ASBE study

Clinical Utility of a Non endoscopic Device EsoCheck and Biomarker EsoGuard as **A**lternative to Endoscopy for **S**creening for **B**arrett's **E**sophagus in At Risk Population (**ASBE**)

A Randomized Controlled, Virtual Patient Trial

Principal Investigator: Victoria T. Lee MD
Vice President Medical Affairs Lucid Diagnostics

Study sponsor: Lucid Diagnostics
360 Madison Avenue
Floor 25
New York, NY 10017

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1. PROTOCOL SYNOPSIS

Title	Clinical Utility of a Non endoscopic Device EsoCheck and Biomarker EsoGuard as **A**lternative to Endoscopy for **S**creening for **B**arrett's **E**sophagus in At Risk Population (ASBE) A Randomized Controlled, Virtual Patient Trial
Rationale	A randomized controlled virtual patient trial is a means of obtaining clinical utility data for reimbursement. This trial will obtain clinical utility data on EsoGuard® (EG) a biomarker assay (laboratory developed test/LDT), and EsoCheck® (EC), an FDA cleared, non-endoscopic esophageal cell collection device, which when used in combination has been identified by the AGA and ACG as a reasonable, non-endoscopic alternative for screening of Barrett's Esophagus (BE) and esophageal adenocarcinoma (EAC).
Study objectives	**Primary objective** To determine the impact of EsoCheck/EsoGuard on health care provider's decision for endoscopy referral **Secondary objective** To determine the impact of EsoCheck/EsoGuard on health care provider's patient risk assessment for BE
Study design	A Randomized Controlled, Virtual Patient Trial. Eligible participants will sign the IRB approved ASBE participant Informed Consent Form (ICF). The participants complete two rounds of questions concerning the assessed risk for BE and upper endoscopy referral of 6 patient cases (clinical vignettes). Per round, there will be 3 different questionnaires consisting of 6 clinical vignettes (A/B/C). Participants will be randomized to questionnaire A, B or C according to the randomization scheme.
Study population	Primary care physicians and other physicians whose scope of practice includes disease screening, and/or diagnosis and management of patients with esophageal disease. • At least 80% of the overall study population will be primary care physicians, family medicine physicians, and other general practitioners; • ≤20% will be other types of physicians/specialists.
Number of participants	Minimum of 100. Around 200 will be invited to participate.
Expected duration of accrual	Approximately 3, but up to 6 months.

2. INTRODUCTION AND SCOPE

EsoCheck® (EC) is an FDA cleared, non-endoscopic cell collection device designed to sample cells from a targeted region of the esophagus; EsoGuard® (EG) is a laboratory developed test (LDT) performed in a Clinical Laboratory Improvement Amendment (CLIA) certified and College of American Pathologists (CAP) accredited lab that utilizes set of genetic assays and algorithms which examines the presence of cytosine methylation at 31 different genomic locations on the vimentin (VIM) and Cyclin-A1 (CCNA1) genes. Using EsoCheck and EsoGuard in combination may offer an accurate, lower cost, minimally invasive, non-endoscopic, approach to screen for BE with and without dysplasia, and for esophageal adenocarcinoma (EAC), as compared with the current gold standard, namely diagnostic upper endoscopy of the esophagus plus biopsies.

EsoCheck/EsoGuard has been clinically validated in a developmental study published in 2018 and shown to have a >90% sensitivity and >90% specificity in non-endoscopic detection of BE or EAC (Moinova 2018). EsoCheck administration is a simple, non-endoscopic, office-based procedure that can be performed by a variety of healthcare providers including physicians, nurse practitioners, physician assistants, nurses and others. It allows for planned, point-of-care screening of the at-risk patient population to provide a convenient and early datum for providers to assist in medical decision making.

Non endoscopic minimally invasive cell-collection devices like EsoCheck/EsoGuard may be considered as an acceptable alternative to upper endoscopy or as an option to screen for BE as mentioned in the 2022 American College of Gastroenterology (ACG) and American Gastroenterological Association (AGA) guidelines for screening in Barrett's Esophagus (Shaheen 2022; Muthusamy 2022).

A randomized controlled virtual patient trial is a means of obtaining clinical utility data for reimbursement (Peabody 2019).

AIM

This prospective randomized, controlled, virtual, patient study aims to assess the impact of EsoCheck/EsoGuard on health care provider's decision for upper endoscopy referral.

3. TRIAL DESIGN

This will be a prospective randomized, controlled, virtual, patient study to measure the impact of EsoCheck/EsoGuard on health care provider's decision for upper endoscopy referral.
Around 200 US physicians will be asked to participate in this study and at least 100 will be enrolled.

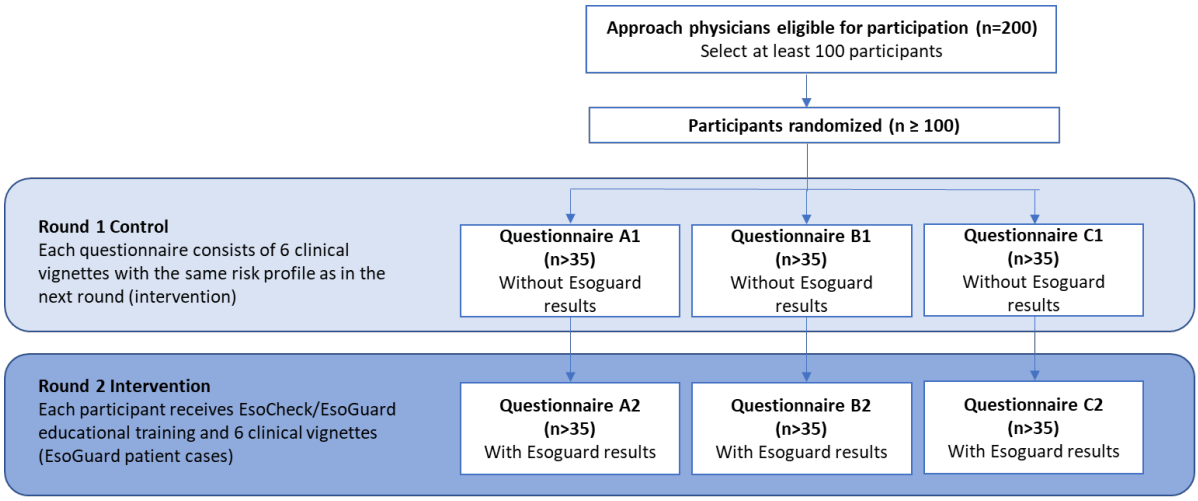
Physicians eligible for participation are those whose scope of practice includes preventative care and disease screening – namely screening of BE, such as primary care physicians, family medicine physicians, and general practitioners; physicians whose scope of practice include diagnosis and management of esophageal disease may also participate.

- At least 80% of the overall study population will be primary care primary care physicians, family medicine physicians, and general practitioners;
- ≤20% will be other physicians/specialists.

Eligible participants will sign the IRB approved ASBE participant Informed Consent Form (ICF).

The participants will complete two rounds of questions concerning the assessed risk for BE and decision for endoscopy referral of 6 patient cases (clinical vignettes). Per round, there will be 3 different questionnaires consisting of 6 clinical vignettes (A/B/C). Participants will be randomized to questionnaire A, B or C according to the randomization scheme. The link to the online questionnaires will be sent by email. The questionnaires should be completed within approximately ten (10) business days, and no more than twenty (20) business days after receiving the link. After the first round has been completed, an EsoCheck/EsoGuard educational information package and the second round of 6 clinical vignettes including EsoGuard results will be sent.

Flowchart



- The intervention group consists of 8 EsoGuard patient cases (clinical vignettes) (3 positive and 5 negative for EsoGuard).
- Per round, there will be 3 different questionnaires consisting of 6 clinical vignettes (A/B/C).
- In the intervention round the 3 questionnaires will have the same 5 negative EsoGuard cases, and 1 (different) positive EsoGuard case per questionnaire.
- In the control round each questionnaire will consist of clinical vignettes with the same risk profile as in the intervention group with a different description and in a different order.

4. STUDY OBJECTIVES

This study has the following objectives:

Primary objective

To determine the impact of EsoCheck/EsoGuard on health care provider's decision for upper endoscopy referral.

Secondary objective

To determine the impact of EsoCheck/EsoGuard on health care provider's patient risk assessment for BE.

5. STUDY POPULATION

Inclusion criteria

1. Board-certified physicians whose scope of practice includes preventative care and disease screening, and/or those whose scope of practice include diagnosis and management of esophageal disease (examples include but are not limited to primary care physicians/ general practitioners, family medicine physicians, gastroenterologists, and foregut surgeons);
2. Have between 1 to 40 years of post-residency clinical experience within their field of practice;
3. Have an active panel (whether as part of a group practice, or individually) of over 1000 patients with an adult patient load of more than 50%.

6. STUDY PROCEDURES

The participants will complete two rounds of questions concerning the assessed risk for BE and upper endoscopy referral of 6 patient cases (clinical vignettes). Per round, there will be 3 different questionnaires consisting of 6 clinical vignettes (A/B/C). Participants will be randomized to questionnaire A, B or C according to the randomization scheme.

The link to the online questionnaires will be sent by email. The questionnaires should be completed within approximately ten (10) business days, and no more than twenty (20) business days after receiving the link.

After the first round has been completed, an EsoCheck/EsoGuard information package and the second round of 6 clinical vignettes including EsoGuard results will be sent.

6.1 Round 1 Control

The control round consists of 8 virtual patient cases (clinical vignettes). The 3 questionnaires (A/B/C) will consist of 6 clinical vignettes with the same risk profile as in the intervention round with a different description and in a different order.

The following baseline and self-assessment questions will be asked:

- Location of practice
- Type of practice
- Number of MDs associated with the practice
- Years of practice
- Proportion of patients covered by Medicare/Commercial insurance (<50% Medicare/>50% commercial; 50/50; >50% Medicare/<50% commercial)
- Estimate of number of GERD patients seen per week (<10; 10-20; ≥20)
- Rate your knowledge of Barrett's Esophagus (BE), esophageal adenocarcinoma (EAC), and associated risk factors (1 = not knowledgeable at all; 2 = not very knowledgeable; 3 = somewhat knowledgeable; 4 = very knowledgeable; 5 = expert)
- Rate your knowledge of the options and indications for BE screening (1 = not knowledgeable at all; 2 = not very knowledgeable; 3 = somewhat knowledgeable; 4 = very knowledgeable; 5 = expert)
- Rate the frequency in which you refer your GERD patients for endoscopic BE screening, as part of your standard practice (<20%; 20-40%; 40-60%; 60-80%; ≥80%)

The following questions will be asked per clinical vignette:

1. What level of risk for BE (and/or EC) do you think this patient has?
    - Low
    - Intermediate
    - High
2. Do you refer this patient for upper endoscopy?
    - Yes, I would refer this patient for endoscopy
    - No, I would not refer this patient for endoscopy

6.2 Round 2 Intervention

The intervention round consists of 8 EsoGuard patient cases (clinical vignettes) (3 positive and 5 negative for EsoGuard). The 3 questionnaires (A/B/C) will have the same 5 negative EsoGuard cases, and 1 (different) positive EsoGuard case per questionnaire.

The following questions will be asked per clinical vignette:

1. What level of risk for BE (and/or EC) do you think this patient has?
    - Low
    - Intermediate
    - High
2. Do you refer this patient for upper endoscopy?
    - Yes, I would refer this patient for endoscopy
    - No, I would not refer this patient for endoscopy
3. Did the EsoGuard result influence your decision to refer or not refer the patient for upper endoscopy?
    - Yes; the EsoGuard result had an impact on my decision
    - No; the EsoGuard result had no impact on my decision

The following self-assessment questions will be asked of each participant at the end of round two (scale 1 very low to 5 high):

- Rate your understanding of EsoCheck/EsoGuard and its indications?
- How likely are you to use EsoCheck/EsoGuard for BE screening in your own practice?
- How likely are you to refer this technology to others or use in their practices?

7. STATISTICAL ANALYSES

7.1 Case Selection

The enrollment period is expected to be 3-6 months. Around 200 primary care physicians and other physicians whose scope of practice includes disease screening, and/or diagnosis and management of patients with esophageal disease in the United States will be invited and a minimum of 100 will participate.

7.2 Power Justification

No data exist regarding the expected endoscopy referral rate for patients at risk for BE with an EsoGuard test result by primary care physicians. It is expected that if at least 100 providers participate and complete both rounds the objectives can be met. Previous randomized controlled, virtual patient trials enrolled between 81 and 202 participants (Peabody, 2019).

7.3 Statistical formulation and statistical analysis plan of the objectives

Primary objective: To determine the impact of EsoCheck/EsoGuard on health care provider's decision for upper endoscopy referral.

The impact will be measured by assessing the change in the percentage/rate of virtual patient cases who will be referred for endoscopy in the intervention round compared to the control round.
Statistics summarizing the agreement between the EsoGuard result (positive or negative) and the health care provider's decision (referral or no referral deemed necessary) include:

- positive agreement; percentage of EsoGuard positive virtual patient cases that were referred for endoscopy
- negative agreement; percentage of EsoGuard negative virtual patient cases that were not referred for endoscopy
- positive predictive value (PPV); percentage of referred virtual patient cases that are EsoGuard positive
- negative predictive value (NPV); percentage of non-referred virtual patient cases that are EsoGuard negative
- percentage of concordance

The participant-reported impact of EsoGuard results on their clinical decision making will be measured by assessing the proportion of patient cases in round 2 for which the provider answered the question, "*Did the EsoGuard result influence your decision to refer or not refer the patient for upper endoscopy"*, with, "*Yes; the EsoGuard result had an impact on my decision"* divided by all patient cases in round 2.
The provided answers will also be reported in a table with counts and percentages.

Secondary objective: To determine the impact of EsoCheck/EsoGuard on health care provider's patient risk assessment for BE.
The impact will be measured by assessing the change in the provider's virtual patient risk assessment for BE in the intervention round compared to the control round.
The provided answers will be reported in a table with counts and percentages.

The baseline and self-assessment questions, Round 1 Control, and Round 2 Intervention, will be reported in a table with counts and percentages.

8. ETHICAL CONSIDERATIONS

All participants must be appropriately informed about the participation in this study and sign an IRB approved consent form. Data will be collected for this research project in accordance with applicable laws and guidelines.

The protocol has been written and the study will be conducted according to the ICH Harmonized Tripartite Guideline for Good Clinical Practice.

9. REFERENCES

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