in research as follows:

  "Hi, I am _____. I am a research nurse with the GI department. I would like to talk to you about a research study. Would you be interested in hearing about a study that you may qualify for? If you are feeling too distracted or anxious because of your procedure, or you aren't interested, it's okay to say no."

  If the potential subject answers "yes", proceed with the study description and consenting process using IRB approved ICF.

  If the potential subject answers "no", the potential subject will be thanked for their time and the research nurse will walk away. *"Thank you for your time".*

Timepoint	Procedures						
	Informed Consent	**ROI signature**	**Questionnaire completion with coordinator**	**EsoCheck**	**EsoGuard**	**Upper Endoscopy**	**Tissue Samples Collected**
Day of scheduled procedure	**X**	**X**	**X**	**X**			
Send samples and receive results					**X**		
If positive, subject requested to complete SOC upper endoscopy						**X**	**X**
If negative, 100 volunteers to complete research upper endoscopy						**X**	**X**

7.0 STUDY CONDUCT

Patients are sent to screening colonoscopy and other endoscopic procedures through open access scheduling where they see their treating gastroenterology endoscopist on the day of the endoscopic procedure in the UH endoscopy suite locations. Ensuring the patient understands their scheduled procedure, consent is obtained by their treating gastroenterologist/team at that time.

Patients who are scheduled for a screening colonoscopy and other endoscopic procedures with a UH gastroenterologist will receive endoscopy prep information by mail or email. A copy of the DHI Clinical Research Opportunity Flyer will be included with this endoscopy prep information. This will allow patients to independently review their opportunity for research and determine if they are interested in participating in research. They can choose to "opt-out" of the opportunity by calling the designated study coordinator listed on the flyer.

Scheduled endoscopy patients wait in the pre-op waiting room in their UH endoscopy suite location. While they are waiting, they will openly be exposed to copies of the DHI Clinical Research Opportunity Flyer located in the waiting room for their review. The flyer will offer the potential research subject an "opt-out" option for research. This will allow patients to independently review their opportunity for research and determine if they are interested in

participating in research. They can choose to "opt-out" of the opportunity by telling their admitting nurse they do not want to be approached for research.

The study coordinator will review the potential study subject's scheduled procedure and will identify patients with age of ≥ 50 years who have no chronic GERD and have at least two other factors for BE/EAC (male gender, white race, smoking history, central obesity, or family history). Eligible colonoscopy patients who have not expressed their desire to "opt-out" of research , with permission from the physician performing their procedure (whom patient will meet on the day of the scheduled procedure), will be approached by a member of the study team to acquaint them with the following: an introduction to the study using the research informational flyer, the privacy and quiet of the enclosed area, given adequate time to consider their participation and ask and have questions answered, with possible family around, and **before any scheduled sedation**. They will be asked questions to confirm their eligibility.

The study team member will initially and purposefully allow the potential subject to "opt-out" of being approached for study inclusion. The study team member will assure the subject that they will not need to participate in the study to receive their scheduled clinical care and they will receive their prescribed medical care whether they decide to participate in the research, or not. If the potential subject is agreeable and found to be eligible, they will be presented with the consenting process by the Human Research Protections Certified member of the research team.

If they agree to participate and have signed and dated the approved informed consent form, they will then be asked to complete the study Questionnaire, Release of Medical Information Form with the study team and then undergo the EsoCheck procedure prior to their scheduled endoscopic procedure.

Once eligibility has been established the study will be explained in detail by one of the study team. Specifically, it will be explained that participation requires the following:

1. Written informed consent to participate in the study.
2. Donation of biofluids or tissue collected during non-endoscopic sampling (EsoCheck Procedure).
3. Signature of "Authorization for Release of Medical Information" form (Appendix G) by affected subjects or their authorized representative to allow researchers to obtain surgical reports, pathology reports, chart summaries, and/or paraffin-embedded tumor blocks and matching H & E slides related to the diagnosis of BE and/or EAC.
4. Completion of a Study Questionnaire that asks questions about reflux symptoms and patient's attitudes toward non-endoscopic screening.
5. Performance of an EsoCheck procedure; the EsoCheck sample will subsequently be tested with the EsoGuard assay.
6. Patients whose EsoGuard assay results comes back positive, suggesting that they may have BE, will be recommended an EGD and contacted to undergo EGD. This will be a standard of care billable EGD. EsoGuard assay results may take up to two weeks from the date when the sample is obtained. Patients will be contacted by phone and results will be discussed with them. The patient will then have the opportunity to schedule an EGD at their convenience.

7. Selected patients whose EsoGuard assay comes back negative will also be offered a research EGD if they consent. . EsoGuard assay results may take up to two weeks from the date when the sample is obtained. Patients will be contacted by phone and results will be discussed with them. If the patient chooses, they will then have the opportunity to schedule an EGD at their convenience. This will be a research EGD.
8. Patients who participate in the research study and undergo EC/EG will be provided $20 as a token of appreciation along with a parking pass. In addition, those who are EC/EG negative and undergo a research EGD will be offered $60 as an additional token of appreciation along with a parking pass.

The study Questionnaire obtains details regarding GERD symptoms, environmental exposure history, family history, height, weight, and prior upper endoscopy along with attitudes toward non-endoscopic screening. The questionnaire will take approximately 5 to 15 minutes to complete. The gastroesophageal reflux questionnaire (GERQ) is a validated measure of reflux symptoms and environmental exposure history developed by the Mayo Clinic(24).

The EsoCheck procedure is performed according to its Instructions for Use (Appendix 1). Samples collected are sent by study coordinators to ResearchDx/PacificDx, a licensed CAP/CLIA Laboratory, 5 Mason, Suite 100, Irvine CA 92618 where the EsoGuard assay will be performed. The EsoGuard test extracts DNA from the esophageal samples. DNA is reduced with bisulfite and then assayed for methylated Vimentin and methylated CCNA1 using specific primers. % methylated Vimentin > 2% or % methylated CCNA1 > 0.5% is considered positive.

Patients who have a positive EsoGuard assay will then be offered and undergo standard of care EGD. They will be informed that this endoscopy will be billed to insurance. EsoGuard is an approved laboratory developed test. Up to 100 patients who have a negative EsoGuard assay will also be offered a research EGD free of charge if they choose to participate further in research. Patients with BE or EAC at EGD will have standard of care screening and diagnostic biopsies. Biopsies from BE and EAC will be directed by using high definition narrow band imaging. Biospecimens will also be snap frozen at bedside and stored for future research assays.

In patients found to have BE, biopsy specimens for routine histology will be obtained at 2-cm intervals along the entire length of the Barrett's epithelium following standard of care “Seattle” protocol. In patients with a normal esophagus or BE, additional brushings or biopsies will be obtained for research purposes from areas of columnar appearing mucosa and also from normal squamous mucosa at least 3cm proximal to the squamocolumnar junction, normal gastric mucosa, or normal duodenal mucosa for control purposes. A total of up to 12 additional research brushings or biopsies will be obtained.

8.0 DRUG INFORMATION

Patients may be offered Cetacaine, a topical anesthetic spray and/or viscous lidocaine applied to the pharynx to minimize gag reflex for the balloon capsule procedure.

9.0 STATISTICAL CONSIDERATIONS

EsoCheck/EsoGuard positive will mean the reporting of a "positive" result for an EsoGuard test run on a sample obtained via EsoCheck. EGD positive will mean a result of BE (whether or not dysplasia is also present) and/or EAC based on the visualization of salmon-colored mucosa on EGD as well as the reported pathologic finding of intestinal metaplasia, dysplasia and/or neoplasia.

A two by two table will be constructed comparing results from EC/EG and result from EGD histology.

	EGD Positive	EGD Negative	Total
EsoCheck/EsoGuard Positive	*PP*	*PN*	*PP+PN*
EsoCheck/EsoGuard Negative	*NP*	*NN*	*NP+NN*
Total	*PP+NP*	*PN+NN*	*n*

where
PP is the number of patients who test positive via EsoCheck/EsoGuard then positive via EGD,
PN is the number of patients who test positive via EsoCheck/EsoGuard then negative via EGD,
NP is the number of patients who test negative via EsoCheck/EsoGuard then positive via EGD,
NN is the number of patients who test negative via EsoCheck/EsoGuard then negative via EGD.
$n = PP+PN+NP+NN$ and represents the total sample size.

Primary Aim 1. Calculate positive predictive value for patients who have EC/EG then undergo EGD.

For patients who are predicted to be positive via EsoCheck/EsoGuard to undergo EGD. The estimated EGD positive rate for Strategy B is $\Pi_B = PP/(PP+PN)$.

Π_B will be calculated and reported with 95% confidence intervals.

Primary Aim 2. Calculate proportion of patients who have negative EC/EG and are also confirmed to be negative for BE when they undergo EGD.

Study population and justification of sample size:
The prevalence of BE in male patients with chronic GERD symptoms who have two other risk factors is 7-10%.(21) A study that performed EGD on 822 men undergoing colonoscopy reported that up to 7% of those without GERD who met criteria similar to what we will use for this study had BE.(25) Furthermore, using the M-BERET BE risk prediction model developed at the University of Michigan, we tested various scenarios that fit our inclusion criteria and found the prevalence of BE for the proposed study population would be expected to be between 4-6%. To be conservative, we have estimated the PPV using a sample size of 500 subjects for the lower

estimated prevalence of 4% and 5%. Our goal is to develop a screening test with a minimal threshold PPV of 20%.

We propose to recruit 500 patients for EC/EG based on the following analysis. If we assume a 5% prevalence of BE in the study population, with a 90/90 sensitivity/specificity for the EsoGuard assay(26), then 70 would undergo endoscopy, of whom 22 would be true positive (true PPV 32% with 95% CI of 26.3-39.1%). If we assume a 4% prevalence of BE in the study population, with a 90/90 sensitivity/specificity for the EsoGuard assay(26), then 66 patients would undergo endoscopy, of whom 18 would be true positive (true PPV 27% with 95% CI of 21.6-33.7%).

The majority of these patients will have a negative EsoGuard assay. Of those with a negative EsoGuard assay, we will recruit up to 100 patients for a research EGD.

Assuming that the sensitivity of EsoGuard is 90% and the prevalence of BE in our population is 5%, the expected rate of missed BE will be 0.5% in EsoGuard negative patients. If we perform EGD on 100 patients then we will be able to estimate a miss rate of 0.5% with a 95% confidence of $\pm$ 1.4%. Even if we assume that the sensitivity of EsoGuard is only 80%, then the expected rate of missed BE will be 1% in EsoGuard negative patients. If we perform EGD on 100 patients, then we will be able to estimate a miss rate of 1% with a 95% confidence of $\pm$ 2%, i.e. a positive test result defines a population with a 27-fold enrichment for BE versus a test negative population.

The research EGD procedure will be billed to research; therefore, patients will not have to pay for EGD costs if they have a negative EsoGuard assay result. The performance of research EGD on 100 patients with negative EsoGuard assays will allow us to estimate the proportion of BE patients that are missed by an EC/EG strategy in these patients.

400 subjects will be recruited at UH locations. We plan to extend enrollment for this study to other sites by 100 subjects to obtain a planned final enrollment of 500.

10.0 PATIENT CONSENT AND PEER JUDGEMENT

All institutional, NCI, FDA, state and Federal regulations concerning informed consent and peer judgment will be fulfilled.

11.0 RECORDS TO BE KEPT

To ensure confidentiality for patients participating in the study, numbers will be assigned to each subject. Each study coordinator and PI has access to participant identifiers and the assigned numbers at their respective institutions. Questionnaire information will be identified by a code number. All subject records (hard copy) will be stored in locked file cabinets at the institution where the patient was enrolled. All coded information (questionnaire data, pathology reports, surgical reports, endoscopy reports and lab analysis results) collected about a participant will be entered into Labmatrix and Veeva Vault, secure electronic databases. The information stored in these databases is protected under HIPAA and all individuals with access to the information follow government regulations to protect the privacy of research study subjects.

If participants are patients at the institution where they are recruited, results from research and other information obtained during the study will not be placed in the patient's medical record. If standard of care lab test results are confirmed in a CLIA laboratory it is appropriate to include those results in the patient's medical record. Esoguard and possible research EGD results will be shared with research participants and their physician. Esoguard results will be placed in EMR by study investigators and copied to the primary physician. Patients will also be called by phone with results.

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