Advanced Gastrointestinal Endoscopic Imaging

NCT01034670

September 15, 2021

1. PURPOSE OF THE STUDY

a. Brief Summary

Develop new methods to detect and manage malignant and premalignant conditions of the gastrointestinal tract.

b. Objectives

Current endoscopy techniques cannot reliably differentiate between early premalignant conditions and normal mucosa. We hope to develop new techniques to improve this and will be combining macroscopic and microscopic imaging tools with molecular probes.

To improve visualization during the endoscopic procedure, we will be using an overtube (a sleeve that fits over the scope) and a cap (a small clear plastic cap that is attached to the tip of the endoscope). The physician performing the procedure will subjectively rate the stability of the endoscope tip and the quality of the visualization with the cap and overtube.

We also hope to assess techniques to better perform polypectomy (which is performed for the purpose of reducing risk of colorectal cancer). We will assess the utility of EverLift, which is a Submucosal Lifting Agent. EverLift has been FDA approved for the indication of endoscopic procedures for "submucosal lift of polyps, adenomas, early-stage cancers, or other gastrointestinal lesions prior to excision with snare or other appropriate endoscopic device." We will be assessing the ability to EverLift to provide adequate submucosal lift, in accordance with tis FDA indication. We will be using snare or other appropriate endoscopic devices to perform polypectomy, and will be assessing the completeness of excision of the polyps and adenomas.

We will also be including patients with active or recent COVID-19 to study whether the infection may have an impact. This will have importance in helping manage COVID-19 patients in the future. We will be looking for residual COVID DNA in biopsies in patients who have active or recent COVID-19.

c. Rationale for Research in Humans

There are no adequate animal endoscopy models to allow detection of premalignant endoscopic findings, and the molecular probes are being developed for human targets

such that cross reactivity with animal markers are unlikely. Cross reactivity with target molecules on mouse, and other animals. cells will be evaluated to see if there is a suitable animal model. There are also no effective animal endoscopy models that would allow real-time assessment of efficacy of polypectomy.

2. STUDY PROCEDURES

a. Procedures

Participants will be undergoing medically necessary endoscopy procedures or will be receiving regularly scheduled care in the gastroenterology or general surgery departments. Patients that are not undergoing medically necessary endoscopy procedures will have three tubes of blood (30ml) collected for the study and will not undergo any of the other portions of the protocol described below.

The remainder of the study will consist of additional imaging performed in conjunction with the regularly scheduled endoscopy during which the newer imaging techniques will be used to detect premalignant conditions. This will include wide field fluorescence, microscopy, Ramanspectroscopy, computerized image analysis, and/or ultrasound. In addition, two or three tubes of blood (20-30 ml) will be collected from study subjects.

For the wide field fluorescence we will use an Olympus endoscope that can operate in the white light mode like a standard endoscope, and in a fluorescence mode where the input light is filtered as is the collected light. This exam will not require an additional endoscope.

If a polyp is removed as part of routine clinical care during the endoscopy procedure, we will add tranexamic acid to the injection fluid that is used to facilitate the polyp removal in half of the cases. This will allow us to assess whether the tranexamic acid improves imaging by eliminating trace amounts of bleeding at the polyp site.

If a polyp <=3mm is to be removed as part of routine clinical care during the endoscopy procedure, we will remove half of the polyps using cold biopsy forceps and the other half using cold snare. Biopsies will be performed at the margins of the polypectomy site. This will allow us to assess whether cold biopsy forceps or cold snare is more effective at adequately removing polyps. While biopsies are routinely performed in clinical practice to check for completeness of resection, the biopsies performed at the margins of the polypectomy site are done for research purposes. However, biopsies of the margins are of minimal increased risk.

If a polyp >3mm is to be removed as part of routine clinical care during the endoscopy procedure, we will remove half of the polyps using an submucosal injection agent (EverLift) and the other half of the polyps without a submucosal injection agent. EverLift will be used to provide submucosal lift of the polyp or gastrointestinal lesion prior to excision with snare or other appropriate endoscopic device, as consistent with its FDA approval. Biopsies will be performed at the margins of the polypectomy site. This will allow us to assess whether using an injection agent increases the completeness of polyp resection as well as improve intra-procedural hemostasis. While biopsies are routinely

performed in clinical practice to check for completeness of resection, the biopsies performed at the margins of the polypectomy site are done for research purposes. However, biopsies of the margins are of minimal increased risk.

For the Raman spectroscopy we will put a Raman fiber optic scope into the instrument channel of an Olympus endoscope. This procedure will only use a single endoscope.

This Raman scope is deployed like any other instrument that fits into the channel of the endoscope. But since we will need to biopsy the tissues after Raman spectroscopic examination, the procedure will take more time as we put the Raman scope into the endoscope, remove it and put the biopsy forceps into the channel. The Raman spectroscopic imaging will involve using a 785 nm laser with a 1mm spot size. We have calculated the maximum permissible exposure to the tissue and we will be using a low power laser illumination that is under the maximum permissible exposure to tissue as recommended by the ANSI standards. Additionally, a safety mechanism is in place where the laser illumination is controlled through a shutter that can only be opened while acquiring spectra with the acquisition software we intend to use to operate our device.

For the microendoscopy we will put a minimicroscope, also called aminiprobe, into the instrument channel of an Olympus endoscope. This procedure will also use only a single endoscope. These minimicroscopes are deployed like any other instrument that fits into the channel of the endoscope. But since we will need to biopsy the tissues after microscopic examination, the procedure will take more time as we put the microscope into the endoscope, remove it and put the biopsy forceps into the channel.

As part of this program we will be developing miniaturized ultrasound systems. As these are developed and we can better describe them to the IRB, we will amend our protocols with sufficient detail that the panel can review these instruments. No experimental ultrasound will be performed until we have approval for these new tools from the IRB.

We will use an overtube (a plastic sleeve that fits over the scope)and a cap (a small clear plastic piece fitted to the end of the endoscope)to stabilize the endoscope tip during the procedure. The physician performing the procedure will rate the stability of the endoscope tip with the cap and overtube.

When endoscopic biopsies are performed for clinical purposes during the endoscopy, a portion of the biopsy material will also be analyzed using the microscope and biomarker assays like western blots or immunohistochemistry or immunofluorescence imaging.

We intend to take one biopsy of normal tissue per study that the patient enrolls in. The physician, Shai Friedland will take a biopsy using the same standard procedures for taking tissues for biopsy when taking tissue samples for histological assessment. The additional tissue collected will impact the study by determining what useful targeting biomarkers are generally overexpressed in normal vs tumor areas. The tissues will be evaluated for various biomarkers overexpressed on normal vs tumor tissue. This will be very important in helping us determine how to better target these tumors in the future.

We will also be including patients with active or recent COVID-19 to study whether the infection may have an impact. We will be looking for residual COVID DNA in biopsies in patients who have active or recent COVID-19. This will have importance in helping manage COVID-19patients in the future.

b. Procedure Risks

The participants will have their regularly scheduled endoscopy procedures and the research component will consist of an additional 5-15 minutes during which the advanced imaging techniques will be used to attempt to detect premalignant lesions. The new imaging tools are either developed by companies that make ultrasound equipment (wide field fluorescence by Olympus) and involve only slight modifications to existing systems, or they are microscopes designed for clinical use

c. Use of Deception in the Study

No deception

d. Use of Audio and Video Recordings

Endoscopy videos will be obtained. There will be no patient-identifying information on these videos. The videos may be shown at scientific meetings and will be kept as part of the study data.

e. Alternative Procedures or Courses of Treatment

The alternative is not to participate. In this case only the standard medically indicated endoscopic procedure will be performed.

f. Will it be possible to continue the more (most) appropriate therapy for the participant(s) after the conclusion of the study?

Yes. All patients will continue to receive their appropriate medical therapy.

g. Study Endpoint(s)

The study duration is limited to the endoscopic procedure.

3. BACKGROUND

a. Past Experimental and/or Clinical Findings

Prior studies by our group and others have shown that it may be possible to detect premalignant lesions using optical probes that selectively enhance the signal tumors of the GI.

b. Findings from Past Animal Experiments

Prior animal experiments have demonstrated that optical detection techniques during endoscopy are feasible.

4. RADIOISOTOPES OR RADIATION MACHINES

N/A

5. DEVICES USED IN THE STUDY

a. Investigational Devices (Including Commercial Devices Used Off-Label)

Investigational Device 1	
Name:	Dual axis endoscopic microscope
Description:	This is a device that is used in the accessory port of a standard endoscope and allows visualization of microscopic areas of mucosa.
Significant Risk? (Y/N)	No
Rationale for Non-Significant Risk	low level of light that does not pose a significant risk to tissue
Investigational Device 2	
Name:	Wide field fluorescence system
Description:	This is a modification to the existing narrow band endoscope from Olympus that incorporates different filters on the source and collecting optics to enable fluorescence imaging. It is used as is a standard endoscope.
Significant Risk? (Y/N)	No
Rationale for Non-Significant Risk	This instrument is much like a standard endoscope and is used in the same way. The only difference is that the emission and excitation sources are filtered to enable fluorescence imaging.
Investigational Device 3	
Name:	Raman Endoscope
Description:	This is a device that is used in the accessory port of a standard endoscope and allows visualization of the chemical components intrinsic to the tissue, and any FDA approved dyes that are routinely administered during endoscopy.
Significant Risk? (Y/N)	No
Rationale for Non-Significant Risk	The device operates similarly to the other devices that have already been used in humans under this IRB protocol as it is being sent through the accessory channel of an endoscope. Low levels of light that do not pose a significant risk to tissue will be used. Additionally we have installed a shutter that only allows the light from the probe to illuminate the tissue area during spectral acquisition as an additional safety precaution.
Investigational Device 3	
Name:	Dynamically digitizing overtube
Description:	This is a flexible sleeve that fits over the endoscope. After advancing the endoscope to the appropriate position, application of vacuum to the overtube makes it more rigid so that the endoscope tip is stabilized.
Significant Risk? (Y/N)	No
Rationale for Non-Significant Risk	The risk of trauma to the digestive organs or other adverse events from overtube use is very low (< 0.5%).
Investigational Device 3	
Name:	Endovigilant CAD
Description:	Deep learning-based image analysis software for analyzing endoscopy images
Significant Risk? (Y/N)	No
Rationale for Non-Significant Risk	Image analysis software does not pose a significant risk to patients undergoing endoscopic procedure
Investigational Device 3	
Name:	Pathfinder Endoscope Cap
Description:	This is a short transparent single-use plastic cap that is placed at the tip of the endoscope to improve visualization. Caps are commonly used in endoscopic procedures. The Pathfinder Endoscope cap is very similar in design to existing FDA-cleared caps that are commonly used but is made of a slightly thinner plastic to allow it to fit through the Pathfinder Overtube. We believe this does not significantly change the risk The risk of bleeding or perforation from using a cap is <1 in 5000.
Significant Risk? (Y/N)	No
Rationale for Non-Significant Risk	Endoscope caps are widely used during endoscopy to improve visualization. They are known to pose non-significant risk. They are not

	intended as an implant not are they used in supporting or sustaining human life. The use of these caps does not pose a serious risk to the health, safety, or welfare of a subject

b. IDE-Exempt Devices

IND-Exempt Device 1	
Name:	CellVizio
Description:	Minimicroscope--this is an FDA approved fiber-based microscope that we will use according to the manufacturers protocols.
IND-Exempt Device 2	
Name:	EverLift
Description:	We will assess the utility of EverLift, which is a Submucosal Lifting Agent. EverLift has been FDA approved for the indication of endoscopic procedures for "submucosal lift of polyps, adenomas, early-stage cancers, or other gastrointestinal lesions prior to excision with snare or other appropriate endoscopic device." It is similar to other submucosal lifting agents on the market such as Eleview. The ingredients are primarily methylene blue and hydroxyethyl cellulose. Methylene blue is commonly used in endoscopic procedures. Given the similarities to the predicate device (Eleview), it is felt to have similar safety profile. We will be using EverLift in accordance to its indication as written above (taken from the FDA approval documentation).

6. DRUGS, BIOLOGICS, REAGENTS, OR CHEMICALS USED IN THE STUDY

a. Investigational Drugs, Biologics, Reagents, or Chemicals

N/A

b. Commercial Drugs, Biologics, Reagents, or Chemicals

Commercial Product 1	
Name:	tranexamic acid
Dosage:	100mg

7. DISINFECTION PROCEDURES FOR MEDICAL EQUIPMENT USED ON BOTH HUMANS AND ANIMALS

N/A

8. PARTICIPANT POPULATION

a. Planned Enrollment

1,000 patients at VA Palo Alto and 100 patients at Stanford will have a variety of cancers (esophagus, stomach, colon) and premalignant conditions (polyps, etc.) of the esophagus, stomach and colon. Up to 1/2 of the patients will be normal. We plan to compare the imaging results in normal patients, patients with premalignant conditions and patients with gastrointestinal cancers.

In addition, up to 50 patients at VA Palo Alto and 50 patients at Stanford who are treated in the gastroenterology and surgery departments will be enrolled for just the blood draw component of the study.

We will also be including patients with active or recent COVID-19 to study whether the infection may have an impact. We will be looking for residual COVID DNA in biopsies in patients who have active or recent COVID-19. This will have importance in helping manage COVID-19 patients in the future.

b. Age, Gender, and Ethnic Background

Age 18+, both genders and all ethnic backgrounds.

c. Vulnerable Populations

No vulnerable subjects

d. Rationale for Exclusion of Certain Populations

Children are not included because the endoscopy units only serve adult patients

e. Stanford Populations

N/A

f. Healthy Volunteers

N/A

g. Recruitment Details

Patients who are scheduled for endoscopy by one of the investigators will be asked if they are interested in participating in the study.

In addition, patients treated in the gastroenterology and surgery departments who have undergone endoscopy by one of the investigators will be asked if they are interested in participating in the blood draw component of the study.

h. Eligibility Criteria

i. Inclusion Criteria

The study will be open to all patients undergoing endoscopy that do not have exclusion criteria.

ii. Exclusion Criteria

Patients with unstable vital signs will not be included.

i. Screening Procedures

Patients scheduled for endoscopy by one of the investigators will be asked if they would like to participate in the study. If they are interested, then they will be enrolled.

j. Participation in Multiple Protocols

We will ask all patients if they are participating in any other studies. If they are participating in any other study then we will ask them for more information to determine

whether there could be any harm from participating in both studies and if there is then they will not be enrolled.

k. Payments to Participants

no payment

l. Costs to Participants

no costs

m. Planned Duration of the Study

We expect the total study duration would be 17 years.

The study will take 5-15 minutes during the regularly scheduled endoscopy.

Analysis of data will take approximately 2 years.

9. RISKS

a. Potential Risks

i. Investigational devices

There is a very low (< 1 in 5000) risk of perforation of the gastrointestinal tract and a low (< 1 in 1000) risk of bleeding from operating the investigational microscope device during endoscopy. The nano-devices pose little to no risk as they are composed of inert gold and are cleared from the body within 24 hours therefore qualifying as a non-implant and there is no evidence of them crossing over into the circulation after extensive animal studies (see attached papers sent to Anastasia Doherty).There is a very low(<1 in 5000) of perforation or bleeding from the Pathfinder Endoscope Cap used in the study.

ii. Investigational drugs

There is a very low (< 1 in 5000) risk of an allergic reaction to tranexamic acid. The risk of other adverse events such as infection or thrombosis are very low with submucosal injection as performed in the study.

iii. Commercially available drugs, biologics, reagents or chemicals

N/A

iv. Procedures

There is a very low (< 1 in 5000) risk of perforation of the gastrointestinal tract and a low (< 1 in 1000) risk of bleeding during the study portion of the endoscopy.

There is a very low risk of an adverse event from the blood draw (< 1 in 1000).

There is a very low risk of an adverse event from biopsies of resection site (<1 in 1000 risk of bleeding, <1 in 1000 risk of infection). There is a very low risk of adverse event from polypectomy of a small polyp - there is no evidence to suggest either technique

(cold snare or cold biopsy) is safer than the other. There is also no evidence to suggest either technique (submucosal lift versus no submucosal lift) influences the safety of the procedure.

v. Radioisotopes/radiation-producing machines

N/A

vi. Physical well-being

With the exception of the rare potential complications described above, we do not expect any harm to the participants' physical well-being.

vii. Psychological well-being

The patients are sedated during their medically-necessary endoscopy procedures and we do not expect any harm to their psychological health.

viii. Economic well-being

no expected effect

ix. Social well-being

no expected effect

x. Overall evaluation of risk

Low

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b. International Research Risk Procedures

N/A

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c. Procedures to Minimize Risk

All of the patients undergo continuous vital signs monitoring by trained endoscopy nurses during the procedure. They are monitored continuously during the procedure and during recovery for any evidence of complications.

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d. Study Conclusion

The study will be completed during the endoscopy procedure.

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e. Data Safety Monitoring Plan (DSMC)

i. Data and/or events subject to review

Complications from the endoscopy, including any complications that could potentially be due to the study.

ii. Person(s) responsible for Data and Safety Monitoring

The investigators and protocol director will be responsible for monitoring the data.

iii. Frequency of DSMB meetings

Possible adverse events will be reviewed daily.

iv. Specific triggers or stopping rules

If any adverse events occur, the protocol will be suspended until the PD investigates the event and determines whether or not it is related to the study.

v. DSMB Reporting

The PD will inform the IRB if any adverse events relating to the study occur.

vi. Will the Protocol Director be the only monitoring entity? (Y/N)

Yes

f. Risks to Special Populations

N/A

10. BENEFITS

This study will potentially improve our ability to detect (and therefore treat) premalignant and malignant disorders of the GI tract.

11. PRIVACY AND CONFIDENTIALITY

All participant information and specimens are handled in compliance with the Health Insurance Portability and Accountability Act (HIPAA) and privacy policies of Stanford University, Stanford Health Care, and Stanford Children's Health.