H-53483- EFFECTIVENESS AND PERFORMANCE OF A MOBILE, AUTOMATED, OPTICAL BIOPSY TECHNOLOGY FOR ESOPHAGEAL CANCER SCREENING: A CLINICAL STUDY IN BRAZIL AND THE UNITED STATES

Concise and Focused Presentation

You're invited to join a research study during an upper endoscopy procedure with a long, bendy tube with a light and camera placed down your throat to check your esophagus.

For the study, we'll use a tool called an artificial-intelligence mobile high-resolution microendoscope (AI-mHRME). This AI is a computer program that takes pictures of the cells in your esophagus during endoscopy. The AI identifies and assists doctors in finding abnormal cells. Your participation is voluntary and contributes to medical research.

We use Proflavine Hemisulfate, a dye, to look at the esophageal cells during the procedure. This safe dye is easily washed away with water. The study doctor sprays your esophagus with Proflavine and the study doctor inserts the AI-mHRME through the endoscope to take pictures of your esophageal cells. Using the AI-mHRME, the study doctor will look at 1-4 abnormal and 1-2 normal areas in your esophagus. Afterwards, the study doctor will collect 1-2 research biopsies from normal areas for comparison. The AI-mHRME imaging, proflavine spray, and biopsy collection will add about 16-18 minutes to the endoscopy procedure. Using Proflavine and AI-mHRME shouldn't make the endoscopy riskier. We take standard precautions to avoid any issues.

Participating in this study helps your study doctor understand changes in your esophageal cells. The study information will help others in the future. You'll still get the usual endoscopy care if you decide not to join the study. You will not incur any costs from participating in this study. We will not pay you to take part.

There are potential risks to the study procedures, mentioned below. There could be other risks we don't know about. Let the study staff know about any side effects immediately, even if you don't think they're connected to the study procedure. For these risks, we have procedures to treat you in the endoscopy room.

- Allergic Reaction: There's a rare chance of a severe allergic reaction to Proflavine, which could cause difficulty breathing and a drop in blood pressure. The Principal Investigator has used Proflavine in other studies before without any harmful events.

- AI-mHRME: Using the imaging probe poses no known risks.

- Anesthesia: There may be risks due to the extra time spent under sedation, such as decreased blood pressure.

- Inhaling Fluid Into Lungs: Under anesthesia, there's a small risk of inhaling fluid, such as proflavine, into the lungs. This could cause lung inflammation.

- Biopsies: There may be hoarseness, sore throat, difficulty/pain in swallowing, bleeding/infection, or discomfort. For the study, we will collect 1-2 biopsies from a Lugol's normal area. Lugol's normal area is

the area of your esophagus that was stained a dark color with the Lugol's iodine spray that is used by doctors to see any areas in the esophagus that may be pre-cancerous or cancerous. These extra biopsies does not change the risks from biopsy collection.

- Pregnancy: Insufficient information is available regarding the use of Proflavine in pregnancy, and drugs can have harmful effects on the fetus. You will not be enrolled in the study or have standard of care endoscopy performed if you are pregnant.

- Loss of Privacy: To protect your privacy, the study will minimize the risk of sharing information by removing personal details and storing data securely. Study results and publications will be anonymous and won't include identifiable information.

The total duration of the research study will be 7 days. Day 1 will be the enrollment, consent, questionnaire, and AI-mHRME procedure. We will call you 7 days later to ask how you are recovering from the procedure and if you have any problems. We will review your medical records 6 months after the procedure for any final diagnoses.

Background

You are invited to take part in a research study. Please read this information and feel free to ask any questions before agreeing to participate in the study.

Esophageal cancer is the 6th most common cause of cancer-related mortality worldwide. While esophageal squamous cell neoplasia (ESCN) carries a significant global burden, those in certain underserved geographic regions (South America, eastern Africa, eastern Iran, and northern China) have a particularly high number of new cases of ESCN (incidence) and number of people who die from ESCN (mortality rates) due to lack of endoscopic screening capacity. Endoscopy with Lugol s chromoendoscopy or digital chromoendoscopy has shown high sensitivity for screening (>95%) or how well it can correctly identify a person with ESCN. Lugol's chromoendoscopy has poor specificity (<60%), which is how well a test can correctly identify a person who does not have ESCN. Lastly, Lugol's generates false-positive results due to confounding inflammatory areas, meaning that other inflamed areas in the esophagus near the ESCN may skew the test results. As a result, standard-of-care endoscopy produces many unnecessary biopsies, increasing the risk and cost of endoscopic screening and surveillance.

Our team has studied this microscope (HRME) in both China and Brazil with artificial intelligence (AI) software that can tell whether the esophagus's lining has cancer. The AI is a computer software program that can perform a human task; in this study it was for identifying any cells that look abnormal in the esophagus. This software assisted doctors in seeing anything that was out of the ordinary in the esophagus lining. In these studies, we saw that 1 in 6 patients could walk out of the procedure without ANY biopsy, and almost 1 in 5 patients had their treatment plan changed correctly because of the HRME diagnosis. In addition, the use of the computer software with the HRME increased the confidence level of the doctors, which allowed the doctors to correctly treat, not treat, or biopsy 64% of the time. When these doctors were interviewed, they uniformly favored this computer-assisted HRME

approach. However, some doctors were unsure how to get the equipment into their endoscopy centers for routine use in their patients. Since the computer-assisted HRME is currently in research studies, some doctors interviewed were unsure how the equipment could be purchased, used, and maintained in their clinical centers.

As part of research conducted with HRME, we use Proflavine Hemisulfate, a staining dye, to dye the esophagus where we see any abnormal areas to help us better see the cells when the probe is against the esophageal lining. Dr. Sharmila Anandasabapathy is the sponsor for this investigational drug, and it is safe to use inside the body. Proflavine is an antibacterial agent used as a topical antiseptic in wound dressings and umbilical cord care. As a liquid that can dye nucleic acids like DNA or RNA, which are genetic material found inside cells, proflavine is also an effective optical contrast agent for visualizing cell nuclei.

This research is funded by the National Institutes of Health (NIH).
A description of this clinical trial will be available on http://www.ClinicalTrials.gov, as required by U.S. Law. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time.

Purpose
This study aims to enhance and assess the impact of an artificial intelligence mobile high-resolution microendoscope (AI-mHRME) on diverse populations in the USA and Brazil. For this study, AI technology is a computer software program that can perform human tasks. It was developed to help look at the cells in the esophagus and tell doctors if any cells look abnormal.

We plan to enroll patients scheduled for routine endoscopy who are either under surveillance or screening for ESCN. The AI-mHRME probe will capture images of the esophagus in abnormal areas, and the study doctor's diagnosis during the procedure will be determined. These images will be compared to the pathology results from collected biopsies.

A challenge in the community is that most doctors are unfamiliar with interpreting these microscopic HRME images. The research aims to test a computer software program designed to interpret these HRME images, aiding doctors in diagnosing high-risk patients undergoing LCE followed by HRME for esophageal cancer screening. We will compare the results of LCE to HRME and clinical interpretation. The goal is to develop a precise and swift diagnosis, enabling the use of this low-cost technology in low-resource or community settings and improving the care of patients at risk of developing esophageal cancer.

Procedures
The research will be conducted at the following location(s):
Baylor College of Medicine, Baylor St. Luke's Medical Center (BSLMC), HCHD: Harris County Hospital District Ben Taub, Rice University, and UT: MD Anderson Cancer Center.

Research Procedure: The study procedure will begin following the routine endoscopic assessment. The

study doctor will spray your esophagus with 2 teaspoons (10 mL) of Proflavine Hemisulfate using a spray catheter. Proflavine is a safe staining dye for use in your esophagus. It will color the cells in the esophagus to make it easier for the study doctor to see them for abnormalities. Next, the study doctor will rinse the Proflavine with water from the endoscope. Then, the study doctor will insert the sterile and disinfected AI-mHRME probe through the endoscope biopsy channel until it gently touches the esophageal lining. The AI-mHRME probe is attached to a computer where there is the AI program. This program allows the study doctor to see the cells on the screen, and the program can produce a score that helps the study doctor determine if there are any abnormalities. During this time, the study doctor will move the AI-mHRME probe so that it can touch the esophagus wall and move it around to capture photos. The focus will be to look at any areas in the esophagus that may appear abnormal or irregular under Lugols chromoendoscopy (LCE, standard endoscopy) and AI-mHRME. This means these are areas where the iodine used in LCE did NOT stain.

The study doctor will assess and look at one to four LCE abnormal areas and two LCE normal areas with the AI-mHRME. LCE abnormal areas are where the Lugol's iodine did not stain the lining of the esophagus, and LCE normal areas are where Lugol's iodine stained the lining of the esophagus a dark color. This can be seen by doctors during routine endoscopy and helps the study doctor identify any areas in the esophagus that may be pre-cancerous or cancerous. After viewing the esophagus with the AI-mHRME, the study doctor will take one to two biopsies from the LCE normal areas for comparison to the LCE abnormal areas (standard of care) and the HRME images by the pathologist.

A study coordinator will collect data throughout this procedure, including the time and date of procedures, esophageal descriptions, study doctor's interpretations of LCE and AI-mHRME, and LCE abnormal and normal biopsy collection sites. After the study procedure and endoscopy, the study coordinator will access your medical records to confirm any previous endoscopy procedures you have had and their corresponding pathology results. Lastly, the study coordinator will access your pathology results in your medical record for the endoscopy procedure you had today to collect data on the results.

The total time of the study procedure with HRME and biopsy collection will add no more than 16-18 minutes of time to your upper endoscopy procedure.

During the study procedure, research technicians from Rice University will accompany the study coordinator in the endoscopy room. They will operate the HRME device and laptop that collects the images from the AI-mHRME probe the study doctor will use during endoscopy.

Results and Follow-up: You will not receive the AI-mHRME imaging results. However, within 7 days of your procedure, the study doctor or coordinator will contact you to check for any side effects you may be experiencing.

Investigational Devices: The AI-mHRME, equipped with a powerful microscope, is considered investigational and not yet FDA-approved for general use. The AI-mHRME has an Investigational Device Exemption (IDE) from the Federal Drug Administration (FDA), allowing its medical use in the

clinic for data collection and research, but not for commercial or general use in the public. The AI-mHRME probe also requires using the investigational contrast dye Proflavine to enhance the visibility of abnormal areas in the esophagus. Proflavine is monitored under an FDA-approved Investigational New Drug (IND) status under Dr. Anandasabapathy's supervision at Baylor College of Medicine.

The total study participation period will be 7 days, starting from the day of your endoscopy procedure and ending with the 7-day follow-up phone call. After 6 months following the endoscopy procedure, research staff will also review your medical chart to see if you had another endoscopy, and if you received a diagnosis and any treatment.

Lastly, you may be invited to participate in an interview about the AI-mHRME after you have had your endoscopy. This interview will be conducted over phone or video conference app., and we will contact you to schedule a date and time. Please indicate your interest in the interview below with your initials:

_____ YES

_____ NO

Clinically Relevant Research Results

The results generated from this research study are not expected to have any clinical relevance to you.

Sharing and Future Research Studies with Identifiable Private Information

Your identifiable private information collected as part of this research, even if the identifiers are removed, will not be used or distributed for future research studies.

Sharing and Future Research Studies with Identifiable Biospecimens

Your identifiable biospecimens collected as part of this research, even if the identifiers are removed, will not be used or distributed for future research studies.

Research related health information

Authorization to Use or Disclose (Release) Health Information that Identifies You for a Research Study

If you sign this document, you give permission to people who give medical care and ensure quality from Baylor College of Medicine, Baylor St. Luke's Medical Center (BSLMC), HCHD: Harris County Hospital District Ben Taub, Rice University, and UT: MD Anderson Cancer Center to use or disclose (release) your health information that identifies you for the research study described in this document.

The health information that we may use or disclose (release) for this research includes:

- Information from health records such as diagnoses, progress notes, medications, lab or radiology findings, etc.
- Specific information concerning alcohol abuse

- Demographic information (name, D.O.B., age, gender, race, etc.)
- Photographs, videotapes, and/or audiotapes of you
- Identifiable biospecimens

The health information listed above may be used by and or disclosed (released) to researchers, their staff and their collaborators on this research project, the Institutional Review Board, Baylor College of Medicine, Baylor St. Luke's Medical Center (BSLMC), HCHD: Harris County Hospital District Ben Taub, Rice University, UT: MD Anderson Cancer Center, NATIONAL CANCER INSTITUTE (NCI) and their representatives, and NATIONAL INSTITUTES OF HEALTH (NIH) and their representatives.

Agents of the U.S. Food and Drug Administration may inspect the research records including your health information. Agents of regulatory agencies such as the U.S. Department of Health and Human Services will be permitted to inspect the research records including your health information.

The data coordinating center will have access to the research records including your health information.

A Data and Safety Monitoring Board will have access to the research records including your health information.

Use or Disclosure Required by Law

To help us protect your privacy, we have obtained a Certificate of Confidentiality from the National Institutes of Health. The researchers can use this Certificate to legally refuse to disclose information that may identify you in any federal, state, or local civil, criminal, administrative, legislative, or other proceedings, for example, if there is a court subpoena. The researchers will use the Certificate to resist any demands for information that would identify you, except as explained below.

The Certificate cannot be used to resist a demand for information from personnel of the United States Government that is used for auditing or evaluation of Federally funded projects or for information that must be disclosed in order to meet the requirements of the federal Food and Drug Administration (FDA).

You should understand that a Certificate of Confidentiality does not prevent you or a member of your family from voluntarily releasing information about yourself or your involvement in this research. If an insurer, employer, or other person obtains your written consent to receive research information, then the researchers may not use the Certificate to withhold that information.

Information regarding study participation will be included in your medical records.

The Certificate of Confidentiality will not be used to prevent disclosure of child abuse, neglect, or harm to self or others to state or local authorities.

Baylor College of Medicine, Baylor St. Luke's Medical Center (BSLMC), HCHD: Harris County Hospital District Ben Taub, Rice University, and UT: MD Anderson Cancer Center are required by law to protect your health information. By signing this document, you authorize Baylor College of Medicine, Baylor St. Luke's Medical Center (BSLMC), HCHD: Harris County Hospital District Ben Taub, Rice University, and UT: MD Anderson Cancer Center to use and/or disclose (release) your health information for this research. Those persons who receive your health information may not be required by Federal privacy laws (such as the Privacy rule) to protect it and may share your information with others without your permission, if permitted by laws governing them.

Please note that the research does not involve treatment. Baylor College of Medicine, Baylor St. Luke's Medical Center (BSLMC), HCHD: Harris County Hospital District Ben Taub, Rice University, and UT: MD Anderson Cancer Center may not condition (withhold or refuse) treating you on whether you sign this Authorization.

Please note that you may change your mind and revoke (take back) this Authorization at any time. Even if you revoke this Authorization, researchers, their staff and their collaborators on this research project, the Institutional Review Board, NATIONAL CANCER INSTITUTE (NCI) and their representatives, NATIONAL INSTITUTES OF HEALTH (NIH) and their representatives, regulatory agencies such as the U.S. Department of Health and Human Services, FDA, Baylor College of Medicine, data coordinating center, Data and Safety Monitoring Board, Baylor St. Luke's Medical Center (BSLMC), HCHD: Harris County Hospital District Ben Taub, Rice University, and UT: MD Anderson Cancer Center may still use or disclose health information they already have obtained about you as necessary to maintain the integrity or reliability of the current research. If you revoke this Authorization, you may no longer be allowed to participate in the research described in this Authorization.

To revoke this Authorization, you must write to: Dr. Mimi Tan, Attn: Arlene Zamora, Gastroenterology, Ben Taub Hospital, 1504 Taub Loop, Houston, TX 77030

This authorization does not have an expiration date. If all information that does or can identify you is removed from your health information, the remaining information will no longer be subject to this authorization and may be used or disclosed for other purposes.

No publication or public presentation about the research described above will reveal your identity without another authorization from you.

Potential Risks and Discomforts

1. Allergic Reaction (Anaphylaxis): You may have a severe allergic reaction to the Proflavine contrast dye, resulting in difficulty breathing and a drop in blood pressure. If such a reaction occurs, we have procedures to treat you in the endoscopy room. However, this Principal Investigator has used Proflavine in other studies before without any harmful events.

2. Specimen Imaging Probe (AI-mHRME): You will have minimal to zero risks when we use the imaging probe during the endoscopy procedure. No risks are associated with using the imaging probe

(AI-mHRME).

3. Anesthesia: You may have additional risks due to the extended duration of sedation, potentially leading to decreased blood pressure. We have procedures to treat you in the endoscopy room.

4. Inhaling of Fluid into the Lungs (Aspiration): You may have a risk of lung inflammation if you inhale fluid in the lungs during endoscopy, including proflavine. While you are under anesthesia, we will implement safeguards to minimize the chances of this happening. We will meticulously monitor your breathing and vital signs for any alarming changes. If you experience any symptoms that the study doctor did not previously explain, you should notify the study team promptly.

5. Biopsies: There is the possibility of some hoarseness, sore throat, difficulty and/or pain in swallowing, bleeding or infection, as well as discomfort at the surgical site. One to two biopsies will be collected from LCE normal areas in the esophagus for the study procedure. This additional biopsy does not increase or change the risks due to biopsy collection.

6. Pregnancy: Insufficient information is available regarding the use of Proflavine in pregnancy, and drugs can have harmful effects on the fetus. You will not be enrolled in the study or have standard of care endoscopy performed if you are pregnant.

7. Loss of Privacy: There is the potential for the loss of confidentiality. You will give consent for the HRME procedure on the day of your endoscopy in a private area. You will be assigned a study ID number for all forms, images, and communications. All your data will be coded and de-identified using this assigned study ID. Any study documents with your Protected Health Information (PHI) will be redacted before being sent for data monitoring/entry. All your PHI that we collect for the study will be stored securely. We will minimize intrusion on your privacy. The only additional times we will contact you will be 7 days after the endoscopy procedure to follow up on your symptoms and check for adverse events. We will review your medical records 6 months after the procedure for any final diagnoses. Only the study coordinator or the Principal Investigator will contact you for follow-up. Your participation in the study will only be discussed between you and the study team.

There may be unknown risks or discomforts involved. Study staff will update you in a timely way on any new information that may affect your decision to stay in the study. There is a small risk for the loss of confidentiality. However, the study personnel will make every effort to minimize these risks.

Potential Benefits

You will receive no direct benefit from your participation in this study. However, your participation may help the investigators better understand the changes in your cells during your scheduled procedure. This increased insight could contribute to developing more effective methods for detecting esophageal cancer in the future. Additionally, the knowledge gained from this research has the potential to benefit the general population by advancing our understanding of esophageal cancer detection methods and improving overall healthcare practices. Your participation is valuable in contributing to advancements

that can positively impact medical care for others.

Alternatives

The following alternative procedures or treatments are available if you choose not to participate in this study: If you decide not to participate in the study, you will still receive the standard of care, and your scheduled endoscopy procedure will proceed as planned. Your medical care will remain the same, regardless of your decision to participate or not in the study. It is entirely your choice, and declining participation will not affect the quality or nature of the care you receive during the routine endoscopy. If you decline to participate, you will not have the AI-mHRME, Proflavine, and one normal area biopsy done during your upper endoscopy..

Subject Costs and Payments

Participating in this research will not incur any costs for you. The standard of care procedures, including the biopsy and endoscopy, are not covered by the study and will be billed to you and/or your insurance company. The study will cover the costs associated with the AI-mHRME and Proflavine Hemisulfate.

You will not receive any payment for participating in this study. Your involvement is entirely voluntary and aims to contribute to valuable medical research. If you have any questions or concerns about the financial aspects of the study, please feel free to talk with the study coordinator or your healthcare provider.

You will not be paid for taking part in this study.

Research Related Injury

All research activities will take place on-site in a hospital setting. In the event of any injuries, they will be managed according to the standard of care in a hospital setting.

If you experience an injury related to this study, the medical care you receive will be your responsibility or covered by your insurance, similar to any other medical care. The research team is committed to providing appropriate medical attention and managing adverse events following established medical practices. If you have any concerns or questions about this aspect of the study, feel free to discuss them with the study coordinator or your healthcare provider.

In the event of injury resulting from this research, Harris Health (Ben Taub Hospital) is not able to offer financial compensation nor to absorb the costs of medical treatment. However, necessary facilities, emergency treatment, and professional services will be available to you, just as they are for the general community.

Research personnel will try to reduce, control, and treat any complications from this research. If you are injured because of this study, you will receive medical care that you or your insurance will have to pay for just like any other medical care.

Subject's Rights

Your signature on this consent form means that you have received the information about this study and that you agree to volunteer for this research study.

You will be given a copy of this signed form to keep. You are not giving up any of your rights by signing this form. Even after you have signed this form, you may change your mind at any time. Please contact the study staff if you decide to stop taking part in this study.

If you choose not to take part in the research or if you decide to stop taking part later, your benefits and services will stay the same as before this study was discussed with you. You will not lose these benefits, services, or rights.

The investigator, MIMI TAN, and/or someone he/she appoints in his/her place will try to answer all of your questions. If you have questions or concerns at any time, or if you need to report an injury related to the research, you may speak with a member of the study staff: MIMI TAN at (713) 798-5987 during the day and (713) 798-1000 and ask for the gastroenterologist (GI doctor) on call after hours, and/or ADRIANNA MALIGA at 713-798-5987 after hours.

Members of the Institutional Review Board for Baylor College of Medicine and Affiliated Hospitals (IRB) can also answer your questions and concerns about your rights as a research subject. The IRB office number is (713) 798-6970. Call the IRB office if you would like to speak to a person independent of the investigator and research staff for complaints about the research, if you cannot reach the research staff, or if you wish to talk to someone other than the research staff.

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Signing this consent form indicates that you have read this consent form (or have had it read to you), that your questions have been answered to your satisfaction, and that you voluntarily agree to participate in this research study. You will receive a copy of this signed consent form.

Subject	Date
Investigator or Designee Obtaining Consent	Date
Witness (if applicable)	Date
Translator (if applicable)	Date