# Protocol Title: The Acceptability of a Rapid Esophageal Adenocarcinoma Risk Test (REACT)

NCT03366012

STUDY PROTOCOL

Date: November 30, 2022

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## 1. Background and Rationale for Study

The incidence of esophageal adenocarcinoma (EAC) has risen 10-fold over the past half century and continues to have a dismal prognosis. [1-3] Even though it has been established that Barrett's esophagus (BE) is the precursor lesion to EAC, more than 90% of EAC patients are never diagnosed with BE beforehand. [4-6] Thus, the opportunity is missed to identify most patients at high risk for EAC who could benefit from surveillance and early endoscopic therapy, which in turn may lower EAC mortality. [5, 7-9] Upper endoscopy is the only means to diagnose BE, yet widespread endoscopic screening is impractical and expensive. There is an urgent need to develop minimally-invasive methods of BE screening that can be easily performed in the primary care setting to allow for efficient and cost-effective interventions to decrease EAC mortality.

The Cytosponge is a tethered cell sampling device that is swallowed and then withdrawn through the mouth. Prior studies have shown that, using this device, immunohistochemical staining for trefoil factor 3 (TFF3) is specific for Barrett's esophagus tissue. [10] In a large case-control study (BEST2 [11]) of 647 patients with BE and 467 patients without BE, the Cytosponge was administered prior to upper endoscopy. The test was associated with 79.9% sensitivity and 92.4% specificity. The large majority (93.9%) of patients were able to swallow the Cytosponge successfully, and 97.9% of patients rated the experience as 3/10 (mildly unpleasant) or higher. There were three serious adverse events, none of which were attributed to the Cytosponge. On endoscopy, 16.7% of patients had mild oozing of blood in the esophagus from the Cytosponge, but there were no cases of major bleeding.

Enrollment has begun for the BEST3 trial in the United Kingdom. The BEST3 Trial will assess whether the Cytosponge test for patients with reflux symptoms will be effective in increasing the detection of Barrett's esophagus in primary care and to evaluate its cost effectiveness. It will also give further information on the diagnostic accuracy of the Cytosponge test and will also evaluate the patient acceptability of this new diagnostic test. This is a study of over 9,000 patients and is being conducted in primary care clinics throughout the UK. Eligible subjects are invited for Cytosponge testing, with follow up endoscopy performed for those with a positive test. Additionally, a subset of patients ineligible for testing or who test negative will be invited to undergo upper endoscopy.

We now propose to study the Cytosponge test in the primary care setting here in the United States to assess participation rates, tolerability, safety, and performance. In addition to testing samples for TFF3, we will also assess for p53 expression; emerging data indicates that p53 expression is an important predictor of future dysplastic Barrett's esophagus or esophageal adenocarcinoma.

## 2. Objectives

***Primary Objective***

The primary objective of the study is to pilot a Barrett's esophagus screening program using the Cytosponge test in the primary care setting. This will be assessed by two outcomes: 1) participation rates among eligible patients seen at CUMC primary care practices; and 2) patient tolerability of the Cytosponge test as assessed by questionnaire.

***Secondary Objectives***

Secondary objectives include the following:

- To assess the positive predictive value of the Cytosponge test in the primary care setting. We will calculate the proportion of patients with a positive Cytosponge test who have Barrett's esophagus confirmed on follow up endoscopy.

- To assess safety of the Cytosponge test in the primary care setting.

## 3. Overview of Study Design

We will prospectively enroll 100 patients to undergo Cytosponge testing. We plan to use data generated from this study to design a follow up study, refining patient selection and recruitment methods as necessary.

***Study Population***

*General Considerations*

The purpose of Cytosponge testing is to identify patients with Barrett's esophagus, so that surveillance can be instituted to facilitate the early detection of dysplasia and cancer, and interventions can be instituted to reduce esophageal cancer mortality. The risk of BE varies greatly by age, sex, race, and other factors including a history of GERD symptoms, obesity, and smoking. Inclusion and exclusion criteria have been developed in order to maximize BE detection, but without being too restrictive in patient selection. While difficult to anticipate precisely, we have designed criteria for screening with the goal of diagnosing BE in 5-10% of screened patients.

*Inclusion Criteria*

***Males:***

- Ages 50-75 AND at least one of the following:
    - Gastro-esophageal reflux disease (GERD)*
      OR
    - Family history (first degree relative) with Barrett's esophagus or esophageal adenocarcinoma
      OR
    - BMI≥30
      OR
    - History of cigarette smoking (at least 10 pack years)

***Females:***

- Ages 50-75 AND GERD* AND either:
    - Family history (first degree relative) with Barrett's esophagus or esophageal adenocarcinoma
      OR
    - BMI≥30
      OR
    - A history of cigarette smoking (at least 10 pack years)

*GERD defined as either a history of frequent heartburn or fluid regurgitation symptoms (at least weekly for 6 months) OR regular use of proton pump inhibitors or histamine-2 receptor antagonists.

*Exclusion Criteria*

- History of gastric or esophageal cancer
- History of esophageal surgery
- Known untreated esophageal stricture or uninvestigated dysphagia
- Previous upper endoscopy within 10 years
- Cancer within 3 years except for non-melanoma skin cancer

- Portal hypertension, with or without known varices
- Uncontrolled coagulopathy
- Uncontrolled major comorbid illness
- Inability to tolerate or contraindication to upper endoscopy
- Inability to give informed consent

***Identification of Study Subjects***

The schedules will be reviewed from participating primary care providers (PCPs). The electronic medical records will be reviewed to identify potentially eligible study subjects. Additionally, the study team will work with CUIMC IT department and TRAC committee to generate a recurring report using the inclusion/exclusion criteria of the study. The TRAC report will list patients with upcoming appointments with participating PCPs who are potentially eligible study subjects, based on the information already present in their electronic medical records.

The insurance of potentially eligible subjects will be ascertained to determine whether a possible follow up endoscopy would be in-network or out-of-network. The participating PCPs will be notified of which subjects are potentially eligible. During the subject's office visit, the PCP will introduce the study to the patient prior to a member of the research team contacting the patient. If the patient indicates to the PCP that they are not interested in participating in the research study, the research team will not approach the patient.

***Informed Consent***

At the conclusion of the visit with the PCP, a member of the Research Team will approach the subject regarding participation in the study, including background of the proposed study, inclusion and exclusion, the benefits and risks of participation. If this is of interest to the subject, the informed consent form is discussed and presented. The subject must sign the consent form prior to enrollment.

***Study Procedures***

The Cytosponge (Medtronic) is a tethered capsule on a string that a patient can swallow while sitting in a chair in an office. The capsule dissolves, exposing a small spherical brush. After 5 minutes, the string with the attached sponge is then withdrawn from the patient, capturing a small sample of cells from the esophagus that can accurately determine whether or not a patient has Barrett's esophagus.

The Research Nurse will conduct all procedures by asking subjects to be seated upright and swallow the tethered capsule sponge with sips of water. After an interval of 5 min, the capsule sponge will be pulled out with steady traction using the string attached to the capsule sponge. The sponge will then be placed in 20 mL CytoRich Red Preservative Fluid. Subjects will then complete a tolerability questionnaire which allows patients to grade discomfort during the procedure on a Likert scale of 0-10. Participants will also be asked if they would have the procedure again (yes/no).

Immunohistochemical testing for trefoil factor 3 (TFF3) and p53 expression is performed on tissue samples collected from the Cytosponge. The subject exits the study in the event of a negative TFF3 test and normal p53 expression. In the event of a positive TFF3 test or abnormal expression of p53, the subject will be informed of the test results and scheduled for an upper endoscopy. During the upper endoscopy, notation will be made with regard to endoscopic evidence of Barrett's esophagus and any other endoscopic findings. If Barrett's esophagus is suspected, four-quadrant biopsies will be taken every 2 cm per standard clinical practice to assess for the presence of intestinal metaplasia and/or dysplasia.

***Study Evaluations***

The primary outcomes will be:

- Participation rates – defined as the proportion of patients who agree to undergo Cytosponge testing among number of eligible patients offered Cytosponge testing.
- Tolerability – after undergoing the Cytosponge test, subjects will be asked to rate tolerability using a Likert scale (1 to 10) and whether they would be willing to undergo Cytosponge testing again.

Secondary outcomes of Cytosponge testing include:

- Positive predictive value of the Cytosponge TFF3 test: PPV = (# of patients with endoscopic and histologic evidence of Barrett's esophagus on upper endoscopy) / (# of patients with TFF3-positive Cytosponge test who undergo a follow up endoscopy)
- Positive predictive value of the Cytosponge p53 expression test: PPV = (# of patients with endoscopic and histologic evidence of Barrett's esophagus associated dysplasia on upper endoscopy) / (# of patients with abnormal p53 Cytosponge test who undergo a follow up endoscopy)
- Safety: we will record and report all adverse events (AEs) and serious adverse events (SAEs) related to Cytosponge testing.

***Statistical Methods***

Data will be summarized with proportions, means, or medians as appropriate with 95% confidence intervals. The sample size of 100 patients was chosen as a convenience sample that represents a feasible enrollment target and that will provide critical data for the design of larger Cytosponge testing studies. We have developed the inclusion and exclusion criteria such that the anticipated prevalence of BE in the study population will range from 5-10%. With a 5% true BE prevalence in our study population, 11% of subjects are expected to test TFF3-positive. With a 10% true BE prevalence, 15% of subjects are expected to test TFF3-positive

## 4. Risks and Benefits Assessment

***Risks***

Cytosponge testing is overall well tolerated. In the aforementioned BEST2 trial [11], 97.9% of patients rated the experience (undergoing Cytosponge testing) as 3/10 (mildly unpleasant) or higher. There were three serious adverse events, none of which were attributed to the Cytosponge. On endoscopy, 16.7% of patients had mild oozing of blood in the esophagus from the Cytosponge, but there were no cases of major bleeding.

In total, over 9,000 patients have undergone testing with the Cytosponge (EuroPlaz, United Kingdom) in the United Kingdom and the United States. Three detachments have occurred (<1 in 1,000) upon withdrawal of the tethered device. In all cases, the Cytosponge was retrieved by endoscopy, and subjects recovered without further complications.

Cytosponge testing may produce false positive results, which may lead to undue anxiety and worry. Additionally, patients with a positive Cytosponge test but without Barrett's esophagus will still undergo a follow up endoscopy. Severe complications from upper endoscopy are rare (<1%), and include bleeding infections, aspiration, and intestinal perforation.

***Benefits***

There are no direct benefits to participation in the study. Detection of Barrett's esophagus by undergoing Cytosponge testing could lead to early detection of dysplasia or esophageal adenocarcinoma. However, it is unclear whether early detection leads to lower esophageal cancer mortality or improved outcomes overall.

***Adverse Event Reporting***

*Adverse Event Classification Definitions*

All adverse events (AEs) will be recorded. The intensity of adverse events will be evaluated using the following criteria:

- Mild – noticeable to the patient but does not interfere with routine activity
- Moderate – interferes with the patient's routine activity but responds to symptomatic therapy or rest
- Severe – significantly limits the patient's ability to perform routine activities despite symptomatic therapy

A Serious Adverse Event (SAE) is any untoward medical occurrence that:

- results in death
- is life-threatening
- requires in-patient hospitalization or prolongation of existing hospitalization
- results in persistent or significant disability/incapacity
- results in medical or surgical intervention to prevent permanent impairment to body structure or a body function.

*Unanticipated Problem (UP)* will be defined as any incident, experience or outcome involving risk to subjects or others in any human subjects research that meets all of the following criteria:

- Unexpected (in terms of nature, severity or frequency) given (a) the research procedures that are described in the IRB-approval protocol and informed consent document and (b) the characteristics of the subject population being studied;
- Related or possibly related to participation in such research (i.e., there is a reasonable possibility that the incident, experience or outcome may have been caused by the procedures involved in such research); and
- Suggests that the research places subjects or others at a greater risk of harm (including physical, psychological, economic or social harm) than was previously known or recognized.

*Unanticipated Adverse Device Effect (UADE)* are any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem or death was not previously identified in nature, severity or degree of incidence in the investigational plan or application or any other unanticipated serious problem associated with a device that relates to the rights, safety or welfare of subjects.

*Adverse Event Review and Relationship Determination*

The Investigator will report their assessment of the adverse event with respect to severity and causality. The Investigator will also assess all Serious Adverse Events considered device-related for potential regulatory reportability. The following lists the potential event attribution categories:

- Device-Related: An adverse event is considered to be device-related when it is reasonable to believe that the event may have been caused by or is related to the investigational device.
- Procedure-Related: An adverse event is considered to be procedure-related when it is reasonable to believe that the event is not specific to the investigational device. Other products may have contributed to the occurrence of the event.
- Pre-Existing Condition Related: An adverse event is considered to be related to a pre-existing condition when it is reasonable to believe that the event is associated with the subject's pre-existing condition and is not specific to the investigational device or procedure. Pre-existing conditions that are exacerbated after the index procedure and have been determined to not be device-or procedure-related will be categorized as related to a pre-existing condition.
- Concomitant Medications: An adverse event that is associated with concomitant medications and is not otherwise specific to the investigational device.
- Intercurrent Condition: An adverse event that is believed to be directly associated with a new medical condition/co-morbidity/diagnosis that arises following the index procedure.
- Intercurrent Intervention: An adverse event that arises from, or is associated with, an intervention that was performed after the index procedure for reasons other than to address a device- or procedure-related complication.

***Data and Safety Monitoring Plan***

The PI and study team will continuously monitor any and all AE's and UP's as they arise. The Herbert Irving Comprehensive Cancer Center (HICCC) DSMP board, led by Dr. Joseph Jurcic, will conduct the data and safety monitoring, together with an independent internal study monitor. The initial review will consist of a comprehensive evaluation of the first 3 patients enrolled, and then will commence annually. Safety, regulation accountability, and enrollment data will be reviewed by the study monitor. Any unanticipated problems and unanticipated adverse device effects will be reported promptly to the Columbia University IRB, no later than 7 days after the occurrence or PI knowledge of the event.

## 5. Costs

There will be no costs to the subject for Cytosponge testing. Follow up upper endoscopy will be performed in patients with a TFF3-positive test or abnormal p53 expression to confirm a Barrett's esophagus diagnosis. The endoscopy will be billed to the patient's insurance as standard of care.

## 6. Subject Completion

***Completion***

Subjects complete participation in the study upon receiving a negative Cytosponge test or after the follow up endoscopy in the event of a positive Cytosponge test.

***Withdrawal***

Subjects may withdraw from the study at any time.

## 7. Ethical Aspects

***Institutional Review Board (IRB)***

Prior to initiating the study, the investigators will obtain written approval to conduct the study from the Columbia University IRB. Should changes to the study become necessary, protocol amendments will be submitted to the Columbia University IRB.

***Informed Consent***

The Informed Consent Form must have prior approval of the Columbia University Institutional Review Board (IRB). Failure to obtain informed consent renders the subject ineligible for the study. The original copy of the signed consent form will be kept in the Investigator file in a locked cabinet. A copy will be provided to the subject. Subjects will be assured that they may withdraw from the study at any time for any reason.

***Confidentiality of Study Data***

All subjects will be assigned an alphanumeric study ID code. A password-protected computer file containing the list of patients and their corresponding study ID will be maintained separately. This file will be stored on a password-protected encrypted end-point device and will be accessible only to the PI and the Study Coordinator. Study data will be recorded on Case Report Forms, which will only be labeled with the study ID code. The password-protected electronic study database will only be accessible by the PI and study coordinator.

## 8. Administrative Requirements

***Protocol Modifications***

Minor deviations from the investigational plan must be medically considered to be minor and should not offer increased risk to the subject nor affect the validity of the trial. Significant changes to the protocol will require that the protocol be formally amended. Protocol amendments must be approved by the Columbia University Institutional Review Board.

***Electronic Data Entry***

The study database will be accessible only to the study investigators through a password-protected computer. The PI and study team will have access to deidentified data in the form of statistical summaries and data analytic files (SAS, SPSS, etc.) generated from the database, but these database products will not contain explicit patient identifiers. Individual level patient data in these analytic files will be identified only by a sequential study ID number. Direct database access will be through a secure Citrix gateway requiring an individually assigned userid and password. Data entry and modification will be electronically audited, ensuring that each entry or change to the database, the individual responsible, and the date of change, can be documented. Access to database products (reports, analytic files) will be through secure VPN access with userid and password assigned to each authorized individual. All project data and database projects will be stored on a physically and electronically secure server cluster maintained by Columbia University Data Coordinating Center IT staff, under the supervision of Dr. Howard Andrews, director of the DCC.

## 9. References


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