Protocol Title:	Early feasibility study of endoscopic optical coherence tomography for screening and diagnosis of colorectal precancerous and malignant polyps
NCT#:	NCT05179837
Version:	05/31/2023

Early feasibility study of endoscopic optical coherence tomography for screening and diagnosis of colorectal precancerous and malignant polyps

Washington University School of Medicine
Division of Gastroenterology
660 South Euclid Avenue, Campus Box 8124
St. Louis, MO 63110

Protocol #: 202103151
Version Date: 31 May 2023

Principal Investigator: **Vladimir Kushnir, M.D.**
Phone: (314) 362-3685
E-mail: vkushnir@wustl.edu

Sub-Investigators	**Modality**
Quing Zhu, Ph.D.	Biomedical Engineering
Vladimir Lamm, M.D.	Gastroenterology
Esther Lu (Jingxia Liu), M.S, Ph.D.	Biostatistics

Study Device: Optical coherence tomography (OCT) probe
NCT#: Pending
Funded by: Departmental funds

STATEMENT OF COMPLIANCE

The trial will be carried out in accordance with International Conference on Harmonisation Good Clinical Practice (ICH GCP) and the following:

- United States (US) Code of Federal Regulations (CFR) applicable to clinical studies (45 CFR Part 46, 21 CFR Part 50, 21 CFR Part 56, 21 CFR Part 312, and/or 21 CFR Part 812)

National Institutes of Health (NIH)-funded investigators and clinical trial site staff who are responsible for the conduct, management, or oversight of NIH-funded clinical trials have completed Human Subjects Protection and ICH GCP Training.

The protocol, informed consent form(s), recruitment materials, and all participant materials will be submitted to the Institutional Review Board (IRB) for review and approval. Approval of both the protocol and the consent form must be obtained before any participant is enrolled. Any amendment to the protocol will require review and approval by the IRB before the changes are implemented to the study. In addition, all changes to the consent form will be IRB-approved; a determination will be made regarding whether a new consent needs to be obtained from participants who provided consent, using a previously approved consent form.

Table of Contents

PROTOCOL SUMMARY

Title:	Early feasibility study of endoscopic optical coherence tomography for screening and diagnosis of colorectal precancerous and malignant polyps.
Study Description:	Colorectal cancer arises from the mucosal layer of the colon. Current screening is performed by flexible endoscopy, which involves visual inspection of the mucosal lining of the colon and rectum with an optical camera mounted on the endoscope, with abnormal areas being biopsied. This method is somewhat limited in that there are no readily available surface pattern or morphological classification systems with adequate sensitivity or specificity to evaluate extent of submucosal invasion (deep, superficial, or none). Optical coherence tomography (OCT) using pattern recognition is a high-resolution imaging modality. There is currently an unmet need to predict depth of invasion for colonic tumors to decide on applicability of endoscopic (endoscopic submucosal dissection or endoscopic mucosal resection) vs. surgical therapy. Our hypothesis is that OCT will have a higher diagnostic accuracy for determining depth of submucosal invasion compared to existing modalities. We will first aim to assess the procedural feasibility and safety of using an OCT probe during routine colonoscopy with an early feasibility study. This study will identify appropriate modifications to the device and help with development of subsequent clinical study protocols. The eventual goal is to assess the diagnostic accuracy of OCT imaging for predicting depth of invasion of colonic tumors.
Objectives:	Primary Objective: To demonstrate the procedural feasibility of OCT during routine colonoscopy. Secondary Objective: • To describe the safety of the OCT probe during routine colonoscopy. • To evaluate the quality of OCT images using a machine learning algorithm. • To explore the diagnosis agreement between OCT imaging and pathology when a lesion is biopsied.
Endpoints:	Primary Endpoint: Whether a lesion can be adequately evaluated with OCT within 5 minutes during a standard of care colonoscopy. Secondary Endpoints: • Adverse events related to OCT imaging during routine colonoscopy. • Whether OCT image is successfully captured using machine learning algorithm.

	• Weighted kappa
Study Population:	Fifty-four adults undergoing standard of care colonoscopy for the evaluation of colonic polyps will be enrolled in this study.
Phase:	N/A
Description of Sites / Facilities Enrolling:	This study will enroll patients at Washington University School of Medicine.
Description of Study Intervention:	The OCT probe (Section 12, Figure 1) is attached to an approximately 3-meter wire that is attached to the OCT fiber probe system setup. This setup consists of a power supply unit, and a control platform that controls fiber probe rotation and retraction. The OCT probe will be advanced through the colonoscope instrument channel (Section 12, Figure 2).
Study Duration:	12 months (enrollment) + 1 day (participation) + 2 days (follow-up) + 6 months (analysis)
Participant Duration:	3 days

1.0 INTRODUCTION

1.1 Study Rationale

Endoscopic submucosal dissection (ESD) and endoscopic mucosal resection (EMR) are used to treat superficial colorectal neoplasms but are contraindicated by deeply invasive colorectal cancer. Estimating depth of invasion is crucial to guiding treatment strategies. Current methods for estimating this depth are not readily available, expensive, or lack accuracy. There have been no in vivo studies using optical coherence tomography to differentiate between different types of polyps. We would like to determine the procedural feasibility and safety of using an optical coherence tomography (OCT) probe for evaluation of colonic polyps during routine colonoscopy.

If this feasibility study is successful we will then plan a study of patients with large complex polyps referred for EMR or ESD to Washington University, where we would evaluate the accuracy of the OCT probe for determining depth of submucosal invasion.

1.2 Background

1.2.1 Colonoscopy Polyp Detection Rate and Adenoma Detection Rate

Guidelines support performance targets for adenoma detection rate of 25% for a mixed gender population (20% in women and 30% in men). Polyp detection rate (PDR) and adenoma detection rate (ADR) increase with age, with one study showing a PDR/ADR ratio of 16.9%/6.3% for patients in their 20s, 33%/14.0% for patients in their 30s, 43.5%/28.7% for patients in their 40s, 54.3%/38.4% for patients in their 50s, 61.2%/46.2% for patients in their 60s, 68.7%/55.8% for patients in their 70s, and 65.9%/56.1% for patients in their 80s ($P < 0.001$) [1]. Polyp detection rate is relevant for patient selection. Because we want to maximize the chance that a patient will have a polyp (hyperplastic, adenoma, etc.) that OCT can image, inclusion criteria will include age 40 years or older.

1.2.2 Diagnostic Accuracy of Depth of Invasion

Being able to differentiate between deep (> 1mm) and superficial (<1 mm) submucosal is a crucial branch point in clinical decision making. Deep submucosal invasion carries an 8-23% risk of lymph node metastasis. These lesions should be referred to surgery. On the other hand, if a lesion has superficial submucosal invasion and the endoscopist completes "en bloc" resection with EMR or ESD, then this is considered curative. While NICE 3 classification (Section 12, Figure 3) has up to a 94% accuracy for lesions with deep submucosal invasion, there are no readily available surface pattern or morphological classification systems with adequate sensitivity or specificity for superficial submucosal invasion [2]. Increasing diagnostic accuracy for lesions with superficial submucosal invasion would aid in the decision-making process of whether or not to refer a patient with a suspicious polyp to colorectal surgery or for endoscopic therapy.

Current options for estimation of invasion depth include gross features on endoscopy, narrow band imaging, magnifying chromoendoscopy, endoscopic ultrasonography, endocytoscopy, and confocal laser endomicroscopy. The only modality in widespread use is narrow band imaging, which does not require the use of magnification or dye spray.

Narrow band imaging using the NICE classification is limited in identifying superficial submucosal invasion. JNET (Section 12, Figure 4) was formed to help better differentiate between low grade intramucosal neoplasia and superficial submucosal invasion. This classification has an accuracy of <80% for lesions with superficial submucosal invasion and requires magnifying chromoendoscopy, which is not readily available [3]. Endoscopic ultrasonography is comparable to magnifying chromoendoscopy with neither modality having sufficient diagnostic accuracy for depth of invasion [4].

1.2.3 Optical Coherence Tomography (OCT)

In prior work, several research groups have demonstrated promising results that suggest OCT, an established high resolution imaging modality [5,6,7], may address the shortcomings of traditional camera endoscopy in the upper gastrointestinal tract [8,9,10] or large intestine [11,12,13]. OCT has been shown to accurately differentiate abnormal from normal tissue in multiple organs as an “optical biopsy” tool [14,15,16] in both murine and human colorectal models [17,18,19,20]. However, clinical application of the technology is complicated by the large volume of data generated and the subtle qualitative differences between normal and abnormal tissue.

The success of convolutional neural networks (CNN) in computer vision tasks has popularized deep learning for CAD imaging [21,22,23]. CNNs have successfully been applied to OCT images for ophthalmological, esophageal, and cardiac diseases [24,25,26]. Moreover, CNN has also been applied to colon cancer diagnostics in an image classification [27,28,29].

The Zhu lab reported the use of pattern-recognition OCT(PR-OCT) in differentiating normal from neoplastic colorectal tissue (Section 12, Figure 5). Using RetinaNet, a novel neural network architecture for pattern recognition tasks, a dentate structural pattern was used as a structural marker of normal specimens and in PR-OCT prediction. This method leverages the recent advancement in object detection, which localizes and classifies the diagnostic features at real-time, and achieves an accurate classification result. This initial study demonstrated the feasibility of using PR-OCT as an "optical biopsy" tool to assist physicians in real-time for mucosal neoplasms screening [30].

The current OCT system developed by Zhu et al has so far been tested on a limited number of specimens in an ex-vivo study using specimens collected after surgical

resection (16 normal, 2 adenomatous polyps, 4 treated areas (2 complete responders, 2 non-responders). Using OCT and training this input with deep learning, the Zhu lab achieved a sensitivity and specificity of 100% and 99.7%, respectively for normal vs cancerous tissue in an ex-vivo model.

Currently, there are limited studies that focus on determining sensitivity and specificity of OCT for evaluation of different types of polyps. Further, there are no studies using this technology in real time for colorectal cancer screening.

1.3 Study Design

1.3.1 Overall Design

This is a one-arm non-blinded study to investigate the feasibility of an OCT probe for the patients undergoing routine screening or surveillance colonoscopy. Time added to length of overall procedure will serve as a surrogate endpoint towards evaluating ease of procedure for the endoscopist and endoscopy staff. We expect to find polyps in the enrolled patients. One polyp per patient will be imaged. A population of patients undergoing routine colonoscopy on the 8th floor of Center for Advanced Medicine will be targeted. The duration of each patient's participation will last from the time of screening to 48 hours after the colonoscopy to evaluate for adverse events.

Patients will be screened for the study prior to undergoing routine colonoscopy. The OCT probe system setup will be placed in a pre-determined room in the GI endoscopy suite on 8th floor of Center for Advanced Medicine. Once a polyp is found (hyperplastic, adenoma, or malignant appearing), the OCT probe will be advanced through the channel of the colonoscope. Image capture is expected to take around 3 minutes. We will have a goal of imaging one polyp per patient. If no polyps are found then the OCT probe will be used to image an area of normal colonic mucosa.

1.3.2 Scientific Rationale for Study Design

Our goal is to assess feasibility of using OCT probe during routine colonoscopy. Therefore, we are going to screen patients 40 years of age or older for inclusion in this study because these patients have a higher chance of having polyps that can be imaged. Because we are assessing the feasibility of a new device, there will be no blinding or randomization. The secondary objective of correlating OCT images with pathology is exploratory in nature.

1.4 Risk/Benefit Assessment

1.4.1 Known Potential Risks

Known potential risks include added procedure sedation time as a result of OCT

imaging. We expect each polyp to be imaged within the span of 3 minutes and do not expect adding more than 5 minutes to total procedure time. Risk of infection and bleeding is <1% in standard of care colonoscopy. We don't expect the OCT probe to increase these risks. A table of common adverse events during a routine colonoscopy (with rates in percentages) is presented below. Adverse event rates in this study will be compared to the historic AE rates from this table.

Adverse Events 30 days After Outpatient Screening or Follow-Up Colonoscopy [31]

	Screening	Surveillance	No Polypectomy	Polypectomy
Death	0.03%	0.06%	0.02%	0.05%
Perforation	0.04%	0.12%	0.03%	0.07%
Hemorrhage	0.27%	0.38%	0.08%	0.50%
Diverticulitis	0.18%	0.22%	0.18%	0.20%
Abdominal pain	2.64%	2.21%	2.62%	2.56%
Any serious adverse event*	0.47%	0.68%	0.27%	0.74%
Hospitalizations	1.11%	1.61%	0.94%	1.43%
Emergency Department or Urgent Care Visit	2.26%	3.01%	2.23%	2.47%

*Serious adverse events include perforation, hemorrhage, or diverticulitis.

1.4.2 Known Potential Benefits

There is no direct benefit to the patient. We hope that this feasibility study will answer the question of whether or not this OCT probe is feasible in routine colonoscopy. This may lead to another study of assessing the diagnostic accuracy of the OCT probe.

1.4.3 Assessment of Potential Risks and Benefits

OCT is an older technology used by many research groups and commercially in eye clinics. The probe is made by Dr. Zhu's lab. We anticipate that the potential benefits outweigh the minimal risks.

2.0 OBJECTIVES AND ENDPOINTS

Objectives	Endpoints
Primary	
To demonstrate the procedural feasibility of OCT during routine colonoscopy	Whether a lesion can be adequately evaluated with OCT within 5 minutes during a standard of care colonoscopy.
Secondary	
To describe safety of OCT probe during routine colonoscopy	Adverse events related to OCT imaging during routine colonoscopy
To evaluate the quality of OCT images using a machine learning algorithm.	Whether OCT image is successfully captured using machine learning algorithm
To explore the diagnosis agreement between OCT imaging and pathology when a lesion is biopsied.	Weighted kappa

3.0 STUDY POPULATION

3.1 Inclusion Criteria

1. Undergoing standard of care colonoscopy for the evaluation of colonic polyps.

2. At least 40 years of age.

3. Ability to understand and willingness to sign an IRB approved written informed consent document (or that of legally authorized representative, if applicable).

3.2 Exclusion Criteria

1. Pregnant and/or breastfeeding.

2. Unable to tolerate sedation.

3.3 Inclusion of Women and Minorities

Both men and women and members of all races and ethnic groups are eligible for this trial.

4.0 REGISTRATION PROCEDURES

Patients must not start any protocol intervention prior to registration through the Siteman Cancer Center.

The following steps must be taken before registering patients to this study:

1. Confirmation of patient eligibility
2. Registration of patient in the Siteman Cancer Center database
3. Assignment of unique patient number (UPN)

4.1 Confirmation of Patient Eligibility

Confirm patient eligibility by collecting the information listed below:

1. the registering MD's name
2. Patient's race, sex, and DOB
3. Three letters (or two letters and a dash) for the patient's initials
4. Copy of signed consent form
5. Completed eligibility checklist, signed and dated by a member of the study team
6. Copy of appropriate source documentation confirming patient eligibility

4.2 Patient Registration in the Siteman Cancer Center OnCore Database

All patients must be registered through the Siteman Cancer Center OnCore database.

4.3 Assignment of UPN

Each patient will be identified with a unique patient number (UPN) for this study. All data will be recorded with this identification number on the appropriate CRFs.

4.4 Screen Failures

Screen failures are defined as participants who consent to participate in the clinical trial but are not subsequently entered in the study. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants, to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any serious adverse event (if applicable).

5.0 STUDY PROCEDURES

5.1 Recruitment

Adult patients scheduled to undergo a routine colonoscopy for screening or surveillance of colon polyps, evaluation of GI bleeding, post-colon cancer resection surveillance, or reassessment of prior colon polyp will be screened for the study. Patients will be identified as candidates for the study from the BJH Surgery schedule the day before they come in. One of the investigators or a research assistant will discuss the study with potential participants in the pre-endoscopy area. Those subjects who qualify for the study based on eligibility criteria will be invited to participate. The consent process will take place in the

pre-endoscopy area. Those patients who wish to participate will sign the informed consent document and proceed to colonoscopy.

5.2 Study Procedures

After consent, the endoscopist will perform a standard of care colonoscopy. We will enroll 54 participants in the study and expect approximately 40 of these participants to have polyps. If a polyp is found, then OCT will be used to image that polyp. Patients with polyps, regardless of number found, will have either one tubular adenoma (NICE type 2) imaged OR one hyperplastic polyp (NICE type 1) imaged. These polyps can be distinguished endoscopically using the NICE classification (see Section 12, Figure 1). If no polyps are found, then one area of normal mucosa will be imaged. We will have a goal of imaging an equal number of tubular adenomas and hyperplastic polyps. We will have a running log of the number of imaged tubular adenomas and hyperplastic polyps imaged to ensure that equal amounts of each type are imaged. If on the rare chance a malignant appearing colonic tumor (NICE type 3) is found, this and no other polyps will be imaged with OCT.

Duration of using OCT probe as well as duration of the colonoscopy will be kept by endoscopy staff with a stopwatch. Initiation of colonoscopy will be time 00:00. There will then be time marks for initiation of OCT imaging, end of OCT imaging, and end of colonoscopy. In this way, the exact duration of OCT and the full duration of colonoscopy with OCT will be captured.

Duration of OCT imaging will be from the time of guiding the OCT probe through the colonoscope to imaging, and withdrawal of OCT probe. The maximum time allotted to obtain OCT imaging will be 10 minutes. Any OCT imaging that reaches the 10-minute mark will be stopped so that routine colonoscopy can resume. A log of total procedure duration is kept for every standard of care colonoscopy.

When a polyp or area of normal mucosa to be examined with OCT is identified, the location of the area imaged will be documented (sigmoid, descending colon, transverse colon, ascending colon, cecum, etc.) by a registered nurse. The OCT catheter probe will be guided through the instrument channel of the colonoscope with the colonoscope still in the patient. This will take under approximately 5 seconds. The OCT probe will then be moved to make contact with the mucosa. The probe will then take several hundred high-resolution images of the lesion, with an expected duration of 2-3 minutes. During this time, the endoscopist will maintain view of the lumen and/or polyp. After completion of OCT imaging, the OCT probe will be removed, which will take approximately under 5 seconds. Colonoscopy will then resume to complete a full routine examination.

All procedures will be performed by a gastroenterologist experienced in advanced imaging techniques or by a fellow under direct supervision.

There will be a toxicity assessment at baseline and at the observation period after colonoscopy. Patients will also be contacted by phone approximately 48 hours after colonoscopy to collect information on any AEs experienced.

The standard of care pathology report for any area biopsied will be accessed from the medical record when available in order to compare the pathological findings with the diagnosis determined by OCT imaging.

5.3 Definitions of Evaluability

A patient must have had at least one colonic polyp or area of normal mucosa selected for OCT imaging in order to be evaluable for the feasibility endpoint. Any patient who does not have any area of mucosa imaged by OCT (either due to poor bowel prep, anesthesia complications, etc.), will be considered inevaluable for the feasibility endpoint and will be replaced.

All patients who undergo colonoscopy using the OCT probe are evaluable for toxicity and evaluation of imaging quality. Patients are evaluated for AEs from time of colonoscopy until 48 hours after colonoscopy.

6.0 REGULATORY AND REPORTING REQUIREMENTS

The entities providing oversight of safety and compliance with the protocol require reporting as outlined below. Please refer to Appendix A for definitions and Appendix B for a grid of reporting timelines.

Adverse events will be tracked from time of colonoscopy through 48 hours after end of colonoscopy. All adverse events must be recorded on the toxicity tracking case report form (CRF) with the exception of:

- Baseline adverse events, which shall be recorded on the medical history CRF

Refer to the data submission schedule in Section 7 for instructions on the collection of AEs in the EDC.

Reporting requirements for Washington University study team may be found in Section 6.1.

6.1 WU PI Reporting Requirements

6.1.1 Reporting to the Human Research Protection Office (HRPO) at Washington University

Reporting will be conducted in accordance with Washington University IRB Policies.

Pre-approval of all protocol exceptions must be obtained prior to implementing the change.

6.1.2 Reporting to the Quality Assurance and Safety Monitoring Committee (QASMC) at Washington University

The PI (or designee) is required to notify the QASMC of any unanticipated problems involving risks to participants or others occurring at WU or any BJH or SLCH institution that has been reported to and acknowledged by HRPO. (Unanticipated problems reported to HRPO and withdrawn during the review process need not be reported to QASMC.)

QASMC must be notified within **10 days** of receipt of IRB acknowledgment via email to qasmc@wustl.edu. Submission to QASMC must include the myIRB form and any supporting documentation sent with the form.

6.2 Exceptions to Expedited Reporting

Events that do not require expedited reporting as described in Section 6.1 include:

- planned hospitalizations
- hospitalizations < 24 hours
- respite care
- events related to disease progression

Events that do not require expedited reporting must still be captured in the EDC.

7.0 DATA SUBMISSION SCHEDULE

Case report forms with appropriate source documentation will be completed according to the schedule listed in this section.

Case Report Form	Submission Schedule
Original Consent Form	Prior to registration
On-Study Form Medical History Form	Prior to colonoscopy
Colonoscopy Procedure Form OCT Data Form	Following colonoscopy
Toxicity Form	Baseline Post-colonoscopy observation period 48 hours following colonoscopy

7.1 Adverse Event Collection in the Case Report Forms

All adverse events that occur beginning with colonoscopy (minus exceptions defined in Section 6.0) must be captured in the Toxicity Form. Baseline AEs should be captured on the Medical History Form.

8.0 SCHEDULE OF ACTIVITIES

	Screening	Colonoscopy	48 hours after colonoscopy
Informed consent	X		
Pregnancy test[1]		X	
Colonoscopy		X	
AE monitoring		X	X

1. Women of childbearing potential only

9.0 DATA AND SAFETY MONITORING

In compliance with the Washington University Institutional Data and Safety Monitoring Plan, the Principal Investigator will provide a Data and Safety Monitoring (DSM) report to the Washington University Quality Assurance and Safety Monitoring Committee (QASMC) semi-annually beginning six months after accrual has opened (if at least one patient has been enrolled) or one year after accrual has opened (if no patients have been enrolled at the six-month mark).

The Principal Investigator will review all patient data at least every six months, and provide a semi-annual report to the QASMC. This report will include:

- HRPO protocol number, protocol title, Principal Investigator name, data coordinator name, regulatory coordinator name, and statistician
- Date of initial HRPO approval, date of most recent consent HRPO approval/revision, date of HRPO expiration, date of most recent QA audit, study status, and phase of study
- History of study including summary of substantive amendments; summary of accrual suspensions including start/stop dates and reason; and summary of protocol exceptions, error, or breach of confidentiality including start/stop dates and reason
- Study-wide target accrual and study-wide actual accrual
- Protocol activation date
- Average rate of accrual observed in year 1, year 2, and subsequent years
- Expected accrual end date
- Objectives of protocol with supporting data and list the number of participants who have met each objective
- Early stopping rules with supporting data and list the number of participants who have met the early stopping rules
- Summary of toxicities
- Abstract submissions/publications
- Summary of any recent literature that may affect the safety or ethics of the study

The study principal investigator and Research Patient Coordinator will monitor for serious toxicities on an ongoing basis. Once the principal investigator or Research Patient Coordinator becomes aware of an adverse event, the AE will be reported to the HRPO and QASMC according to institutional guidelines.

10.0 STATISTICAL CONSIDERATIONS

10.1 Study Design

This is a one-arm non-blinded study to investigate the feasibility of an OCT probe for patients undergoing routine screening or surveillance colonoscopy. The primary objective is to demonstrate the procedural feasibility of OCT during routine colonoscopy. Secondary objectives aim to describe the safety of the OCT probe, evaluate the quality of OCT images using a machine learning algorithm, and explore the diagnosis agreement between OCT imaging and pathology when a lesion is biopsied. OCT imaging through a catheter directed probe during routine colonoscopy will be measured by the duration of the entire procedure as well as duration of the OCT procedure itself.

10.2 Endpoints

Primary endpoint is whether a lesion can be adequately evaluated with OCT within 5 minutes during a standard of care colonoscopy. If the proportion of the patients whose procedure length using an OCT probe during routine colonoscopy is within 5 minutes is greater than 75%, then the feasibility is defined in this study.

Secondary endpoints include:

- AEs related to OCT imaging during routine colonoscopy
- Whether OCT image is successfully captured using machine learning algorithm, coded as "good" or "noisy". The OCT imaging catheter will be calibrated before each patient study to ensure that the catheter system is working properly. In an in vivo study of the catheter, we expect some images will be distorted due to patient movement, sub-optimal contact with the mucosa, etc. The machine learning algorithm will judge image quality based on number of colonic crypts visualized (see Section 12, Figure 5). We hypothesize that the proportion of good OCT images is greater than 90%.
- Weighted Kappa. Clinical pathology is the gold standard for diagnosis. Diagnosis from both OCT and clinical pathology will be assigned as normal mucosa, hyperplastic polyp, tubular adenoma, sessile serrated adenoma, or colorectal cancer. Based on ex vivo data from Dr. Zhu's lab, we hypothesize that there will be an over 80% agreement rate in this feasibility study.

10.3 Sample Size Calculation

The sample size calculation is based on the primary endpoint of feasibility only. The primary hypothesis is that the proportion of the patients who have OCT imaging which adds 5 minutes or less to the duration of standard of care colonoscopy is greater than 75%. The null hypothesis for feasibility is 75% and the alternative hypothesis is 90%. H0: $p<75\%$ Ha: $p>75\%$ (expect it to be 90% in clinical practice). A sample size of 54 patients achieves 80.1% power to detect a difference of 15% using a two-sided exact test at a significance level of 5% with the assumption that the proportion is 75%.

10.4 Accrual

We perform screening and surveillance colonoscopies in about 10-15 patients per day at Barnes Jewish Hospital with similar characteristics and estimate approximately 5-10 patients/day may be eligible for and will participate in this trial. We anticipate enrolling our goal of 54 patients in about 3-4 weeks.

10.5 Statistical Analyses

10.5.1 Patient Disposition

The number of patients discontinued, the reasons for discontinuation, and the duration of OCT imaging administered will be summarized by patient and by reason for discontinuation.

10.5.2 Protocol Deviations

All significant deviations will be summarized by patient and by type of deviation.

10.5.3 Demographics and Baseline Characteristics

Subject demographic and clinical characteristics will be summarized to characterize the population. Descriptive summaries will include means, standard deviations, medians, ranges for continuous variables and frequency and percentage for categorical variables. They are presented by total and each arm, respectively.

10.5.4 Endpoint Analysis

Proportions of the patients whose procedure length using an OCT probe during routine colonoscopy is within 5 minutes and who have good OCT images, as judged by a machine learning algorithm, will be provided. Their associated 95% confidence intervals (CIs) will be calculated assuming a binomial distribution. The descriptive statistics will be presented including frequency, type, and severity of AEs related to OCT imaging during routine colonoscopy. Weighted kappa and 95% CI will be computed for the agreement between OCT imaging and pathology for all enrolled patients. All analyses will be conducted using SAS (SAS Institute, Cary, NC) at the two-sided 5% significance level.

10.6 Early Stopping Rules

Toxicity, defined as study-related grade 3-5 SAEs, will be reviewed on a continuous basis. Early stopping will be based on the toxicity rate (TR) using the repeated significance testing of Pocock boundary with 80% power and 0.05 overall Type I error. We assume that no more than 5% is acceptable and a maximum-tolerated TR is 30%. The study will be halted if a study-related grade 3-5 SAE occurs in the first 2 patients, or 2 of the first 8 patients, or 3 of the first 15 patients, or 4 of the first 24 patients, or 5 of the first 34 patients,

or 6 of the first 45 patients. R function-toxbdry was used for calculations.

11.0 REFERENCES

1. Bae T, Ha Y, Kim C, et al. Distribution of the colonoscopic adenoma detection rate according to age: is recommending colonoscopy screening for koreans over the age of 50 safe?. *Ann Coloproctol*. 2015;31(2):46-51. doi:10.3393/ac.2015.31.2.46
2. Shaukat A, Kaltenbach T, Dominitz JA, et al. Endoscopic Recognition and Management Strategies for Malignant Colorectal Polyps: Recommendations of the US Multi-Society Task Force on Colorectal Cancer. Am J Gastroenterol 2020; 115:1751-1767.
3. Sumimoto K, Tanaka S, Shigita K, et al. Diagnostic performance of Japan NBI Expert Team classification for differentiation among noninvasive, superficially invasive, and deeply invasive colorectal neoplasia. Gastrointest Endosc 2017; 86:700-709.
4. Lee BI, Matsuda T. Estimation of Invasion Depth: The First Key to Successful Colorectal ESD. Clin Endosc 2019; 52: 100-106.
5. Huang D, Swanson EA, Lin CP, et al. Optical coherence tomography. Science 1991; 254: 1178–1181.
6. Chen CL, Wang RK. Optical coherence tomography based angiography. Biomed opt express 2017;8: 1056–1082.
7. Pahlevaninezhad H, Khorasaninejad M, Huang YW, et al. Nano-optic endoscope for high-resolution optical coherence tomography in vivo. Nat photonics 2018;12: 540.
8. Gora MJ, Quénéhervé L, Carruth RW, et al. Tethered capsule endomicroscopy for microscopic imaging of the esophagus, stomach, and duodenum without sedation in humans (with video). Gastrointest endosc. 2018;88: 830–840.
9. van der Sommen F, Curvers WL, Nagengast WB. Novel developments in endoscopic mucosal imaging. Gastroenterology 2018; 154:1876–1886.
10. Ahsen OO, Lee HC, Liang K, et al. Ultrahigh-speed endoscopic optical coherence tomography and angiography enables delineation of lateral margins of endoscopic mucosal resection: a case report. Therap Adv Gastroenterol 2017: 10:931–936.
11. Kirtane TS, Wagh MS. Endoscopic optical coherence tomography (OCT): advances in gastrointestinal imaging. Gastroenterol Res Pract 2014;2014: 376367.
12. Gora MJ, Suter MJ, Tearney GJ, Li X. Endoscopic optical coherence tomography: technologies and clinical applications. Biomed Opt Express 2017; 8:2405–2444.
13. Welge WA, Barton JK. In vivo endoscopic Doppler optical coherence tomography imaging of the colon. Lasers Surg Med 2017; 49:249–257.
14. Panta P, Lu CW, Kumar P, et al. Optical Coherence Tomography: Emerging In Vivo Optical Biopsy Technique for Oral Cancers. In: Panta P. (eds) Oral Cancer Detection. Springer, Cham.
15. Freund JE, Faber DJ, Bus MT, et al. Grading upper tract urothelial carcinoma with the attenuation coefficient of in-vivo optical coherence tomography. Lasers Surg Med 2019; doi: 10.1002/lsm.23079.
16. Hariri LP, Mino-Kenudson M, Lanuti M, et a;. Diagnosing lung carcinomas with optical coherence tomography. Ann Am Thorac Soc 2015; 12:193–201.
17. Zagaynova E, Gladkova N, Shakhova N, et al. Endoscopic OCT with forward-looking probe: clinical studies in urology and gastroenterology. J Biophotonics 2008; 1:114–128.
18. Adler DC, Zhou C, Tsai TH, et al. Three-dimensional endomicroscopy of the human colon using optical coherence tomography. Opt Express 2009; 17:784–796.

19. Li Y, Zhu Z, Chen JJ, et al. Multimodal endoscopy for colorectal cancer detection by optical coherence tomography and near-infrared fluorescence imaging. Biomed Opt Express. 2019; 10:2419–2429.
20. Mavadia-Shukla J, Fathi P, Liang W, et al. High-speed, ultrahigh-resolution distal scanning OCT endoscopy at 800 nm for in vivo imaging of colon tumorigenesis on murine models. Biomed Opt Express 2018; 9:3731–3739.
21. Esteva A, Kuprel B, Novoa RA, et al. Dermatologist-level classification of skin cancer with deep neural networks. Nature 2017; 542:115.
22. Lu Y, Yu Q, Gao Y, et al. Identification of metastatic lymph nodes in MR imaging with faster region-based convolutional neural networks. Cancer Res 2018; 78: 5135-5143.
23. Litjens G, Kooi T, Bejnordi BE, et al. A survey on deep learning in medical image analysis. Med Imaage Anal 2017; 42:60–88.
24. Lee CS, Baughman DM, Lee AY. Deep learning is effective for classifying normal versus age-related macular degeneration OCT images. Ophthalmol Retina 2017; 1:322–327.
25. Kermany DS, Goldbaum M, Cai W, et al. Identifying medical diagnoses and treatable diseases by image-based deep learning. Cell 2018; 172:1122–1131.
26. Abdolmanafi A, Duong L, Dahdah N, et al. Deep feature learning for automatic tissue classification of coronary artery using optical coherence tomography. Biomed Opt Express 2017;8:1203–1220.
27. Chen PJ, Lin MC, Lai MJ, et al. Accurate classification of diminutive colorectal polyps using computer-aided analysis. Gastroenterology 2018; 154:568– 575.
28. Sirinukunwattana K, e Ahmed Raza S, Tsang YW, et al. Locality sensitive deep learning for detection and classification of nuclei in routine colon cancer histology images. IEEE Trans Med Imaging 2016; 35:1196– 1206.
29. Urban G, Tripathi P, Alkayali T, et al. Deep learning localizes and identifies polyps in real time with 96% accuracy in screening colonoscopy. Gastroenterology 2018;155(4): 1069-1078.
30. Zeng Y, Xu S, Chapman WC Jr, et al. Real-time colorectal cancer diagnosis using PR-OCT with deep learning. Theranostics 2020;10:2587-2596.
31. Rutter CM, Johnson E, Miglioretti DL, et al. Adverse events after screening and follow-up colonoscopy. Cancer causes control 2012;23:289-296.

12.0 FIGURES

Figure 1. The OCT fiber probe laser focusing structure is depicted in Fig. 2. It is composed of a lead-in single mode fiber (SMF), a no-core fiber (NCF) for laser expansion, and a segment of gradient index (GRIN) fiber for laser focusing. The diameter of the GRIN fiber can be changed to realize different resolutions and working distances. The working distance is defined as the distance between the laser focus and the GRIN fiber end-face. In our experiments, GRIN fiber with a 230 um diameter is used to realize a resolution of around 25 um and a working distance of around 1.8 mm in air. The lengths of the GRIN fiber and NCF are 1300 um and 400 um, respectively.

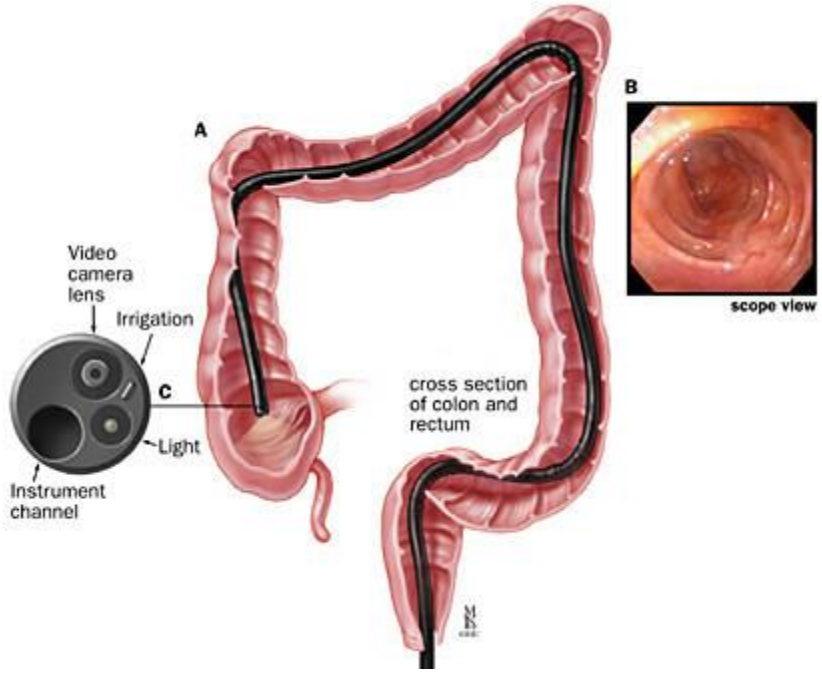
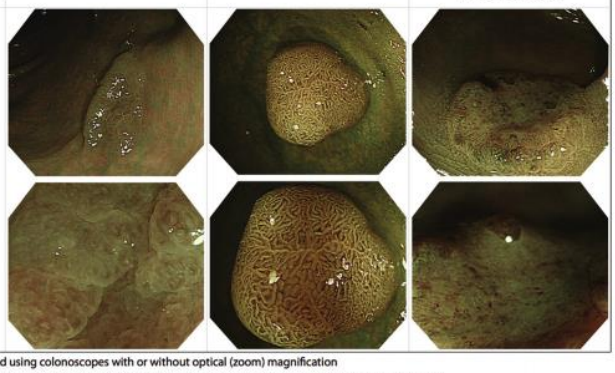


Figure 2. Colonoscope instrument channel.

NBI International Colorectal Endoscopic (NICE) Classification*

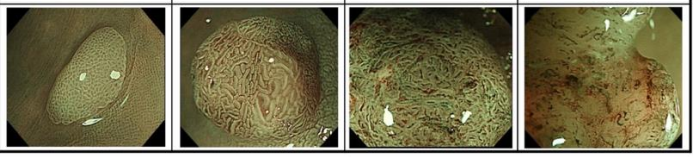
	Type 1	Type 2	Type 3
Color	Same or lighter than background	Browner relative to background (verify color arises from vessels)	Brown to dark brown relative to background; sometimes patchy whiter areas
Vessels	None, or isolated lacy vessels coursing across the lesion	Brown vessels surrounding white structures**	Has area(s) of disrupted or missing vessels
Surface Pattern	Dark or white spots of uniform size, or homogeneous absence of pattern	Oval, tubular or branched white structure surrounded by brown vessels**	Amorphous or absent surface pattern
Most likely pathology	**Hyperplastic**	**Adenoma*** **	**Deep submucosal invasive cancer**
Examples			

* Can be applied using colonoscopes with or without optical (zoom) magnification

** These structures (regular or irregular) may represent the pits and the epithelium of the crypt opening.

*** Type 2 consists of Vienna classification types 3, 4 and superficial 5 (all adenomas with either low or high grade dysplasia, or with superficial submucosal carcinoma). The presence of high grade dysplasia or superficial submucosal carcinoma may be suggested by an irregular vessel or surface pattern, and is often associated with atypical morphology (e.g., depressed area).

Figure 3. NICE classification.

	Type 1	Type 2A	Type 2B	Type 3
Vessel pattern	・Invisible ※1	・Regular caliber ・Regular distribution (meshed/spiral pattern) ※2	・Variable caliber ・Irregular distribution	・Loose vessel areas ・Interruption of thick vessels
Surface pattern	・Regular dark or white spots ・Similar to surrounding normal mucosa	・Regular (tubular/branched/papillary)	・Irregular or obscure	・Amorphous areas
Most likely histology	Hyperplastic polyp/ Sessile serrated polyp	Low grade intramucosal neoplasia	High grade intramucosal neoplasia/ Shallow submucosal invasive cancer ※3	Deep submucosal invasive cancer
Endoscopic image				

*1. If visible, the caliber in the lesion is similar to surrounding normal mucosa.

*2. Microvessels are often distributed in a punctate pattern and well-ordered reticular or spiral vessels may not be observed in depressed lesions.

*3. Deep submucosal invasive cancer may be included.

Figure 4. JNET classification.

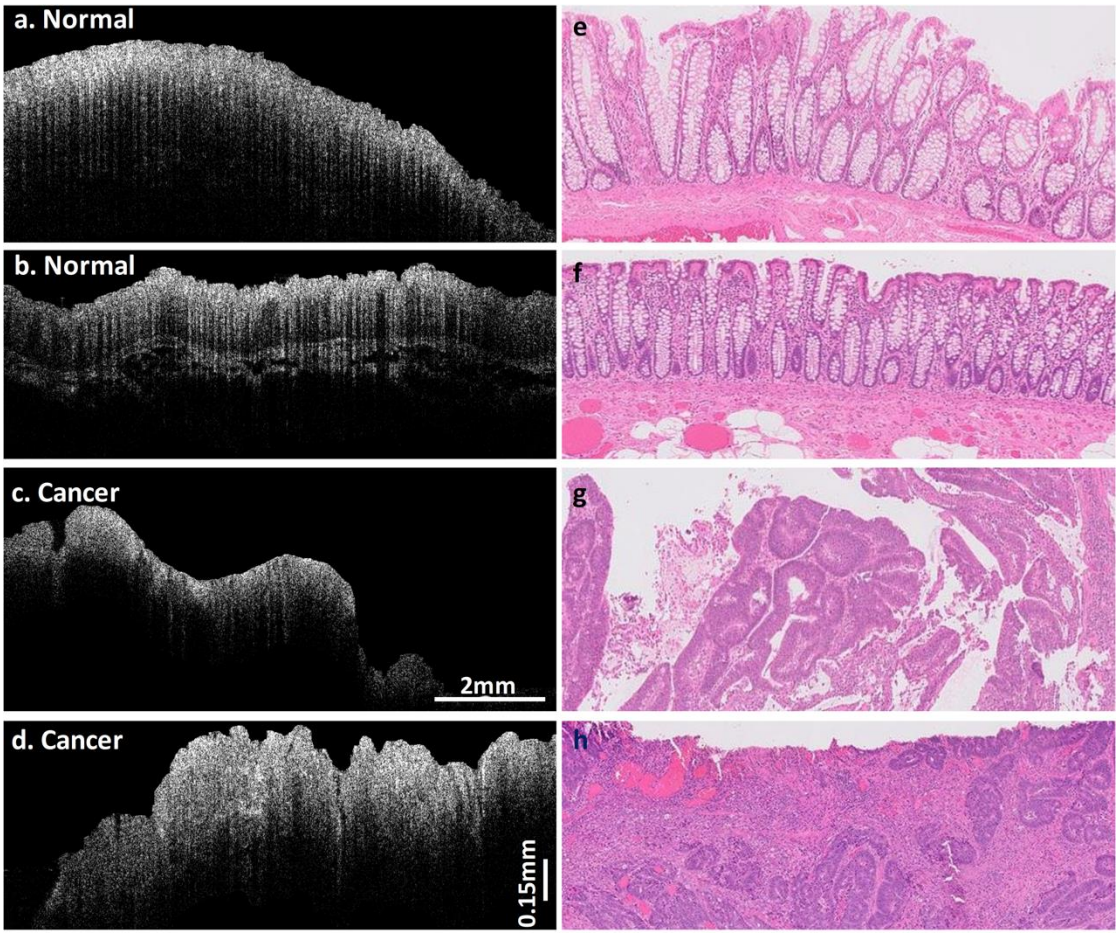


Figure 5. OCT imaging of normal colon tissue and colon cancer on left, corresponding pathology on right.

APPENDIX A: Definitions for Adverse Event Reporting

A. Adverse Events (AEs)

As defined in 21 CFR 312.32:

Definition: any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug-related.

Grading: the descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 will be utilized for all toxicity reporting. A copy of the CTCAE version 5.0 can be downloaded from the CTEP website.

Attribution (relatedness), Expectedness, and Seriousness: the definitions for the terms listed that should be used are those provided by the Department of Health and Human Services' Office for Human Research Protections (OHRP). A copy of this guidance can be found on OHRP's website:
http://www.hhs.gov/ohrp/policy/advevntguid.html

B. Suspected Adverse Reaction (SAR)

As defined in 21 CFR 312.32:

Definition: any adverse event for which there is a reasonable possibility that the drug caused the adverse event. "Reasonable possibility" means there is evidence to suggest a causal relationship between the drug and the adverse event. "Suspected adverse reaction" implies a lesser degree of certainty about causality than adverse reaction, which means any adverse event caused by a drug.

C. Life-Threatening Adverse Event / Life Threatening Suspected Adverse Reaction

As defined in 21 CFR 312.32:

Definition: any adverse drug event or suspected adverse reaction is considered "life-threatening" if, in the view of the investigator, its occurrence places the patient at immediate risk of death. It does not include an adverse event or suspected adverse reaction that, had it occurred in a more severe form, might have caused death.

D. Serious Adverse Event (SAE) or Serious Suspected Adverse Reaction

As defined in 21 CFR 312.32:

Definition: an adverse event or suspected adverse reaction is considered "serious" if, in the view of the investigator, it results in any of the following outcomes:

- Death
- A life-threatening adverse event

- Inpatient hospitalization or prolongation of existing hospitalization
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- A congenital anomaly/birth defect
- Any other important medical event that does not fit the criteria above but, based upon appropriate medical judgment, may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed above

E. Protocol Exceptions

Definition: A planned change in the conduct of the research for one participant.

F. Deviation

Definition: Any alteration or modification to the IRB-approved research without prospective IRB approval. The term "research" encompasses all IRB-approved materials and documents including the detailed protocol, IRB application, consent form, recruitment materials, questionnaires/data collection forms, and any other information relating to the research study.

A minor or administrative deviation is one that does not have the potential to negatively impact the rights, safety, or welfare of participants or others or the scientific validity of the study.

A major deviation is one that does have the potential to negatively impact the rights, safety, or welfare of participants or others or the scientific validity of the study.

APPENDIX B: Reporting Timelines

Expedited Reporting Timelines		
Event	**HRPO**	**QASMC**
Unanticipated problem involving risk to participants or others	Report within 10 working days. If the event results in the death of a participant enrolled at WU/BJH/SLCH, report within 1 working day.	Report via email after IRB acknowledgment
Major deviation	Report within 10 working days. If the event results in the death of a participant enrolled at WU/BJH/SLCH, report within 1 working day.	
A series of minor deviations that are being reported as a continuing noncompliance	Report within 10 working days.	
Protocol exception	Approval must be obtained prior to implementing the change	
Complaints	If the complaint reveals an unanticipated problem involving risks to participants or others OR noncompliance, report within 10 working days. If the event results in the death of a participant enrolled at WU/BJH/SLCH, report within 1 working day. Otherwise, report at the time of continuing review.	
Breach of confidentiality	Within 10 working days.	
Incarceration	If withdrawing the participant poses a safety issue, report within 10 working days. If withdrawing the participant does not represent a safety issue and the patient will be withdrawn, report at continuing review.	

Routine Reporting Timelines		
Event	**HRPO**	**QASMC**
Adverse event or SAE that does not require expedited reporting	If they do not meet the definition of an unanticipated problem involving risks to participants or others, report summary information at the time of continuing review	Adverse events will be reported in the toxicity table in the DSM report which is typically due every 6 months.
Minor deviation	Report summary information at the time of continuing review.	
Complaints	If the complaint reveals an unanticipated problem involving risks to participants or others OR noncompliance, report within 10 working days. If the event results in the death of a participant enrolled at WU/BJH/SLCH, report within 1 working day. Otherwise, report at the time of continuing review.	
Incarceration	If withdrawing the participant poses a safety issue, report within 10 working days.	

Routine Reporting Timelines		
Event	**HRPO**	**QASMC**
	If withdrawing the participant does not represent a safety issue and the patient will be withdrawn, report at continuing review.	