AWARD NUMBER: W81XWH-18-1-0371

TITLE: Optical Imaging Falloposcope for Early Ovarian Cancer Detection: In Vivo Feasibility and Safety

PRINCIPAL INVESTIGATOR: Jennifer Barton, Ph.D.

CONTRACTING ORGANIZATION: The University of Arizona

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Jennifer Barton

E-Mail: barton@email.arizona.edu

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UNIVERSITY OF ARIZONA
ARIZONA BOARD OF REGENTS
888 N EUCLID AVE RM 510
TUCSON AZ 85719-4824

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14. ABSTRACT

The goal of our project is to demonstrate that advanced imaging of the fallopian tubes and proximal ovary surface can be performed in women via a minimally invasive approach (no tissue cutting, endoscope introduced into the fallopian tube through a conventional hysteroscope), with no clinically relevant tissue damage, and in a reasonable period of time. This year, we we have built and certified a portable, operating room-ready falloposcope imaging system. We replaced large light sources with small fiber-coupled laser diodes, created a compact OCT system, rack mounted the hardware, built disposable, simplified but high performance falloposcopes, wrote improved software, and fully tested an operating room-ready, easily manufacturable, falloposcopy system. All University of Arizona and Banner University Medical Center approvals have been obtained. We have tested the system in phantoms and have a journal manuscript on the falloposcope accepted. We are awaiting the reopening of clinical research at Banner, closed due to high volume of COVID-19 patients, to begin in vivo trials.

15. SUBJECT TERMS
Endoscope, Fallopian Tube, Falloposcope, Fluorescence Imaging, Optical Coherence Tomography, Ovarian Cancer, Ovary, Uterine Tube

16. SECURITY CLASSIFICATION OF:			17. LIMITATION OF ABSTRACT	18. NUMBER OF PAGES	19a. NAME OF RESPONSIBLE PERSON
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W81XWH1810371 Optical Imaging Falloposcope for Early Ovarian Cancer Detection: In Vivo Feasibility and Safety

1. **INTRODUCTION:**

The purpose of this project is to demonstrate that advanced imaging of the fallopian tubes and proximal ovary surface can be performed in women via a minimally invasive approach (no tissue cutting, endoscope introduced into the fallopian tube through a conventional hysteroscope), with no clinically relevant tissue damage, and in a reasonable period of time (15 minutes or less). We are conducting two specific aims. In the first aim, we have built and certified a portable, operating room-ready falloposcope imaging system to improve upon our previous prototype. We have replaced large light sources with small fiber-coupled laser diodes, created a compact OCT system, rack mounted the hardware, built disposable, simplified but high performance falloposcopes, wrote improved software, and fully tested an operating room-ready, easily manufacturable, falloposcopy system. In the second aim, we will perform falloposcopy on twenty volunteers undergoing endometrial ablation with salpingectomy, and statistically assess the outcomes of performance of the falloposcope system as well as intra- and inter-patient image feature variability of the imaged tissue.

2. **KEYWORDS:**

Endoscope, Fallopian Tube, Falloposcope, Fluorescence Imaging, Optical Coherence Tomography, Ovarian Cancer, Ovary, Uterine Tube

3. **ACCOMPLISHMENTS:**

1. **What were the major goals of the project?**

The Statement of Work, together with percent complete, is give below. Tasks 1-5, which include all of Specific Aim 1, are complete. Task 6 associated with Specific Aim 2, is complete. The final two tasks, involving conducting the study and analyzing data, have not been started. This situation is described further in Section 5, Problems/Changes.

Specific Aim 1 Build and certify a portable, operating room (OR)-ready falloposcope imaging system	**Timeline**	**% Complete**
Major Task 1: *Build a portable MFI system*	Months	
Identify, order, and receive optimum laser wavelengths based on previous classification study and current availability power output, and cost.	1-3	100%
Combine lasers and couple into falloposcope MFI illumination fiber. Package into rack mount system.	3-9	100%
Convert proximal MFI imaging system from current microscope body to a compact cage mount system, affixed in instrument rack.	5-9	100%
Milestone Achieved: Functional, compact, portable MFI system.	9	*100%*
Major Task 2: *Incorporate a portable OCT system*		
Design a new OCT system with best available components, to meet resolution requirement of 5 μm axial. Order and receive components.	1-4	100%
Assemble components on compact breadboard with robust mounting hardware, test functionality, affix in instrument rack	4-9	100%

Milestone Achieved: Functional, compact, portable OCT system.	9	*100%*
Major Task 3: *Build disposable falloposcopes*		
Refine the specifications for a GRIN lens to replace the original 3 element design	1-3	100%
Specify, order, obtain and test multi-durometer endoscope sheath designs from a disposables OEM (Vention Medical – Sunnyvale, CA)	1-6	100%
Build 30 disposable final-design falloposcopes, 10 for sterilization survivability, testing and spares; 20 for the feasibility and safety study	6-18	100%
Test endoscopes for mechanical and optical properties, physician usability, sterilization survivability	12-18	100%
Milestone Achieved: 30 endoscopes built; 20 ready for human pilot trial	18	*100%*
Major Task 4: *Rack assemble and write integrating software, test system*		
Assemble all components on a rack that can be cleaned/draped prior to entry, and upon leaving, the OR	9-14	100%
Write integrating software in LabVIEW	4-14	100%
Confirm functionality of the falloposcope system: size/portability, data acquisition, software interface	14-16	100%
Milestone Achieved: Portable falloposcope system complete and functionality tested.	16	*100%*
Specific Aim 2 Perform a safety and feasibility study in women		
Major Task 5: *Obtain certifications and approvals*		
Submit UA IRB approval and related material for DoD's HRPO approval	14-18	100%
Receive UA IRB approval and HRPO approval before initiating human subjects/HAS related studies	18	100%
Certify falloposcope system with standard clinical engineering review for electrical safety, laser safety, materials, sharp edges, etc. to be used in humans at the BUMC Ob/Gyn operating room	16-18	100%
Milestone(s) Achieved: All certifications/ permissions in place to begin human study	18	*100%*
Major Task 6: *Recruit, consent, and image 20 volunteers*		
Recruit volunteers from the pool at BUMC undergoing endometrial ablation with salpingectomy.	20-34	Not started
After endometrial ablation, introduce the falloposcope through the hysteroscope already in place, and advanced to image the right and left fallopian tubes in a non-significant risk study.	20-34	Not started
Milestone Achieved: 20 volunteers imaged	34	*0%*
Major Task 7: *Analyze data*		

Analyze data relating to success of the procedures (e.g. ability to enter the ostium, timing)	24-35	Not started
Analyze data relating to imaging (e.g. intra- and inter-volunteer variation in image intensities as a function of wavelength)	24-35	Not started
Evaluate tissue grossly for evidence of damage by the falloposcope. Obtain representative histological sections and examine for microscopic evidence of damage and confirm the normal status of the tissue.	24-35	Not started
Write final manuscripts and reports	30-36	Not started
Milestone Achieved: Analysis and manuscripts complete	36	*0%*

2. **What was accomplished under these goals?**

We have completed the falloposcope hardware and software, built 30 falloposcopes, and conducted testing. The entire system is described in detail in *Translational Biophotonics* Manuscript ID tbio.202000011 entitled "Re-engineering a Falloposcope Imaging System for Clinical Use." The manuscript has been accepted for publication. Appendix A includes the accepted manuscript, which contains a detailed description of the system, endoscopes, the specifications and measured performance. We have completed building falloposcope assemblies, and have them safely secured and numbered in a room set up for this purpose.

We wrote sterilization procedures, user manuals, and completed setting up the contract to utilize Banner-University Medical Center (BUMC) operating room and anesthesiologist time (BUMC is the University of Arizona clinical partner and the hospital is within the University of Arizona footprint, but we were required to set up a contract to pay for any expenses beyond the patient's standard of care procedures). We completed procedures for assuring sterilization and safety of the equipment, passed sterilization tests, and received clinical engineering electrical safety and laser safety approval. We received one protocol amendment to expand the eligible patient population to any woman undergoing a salpingectomy with cervical dilation. We received our annual renewal in July 2020. All protocol actions have also been approved by the U.S. Army Medical Research and Development Command (USAMRDC), Office of Research Protections (ORP), Human Research Protection Office (HRPO). We are ready to begin human subjects testing.

3. **What opportunities for training and professional development has the project provided?**

The PI, Jennifer Barton, had opportunities to present the work on this project at the following events: National Ovarian Cancer Coalition Valley of the Sun Retreat, July 19, 2019; Vanderbilt University Biomedical Engineering Department Seminar, August 27, 2019; National Taiwan University Photonics Seminar, December 4, 2019; OPTIC Taiwan Conference Invited Speaker, December 6, 2019; University of Arizona Collaborative Cancer Grand Rounds, July 10, 2020.

Kelli Kiekens presented the falloposcope at the OSA Conference on Lasers and Electro-Optics, which was held virtually due to COVID-19, on May 11, 2020. She also had the opportunity to learn about the Banner process for admitting developmental hardware into the hospital with multiple meetings and presentations to Banner committees on devices, sterilization, and contracting. She presented a poster on the falloposcope to the Wyant College of Optics Industry Affiliates Board.

4. **How were the results disseminated to communities of interest?**

The presentation at the National Ovarian Cancer Coalition Valley of the Sun Retreat, July 19, 2019, gave the PI an opportunity to interact with ovarian cancer survivors and their supporters, and to help update them on the research being performed to diagnose ovarian cancer early.

Additionally, Kelli Kiekens and Ricky Cordova had the opportunity to present at the University of Arizona Innovation Showcase on Jan 30, 2020. This event highlighted the intellectual property arising out of University of Arizona, and was attended by university, industry and community members.

5. **What do you plan to do during the next reporting period to accomplish the goals?**

As soon as BUMC permits human subjects work to begin, we will immediately begin the clinical pilot project and data analysis described in Tasks 6 and 7. We do not plan any deviations from the Statement of Work.

4. **IMPACT:**

1. **What was the impact on the development of the principal discipline(s) of the project?**

We have created detailed standard parts list and operating procedures (SOPs) for construction of the falloposcope. They are available upon request now, and will be published with graduate student Kelli Kiekens' dissertation. Our designs for the falloposcope, involving a modular multi-lumen extrusion, ferrule, coating, functional handle, and rack design are a model that other groups can follow when developing miniature endoscopes. Several of the techniques for producing and assembling are unique as far as we are aware.

2. **What was the impact on other disciplines?**

Nothing to report.

3. **What was the impact on technology transfer?**

The University of Arizona has applied for a patent on the falloposcope technology (during a previous contract W81XWH-13-1-0131), and in this last year the investigators have been responding to comments from the US Patent Office. A provisional patent was filed on improvements to the falloposcope created under this contract: 62/897,744 - Provisional Application filed 9/9/19. The investigators continue to talk with potential licensees in medical device industry. This work, showing feasibility *in vivo*, is instrumental in attracting attending of potential licensees.

4. **What was the impact on society beyond science and technology?**

Nothing to Report.

5. **CHANGES/PROBLEMS:***:*

1. **Changes in approach and reasons for change**

There have been multiple changes. First, co-investigator Kenneth Hatch, M.D. has retired. He was one of two physicians on this project. Andrea Aguirre, M.D., an accomplished gynecological surgeon, has stepped up to replace him. This change in co-investigator has been approved.

Second, subcontractor Glannaventa (John Black, Ph.D., subcontract PI) has determined that he is unable to continue as a subcontractor. Fortunately, Dr. Black completed most Glannaventa SOW tasks, and transferred the knowledge necessary to perform Year 3 data analysis to Dr. Barton and students. We request that we transfer Year 3 Glannaventa tasks to UA to complete. We have the necessary personnel and skills to complete them.

COVID-19 has been a major disruption. All laboratory activities were halted for about three weeks. Clinical research was shut down by Banner University Medical Center in March, and remain closed. More information is given in the sub-sections below.

2. **Actual or anticipated problems or delays and actions or plans to resolve them**
The shutdown of clinical research has made us late with our pilot clinical study, which was scheduled to begin in March 2020. At this time, we do not know when we will be able to commence, although there are informal suggestions that, should COVID-19 cases in Arizona continue to fall, clinical research will be allowed on an exception basis beginning in late Fall 2020. Our procedure causes minimal increased COVID-19 exposure risk to the patient or operating room personnel (simply extends operating room time by 15 minutes), but has the potential for significant risk to Barton lab personnel who must enter the hospital, set up equipment, and be present for up to several hours for the complete procedure to be performed. Risk will continue to be assessed. Likely, the delay will require that the investigators request a no-cost extension, should the 20 patients and data analysis not be complete by July 14, 2021.

3. **Changes that had a significant impact on expenditures**
We have reduced as many expenses as possible during this time that we are waiting on clinical research to re-open. The program coordinator who is responsible for helping to set up the pilot clinical study has been moved from 50% time to 10% time. The 10% time enables him to continue with renewals, updates, etc. as required to maintain our protocols, and he can remain at 10% until we begin pilot studies. The biostatistician Denise Roe, who was scheduled to begin working on this project in year 3, has agreed to delay start until at least January 15, 2021 at which time hope to have data to begin analyzing. Dtudents are spending minimal time on the project and some instead are engaging in outside internships this summer. These cost savings should allow work to proceed into a no-cost extension period.

4. **Significant changes in use or care of human subjects, vertebrate animals, biohazards, and/or select agents**
Nothing to report. Human subjects protocols are approved and current. One modification to expand the eligible patient pool has been approved by both UA and DoD.

6. **PRODUCTS:**

1. **Publications, conference papers, and presentations**.
- Kelli C. Kiekens, Gabriella Romano, Dominique Galvez, Ricky Cordova, John Heusinkveld, Kenneth Hatch, William Drake, Zaynah Kmeid, Jennifer K. Barton. "Re-engineering a Falloposcope Imaging System for Clinical Use, Translational Biophotonics, accepted August 3, 2020. https://doi.org/10.1002/tbio.202000011
- Kelli C. Kiekens, Jennifer K. Barton. "3D printed lens for depth of field imaging." OSA Continuum, 2(11):3019-3025, 2019. https://doi.org/10.1364/OSAC.2.003019

2. **Other publications, conference papers, and presentations.**
- Kelli Kiekens, Dominique Galvez, Gabriela Romano, Ricky Cordova, Jennifer Barton. "Falloposcope Modifications for Clinical Trials." OSA CLEO: Conference on Lasers and Electro-Optics, May 11, 2020, virtual, presentation #AM4I.5.

3. **Website(s) or other Internet site(s)**
None.

4. **Technologies or techniques**
   We are developing detailed Standard Operating Procedures for fabrication and testing of the falloposcope. Many of these techniques will be applicable to others wanting to build similar miniature endoscopes. It is our intention to include all these SOPs into Kelli Kieken's dissertation, which will be published and made available to the community.

5. **Inventions, patent applications, and/or licenses**
   A provision patent was filed on improvements to the falloposcope created under this contract: 62/897,744 - Provisional Application filed 9/9/19.
6. **Other Products**
   N/A

7. **PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS**
1. **What individuals have worked on the project?**

Name:	Jennifer Barton
Project Role:	Principal Investigator
Researcher Identifier (e.g. ORCID ID):	0000-0003-4897-9361
Nearest person month worked:	1
Contribution to Project:	Dr. Barton performed roles of project leadership, overseeing personnel, and contributing to design, building and testing of the endoscope.
Funding Support:	This project

Name:	John Black, Ph.D.
Project Role:	Subcontract (Glannaventa) PI
Researcher Identifier (e.g. ORCID ID):	0000-0001-6374-3125
Nearest person month worked:	1
Contribution to Project:	Dr. Black aided with design of the falloposcope, especially the multi-lumen extrusion, assembly techniques, and contact with appropriate vendors.
Funding Support:	This project

Name:	Richard "Ricky" Cordova
Project Role:	Research Technician
Researcher Identifier (e.g. ORCID ID):	0000-0001-9201-9603
Nearest person month worked:	2

Contribution to Project:	Mr. Cordova has continued endoscope design and optimization of parts and mechanics
Funding Support:	Lauder Family Office

Name:	Kenneth Hatch, M.D.
Project Role:	Co-I, physician
Researcher Identifier (e.g. ORCID ID):	NIH Commons: KHATCH
Nearest person month worked:	1
Contribution to Project:	Dr. Hatch aided with design and testing of the falloposcope and human subjects protocol.
Funding Support:	This project

Name:	John Heusinkveld, M.D.
Project Role:	Co-I, physician
Researcher Identifier (e.g. ORCID ID):	0000-0002-5708-2647
Nearest person month worked:	1
Contribution to Project:	Dr. Heusinkveld aided with design and testing of the falloposcope and human subjects protocol.
Funding Support:	This project

Name:	Kelli Kiekens
Project Role:	Graduate Student
Researcher Identifier (e.g. ORCID ID):	0000-0003-3434-3127
Nearest person month worked:	6
Contribution to Project:	Ms. Kiekens has developed the assembly protocol for the endoscope, including standard operating procedures and documentation.
Funding Support:	University of Arizona institutional funds

Name:	Photini Faith Rice
Project Role:	Research Specialist
Researcher Identifier (e.g. ORCID ID):	0000-0001-7100-4023

Nearest person month worked:	6
Contribution to Project:	Ms. Rice assisted with the technical development of the falloposcope system, obtained certifications and assisted with writing the human subjects protocol.
Funding Support:	This project

Name:	Andrew Rocha
Project Role:	Graduate Student
Researcher Identifier (e.g. ORCID ID):	0000-0002-9030-7609
Nearest person month worked:	3
Contribution to Project:	Mr. Rocha performed optical and mechanical design and assembled and tested endoscopes.
Funding Support:	This project, University funds

Name:	Christopher Ussery
Project Role:	Project Coordinator
Researcher Identifier (e.g. ORCID ID):	0000-0001-6715-8708
Nearest person month worked:	5
Contribution to Project:	Mr. Ussery performed clinical coordination services, including obtaining Banner hospital approvals, sterilization assurance, clinical engineering, and contract coordination.
Funding Support:	This project

Name:	Zaynah Kmeid
Project Role:	Undergraduate Research Assistant
Researcher Identifier (e.g. ORCID ID):	0000-0002-1583-6885
Nearest person month worked:	1
Contribution to Project:	Ms. Kmeid assembled and tested endoscopes
Funding Support:	This project

Name:	Steven Santaniello
Project Role:	Undergraduate Research Assistant
Researcher Identifier (e.g. ORCID ID):	0000-0003-0223-1163
Nearest person month worked:	2
Contribution to Project:	Mr. Santaniello assembled and tested endoscopes
Funding Support:	This project

2. **Has there been a change in the active other support of the PD/PI(s) or senior/key personnel since the last reporting period?**
Currently Active, New, and Ended support for all key personnel is given below.

BARTON, J.K.
ACTIVE

W81XWH1810371 (Barton) 07/15/18-07/14/21 1.2 calendar
US Army Medical Research Acquisition Activity $885,184 (Total Cost)
Optical Imaging Falloposcope for Early Ovarian Cancer Detection: in vivo Feasibility and Safety
The purpose of this project is to test the feasibility of an imaging-only endoscope that traverses the uterus and fallopian tubes to the ovary, to detect early ovarian cancer.
SUBJECT GRANT

1R01EB020605 (Barton) 9/15/16 – 6/30/21 1.8 calendar
NIH/NIBIB $225,000
Advanced Salpingoscope for Minimally-Invasive Imaging of the Fallopian Tubes
The goal of this project is to build an endoscope that can image the ovaries and fallopian tubes with wide field, optical coherence tomography, and multiphoton microscopy, but accessing through the vagina wall.

R21CA229707 (Barton) 08/01/18-07/31/21 0.6 calendar
NIH/NCI $150,000
Molecular and Imaging Assessment of Fallopian Tube Health
The overall goal of this project is to show ex vivo proof of principle of a combined method for differentiating fallopian tubes of normal risk, high risk, and ovarian cancer patients.

T32HL007955 (Barton) 4/1/00 - 6/30/21 1.2 calendar
NIH/NHLBI $281,334
Cardiovascular Biomedical Engineering
Barton is the Program Director for this grant, which funds pre-doctoral student training in the field of cardiovascular biomedical engineering.

3P30CA023074 (Sweasy PI, Barton prog. co-leader) 7/14/16 - 6/30/21 0.5 calendar
NIH/NCI $2,301,904
University of Arizona Cancer Center – Cancer Center Support Grant
This is the overall Arizona Cancer Center support grant. Dr. Barton is Co-Leader of one of the four scientific programs, Cancer Imaging.

ECCS-1828132 (Zhang, Barton co-I) 10/1/2018-9/30/2021 0 Calendar
NSF $855,319
MRI: Development of Integrated Multi-Access Entangled Photon Sources and Single-Photon Detector Array Instrument for Interdisciplinary Quantum Information Research.
This grant will develop novel quantum sources and detectors for distribution and use around the University of Arizona. Barton's role is to evaluate quantum entangled photons for use in biomedical imaging applications.

N/A (Barton) 5/1/2019-11/30/2020 0 Calendar
American Society for Laser Medicine and Surgery $2,500
Combined optical coherence tomography and autofluorescence imaging for screening of early-stage esophageal cancer. These funds will help support graduate student Travis Sawyer to build a prototype optical coherence tomography-fluorescence imaging endoscope for detection of esophageal dysplasia.

NEWLY FUNDED
5U01CA200469 (Shih PI, Barton sub PI) 10/01/19-9/30/20 0.6 calendar
NIH/NCI $127,585
Development of in vitro diagnostic multivariate assay
Barton is subcontract PI on this pilot project funded by the Early Detection Research Network. This pilot grant funds an endoscope with cell collecting capability and ability to visualize fluorescent contrast agent targeted to STIC lesions.

ENDED
1R01CA195723 (Barton) 9/1/15 - 8/31/19 NCX 2.4 calendar
NIH/NCI $466,735 average
Validating a mouse model of ovarian cancer for early detection through imaging
The goals of this grant are to develop and validate a mouse model for ovarian cancer and to determine the image characteristics of the earliest cancerous changes.

BLACK, J.F.
ACTIVE
1853242 (Mowery, Black consultant) 04/01/19-03/31/21 (est.) 3.0 calendar (est.)
NSF SBIR Phase 2 Award $747,753 total
OCT-Compatible Imaging Adaptor for Precision Vascular Access via Hollow-Bore Needles
This SBIR Phase II project supports development of a commercially viable real-time optical imaging device to address the problem of failed first-time vascular access.

NEWLY FUNDED
None

ENDED
W81XWH1810371 (Barton, Black subcontract PI) 07/15/18-07/14/21 1.8 Y1, 0.6 Y2 cal.
US Army Medical Research Acquisition Activity $885,184 (Total Cost)
Optical Imaging Falloposcope for Early Ovarian Cancer Detection: in vivo Feasibility and Safety
The purpose of this project is to test the feasibility of an imaging-only endoscope that traverses the uterus and fallopian tubes to the ovary, to detect early ovarian cancer.
SUBJECT GRANT- Subcontract ended at the end of year 2.

HEUSINKVELD, J.
ACTIVE
W81XWH1810371 (Barton, Heusinkveld Co-I) 07/15/18-07/14/21 0.6 calendar
US Army Medical Research Acquisition Activity $885,184 (Total Cost)
Optical Imaging Falloposcope for Early Ovarian Cancer Detection: in vivo Feasibility and Safety

The purpose of this project is to test the feasibility of an imaging-only endoscope that traverses the uterus and fallopian tubes to the ovary, to detect early ovarian cancer.
SUBJECT GRANT

R21CA229707 (Barton, Heuskinveld Co-I) 08/01/18-07/31/21 0.48 cal. y2-3
NIH/NCI $150,000
Molecular and Imaging Assessment of Fallopian Tube Health
The overall goal of this project is to show ex vivo proof of principle of a combined method for differentiating fallopian tubes of normal risk, high risk, and ovarian cancer patients.

NEWLY FUNDED, ENDED
None

HATCH, K.D. (retired 3/31/20)
ENDED
W81XWH1810371 (Barton, Hatch Co-I) 07/15/18-03/3120 0.6 calendar
US Army Medical Research Acquisition Activity $885,184 (Total Cost)
Optical Imaging Falloposcope for Early Ovarian Cancer Detection: in vivo Feasibility and Safety
The purpose of this project is to test the feasibility of an imaging-only endoscope that traverses the uterus and fallopian tubes to the ovary, to detect early ovarian cancer.
SUBJECT GRANT

1R01EB020605 (Barton, Hatch Co-I) 9/15/16 – 3/31/20 0.6 calendar
NIH/NIBIB $225,000
Advanced Salpingoscope for Minimally-Invasive Imaging of the Fallopian Tubes
The goal of this project is to build an endoscope that can image the ovaries and fallopian tubes with wide field, optical coherence tomography, and multiphoton microscopy, but accessing through the vagina wall.

AGUIRRE, A. (new as of year 3)
ACTIVE
W81XWH1810371 (Barton, Aguirre Co-I) 07/15/20-07/14/21 0.6 calendar
US Army Medical Research Acquisition Activity $885,184 (Total Cost)
Optical Imaging Falloposcope for Early Ovarian Cancer Detection: in vivo Feasibility and Safety
The purpose of this project is to test the feasibility of an imaging-only endoscope that traverses the uterus and fallopian tubes to the ovary, to detect early ovarian cancer.
SUBJECT GRANT

ROE, D.
ACTIVE
W81XWH1810371 (Barton, Roe Co-I) 7/15/18 – 7/14/21 0.23 calendar
US Army Medical Research Acquisition Activity $885,184 (Total Cost) (y3 only)
Optical Imaging Falloposcope for Early Ovarian Cancer Detection: In Vivo Feasibility and Safety.
The goal of this study is to test the feasibility of a minimally invasive, inexpensive, and highly sensitive falloposcope, which will allow the testing for the first time in vivo, or in a living person.
SUBJECT GRANT

R25HL126140 (Garcia, Roe Co-I) 9/15/14 – 12/31/23 0.60 calendar
NIH/NHLBI $433,087
Arizona Pride-25: Translational Approaches to Health Disparities in the Lung.
The goal of this project is to have sustained reductions in health disparities through impactful basic, behavioral, clinical, and social sciences research and an impactful increase in the proportion of successful next generation UBR research leaders.

P30CA023074 (Sweasy, Roe Core lead) 07/01/16 – 06/30/21 3.36 calendar
NIH/NCI $2,277,437
Arizona Cancer Center – Cancer Center Support Grant.
The major goal of this project is to provide organizational infrastructure for the promotion of interdisciplinary research and the collective use of resources.

R01CA186700 (Thomson, Basen-Engquist, Roe Co-I) 01/01/15 – 12/31/20 (NCE) 0.60 calendar
NIH/NCI $479,334
Study of Biomarkers in Ovarian Cancer: Modulation by Activity and Diet Intervention.
The goal of this research is to evaluate the biological mechanisms associated with ovarian cancer survival using samples collected in a randomized, attention-control study of 1070 women with prior invasive disease.

R01CA241709 (Karellas, Roe Co-I) 06/1/19 – 05/31/24 0.24 calendar
NIH/NCI $659,131
Upright, Low-dose, High-resolution, 3D Breast CT.
The goal of this project is to design, develop and clinically evaluate a new generation of breast CT that will use upright patient positioning similar to mammography, but without breast compression, and at radiation dose similar to mammography to provide full 3D images of the breast.

ENDED
R01CA172444 (Chow, Roe Co-I) 9/11/13 – 6/30/20 0.48 calendar
NIH/NCI $218,390
Metformin for Reduction of Obesity-Associated Breast Cancer Risk.
The goal of this project is to conduct a Phase II clinical trial of metformin to determine the potential activity of metformin on breast cancer risk reduction.

1U01CA214254-01 BSWRI (Roe sub PI) 09/01/17 – 7/31/21 0.99 calendar
NIH/NCI (Sub-recipient from Baylor University) (Year 1)
Noncoding RNA Biomarkers for Noninvasive and Early Detection of Pancreatic Cancer
Dr Roe will provide statistical collaborative support for the proposed studies.

SU2C-AACR-CT03 (Roe sub PI) 05/01/17 – 12/31/19 0.78 calendar
TGen (sub-AACR) $35,576
A SU2C Catalyst Randomized Phase II Trial of the PD1 Inhibitor Pembrolizumab (Keytruda) with or without a Vitamin D Receptor Agonist Paricalcitol (Zemplar) in Patients with Stage IV Pancreatic Cancer.
The goal of this study is to determine the effects that pembrolizumab with or without the addition of paricalcitol may have on pancreatic cancer.

R34DK118486 (Hingle, Roe Co-I) 09/15/18 – 06/30/20 0.96 calendar
NIH/NIDDK $151,353
Type 2 Diabetes Prevention in Community Health Care Settings for at Risk Children and Mothers.
The goal of this project is to test the feasibility and acceptability of a family-focused lifestyle behavior change intervention delivered to mothers with prediabetes and their 8-12-year-old children by staff at a Federally Qualified Health Center (FQHC).

NEW
P01CA229112 (Curiel-Lewandrowski, Roe Core Leader) 09/10/2019-08/31/2024 1.20 calendar
NIH/NCI $974,965
Targeted Prevention for Non-Melanoma Skin Cancer
Core B – Biostatistics and Bioinformatics Core

The overall goal of this grant is to identify, develop, and clinically evaluate novel non-melanoma skin cancer chemopreventive agents, biomarker discovery and to evaluate these candidate agents in early human studies.

R01CA245920 (Altbach, Roe Co-I) 12/01/2019 – 11/30/2024 0.36 calendar
NIH/NCI $346,214
Advancing MRI Technology for Early Diagnosis of Liver Metastases
We expect our proposal to yield technology improvements that will increase precision of care and outcomes in patients with metastatic malignancies, in particular those with colorectal cancer.

41010481702/1U01CA214254-01 (Goel, Roe Site PI) 04/01/2018 – 03/31/2023 0.99 calendar
Beckman Res. Inst. of The City of Hope/NCI $749,507
Noncoding RNA Biomarkers for Noninvasive and Early Detection of Pancreatic Cancer
Dr. Roe will contribute to this project by providing statistical design, oversight of statistical analyses, assistance in the reporting of results to investigators as well as assistance in manuscript preparation.

R01CA253302 (Bea, Roe Co-I) 07/01/2020 – 06/30/2023 1.20 calendar
NIH/NCI $250,000
Adipose and Lean Soft Tissue Depots, Cancer Risk and Mortality in Postmenopausal Women
This study will inform etiological understanding, improve risk assessment, and, most importantly, enhance our ability to target interventions and cancer prevention efforts.

R01MD014127-01A1 (Gachupin, Roe Co-I) 04/13/2020 – 12/31/2024 1.20 calendar
NIH/NIMHD $467,734
Achieving American Indian Youth Energy and Mental Health Balance.
The goal of this project is to develop and test a culturally relevant, community-led intervention that incorporates the principles of Mind-Body Medicine (MBM) skills training and parental/caregiver engagement to support AI youth in achieving healthy lifestyle choices and in reducing risk for obesity and related metabolic diseases.

61998.2006995.669308/U01CA214254-03 (Roe, Primary) 08/01/2019 – 07/31/2022 0.65 calendar
Beckman Research Institute of The City of Hope (NCI) $64,680 (TC)
Noncoding RNA Biomarkers for Noninvasive and Early Detection of Pancreatic Cancer
Dr. Roe will provide statistical collaborative support for the proposed studies.

3. **What other organizations were involved as partners?**
Nothing to Report.

8. **SPECIAL REPORTING REQUIREMENTS**
N/A

9. **APPENDICES:**
Kiekens KC, Romano G, Galvez D, Cordova R, Heusinkveld J, Hatch K, Drake W, Kmeid Z, Barton, JK. Re-engineering a Falloposcope Imaging System for Clinical Use. Translational Biophotonics, *accepted* 2020.

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ARTICLE TYPE

Re-engineering a Falloposcope Imaging System for Clinical Use

Kelli C. Kiekens[1] | Gabriella Romano[2] | Dominique Galvez[1] | Ricky Cordova[2] | John Heusinkveld[3] | Kenneth Hatch[3] | William Drake[1] | Zaynah Kmeid[2] | Jennifer K. Barton*[1,2]

[1]Wyant College of Optical Science, University of Arizona, Arizona, USA
[2]Biomedical Engineering, University of Arizona, Arizona, USA
[3]Obstetrics and Gynecology, University of Arizona, Arizona, USA

Correspondence
*Jennifer K. Barton, T W Keating Blg, Rm. 102, Tucson, AZ 85721. Email: barton@email.arizona.edu

Present Address
T W Keating Blg, Rm. 102, Tucson, AZ 85721

Abstract

High grade serous carcinoma of the ovary is believed to originate in the fallopian tubes. A sub-millimeter diameter endoscope with advanced imaging capabilities may take advantage of the natural pathway of the female reproductive tract to image the fallopian tubes in a minimally invasive procedure for early detection of cancer. Our lab previously built a prototype benchtop fallopian tube endoscope with pseudo-white light imaging, multi-spectral fluorescence imaging, and optical coherence tomography. This endoscope was approximately 0.9mm in diameter, flexible, and steerable in one direction. Several modifications have been made to create a falloposcope imaging system which is ready for clinical use. This new design includes a multi-lumen extrusion, a revised handle design, simplified lens design, and redesigned subsystems resulting in improved mechanical characteristics, biocompatibility, and portability while maintaining image quality. Additionally, these clinical endoscopes are single use, considerably less expensive, and faster to build as compared to the prototype.

KEYWORDS:
multispectral fluorescence imaging; optical coherence tomography; micro-endoscope; ovarian cancer; early detection

1 | INTRODUCTION

No adequate screening mechanism is currently available for detection of early ovarian cancer. Current methods include palpation, transvaginal ultrasound, and the CA-125 blood marker. However, in a study of nearly 40,000 women, the positive predictive value for cancer in women who had both a CA-125 value over 70 units/milliliter and an abnormal transvaginal ultrasound was only 25% [1]. As a result, approximately 60% of ovarian cancers are not diagnosed until late stage [2]. High-risk women, such as those with a BRCA gene mutation, may undergo prophylactic salpingo-oophorectomy [3], which is effective at reducing the risk of cancer, but may increase the risk of cardiovascular mortality if performed before the age of 45 [4]. Recent studies have shown that at least some ovarian cancers may originate from the fallopian tubes (FTs) near the fimbria, suggesting that in vivo imaging of the FT may identify ovarian cancer precursors such as serous tubal intraepithelial carcinoma (STIC) [5]. Further, the FTs could be accessible in a minimally invasive fashion via the natural pathway through the reproductive tract.

Ex vivo studies of FTs and ovaries have shown a decrease in the autofluorescence of cancerous tissue at multiple excitation and emission bands [6–8]. Additionally, optical coherence tomography (OCT) provides cross-sectional imaging capability and can identify structural changes of FT [9] such as a thickening of the epithelium, a hallmark of STIC, or loss of organized structure, a hallmark of cancer. By combining multispectral fluorescence imaging (MFI) and OCT into a single miniature endoscope, it may be possible to achieve high sensitivity and specificity for early-stage ovarian cancer detection.

Our lab previously built a prototype fallopian tube endoscope (the "falloposcope"), which provided proof-of-concept

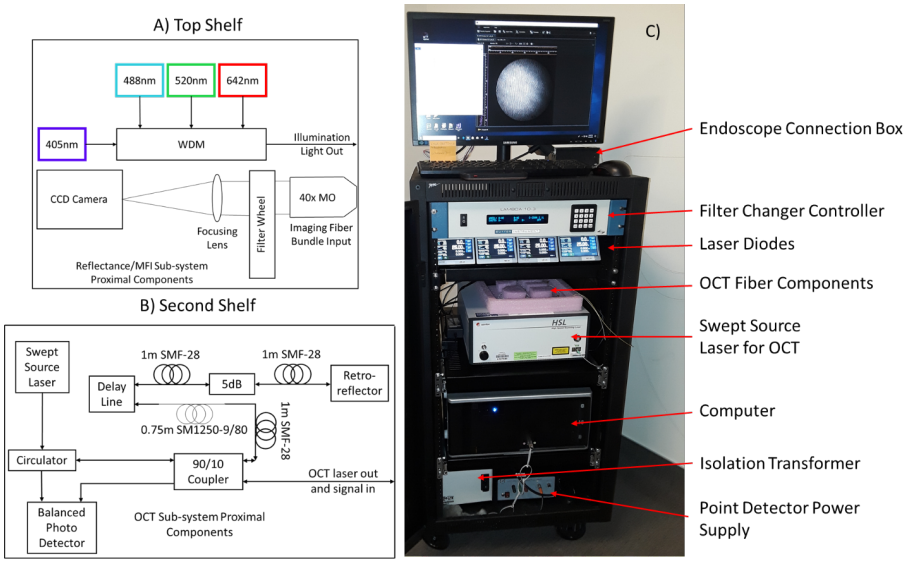

FIGURE 1 A) Detailed block diagram of the components used in reflectance imaging and MFI which are all housed on the top shelf. The four colored boxes represent the four laser diodes. Wavelength Division Multiplexer (WDM), 40x Microscope Objective (MO) B) Detailed block diagram of the components used for OCT which are all housed on the second shelf. C) Picture of the proximal rack with the major components labeled.

for miniaturizing all desired imaging functionality in an endoscope with a sub-millimeter size constraint[10]. However, this system was not suitable for clinical use due to being attached to benchtop MFI and OCT systems, it was costly and time-consuming to assemble, had sub-optimum mechanical characteristics, and was not biocompatible. In this paper, we present the results of a complete second-generation falloposcope imaging system which was re-engineered with an emphasis on meeting clinical requirements, improving manufacturability, and reducing cost. Multiple rounds of usability testing with the collaborating gynecological surgeons were performed to refine the design. Modifications have led to a simplified, capable system which has received clinical engineering safety approval. This clinical falloposcope imaging system will be evaluated for feasibility in a pilot clinical trial of 20 women.

2 | SYSTEM REQUIREMENTS

The clinical goal is to image women at high risk for ovarian cancer in an outpatient procedure to delay or avoid unnecessary salpingo-oophorectomies. Therefore, the procedure must be minimally invasive. A hysteroscope and an introducing catheter will guide the falloposcope through the uterus to the FT ostium. The ostium opening is only about 1mm in diameter and FTs have an average length of 11 to 12cm[11], driving the length and diameter requirements that need to be met bt the falloposcope. Saline or carbon dioxide will be pumped through the introducing catheter, around the falloposcope, and into the FT to help open the ostium and displace plicae. FTs are not a straight path, so the falloposcope must be flexible and steerable to navigate the length of the lumen.

Real-time reflectance imaging enables navigation to the distal end of the FT with a desired field of view (FOV) of at least 60°. A two-step process to detect abnormal areas will be performed during retraction of the falloposcope. First, MFI will be used as a general screening for suspect areas. STIC lesions are superficial and may be as small as hundreds of microns in diameter. Therefore, the MFI will require an image resolution of at least 100µm to highlight suspicious regions within the working distance of 3 to 7mm. Exposure time is limited to 100ms to minimize motion artifact. When suspicious areas are identified, the endoscope will be manually rotated to the orientation where the side-firing OCT can contact the tissue. The endoscope will be advanced forward again, past the area of interest, and the OCT scanning as well as MFI will be recorded during the pullback over the region of interest. An axial resolution of at least 20µm is required for OCT to identify the abnormally thickened epithelium. This procedure, in addition to the fixed orientation of OCT and MFI within the endoscope, enables co-registration of the two modalities.

The falloposcope must be biocompatible and sterilizable. The falloposcope is single human use to avoid the risk of patient cross-contamination and the need for reprocessing. Being single use imposes requirements including similar performance between falloposcopes, rapid manufacturing, and relatively low cost. The proximal system components must be

portable and comply with all electrical and laser safety requirements for medical devices. A detailed list of all falloposcope imaging system requirements was decided upon in conjunction with our physician collaborators. This list, including pass or fail criteria as well as the measured performance, is provided in Table 1 in the results section.

3 | SYSTEM DESCRIPTION

The system description below is separated into four sections: the proximal components which are arranged in a portable rack, mechanical considerations of the falloposcope, design of reflectance and MFI subsystems, and design of an OCT subsystem.

3.1 | Proximal Components

To make the clinical falloposcope imaging system portable, all proximal components were arranged to fit inside a partial-size server rack (Middle Atlantic Products, PN: PTRK-21, Fairfield, NJ, USA). Three fiber bulkhead connectors on the top of the rack provide a convenient interface for a falloposcope. A protective box provides strain relief at the connection points.

The rack has 3 shelves to organize the equipment. The top shelf holds the all the components for reflectance and MFI systems including the laser diode illumination sources and wavelength division multiplexer (WDM) for illumination, as well as the relay optics, filter wheel with rack-mounted filter changer controller, and camera for imaging. The second shelf holds all components related to the OCT system including swept source laser, fiber components, and balanced photo detector. The third shelf holds the computer tower. Power management is located on the base of the rack, including an isolation transformer (Tripp Lite, PN: IS1000HG, Chicago, IL, USA) to conform to electrical safety standards and protect all rack components. Figures 1 A and B are block diagrams of the components housed on the corresponding shelves. Figure 1 C is a picture of the assembled rack with major components labeled.

3.2 | Falloposcope mechanics

To provide better biocompatibility, steerability, and manufacturability, the mechanics of the falloposcope were completely redesigned. A custom multi-lumen extrusion (MLE) of polyether ether ketone (PEEK) replaced polyamide tubing as the main body of the falloposcope because the polyamide tubing tended to kink and had sub-optimum steering capability. A minimum wall thickness of 50μm and a symmetric design of the MLE was preferred by the manufacturer (Apollo Medical Extrusions, Atlanta, GA, USA). The final design has an external diameter of 710 μm with six channels so that each of the fibers and wires are individually protected. The largest channel (300μm diameter) houses the imaging fiber bundle, the medium channel (200μm) holds the OCT probe, and the four small channels (110μm) contain the two pull wires and illumination fiber, with one channel remaining open.

A custom metal ferrule was fabricated (Major Precision Engineering, Inc., Tempe, AZ, USA) with the same outer diameter and six "U" shaped slots matching the size and position of the MLE channels. The ferrule aids in the alignment of the lens with the fiber bundle, and provides an attachment point for all fibers and pull wires, which are otherwise loose in their individual channels through the MLE. Figure 2 is a labeled rendering showing all of the components in the final distal assembly with an inset cross-section view of the MLE.

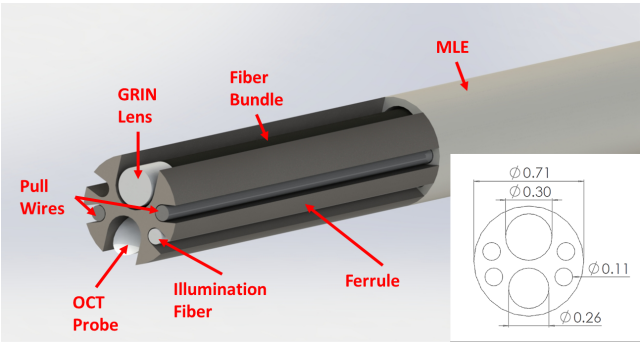

FIGURE 2 Rendered computer model of the falloposcope distal tip with all components labeled. The inset is a dimensioned cross section of the MLE in millimeters. GRIN – Gradient Index, MLE – Multi-Lumen Extrusion

A 14cm length of transparent, thin walled, medical grade heat shrink tubing (Nordson Medical Corp., PN: 103-0139, Westlake, OH, USA) protects the distal tip of the falloposcope. A few millimeters of this heat shrink extending, past the end of the falloposcope, is folded back on itself, and a short piece of a larger diameter heat shrink (Nordson Medical, PN: 103-0140) is used to hold and seal the end. This process results in the falloposcope being encapsulated in biocompatible material with a smooth surface for safety and sterilizability. Additionally, this method guarantees an air interface at the 48° distal polish of the OCT probe. The thin layer covering the distal face minimizes back reflection from the illumination fiber into the fiber bundle[12]. Another, thicker heat shrink tube (Nordson Medical, PN: 103-0454) is used on the proximal 56cm of the MLE, which is not inserted into the FT, to provide more structural

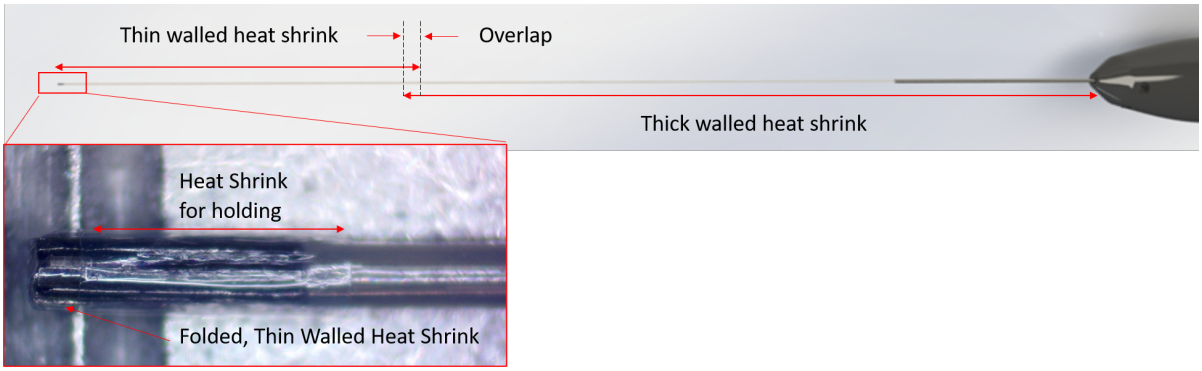

FIGURE 3 Thin walled heat shrink is put over the front portion of the fallopocope and folded back on itself at the tip. A short segment of a larger diameter heat shrink holds the folded over portion as shown in the picture of the falloposcope tip. A thicker walled heat shrink is used on the non-insertable portion of the falloposcope.

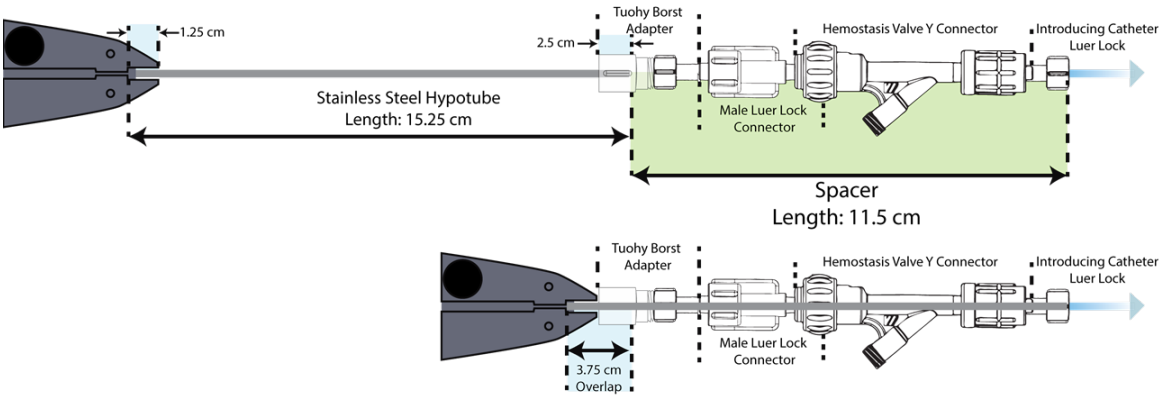

FIGURE 4 Components attached to the back end introducing catheter with the falloposcope handle and hypotube in the retracted position so the falloposcope would be just inside the distal tip of the introducing catheter (top). The same components in the fully extended position so the falloposcope extends 11.5cm out of the introducing catheter (bottom).

rigidity. A diagram of the use of heat shrink is shown in Figure 3.

A 15.25cm length of custom stainless steel hypotube (Vita Needle, Needham, MA, USA) covers the most proximal portion of the MLE where it exits the falloposcope handle. The hypotube provides protection and rigidity at this juncture to push the falloposcope forward through the introducing catheter. The introducing catheter (Cook Medical, PN: J-SSG-554086, Bloomington, IN, USA) has an attached luer lock which mates to a hemostasis valve Y connector (Qosina, PN: 80325, Ronkonkoma Long Island, NY, USA) to enable the introduction of saline or carbon dioxide into the FTs. A male luer lock (Qosina, PN: 71637) and a Tuohy Borst adapter (Qosina, PN: 80402) prevent backflow and add additional length to allow the distal tip of the falloposcope to extend a set maximum length (in our case 11.5cm) from the tip of the introducing catheter.

When the hypotube is inserted into the Tuohy Borst adapter, the tip of the falloposcope is just proximal to the end of the introducing catheter. The handle can then be pushed forward until the hypotube reaches the introducing catheter and the Tuohy Borst adapter contacts the handle, providing a hard stop. Figure 4 shows a diagram of this assembly and demonstrates the spacing necessary that provides a hard stop at the 11.5cm maximum extended length.

An improved handle was 3D printed in two halves to assemble with mechanical functionalities within the handle. The two pull wires wrap around a pulley which is attached to a steering wheel on the outside of the handle. When the wheel is turned, one pull wire is tightened and the other loosened, causing the tip of the falloposcope to turn in the direction of the

wire being pulled. The imaging fiber bundle and the OCT fiber pass through the handle in a straight central channel, while the illumination fiber follows a separate lateral channel which contains a custom mode scrambler described in the following section. Vinyl tubing on the proximal side of the handle provides protection for all three fibers between the handle and the connection box on the rack. Figure 5 shows a computer rendering of the 3D printed handle with the exterior material made partially transparent to display the internal assembly.

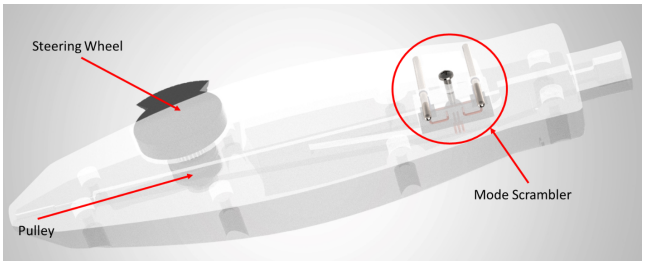

FIGURE 5 A computer rendering of the handle designed for this falloposcope. The outer material has been made partially transparent, so the internal mechanical assemblies are visible. This displays the interaction of the pulley and steering wheel as well as the assembly of the mode scrambler.

Additionally, UV illumination limits optical material choices and raises concern of possible mutagenicity on reproductive organs.

A specialized illumination fiber with an outer diameter of 100um, core diameter of 80 µm, and a numerical aperture (NA) of 0.66 (Polymicro Technologies, PN: FSU085100, Phoenix, AZ, USA) was chosen for its small diameter as well as its ability to illuminate the entire field of view of the imaging system. However, the output fiber of the laser diodes has an NA near 0.12, creating an underfilled condition when coupled into the high NA fiber, resulting in a much narrower illumination cone than needed. This situation can be rectified by introducing controlled bends in the fiber, which couple the light into higher order modes resulting in a more uniform output near the supported 0.66 NA (82.6°). Figure 6 illustrates this mode scrambling effect.

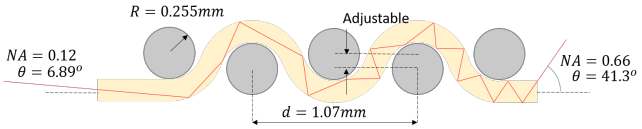

FIGURE 6 Example of mode scrambling within the fiber due to induced micro-bends which results in an output angle that is larger than the input angle of the light (not to scale).

3.3 | Reflectance and MFI subsystems

Illumination wavelengths were chosen that could create narrow-band reflectance images, pseudo white-light images, and fluorescence contrast between normal and cancerous tissues based on our previous ex vivo MFI study [6]. Four commercially available, single-mode fiber coupled laser diodes at wavelengths of 642nm, 520nm, 488nm, and 405nm (Thorlabs, LP642-SF20, LP520-SF15, LP488-SF20, and LP405-SF10, respectively, Trenton, NJ, USA) were chosen for the system. A custom fiber coupled wavelength division multiplexer (WDM) (OZ Optics, Ontario, Canada) combines all four wavelengths into the same output fiber.

Reflectance imaging can be performed with the 642nm, 520nm, and 488nm wavelengths separately or combined. Pseudo-white light imaging may be accomplished by overlaying sequential images at each wavelength in the case of minimal sample and falloposcope movement. All wavelengths may also be used for fluorescence imaging, with the blue and green wavelengths capable of exciting endogenous tissue fluorophores and the red wavelength appropriate for exogenous dyes such as Cyanine 5. Ultraviolet (UV) wavelengths used in the prototype system were eliminated because they did not provide a significant increase in cancer discriminating ability compared blue wavelengths based on our previous study [6].

A custom mode scrambler is incorporated in the handle, consisting of three pieces of 24-gauge wire on one side, and two pieces of 24-gauge wire on the other side, sandwiching the illumination fiber. The distance separating the two sides is adjusted until the desired output is achieved.

Illumination light from the tissue, both reflectance and fluorescence, is collected by a gradient index (GRIN) lens (GRINtech, PN: GT-IFRL-025-005-50-CC, Jena, Germany) and focused onto the face of a 3000 element, miniature imaging fiber bundle (Fujikura, PN: FIGH-03-200S, Tokyo, Japan). The GRIN lens replaced the custom three element lens assembly used in the prototype which was challenging to align. The GRIN lens has an outer diameter of 250µm, while the imaging circle diameter of the fiber bundle is only 186µm. This eases the alignment tolerance by allowing some mismatch between the fiber bundle and lens. The proximal end of the fiber bundle is imaged onto a CCD detector (Retiga, PN: R6, Surrey, BC, Canada) using an infinity corrected 40x microscope objective (Olympus, PN: PLN-40x, Center Valley, PA, USA) and an achromatic focusing lens (focal length = 150mm).

A filter wheel (Sutter Instruments, PN: LB10-3, Novato, CA, USA) located between the microscope objective and the focusing lens has an open slot for reflectance imaging, along with four filters (Omega Optical, Inc., PN: 420LP RapidEdge,

510LP RapidEdge, and 540LP RapidEdge, Brattleboro, VT, USA and ThorLabs, PN: FEL0650) to block the 405, 488, 520, and 642nm laser lines, respectively, for MFI.

3.4 | OCT subsystem

The falloposcope lacks a distal beam scanning mechanism due to distal size constraint, instead relying on proximal pullback in a relatively slow "m-scan" or "waterfall" presentation mode. Resolution was prioritized over speed, leading to the choice of a 20 kHz swept source laser (Santec, PN: HSL-2100-WR, Aichi, Japan) in conjunction with a fiber coupled, balanced photo detector (Santec, PN: BPD-200) to accomplish Fourier domain OCT. The laser has a central wavelength of 1319nm, which provides good depth penetration in tissue, and a full width half max bandwidth of 114nm, which yields a theoretical axial resolution of approximately 6.7µm in air[13].

The circulator (Thorlabs, PN: CIR-1310-50-APC), 90/10 beam splitter (Thorlabs, PN: TW1300R2A2), fiber coupled 330ps delay line (OZ Optics, PN: ODL-600-11-1310-9/125-S-60-3A3A-1-1-330), and retroreflector (Thorlabs, PN: P5-SMF28ER-P01-1) are all fiber or fiber-coupled, off-the-shelf components helping to reduce the overall cost and size of the system while making the system robust enough to withstand shock and vibrations during transportation. SM1250-9/80 fiber runs the length of the falloposcope body due to its small outer diameter (170 µm), whereas jacketed SMF-28 is utilized elsewhere. An equivalent length of SM1250-9/80 fiber was included in the reference arm to compensate for wavelength dispersion mismatch between SM1250-9/80 and SMF-28 fibers.

The all fiber OCT probe contains segments of multimode (Thorlabs, FG105LCA) and GRIN (Thorlabs, GIF625) fibers spliced to the SM1250-9/80 fiber and cleaved to length for beam expansion and focusing. The length of each segment of fiber was calculated for a desired spot size of 16µm and a focal distance of 200-250µm using the method described by C. Wang et al.[14]. The final segment of multimode fiber is polished at 48 degrees to make the OCT probe side firing while mitigating back reflection from the exit face[10].

Each falloposcope is manufactured to have minimal variation in the length of the OCT channel; however, it is not practicable to make them the exact same length as each other. A delay line was incorporated into the reference arm which allows for adjustment of up to 7 cm of fiber length variation between falloposcopes.

4 | RESULTS (PERFORMANCE)

Table 1, at the end of the results section, is a summary of the system requirements, measurement (if applicable), and pass/fail determination for each requirement.

4.1 | Mechanical

The complete falloposcope measured 790µm in outer diameter. Figure 7 left) shows the distal tip of a falloposcope placed on a penny. For comparison, the falloposcope appears similar in size to the word "LIBERTY" on the front. The falloposcope easily fits through the introducing catheter and extends to a maximum of approximately 11.5cm out the catheter tip.

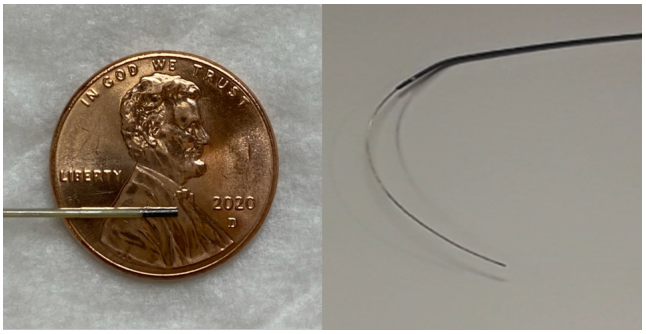

FIGURE 7 Left) The distal tip of the falloposcope shown on the front face of a penny. The diameter is visually similar in size to the text height. Right) Falloposcope extended at the maximum distance from the introducing catheter and deflected by approximately 90 degrees.

The MLE provides structure and protection of the individual components while maintaining flexibility. The pull wires are confined to channels on opposite sides of the falloposcope, which enables steering in two directions within a plane. Approximately 90 degrees of deflection is achieved when the falloposcope is fully extended out of the introducing catheter, as shown in Figure 7 right). All other mechanical aspects of the falloposcope function as designed, including saline or carbon dioxide instillation through the introducing catheter the valve Y connector.

4.2 | Imaging Subsystems

The mode scrambler enabled simple adjustment of the output illumination cone up to 75 degrees (0.61 NA). To test the imaging resolution and FOV, a 1951 USAF resolution target was imaged at distances of 3mm, 5mm, 7mm, and 10mm from the falloposcope tip. Images were captured with the room lights

off, while the 488, 520, and 642 nm lasers simultaneously illuminating the target. The images were analyzed in ImageJ (NIH, Version 1.8.0_112), defining resolvable as a minimum modulation contrast of 15.21% for both the horizontal and vertical bars. FOV was measured by imaging a one lp/mm pattern at each distance. In ImageJ, the known width of one line pair (1mm) was used to set the scale, then the distance over the entire imaging circle was measured. Figure 8 A shows the comparison of the minimum resolvable feature size and the FOV for both the prototype falloposcope (dashed lines) [10] and the current design (solid lines).

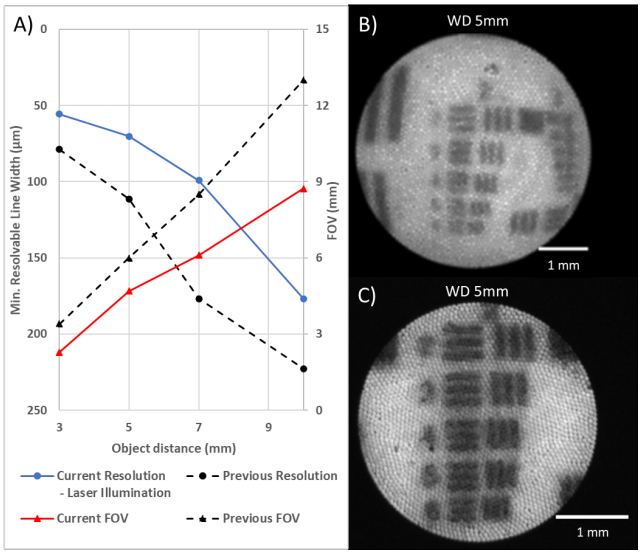

FIGURE 8 A) Plot of the prototype falloposcope (dashed lines) and the clinical version (solid lines) showing the resolution and FOV at object distances between 3mm and 10mm from the tip. B) Image of group 2 of a 1951 USAF resolution target taken with the prototype falloposcope. C) Image of the same group of the resolution target taken with the clinical falloposcope.

The solid blue line is the minimum resolvable feature size. Within the working distance of 3mm to 7mm, the minimum resolvable line width is better than 100µm. While the clinical falloposcope has better resolution than the benchtop prototype, the FOV is only 47°. A smaller FOV over the same imaging area results in an increased magnification which gives us better resolution, as seen by comparing Figures 8 B (prototype) and 8 C (current falloposcope). Using the GRIN lens instead of the custom three lens system dramatically reduced cost and time to build each falloposcope, with an acceptable trade-off of resolution for FOV. Images of the USAF resolution target were taken at a 5mm working distance for each laser wavelength to confirm that the chromatic aberrations from the GRIN lens were insignificant.

The axial resolution of OCT was measured as the FWHM of the signal from a strong reflector, and found to be 10.7µm. To measure the lateral resolution, a falloposcope was pulled back over a Ronchi ruling with 30 lp/mm using a motorized stage. The observed difference between the highly reflective and non-reflective lines on an OCT scan verified a lateral resolution of at least 17µm. Figure 9 shows example images of all modalities of the clinical falloposcope imaging system. Individual narrowband images were taken with the 488nm, 520nm, and 642nm lasers, then overlaid to create a false color image (Figure 9 A) of fallopian tube surgical discard tissue from a female reproductive tract. Figure 9 B) is a monochromatic reflectance image of the same sample as shown in Figure 9 A) using 488nm, 520nm, and 642nm illumination wavelengths simultaneously. Figure 9 C) is a picture of the falloposcope illuminating the tissue used to capture Figures 9 A) and B) with the 520nm source. Figure 9 D) is an OCT scan of an *ex vivo* segment of fallopian tube sliced along the length of the tube and laid open as the tissue was pulled back using a motorized stage while the falloposcope was held in place. The scan shows fluid filled pockets beneath the surface of the tissue. Figure 9 E) is an auto-fluorescence image of the tissue sample illuminated with 405nm light. Figure 9 F) is a picture of the falloposcope illuminating the sample with the 405nm source as was used to capture Figure 9 E).

4.3 | Clinical Readiness

The usability of the falloposcope was assessed by a gynecological surgeon during mock imaging tests of sow reproductive tract, which was dissected to access the distal uterus and fallopian tubes. The connective tissue was cut, and the tube straightened out to better approximate the path of the human fallopian tube. In clinical use, the falloposcope will be introduced through a standard hysteroscope and introducing catheter which will position the falloposcope at the ostium. The falloposcope will traverse the introducing catheter and emerge at the correct angle to enter the fallopian tubes. The testing revealed the capability and challenges of navigating through the fallopian tubes. Comments from initial trials resulted in design changes made to the steering wheel and handle dimensions. Figure 10 shows the tip of the falloposcope partially traversed through the FT while the surgeon is injecting saline through the y connector on the back of the introducing catheter.

To test clinical requirements for being biocompatible and sterilizable, one fully-tested endoscope was designated as a qualification unit and went through hydrogen peroxide sterilization. Sterilization was confirmed by hospital infection control staff, then it was brought back to the lab and tested for

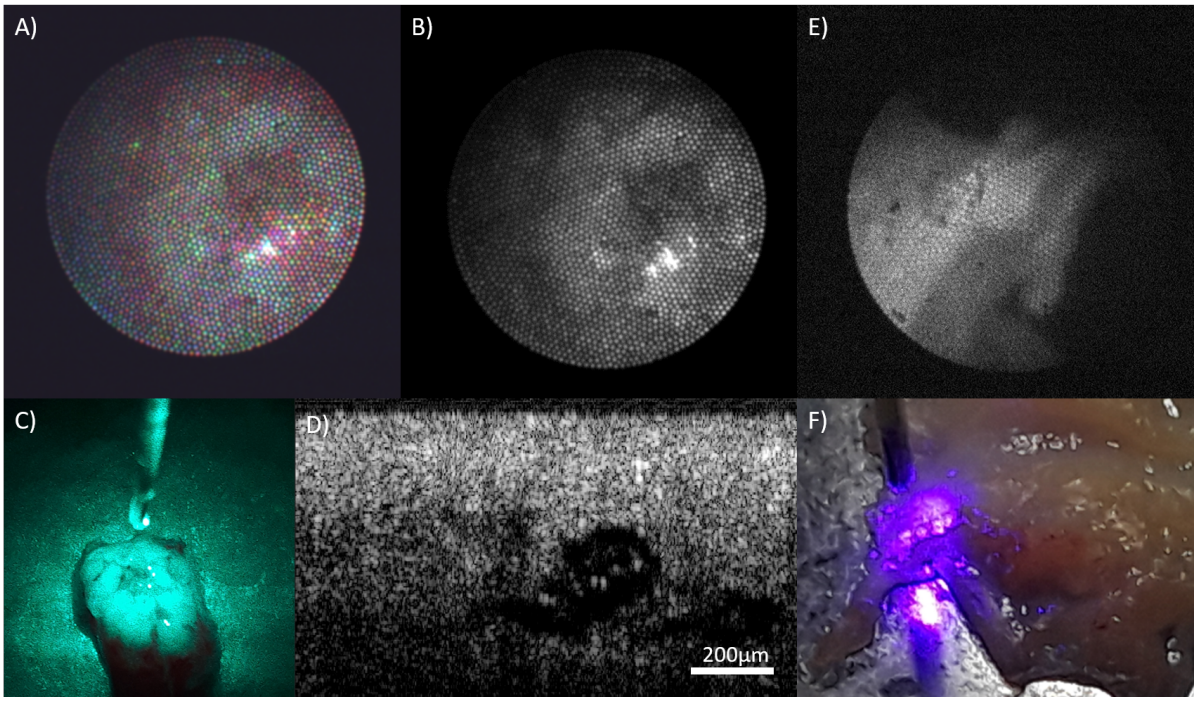

FIGURE 9 A) False color image of human surgical discard tissue from a female reproductive tract. B) Monochromatic reflectance image of the same sample using 488nm, 520nm, and 642nm illumination wavelengths simultaneously. C) Picture of the falloposcope illuminating the tissue imaged in A and B with 520nm light. D) OCT scan of a fallopian tube wall using a motorized stage for a linear pullback to be performed. Fluid filled pockets are visible beneath the surface. E) Auto-fluorescence image of the the surgical discard tissue excited with a 405nm laser. F) Picture showing the falloposcope illuminating the tissue sample with 405nm light used to acquire image E).

performance to ensure no degradation in operational or image quality was observed. Currently, the time to build and test one falloposcope is approximately 12.5 hours with a material cost of $750 per falloposcope (not including components contained within the rack). Each falloposcope is verified to have similar performance based on passing a go/no go test for all imaging functionalities. The system has passed the hospital's clinical engineering electrical leak current safety test [IEC 60601-1 Part 1, third edition, Part 1, section 8.7.3d] and all laser powers are set to be below the ANSI Z136.1 standard with a safety factor of two.

FIGURE 10 Falloposcope being used by a gynecological surgeon in a straightened segment of sow fallopian tube. Light emitted from the probe tip can be see through the tissue.

5 | DISCUSSION

All system requirements were met except for the FOV of the imaging channel. While it is smaller than desired, it was still deemed acceptable for the purpose of the clinical trials. Currently, the only off-the-shelf lens with an outer diameter of 250µm is the GRIN lens used here. To achieve the desired 60° FFOV, a custom lens is required. Our lab has been looking into replacing the GRIN lens with a 3D printed lens [15] giving us optical design flexibility while keeping cost and manufacturing time low. Another future improvement to this project is to

TABLE 1 Summary of the requirements for the system separated by functionality, along with the results and if the performance passes or fails the criteria.

Sub-system	Description	Requirement	Result	P/F
Illumination	Spot Size	Fill FFOV	Up to NA = 0.61	Pass
Reflectance Imaging	Refresh Rate	>30Hz	Limited by monitor, 60Hz	Pass
	Resolution	≤100 μm for WD = 3-7mm	See Figure 8	Pass
	FOV	> 60^o FFOV	47^o FFOV	Fail
	Laser Power	<3.2mW	≤1.5mW	Pass
MFI	Filter OD	>4 OD at laser line	>5OD	Pass
	Exposure Time	≤ 100ms	100ms	Pass
	Laser Power	<3.2mW	≤3mW	Pass
OCT	Axial Resolution	≤20μm	10.7μm	Pass
	Lateral Resolution	≤ 17μm	≤ 17μm	Pass
	Laser Power	≤8.2mW	<5mW	Pass
Mechanical	Diameter	<1mm	790μm	Pass
	Channel for Saline/CO_2	Functional	Tested Functional	Pass
	Extended Length	11-12cm	11.5cm	Pass
	Flexible	≤30mm bend radius	limited by 25mm bend radius of imaging fiber bundle	Pass
	Steerable	±60^o	> ±60^o	Pass
	Biocompatible and Sterilizable	hydrogen peroxide sterilization	Pass sterilization with no performance degradation	Pass
Falloposcope Assembly	Similar performance between falloposcopes	Go/No Go tests	Pass Go/No Go test	Pass
	Parts Cost	< $1000/probe	$750/probe	Pass
	Time to production	< 5 work days/probe	12.5 hrs/probe	Pass
Proximal Components	Transportable	N/A	Endured multiple trips to and from the hospital	Pass
	Easy/Quick connection to falloposcope	<3minutes	<3minutes	Pass
	Electrical Safety	≤100μA - Normal Conditions	0.3μA - Normal Conditions	Pass

incorporate a motorized pull back mechanism inside the handle for automated OCT scanning.

So far, 10 falloposcopes have been constructed and verified to have similar performance by go/no go tests. The next step for verification of the falloposcope system is a pilot test in women who are presumably cancer-free, and are undergoing a procedure including cervical dilation with salpingectomy as their standard of care. For the women who consent to participate, the physician will pause the planned procedure, place a hysteroscope in the uterus, insert the introducing catheter and falloposcope, and image the FTs. This study will test the feasibility of using the falloposcope imaging system in humans and will accumulate an image data base of normal tissue. Once the present study is completed, the next study will aim to perform imaging in high-risk women for the detection of cancer.

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CONFLICT OF INTEREST

The authors declare a conflict of interest in that a patent on the falloposcope has been submitted by University of Arizona (WO2016126879A1).

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6 | BIBLIOGRAPHY

References

[1] Edward E. Partridge, Robert T. Greenlee, Thomas L. Riley, John Commins, Lawrence Ragard, Jian-Lun Xu, Saundra S. Buys, Philip C. Prorok, Mona N. Fouad, *Obstetrics & Gynecology* **2013**, *121* (1), 25–31.

[2] American Cancer Society, *Cancer Facts and Figures*, **2018**, Available from: https://www.cancer.org/content/dam/cancer-org/research/cancer-facts-and-statistics/annual-cancer-facts-and-figures/2018/cancer-facts-and-figures-special-section-ovarian-cancer-2018.pdf [last accessed May 2020].

[3] Amy P.M. Finch, Jan Lubinski, Pål Møller, Christian F. Singer, Beth Karlan, Leigha Senter, Barry Rosen, Lovise Maehle, Parviz Ghadirian, Cezary Cybulski, Tomasz Huzarski, Andrea Eisen, William D. Foulkes, Charmaine Kim-Sing, Peter Ainsworth, Nadine Tung, Henry T. Lynch, Susan Neuhausen, Kelly A. Metcalfe, Islay Thompson, Joan Murphy, Ping Sun, Steven A. Narod, *Journal of Clinical Oncology* **2014**, *32* (15), 1547–1553, PMID: 24567435.

[4] Cathleen M. Rivera, Brandon R. Grossardt, Deborah J. Rhodes, Robert D. Jr Brown, Véronique L. Roger, L. Joseph III Melton, Walter A. Rocca, *Menopause* **2009**, *16* (1), 15–23.

[5] C.P. Crum, R. Drapkin, D. Kindelberger, F. Medeiros, A. Miron, Y. Lee, *Clinical Medicine & Research* **2007**, *5* (1), 35–44.

[6] Tyler H. Tate, Brenda Baggett, Photini F. S. Rice, Jennifer W. Koevary, Gabriel V. Orsinger, Ariel C. Nymeyer, Weston A. Welge, Kathylynn Saboda, Denise J. Roe, Kenneth D. Hatch, Setsuko K. Chambers, Urs Utzinger, Jennifer K. Barton, *Journal of Biomedical Optics* **2016**, *21* (5), 1 – 9.

[7] Jessica Mcalpine, S. Hallani, S. Lam, Steve Kalloger, Margaret Luk, D. Huntsman, Calum Macaulay, C. Gilks, Dianne Miller, Pierre Lane, *Gynecologic Oncology* **2011**, *120*, 385–92.

[8] Ronie George, Michalis Michaelides, Molly Brewer, Urs Utzinger, *Lasers in surgery and medicine* **2012**, *44*, 282–95.

[9] Mikhail Yu. Kirillin, Natalia M. Shakhova, Olga G. Panteleeva, Ekaterina Yunusova, Ekaterina Donchenko, *Journal of Biomedical Optics* **2012**, *17* (8), 1 – 6.

[10] Molly Keenan, Tyler H. Tate, Khanh Kieu, John F. Black, Urs Utzinger, Jennifer K. Barton, *Biomed. Opt. Express* **2017**, *8* (1), 124–136.

[11] Carlton A. Eddy, Carl J. Pauerstein, *Clinical Obstetrics and Gynecology* **1980**, *23* (4), 1177–1194.

[12] Elizabeth Swan, Tyler Tate, Molly Keenan, John F. Black, Urs Utzinger, Jennifer Barton, in *Endoscopic Microscopy X; and Optical Techniques in Pulmonary Medicine II*, (Eds: Melissa J. Suter, Stephen Lam M.D., Matthew Brenner, Guillermo J. Tearney M.D., Thomas D. Wang), International Society for Optics and Photonics, SPIE, **2015**, pp. 93 – 98. https://doi.org/10.1117/12.2078671.

[13] C. Boudoux, *Fundamentals of Biomedical Optics 1st ed.*, Pollux, **2017**, chapter 16.

[14] Chi Wang, Chen Fang, Zhi Tang, Yingjie Yu, Youxin Mao, Bo Qi, *Optical Engineering* **2011**, *50* (9), 1 – 10.

[15] Kelli C. Kiekens, Jennifer K. Barton, *OSA Continuum* **2019**, *2* (11), 3019–3025.

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