Optical Coherence Tomography:
A Minimally-Invasive Diagnostic Tool For Patients With AIN

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Abstract

**Background:** Optical coherence tomography (OCT), a near-infrared imaging technology that produces cross-sectional images of the internal microstructure of biologic tissues, has previously been used to detect squamous cell carcinoma, but not within the anal canal. We hypothesized that OCT could distinguish between patients with anal intraepithelial neoplasia (AIN) and controls.

**Materials and Methods:** We obtained OCT images of the anal canal in 30 patients at high-risk for AIN and 30 controls. High-risk AIN patients underwent high-resolution anoscopy ± biopsy to confirm presence or absence of disease. A blinded analyst measured images for epithelial thickness and brightness. Using criteria from cervical dysplasia literature, 3 blinded and 2 unblinded colorectal surgeons with no prior OCT experience evaluated images for presence of AIN. Sensitivity, specificity, positive predictive value, negative predictive value and kappa statistic, a measure of intra-rater agreement, were calculated.

**Results:** OCT was well-tolerated by all patients. AIN patients had a higher prevalence of immunosuppression (52% vs 13%, $p=0.001$). Epithelial thickness and brightness were not significantly different between groups. Sensitivity for blinded investigators was 8-31% with 85-78% specificity. Sensitivity for unblinded investigators was 31-77% with 71-75% specificity with a kappa statistic of 0.11.
Conclusions: Interpretation of OCT images by naïve observers had better sensitivity, specificity, and negative predictive value when pre-test probability was high. This may improve with observer experience and advancements in technology. Further characterization of the anal canal with newer models for OCT imaging is needed to determine the utility of OCT as a non-invasive clinical adjunct for detection of AIN.
Acknowledgments

Thank you to the colorectal surgeons that generously allowed me into their operating rooms and clinics to recruit patients and perform exams, painstakingly reviewed patient images, and provided moral support, encouragement, and enlightenment: Mary R. Kwaan, M.D., M.P.H., Robert D. Madoff, M.D., Genevieve Melton-Meaux, M.D., M.A., James W. Ogilvie, Jr., M.D., M.S., and David A. Rothenberger, M.D., Division of Colon and Rectal Surgery, Department of Surgery, University of Minnesota. Thank you to the biostatistics department and the graduate students that helped with my statistics, Andy Wey and Tingting Zhao, and the biostatistician that masterminded it all, Joe Koopmeiners. I had no idea what bootstrap adjustments were before I met them. I would also like to acknowledge the clinic staff in PWB-1E, Riverside Endoscopy Center, and the operating room staff at UMMC who welcomed me as a researcher and put up with my interruptions into their normal routines. Finally, I would like to thank Nancy Tresser, M.D., M.B.A., Katy Ledford, B.S., and the Imalux Corporation for teaching me about OCT, measuring the images, and lending me the imaging system, without which we would not have been able to perform this work.
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Introduction and Background

Anal intraepithelial neoplasia (AIN) is a known precursor to invasive squamous cell cancer (SCC) of the anus. AIN is strongly associated with receptive anal intercourse in men who have sex with men (MSM), HIV positivity, and infection with high-risk HPV. AIN and cervical intraepithelial neoplasia (CIN) both have similar histologic features in histologically similar parts of the body, both serve as precursors to invasive cancer, and both are strongly associated with oncogenic HPV. Approximately 91% of patients with high grade AIN are HPV+ and 81% of patients with invasive SCC of the anus are HPV+.

Despite increased understanding of the biology of anal dysplasia and anal cancer, and improved medical therapies for HIV positivity, there appears to be a growing incidence of anal cancer especially among HIV-positive patients. The National Cancer Institute estimated that 6230 people in the US would be diagnosed with anal cancer and that 780 men and women would die from anal cancer in 2012. While the overall anal cancer incidence is low in the general U.S. population (1.4-1.8/100,000), it is substantially higher in high-risk groups. A large multicenter cohort study in MSM showed that the incidence in all MSM is 14/100,000, and in HIV-positive MSM the incidence is 69/100,000 (pre-HAART era) and 137/100,000 (post- HAART era). The overall anal cancer rate in MSM is similar to the rate of cervical cancer in women prior to the implementation of cervical Pap testing. AIN is much more prevalent than anal cancer, with estimated prevalence rates of up to 52% of MSM patients that are HIV positive and 25% prevalence in MSM patients that are HIV negative.
Current evaluation of AIN has been modeled after established methods for cervical cancer screening. The general recommendation for patients at high-risk of developing AIN is to undergo screening with anal cytology, akin to a Pap smear of the anal canal. If this is found to have any abnormalities, high resolution anoscopy (HRA) may be recommended. HRA utilizes a high-resolution microscope to examine the tissues of the anal canal during anoscopy. Abnormal areas are identified with gross visual inspection as well as acetic acid application and acetowhite staining, similar to standard colposcopic techniques. Further areas of high grade AIN may be identified by Lugol’s Iodine staining. Biopsies are then taken of abnormal areas and histologic examination and grading using the Bethesda criteria is then performed.\textsuperscript{7}

There is no formal recommendation for treatment of AIN. Current options include close observation and follow-up, excision, ablation, infrared coagulation and topical treatments such as imiquimod. Because of the risk of anal stenosis, abscess, pain, and high morbidity associated with excision or cautery of the anal canal, often times, high-grade dysplasia is closely monitored with high-resolution anoscopy and biopsy. Treatment of precursor lesions can reduce the risk of invasive anal cancer, but there is also a high recurrence rate for all modalities. A recent study of AIN treated by infrared coagulator had a recurrence rate 65% with a median time to recurrence of 217 days.\textsuperscript{8} Studies of surgical treatment for AIN showed a recurrence rate of 45-79%.\textsuperscript{9-10} Thus, close follow-up every 6 months and treatment of recurrent dysplasia is essential to treatment plan.

Optical coherence tomography (OCT) is a non-invasive, near-infrared high-resolution imaging technology that can produce cross-sectional images of the internal
OCT uses low-coherence interferometry to produce 2-D optical scattering. This backscattering is then measured to produce images based on the intensity of the light; principles similar to ultrasound technology except with light instead of ultrasound waves. These high-resolution images of the microarchitectural structures are produced in real-time, thus producing a type of “optical biopsy” and can scan up to depths of 2 mm. Images can be saved to a file and viewed in real-time or at a later date.

OCT is widely used in ophthalmology to image the retina for pathologies such as macular degeneration and retinal detachment. Its application in a probe-based system has been widely studied in various medical fields such as dermatology, urology, gynecology, and gastroenterology. OCT has even been used to evaluate cervical intraepithelial neoplasia (CIN) with reported sensitivities as high as 95-98%. The ability of OCT to produce an optical biopsy using a small probe without actual biopsy, allows for a minimally-invasive way to image the anal canal and, perhaps, produce a better image for evaluation of AIN. This tool may also lead to visually-guided biopsies, ablation or other treatments of AIN, enhance sensitivity and specificity of current diagnostic and screening procedures, as well as allow for direct monitoring of dysplastic areas without biopsy. A minimally-invasive means of examining the anal canal could also potentially increase the compliance with anal dysplasia screenings in high-risk patients.

The aim of this project was to evaluate the utility of OCT as a diagnostic tool for AIN using both surgeon-rated interpretations of OCT images and objective measurement of epithelial thickness and brightness. We hypothesized that OCT can be used to diagnose AIN.
Materials and Methods

Study site and subject selection

We performed a prospective, cross-sectional comparative study of patients at high-risk for AIN (cases) and presumed healthy controls from November 2011 to October 2012. This study was approved by the Institutional Review Board at the University of Minnesota. Informed consent was obtained from all patients prior to enrollment in the study. All procedures took place in the clinics or operating rooms of our tertiary care medical center or at an affiliated endoscopy center.

Patients were defined as “high-risk” if they were known to be HIV+, a man who has sex with men with abnormal anal cytology findings, have a previous history of AIN, or have other HPV-related disease in the anogenital region such as high-grade vulvar intraepithelial neoplasia (VIN). These patients were recruited from the anal microscopy clinic at the University of Minnesota. Patients in the control group were recruited from the colon and rectal surgery clinic at the University of Minnesota Department of Surgery if they were seeking treatment for benign anorectal conditions, screening or surveillance colonoscopies, or examinations in the operating room. We excluded patients with inflammatory bowel disease, rectal or anal cancer, active perirectal abscess, known previous AIN, or physical exam finding or pathology result concerning for AIN or anal cancer.

The following demographic information was recorded from each patient: age, sex, AIN disease status, HIV status (if known), immune status. Immunosuppressed patients
were defined as those with a diagnosis of HIV, a previous solid organ or bone marrow transplant, or on immunosuppressant medications such as methotrexate or cyclosporine.

**OCT imaging procedure**

The Niris® 1300 operating system (Imalux Corporation, Cleveland, OH), which consists of a reusable fiber-optic probe connected to an imaging console, was used to obtain OCT images of the anterior, posterior, right lateral, and left lateral portions of the anal canal in all patients (Figure 1). The OCT imaging console contains an optical fiber-based interferometer with super luminescence diode that provides the near-infrared light necessary for OCT, scanning to a depth of 1.5mm and laterally with a range of 1.6-2.5mm. The probe is long and flexible and its width is 2.7mm, thus allowing it to be inserted into the finger of an examination glove and can also be used down the channel of an endoscope. Before a patient’s scheduled anal exam in the anal microscopy or colorectal surgery clinic, a digital rectal examination was performed with the OCT probe in place and OCT images taken through the glove. The probe scans laterally continuously, producing real-time images on the imaging console. OCT images were obtained from the anterior, posterior, right lateral and left lateral positions of the anal canal. Additional images may have been taken and saved if there was a known mass or abnormality in the anal canal (*i.e.* skin tag, scar tissue) or appeared as abnormal on the OCT monitor. All OCT imaging procedures were performed by the same surgeon investigator. Images were saved to a hard drive for later review. An ID number was created for each patient enrolled in the study and included with the image files as well as notations of each image’s location in the anal canal. OCT images were then shuffled so as
to mix groups and then assigned new ID numbers and compiled into an image database. No patient identifiers were included with the images.

After OCT examination, the patient’s scheduled procedure or HRA was then performed. All OCT examinations occurred prior to application of acetic acid during HRA. Results from biopsies obtained during HRA or procedures were recorded and later correlated with imaging findings. The performing surgeon’s impression of HRA examination and location of any suspicious areas were also recorded. All suspicious areas of AIN were treated with cautery ablation.

OCT image interpretation

Images were reviewed by five surgeon investigators and assessed for presence of AIN. Three investigators who were blinded to patient group status reviewed images from both cases and controls. Two investigators were made aware of patient group status but were not provided with additional clinical information such as patient age, HRA findings or immunosuppressed status. These unblinded investigators included the investigator performing the OCT procedure, although images were not interpreted in real-time. All investigators were inexperienced at interpreting OCT images and received the same training via an instructional CD that contained diagnostic criteria derived from the CIN literature, example images from CIN studies of OCT, and annotated images from control patients interpreted by an experienced OCT individual (representative from the Imalux company) (Figure 2). Images were interpreted using the criteria established for diagnosis of cervical intraepithelial neoplasia as described by Escobar et al (2004). These criteria specify that non-diseased tissues must demonstrate visualization of a distinct two-layer
architecture (i.e. epithelial layer and underlying stroma, with sharp interface in between the two representing an intact basement membrane), while tissues with intraepithelial neoplasia demonstrate increasing irregularity of the epithelial layer and higher levels of backscattered epithelium. For each patient, investigators reviewed images from all 4 quadrants of the anal canal. Investigators were asked to determine if dysplasia (AIN 1-3) was present (yes/no) in any quadrant, and, if present, record the location of the dysplasia.

All images in the image database were also sent to a blinded analyst at the Imalux corporation with experience in OCT image measurement. No clinical information was included with the images. Images were measured for epithelial thickness as well as mean backscattering intensity of the epithelial layer which is a measure of brightness.

Statistical analysis

Patient demographics of the cases and controls were compared using Student’s t and chi-square tests (alpha=0.05). Epithelial thickness and mean brightness for images from biopsy-proven quadrants with AIN were compared to images from non-diseased areas. Generalized estimating equations\textsuperscript{18} with an exchangeable working correlation structure were used to account for repeated measurements on the same individual. Using HRA with or without biopsy as the gold standard for a diagnosis of AIN, we determined sensitivity and specificity of OCT in the high-risk patient group. The sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) were calculated for each investigator and 95% confidence intervals were calculated using the non-parametric bootstrap to account for multiple measurements on the same individual.
The kappa statistic was calculated for the unblinded group and confidence intervals for the kappa statistic were calculated using the bootstrap.

**Results**

We recruited 30 patients at high-risk for AIN and 30 controls for a total of 60 patients during the study period. All patients tolerated digital rectal exam with the OCT probe well and each exam lasted no longer than 2-4 minutes. Overall, 240 images were collected for all 60 patients. The mean age of the cohort was 52.2 years (range 20-85) and approximately half of the patients (48%) were male. The majority of control patients were being seen in the colorectal surgery clinic for screening colonoscopies (30%), hemorrhoidectomies (30%), or skin tag or anal fissure procedures (17%). Demographics for the patients at high risk for AIN are shown in Table 1. Twenty-one of the 30 (70%) patients in the high-risk group had presence of AIN or squamous cell carcinoma confirmed in at least one of the quadrants of the anal canal with either biopsy or HRA. Lesions was more commonly found in the left (60%), right (60%), and anterior (55%) quadrants of the anal canal while lesions were found in the posterior quadrant only 35% of the time.

There were no significant differences in age or gender between the high-risk group and control groups (Table 2). High-risk AIN patients had a higher prevalence of immunosuppression than controls (52% vs 13%, \( p=0.001 \)). Epithelial thickness and measurement of brightness were not significantly different between the high-risk AIN group and control group (Table 2).
Amongst the blinded investigators, OCT had a sensitivity ranging from 8.3-33%, specificity 61.8-85.3%, PPV of 28.6-50.0%, and NPV of 56.8-61.6% (Table 3). Between the two unblinded investigators, sensitivity ranged from 31.2-77.1%, specificity of 70.6-75.0%, PPV 46.9-64.9%, and NPV 60.7-81.4%. The inter-rater kappa statistic was 0.11 (95% CI -0.02-0.25).

**Discussion**

OCT has been used to obtain “optical biopsies” in a variety of animal models and human tissues such as the retina, bladder, esophagus, and cervix. Our study is the first to use OCT to image the anal canal and to evaluate its potential as a minimally-invasive diagnostic tool for AIN. We found that OCT examination of the anal canal was well-tolerated by patients undergoing procedures in both the operating room and clinic setting. With the OCT probe in the finger of an examination glove, we were able to obtain images of the anterior, posterior, right lateral and left lateral portions of the anal canal without the use of an anoscope. The distinctive two-layer architecture of the epithelial layer and underlying stroma were visualized in most images.

We were unable to detect significant differences in epithelial thickness or brightness between areas of confirmed dysplasia and normal tissue in our cohort. This may have been due to sampling error, as our selected OCT images were not obtained under direct visual guidance during anoscopy. The width of the probe is only 2.7mm and thus, only a small area of each quadrant of the anal canal was sampled. The obtained anal canal images may have been taken from non-diseased or mildly diseased areas as opposed to focused areas of high-grade AIN identified during HRA. In addition, we may
not have detected differences between groups because of a higher than expected rate of false positives in the control group. Atrophy, metaplasia, and inflammation are known to mimic histopathological findings of CIN-2\textsuperscript{19-20} and we suspect this may be true for AIN. Diarrhea from the colonoscopy preparation or irritation from hemorrhoids or anal fissures may have potentially caused changes in the anal canal tissues that also lead to epithelial thickening or an increase in brightness as measured by OCT. Moreover, 13% of patients in the control group were immunosuppressed and may have had undiagnosed inflammation or dysplasia of the anal canal. We also may not have had enough patients with moderate to severe dysplasia in our cases group to detect a significant difference in epithelial thickness or brightness compared with non-diseased areas of the anal canal.

The results of our study show that sensitivity, specificity, and precision of OCT to detect AIN was widely variable between investigators and varied based on the amount of clinical information accompanying the images. When investigators were informed of patient group status (high-risk for AIN or presumed healthy control), the sensitivity, specificity, NPV and PPV were higher than when investigators were blinded to group status. Additional clinical information such as HRA findings, previous history of AIN, anal canal biopsies, history of VIN, or an immunosuppressed status may change the suspicion level of investigators and the amount of time spent interpreting each image. If OCT was used in the clinical setting, such clinical information would likely be available for physicians performing OCT, and further determination of sensitivity and specificity of OCT under such real-world conditions may be warranted. Interpretations of images may also vary when read in real-time versus at a later date.
Several studies have evaluated OCT as a potential diagnostic or screening tool for CIN with reported sensitivities of 29-95% and specificities of 11-93%. In line with our observations, the sensitivity and specificity of OCT to detect CIN 2 has been shown to vary with the amount of clinical information available to investigators. For example, in a study of 212 women, Escobar et al determined sensitivity and specificity of OCT for detecting CIN 2 in the cervix with varying amounts of clinical information available: patient age only; results from visual inspection with acetic acid (VIA) with a non-magnified digital image of the cervix; and Pap test results, colposcopic diagnosis by quadrant, and magnified digital photograph of the cervix. The overall sensitivity of OCT for detecting CIN-2 by investigators with minimal clinical information was 56% and specificity was 59%, while the addition of VIA results decreased sensitivity to 53% but increased specificity to 61%, and full knowledge of colposcopic findings decreased sensitivity to 46% and increased specificity to 69%. These results, along with the findings in our own studies, suggest that the addition of clinical information may bias investigators in their interpretation of OCT images. In addition, there may be high intra-rater and inter-rater variability in image interpretation and sensitivity and specificity estimates may depend on physician experience with OCT image interpretation or image interpretation using other modalities (i.e. ultrasound, histopathology). Further research with standardization of OCT training of observers or characterization of prior observer experience in other modalities may help delineate such factors.

Other studies involving OCT evaluation of the cervix have tested the utility of OCT as an adjunct to VIA or colposcopy. Wulan et al obtained OCT images from abnormal areas of the cervix identified by VIA in 182 patients. Images were then read in
real-time. Standard colposcopy with biopsy was performed and comparisons between VIA-guided OCT images and histopathology results were then compared. The addition of OCT as an adjunct to VIA increased sensitivity from 31% to 50% while specificity decreased from 96% to 80%. In a similar study examining the utility of OCT as an adjunct to colposcopy, however, sensitivity decreased from 60% to 29% while specificity increased from 83% to 93%. Escobar et al also found that OCT decreased sensitivity of VIA for the detection of CIN 2 from 76% to 53% but increased specificity of VIA from 34% to 61%. Thus, OCT may not serve as a useful initial screening tool, but may be useful as a secondary screen prior to biopsy.

Based on preliminary work in the CIN literature, OCT may similarly have potential to serve as a useful adjunct for diagnosis of AIN. Current estimates of sensitivity and specificity for anal cytology are widely variable in the literature with sensitivity ranging from 8-88% and 60-94%, respectively, with agreement between cytologic rating and histologic grade of only 0.2. For high-grade dysplasia, anal cytology has been shown to have only a sensitivity of 16-29% and specificity of 91-97%. Studies have also shown that the sensitivity and specificity of anal cytology varied based on immune status. The sensitivity and specificity of anal cytology improve among patients with HIV while the estimates improved with lower CD4 cell counts. Like anal cytology, OCT may prove to be more sensitive and specific in selective patient populations such as HIV-positive patients or patients with a previous history of AIN. For HRA, studies have shown estimates of sensitivity at 90-100%, specificity 19.2-71%, PPV 41.7-47.62%, NPV 75-100%. As demonstrated in the CIN literature, OCT may have
the ability to further increase the specificity of HRA and decrease the number of biopsies needed for diagnosis or surveillance of AIN.

Limitations of our study include the lack of previous experience with OCT image acquisition and image interpretation. All investigators were previously inexperienced with OCT image interpretation and although instructional methods were provided to all investigators, there was no testing of efficacy of instruction. As our own center’s experience with OCT image acquisition and image interpretation increases, we may find that sensitivity and specificity of OCT to detect dysplasia increases, as has been demonstrated in the CIN literature. Our study was also limited by the current model of OCT and nature of the probe used. Currently, the OCT model used in this study only images at the surface of the 2.7mm diameter probe and does not allow for a wide field of view when obtaining images. A larger, rounded probe with the ability to scan radially, or a higher-resolution model may improve the ability to detect abnormal areas of the anal canal. We also did not obtain biopsies in the control group of patients and therefore could not confirm that AIN or inflammation was present in our presumed normal OCT images. Further studies involving obtaining images from high-risk only patients in areas confirmed to be normal or diseased by VIA may also provide a better estimate of OCT’s true potential as a diagnostic tool for AIN.

Advances in OCT technology continue to develop for use in CIN diagnosis and other medical fields. Gallwas et al\textsuperscript{35} recently described their experience using OCT models with 3-D capabilities to produce better quality images for detection of CIN. Three-dimensional OCT models have also been described for use in the colon to diagnose a variety of pathologies.\textsuperscript{36} Preliminary studies of fluorescence-guided OCT in a mouse
model have also shown potential use in colon cancer screening. Fourier-domain OCT has improved on traditional OCT technology by increasing imaging speeds, allowing imaging of larger areas of tissue such as the esophagus and coronary arteries for diagnosis of various disease processes. For example, Khandhar et al recently used Fourier-domain OCT to evaluate intimal thickening in the left anterior descending artery in heart transplant recipients. Higher resolution OCT with faster imaging speeds, faster processing speeds, development of a probe more suitable for the anal canal, Fourier-domain OCT, or perhaps computer-based readings of OCT images may be useful non-invasive alternatives or adjuncts for current practices for screening and diagnosis of AIN.

**Conclusions**

In conclusion, OCT examination of the anal canal was well-tolerated in the outpatient setting. Significant differences in epithelial thickness or brightness could not be detected between presumed normal controls and patients at high-risk for AIN. The ability to detect AIN in patients at high-risk for AIN varied based on physician experience and amount of accompanying clinical information. As we gain more experience with OCT, it may prove to be a useful adjunct to existing methods of screening and diagnosis of AIN, especially as the OCT technology and equipment continue to advance.
References

15. Drexler W. Cellular and functional optical coherence tomography of the human


Figure 1: OCT imaging system and probe
Figure 2: Example annotated OCT image of the anal canal
Table 1: Characteristics of the high-risk AIN group

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>n(%)</th>
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<tbody>
<tr>
<td><strong>Reason for exam</strong></td>
<td></td>
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<tr>
<td>VIN/cervical HPV</td>
<td>9 (30.0)</td>
</tr>
<tr>
<td>Previous AIN</td>
<td>15(50)</td>
</tr>
<tr>
<td>Referral</td>
<td>10(33.3)</td>
</tr>
<tr>
<td><strong>Histology results</strong></td>
<td></td>
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<tr>
<td>AIN 1</td>
<td>11(37)</td>
</tr>
<tr>
<td>AIN 2-3</td>
<td>8 (27)</td>
</tr>
<tr>
<td>Invasive carcinoma</td>
<td>2 (7)</td>
</tr>
<tr>
<td>Negative for dysplasia</td>
<td>9(30)</td>
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Table 2: Comparison of the high-risk AIN group and controls

<table>
<thead>
<tr>
<th>Variable</th>
<th>AIN patients (n=30)</th>
<th>Controls (n=30)</th>
<th>p-value</th>
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<tbody>
<tr>
<td>Age, mean years (SD)</td>
<td>50.7(14)</td>
<td>53.7(19)</td>
<td>0.48</td>
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<tr>
<td>Male, n(%)</td>
<td>12(41%)</td>
<td>17(55%)</td>
<td>0.29</td>
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<tr>
<td>Immunosuppressed</td>
<td>15(52%)</td>
<td>4(13%)</td>
<td>0.001</td>
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<tr>
<td>Epithelial depth, mean µm (SD)</td>
<td>98.2(36.6)</td>
<td>90.8(32.2)</td>
<td>0.90</td>
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<td>Epithelial brightness, mean dB (SD)</td>
<td>57.8(11.2)</td>
<td>59.1(11.6)</td>
<td>0.23</td>
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Table 3: Summary of sensitivity, specificity, PPV and NPV for blinded and unblinded investigators

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<th>PPV</th>
<th>NPV</th>
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<td>Bootstrap Estimate</td>
<td>0.312</td>
<td>0.779</td>
<td>0.500</td>
<td>0.616</td>
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<td>95% CI</td>
<td>(0.140, 0.490)</td>
<td>(0.653, 0.896)</td>
<td>(0.263, 0.720)</td>
<td>(0.489, 0.740)</td>
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<tr>
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<td>0.333</td>
<td>0.618</td>
<td>0.381</td>
<td>0.568</td>
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<tr>
<td>95% CI</td>
<td>(0.151, 0.543)</td>
<td>(0.439, 0.783)</td>
<td>(0.211, 0.542)</td>
<td>(0.412, 0.721)</td>
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<tr>
<td><strong>Blinded3</strong></td>
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<tr>
<td>Bootstrap Estimate</td>
<td>0.083</td>
<td>0.853</td>
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<td>0.569</td>
</tr>
<tr>
<td>95% CI</td>
<td>(0.0, 0.179)</td>
<td>(0.750, 0.944)</td>
<td>(0.000, 0.571)</td>
<td>(0.449, 0.686)</td>
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<tr>
<td><strong>Unblinded1</strong></td>
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<tr>
<td>Bootstrap Estimate</td>
<td>0.771</td>
<td>0.706</td>
<td>0.649</td>
<td>0.814</td>
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<tr>
<td>95% CI</td>
<td>(0.651, 0.894)</td>
<td>(0.562, 0.824)</td>
<td>(0.529, 0.767)</td>
<td>(0.674, 0.927)</td>
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<tr>
<td><strong>Unblinded2</strong></td>
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<td>(0.164, 0.476)</td>
<td>(0.656, 0.846)</td>
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<td>(0.471, 0.741)</td>
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