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CENTER FOR DEVICES AND RADIOLOGICAL HEALTH

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PUBLIC WORKSHOP - FORUM ON LASER-BASED IMAGING

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Tommy Douglas Conference Center
10000 New Hampshire Avenue
Silver Spring, Maryland

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SESSION 1: OPTICAL COHERENCE TOMOGRAPHY (OCT)

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M E E T I N G

(8:35 a.m.)

DR. EYDELMAN: Good morning, everyone. On behalf of the FDA, it gives me great pleasure to welcome all of you to today's forum.

The Center of Devices and Radiological Health has a mission to facilitate medical device innovation by advancing regulatory science, providing industry with predictable, consistent, transparent, and efficient regulatory pathways. We do this by challenging the status quo and ourselves to force a positive change. We harness the creativity of our staff and stakeholders. We rapidly test and adapt new approaches to more effectively and efficiently accomplish our mission. We make decisions based on sound science using the best available data, methods, information, and tools. We value and take into account differing internal and external perspectives.

Collaboration is a word that you hear very often around FDA and for a good reason. It is an essential element of many approaches we apply to achieve our public health mission. Proactively working with stakeholders in the medical device ecosystem to solve both shared problems and problems unique to others allows us to serve the American public better and to achieve our vision.

Today's event is a true collaboration between 11 professional organizations and academic institutions and FDA. These parties have gotten together and for the last year have pondered the question of how to expedite innovation of laser-based imaging devices. The committee worked very hard to try to identify the key questions and key topics that need to be addressed today. And I'm delighted that they have come up with an outstanding agenda for today.

You will hear about OCT's regulation, novel applications of leading-edge OCT for diagnosis and treatment of glaucoma, anterior segment, and retina diseases. We will

discuss clinical standards for assessment in AI-assisted segmentation. For the first time ever in the regulatory world, we'll be discussing AO. We will cover its clinical uses, research applications and how they can lead to clinical trials, and regulatory considerations. Also for the first time, from the podium, we will be discussing a possibility of using nonclinical data sources to provide adequate information for AO and OCT. And you'll hear about an exciting new program, called Medical Device Development Tool, that we have developed at CDRH.

And last but certainly not least, we're delighted to bring to you today a reimbursement session. We realize that our devices are only good once they reach the public. In other words, we need to make sure that once approved, they can be sold and bought. Hence, we have put together for the first time, together with an ophthalmic innovation workshop, a reimbursement session, and there we will discuss reimbursement considerations as well as address a CDRH payer program.

Today's goal is to deliver transformational change by combining the best internal and external talent to shorten the time from conception to market, and each one of you is the change agent. Together, we will help bring the U.S. as the world's leader in regulatory science and medical device innovation and assure that patients in the U.S. have access to high-quality, safe and effective medical devices of public health importance first in the world.

Thank you.

(Applause.)

DR. MYUNG: Thank you, Dr. Eydelman, and good morning, everyone. It's a privilege to be here with you. My name is David Myung, and I'm here with Dr. Mark Blumenkranz representing the Byers Eye Institute at Stanford and its ophthalmic innovation program, which I've had the honor of serving on the planning committee and to be co-sponsoring today's event along with the FDA and 10 of our nation's leading professional vision health

organizations whose efforts, commitment, and support for this forum -- it would not be possible to have this forum without them. I'd like to acknowledge them here, right now:

- The American Academy of Ophthalmology;
- The American Academy of Optometry;
- The American Academy of Pediatric Ophthalmology and Strabismus;
- The American Optometric Association;
- The American Society for Cataract and Refractive Surgery;
- The American Society of Retinal Specialists;
- The American Glaucoma Society;
- The American Uveitis Society;
- The Cornea Society; and
- The Retina Society.

The gathering of these 12 organizations is a testament to just how important laser-based imaging modalities have become to clinical practice and to patient outcomes and also the growing importance that they will continue to have as new technologies come to the fore and are accelerated into the marketplace, which is the very subject of today's events.

We're truly excited to have a lineup of world-class speakers today in the field serving as speakers and panelists, and on behalf of the planning committee, I want to thank them, our speakers and panelists, Dr. Eydelman and FDA for their vision and initiative for putting this whole day together, and everyone here in person and also online via webcast, for joining us today.

Please join me now in welcoming Brad Cunningham from the FDA, who will be talking to us about the FDA's approach, its regulatory approach to OCT devices. Brad is the Chief of Diagnostic and Surgical Devices at the Office of Device Evaluation at CDRH. So let's give him a warm welcome.

(Applause.)

MR. CUNNINGHAM: Well, good morning. And I guess I have the distinct honor of being the first presenter of the main session. So like Dr. Eydelman said, I'm really excited to be here, and I think this is a fantastic turnout, so thank you all for coming. I am the Branch Chief for the Diagnostic and Surgical Devices Branch in the Office of Device Evaluation, and I really look forward to today's discussion.

So I'll start this to get us on the same page with a pared-down version of the medical device definition, which can be found in Part 201(h) of the Food, Drug, and Cosmetic Act. But put simply, to be a medical device you have to be -- the device has to cure, mitigate, treat, prevent a disease or condition, and has to affect the structure or function of the body. The most important part is that it cannot achieve its primary mechanism of action through a chemical action or through being metabolized.

Devices are separated into three classes, Class I, II, and III, with Class I being the lowest risk and Class III being the highest risk. These determinations are based on the technology and intended use.

Class I are subject to general controls. I show them here on the slide. I think it's important to point out that most Class I devices are exempt from premarket notification or premarket review.

Class II devices, moderate risk, are subject to everything that was on the previous slide but also additional special controls and most notably of which is the 510(k) or premarket notification. There are some that are exempt from it, but most, by and large, are subject to the premarket review process.

Class III are highest risk devices and are subject to the most rigorous premarket review, which is our premarket approval application. And there are some additional controls, for example, a premarket manufacturing inspection as well as post-approval

reporting requirements, among others.

I just wanted to point out some basic examples of devices and their classification for ophthalmic, and you can see right in the middle, under Class II is OCT devices, as well as software, as a medical device. I think it's relevant to today's discussion.

These are the various application types for devices, and I will be just briefly covering those top two rows there, premarket notification and de novo classification.

So starting with 510(k), it's a premarket notification submission or because of its section in the Food, Drug, and Cosmetic Act, it's known as a 510(k), which is a mechanism by which Class I, some Class I and most Class II devices are brought to market. As part of our evaluation, we determine whether a new device, the subject device, is substantially equivalent to a legally marketed device of its same intended use and similar technology, called a predicate device.

There's definitely a lot that goes into this, but I tried to pare it down to one slide. In general, if the device has the same intended use, and that has to be true, if it has the same intended use and the same technology, the device is deemed to be substantially equivalent to its predicate. If it has the same intended use but different technological characteristics, it can still be determined as SE, or substantially equivalent, so long as those new technological differences don't raise different types of safety and effectiveness questions and that those can be addressed through some type of performance testing or rationale or otherwise.

For those devices that didn't quite meet the cut and were determined to be not substantially equivalent, or NSE, because of those reasons of new intended use or new technologies, they were automatically deemed as Class III as per our original regulatory paradigm and therefore subject to premarket approval application. In 1997 with the Food and Drug Administration Modernization Act, there was the de novo classification process

brought into light. This pathway allowed FDA to classify devices that were deemed NSE and automatically classify to Class III and put those into Class I or Class II. The program was again modified in 2012 with the FDA Safety and Innovation Act, which allowed for something very important, and that's a direct de novo, removing the requirement for an NSE decision prior to submitting.

Through the classification process, we make the determination of whether general controls alone or whether general and special controls can be effective to adequately regulate the device in the Class II or Class I realm.

Consistent with the Medical Device User Fee Amendments that were passed in 2017, and it's part of the FDA Reauthorization Act, we are aiming to complete, at least for FY 2019, at least 55% of those de novo applications within 150 days. At the end of our review, if a favorable decision is reached, we will create a new regulation, and that will be designed around the intended use and technology of the device that was the subject of the application. Once it's there, it will now serve as a suitable predicate for anything else that comes within that device classification reg.

So then moving on to something a little bit more relevant, OCT technology is regulated under 886.1570, which is a Class II regulation for ophthalmic devices. The first OCT device, Well-Found SE-2 (ph.), a different type of device, was placed under this regulation after it was determined to be safe and effective back in 1994. Along with that clearance we did create a special product code, OBO, which is designed specifically for OCT devices. To date, we have rendered a substantial equivalence determination for 48 different devices.

All 510(k) submissions are required to include an indications for use statement. This statement should include a general description of the disease or condition the device will diagnose, treat, mitigate, or cure, including a description of the patient population for

which the device is intended. The notes underneath there show the various types of indications for diagnostic devices, and I will point out that for OCT, we have seen only the first three that are currently legally marketed for imaging only or qualitative looks, quantitative that aren't disease specific, and then aid in diagnostic indications.

So there are various amounts of indications that are currently cleared, and this slide shows them here. I won't go through them all, but I will point out that there are indications for viewing your visualization only, there are quantitative indications, and there are those for diagnostic aids, and typically, with the diagnostic aid indications, manufacturers will elect to include a reference database.

On this slide I'll sort of do the reverse and show things that are not currently cleared. I attempt to show sort of main categories, but I will note that this slide is not all inclusive, and certainly, while there may be references to these types of uses in literature or are currently in clinical practice, ophthalmic OCTs have not yet been cleared for these.

All marketing submissions for OCT devices should include information to characterize its performance. This typically includes precision and agreement testing. Measurement precision is the closest of agreement between test results. Agreement testing is testing that serves, at least in OCTs, as a surrogate for accuracy. This testing assesses the performance of the subject OCT compared to the predicate or a selected predicate device.

And the last part, while it's not a required addition to any OCT device, as I mentioned, some manufacturers elect to include a reference database, and there are certain testing recommendations around this.

Repeatability is precision assessed under conditions that reasonably vary as little as possible. That is, the test results are typically obtained in one session, within a short period of time, on the same device and with the same operator.

Reproducibility is precision assessed in conditions that reasonably vary as much as

possible. So you have potentially varying time, environmental conditions, device operators, manufacturing lots, etc. This type of testing can assess things like within-operator variability or between-operator variability as well as between-device variability.

So the data collected through these testing types allows for evaluation of things like standard deviation and a coefficient of variation to help characterize the device. Because a device can perform differently within each type of patient population, as varying types of pathology may affect the measurement, we typically ask for separate evaluations among these populations and the applications.

Agreement testing allows for a direct comparison of the OCT device to a predicate device. An agreement study takes measurements on study eye with the new device and the predicate device, ideally randomizing in that order. Analyses are performed separately for each set of patients and each device, and from these results we can obtain differences between the subject and the predicate device, such as mean percent and absolute differences, but I will point out that there are no simple criteria for the limits of agreement in terms of how close the results need to be, but large differences, even systematic differences, need to be justified in some way.

So there has been a lot of steady growth and innovation in the field of ophthalmic imaging. OCTs certainly continue to evolve and to incorporate new and improved technology and uses, scan patterns, measurement, things like that. One area of growth we have seen, and expect to see more of, is software improvements. It would include more advanced analytics. OCT is a great example of a SiMD, or S-i-M-D, software in a medical device; even though the optics and electronic components are critical to the OCT performance, the analyses processing and outputs are heavily dependent on software, which gets us into the digital health space and artificial intelligence.

The use of digital health technology is providing innovative ways for us to monitor

our health and well-being. These advancements are leading to improved healthcare and health outcomes. Not only do we continue to facilitate digital health innovation and stay true to our mission of ensuring that U.S. patients and healthcare providers have access to high-quality, safe and effective medical devices, we also continue to advance regulatory science to optimize regulation to suit these digital devices.

This is probably the most exciting area that I've had the privilege of being involved with recently. Artificial intelligence is a broad term that generally describes a concept of programming computers to mimic human capabilities. Within the umbrella of AI there are machine-learning and deep-learning capabilities. And then even within machine-learning, there are certainly different aspects of how to train those, but generally, ML as a subset of AI is essentially computers having the ability to learn without being explicitly programmed to do so. And then within that, the smaller subset of deep-learning, this is something that does not require feature engineering and uses artificial neural networks that are meant to mimic thought processes in the human brain.

Incorporation of AI into ophthalmic imaging, I believe, can certainly lead to earlier disease diagnosis, more accurate results, new observations or patterns in the data sources, and possibly even personalized diagnoses or diagnostics.

So actually, really timely was a paper, a discussion paper that was released last week, and this provides a great background on AI ML in our post-regulatory framework. This paper is not guidance, it's not even draft guidance, but it is meant to provide our current thoughts on what a regulatory framework would look like for these types of devices.

There are definitely a few underlying concepts that are key to having created this paper, and most notably, our traditional regulatory paradigm was not meant for these types of devices. These are highly iterative, autonomous, and adaptive devices that require sort of a new total product lifecycle approach to facilitate a rapid cycle of development and

allow these devices to continually improve.

One critical concept, and definitely as a take-home point in the discussion in the paper, is to understand when would a continuously changing AI ML require premarket submission for an algorithm change. To help answer that question, our paper goes into a proposed framework for this very point. With AI ML, we anticipate that many changes will involve algorithm architecture modifications that would go through retraining, which would generally require a premarket review if looking at our software modification guidance.

Types of modifications generally fall into three categories: changes to performance, changes to inputs, and changes to intended use. We would base the decisions around the AI ML evolution in SaMD pre-specifications, or SPS. This is essentially a document that we would -- it would have to go out premarket between FDA and the manufacturer that would outline the various types of changes we expect that may occur. The algorithm change protocol, or ACP, would ascribe those methods that would go into qualifying the changes described in the SPS.

We do expect, generally speaking, that SaMD developers will embrace the principles of culture, of quality, and organizational excellence, as well as good machine-learning practices to ensure algorithm changes are done safely and responsibly. In addition, we also believe real-world evidence will be helpful in observing indicators of performance.

So there's likely some link between software advances and the steady growth in innovation in the field of ophthalmic imaging. OCT is continuing to evolve to incorporate new and improved technology. Accordingly, we've seen a rise in 510(k) submissions over the past few years and a dramatic increase in the number of pre-submissions that have been coming in.

Unlike previous iterations of the Medical Device User Fee Amendments, MDUFA IV includes of a concept of a shared goal and uses total time to decision as one of the main

points and not just FDA days alone for goals. For FY19, a TTD is 120 days for 510(k) submissions. I ran a recent report for 2018 and found that our current TTD for OCT devices is at about 144 days.

So making a few observations about these, I believe there are some reasons for this, and I believe they can be addressed, which leads us right into the OCT pilot program. This was launched last October, and it was posted in the *Federal Register* to announce the program to -- essentially, the program was designed to explore ways to yield more consistent premarket applications, improve predictability of the 510(k) process for OCT devices, and then to fine -- refine, rather, testing recommendations.

The pilot program is open to nine participants on a first-come/first-serve basis, and they were required to meet certain eligibility criteria. The general goals of the program are to improve consistency and predictability of the 510(k) process, to reduce the total time to decision, and to increase the collaboration between FDA and stakeholders to refine these initial testing recommendations.

So what we see is that to each of the nine participants we sent an initial set of testing recommendations with the first part of that document describing the basic device characteristics that we would expect in each application to be defined, as well as some fundamental safety information that would need to be qualified for each device.

We also recommended that all submissions include information to non-clinically assess the OCT characteristics, including spatial performance testing and sensitivity and things of that sort as well as, if applicable, OCT angiography and any ancillary or auxiliary functions.

And, lastly, our initial recommendations included a lot of clinical performance testing. We had that parsed out for some that would apply to all OCTs as well as those that would be for imaging only or those that put out quantitative values or measurements.

The pilot is one of the ways that we try to expedite innovation in the area of ophthalmic imaging. We do look to collaborate with these nine participants to further refine those testing recommendations with the aim of reducing the goal to reduce TTD. We also look to combine that feedback with today's discussions in hopes to move towards improving regulatory science for OCT.

With that in mind, along with our co-sponsoring organizations, we have identified areas that need to be addressed to help promote the development of imaging devices for use in clinical practice. While we have done a lot internally, we recognize a strong synergy of collaboration with our external stakeholders to help expedite innovation. To that end, we look forward to today's discussion of new OCT functionalities and measurements and the related validation strategies.

Thank you.

(Applause.)

DR. WEIKERT: All right. Good morning, I'm Mitch Weikert. I'm a cornea cataract and refractive surgery specialist at Baylor College of Medicine in Houston, Texas. I'd like to thank Drs. Eydelman, Myung, and Blumenkranz for allowing me to speak this morning. I'm going to talk about novel applications of leading-edge OCT in the diagnosis and treatment of anterior segment disease.

As disclosures, I do some consulting for Alcon and Ziemer, both of which have not a real significant presence in this space.

So OCT we know as low-coherence interferometry, and over the last decade or longer, we've seen pretty much an incredible evolution in it, from time domain through spectral domain, and now with swept-source OCT, which has led us to have faster scan speeds, higher resolution, and deeper penetration, which has just improved not only the accuracy of our measurements but also the applications that we're able to use it for.

So for anterior segment OCT, currently we have maybe four different areas that I like to think that we use it. Clinical imaging is really what we started with using OCT in the anterior segment for, but now we use it for biometric applications. We also have biomechanical assessment abilities with it, and then, finally, we've got intraoperative guidance to use it for as well. So I'm going to go through each of these different categories.

And clinical imaging, again, that's what we really started using OCT for. So, you know, we can really apply imaging to any pathologic condition that affects the anterior segment, so I'm just going to go through a bunch of case examples of what we have used it for.

Post-LASIK poor vision. This was a patient that had had LASIK and complained of monocular diplopia in the right eye, had a slight decrease in the acuity of that eye as compared to the fellow left eye. When we looked at the surface topography here, the reflected mire shows some spreading just superior to the visual axis, which is then mirrored in the corneal topography showing flattening in that area, and when you looked at the patient clinically, you can just see a little faint haze in the cornea there.

So with our abilities to image the cornea now with high-resolution OCT, we can actually look at the thickness of the epithelium, and we see in that same area we have thickening of the epithelium, and this patient was scheduled for a flap lift and enhancement of their LASIK but came to us for a second opinion prior to undergoing that, and when we actually looked at the high-resolution image, we can see the flap thickness here, and when we look at the epithelial thickness, we see in that area where we saw the thickening and flattening, that the actual flat stroma is incredibly thin, so they're not a good candidate for a flap lift, so we sent them for topographic-guided ablation, and they did well.

This was a patient that came in that had a foreign body in his eye after LASIK, and we usually just pop these off with a little needle in the clinic, and we went to do that, and

actually, the little foreign object just kind of slid along the corneal surface. When we got the OCT, we could see that the little foreign body was indeed under the flap, so we just lifted the flap up and took it out.

What about DMEK? DMEK is Descemet's membrane endothelial keratoplasty, where we replace the corneal endothelium with a layer of Descemet's with new donor endothelium, and we'll put that into the eye, we put gas underneath, and then eventually the gas goes away and the membranes just stick to the back of the cornea. Well, this is the case where the patient had a little edema following surgery, and we can see that our Descemet's is actually detached. So in the clinic we'll put a little bit more air in, and they usually do very well and attach.

This is a similar case, but we can see that the Descemet's is detached but actually scrolled, and it can be hard to see this through an edematous cornea. So this might change the way that you manage this and maybe not put the gas back in just at your slit lamp in the clinic.

We see a lot of different causes for corneal opacity. This is a patient with something called macular corneal dystrophy, and here we can just see, with our high-resolution image, the little bumpy edge of our Bowman's membrane and then the epithelium over it, which kind of smoothes and does some masking, but this allows us to judge depth of opacity so we can gauge whether or not these patients are amenable to, say, laser treatment to improve the clarity of their cornea.

This is a case of corneal opacification following cataract surgery. We can see this white spot at the leading edge of our cataract incision. One month later, it's increased in size, and when we do our OCT, we can see that's a collection of epithelium underneath Descemet's membrane in the cornea, so this patient was elected to be followed.

One area of great use for OCT, led by Carol Karp in Miami, is the use in managing

ocular squamous surface neoplasia. And we can see this papillary lesion on the corneal surface and this classic appearance of the epithelium where we see thickening and hyper-reflectivity and then this very sharp boundary. So this can help guide us and maybe eliminate the need for doing a corneal biopsy, etc., in the management of these patients.

Biometry is another area of measuring the eye. It's become the gold standard for axial length measurement, and when we first got these systems, it would measure the length from the anterior corneal surface to the retina or the retinal pigment epithelium, actually, and then that data, when it was approved, would actually regression fit to ultrasound data. So we are a little underrepresented at the extremes of axial length, but it does really great. But we know when we get the long eyes or short eyes, our calculations can be off some. But then as OCT involved, or evolved, we were able to measure, again, the length of these different segments of the eye. But when the machines actually give us the length of the entire eye, it goes back to that regression fit using kind of a fixed index of refraction that averages through the entire eye.

So we would think that if we could actually use the segmented measurements, we might get better results, and this just shows the difference between what's displayed versus what you would get if you segmented the axial lengths, and we can see they cross at around 27 mm in axial length. But when you look at the eyes that are shorter at that, perhaps that displayed axial length is a little shorter than it really should be or if you're above that, maybe that axial length is a little bit longer than what it should be, and that kind of mirrors the calculation errors we get with our intraocular lenses.

When we look at this for the different refractive prediction errors, we can see -- it's a lot of graphs here. Each graph is a different formula. The blue line is if you do that calculation using the displayed axial length, the red line is if you use the segmented axial length, and we can see the red lines are flatter, they're closer to zero, so the prediction

errors are actually lower when you use that segmented axial length. So that's another area where OCT could improve our IOL calculation results.

What about measuring the cornea? We know we typically measure the cornea by reflecting off the anterior surface of the cornea. Why do we do that? Well, it's very reproducible, we don't have to measure it to quite the same resolution, meaning our measurements are on the order of millimeters, not microns. But with OCT development, and even like Scheimpflug development, we get cross-sectional images of the cornea, and then we can measure curvature in that way, too, but we're actually measuring elevation and converting that to curvature, which is a little bit more difficult process and a little bit more prone to inaccuracy and variation, but with the increased resolution of OCT, now we're able to maybe do that and improve our measurements of the cornea.

So we can see here, we can actually measure the front and the back surface and get what we might call a total keratometry to possibly improve our corneal measurements in cataract surgery.

We can also use this to measure the tilt of the crystalline lens and the intraocular lens as well, and we've done this in the past, and we found that the tilt of the intraocular lens after surgery kind of correlates with the tilt of the crystalline lens before surgery, and that can actually have an effect, maybe, on induced astigmatism with cataract surgery. So we looked at that and modeled that, and we found that if you tilt just a monofocal aspheric intraocular lens, that tilt on average induces not much, maybe a little over a tenth of a diopter, but if you get to those more extreme clinical levels of tilt, we can see induced astigmatism of a half a diopter maybe, depending on the lens power.

And here we can see that if we then apply that to toric intraocular lenses, if we put a toric intraocular lens at very high power, say 28 diopters, and that lens is aligned vertically, we're actually going to potentially get some over-correction where, if we have to orient that

toric intraocular lens horizontally, we may be prone to under-correction. So this tilt may be another source of error in our use of toric IOLs, and maybe being able to measure a crystalline lens tilt prior to that might help in our accuracy as well. And that effect changes, as you might expect, as that intraocular lens power increases also.

What about post-LASIK? Well, we know that IOL calculations after corneal refractive surgery can be very problematic. We're changing the relationship between the front surface of the cornea and the back surface of the cornea, which subsequently affects its refractive power, and it's a big source of error in these calculations. It also affects how the formula predicts where that intraocular lens will sit postoperatively.

So as an example, this is a patient who had LASIK, so he underwent cataract surgery, and we did our multiple calculations, which we always do, to try to predict what lens we should put in this patient. The patient had monovision and wanted to be targeted for near after surgery.

So you can see here, with this OCT device we're able to measure the net corneal power, the combination of the altered front surface and the back surface, as well as the power of both the anterior and posterior corneal surfaces, and we can implant that into our calculator spreadsheet which will employ a bunch of different formulas, and we can see here, we get results and lens recommendations for all these different formulas. If you look at the bottom, you can see the min and the max are, you know, the minimum IOL power recommended versus the maximum, and you can see here that the spread is about 2½ diopters, and even if you're not a cataract surgeon here, I think you can guess that that kind of makes it more difficult on choosing or picking what you want to use.

When we look at the refractive prediction error for this, we chose a 23 diopter lens because that went along with several formulas we had confidence in. That patient actually ended up a lot more myopic than we targeted, and when we went back and looked at the

refractive prediction errors for this anecdotal patient, we found that in this case the OCT did give us better refractive prediction results than we might see with others.

And if we look here for these different formulas and we looked how these formulas did, we can see that the OCT, on average, across these hundred patients had a little bit lower refractive prediction error, and when we averaged that with other values, it actually got the best results.

What about biomechanical assessment? When we do refractive surgery, we're essentially weakening the cornea because we're thinning it with PRK, and then with LASIK we're going even deeper; we make our flap, we laser under the flap, and put the flap back down. So we're removing cornea, and we're weakening the cornea. So a big goal in our preoperative evaluation is to assess who are good candidates and who are not good candidates, who might we excessively weaken their cornea and who might be safe to have these procedures.

So, currently, most of our methods actually are indirect. We measure the shape of the cornea, and we try to infer is that cornea a little bit more prone to weakness than other corneas. We've employed OCT to try to improve these results. And David Huang's group out of Oregon has looked at different pachymetric relationships across the cornea, which again are available with high-resolution OCT, and they looked at different relationships between different areas of the cornea, say the thinnest part of the cornea, maybe the superior compared to the inferior thickness, the superior temporal compared to -- I'm sorry, the superior nasal compared to the inferior temporal thicknesses, put that together with a five-variable regression formula to come up with a risk scoring system, and that scoring system ends up with a sensitivity of about 90% and a specificity of about 93, which is okay. Maybe not as good as we want it to be but still on par with a lot of the other methods that we have available to us. But this is to distinguish keratoconus from regular eyes, and often

we can do that clinically and don't need a scoring system to do that. We really want to identify what we call these subclinical or forme fruste keratoconus patients. And now being able to look at epithelial thickness patterns may help with that as well.

This, again, looks at thickness but not the thickness of the entire cornea, just the thickness of the epithelium, and we can see in these keratoconus patients or these subclinical keratoconus patients at the bottom, we can see that there's a little thinning typically over the apex of that cone and the epithelium, which can mask the overall curvature of the cornea. And when we look at, again, similar relationships of the epithelium across different aspects of the cornea, coming up a with a risk scoring system, in this case we can see improved sensitivity to about 96% and specificity of about 100% in this group of patients. But, again, this is a development set, maybe not a validation set.

What about actually measuring the biomechanical strength of the cornea? Well, OCT elastography may benefit us in this respect. We know the cornea is viscoelastic. There's a nonlinear relationship between the amount of stress or force you apply to the cornea versus the displacement or change in shape that you get along with that. And these are spatially dependent. The front of the cornea behaves differently than the back of the cornea, and maybe characterizing this can help us, again, assess patients that are at higher risk.

This is just one example of this where a flat glass applanation lens is coupled to a swept-source OCT, indented the cornea, measuring the force required to do that indentation and then using the OCT to look at the speckle displacement of the different levels of the cornea, and you can see here the yellow across the middle is the change in displacement horizontally of those speckles, and if you look at the scale to the right, you can see that's around very low, close to zero. But then if you look at the vertical displacement in red, you can see a much bigger displacement measured in that cornea with

the known force applied. So you can see on the top right graph, you can see that blue line is the anterior cornea kind of stress/strain relationship being higher, and that means it is a stiffer cornea compared to the red, which is a little deeper into the cornea. So you can actually spatially resolve differences in corneal stiffness between the front of the cornea and the back of the cornea.

I'm going to finish with some intraoperative applications. There are kind of two systems that are available right now. We've used these in lamellar keratoplasty. This is a DSEK where you can see that we're putting that lamella of corneal tissue in, and it looks great once we've injected the air, but it is very surprising to me how much fluid can remain in the interface when you really can appreciate that under the microscope. So as we stroke across here, we can milk out that fluid in the interface and probably improve our postoperative adherence of the corneal lamella that we implanted.

This is DMEK. Again, we're implanting a much thinner layer of cornea, and it likes to scroll up, so it can be often difficult to determine the orientation of the graft. And here we can see, with the OCT images live, to the right we can see the scrolling and know that it scrolls up, which is really what we want, and we can use that to monitor as we tap and replace the cornea. And then we can see here, as we inject our bubble, we'll notice that green line of the Descemet's going up against our cornea, and we can verify our detachment here. Or, I'm sorry, our attachment there.

Oliver Findl, I don't have a slide here, has also used OCT intraoperatively to try to predict lens position postoperatively and has found that it helps to increase the accuracy of determining where that final lens position is postoperatively. So that holds promise as well.

So quickly, to conclude, we all know that OCT has substantially improved in image quality, and that's led to improvements in speed, resolution, and penetration, our ability to go deeper into the eye, which has a myriad of applications in the anterior segment, and

we've certainly seen that evolution clinically over the last several years.

So thank you very much.

(Applause.)

DR. REPKA: Thank you, Dr. Weikert.

Now we'll have an official introduction. Our next speaker is Dr. Yasmin Bradfield from the University of Wisconsin.

DR. BRADFIELD: I don't see the --

DR. REPKA: You don't see --

DR. BRADFIELD: -- slide advancer.

DR. REPKA: All right.

DR. BRADFIELD: Did you take it? Did somebody take that? Okay, you can give my talk.

(Laughter.)

DR. REPKA: That would be helpful.

DR. BRADFIELD: No problem. Thank you. It will make it a lot of easier for my talk to do today.

DR. REPKA: He's going to get that for us.

DR. BRADFIELD: Okay, terrific.

So I thank the organizers today for putting together such a novel and innovative conference, and I'm very pleased to be here. What I wanted to talk about today is clinical standards for assessment of novel anterior segment measurements, and I have no financial interests.

So when we think about what the best way is to validate anterior segment OCT measurements, we have to think about what is a clinically accepted way that is also scientifically accepted. So we need agreement, accuracy, and reproducibility of these new

data. We also need large population studies to even determine what is the normal variance before we can look at ocular disease. So we also want to make sure that we can determine if there are differences between ethnicities, and there are some charts that show us, even within Asian subgroups, there are gender and age.

So what I wanted to talk about today is to go over where are we in 2019. What is the current state of our technology today, which structures have been imaged by anterior segment OCT, what has been used as a comparison to validate this new data, and are there large population studies available?

Well, we know that there has been an evolution of OCTs over time, with the first generation being the time domain OCT. This then evolved into spectral domain, which gave us faster image acquisition time as well as better resolution, and now swept-source OCT is developed, and this allows deeper tissue penetration, giving us better detail in the deeper areas of the anterior segment, and then microscope-integrated OCT, which has rare publications but we know it's out there.

This is what I use in my operating room. I have a large pediatric glaucoma practice, and I use a mobile anterior segment OCT device, a handheld one, in the operating room. On my infants and young children with glaucoma, I'm able to take really nice videos of angle structures, looking at their aqueous outflow and then later pick the best images.

So what clinical ocular conditions have been useful with anterior segment OCT images? You know, you heard a lot about cornea intraocular lenses at the last talk. So this is not a comprehensive list, but for instance, when I asked my cornea faculty, my department, what she finds useful in her patients with anterior segment OCT, she points to a lot of these qualitative parameters right here, and she says, you know, I really don't know what the normal measurements are aside from corneal thickness, so even if I had to do calipers and the photographers, which are the staff that take our OCTs in the clinic, use

them for me, I really don't know what to compare them to. So there's a lot of work that still needs to be done.

I just want to point out this last area here, this angle of closure, narrow angle, and just normal adult human angle measurements such as the angle opening distance and the TISA have been well studied, looking at what angle structures can put our patients at risk for angle-closure glaucoma. This has been a high interest in Asian countries where the rate of angle closure is higher than in the United States. So these measurements have really been consistent and pretty much validated with these newer OCT devices.

There's been emerging data looking at anterior segment structures that are imaged on aqueous outflow pathways in both adult and pediatric glaucoma and some of these other ocular conditions.

However, when we look at what are real established parameters, because if we want to start looking at clinical trials and looking at large population studies, we need to know what normal is and we really don't have that yet, there are very few parameters where it's widely accepted and some of those are just on the top, but if we're looking at primary and secondary outcomes, we need to have a large database of what's normal across ages and ethnicities.

And then we can start looking at really more interesting things like exploratory outcomes of what, for instance, is Schlemm's canal size? What change of the size can we see if we introduce glaucoma drugs as well as glaucoma surgery? These are the things that make it fascinating to study with this new technology.

There have, however, been established devices that have been used to validate, trying to validate, this new data and ultrasound biomicroscopy, or UBM, has been the most published.

This is an example. On the right side you can see the images of a pediatric patient

with glaucoma and UBM images. On that one left side is anterior segment OCT, and you could see that, you know, the landmarks are there and the structures may be similar, but the resolution and detail is much better on the anterior segment OCT.

Here's another example comparing, on the right side, a UBM image of an angle and then on the left side, similar angle structures, but just much better detail. And then there's actually software that allows you to use calipers to measure in micrometers what some of these outflow pathways are.

B-scan ultrasound has been another established device that has been used and published to compare data versus anterior segment OCT, and for instance, if you look here, the B-scan ultrasound images are on the right, anterior segment OCT on the left, and look at this much higher resolution on the top, iris melanoma that you can see on anterior segment OCT as well as this posterior iris cyst. So the details and resolution are just much better with this new technology.

Well, we have to also understand that not all anterior segment OCT images are the same. There really is no standardization of obtaining these images, and we know that with every new iteration and upgrade of technology, there's a learning curve. So our clinical staff, which is our photographers that take these images, have to image these with many patients over a few months to get used to these new devices.

We know that there are environmental factors that can affect the images that we get. Lighting, for instance, can really affect the iris configuration, and we know that even if you're taking serial measurements in an individual patient, the measurements will change depending on what lighting conditions were when the images were taken. There's controversy if there's diurnal variances. There are publications that haven't really resolved that yet. And then we also know that there are changes in Schlemm's canal size with the combination. So if you're not controlling that, the measurements are going to be different.

So there's no standardized scanning protocol, but what about reproducibility of these current measurements?

Well, so now, just recently in the past year, there has been some small reproducibility data published in the literature. We know, for instance, if you look over here, the top is the Casia image and the bottom is Spectralis, and the landmarks actually look very similar. So in this small study of healthy adult eyes, it was found that there was actually high intra- and inter-device reproducibility of measurements, so that's a good thing.

However, there's another study that came out after that that said, well, wait a minute, if you use a first-generation model of OCT, you can't actually compare those measurements with the newer devices because the devices actually are not reproducible, the measurements are not the same.

So this is a study that looked at Schlemm's canal in a pediatric population and actually found that the size of Schlemm's canal seemed to increase with older age, and this was very similar to prior findings using UBM. So it's important to reproduce studies and see if the findings are similar with this new technology.

But we know that we do need not only larger studies but more measurements per eye in each study, and we've seen this with other new devices as well. If you look, you can see that there's a large deviation of the range and mean values if you're not using several measurements per eye, so we have to be aware of that.

So what do we do, however, if we're finding new things on anterior segment OCT that we can't actually compare to prior established devices, such as abnormal tissue in a glaucoma angle or these new aqueous outflow pathways that we're imaging, and we really haven't seen that before, to use other devices for comparison. But what about this child that came to my clinic with a globe mass, wanting to know if we could surgically excise it; what do I do with the image that I got because I don't have a comparison? Or another

patient of mine with pediatric glaucoma that came in with new deposits in his tube shunt, and these are the images that I got, but what do I compare it to, to know what is normal?

Alex Well (ph.) and his group had created this really interesting 3-D model looking at Schlemm's canal in healthy adult patients, as well as his glaucoma patients, and he has found these, and he was able to image these collector channels that are part of this aqueous outflow pathway that's a novel finding.

We know that there is intrascleral lumen that we've seen, we were able to reproduce this on images. This is Kagemann's group who's looked at this, and they actually have their own software that they customized in order to determine the high detail within deep tissue of the anterior segment, looking at these structures. But the other thing that they did that was interesting is that they used Doppler to determine if what they're looking at was the blood vessel versus Schlemm's canal. That that's what we need to start doing is, is looking at what is the function or clinical significance of these structures and to identify them appropriately.

We've been able to look and reproduce the abnormal tissue angle found in pediatric glaucoma compared to a prior image on the left that was done by Gupta.

We can use histopathology to confirm new findings if we have nothing else to compare it to. This, for instance, is a really nice histopathology slide which verified a structure, a new structure called BELL, which is this extracanalicular matrix around Schlemm's canal. So we can certainly do this in animal studies.

We have to think about, though, does anatomy correlate with function? So this is a paper that came out in which this group actually found that Schlemm's canal size in this pediatric population, after cataract surgery, did not increase with -- effort compared to what is normally seen in children without cataracts, and they postulated that maybe this contributes to their risk of developing glaucoma after cataract surgery.

Kagemann and Schuman's group found that under high intraocular pressure conditions, Schlemm's canal is compressed and may not be visible. And so we have to understand that when you were taking these images, there's a dynamic aspect to it, and depending on the environmental factors, you may or may not see structures that are really there.

We also know that anatomy sometimes does not equal function. So, for instance, you know, we assume that a larger Schlemm's canal is better; however, how do we know that? How do we know that a large Schlemm's canal does not mean that there's fluid stasis and really not better aqueous outflow?

This is an example of looking at function in parallel to anterior segment structures, and this is by Huang's group, and he's actually been performing aqueous angiography looking at aqueous outflow in his normal adult healthy patients, and what he has found is that actually not all quadrants are the same. So if we're imaging anterior segment outflow structures in one quadrant, you know, we have to understand that this may not represent the entire eye, and that's what he's finding. So doing these function studies in parallel to the structure studies, I think, are very important.

Is there a role for animal models to validate this new data? And there certainly is. There's a lot of interest in looking at mice and rodents and specifically looking to see if we can develop a drug delivery system. So this is a nice example showing anterior segment OCT on the left, of inflammatory precipitates that are on the endothelium of a mouse eye, and on histopathology, you can actually see those same precipitates. So that really confirms what that structure is and the clinical significance of it.

This is a really nice example of anterior segment OCT and showing fluid gel over the cornea and looking on the right with these macrophages. So the thought is that can you introduce drugs in these fluid gels that get absorbed into the cornea and anterior chamber

to treat things such as infection or inflammation?

Gillian Anderson is a veterinary ophthalmologist in our department, and she has a colony of cats with congenital glaucoma, and she has been doing parallel function studies with structure studies looking at anterior segment OCT under aqueous outflow as well as aqueous angiography. So, again, these are really important studies to do.

Well, lastly, I just want to tell you that when you're really looking at all of the data that's out there, this was the largest review so far, this was just published a few months ago, on all of the anterior segment OCT publications, and based on this, we really don't have great population studies that are large studies across age, gender, ethnicity, so there is a big gap of knowledge of even what's normal.

So, in conclusion, we do need large population studies to determine what's normal, as well as a standard standing protocol. So we're definitely not there yet, we're making progress, but we have a long ways to go before we can determine what is normal and what is ocular disease.

There's definitely a role for image software processing technology to enhance the images that we're finding.

We need to perform parallel function studies in addition to the structure studies to understand the clinical significance of what we're imaging.

And finally, you know, there really is a huge potential use for this. We've never been able to see some of these structures in detail without this technology, so we don't really have much to compare this with, and there's high potential in performing studies looking at ocular disease in a way we've never had before, and hopefully, this will lead to individualized patient treatment.

Thank you very much.

(Applause.)

DR. REPKA: Thank you, Yasmin.

So our next speaker will be Dr. Joel Schuman, chair at NYU, who will at least move us into glaucoma.

DR. SCHUMAN: Good morning. And I'd like to thank the organizers for including me in this panel and especially Malvina for putting this together and coming up with the concept.

These are my disclosures.

And I'm going to talk about novel applications of leading-edge OCT in the diagnosis and treatment of glaucoma. First, I'm going to talk about visible-light OCT, and there are certain advantages of using visible light for OCT. You have higher axial resolution, so with visible light you can get about a 2 µm axial resolution in tissue in the eye, about 1 to 1.4 µm in air. And then with near infrared, you're really working at 3 to 5 µm best resolution.

With visible-light OCT, it's also easier to do retinal oximetry, and because the visible-light OCT allows you to see the 10 times higher hemoglobin absorption coefficient compared to near infrared, you can measure the deoxyhemoglobin more distinctly.

This is an example of a series of B-scans taken with different OCT technologies, the top left being the visible-light OCT; top right, swept-source OCT; and the bottom two being commercially available near-infrared OCT devices. And I think that you can see the difference in terms of the discernibility of laminations within the retina.

This is a similar set of images from Vivek Srinivasan's work comparing near-infrared on the left and visible-light OCT on the right, and you can see again, in the study, the difference in the visibility of the laminations in the retina, and in fact, more layers can be discerned posterior to the RPE than can be seen with near-infrared OCT.

It's even possible to see layers within layers that we had assumed before were fairly uniform. So, for instance, the inner plexiform layer in this expanded image may actually be

five layers; there may be five layers that are discernible within the inner plexiform layers, so there may be bright, dark, bright, dark, bright within the inner plexiform layer, as you can see here, although in this image, it may take a little bit of imagination.

With regard to retinal oximetry, the O_2 saturation is what is being measured, and because of where visible light falls on the absorption spectrum relative to near infrared, visible light is optimal for measuring the oximetry in blood.

This is an example of a set of images in a rat, and so you're looking at the rat optic nerve in a series and the vasculature on the left, and then a B-scan on the top image under B, and then a series of cuts through a vessel underneath that B-scan. And so that's the visible-light OCT spectroscopic processing. And then in the next panel you see the extraction of the OCT signal from the blood or vessel wall, and then that's fit to the known values for hemoglobin absorption. And then you see the color coding in that last image on the right of each of those vessels with regard to O_2 saturation.

We did this in humans and here, what I'm going to show you are visible-light OCT scans in a healthy volunteer, a pair of major retinal artery and vein superiorly and inferiorly, and this is just using raster scans to cut across the vessels. You see the parameters that we used here. We also did a circular scan around the optic nerve head using the parameters that are shown, and I'll show you that as well. And then we did the spectroscopic analysis on the rest or circular scans using a short-time Fourier transform, and then we did an O_2 saturation estimation with wavelength-dependent OCT amplitude from the same depth location across multiple A lines which were averaged.

So this is a series of raster scans, these are the B-scans that were taken across the vessels, and here you see the fifth to a vein, the venous SO_2, and this is the average spectrum from four B-scans that were used for the spectral fitting.

And here I'm showing you the sampling locations for the vein and the artery. The

vein has an O_2 saturation of 0.592, whereas the artery has an O_2 saturation of 1, and you can see the spectral fitting underneath the en face and B-scan images.

And then in a circumpapillary scan, which has the advantage of sampling all of the vasculature leaving and coming back, or all the blood leaving and coming back to the optic nerve, you can see that similar measurements can be made, and so you see the superior and inferior major artery and vein and their oxygen saturations. Superiorly, the vein has 0.621 and the artery 0.1, and inferiorly, the venous oxygen saturation is 0.593 and the artery is again 1.

Let me just go back for a second. So I think that the potential applications for this are broad, and we don't know if, in glaucoma, a sick retina would demand more oxygen or if it would use less oxygen. We would expect a dead retina would use less oxygen. But even something as simple as this still remains to be seen. In diabetic retinopathy and multiple other applications, oximetry may be of great value, and there may be value in applications we haven't even thought about yet.

The last thing that I wanted to talk about was visualization of retinal ganglion cells, and here you see work from Ethan Rossi in which he showed retinal ganglion cells with adaptive optics confocal scanning laser ophthalmoscopy, and each of the little bumps that you're seeing is a retinal ganglion cell.

This work was expanded on with adaptive optics OCT by Don Miller here, and what you see is by using AO OCT with multiple repeats and averaging, you can visualize the individual retinal ganglion cell bodies in the retinal ganglion cell layer, and they are localized spatially, as you would expect, and this provides the opportunity of looking at individual ganglion cell bodies and how they change during the process of disease.

And, finally, this is a repeat of Ethan Rossi's work using a PSI prototype unit with high-offset imaging using AOSLO, and again, you can see the retinal ganglion cell bodies in

the appropriate locations in the retina.

So retinal oximetry is possible with visible-light OCT. We can improve retinal layer segmentation with visible-light OCT, and retinal ganglion cells can be visualized with adaptive optics OCT and also adaptive optics SLO, and the visualization of retinal ganglion cells, which is really giving us a revolutionary opportunity to characterize the cellular changes that occur in glaucoma and the cells that are damaged by the disease, and these things offer the potential to identify disease and progression or response to treatment by structural and other-than-structural means.

I want to recognize my collaborators and especially Hao Zhang here at Northwestern, who developed and built the visible-light OCT that we used and, of course, Jim Fujimoto, whose work in OCT is legendary. Also, the people that I get to work with in a laboratory at NYU, a fantastic group of people who are doing cutting-edge work in this area.

Thank you very much.

(Applause.)

DR. REPKA: And, Joel, thank you very much for those comments.

Our next speaker is Dr. Richard Spaide, also from NYU.

DR. SPAIDE: So howdy. I'm supposed to give some patter right now because there's a computer situation, but thank you for allowing me to speak here. The faster the computer, the less time this is going to take.

DR. REPKA: Because Joel ran ahead.

(Off microphone comment.)

DR. REPKA: Yes.

DR. SPAIDE: I've got the clicker. So these are my disclosures. This talk starts with a Michelson interferometer. You learned about that in high school physics class, where light goes in through an instrument that is a beam splitter, split into two parts; one goes to a

reference arm, and at least in biologic imaging, one goes to the sample arm. These get combined back together and detected by a detector. Now, if they're the same path length, those waves are going to reinforce each other through constructive interference, and we'll be able to detect that. If we move one of those mirrors just by a fraction of a wavelength, those waves are going to come in, and they're going to interfere with each other, and we'll be able to measure that.

So with a Michelson interferometer, we can measure very small differences in path length. The problem is if the path length differs by more -- by multiples of a half wavelength and it could be 2- or 5,000, it doesn't matter what, we can't tell the difference from that and when the sample arms and the reference arms are equal in length.

So it would be good to be able to use an interferometer to measure things inside the eye, particularly depth ranging or looking at different structures. So there was a tricky solution made by Jim Fujimoto, and that was to use short coherence wave light, and to make that, you just add a bunch of different wavelengths together at the same time, they're all coherent with each other, and you remember from the summation of sinusoidal waves, we can end up with a more complex sort of wave and that wave changes with time, although it is coherent. So a wave here, say a light wave here, really wouldn't interfere very well with something from here, but this wave can interfere with this one because of spatial coherence.

So this idea is employed in spectral domain OCT where a broad band of light source is used and it's put into a spectrometer -- I'm sorry, put into a reference arm and also into the sample arm, and if you get a reflection from a reflector and that reflector is somewhat near the same length as the path length is for the reference arm, you get an interferogram that has a relatively low frequency. If we have a deeper reflector, the interferogram is a higher frequency and so forth, this has even a higher frequency. And so that's kind of the --

the ingenious part of spectral domain OCT is that the interference fringes change with depth, so we can estimate the amount of reflection and also estimate the depth.

Now, your eye has a lot of different reflectors inside of it so we get a pretty complex signal, and this is decoded with a Fourier transform and we get an A-wave, and we add a bunch of A-waves together and we get a B-wave, a B-scan.

The resolution of OCT is related to coherence length of the light which, in turn, is related to the central wavelengths where it's divided by the bandwidth of the light source. So you can see that the shorter the wavelength used, the better the resolution. The problem, though, is that shorter wavelengths have somewhat higher scatter. Most commercial spectral domain OCTs work around 8,200 nm.

You already heard from Joel Schuman about visible-light OCT. These use shorter wavelengths, and you remember that the wavelength squared part is important in terms of resolution of an OCT. So visible-light OCT is commonly reported to have a resolution of less than 2 µm, some less than 1 µm, and that sounds great, but then you look at the images, and you'll say where is that 2 µm resolution because it doesn't look all that much better than OCTs that we commonly use in the clinic.

I just want to point out that the image on the left is without motion correction and the right with motion correction, and that was on an anesthetized rat, so you don't know how much motion it could have been, although some do actually show what looks like improved resolution and we all hope for improved resolution, certainly in the lateral resolution, and we're going to learn more about that later with adaptive optics, but you can imagine if you have less than 2 µm resolution in both directions, you're going to easily be able to look at cells or quantify different aspects that's going on, on a cellular level.

One thing with visible-light OCT is we can estimate the extension coefficient from the interferogram, and the oxygenated hemoglobin has a different extension coefficient

than hemoglobin does, and this is from a paper by Pi et al., and they can estimate the oxygen saturation inside of blood vessels. Now, we can measure the blood flow in bigger blood vessels from Doppler or from other methods, so you can imagine that just by putting those two things together, we can estimate the oxygen usage by areas of tissue inside the retina, and we can look at one disease versus another and so forth.

Remember that there is -- with spectral domain, that -- well, the problem with spectral domain is that there's a sensitivity with depth, and the deeper things are, the less well we see them. And this was used, this ordinary SD OCT. This is the idea behind EDI OCT where this whole thing was flipped around and the larger sensitivity is put deeper inside of the eye near the sclera. That led us to look at the choroid.

With swept-source OCT, we use a different kind of idea in which we sequentially scan through different wavelengths in order and build up the interferogram over a short period of time. That interferogram is analyzed by a Fourier transform much the same way as the spectral domain OCT, and then we get an A-scan, we take a lot of A-scans, and we make a B-scan out of that.

Recall that there's a sensitivity roll-off with depth with spectral domain OCT, and that's what really hurts that kind of imaging. Swept source also has a falloff, but much less so. So we get images that look different, we can see both the vitreous, the retina, and the choroid instead of having to pick, say, just looking at the retina or look at the choroid.

The light source that's used generally is based on a VCSEL laser for most current spectral domain OCT devices that the center wavelength is around 10, 15 nm. This, as you remember from that mathematical equation, would give somewhat lower resolution, but on the other hand, there's tradeoffs that we get, and that detector is much simpler, and we're able to scan at a much higher speed.

Scanning speed among commercial devices is still kind of close together, and it's still

a little bit like kindergarteners arm wrestling, deciding which one is better between commercial swept-source and commercial spectral domain OCT devices. But what you want to look for is the future, really, in a sense, particularly for this meeting, and swept-source OCT instruments have at least 10 times faster speed than current instruments do.

High-speed scanning gives us a number of different advantages, including the ability to cover larger areas of the retina, or we can repetitively scan one area of the retina to get OCT angiographic images that we'll talk about later. The problem with high-speed scanning, though, is that the power that we have available is limited by ANSI standards. So we can only spend a certain amount of time at each spot.

Recall that we have a raster scan going across the fundus in which we scan across, and there's a fly-back, and then there's continued scanning like this in a raster sort of pattern. If we have a relatively low scanning speed, we can spend time at each spot and gather a signal. On the other hand, if we increase the scanning speed by 10, we're not getting 10 times more signal, we're actually getting one-tenth the signal per each thing, and noise doesn't scale down the same way that signal does.

Well, let's look at some of the advantages of swept-source OCT. This is sort of an addition to swept-source OCT that I developed with Topcon, which uses swept focusing with windowed averaging of the signal, and we used kind of a software approach to enhance the visualization of the vitreous, and you'll notice that there's a very sharp rendition of the vitreous, and you can see the various types of bursa inside the vitreous. And one time we had the idea that these bursa maybe were degenerative in nature, but if you scan any number of people of different ages, they have those exact same bursa and that same kind of pattern, and it makes you wonder if there was an evolutionary advantage to developing bursa inside the vitreous.

Even if we don't look at the vitreous and we look at structures deeper inside the eye,

here's a scan of a high myope, and you can see through not only just the retina, choroid, and the sclera, we can see hundreds of microns beyond the eye into the orbit and see blood vessels in the orbit, including the fat.

Here's a patient who had a hemorrhage, and you can image through the hemorrhage and through the hemorrhagic pigment epithelial attachment and still see the choroid perfectly well because of the longer wavelength light source and also because there's lower roll-off and sensitivity with this imaging method.

Shookuwan Masuey (ph.) developed or is working with Canon on a prototype that scans a 23 mm wide scan and is 5 mm deep, and she recently published papers about the vitreous attachment to the retina and tractional changes of the inducing pathology in myopes.

Either type of OCT methodology, though, produces light that goes inside the eye and that's evaluated. Now, if you have a reflector that's stationary over time, the reflection stays constant. On the other hand, if there's something moving inside the eye, the reflection is going to change with time.

Here's a series of pictures I took with an iPhone of just this water going down a trough, and they're just being replayed repeatedly. Now, we can take all of these images and stack them up in a stack and look down through each column of pixels and then look at the variance of those images. So in areas where the image has changed with time, you're going to have higher variance, and in areas like the grass or the farm building, there won't be any change. So we can assign the areas with high variance to be white and the areas of low variance to be black, and you can end up with an image that looks like this. And that, plus or minus, is how OCT angiography works. We take repeated OCTs of an area and just look at the difference over time, and the difference over time is counted for by motion, most times. Now, the patient can move back and forth, but if the patient doesn't move,

that's the basis of OCT angiography.

It is a powerful technique that allows us -- because OCT is depth resolved, right, we can pick out different depths inside the retina and look at the vascularity in those depths. And here's the deep vascular plexus, for instance. So when we look at this, we can start to get the idea of different kinds of diseases inside the eye, so at the macula, certainly, by looking at the circulation.

Now, you'll notice in this slide there is certain capillary density in the superior part of the image or the upper part of the image, but in the bottom part of the image there's kind of a swath where there's less vascularity, but it doesn't seem to follow any one blood vessel in particular. I'm sure a lot of people in the audience already know what this disease is, but here we have just a regular color picture, and again, you can see there's an absence of this sort of brighter sort of reflection coming off the retina inferiorly, where it's sort of a swath-shaped area with decreased reflectivity.

We can look at the ganglion cell thickness and get a better idea of what's going on, where you see this again, a swath sort of area of loss of the ganglion cells. Follow that back to the nerve, and you can see the radial peripapillary capillary network, an area that we don't ordinarily see well by any other method of imaging, including fluorescein angiography, that there's a defect here. Now, as it turns out, this patient has a defective nerve fiber layer because she has low tension glaucoma. But if you look at the whole picture, we have multiple different ways of looking at the ganglion cells and what supplies the blood vessel. I don't want to get into any kind of discussion of what comes first, the chicken or the egg, but they do happen together, and they give us information that we wouldn't ordinarily have by looking at all of this stuff at one time.

So we have loss of ganglion cells and axons in glaucoma, but curiously, we also have that in other diseases, systemic diseases, like dementia and Alzheimer's disease and

Parkinson's disease and schizophrenia and the like, and they have also a loss of superficial vascular plexus in correlation with how much their ganglion cells were lost. And this gives the idea that we can measure both the cellular kind of changes that happen in neurodegenerative diseases, but also understand the vascular sort of correlates to that. It also raises the idea that glaucoma itself may be a neurovascular disease, and from that, we can learn a lot about the neurovascular unit in the eye.

If we look at diabetics before they develop vascular disease, they have a number of different abnormalities. They have decreased dark adaptation, reduced light sensitivity, difference with huge discrimination, they have a bunch of different abnormalities of ERGs before any retinal vascular change. When we talk about diabetic retinopathy, we never talk about any of that stuff. We always talk about IrMAs and microaneurysms and the like, but there's plenty of stuff that happens inside the retina that happens before any vascular disease occurs.

One thing we know about in particular is there's a tremendous amount of ganglion cell loss in diabetics, and curiously enough, this is more pronounced in people who have peripheral vascular neuropathy than people who don't, on a match basis. You also have photoreceptor loss. And these things are not just in animal models and humans but also have been observed in culture.

So it gives you the idea that diabetic retinopathy, in addition to having vascular changes, is also a neurodegenerative disease. It's certainly more than a vascular disease, and if you think about it from that standpoint, is really getting like a stronger anti-VEGF agent really going to be that much of a big breakthrough in the continuing improvement and development in our ability to treat diabetes with all of these other things going on? Even if we treat somebody with diabetic macular edema, the edema goes away, and oftentimes their vision doesn't come up to be where my vision is or what your vision is.

So it seems that we're going to have a bigger payoff addressing the neurodegenerative part of these diseases, and you can apply that same kind of logic to glaucoma, is having an additional medicine that lowers the pressure by 1 mmHg really going to be that big of a deal, or would we be better off looking at the neurodegenerative part? I think this is really where one big opportunity for meaningful research is for OCT and OCT angiography, because we look at this, living people, and understand the physiology of what's going on.

I'm going to show you just a couple other things to close this talk. This is integrating the structural as well as the angiographic OCT data into volume rendering, and this is -- it looks better in the dark, but it's kind of a cool image in that this patient -- the retinal capillary macular aneurysms and the different layers of edema are also color coded in this volume-rendered image.

Jim Fujimoto, just working on the 800 kHz A-scan rates, swept-source OCT, and it has -- you can play frame rate videos of small areas of retina, and you can see the pulsatile flow inside ocular vessels. At Duke University, they're developing kind of this, almost the same speed, 400 kHz speed OCT in which they do volume rendering real time during surgery, and through kind of a sparser sort of scan matrix, you can actually see surgery being done from an offset position while you're doing the surgery itself.

So I think that it's hard to cover all the topics that are available in 15 minutes, but I think you can see that this is a very exciting area, and I didn't mention some of the topics. Choriocapillaris is a 15-minute talk all by itself, but I think that you can see, with the current improvements and ongoing improvements in OCT, that we're going to have a better understanding of the structural anatomy of the retina. And certainly, to learn about the physiology of the retina, and I think that because these are going to generate much more data than we used to measure, I knew that from a project that I just recently submitted

about the glaucoma versus diabetes thing, I think that big data approaches are going to help us analyze this information.

So thank you.

(Applause.)

DR. REPKA: Thank you, Dr. Spaide.

The final speaker for this portion of the meeting will be Dr. SriniVas Sadda, who is president of Doheny Eye Institute at UCLA, so hopefully he's awake enough now to speak. Good morning.

DR. SADDA: Red eye is always great. Thank you, Mike. So it's really a pleasure to be able to speak at this meeting, and I appreciate the invitation. So I'll just wait for my slides. Oh, I can't give Rick's talk, so I need my own. No one can give Rick's talk except Rick.

(Pause.)

DR. SADDA: This does look like one I can give. Okay, great. So thank you. So this is on clinical standards for posterior segment measurements. These are my relevant disclosures.

And so I think we all recognize that because of its high resolution and contrast, OCT has really lent itself to quantitative assessments, we love it for that reason, and there are many that have, as Cunningham talked about, that have been reviewed by the FDA, and we use these, some of these, in clinical practice, but there are a whole host of novel measurements that people have been using in various different research studies. Some of these have been quantified using AI-based approaches now. Mike Chiang will talk about that in the next talk after the break.

But to really look at the issue, I think, at hand and what I was asked to discuss was what are some of the considerations before we could actually think about using these measurements with confidence. What are some standards of value here? And we've

gotten excellent guidance from the FDA, but Cunningham has told us a bit about important measures of precision, in particular, repeatability using the same device with the same eye, same operator, to look at that variability, then reproducibility, which probably is more important for us in clinical trials and clinical practice, to look at the same eye but different devices and different operators. Those are obviously very relevant.

But it's not just precision, of course; it's accuracy, the closeness of the measurement of the device to a true value, and I guess, technically, you know, to really know this, you know, you really would want histology, and that's a pretty high bar, so sometimes we have to settle for other types of validation which is agreement, and I'm going to talk about a little bit about this with regards to manual segmentation against human experts.

So, fortunately, with OCT we do have good studies that have looked at accuracy, at least in normals, between histology and structural OCT, and most recently, just published recently, was the first correlation with OCT angiography, which is especially important because, you know, we have these projection resolution techniques and the like; how do we know that they're actually not creating other artifacts? So these kinds of studies, I think, are very important to move quantitative measurements in OCT forward.

But a challenge with demanding histologic correlation for all of these types of validations is that with each advance in technology analysis, that's actually pretty difficult to do, and of course, as much as we'd like to say histology is perfect, it of course isn't, and it's also not void of artifact, and when you're assessing vascular structures, for example the choroid, it's really difficult to take your histology choroidal measurements and then try to line them up with our clinical measurements.

So we've always been in search of alternative reference standards to assess accuracy. I think in the afternoon we'll hear about the use of phantom eyes, and I think this can be very useful, but these, of course, represent an idealized perfect eye, and the

question is, are there other alternatives that we can use to help us with some of the measurements we obtain? And this is where, I guess, serendipity is useful because, you know, we do have FDA-cleared devices that can be put inside the eye that we know what their size is, that can be used essentially as intraocular rulers, like the retinal prosthesis, to validate some measurements, and it has been done for planar imaging devices already, and of course, this could be applied to OCT as well, as a type of reference tool.

In any event, you know, with regards to accuracy again, I guess the final word I'd want to emphasize is that most of our evidence comes from normals, whether it's normal animals and the like, and we extrapolate to diseased eyes. We have some histopathologic correlation for some of the features that we're interested in, but not all of them, and as I've already mentioned, histology may not be perfect.

On the other hand, maybe this is blasphemy here, but I'll say, well, how critical is accuracy? Obviously, it's important. But I would also argue that if an OCT-derived measurement is repeatable, correlates strongly with another clinical outcome of interest, for example, some visual function variable, it may still be viable as a useful biomarker of whether or not we can claim that it actually is the structure that we thought we might be interested in measuring.

So let me move on to agreement, from accuracy. As I said, accuracy may be a high bar for us. Agreement is something that we often settle on as a useful strategy to validate some of our measurements, and I'll use the example of RP elevation analysis or drusen analysis where, again, many of these studies have been done to look at the agreement between manually segmented drusen, for example, and automated measurements to give us some confidence of these measurements may be of some value.

The one thing I would emphasize, that I think it's important not just simply to look at the net area or volume measurement generated by these approaches but actually look at

the actual accuracy of the position of the inner and outer retinal boundaries of the structure of interest. I think that's actually very relevant for judging how precise the tool actually is.

In any event, you know, that same kind of approach can be applied not just for drusen analysis but looking at all the other retinal layers. This has become a topic of great interest recently, and again, I think that you have to scrutinize the absolute mean differences and the actual boundary positions relative to ground truth.

You could also do segmentation off of en face OCT, and this has become of recent interest in segmenting atrophy, especially since we have some definitions, so these consensus definitions for atrophy on OCT now, and we're able to do these types of segmentations. But, again, any time you're measuring something new with OCT, I do think that it's good to look at agreement relative to previous technologies.

And so comparison, for example, with regards to atrophy with autofluorescence measurements, I think that's a very useful approach. And it's important to recognize that even when you have good agreement with autofluorescence and OCT, they're very correlated in terms of measurements of atrophy, but we all recognize that it may not be measuring exactly the same thing. The nice thing is that these kinds of things are amenable now to some deep blurring type of approaches, but I'll leave that to Michael Chiang to talk about.

I was also asked to talk a little bit about photoreceptor-related metrics because we obviously recognize that there are diseases that may affect the outer neurosensory retina preferentially and less so perhaps to RPE, so that gets me to this easy metrics story. And the reason this kind of, I think, arose was because we've sort of recognized, with retinal degenerative diseases, visual field can be a challenge at times because there can be significant variability. So you can imagine if you're trying to do a therapeutic trial for a

retinal degenerative disease, that could be quite a challenge to be able to do. And at the same time we recognize that these inherited retinal disorders can affect the outer retina of photoreceptors, and we can see those changes in the ellipsoids of band, and that can correspond to visual field alterations.

We recognize that the ellipsoid zone or the IS/OS junction is easy to identify and quantify, and so it lends itself to a potential measurement. David Birch was one of the first to propose this and demonstrated that it could be done repeatedly and could be useful for monitoring the progression of RP over time, demonstrated that this could correlate with other visual field-derived parameters, but a similar question of whether a single B-scan measurement like EZ width is satisfactory for assessing a degenerative disease process, especially, you know, there may be a concern, does the degenerative disease actually progress at the same rate in all directions? And, certainly, in some diseases it probably does.

Here's an example of a patient with RP, and again, because of the potential variability, people have suggested using EZ area as opposed to EZ width. It's kind of like more thoughts on goal. And if you have a good segmentation, this can be obtained straight from the en face maps, like in this example here. But I will say that you don't always have great segmentation, and sometimes another strategy one can resort to is simply measuring an EZ width on every single B-scan and the volume, and you know, multiple widths can essentially give you an area. That's another strategy that can be used, although obviously, that's somewhat more time consuming.

For diseases where there are relatively circular areas of preservation, not shockingly, there is a good correlation between EZ area and EZ width, and again, it also correlates nicely with visual field, but there are some limitations of this type of EZ measurement. You can imagine that, you know, if you're going to be treating or intervening early in the

disease, you have to be able to see the margins of the EZ, so you have to be able to scan wide areas, potentially. Maybe as Rick pointed out with swept-source OCT and dense scanning of large regions, it's going to be less of an issue, but it is still a consideration.

But I think the more important thing that I want to emphasize is, well, what about diseases where the area of preservation may not be circular, for example, a condition like MacTel or other inherited conditions where the area of preservation is not circular? And the disease I thought I would highlight is choroideremia, in part because it's a topic of interest, so there's multiple trials now in progress for choroideremia. And, of course, you have these stellate non-circular areas of photoreceptors preservation, so you can understand why somebody might be skeptical about using EZ width in a condition such as this.

And, of course, you know, there are some challenges, particularly with the choroideremia, that I don't want to spend too much time on. The high reflectivity of the choroid sometimes interferes with automated segmentation. So if you're going to do en face strategies, that's a problem. But you can obviously adjust all of the segmentations on every B-scan to produce an en face map, or you can do the manual segmentation of individual B-scans. That certainly can be performed to produce an EZ area, and this can be done quite repeatedly, and of course, again, I think any time you get an OCT measurement, if there's an opportunity to correlate it with another measure, for example, like autofluorescence, I believe that's something that's useful to demonstrate that type of agreement, and that certainly can be done with, you know, with the preserved autofluorescence versus the preserved EZ area; there is a nice relationship.

Lastly, in the last 5 minutes that I have, I'll talk about repeatability and reproducibility. Again, these are critical to establish for any proposed measurement. It's sort of you need to establish the coefficient of variability because you need to know the size

of the fuzzy borders. That's essential to understand the sample size for any trial, especially critical in multicenter trials, as is reproducibility. You want to know that all the sites are going to be doing this the same way. And you really need to understand, I believe, the factors which impact reproducibility and reliability.

We were interested long ago, back in the old OCT days, when we were looking at neurofiber layer measurements and we could see that there was a difference from scan to scan, and it seemed that the best predictor of this difference was really the signal strength difference between the scans. It really highlighted the importance of optimizing image quality and actually established some of the standards that we use in clinical trials for what is the minimum image quality we might need in order to reduce the type of variability. Of course, we found something similar with spectral domain OCT. And, again, image quality is something that's important to highlight.

I would emphasize that it's even more important with OCT angiography, so maybe I'll transition to that because I wanted to say something about OCT angiography in this talk. And we've heard a little bit about metrics from OCT angiography. You know, clearly, it's a high-contrast technology. It allows us to separate the vascular and nonvascular regions. So it really lends itself to quantitative analysis, and it appears relevant to both glaucoma and retinal diseases.

The common approach is that you binarize the image, and then you can compute a vessel density, if you will, or you can further skeletonize the image and then do a vessel length density, which is the total length of the vessels divided by the area. Of course, you can also quantify the FAZ, and what about the reproducibility and repeatability? There were many studies that looked at repeatability for just all the different manufacturers' devices. There are fewer studies that have looked at reproducibility, which again, to distinguish, you know, again this is a study where we used three different OCT devices from

the same manufacturer in this particular analysis. But, again, repeatability, the same device, the same eye, the same operator, which again, in this particular study, we could do that for each of the three devices and look at the coefficient of variation.

But more important is reproducibility, right? For a clinical trial you have different, you know, instruments and different centers, even if they're from the same manufacturer, and you want to know what is the reproducibility. And, again, we're able to study this in the study to establish, you know, how variable, for example, is vessel density. But the most important thing, I think, that we learned from that is that signal strength is an important predictor of variability, and again, for OCT angiography, I think that's something that's critical to try to standardize.

We have other challenges of OCT angiography. I would say multiple devices and many studies that have compared between different devices, depending on the study, have shown anywhere from moderate to poor agreement. It depends on the particular metric. I don't have time to get into that detail. But some of this relates to the fact that these different devices use different segmentations, and so we don't have standardization of this.

Lastly, Rick mentioned this, so I thought I'll say something about this, about the choriocapillaris. You know, if we can obtain images like this with our OCT angiography devices, you know, why do we think this is the choriocapillaris? Well, it kind of looks like it when we look at histology, but actually, this image was obtained like quite a bit below where the anatomic location of the choriocapillaris should be. So we're actually probably imaging projection artifact, which is another interesting question. But these metrics, we think, could be of some value because they seem to appear to predict disease progression.

But I wanted to emphasize, and I thought the choriocapillaris I'll use as the poster child to emphasize how sometimes you can have metrics which have a long way to go before they're ready for primetime, and choriocapillaris is very much the face. A lot of

controversies still on where should we position the slab to extract the choriocapillaris? I showed you an image from a slab that was deeper into the choroid that looked like the choriocapillaris.

And so again, you know, if you modulate the slab position, and we've done studies like this and you get slightly different -- I'm kind of moving the slab down here -- slightly different images of the choriocapillaris, which actually translates to some differences in terms of the -- if I can get to the end here, the quantitative metrics, they actually differ based on the slab position and you could also modulate the slab thickness. I'm just making the slab thinner and thinner here. And it also has an impact on the quantitative metrics. So these are all things to think about.

So, to summarize, I think the accuracy and precision of all of these novel posterior segment OCT and OCT measurements really has to be studied carefully and established before they can be used reliably.

Histology may be the ultimate reference standard to establish accuracy in some of these cases. Sometimes that's not possible.

And agreement with other reference imaging modalities, I highlighted autofluorescence as a useful potential validation source. It certainly can increase our confidence in these measurements.

And while accuracy is important, I would argue that it may not be essential if the metrics are reproducible and show a strong correlation with other outcomes or markers of interest.

I did point out how image quality, segmentation issues, acquisition protocols, differences between device and algorithms, and other specific attributes of disease can impact the reliability of these measurements and must be addressed.

Thank you.

(Applause.)

DR. REPKA: Thank you, Vas.

I think it's amazing that all of the speakers stayed strictly on time. We do have a -- well, they were highly accurate in their projection of time, then, I suppose. We do have a coffee break slotted for this time. We'll resume at 10:35. Visit the instruments that are here outside the meeting room. Thanks.

(Off the record at 10:18 a.m.)

(On the record at 10:35 a.m.)

DR. BLUMENKRANZ: Thank you very much. So we'll continue our program. Now we're about a couple minutes behind, but we're doing all right so far. So I'd like to introduce Michael Chiang, who's going to be speaking on clinical -- excuse me, on AI-assisted segmentation. Michael is Professor of Ophthalmology and Medical Informatics at the Casey Eye Institute at Oregon Health & Science University and an important member of the American Academy of Ophthalmology working on these areas.

Michael.

DR. CHIANG: Mark, thank you very much, and thanks for the invitation to come here and speak. I'm actually going to be not talking about a single thing related to OCT and, you know, the reason for that is that I actually, about a week ago, prepared some slides involving some work that some folks in Moorfields, you know, people like Aaron Lee, Philippe Alena (ph.), had done involving OCT segmentation. But I couldn't make all the points that I really wanted to make here that I think will be interesting for discussion. And so this is going to be a talk about segmentation in retinopathy prematurity images, and I hope this is going to, you know, be able to stimulate some discussion in the panel coming up afterwards.

These are my financial disclosures, and you know, most importantly, I want to

highlight that I'll be presenting work that a group of people have done, and it's a collaborative group that I manage involving informatics and ROP.

So why do we care about ROP, this disease? It's one of the leading causes of childhood blindness in the U.S. and throughout the world. The way it's diagnosed is that you do a bedside ophthalmoscopic exam in the neonatal intensive care unit, and the problem is that, you know, doctors can't get to these units, it takes a long time, nobody wants to do it, there's enormous medical legal liability, and so there's this avenue for artificial intelligence.

And the international classification of ROP in the 1980s was really revolutionary in terms of some of the things that came up in the panel earlier. It provided an international classification standard for ROP exams. So before then, the examination was completely descriptive and unstructured and, you know, because of this, we've gotten standard parameters, and these parameters are things like zone, stage, clock-hour, extent, and plus disease. And, you know, when everyone in the world speaks the same language, we can then standardize diagnosis and do multicenter trials, and because of these multicenter trials, we know that of all these parameters, something called plus disease is by far the most critical parameter for identifying who's going to go blind and who needs to be treated.

So plus disease is either a yes or a no. If you have plus disease, the baby is going to go blind; you need to treat the baby. And there's actually a new intermediate pre-plus category. So it's plus, pre-plus, or normal.

And so what is plus disease? It means tortuosity of the arteries and dilation of the veins in the central retina. So remember those terms, tortuous arteries, dilated veins in the central retina. The problem is that ophthalmologists are not very good at diagnosing plus disease. You know, so 10 years ago we did something that was very simple, and we put up a standard, a series of images up on the web, invited 20 world experts to go in and diagnose

is it plus, is it pre-plus, or is it normal?

And so in this image here on the left there's a little bit of dilation, a little bit of tortuosity. Fifteen percent called this plus, 85% called it not plus. The image on the right split 50/50, okay. Half called it plus, half called it not plus. And we see this all the time, 50/50, 60/40. And so the problem is that if something is so important that it determines whether you need to treat and if the world experts split 50/50, you know, it's just not good.

And so it happened that maybe 7 years ago I was on a panel, and so it's an ROP panel, and one of the people on the panel said, well, plus disease is kind of like the U.S. Supreme Court justice in the 1960s, Potter Stewart, described pornography as being -- they were arguing, of course, a case on pornography, and he said I can't define it, but I know it when I see it because it just looks bad. And he says, well, plus disease is like that and, you know, investors just looked angry, and you know, that comment just bugged me for a few months because how can we be scientific and systematic, you know, if we say things just look bad? But that is what clinicians do all the time. Okay, we just don't like the way something looks; it makes us uncomfortable.

And so we thought we'd do a qualitative study. We got the seven world experts, okay, they were people who had come up with that original classification system, they practiced for decades, and we videotaped them while making diagnoses, and they annotated, you know, what part of the images worries them or reassures them and had a psychologist go through and -- you know, go through all of that and come up with mental models. And, you know, they're all looking at different parts of the retina.

Okay, Expert Number 1 diagnosed as plus, Expert 2 diagnosed pre-plus, Expert 3 diagnosed as normal, and the process was completely different that they used to come up with that diagnosis. So we've got differences in outcome as well as differences in process. Okay, so this is -- I would argue that this is clinical diagnosis overall.

And Brad Cunningham introduced this concept of artificial intelligence. I'm not going to, you know, go through that except to say that you've got the umbrella term AI. Within that is machine learning, and a subset of machine learning is what we'll call deep learning. Okay, so I'll give some examples of machine learning and deep learning with regard to segmentation.

And I want to call out, you know, Jayashree Kalpathy-Cramer, Stratis Ioannidis, and Deniz Erdogmus. They're collaborators at Harvard and Northeastern Universities, and we've built up a team of Ph.D. students and post-docs in Oregon and in Boston to do this work.

So by way of overview, you know, with machine learning, so classic machine learning, we start with segmentation, basically what are the vessels, what are the retinal vessels, and what's the background. We then extract the features, and in a classic machine-learning approach, these features are predefined. So for ROP there are things like vascular curvature, branching, and dilation. We come up with mathematical definitions and how to quantify those.

We then do what I'll call a feature representation, meaning combine those features mathematically, for example, the mean of the vascular curvatures are the two largest values, you know, some Gaussian mixed model, and then after that, we classify. Any of the terms that you'll see in the literature are going to be things like support vector machine, so a *k*-nearest neighbors method, and these are basically machine-learning methods to combine the features and come up with your diagnosis.

So with that machine-learning approach for segmentation, you know, this is just an example of something that we did with a Ph.D. student, Ezra Kinasiglu (ph.), at Northeastern University about 7 years ago. You start with that original image, do a little preprocessing to, you know, emphasize the key features, and then, you know, we used what I'll call a clustering algorithm, it's an unsupervised algorithm, so you do not train it with any

gold standard data. And the clustering algorithm basically identifies mathematical features for what's likely to be a vessel versus not a vessel. And, you know, once we've got that, we threshold it to put it onto a black light screen, and so you see here, this looks a lot messier than this. And then we post-process it to remove some of the noise.

And so this is your segmented image. Here's your original image, here's your segmented image from this clustering, sort of machine-learning algorithm. So it looks pretty good, but it's not perfect.

When we evaluated a set of images using these segmentation algorithms, here's the original retinal images. Here's a manual segmentation. So an expert literally uses Photoshop, traces over the vessels, and comes up with, you know, what we'll call a gold standard for evaluation, and these are the automated segmentations. So you'll see that you can roughly tell that they match the original pattern, but there's a lot of noise. And the accuracy for a hundred images was 94%, if you go pixel by pixel. If you look from a sensitivity perspective, it's 64%. And from a specificity perspective, it's 95%. And that makes sense when you look at the images. There's a lot more background than actual vessel here. So these perform pretty well, but they're not perfect.

And when we use these segmented images in machine-learning algorithms to diagnose ROP -- plus, pre-plus, or normal -- the area under the ROC curve is not really that good, it's about 0.75, you know, presumably because the segmentation isn't that good.

But on the other hand, we did some studies where we did manual image segmentation, so we'd go back here, we use this image instead of this image, into one of these machine-learning algorithms that's based on feature extraction. Okay, what are the features? In this case, the best one that we found was a metric called acceleration, which is basically, you know, how quickly is your vessel changing directions. It's actually mathematically the second derivative of your XY position. So it's kind of like tortuosity.

And, you know, how do we evaluate using a reference standard if everybody has a different diagnosis for plus, pre-plus, or normal? We had a panel of experts, okay, so three people look at each image. You get an ophthalmoscopic exam, combine all of that, and that's your reference standard. So eight different world experts, did you get the right answer, plus, pre-plus, or normal? The lowest was 79%, the highest was 99%. On the average, they're 87% accurate. The computer system was 95% accurate. Now, this is using manual segmentation.

Now I want to move into deep learning because deep learning is a little bit different in the sense that we go through the same process; you go from retinal image to a vessel map using a so-called deep-learning method. I'll talk a little bit more about that. You take that vessel map, that segmentation, and then you classify it by looking at features. Okay, so you go from low-level features to mid-level features to high-level features and then, based on that, cluster into diagnoses. In this case, what's your probability of normal, what's your probability of pre-plus, what's your probability of plus.

And the principle of deep learning is that instead of coming up with features that are defined by experts a priori, the system, through a series of convolutions, goes back and forth and maps features, you know, what they think are the features to the diagnoses and then what the different weights are. And so in a sense, the system, using a black box approach, comes up with that diagnosis, you know, because of the abundance of big data and because of the abundance of processing power these days.

So how does this work for segmentation? Well, we started with 200 retinal photographs, annotated them in Photoshop with these manual segmentations that serve as a gold standard. We trained a deep-learning system to learn segmentation by mapping the original retinal images to the manual segmentations, and that's basically using a unit architecture; it's an open source algorithm for things like segmentation. And then we take

those segmentations, feed them into another convolutional network to make a plus disease diagnosis, so plus, pre-plus, or normal. So it's a two-step process. Number one, we segment the image. Number two, we make a diagnosis based on that segmented image.

And so these are some examples of the segmentation, again, trained on 200 manual segmentations. Here's your original image, here's that manual gold standard segmentation, and here's the automated segmentation using deep learning. They look really, really good. So when we use that for diagnostic classification, we actually get really, really good results.

So this is fully automated; there's no manual segmentation, nothing. And the area under the ROC curve for diagnosing plus disease was 0.98, so near perfect discrimination. And when we tested in independent tests out of a hundred images, we compared to that reference standard, which is, again, four experts looking at each image, majority vote, the computer system was 91% accurate for diagnosing plus versus pre-plus versus normal. Recruited eight world experts; they were on average 82% accurate. So the computer system beats seven out of eight experts on an independent dataset.

And, in fact, we've done some studies where if you take that output of deep learning and if you convert it to a number from 1 to 9, you can create a quantitative scale for categorizing plus disease, really similar to some of the OCT stuff this morning, and that when we do that, we can actually come up with actually very, very accurate methods for screening populations, where if you draw the line over here, higher than this number is -- lower than this number is observed, we can get actually very high sensitivity and specificity from a screening perspective.

So the last thing I want to talk about is image quality. You know, we all know that there are good images, there are bad images, and there are in-between images, and you know, if we want to run systems like this, we've got to have ways to identify bad images to filter them out because you can't segment and analyze images that are poor quality. So the

question is could we take 6,000 posterior pole images, grade them by a series of three experts. Every expert would say, you know, the image is acceptable quality for a diagnosis, it's not acceptable, or it's possibly acceptable. Okay, so we take a majority vote of those quality gradings, that's your gold standard, and based on that, we can train a deep-learning system to identify if your image is acceptable versus not acceptable.

So does this work? The answer is that it actually works pretty well. So we evaluated on these 6,000 images. The area under the ROC curve is about 0.96 for identifying acceptable quality images versus not acceptable quality images. And, in fact, we had six experts take a series of 30 images and rank them from 1 to 30 in terms of quality. You've got your worst quality, you've got your highest quality, and we did that through a series of comparisons. What's high quality, one versus two, one versus three, one versus four? And if you do that several hundred times, you can rank them from 1 to 30.

So each expert ranks it in quality, the computer system ranks it in quality, and you can get correlation coefficients. How well does one person correlate with another person? And the computer system has a correlation coefficient of 0.9 compared to the overall consensus rank ordering of quality. So I really think this kind of has potential to work, and we can feed it into these deep-learning systems to be able to figure out well, you know, is your image good enough quality to analyze?

So this is my last slide, a few bullet points to summarize. Number one, I've tried to make the point that ophthalmic diagnosis is subjective and qualitative. Okay, there's inconsistency in both classification and process. And, obviously, I think there's a role for artificial intelligence in image segmentation and also image quality. You know, we talked about the fact that there is significant better performance for deep-learning methods of segmentation compared to traditional methods, but I don't think this concept of features is dead. In fact, I think that this concept of explainability, what it means to just look bad, I

think it's going to be really, really important for the practice of medicine, and I hope that's something that machine-learning systems and deep-learning systems can really focus on in the future.

And, you know, my last point is that there's a difference in diagnostic classification versus screening, and I hope that there are going to be different levels of oversight for these systems, depending on their intended use.

So thank you very much.

(Applause.)

DR. BLUMENKRANZ: Thank you, Michael.

I'd like to ask the panelists for Panel 1 to come up, please. If you can, bring your name card with you and be seated here at the front, and we will get started as soon as you get up here.

(Pause.)

DR. BLUMENKRANZ: While the panelists are getting seated, I'll tell you a little bit about who we have with us today. We have a distinguished group of experts that have been chosen especially to sort of illuminate some of the topics that you've heard earlier that will benefit from some additional -- I think we might need one extra chair, by the way, please.

UNIDENTIFIED SPEAKER: There's one here.

DR. BLUMENKRANZ: We're going to have to share, I guess. I'm just joking. Don't worry about it, that's fine. So do we have enough chairs here? Okay, great.

So Michael Abramoff is an ophthalmologist, computer scientist, and entrepreneur who is the founder of IDx, the first company to receive FDA clearance.

Dr. Lama Al-Aswad is a faculty member at Columbia and the Harkness Eye Institute, who specializes in glaucoma and cataract surgery and heads up a novel tele-ophthalmology

initiative that includes remote disease screening in kiosk-based acquisition systems.

Frank Brodie is a UCSF-trained ophthalmologist who's a fellow at Stanford in the ophthalmic innovation program, who's established a novel nonprofit organization to provide 3-D printed spectacles to children with severe craniofacial abnormalities.

Brad Cunningham you met earlier in the program; he's the Branch Chief for Diagnostic and Surgical Devices in the Division of Ophthalmic and ENT Devices here at the FDA.

Dr. Alastair Denniston is an internationally noted uveitis specialist, professor, and consultant at the University of Birmingham in England, who's made major contributions in etiology and classification of important uveitic diseases.

Ted Leng is a retinal specialist and member of the faculty at Stanford Byers Eye Institute, where he serves as Director of Clinical and Translational Research. He has special interest and expertise in the use of AI techniques in OCT interpretation.

Mays El-Dairi is a pediatric ophthalmologist at Duke University with extensive experience and expertise in the use of spectral domain OCT for evaluation of optic nerve disease.

Dr. Felipe Medeiros is Professor of Ophthalmology at Duke and Director of the Clinical Research Unit, who has special interest and expertise in the use of OCT for diagnosis and detection of glaucoma and its progression.

And Nadia Waheed is a member of the faculty of the Tufts New England Medical Center where she is Director of the Boston Image Reading Center. She has expertise and is the author of a book on ophthalmic imaging and also expert in the use of imaging for trial design and endpoints.

So you can see that we have tried to select people that can provide insights and additional information on some of the topics we've heard a little bit about.

We're going to start. Actually, if we could have the questions. The first question relates to quantification of retinal vascularity, and I'm going to ask Nadia to comment on that. How does OCT compare to dye-based vascular studies in assessing flow and leakage in the retina, impacts on late staining and low flow, and in general, how do you see this field adding to our knowledge and understanding?

DR. WAHEED: So thank you, Mark.

I think, you know, OCT angiography is really interesting in that it can provide very high resolution of the microvasculature, so, you know, as far as quantification of vasculature goals, OCT angiography is actually, I think, far ahead of some of the traditional dye-based techniques that we've used in terms of being able to quantify vasculature. But, of course, you know, it's not able to visualize some of the things that you would see in dye-based, for example, leakage is not one of the things that OCT angiography can visualize.

I have a couple of slides that I can potentially present, but I think, from a clinical trials perspective, you know, one of the great things about OCT angiography is that it can quantify vasculature, you know, in a relatively repeatable and reproducible manner. You do have to be careful, however. You know, I think some of the other speakers were alluding to this. You do have to be careful when you're switching between devices, so this was, you know, studies that we did.

If you can actually go on to the next slide, please.

This was one of the studies that we did that looked at repeatability and reproducibility within devices and between devices, and as you can see over here, you know, there's a lot of data going on there, but the crux is that looking between devices can be somewhat tricky, especially as you're switching from the spectral domain platforms to the swept-source platforms, but within devices the repeatability and reproducibility of retinal vascular quantification is actually quite good. And as you can see, the coefficient of

repeatability is quite good if you're looking within a device.

Can you go to the next slide, please?

So these are the coefficients of repeatability values between the different instruments, using different strategies for binarization.

Next slide, please.

And I think the final conclusion is that there is variability between the different devices, but within devices that you get pretty good results. Now, the caveat to that, of course, is that there's some, you know, lack of transparency when the images come out from the machines, exactly what kind of enhancements have been applied to them.

So if you go on to the next slide here. And this is my last slide I'll show you.

You know, depending on just -- if you just vary the brightness and contrast and apply different binarization technologies or apply adaptive contrast enhancement in these images, you can change the quantific metrics quite a bit. As long as the same consistent metrics are applied every single time you get images on a particular machine from a patient, you get very repeatable and reproducible results. But if different algorithms are applied at different visits or if there's an adaptive technique that enhances images based on what the quality is, then you can have quite a bit of variability.

I'm just going to end the slides over here. I hope that answers some of the questions that you asked.

DR. BLUMENKRANZ: Thank you, that's very helpful.

I think we'll move on to the second question now, which has to do with establishing gold standards. The FDA is promoting innovation and expediting of the clinical development of optical coherence tomography units and other methodologies as new functionalities are introduced, typically performance data as compared to a gold standard. Does a gold standard comparator exist for the following? And, Nadia, you've spoken a little

bit about its potential for gold standards and reproducibility in retinal vascularity. We have a question about the new technique.

We heard a little bit, and as an aside, in listening to Joel Schuman, who's a world-renown glaucoma expert, speak about retinal applications, and listening to Rick Spaide, who's a world-renown retinal specialist, speak about glaucoma applications, it occurred to me that we've finally come to the point where we can all agree it's kind of like not worrying about whether you're a Mets fan or a Yankees fan; we're all baseball fans. And so it's clear that the technology is bringing us together in ways that we might not have thought about, about looking at different diseases because we're drawn together by the technology rather than the disease, the same methodology.

So, Brad, I'm going to ask you about oximetry a little bit, and then I actually have a plant in the audience, as well, to follow up on this. So in terms of gold standards for retinal oximetry, and we were pleased to hear two different talks about this, so clearly we've already had some review of this.

MR. CUNNINGHAM: So I appreciate you asking me to answer this question, but certainly this is something that we're very interested in. From FDA's perspective, I think we're looking to hear what everyone else has to say, so I'd be happy to turn it back to --

DR. BLUMENKRANZ: Okay.

(Laughter.)

MR. CUNNINGHAM: I mean, certainly, we can come up with plenty to offer, but we're here to hear everyone else's comments as well.

DR. BLUMENKRANZ: Well, I can tell that you're skilled not only in regulatory science but in handling yourself on the podium as well. That's a classic maneuver, but I appreciate it, and I think you're correct.

So, Ted, I mentioned this to you a little bit, and maybe if you have a word or two

about that. Alf Dubra, if you're around somewhere and can get to a microphone, I know Alf is interested in this area, and they have a viewpoint, if you're out there.

DR. LENG: I think, while Alf is getting a microphone, I think just to kind of echo what Rick Spaide had said earlier, I think while there is a technical potential advantage of a higher axial resolution, I think there is, you know, still more work needs to be done on really eking out the last -- (microphone cuts out) -- from the visible-light OCT. And then there's also issues of just practicability. If anyone's ever done that, the light is quite bright and difficult for patients to tolerate, so there's potential exposure issues as well.

DR. BLUMENKRANZ: Correct. Alf, perhaps you want to make a comment.

DR. DUBRA: Yeah. I want to say that purely from the optics point of view, it's one of the most exciting things that will happen to ophthalmology in terms of imaging because one of the most powerful families of techniques available in optics to study what is all the way from the distant stars and planets to air pollution and chemistry in general is this broad family of techniques called spectroscopy, and visible-light OCT seems to be a far more appropriate tool to study the pigments and molecules that are in the retina and the relation to disease. So I think that visible-light OCT has a lot to offer. Like the previous speaker, I'm going to deflect to one of the three world experts on visible-light OCT, and they're hopefully still right behind me. So I'll let him speak of the virtues of the technique.

DR. SRINIVASAN: Vivek Srinivasan, UC Davis.

I am talking in the panel in the afternoon, so I won't extol the virtues of visible-light OCT, but as to the particular panel discussion question, so it says does a gold standard comparator exist for quantification of oximetry, and my argument would be, well, no, not really, as with other ophthalmic techniques. There are several validation studies that can be and have been done. I want to point in particular to a group from Northwestern as well as the Oregon Health & Science University has looked at kind of a sanity check-type

experiment. So you take a rat, you reduce the oxygen, make it mildly hypoxic, saturation in blood flow, change in opposite directions such that the metabolism stays constant. As you make the animal more hypoxic, oxygen metabolism goes down. People have done similar studies with intraocular pressure, and I think these are very important as sanity checks that metabolism is behaving as we expect it to and as other studies have suggested that it should.

There are methods of measuring -- so I should take a step back, that visible-light OCT measures or claims to measure saturation, oxygen saturation, in vessels. Oxygen saturation is, of course, related to TO_2, partial pressure of oxygen in the blood, and there are ways to measure partial pressure of oxygen directly in situ using phosphorus and oxygen-sensitive dyes. So I point to work from Mahnaz Shahidi as well as others that have shown quantification of PO_2 in retinal vessels, so I think there's some opportunity here for cross-validation with saturation measurements or oximetry measurements with visible-light OCT. Thanks.

DR. BLUMENKRANZ: Thank you very much. It's an interesting topic, and obviously, from the amount of attention devoted to it by the speakers as well as this panel, it's clear that that's really one exciting feature, and I think we have --

DR. MEDEIROS: I have a question about that. This is just a thought. I would imagine that the oximetry would be influenced by the amount of light that gets into the eye. So how does the method here actually influence the measurements? Anyone that has more experience on this? Like the fact that you're actually using visible light to collect the measurement, would that influence the oximetry itself?

DR. BLUMENKRANZ: The Heisenberg uncertainty principle, right. Well, I don't know that we'll answer that today, but I think we'll move on, but it raises an interesting question, and it's more of a generic question. Anytime you measure any system, what perturbations

do you induce that essentially change the baseline measurement that you're trying to achieve? And I guess those are interesting questions.

Okay, we'll move on now to the next question, which is essentially functional assessment of metabolic or other functional structural changes, including the optic nerve and retina, is there a gold standard? And I'm going to direct that to Lama, if you're willing to take that on. And I guess I'll add something. Is there a gold standard in glaucoma at the end? And I think I warned you.

DR. AL-ASWAD: There is no sign, symptom, or diagnostic test or metabolic test that's pattern mnemonic for glaucoma. The current diagnosis for glaucoma is based on constellations of IOP diagnostic tests. Some of them are clear-cut, and some of them are not so clear-cut. We depend on IOP, as we said, visual field, corneal thickness imaging technology, OCT the gold standard, adaptive optics now, and other imaging technology.

If you look at the accuracy and what's happening out in the world, there is over-diagnosis, under-diagnosis, and misdiagnosis. According to the claims data in the U.S. between 2002 and 2008, there's evidence that there are regions of over-diagnosis, regions of under-diagnosis, and misdiagnosis for angle-closure glaucoma.

If you look at the Greek study, Salenski (ph.) study, they did a cross-sectional population study, and they recruited 2,500 individuals and they did testing on them, there was 60% of over-diagnosis. The Chineye (ph.) eye study demonstrated 40% of the people that were included in the study, and it was a randomized study, had angle closure when they were diagnosed with open-angle glaucoma. So we have a problem at this point, and we need standardization.

If you look at the accuracy of our imaging study, they're pretty good, but they're not as accurate. If we look at the "isn't true" itself, which we think is the gold standard, it's sensitive and specific mostly in not-advanced glaucoma, and the inferior section is the best

indicator for it. Cochrane, in 2015, did a meta-analysis for 106 studies, approximately 16,000 patients, looked at OCD, DDX, and HRT and they noticed that the sensitivity is 60 to 70%, the specificity was higher, in the 90th -- 93-94%, and that was more accurate for advanced and not mild glaucoma.

Can I show the last slide of mine?

So to echo some of what Michael Chiang said, what Yasmin said, we have a problem right now in the diagnosis of glaucoma. We need consensus for glaucoma.

Just the last slide.

We don't have, right now, standardization in the diagnosis of glaucoma. We don't have an accurate algorithm for resolution of glaucoma assessment. You have a patient that's a glaucoma suspect; they stay a glaucoma suspect for the rest of their life at this point. We don't have clear-cut indications to reduce over- or under-treatment and diagnosis of glaucoma. We do need foundational knowledge for research and development to standardize studies, protocols, inclusion/exclusion criteria. Definition of population is very important. We cannot even define the population for glaucoma suspects or screening. If we do screening, what is the gold standard? What are criteria for considering a patient a glaucoma suspect in screening and outcome measures?

I think the FDA did a great job with the mix, trying to initially define it and have outcomes for it, but we have lack in it in the rest of the glaucoma diseases and diagnoses and management. And I am jealous, from the ROP, because they have standardization, and in glaucoma, after all those series, and the more I do glaucoma, the more I know I don't know that much about standardization in glaucoma. I practice the way I learned, but is that the gold standard?

Thank you.

DR. BLUMENKRANZ: Thank you very much.

I think we'll move on to AI next, and we'll start with AI-assisted segmentation, and I'll ask Ted Leng, who has written about this and thought about it a great deal, for your thoughts on that.

DR. LENG: Thanks, Mark.

Maybe we can also throw up some of our slides we brought, but I think just addressing the question of whether there's a gold standard, it's been pretty apparent here amongst this panel that we're in the very early stages of having gold standards for much at all in ophthalmic, in this forefront of -- (microphone cuts out) -- and it's certainly the same with trying to segment retinal images, whether that be fundus photographs or OCT. For any of you out there who, like myself, have been unfortunate enough to -- and our graduate students, they actually manually segment images. It's quite painstaking and very tiring. And studies have shown that, you know, even the same person, when they go back and retrace their own image a second time, are incorrect, you know, a high percentage of the time.

So I think this is a perennial problem for us, of what is really a gold standard for segmentation and especially as we move into evaluating and validating some of our AI technologies. Our group has been working on the segmentation of inter-retinal fluid for several years now.

And, actually, if you could just advance the last slide.

This is a study from one of my colleagues over at the University of Washington, where they did 200,000 iterations.

One more slide, please, and you can play the video.

And you can see here, over the 200,000 iterations, they did a dataset of about 1,500 scans variable to -- went down and really get great accuracy as far as identifying the retinal cysts in these OCTs. I think their Dice coefficient was 0.9 something. So that gives us really

great performance of these types of algorithms using convolutional neural networks to identify cysts. And those features are essential in the diseases that we're looking at in the macula.

DR. BLUMENKRANZ: Thank you, Ted.

Staying on the topic of AI, I thought we'd move to Mike Abramoff, who -- and I've asked him whether he would care to offer a comment because this hasn't become a reality yet about the use of AI for grading not only fundus images for diabetic retinopathy, but moving on to the next level of OCT for either diabetic retinopathy or AMD or anything that you'd like to comment on in terms of what's your experience or what's your prediction or feelings about what gold standards should look like for another imaging modality.

Michael.

DR. ABRAMOFF: I think the exciting thing with OCT is that we're pretty early with applying image analysis and AI. And so biomarkers that we are familiar with, like neuroretinal thickness, and now we're pretty -- getting pretty good at segmenting those and measuring those. I'm mostly excited about using it to improve patient outcomes, specifically for screening and early diagnosis. So I'm really focused on autonomous use where you do not have a clinician overseeing the result directly.

And so one of the things that we deal with is the lack of consensus of, for example, glaucoma, if you want to do early detection of glaucoma. Maybe we can show my last slide, Slide Number 4. If you're concerned with that and you want to use, for example, OCT to do early diagnosis of glaucoma without visual field, without IOP, what do you compare it to?

The last slide, please. Well, this is not my last slide.

Okay, so we have shown, in multiple studies, that you can predict visual function, specifically visual fields, pretty well from -- last slide, please -- from just OCT, if you do wide-field OCT. And so it seems that at least the visual field can be predicted from OCT, and that

means that maybe an OCT by itself is enough. Of course, you cannot predict an IOP and maybe some other measurements like what the angle looks like. And so, hopefully, we can come to a consensus where it's effective, right? If you want to use it in places like primary care, measuring IOP and looking at anterior segment is really difficult. And so if there's a technique where it can just use OCT and compare that to a reference standard that does, you know, not involve all these other things, that would be very important for advancing this.

DR. BLUMENKRANZ: Thank you very much.

We'll move on now to the anterior chamber angle, and we heard a good talk by Mitchell earlier this morning about various uses, so I'm going to ask Felipe Medeiros about your impressions of OCT in terms of the precision and reproducibility of anterior chamber angle grading and corneal thickness, both as they relate to anterior segment disease and also to perhaps glaucoma as well.

Felipe, if you'd care to comment.

DR. MEDEIROS: Yeah.

DR. BLUMENKRANZ: And specifying a little bit on what kind of gold standards we might be able to use to determine who's right and who's wrong, if you will.

DR. MEDEIROS: So anterior segment OCT for glaucoma, in contrast to posterior imaging, has received a lot less attention, and most of the algorithms still require a lot of human inputting for marking the images and obtaining the parameters. But once you do that, in general, the measurements have been reproducible, and some studies actually have suggested that the measurements from AS OCT are actually more reproducible than human gradings on gonioscopy, which we all know are quite subjective and have relatively poor inter-grader reproducibility.

So, overall, the measurements are reproducible, and we saw some data on that.

However, in about like 15 to 30% of the images, for example, you cannot really see features like the scleral support very well, which would actually be important for the delineation of certain metrics. Some recent work has used AI, and there's a very interesting paper that just came out this month from Ting Ong's group where they used deep learning to automatically classify AS OCT images in a relatively large sample, I think about over 2,000 patients, about 8,000 images, and compared that to gonioscopy for diagnosis of angle closure, and they found an ROC curve area of about 0.96. So it performed actually pretty well for that, and I think approaches like that, that you actually use the whole image without requiring the subjective input to mark the structures, are actually the way to go with AS OCT. That's how I see it going.

DR. BLUMENKRANZ: Thank you very much.

Well, we'll sort of stay in that general area. We've heard a lot about adults. We've heard some about children, certainly Michael's talk on ROP. So I'm going to ask Mays El-Dairi if you could tell us a little bit about opportunities and challenges that exist for other conditions, specifically focusing on pediatric and neuro-ophthalmologic disease using newer OCT modalities.

DR. EL-DAIRI: Thank you. So in the pediatric world, we have multiple other challenges, one, because we really can't sit them down and have stability while imaging. So I'm lucky to be part of the DARSI Lab with Dr. Toth, and we've had access to this kind of OCT for a very long time. So we use it very frequently in ROP. Dr. Chiang already spoke about that. But we also use it nowadays with a child coming in with an onset nystagmus, we do the OCT in the clinic on the spot, and we can diagnose a retinopathy like LCA or like a 5-year-old coming in with features that look like that, and the OCT features are so diagnostic that you can make the diagnosis very early on.

In other parts of peds, we have this large question of papilledema versus

pseudopapilledema, because a lot of times when they have true papilledema the nerve doesn't swell a lot and it looks a lot like pseudopapilledema, and with the use of OCT, like looking at the Bruch membrane opening or the mechanics of how it's bowed can lead us into going down the route of more diagnostic modalities or not. And the other thing is that it's looking at the inner retina in pediatric patients. So a lot of times we don't have the luxury of getting a retinal nerve fiber layer, so we get a lot of our information by looking just at the inner retina or the inner retinal anatomy.

From doing OCTs in multiple diseases whereby we thought it was a pure optic neuropathy, we're actually finding out that sometimes you have a retina component that we didn't know about. Like inserting cases of pediatric glaucoma, we're sometimes finding some changes in the deeper retinal vasculature that we didn't know existed before. If we have a child who cannot do a visual field, sometimes getting a macular mark can make out a visual defect and can help them out functionally as well.

DR. BLUMENKRANZ: Thank you very much.

We'll move on now to Alastair Denniston. What are some of the more promising methods being used to help in uveitis? Is quantification of anterior chamber cell count and differentiation of retina and vitreous infiltrates ready for prime time? And what are some gold standards that you use to be able to identify those particular areas, if any?

DR. DENNISTON: Great, thanks. So it's an interesting time in the field of uveitis at the moment, and the impacts of imaging and particularly quantitative imaging on that. So I would guess, like any other entity, we're interested in imaging both for diagnosis and for monitoring, and I'm going to park diagnosis for the moment and just talk about the monitoring of disease.

So we do have standards in uveitis, but there are issues that have been fairly subjective in how we assess the condition. So the FDA, with the National Eye Institute,

convened a meeting in 2015 where we defined the key variables that we wanted to measure in order to know whether disease was active or inactive in uveitis, and key amongst those were anterior chamber cells, vitreous haze, retinal infiltrates, choroidal infiltrates, and retinovascular leakage. Macular edema is obviously significant, but because of the multifactorial nature of that, that's kind of considered as highly separate. Of course, macular edema is the one thing that we can measure quantitatively and have reliable measurements fairly easily, but the other areas have been a challenge.

So to come back to Mark's question, the anterior chamber cells, yeah, I think that we are pretty well ready for prime time in the sense of, in the sense that we're very close, certainly. So some great work shown at the American Uveitis Society's LA meeting 2 weeks ago, from groups such as ASCRS, and Sharma Cleveland (ph.), the Arant Group (ph.), and Sylvia Lee, all showing really nice approaches to quantitation over large cohorts, including machine-learning approaches actually to help identify the cells. So I think with anterior segment, particularly swept-source platforms, but there was also shown in spectral domain platforms as well, we can do the AC cell counts.

And the interesting aside is that a lot of the patients that we think clinically have zero cells, we are actually picking up, picking up cells now that we're doing this objectively.

So other areas of interest. So vitreous haze, that's something that my group has worked on a lot, and we find that this is a way of basically quantitating objectively what we've been doing for 20 years in terms of estimating vitreous haze, and I don't think that's ready for widespread deployment yet, but you know, we've shown the proof of concept and we've shown reproducibility, and it's a good alternative for clinical trials.

The retinal and choroidal infiltrates, I think we're still sort of borrowing from our medical retinal colleagues and obviously those amongst others. There's a really great paper from King and colleagues, with the Moorfields DeepMind collaboration, showing for other

retinal diseases. And we're looking at applying that technology to our reference datasets for uveitis as well. Thank you.

DR. BLUMENKRANZ: Thank you very much.

Well, we're down to our last question here, and if we have a moment or two, we may be able to take one or two from the audience, but I'm going to ask Frank Brodie. And, Brad, I'll give you a crack at this as well. But what are some of the newer innovative programs that the FDA designed to help innovators developing new medical imaging devices in terms of the clinical regulatory pathway early in the game?

DR. BRODIE: Yeah, that's a great question. And I'm glad Brad's here. You were almost off the hook. You know, there's some really great programs the FDA has started rolling out to allow for kind of a lot of interactive feedback with the FDA early on and this applies not just to diagnostic devices, but also therapeutic devices. One of the ones that Dr. Abramoff's company took advantage of was the breakthrough pathway, and I think that is a really valuable tool that allows, if you have a technology that presents to a pressing need, you know, something that is not well treated or if there's no FDA-approved alternative for it, you get enhanced interaction with the FDA, a lot of informal and formal interaction and really accelerated timelines, and I think it has really helped.

(Off microphone comment.)

DR. BRODIE: Yeah, really helped IDx come to market in a very efficient way and quickly. Another thing is easy -- or sorry, early feasibility study program, which allows for, while you're still in the design phase of trials, to test on a few patients in a very controlled manner to help develop some design elements of your product, and this is a really unique opportunity to get into human trials in the United States earlier than you normally would in a smaller controlled setting.

Brad, what did I miss or what did I mis-say?

MR. CUNNINGHAM: I don't think you actually mis-said anything. Actually, you covered it quite well. I would just sort of echo with what you mentioned about EFS, and I think the take-home point is there is certainly early interaction. As you saw in my presentation earlier, we've seen a pretty high uptick in terms of Q-subs or pre-submissions to us. So we're hoping that's at least somewhat indicative of sort of the stakeholders and FDA both embracing the idea of early interaction and how that can help facilitate innovation. We do, at least internally, reach out, and we do have programs such as Network of Experts, and that's something internally that we utilize to solve some of the really tough questions like what have been discussed today, and those are mechanisms we use to help bring these types of questions, at least, to be addressed and bring these technologies to market faster in a little bit more meaningful way.

DR. BLUMENKRANZ: Thank you.

Well, according to my Apple Watch, we're exactly 2 seconds over, so I'd like to thank the panel for their accuracy, their reproducibility, and the precision of their presentations.

(Applause.)

DR. BLUMENKRANZ: In the interest of everyone getting a full and restorative lunch, we'll allow you to go out and to do that now and to do networking, to visit the exhibits, to talk amongst yourselves, and then we'd like to have you back here at 12:30 sharp for the next session. But thank you all for coming. Thank you, panelists. Thank you, audience. Thank you, everyone.

(Whereupon, at 11:30 a.m., a lunch recess was taken.)

A F T E R N O O N S E S S I O N

(12:33 p.m.)

DR. REPKA: Let's go ahead and get seated so we can start the afternoon.

(Pause.)

DR. REPKA: All right, so we have a couple of announcements. If you're using or would like to use a cab to go back to one of the airports, if you seek out meeting staff or Wade, who's standing here, about 10 minutes before, he can get a cab or get -- I guess call a cab. On the other hand, I suppose there should be no trouble getting a car-share service to find a place since they seem to know where this is.

The web version of this, of course, is going to be available, expect it in about 24 hours. The link for that will be up on the website for this meeting, which is at www.cfom.org slash whatever, laser diagnostic -- oh, golly. Laser diagnosis in imaging.

Anyway, so I'm going to turn this over to Cathy, who's going to continue moderating the session.

DR. CUKRAS: Great. Well, thank you so much, and welcome to this next session on adaptive optics. To start off, we have Alf Dubra coming to us as the Associate Professor of Ophthalmology at Stanford University, and he'll be speaking on adaptive optics introduction and use in imaging devices.

DR. DUBRA: Excellent. Thank you for the introduction, and feel free to fall asleep. I know that it is right after lunch, and there will be two equations.

So let me start by sharing my disclosures, current and past, and I want to make sure that I acknowledge the past ones as well, because I'm very proud of the funding, the support of the lab. I'm very grateful to the funding agencies.

So let me start with a simple mathematical construct, that is, imagine that you have a little rock, in this case the black dot that is on the screen, and you threw it on a very calm

lake, and then you would all be familiar with a set of concentric waves that emanate from that radially outward. So if you were to freeze that lake for a second as the waves are moving, which is totally practical, if you were to put a pencil anywhere on that water and drawing without lifting your pen, were to join all the points in the water that have the same height, that will be a wavefront. And it's not a real physical feature. It's a mathematical construct that we use to study light or waves, in general, and it doesn't have to be at the peak of the wave or the bottom of the wave; it could be anywhere.

So now if you think that you can draw lines perpendicular to those waves, that is also where we use it as a mathematical construct that we call light rays, and we also use a combination of both to deal with light and waves. And imagine that a fraction of those rays or waveforms actually are collected by an imaging system, and you think of an imaging system in a slightly romantic version as a time reversal machine, what you would get is that you revert these phenomena or these wavefronts that emerge from the point actually converge to form an image. So that's what most imaging systems that you know do, like for example your eye.

So that does not mean that you can take a very small object and create an equally small image of it. There's a phenomenon that comes to spoil the party; there's diffraction, which means that if you were to have a really small point, and you might not see it on this screen because it's actually just one pixel, and tried to create an image of that, the image of that object, even if you had a perfect optical system, you would get a bigger dot on the other side. And, in fact, if you were to make that dot brighter and brighter, you will see that actually has some structure to it. So if you have a good optical system like, for example, the cameras in your cell phone or a microscope, this is what you see. So all the images are formed by the addition of these points with rings around them. It's just that the rings are very faint and you don't see them.

So we defined an idea for a solution by the width of this central point, that we typically call an error disk when your lenses are round. I'm sorry about the equation, but the point I want to make here is just that the size of this feature has to do with the diameter of the hole or the lens that you're looking through. So that's why, in adaptive optics, as I'm going to explain later, we always try to use the largest possible aperture if we want to achieve -- to resolve the smallest feature as possible. So that is a limit, and I want to -- there are ways to break that limit, but they have not been demonstrated in the eye, and I don't think that it will be safe to do that in the eye. You have to put too much light.

So what is a real system would not create a perfect spherical shell converging towards the point. You would actually create a bumpy wavefront, and that is what we call an aberration. So the departure of this spherical shape to the real shape is what we call a wavefront error or wavefront aberration, and that means that those rays of light will go to different parts in the image plane, and it will make the image blurry.

As it would be kind of obvious from my cartoon here, if you had a smaller optical system, then the wavefront would look less bumpy, but diffraction would be worse because the aperture is now smaller. So when you design an optical system, you are always kind of trading the two of them.

So, for example, the analogy here, the reason why this is important for ophthalmology is the most current commercial ophthalmoscopes that you know use a very small pupil, to the point that the wavefront appears always almost perfectly spherical and your images are limited by diffraction, not by the imperfections of your optical system. As you use a larger portion of the pupil, then the wavefront aberrations overtake as the phenomenon that blurs your image.

So, anyway, I want to point out that aberrations change not only with pupil diameter but also pupil location. If you enter the eye through different parts of the pupil, you will get

different aberrations. Also, if you image different parts of the retina, you will see that the shape of the aberrations change as well.

And then, to make things more complicated, if you're trying to use many different colors of light, you will see that, first of all, the most obvious phenomenon is that they all focus at different depths in the retina, and this is used, for example, for subjective refraction when you toggle between red and blue. And this is a very well-known phenomenon, and it's been known since like Newton, and it's called longitudinal chromatic aberration, but what is not talked about very often is, and this is a poor drawing, but there are two wavefronts there, one red and one green, and the point I'm trying to make here is that the aberrations also change with wavelengths. Not a lot, but they do change. So if we want to do visible OCT with adaptive optics, this might actually be a limiting factor.

Then the other thing that is important to acknowledge is that the aberrations are not something that are fixed over time, and what I'm showing you here is a different type of interferometer, it's an OCT, and you're looking at the surface of the tear film of various of my friends in the United Kingdom when I was doing my Ph.D., and they were kind enough to volunteer, and the point here is that the surface of the tear film could be very smooth or very rough and can actually induce aberrations that change over time. And this is playing in real time and this is nothing pathological; this is just normal physiological tear film and then you blink, and ta-da, a new wavefront again.

Anyway, so the point I want to make is that, okay, we have wavefront aberrations, so there are ways to measure the wavefront, and of course, the devices have wavefront sensors, and the most elementary form of wavefront sensor that is used in ophthalmology is when you prescribe spectacles in children, for example, with a direct ophthalmoscope. That is a very elementary and subjective wavefront sensing.

The other refractor is a quantitative wavefront sensor, and it only measures two

aberrations, defocus and astigmatism, but there are aberrations nevertheless. And there are a lot of different devices that have come out throughout the years, but the most popular one is not only for retinal imaging, that is what I'm going to talk about today, but also in refractive surgery, it's the Shack-Hartmann wavefront sensor, and it works by taking the light coming back from the eye, splitting it into many different lens slits, each of which forms a little spot, and we measure the position of that spot to figure out the shape of the wavefront.

There are many different wavefront correctors, and again, the most elementary that we use in ophthalmology is spectacles. If you use an ophthalmoscope, then you have the knob that you use to adjust the subject's prescription to correct for that, and that is called a Badal optometer arrangement. You can think of intraocular lenses or refractive surgery as a form of wavefront correction, it's just a permanent one. And then the more modern devices that maybe are more dynamic and allow you to keep up not only with changing the aberrations across the retina but also over time, and one of them is the formable mirror, and that has been the most popular in the eye in retinal imaging.

And when you combine the wavefront sensor and the wavefront corrector, you can actually use a feedback loop and correct for the aberrations of the eye in real time so you can see through this device and the eye combined as if you were looking through a microscope. And then when you do that, you can go from a magnified image that might look blurry to something that looks really sharp and you can see new features.

So the point here is that the way we think about adaptive optics is that it's not an incremental revealing of information, that you get maybe sharper edges of a lesion, you actually see new information. Although there is room for an adaptive optics type of instrument that might not necessarily bring you all the way here, it doesn't have to be a Rolls-Royce, but it could improve the repeatability or the reproducibility of, say, finding the

edges of lesions, as was discussed earlier today. So as much as I obsess myself about pursuing the maximum resolution, there is room for potentially lower resolution adaptive optics.

And this is the type of images that you might have seen more commonly in adaptive optics retina, limiting the cones and rods, but really, you can look -- you can look at anything that you look at with a fundus camera or an OCT. Even, for example, an epiretinal membrane. The point that we're trying to make here is that there's not necessarily new information revealed, although that could be argued, but you might have a more sensitive measure of progression; in this case, just an epiretinal membrane just 2 months follow-up. And you can also see things like the color from these pictures, that you traditionally think like these orange images with -- that might look completely different once you look at the very microscopic scale and rejecting light from different retinas. So it might provide new information.

And then you can also think that you can translate any technique that you have already in the clinic without AO, into AO. You can look at autofluorescence, in this case a short wavelength autofluorescence that reveals the RPE mosaic, or it could be fluorescein angiography.

And the other thing that I want you to remember, if you can take it home as a message, is that not everything in terms of imaging has been done. In terms of ophthalmic imaging, we're actually creating new imaging techniques that have not even been proposed for microscopy, and here, we and others have been using multiple scattered light to reveal new structures.

So in the interest of time, I'm just going to finish here, but there's only one thing that I want you to remember today, is that adaptive optics is not an imaging modality. It is something that you add to an imaging modality to get higher resolution.

And I'll stop here. Thank you.

(Applause.)

DR. CUKRAS: Thank you so much for that.

And taking us from the background to clinical use, Jacque Duncan is going to continue on with our conversation. Jacque is Professor of Ophthalmology at USCF School of Medicine, and she's going to be talking about the clinical uses of adaptive optics.

Jacque.

(Pause.)

DR. DUNCAN: All right, sorry for the brief delay. Thanks for the invitation to participate in this really amazing symposium, and I've learned a tremendous amount already today. Thanks to Alf for giving a really nice background on how adaptive optics works. And I'm going to talk a little bit about clinical uses of specifically adaptive optics scanning laser ophthalmoscopy. Alf mentioned to you there's lots of different ways to use adaptive optics, but I'm going to focus my talk on use of adaptive optics in combination with scanning laser ophthalmoscopy.

I have a number of financial disclosures which really don't have anything to do with what I'm talking about today, most of which involve serving on the data safety monitoring committees for clinical trials and really do not pertain to today's presentation.

So we're here with members of regulatory agencies like the FDA because, as we develop new treatments for retinal diseases, things that matter a lot to patients and regulatory agencies like the FDA include measures of visual function. So we care a lot about how our measures of ophthalmic structures pertain to patients' visual experience of the world.

The ways we typically represent visual function include visual acuity and visual field sensitivity. These are both very subjective measures. They're not terribly precise. They

represent the activity of many different photoreceptors combined together. They can sometimes be unreliable in patients with retinal disease who sometimes have difficulty holding their eyes still or reliably responding to a visual stimulus. And many times the measures represent the activity, not just of the photoreceptors, but other ocular confounding factors like cataract or tear film abnormalities. So they are not terribly precise measures of photoreceptor structure or photoreceptor survival.

So I would argue that it would be helpful to identify and develop new, more sensitive measures of photoreceptor structure and function to help develop treatments for patients with slowly progressive retinal diseases like retinal degenerations, which are sort of the area of my research and clinical interest.

So we have these amazing tools and technologies that we've been hearing about today, and we'd like to be able to use them as a more sensitive way to measure disease progression and response to treatment. If you're thinking about inherited retinal degenerations or other types of retinal diseases, it would be wonderful to image individual photoreceptor cells. It may allow us to evaluate disease progression and treatment response in shorter periods of time than we can do with clinical measures like visual acuity and visual field sensitivity, which I've argued are somewhat subjective and not terribly sensitive.

However, as Alf just mentioned, most of the time, no matter how hard we squint or how much we magnify our clinical images, we can't see individual photoreceptors in living eyes. Well, this is a picture of the adaptive optics scanning laser ophthalmoscope at UCSF that we're using right now to image patients' visual photoreceptors in the macula, in real time in living eyes, noninvasively. So the patient sits here and is positioned with some temple mounts or a bite bar, and the series of mirrors and lenses allows us to obtain high-resolution images of the retina, which Alf described technically a few minutes ago.

The nice thing about adaptive optics is that adaptive optics scanning laser ophthalmoscopy is a really special and somewhat unique way to look at photoreceptors with individual cell resolution that we can then, because it's noninvasive, monitor longitudinally over time. This gives us the opportunity to study individual photoreceptors in living patients and may give us information about patients with specific mutations, allowing for precision medicine.

Other kinds of clinical instruments do not have sufficient resolution to study photoreceptor structure noninvasively in living eyes. So there's lots of different retinal cell types that we can see with adaptive optics SLO which we can't really see with other standard measures. As Alf just mentioned, inner segments and outer segments of photoreceptors can be seen with adaptive optics scanning laser ophthalmoscopes.

So the outer segments are well seen with confocal images, shown at the bottom of this picture, and inner segments are seen by collecting the non-confocally scattered light using split-detector systems. We can visualize retinal pigment epithelial cells using either autofluorescence, as people like Jennifer Hunter and Jessica Morgan have done, or using dark-field imaging with split-detector systems.

And we can visualize retinal vasculature. These are some images from Richard Rosen's group, where a patient was given oral fluorescein, and this very high-resolution angiogram was acquired using adaptive optics to study the individual retinal capillaries with very high resolution right around the foveal avascular zone in a patient with diabetic retinopathy.

So here's some examples of diseases that are particularly well suited to adaptive optics imaging. It allows us to detect retinal diseases that might be amenable to therapy or prevention very early before significant damage has been done. Examples of these include hydroxychloroquine and other types of retinal toxicity, and also diabetic retinopathy and

other retinal vascular disease.

When we think about patients with progressive retinal degeneration, such as photoreceptor disease like chloride dystrophy or retinitis pigmentosa, we can monitor cones longitudinally over time, and this can be helpful not only for clinical care and early diagnosis but ideally as an outcome measure that we could follow in clinical trials.

So here's an example from Joe Carroll and Kim Stepien of a patient with a history of exposure to hydroxychloroquine, and you can see the typical OCT changes where we see loss of the ellipsoids and just next to the fovea, but a really well preserved inner segment/outer segment junction and ellipsoid -- sorry, external membrane band right at the fovea here, indicated by one and also by two. We can see that when we look with adaptive optics at this region represented by one, that the cone mosaic looks entirely normal, but in the region indicated by two, which looks very normal and well preserved on the OCT, we see already that there's been loss of cones, indicating that adaptive optics tells us where cones are being lost before we can even detect photoreceptor degeneration with standard measures like OCT.

This is a picture from Johnny Tam's work when he was a graduate student at UC Berkeley with Austin Roorda. We can use motion contrast to study the retinal vasculature using adaptive optics, and here we can see very early loss of the perifoveal capillaries in a patient with diabetes in a way that is more sensitive and more precise than we can obtain with fluorescein angiography alone.

Subsequent work similar to this was from Richard Rosen's lab shows a patient who had diabetes and who had improvement in their glycemic control over several months. Over a period of 20 weeks, the hemoglobin A1c decreased from 12 to 11, and you can see that there's actually reperfusion of capillaries in response to this improved glycemic control, indicating that this is a very high-resolution way of looking at retinal capillary changes over

time, longitudinally and noninvasively.

Well, again, as I mentioned, I'm really interested in patients with retinal degeneration since most patients with these inherited diseases do not have the opportunity to be cured or even really treated most of the time. We haven't developed therapies to slow their vision loss. Most of them experience slow progressive loss of vision over many decades. And in many broad cone degenerations, visual acuity, one of our standard measures of visual function, tends to be preserved until very late stages of degeneration.

As I mentioned, most standard imaging techniques do not allow us to see the primary site of disease in these patients, the photoreceptors. So objective and sensitive outcome measures, such as perhaps we could acquire with adaptive optics, are urgently needed to help us facilitate development of clinical trials.

We asked, though -- you may say, well, gosh, these are really nice structural images of the photoreceptors, and these little white dots look like cones, as Alf showed a minute ago, but what really matters is how well these cones can function and how well patients can see with them.

This is a study we did where we looked at foveal cone structure in correlation with visual function. If we look at the fovea, a very precise measure of visual function is visual acuity. So we studied a series of 26 patients with different forms of retinal degeneration at locations very close to the foveal center and measured how abnormal the cone spacing was, indicated by Z scores or standard deviations from the mean at that location. We identified the preferred retinal look by modulating the scanning laser, introducing a little flashing circle, so you would precision exactly which cones they were using to look at the stimulus, and we correlated that with visual acuity using standardized measures. We saw that as cone spacing or distance between a cone and their nearest neighbor, indicative of cone loss as cone spacing increased or cones were lost, visual acuity declined, and that was a

statistically significant correlation, although not a linear one, where you have relatively normal cone spacing with normal acuity until at a certain point at which you begin to lose acuity. You could ask at what point does that happen? We asked what the threshold was below average cone spacing where vision becomes abnormal or lower than 20/25. And in our study, visual acuity remained within normal limits or 20/25 or better until cone density was about 50% below average, indicating that cone density is a more sensitive measure of survival of cones at the fovea than visual acuity.

This is similar to prior model-based estimates of cone survival in the assigned computer-based simulations, where they estimated that you could lose 88% of the cones before visual acuity was reduced to 20/25. In our study, it was a little bit lower than 50% in our longitudinal noninvasive study of living eyes with retinal degenerations. Both studies are consistent, indicating that cone images indicate or may provide us with a more direct and sensitive measure of cone survival, certainly, than visual acuity, which is an insensitive measure of cone survival at the fovea.

Austin's going to be speaking more about this, but we can use adaptive optics not only to look at the cones, but also to deliver very precise little flashes of light to individual cones to measure cone sensitivity on a very high-resolution basis. This is called adaptive optics microperimetry, and this will be discussed in greater detail in Austin's talk.

We've heard a lot about the need for validation of measures at today's meeting, and we need to determine and establish what the repeatability of cone spacing measures with adaptive optics is. So we had a study a few years ago where we measured the inner correlation coefficient of grading of cone spacing in normal eyes and eyes with retinal degeneration, and in that study, it was on the order of 0.8 to 0.9, indicating good repeatability in that study. Jessica Morgan has a paper coming out looking at longitudinal measures in normal eyes in NVIS, so watch for that to be coming out very soon.

We can also ask what is the best way to assess content. I talked a lot about cone spacing, but that may not be a very sensitive measure. The most sensitive to cone loss would be the number of neighbors regularity. If you lose a few cones, the regularity of packing decreases. The thing we've chosen to use a lot is cone spacing because we feel like it's very robust to limited image quality. So if you miss a couple of cones, the cone spacing will be relatively low and relatively stable, whereas the cone density, if you miss just a couple, changes dramatically. And this is work by Joe Carroll and Rob Cooper demonstrating the different benefits of different metrics, and I think combining the metrics allows you to have the most complete picture of the mosaic integrity.

Opportunities for imaging include tracking the fate of cones during the course of degeneration. This is a paper where we identified regions of interest in a patient with horizontal cell ROP in which we could see every cone in the mosaic at a given location at baseline 21 months later. Counting the cones and dividing by the area, we derived a cone density at each of these locations, and over about 21 months, we identified about a 24% decrease in cone density from baseline, which did not correspond to any changes that we could measure otherwise with OCT or visual field sensitivity, indicating this is the way you could watch individual cones over time.

This is a picture from Joe Carroll's group showing that you can use different types of adaptive optics images to determine which types of patients might be best candidates for therapy. These are two patients who both had achromatopsia due to a mutation in the CNGB3 gene, and both of them look relatively similar on OCT with this little defect in EZ band right at the fovea. You can see this patient has very sparse cone inner segments at the fovea, whereas this patient has a much more healthy, robust remaining measure of cone inner segments present at the fovea, indicating that this patient might be more likely to benefit from gene replacement or other types of therapy than somebody who has fewer

cones remaining.

And, again, I think adaptive optics SLO is a useful way of looking at the retina when considered in context of other imaging modalities. So this is a patient again from Joe Carroll's lab with GUCY2D-related retinal degeneration. On color photos we see RPE modeling and on fundus -- on fluorescence we see a little bit of -- very little irregularity at the fovea. But when we look at OCT, we can see disruption of the ellipsoid zone band right at the fovea, but then we correspond with OCT en face to see that there are areas that have lost the ellipsoid zone but other areas which remain. And then when we look with adaptive optics SLO using split-detector images, we can see where the cone inner segments persist and identify cones that, again, might be amenable to therapeutic intervention.

So, to summarize, adaptive optics provides a noninvasive and objective way to evaluate and study individual photoreceptors noninvasively over time in living subjects.

Using split-detector AOSLO allows us to image cone inner segments in degenerating retina that can help us see cones that have inner segments which persist even if outer segments are gone, that might be able to be tracked longitudinally, and it may provide us with ideas of which patients might be best candidates for therapy. We need to develop improved tools for analyzing these images over time.

When we use adaptive optics in concert with other imaging modalities, like functional measures with visual acuity and microperimetry and cross-sectional measures using OCT, we can then increase the sensitivity of each of those modalities.

We think, all together, these new tools provide us with sensitive ways to monitor disease progression and response to therapy in patients with retinal degenerations.

And these are my acknowledgements. So thank you for your attention.

(Applause.)

DR. CUKRAS: Thank you so much.

So continuing our string of speakers from California, we're going to have Austin Roorda come speak with us. Austin is Professor of Optometry and Vision Science at Berkeley School of Optometry, and he's going to continue the conversation into the summary of research applications and how these may lead to clinical trials.

DR. ROORDA: Great. Okay, thank you for the invitation. It's a thrill to be here, and I didn't expect such a wide audience and diverse audience, so this is awesome. So I'll talk about research applications, and I'll focus primarily on research applications that are aiming to relate structure to function. And so even if we could refine our AO systems to get to the precision of electron microscopy, we'll never be satisfied unless we can associate what we see with function.

And so I'm just going to give you an example case, and we learned a valuable lesson in this case. A patient presented with complaints in her central visual field, and an OCT image revealed there was an IS/OS break right at the very center of the fovea. Beautiful adaptive optics images we got on this patient revealed what looks to be a complete lesion and a loss of cones in the foveal center.

But when we imaged this patient, we have a way of measuring the PRL, we can see how they behave and fixate while we're taking images, and we noticed that the patient was using that central lesion as their preferred retinal locus. They were putting images they were looking at into that lesion, and so we were curious about that, and so we used microperimetry, adaptive optics microperimetry, to measure function across the lesion, and in this case, the color code indicates green is normal function, red is reduced function, and you can see that there's not a scotoma there as we might have expected. There's actual sensitivity when we deliver light in the very center of this lesion. Now, you might say, okay, well, they have sensitivity because light goes into the lesion, scatters from the choroid, and gets picked up by the cones, the healthy cones outside of it. It's a very small lesion. After

all, it's only about half a degree, less than half a degree in size. But then we use adaptive optics tools to administer a visual acuity test as well, and the patient, more often than not, placed the images that they were looking at within the lesion. And when we measured the performance of those trials where the letter was within the lesion for the entire duration of the trial, so they only used that part of the retina to do the test, this was the tumbling E test, if they were just guessing, they could get it right 25% of the time, but when we looked at the percentage correct of the trials that fell within the lesion, they got 48%.

So not only did they have sensitivity in a lesion that appeared to be devoid of cones, they also have spatial vision. So lesson learned. We were a little bit cocky to think that adaptive optics and OCT should tell us where cones are and where they aren't, but when we apply functional tests, we discover that we can't be so sure. So we really need to do functional testing.

So I'm going to talk a little bit about subjective and then objective functional testing. So we have tools to not only image the retina on a microscopic scale but track it on a microscopic scale and deliver stimuli to individual tests targeting on the scale of an individual cone. So this just shows the letter E stabilized on the retina in our system. But like any microperimetry, you may image and track the retina with infrared light and use visible light to measure visual sensitivity, so we can do that in adaptive optics systems as well.

And I'll just show you now a couple of examples. This is from Jessica Morgan's lab at the University of Pennsylvania, and what we're looking at here is the transition from the island and choroideremia to the edges where there's visual loss. And this is the typical size of a Goldmont (ph.) 3 stimulus, the kind of stimuli that we make. We can make them as small as individual cones. Here, Jessica has made them about a third the size of a Goldmont 3, and it was able to very carefully probe and measure function at the edge of the lesion.

So you can appreciate that this is not an easy test, it takes some time, but you can appreciate how tools like this can be used to really elucidate and understand what's happening at the transition zone in diseases like choroideremia.

My student, Kat, in collaboration with Jacque Duncan at UCSF, has been using microperimetry to measure visual sensitivity in two different RPE patients with different mutations, and you can measure the sensitivity of the target location, but the advantage of using adaptive optics imaging in tandem with that, you can measure the density of the cones and some structural properties of the cones associated with that.

So this is interesting because we have two patients that have pretty much identical cone density, but the sensitivity is quite dramatically different between the two. The sensitivity in the RPGR mutation is lower than it is in the patient with the row mutation. And when we collect a bunch of data from a bunch of subjects and doing the same thing, always relating to sensitivity, the sensitivity to the density, you can see that any ROP patient has lower sensitivity in the remaining cones that they have, but different mutations may be affected differently.

Finally, the ability to do microperimetry in this way with adaptive optics not only allows us to measure cone function, but we can use specialized tests to infer function of other neural layers in the retina. And I won't go into detail except that Will Tuten, who's now faculty at Berkeley, was able to use cone sensitivity measures to infer properties of the horizontal cells and lateral connectivity and lateral inhibition within the retina. And Ally Beam (ph.), who's my student, is using cone sensitivity and adaption to estimate the size of ganglion cell receptor fields.

Now I'm going to focus on objective. Subjective testing is a lot of fun. It's telling us a lot of interesting things. We have a huge brain attached to the sensor so we can learn interesting things, but of course, we'd like to have more objective ways of assessing

function and there's a whole host of objective ways to assess function now that are coming online in adaptive optics systems.

So I'm going to start with Johnny Tam at the NEI. Using ICG, he discovered, using ICG in an attempt to look at the choriocapillaris and choroid, he discovered that there was an uptake of the ICG dye into the RPE cells, and it ended up revealing the mosaic of RPE cells. So, good for structural imaging of RPE cells but may also indicate the uptake of the dye may be some functional indicator of the health of the RPE cell.

Now we're going to move to photoreceptors. There's a bunch of work going on in photoreceptors right now. Don Miller and his team is doing really awesome work, and in particular, they can look at changes in optical path length of the outer segment in response to visible light stimulation. With adaptive optics, they can measure it on a cellular scale and looking at local changes, local differences in the changes, has allowed them to reveal the trichromatic, the mapping of the trichromatic mosaic. When I was a post-doc 20 years ago, it took me 2 years to get one image of one patient. He can do this in a couple of videos now, so it's really remarkable, the strength of OCT technology paired with adaptive optics.

The group at Davis has had an obscenely fast swept-source scanning laser and phase resolved, and they're also doing the same thing. They're measuring changes in the optical path length of the outer segment in response to visible light stimulation. We're getting functional assessments of the response of cones to visible light stimulation.

Ron Sebasin (ph.) is at the University of Washington, and he's going to present this at ARVO this year. He's doing the same technique, but he's got a much faster line scanning system, and he's able to resolve the slow time course changes of cones -- sorry, slow time course changes of cones in response to visible light stimulation. But now he's actually with a high speed, and he can look at the earliest changes in cones in response to light stimulation, and he can see that the earlier response of a cone, an actual brief, very brief,

on the order of milliseconds, decrease in the cone optical path length is actually very repeatable and very much determined by the amount of light that's being delivered. So we have functional optical probes that can look at cone responses on a cellular scale.

Jennifer Hunter at the University of Rochester is using two-photon imaging to look at auto-fluorescent molecules in the retina, and when they use their two-photon imaging to look at cones and rods, they can see changes in the two-photon autofluorescence which are indicative of molecular processes going on in the cones and rods, and with adaptive optics you can differentiate between the two.

Houtman (ph.). There's a group at Vienna doing really remarkable work. They are doing full-field OCT imaging with an obscenely fast camera, and they are able to replicate the optical changes in photoreceptors that you get in response to visible light stimulation. But this is really super exciting. They can also see changes in the ganglion cell layer, optical path length changes in the ganglion cell layer associated with visible light stimulation, and although the path length changes that they're seeing are sort of slow time course, they're not on a scale of action potentials. But stay tuned; we might see that coming in the future.

We had already seen images from Don Miller's lab. Zhuolin Liu, who's now at the FDA, led the effort to image the ganglion cells. Structurally, you could see the ganglion cells, but what's interesting is it took time to get this image because the organelles moving within the ganglion cell would give rise to changes in the speckle pattern, which over time would sort of fill the cell and reveal the structure of the cell. That organelle motility that is required to get the image of the ganglion cells may itself be a functional assay of the health of the ganglion cell.

I'm going to skip this one because it's a bit of a handful, except that if we do want to look for action potentials in ganglion cells with all optical methods and living human eyes, the target is pretty small. We're looking at nanometer scale changes on millisecond time

scales.

So I'm going to finish off. I have 4 minutes left. Wow, that's going so fast, but I'll yield my time to the panel. Yes.

Okay, so finally, the final functional measurement I'm going to talk about is by Jessie Schallek, also at the University of Rochester. You saw some of the images where the adaptive optics videos can reveal flow, and we can use motion contrast to generate nice images of the microvasculature. Jessie is combining split-detector imaging with adaptive optics scanning laser ophthalmoscopy. This is in, I believe it's in a mouse. But he cannot just image the vessel, but he can do a time scan, scanning across one part of the vessel and reveal the train of red blood cells over time flowing through the vessel. He can reveal the train of them, he can separate the different types of cells, he can separate white blood cells from red blood cells, measure the frequency of the flow, and measure the actual shape of the red blood cells. So it's a type of flow cytometry that you could potentially apply in a living eye.

So as you can appreciate, there's a lot of effort going on in the world now of people using adaptive optics to get the cellular-level access but then applying innovative methods to measure the function of the cells, which, of course, we all really need to know and want to know.

So I'll just summarize, then. The cellular-level access that we get with adaptive optics drives the paradigm shift in how we use ophthalmoscopy to study eye disease. The systems that measure structure and function on the cellular scale continue to yield new results. There's a whole lot of exciting stuff that's just been occurring in the last couple of years, and there's an expanding set of technologies that enable subjective and objective structure/function measurements on a cellular scale.

So thanks for your attention.

(Applause.)

DR. CUKRAS: Thank you so much for that.

So next up we're going to have Larry Kagemann talk to us. He's an adjunct professor in the Department of Ophthalmology, NYU Langone, and also lead reviewer of ophthalmic devices for FDA, so perfectly poised to talk to us about regulatory considerations for adaptive optics technology.

Thanks so much.

DR. KAGEMANN: Thank you.

Are we live or Memorex? We're live. Awesome. Good afternoon. It's a pleasure to be here. I'm excited, the FDA is excited, and we look forward to helping transition this technology to the U.S. marketplace.

Looking for a definition of adaptive optics, for the FDA, we have no regulatory definition. You can search the literature and see adaptive optics in its original application for correcting aberrations in telescopes. It was suggested as early as the early '80s that it might be used to correct the optics to do retinal imaging, but that wasn't accomplished until '99 by someone that we know.

But as far as a regulatory definition, if you search the standards, the ISO and ANSI standards for adaptive optics, it doesn't appear. There is no definition that we can hang a hat on from a regulatory perspective. Looking at the clinicaltrials.gov website, there are 46 current trials that include the search term "adaptive optics." So at least within the realm of regulated research, adaptive optics does appear.

So, commercially, we have no cleared or approved devices incorporating adaptive optics technology available commercially in the U.S. We have no guidance, there are no standards for a definition of adaptive optics, so that sets a challenging environment to bring adaptive optics into the marketplace.

This morning, Brad Cunningham gave an outstanding talk that really set me up beautifully to come and talk about -- mine is almost a practical application of Brad's talk. He talked about having to demonstrate. It's our job to ensure that medical devices on the market in the U.S. are safe and effective.

There are several pathways that can be employed, and given similar devices, given the risk level of what we anticipate in adaptive optics-capable SLO or OCT, as we saw, adaptive optics can be employed on existing imaging platforms, and even there they might be controversial, and I've heard arguments while I was sitting listening to the lectures and know it's an independent technology, so it's going to be important to define it.

But, anyway, given that adaptive optics can be employed on existing platforms, we anticipate a 510(k) or a de novo pathway. And the pathway that will bring adaptive optics-capable devices to the U.S. marketplace will depend on the kinds of questions of the technology, the questions of safety, the questions of effectiveness that arise in the new capabilities of devices equipped with adaptive optics.

One potential consideration for discussion is light safety. Obviously, a difference in an adaptive optics-capable device versus a standard clinical device in the focal point on the retina is going to be much smaller, and in concern for the safety of the device, we want to know that we're not going to cause harm to patients.

Happily, the FDA does recognize standards, including a standard for light safety that is applicable for ophthalmic instruments that direct radiation into the eye. It is up to a company, if they wish, to use this to voluntarily comply with the standard. If you claim compliance, we can then use the criteria of the standard to determine the safety of the device. It's also an available option for a company to come in and, with valid scientific reasoning, argue that they wish to not comply with the standard but provide evidence on their own. We will review; we're happy to look at anything that you bring to us.

Another potential topic of discussion in the area of effectiveness is the field of view. As we've seen, the adaptive optics-equipped device is imaging a very small region, and we heard wonderful talks; the previous talks were fantastic in giving us examples of places where they may be incredibly useful clinically, and we look forward to receiving submissions that can bring us that kind of evidence showing that by utilizing this technology for imaging, despite compared to existing technologies and the size of the image, the amount of retina that's included, how this new technology is going to be useful in the future.

Another potential concern is if the technology comes in and there is a claim to visualize specific cell layers such as photoreceptors, how can we confirm that that's what we're seeing? Yes, it looks a lot like photoreceptors, but performance data will be required to demonstrate that whatever is within your labeling as to the structures that you're visualizing, those structures are actually within the image.

There are groups at FDA currently developing phantoms that are creating physical columns roughly the size and space of photoreceptors. Using something like a physical phantom where you have an a priori knowledge of the structures that exist in the physical device that you're imaging, that would provide wonderful support, wonderful evidence that your imaging does contain and is capable of imaging the structures that you propose to image.

Further, if you're looking at, say, automated quantification, not just providing an ability to see photoreceptors but to actually quantify them, there's a whole new level of complication. You need to demonstrate that the quantification is accurate. To do that, you're implying that you have a foreknowledge of the actual density of whatever the structure is within the image. And, again, this would be a great place to employ a physical phantom if you're imaging a structure where you know what's there, you know the size, you know the density, and you can come back and show that an automated algorithm produces

a number that I expect because I knew it was there.

Also, we've had instances where it is burdensome to try to have a physical phantom to image a specific physical characteristic, and in this case, if you're proposing an algorithm to quantify a physical parameter, it was possible to create a dataset mimicking an image of known content. So a synthetic dataset. Synthetic data is used in AI where you would apply a lesion and then go and show your AI can detect that lesion that you know is there because you put it there.

Similarly, if you were to have a dataset and you were to populate that dataset digitally with structures and then apply an algorithm to go and quantify those structures of known characteristics that you've put there, that's another possible way of validating an algorithm associated with quantification of these structures.

So, in summary, our concern will be safety and effectiveness. Safety concerns with the introduction of adaptive optics into an existing technology may be mitigated, I would say, with compliance to an FDA-recognized standard.

As for effectiveness, this is going to be interesting because a lot of the discussion today has been, okay, I have this great functionality, to what can I compare it? And there just isn't anything out there that does the things that adaptive optics does.

So there will be some creativity, and we look forward to seeing what is brought to us. And the regulatory pathway is going to depend on questions concerning the technical characteristics and the indications for use, those things that you say your device can do. When those differ from existing devices, performance data will be required to demonstrate that the device can do what is claimed.

All of that said, the purpose of today's workshop is to foster medical innovation. We're excited to see this technology come to the marketplace. We want to work with you. You saw in Brad's talk the discussion of the pre-submission process. We're eager for you to

come in earlier than later, discuss with us your ideas of how to get to market, what kind of performance data you might need, propose a performance study. We're happy to review these, we're happy to give you our feedback, our detailed feedback on your proposals, and we're eager for your success.

Thank you.

(Applause.)

DR. CUKRAS: Thank you so much.

I'd like to call the panelists up now for a discussion of Question 2.

(Pause.)

DR. CUKRAS: In the meantime, I can introduce our panelists. Jessica Morgan, here, is from the University of Pennsylvania. She is an Assistant Professor of Ophthalmology and the Director of Advanced Retinal Imaging there.

Alf Dubra, we have heard from in his talk.

And we have Richard Rosen, who's a Professor of Ophthalmology at Mount Sinai, who's done extensive work on vascular imaging.

And at the end we have Nicolas Chateau, who is co-founder and CEO of Imagine Eyes, a commercial device.

Okay, so we are here to talk about Question 2. I also want to say that I think this meeting is a wonderful combination of researchers, clinical researchers, basic researchers, as well as industry. So if there are questions from the audience or people who want to chime in, we certainly welcome that.

The first part of this question Larry Kagemann set up really well. It is a question of safety of adaptive optics. As Alf Dubra mentioned in his talk, adaptive optics is a technique, not an imaging method, so I think when we're talking about safety, we really are talking about probably light safety. Down the road in the future, we might be talking about safety

in terms of risk of diagnostic error or interpretation, but I think first to tackle light safety of it, maybe we'll hear from our panelists on that. And we can start with Jessica Morgan, and she did some work on this way back, and David Williams, when she was in David Williams's lab and beyond that and about your thoughts on that.

DR. MORGAN: It's wonderful to be here today. Thank you so much.

I think there's a lot of things we need to consider when we talk about safety and, in particular, light safety with exposing the retina to all of our different multimodal imaging devices. With adaptive optics, as was pointed out in the previous talk, you know, we are focusing a spot on the retina to a very small area. That said, for all of our imaging, we need to take into account how much light we're delivering over a particular area in the retina.

And so I think most of our safety concerns should be followed in that broad context, that there really isn't something specific to adaptive optics when we're talking about scanning over a larger field of view or taking images that encompass a bigger area than just that small focal point.

And so when you think light safety, there are different mechanisms that can cause phototoxicity to the retina, whether it's photochemical or thermal lesions that can occur. And I think that those mechanisms themselves are not specific to AO itself, that we need to be looking again at the broader context of imaging and light exposure per unit area in general. So maybe somebody else wants to wing in there?

DR. CHATEAU: With adaptive optics -- well, first I want to thank the organizers for inviting me to this welcomed thing. About adaptive optics, there are several aspects that are specifics to adaptive optics. We are illuminating smaller fields, so we can have a higher concentration of light on the retina. However, another specificity of adaptive optics, as Alfredo said before -- (microphone cuts out) -- the microphone is interesting.

UNIDENTIFIED SPEAKER: Go ahead.

DR. CHATEAU: Thank you. Another specificity of adaptive optics is that we are collecting the light from the retina through a larger pupil, so we are collecting a higher percentage of the light that is reflected by the retina. So, although when we consider infrared adaptive optics SLO or adaptive optics camera, we can expose the retina for a very long time while staying below or far below the safety limits.

DR. CUKRAS: Does anyone else want to chime in, in terms of the ANSI standards and limits there?

DR. ROSEN: Well, I think one of the real concerns is, currently, we're still at the stage where a lot of the imaging that we're doing is in relatively normal subjects that have good visual acuity and that have resilience of their retinas. And we've seen, from a number of animal studies, that very often situations where you have eyes that have different genetic defects or ones that have some degenerative disease may be more sensitive and vulnerable to what would appear to be acceptable levels of light.

So I think that this is something that we still don't have a lot of experience with. When we talk -- I'll show some -- a couple of images later, but by and large, I think that this will have to be something that's given great consideration, and very often, the studies that are performed before it becomes a mainstream sort of modality are done in normal eyes. So this is something that I think we'll have to look at.

DR. CUKRAS: Yeah.

DR. DUBRA: I also want to point out that there's something -- we're thinking about adaptive optics as potentially causing damage, but one of the things that adaptive optics has already changed the standard is in revealing potentially toxic or damaging phenomena that might not be possible to detect with traditional techniques. A lot of the ANSI data was derived from images, from fundus images with very low resolution. So now that we can see with more resolution, our definition of what is damaged is also changing. So you might

think not only in the context of adaptive optics might cause damage but might also help us understand better damage that we might be causing right now that we don't know because, you know, conventional clinical instruments don't reveal.

DR. CUKRAS: I think that's a great point, and as the sensitivity of our imaging reaches and enables us to see new things, that's certainly a possibility that we could see evidence of damage that we hadn't appreciated.

I think a lot of the questions have been fielded towards the SLO. How about in terms of other modalities of AO applications? Rich, I know you do a lot with vascular imaging and angiography. Are there any additional considerations when we're looking at different wavelengths and whether it's autofluorescence or fluorescein angiography?

DR. ROSEN: So, I mean, Alf could even speak more to this because when we first set up to do fluorescein angiography at this level, he was particularly concerned that we didn't overlap these very small 1.25-degree fields because of the potential toxicity of using a source that was like 488, which has a much higher degree of toxicity for photoreceptors. So we've actually backed away from that, and I know that he has more experience in terms of autofluorescence, which uses a lot of light and a very small field of, well --

DR. MORGAN: Yeah. So I think that for all of these different modalities of imaging, you can change a parameter, your input parameters, for light exposure. So whether that is using visible light to image in reflectance or using visible light for autofluorescence or fluorescein, there are different considerations and different risk levels for causing phototoxicity. That said, you could -- if you just zoomed in with your -- (microphone cuts out) -- or an SLO without adaptive optics, still using the same amount of light per unit area, you're going to end up with the same effects. And so I think it is we really do need to consider total light exposure per area to the retina regardless of whether adaptive optics is part of your imaging system or not, and then also consider definitely taking into

consideration what is the labeling that you're using, how much are you exposing, and what is the mechanism of potential damage that you would be causing?

DR. DUBRA: And if I can put the FDA on the spot here. So there's something that we haven't really discussed, I think, as a community, that is individual devices might be approved by the FDA, and I'm not putting blame on the FDA, I'm saying they might be approved because individually they are below the ANSI safety, you know, maximum permissible exposure. But we never discuss or consider the accumulation of the fact that you might go to the clinic and you might go through color fundus pictures first, and they might take three or four pictures, and then you might go to take an SLO picture of autofluorescence, and then, hey, just for the surgery they had a fluorescein angiography, and the accumulation of all of those might not necessarily be so far below the safety limits as you think you would be. And that is something that, irrespective of the AO, we should discuss.

And also one final point. Jessica was very modest about her first statement. She did a beautiful experiment with Jennifer Hunter, I believe, where they did a comparison of the same retina patch being imaged with an adaptive optics point being scanned across a patch versus all the patch illuminated at once, and they found that the response of the retina was the same. So if you're scanning with an adaptive optics system, don't be distracted or don't think that the AO is necessarily going to make it worse. The same ANSI safety calculations apply.

DR. CUKRAS: Questions out there related to safety of these devices or the safety aspects of their use?

DR. BUCKLAND: Okay, I'm Eric Buckland. My understanding of at least the near-infrared safety is a thermal effect in that it's premised on diffusion of the energy, and if you have an area, I think if I remember, less than 50 µm squared, it's considered

50 µm squared because it just diffuses.

So is there any signal at all that you've seen in AO that you'd cause a differential impact to the photoreceptors that would change that analysis of the safety, or is this all speculation that it might be there and we should look?

DR. ROSEN: Let me just comment. You know, just to add to what Alf said, you know, the issue with AO is it's such a small area that you're looking at, and the context is critical because if you just look at a single small field, you know, it doesn't mean anything until you put it into the context of all of these multimodality approaches. So I think that's where we're going to run into it, and I don't know that there's a formula for this at this point. Maybe Austin knows.

DR. ROORDA: I just want to add -- Eric's right, the ANSI standard assumes a certain finite size of the spot, and in part, that's due to the optics; the other part is due to the eye motion, and the incessant eye motion, even if you have a tightly focused spot, will dither the spot around and diffuse the heat. And so in the eyes of ANSI, whether you have it finely focused or not, it doesn't really make any difference; the energy is delivered over an area that's equivalent to the motion of the eye. That's maybe not entirely true, but in the eyes of ANSI, that's the way they look at it.

Now, in my lab where we think about if we really want to get structure and function, we track the retina, and not only do we focus our spot finely with adaptive optics, but we track it and we keep it locked at one location, and there's nothing in the ANSI standard that tells us what a safe exposure is under those conditions. And so I'm going through, with my IRB right now, how to calculate what a safe level of light is under those conditions. And if anybody's interested to hear about that process, I'd be happy to talk to them.

DR. HUNTER: Hi. Jennifer Hunter, University of Rochester.

I can't help but interject a little bit into the light safety conversation. And Austin,

you're absolutely correct, there is, as far as I'm aware, one publication that actually looked at the use of adaptive optics in light safety studies. However, the results appeared to be fairly inconclusive, and none of the subsequent work that most of us in retinal imaging have been doing have -- I think Vivek suggested that the use of adaptive optics causes excessive safety concerns, particularly citing back to some of the early work that Jessica did.

I also want to be clear. A lot of us within the community talk about the ANSI safety standard as though there's just one, but there's actually several, and the FDA, as we saw, recognizes the Zed 80.36, which is specific to ophthalmic exposures. But a lot of us in the research community, many years before that was developed, have been, probably for the last 20 years or more, using the Zed 136.1, which is a standard for the safe use of lasers in general. It applies not only to eye but to skin, as well to industrial applications, accidental exposures, but also has sections which consider specific ophthalmic exposures. And if you actually sit down with the two standards side by side, there are clear distinct differences between them.

And so as a user trying to apply a light safety standard, it becomes very difficult to know which standard should I comply with. They're developed by slightly different communities of people, and the research going into them is also quite different. And so, therefore, some may be more protective, for example, in the visible regime; others may be more protective in the infrared. And I think, as a community, it becomes very difficult, and I'm curious, from the FDA's perspective and from everyone else's, how do we consolidate this into sort of one unified type of perspective?

DR. DRUM: Hi, I'm Bruce Drum from FDA, and I've spent a significant amount of effort in the last several years working on exactly these problems, along with, well, the currently recognized ANSI standard is supposed to be sort of a stop-gap because the ISO Standard 1504-2, unlike hazard protection, is outdated and we are actively working on

updating it. But we've been struggling mightily with these exact problems about, well, what happens if you have a device that somebody could be exposed to for hours on end or successive devices, so the current ANSI standard doesn't adequately address this question, but we are trying to do that in the update, which will probably at least be another year before it gets published.

With regard to the issue of adaptive optics and effectively very small spots, we were also struggling with that and the question about, you know, if you're just hitting like one or two cones and you kill them, that might not be much of a problem. But if you're doing experiments where you're doing the same thing for a bunch of cones, why then we have to be concerned about what the relevant safety limits are. And, unfortunately, the data are limited with regard to what exposure is actually too much in those cases. The people who are doing research in that area, basic research on cone psychophysics, single-cone psychophysics, are well aware of these issues, and we're looking forward to hopefully the solutions that they come up with.

DR. CUKRAS: Jessica.

DR. MORGAN: That's a good point, Bruce. I'd like to point out, for the adaptive optics microperimetry work in particular, you are focusing a small point on the retina to the same cones repeatedly; however, the visible light that's used for these experiments is incredibly low. We're talking about threshold-level light exposures. And so it's actually not the visible light exposure in these experiments that is something of concern. For me, it's actually more the infrared, that you are imaging in infrared for a very, very long period of time over the same retinal area. But the visible light in those experiments is very, very low, you're working at threshold levels, and so the exposure is incredibly safe. I mean, you're trying to measure a threshold.

DR. DRUM: Right, yeah, we're aware of that. There are experiments going on where

we're looking at super-threshold levels also, and it's not, you know, the amount of light that it takes to stimulate a single cone so that you can easily see it; it is considerably higher than the threshold for a larger spot.

DR. MORGAN: But it is orders and orders of magnitude below --

DR. DRUM: Right.

DR. MORGAN: -- safety limits.

DR. DRUM: Yeah. This is not our main concern. Our main concern is more on the line of extended exposures, like heads-up displays where people might be exposed to a display for hours, at another time for days on end, you know, if they're using this repeatedly, or when somebody's at a teaching institution and a patient gets run, you know, the same test run through by an entire class of fellows --

DR. CUKRAS: Yeah.

DR. DRUM: -- you may have a long total exposure to the same -- to the light.

DR. CUKRAS: Yeah, I don't want to cut off the conversation. It's clearly a lot to talk about, and it's great to have all of these points. I just want to make sure we have a little time to get to our second point for this session, which was to -- unless, Brad, if you -- sorry, if you wanted to jump in off the -- I don't want to not hear what the FDA's response is to these.

MR. CUNNINGHAM: I know that there's much left to go. I was only going to make a comment about the cumulative aspect of things, and when we evaluate devices for potential optical radiation hazards, we're looking at device by device, looking at one thing, what that one offers, what that one -- what the risks are with that, and the idea of going through one set of imaging procedures followed by another followed by another is not something that we can necessarily control or regulate within what we have authority to regulate.

DR. DRUM: One more very quick comment. The standard does consider the situation where you may have a test that uses several devices at the same time, and so we look at the total exposure for all of the devices that are used in those cases.

DR. CUKRAS: Okay, thanks for that.

So just to touch the last few minutes on our second questions of effectiveness. And Larry also set that up, what we could interpret efficacy to be. We can think about it as the ability to perform its intended use, and we've heard how these instruments are providing some new information. So Larry posed how do we confirm we know what we're looking at? How do we know that we're imaging cones? Are there references, are there histologic references we can use to have an agreement or a consensus that we know what we're looking at with these modalities?

DR. ROSEN: You can look at the paper that Alf Dubra and Joe Carroll did originally, comparing to the work that Christine Curcio had done. A very nice comparison with histology. So I think that it's pretty straightforward that we are looking at the photoreceptor matrix. And so I think that, you know, building phantoms is a lot of fun. I mean, everybody likes Legos, but at this point I think that we have a tremendous amount of data available from histopathology, and we're approaching histopathology at this point, so I think that that will answer a lot of those questions.

DR. CHATEAU: For us, it's not always so obvious. When we see bright spots at the retina with adaptive optics, it's not always thoroughly clear that we are seeing photoreceptors or some kind of debris. There are many small white spots that are visible in a geographic atrophy area. So for us to interpret adaptive optics images, very often, it's useful to also look at images from other techniques, like OCT, to make sure that what we see is actually photoreceptors. And I could say similar things when we see dark spots at the retina, small dark spots. It's not always obvious whether they are melamine trapped in

some cells or non-flowing blood cells. There are many examples like that, so the comparison with the other images is still important.

DR. MORGAN: I think that one of the challenges the adaptive optics community has yet to surmount is where are we going to make a clinical impact for using these images? And we need more than just a pretty looking picture in order to make a difference in our diagnoses or treatment regimes for patients.

And I think that for a long time we, in the adaptive optics field, have been saying we're going to track, for instance, individual cellular survival in patients with disease and then follow whether the cells respond to treatment, and I think that we can do that, but we also need to take into account the limits of things like repeatability, reproducibility, and accuracy in our measurements.

And even though we have this pristine image that matches what we think we have in histology, it actually can be difficult to get graders to agree on what is in that image and how many photoreceptors per unit area are observed and observed in multiple images within the same day or observed in multiple images taken over time. And we need those studies in order to understand how much disease progression, for instance, needs to occur before we can know that we're outside of our measurement error currently. We're not at a single-cell reproducibility currently.

DR. CUKRAS: And I think Jacque touched on that, too, in terms of talking about metrics, and we're all excited to have this as a different biomarker, and do we have a consensus as to what metrics we all want to talk about and what are the most robust metrics, and Jacque mentioned cone spacing rather than cone density, but these kinds of considerations -- Alf, sorry.

DR. DUBRA: Yeah. For those of you who are not versed in the adaptive optics retinal imaging, most of what we were collectively talking about in the last couple of minutes is

about the fact that we've been imaging photoreceptors for almost two decades, and we've imaged them using two techniques that will produce images where each cone or rod will produce a bright spot. So for the longest time we've been studying normal subjects and learning about the mosaic geometry and so on, but when it comes to disease, just because you see a bright dot does not mean that you're looking at a photoreceptor cone or rod. It could well be debris, or it could be anything else.

And so that's why maybe to some extent we've not translated this into clinical imaging as much or as fast as we would like to. It's only recently with the multiple scattering imaging modalities, and there's one that I call split detection, but other people call it Morcher pinhole and multi-offset, but the point is that we've been able to add another imaging modality to match the previous one that reveals what we think is the inner segment, and that seems to confirm that or not when you're looking at photoreceptors. It's not, of course, 100 percent but it provides additional information. Is that a good summary?

DR. ROSEN: So we've actually been able to take, from a different perspective, from subjective symptoms of patients and use this modality to investigate and show objective evidence that confirms -- I don't know if we have any time. I have just a case. It's loaded up. Do you have it? I don't know. Do I have the -- do you have the advancer? So here's just one example. This was somebody who came in complaining that -- if it plays. This was a -- for some reason it's not playing on this, but you can see these little green spots, it was a flickering dot that the patient was well aware of. The patient was 20/20, and yet they were really disturbed, and actually, when we looked at the patient with OCT, you really couldn't see it. But when you looked with the adaptive optics, you could actually see that there are some dark photoreceptors here, and when you compare this to the patient's experience where they drew what they saw on an Amsler grid, you could see it quite precisely that it matched what the patient was experiencing. So this was one example.

There was a patient who came in complaining of a dyschromatopsia, everything red. Well, we did see a little disturbance in the outer layers with the OCT. When we looked at the photoreceptor matrix, you could see that there were areas of non-wave-guiding photoreceptors, and you can compare this to a patient who has a rod/cone dystrophy with the same sort of loss of photoreceptors. This was a patient who had taken an illicit form of Viagra that they bought on the Internet.

This was actually a patient who had phototrauma from solar retinopathy, and you can well see it on the OCT, it was useful. But, in fact, this was the lesion that you could see on the adaptive optics, and this is what the patient actually drew on the Amsler grid, which you can see is very close. When we questioned him closer, this was what they saw.

So we're really able to take subjective to objective using this technology and answer some questions that the patients have.

DR. CUKRAS: Just to try to wrap up here. In terms of bringing this to clinical trials, I know it has been used in clinical trials with some success and looking to do more in that. How about the differences in devices and instruments? AO is a tight community, which is wonderful, but the devices are not all exactly the same, and is the phantom model helpful in that regard or in terms of normalizing our quantification potentially? I don't know if there's a quick answer.

DR. ROSEN: It's really to Alf.

DR. DUBRA: A lot of enthusiasm about this topic and potentially a conflict of interest because I'm trying to write a grant to address this topic.

(Laughter.)

DR. CUKRAS: And we'll just wait.

DR. DUBRA: So good reviews, please.

(Laughter.)

DR. CUKRAS: Great. Well, I want to thank all of our panelists for the opportunity to talk here with you today. Thanks.

(Applause.)

(Off the record at 2:00 p.m.)

(On the record at 2:11 p.m.)

DR. ASHFARI: Good afternoon, everyone. Should we get started?

DR. REPKA: Yes.

DR. ASHFARI: Yes. Dr. Repka says we should get started. Dr. Eydelman said to start. And Dr. Repka said that Dr. Eydelman said to start.

Well, welcome to the afternoon session, the second session. We are going to talk about the nonclinical data sources. I'm Natalie Ashfari. And our first speaker is Dr. Anant Agrawal. So as soon as -- (microphone cuts out) -- we'll start. And Dr. Agrawal will talk about synthetic datasets and some images and their utility. Dr. Agrawal from the CDRH here at FDA.

DR. AGRAWAL: All right. Well, that was a short break, so I know everyone's just kind of filing back in. My name is Anant Agrawal. I'm actually with the Office of Science and Engineering Laboratories, the research component of CDRH.

And so we've been seeing lots of beautiful images and hearing about so many different biomarkers in the retina and anterior segment. So clinical data clearly is an important and essential component of understanding how well an imaging device, an ophthalmic imager performs. So now I'm going to be shifting just to non-biological sources of image data. And I'm an engineer and I do love Legos, so this is quite perfect for me. But, really, I think it's important to understand how well these sources can be used, and I think that it's important for the community to come to some agreement on what are the best purposes, contexts of use, and later you'll be hearing about the Medical Device

Development Tool program, which is where a lot of these synthetic sources might fit very well.

So I'm with the Office of Science and Engineering Laboratories, as I mentioned, which is separate from the previous FDA speakers you've been hearing from. Malvina, Brad, and Larry are from currently called the Office of Device Evaluation, the regulatory side of CDRH.

So our lab's mission is to perform research studies, laboratory computational research studies, to understand the safety and effectiveness of medical device technologies currently on the market and coming to market. And so we comprise about 10% of the total staff of CDRH, and in addition to performing research in the lab and again, computationally, we also work with our regulatory colleagues on teams to review the applications. So we're also heavily involved in the review of medical device submissions, and that's how we stay on the cutting edge of what's coming in, and it directly informs the research that we do.

I'd also like to introduce our burgeoning ophthalmic AO imaging community here in the D.C. metropolitan region. So really there are three main institutions involved. First, you've already seen some good examples of work from the National Eye Institute. That AO program is being led by Johnny Tam, and there are a number of collaborators he has, and they have quite advanced multimodal/multi-wavelength AO imaging capabilities in their facility, and they've been looking at different retinal disease biomarkers, also toxic agents, the effect of toxic agents in the retina, as well as therapies using AO.

Here at the FDA, Dan Hammer, Zhuolin Liu, and myself have been using multimodal AO to look at biomarkers all across the retina, from the inner retina, looking at the microglia, and now you've already seen an example of ganglion cells, we've been resolving those in our lab now, too. And then down to the RPE, we just are now looking at a new biomarker of RPE motility, looking at how those organelles move about in the RPE, and

that's another interesting biomarker. And then I'm the phantom guy, so we were also trying to -- and I'll be showing an example of some of the work I've been doing on phantoms for AO and OCT.

And at the University of Maryland Medical Center, Dr. Osamah Saeedi, we've been working very closely with him now, too; he's a glaucoma specialist. And some of the interesting things we've been seeing so far, both with ganglion cells, we've seen actually changes in the size of ganglion cells with the onset of glaucoma, and also, he's looking at interesting blood flow biomarkers as well.

So, again, we're now talking about synthetic images, and so why bother if it's so easy to put an eye in front of an imager or many eyes in front of an imager, why should we really get into using synthetic data? And what we really need to do, though, as I think has already been hinted at from multiple discussions already, is how do we validate and standardize AO and OCT performance? And we haven't talked about it yet. We talked about the safety standards that have been out there from ISO and ANSI, but there's also an ophthalmic posterior segment OCT-specific standard that was written in 2015, and I was involved in helping with some of the content of that. But in the end, the end result was actually a relatively limited document, and I'll actually be touching on that, and I'll show you some of the content of that later.

So in the end, the FDA elected not to recognize it at this point as part of our standards recognition program. And we've already heard from Larry and others that there really aren't any clear clinical gold standards for AO and OCT, and there are a number of reasons for that, and I'll touch on a few of those reasons. For one, we know that OCT and AO imaging are three dimensional in nature, and therefore, standard fundus imaging techniques, in vivo techniques, are not. And so it makes it harder for us to do a direct comparison of the information.

And in addition to that technological difference, when we think about angiography, and that was also discussed earlier, there's definitely different information being derived from OCT angiography as compared to dye angiography, and the technology behind it, of course, is quite different. So that makes it hard to find something to relate the information and have a gold standard for, with OCT.

And, of course, with AO and OCT, we're really talking about unprecedented capabilities and quite exceptional capabilities to image, and both in just what we see with our eyes but also the biomarkers we derive from those images and functional biomarkers, as we also heard about, I mean, relating structure to function is vitally important, and we're getting some really exciting biomarkers. We're seeing now like phase-based biomarkers from these imaging modalities. And so really there's no way to relate that to anything else that we could gold standard or reference to.

And, again, we now know well that AO is providing cellular-level resolution, and in addition, it has this dynamic character, so we actually are able to do personalized imaging unlike ever before. So this makes it very much more challenging for us to validate and standardize the performance.

So I'll break down the synthetic data sources into three main categories: phantoms; model eyes, which are both physical tools for evaluating the performance of an imager; and then synthetic images, which are created in software and either from scratch or basically images that are augmented with software, and we associate most of these synthetic images with machine learning either to create the images or to use these synthetic images.

All right. Now I'll introduce the basic concepts of a phantom. And so what it is, is it takes the precision and principles of an engineering test target, like this well-known USA of 1951 resolution chart, and it combines it with the known physical properties of the tissue of interest, the geometry, the dimensions, also the optical scattering and absorption

characteristics of the tissue, and what you get is a physical model with highly controlled properties. And this way you can do tissue-relevant performance characterization of an imaging device.

And so this is a phantom that we produced a few years back, and it looks very much like a bar chart; the retina is like a bar chart of its own, and so what we did is just make a very controlled bar chart that looks sort of like a retina.

And so some of the benefits you get from a phantom is that, again, you're able to do a very controlled set of imaging where you can then quantify image quality metrics. You can do a very, very careful comparison, detailed comparison of two different devices, which is actually in the 510(k) paradigm of CDRH regulation, it actually can be quite helpful. You can track a single device's performance over time with a very stable and reproducible target. You can also calibrate the measurements. We know we can take measurements with both AO and OCT, so you can actually calibrate those measurements with a control target like a phantom.

And, in addition, you can actually get new information you may not have been able to access about the physics of light propagation since you're creating a sample with known properties, and so therefore, you can actually potentially get more information about what's going on with light transport in the tissue.

And so in the end, we're trying to influence and impact the device life cycle from development and manufacture to regulation.

There are a couple of commercially available OCT phantoms that you may or may not know about. There's one that's more like an engineering test target, produced by Arden Photonics in the UK, and it's a piece of glass with laser-etched features in a very precise manner to allow you to measure some well-known optical imaging properties like distortion and resolution and sensitivity. And so this is just one example of a commercially available

phantom.

The other one that I'm familiar with is actually more like a retina inside of a model eye, produced by Rowe Technical Optics in California. And so this one has a layered structure which has some of the geometry of a real retina, but the layers themselves don't necessarily resemble the retina itself, but still it is, I think, another good example of a commercially available phantom that's out there.

So now I want to get into phantoms that we've been prototyping in our lab as well as some other labs as well. So I'll go back through our history. One of the first we made for retinal OCT imaging or in consideration of retinal OCT imaging was a 3-D point-spread function phantom, and it's a polymer with nanoparticles embedded in it, spaced out so the particles do not interact with each other optically, and so therefore you can map out the point-spread function across the field of view, and we embedded this in a commercially available model eye.

I showed you this on the previous slide. This is the retina phantom we made a few years ago. And then Audrey Bowden's group, which was formerly at Stanford, now I just learned she moved to Vanderbilt, they actually took the phantom design we had and enhanced it to make it even more realistic and actually include disease features as well.

And more recently we produced an optic nerve head phantom, which for the first time we actually put in front of clinical imagers, and we wanted to do side-by-side testing, and Dr. Sadda showed this earlier, and yes, this is an idealized phantom, so therefore, it is, you know -- how much does it tell us about what's going to go on clinically, but it's certainly an important question. But what we can do is tease out the effects of different elements of an imager, the software from the hardware, and so what we found was that actually it's the software that is an important contributor to the differences we might see in measurements; in this case, a cup-to-disk ratio between devices, but the hardware and the scan protocol

seemed to not have much of an effect. So I think that's an important piece of information we can get from the right kind of phantom.

This is our latest phantom that we've produced for multimodal AO imaging, and it's modeling the photoreceptor mosaic and at different eccentricities. So here it's going from close to the fovea, 0.6 degrees, and then 1.53 and 5 degrees. And so what we have here is really an AO-specific resolution target. And we've actually just modeled the outer segments in this form of the phantom, and that lower image there is an illustration of what the phantom looks like. It's a little cube. Actually, it's really only effectively a few hundred microns on its side, and it includes a surface on the back. The top of the phantom is actually the back of the phantom. That surface is textured to actually produce a diffuse reflection for the wavefront sensor to pick up wavefronts very accurately and very uniformly across the pupil, and that was very important to have AO correction operate in a very controlled manner.

And then we could image it. We imaged it in our lab with the system that Dan and Zhuolin built, as well as with Johnny Tam at NEI, and we saw some interesting effects. You know, we actually couldn't resolve with OCT the 0.6-degree structures which actually can be resolved in vivo, but what was going on was we actually were seeing speckle effects unexpectedly that raised some interesting questions about what's going on with the speckle in vivo. We actually enhanced this, in a sense, enhanced the speckle effect with our phantom. So there's something about the retina itself that's actually suppressing this speckle, we believe. So that's where we can get insight into the physics a little bit about what's going on when we do imaging with a phantom.

Okay, now to model eyes. I already showed you an example of a commercially available model eye. We had used that with a couple of our phantoms already, and this model eye is really recreating the refractive structures quite accurately in plastic, and it's a

water-filled eye, and this is actually, I think, one good example of how we could, you know, continue to use this with different types of phantoms.

Alf Dubra's group, and I think he hinted at this at the end of the panel discussion, actually is creating -- taking a different approach, creating a very simple model eye using a single optical element, a single plano-convex lens which can be very carefully calibrated, and therefore, you know the refractive and aberration characteristics very, very precisely. And then when you take an image with your AO imager, you can then compare what you get to those known aberration and refractive characteristics. So I think that's another important way we can use a model eye to help us with in this case it's for AO imagers.

And then this is the model eye that I had built to go along with our multimodal AO phantom, and this is, again, trying to create a very idealized eye with a single achromat, and it has a fluid-filled chamber to help control reflections, and we've put our phantom in the back of that.

So this is just some examples, and there are probably others out there people are making. And actually the standard includes an AO -- I'm sorry, the OCT standard includes a model eye, and they actually designed theirs for an interesting -- or the way it's written, it's for an interesting purpose. It has also a single lens and a neutral-density filter, but it also includes a filament, a very thin filament in the back so as to ensure the co-registration of a fundus image with an OCT image since most imagers include both a fundus imager along with an OCT scanner, so that was why they included this filament in that version of the model eye.

And now I want to highlight actually what else is in the standard with respect to helping us understand the performance of an OCT imager, and there are a few metrics or figures of merits that have been delineated in there. You know, this provides, I think, some general information, but I think it still lacks some specificity on what else we might be able

to glean from doing the right kind of nonclinical evaluation with a phantom or model eye.

Okay. Now, let me shift to software and synthetic image usage, and so with the help of Sina Farsiu, who's doing some very interesting work in this space at Duke University, I'm going to break this into two categories. One is data augmentation, which is maybe the more traditional way we're actually already seeing synthetic images used, and that's where we're either manipulating or enriching datasets of images to improve both manual segmentation of images as well as training AI algorithms to do the segmentation and other kinds of image analyses.

And then there's also model-based data generation, which is actually creating images from scratch, and that way we can actually better understand how well an algorithm is performing.

So I'll show you now a few examples in each of these. So from Joel Schuman's and Gadi Wollstein's group at NYU, along with some folks at IBM, they were using augmentation techniques to show that you can improve the ability to manually segment images. And so here they use a gold standard in their study of an image, which is multiple frames averaged together, and then they actually augmented a single-frame image with different deep-learning methods to be able to see how much improvement they could get in different image quality figures of merits. And so what they saw was the single-frame image, from an SNR standpoint, a mean-squared error standpoint and so on, they saw quite noticeable improvement when they augmented these images with different deep learning-based methods.

Also, for algorithm training, which I think is very important to think about how to train an algorithm with the right set of images, data augmentation can play an important role. And this group from Shandong University in China showed how -- they started with a dataset of only 912 B-scans, and then they performed geometric and photometric

transformations to that set of images to then create a set of 24,000 images from their original 900 and therefore to improve the training of an algorithm. I think that's essential. I think the best opportunity for augmentation in this space is for algorithm training, but then you still need to test on an independent set of non-augmented images.

Now back to model-based data generation, which is where Sina Farsiu's group has been applying some efforts in developing a model, a mathematical model, to actually create an image with signal and noise characteristics similar to what's actually acquired from an imager in vivo. And what they wanted to establish is what are the limits of segmentation accuracy that are possible.

And, interestingly, I found this quite interesting that actually what they observed is that the accuracy of segmentation is actually better than the axial resolution of the OCT instrument, and it gets even better when you use -- the unbiased method is just using single A-scans, whereas the biased method is actually combining A-scans and using the B-scan information as well, but still the fact is that there's an opportunity to achieve segmentation accuracy exceeding the axial resolution of the OCT device.

Okay, so to summarize, then. There are a number of nonclinical physical tools that have been developed mostly in prototype form by our lab and other labs. And I think what's important now -- and I think this meeting gives us an opportunity to come up with what are the most important ways to use these tools. And I've only highlighted actually the posterior segment really, and we saw some great talks in the morning about the anterior chamber, and I think there also is an important space and need for tools in the anterior chamber as well.

Here I'm listing some examples of how we might -- what types of data we might get, whether it's engineering figures of merits, understanding measurement accuracy of these imaging devices, calibrating a device to work over time, as well as thinking about

traceability of post-processing. There are a lot of datasets that are being posted publicly out there, and I think we need to know, okay, if we need to understand how one dataset has been processed, phantoms and other physical tools could help us with that as well.

And, finally, we've seen just in the last couple of years a surge of activity in synthetic image generation and usage in AO and OCT. It's quite nascent, and I think there's a strong potential for augmentation techniques to enhance training of these deep-learning and AI algorithms.

Thank you very much.

(Applause.)

DR. ASHFARI: Thank you, Dr. Agrawal.

Our next speaker is Dr. Hilda Scharen -- Dr. Scharen, perfect -- who is the Director of Medical Device Development Tools Program at FDA's CDRH. Thank you, Dr. Scharen.

MS. SCHAREN: So good afternoon. Just a correction, I'm not a doctor. I have a master's in engineering, so I don't know what happened in the transcription, so I just wanted to make that correction.

So I've been asked to come and talk to you about a fairly recent program; it's a qualification program, the MDDT Program to qualify development tools. And so I'm going to share with you the outline for the presentation this afternoon. So I'm going to be going through a little bit of the vision of the MDDT Program, the benefits of qualification, and also going through a couple definitions of what an MDDT is and what are contexts of use, we refer to as a COU, going through the different types of MDDTs as well as a nonclinical assessment model and use and also briefly covering the MDDT Program phases. So I am going to try to stick to about 10 minutes here.

So this program was launched a little over a year and a half ago, and it's a voluntary program for qualification of MDDTs that are used in evaluating devices subject to regulation

by CDRH. So the intent of this program is really to promote the development and use of tools to streamline device development and regulatory evaluation. As you can see here, the different tool submitters can be individuals, it can be a group, it can be a consortium or an organization, and even FDA can submit tools to go through the qualification process.

So here you can see there are many benefits to the qualification programs that are listed here. I'm just going to highlight a few. So the MDDT Program provides really a mechanism for leveraging the advances in regulatory science which helped to bridge the gap between research and development of medical devices and the delivery of high-quality, safe and effective devices to patients.

One thing I want to point out here that's particularly beneficial is that a qualified MDDT can be used by multiple manufacturers.

So what is an MDDT? It's a method, material, or measurement, and it's used to assess the effectiveness, safety, or performance of a medical device. It's a scientifically validated tool and qualified for a specific context of use (COU) to use in device development and to support regulatory decision making.

So what is a context of use? This is really a key aspect of qualification, and it describes the way the MDDT should be used, its purpose, and the conditions under which the MDDT is qualified. And a complete context of use should include the tool or product area in which the MDDT is proposed to be qualified, the specific output or measure from the MDDT, the role of the MDDT in regulatory evaluation, as well as the phases of medical device development in which the tool measurements can be used.

So there's different types of MDDTs, and CDRH recognizes these three different types, which really can be distinguished primarily by how the tool measures the relevant parameters, so I'm going to briefly touch on the first two, and the one probably of more interest to this group would be the last one.

So the first one. There are clinical outcome assessments, and it reflects how an individual feels or functions. And, currently, we actually have two tools that are qualified in that category of tool types.

The next one is biomarker tests, and that's an objective measure of biologic or pathogenic process or response to an intervention, and we just recently qualified a tool in that tool type, the biomarker tests.

And the last one is nonclinical assessment models we refer to as NAMs, and these are models that can be computational and animal, to measure or predict a parameter of interest, to reduce or replace animal testing as well as reduce the test duration or sample size.

I mean, I know you guys have talked about this a lot today, but in the space of OCT and adaptive optics, there's really a lack of validated tools which can be used for device development and clinical trial, and so I was asked today to come and speak to you about the MDDT Program because this could be an avenue for qualifying new tools which can be validated. And when making qualification determinations, FDA intends to evaluate the tool validity, the predictability, and the extent of prediction or capture.

So here are areas where we're looking for MDD tools to be developed, including the need for computational simulation models for structural algorithms and disease progression algorithms for image trend analysis, phantoms to be used for OCT and adaptive optics, and developing image databases by accepted or validated reference standards.

So what is qualification? It's a conclusion that, based on FDA review and as long as that tool is being used within the context of use, that MDDT can be relied upon to have a specific interpretation or application in medical device development and regulatory review. So CDRH reviewers should accept the MDDT outcomes as long as that tool is being used in the submission within that qualified context of use without the need to reconfirm the

suitability or the utility of the MDDT when used in a regulatory submission. So CDRH encourages tool developers to make the qualified MDDTs publicly available.

So here I'm going to be just going through briefly the different phases of the qualification process, and as you can see here, the first phase is the proposal phase, and this is really the starting point for all MDDTs that are submitted to FDA, and it's used to determine the eligibility and prioritization into the MDDT Program. So this first step is really for a submitter to submit a proposal, and it's designed to really be very short and will only include a description of the tool, a context of use, a discussion of how the tool meets a public health need. In this particular initial phase, we're not looking for any data to be submitted.

So the next two phases highlighted here in the middle are the incubator and prequalification phases, and during this phase, the submitters may seek advice from FDA on their evidence-gathering plan. And so the goal of the incubator phase is for CDRH to work with submitters to foster the development of tools that have potential to significantly improve public health. And the other optional phase is the prequalification phase, and in this phase, submitters of fully developed tools may submit a plan to gather evidence to support the tool qualification.

And as you can see here, the last phase is the qualification phase, and in this phase we're going to be reviewing the data, all the evidence and the justification provided by the tool submitter to support the qualification of the tool.

So these are the key considerations for qualifying an MDDT: the MDDT tool description, the context of use, the public health impact, the strength of evidence, and the assessment of the advantages and disadvantages of using the tool.

I do want to highlight really quickly the tools we currently have in our pipeline in the different phases, just so you can see, and as I mentioned, we have the three qualified tools

here at the bottom of the funnel.

And this is where you can find some additional information about the program.

And so I'm going to just quickly wrap it up here, and I wanted to just conclude that we really believe that, through programs such as the MDDT Program, we're modernizing the regulatory evaluation process and reducing time and resources needed to develop and assess new products, and this really helps promote innovation, it supports the manufacture of high-quality products, and can speed the rate at which safe and effective medical technologies are made accessible to patients.

And so on behalf of the MDDT Program, I want to thank you for your time and interest. Thank you.

(Applause.)

DR. ASHFARI: Thank you, Dr. Scharen.

If we could have our colleagues in Panel 3 come up.

(Pause.)

DR. ASHFARI: While our colleagues are coming up, we are working on Question Number 3, which is: For cases where there is no clinical gold standard comparators for OCTs or AO-equipped imaging platforms, can adequate preclinical (animal models) and/or non-clinical software (i.e., synthetic images) or hardware (i.e., phantoms) comparators be created?

So here we have -- if we could have -- great. So our colleagues here, Dr. Joseph Carroll from the Medical College of Wisconsin; Dr. Vivek Srinivasan from the University of California, Davis; Dr. Daniel Hammer from FDA; and Dr. Alfredo Dubra from Stanford.

So we have this big long question, if you could put up the question, and we are going to break it down to little questions, and just for the sake of time, I won't go into a deep introduction of each of our colleagues on the panel since they are known, I think, to

everyone in the audience.

So let's break it down. The first part. So really what roles do nonclinical sources, such as animal studies, synthetic images, phantoms, play in device development and not just in device development but also in validation, reproducibility, and standardization?

If we could go around and go over that first part of the question. Should we start from Dr. Srinivasan?

DR. SRINIVASAN: Sure, thanks very much.

I'd like to highlight the animal models in particular. So there was some discussion about visible-light OCT and how do we validate this. It's interesting that I think right now there's maybe 10 or so groups around the world that are doing visible-light OCT and about three or four are now in human subjects. So the initial near-infrared OCTs actually started in humans and then took some time because imaging animal eyes is different, then a move to animals and started looking at rats and mice and other primates.

Visible-light OCT has been the opposite development cycle, so all the groups that I know of have started in animals and more recently moved into humans, and I think, in particular, this is important. We heard the discussion about light exposure, light safety in the last panel. While it is possible to do imaging safely, this is exposure more limited in the visible wavelength range, and I think having that opportunity to validate scan protocols and algorithms in an in vivo setting is so more reliable than a phantom experiment; still, in vivo with real microvascular networks, I think, provide significant advantages.

There are other aspects of animal models as well. For instance, transgenic mice, transgenic technology in mice allows numerous opportunities for cross-validation, which I hope we can discuss in the next few questions.

Thank you.

DR. ASHFARI: What do you think, Joe?

DR. CARROLL: Well, I'll just follow up that I agree with animal models and even to the adaptive optics imaging of photoreceptors, using animal models where either they naturally undergo well-specified changes within photoreceptor structures such as hibernation, and being able to track that and see how that changes the resultant images or pharmacologically changing, you know, killing photoreceptors and then also monitoring the changes in the images, offer opportunities for validation that just simply aren't possible within human retinas in such a well-controlled fashion. So I think there is a clear role for animal models.

DR. ASHFARI: Alfredo or Dan.

DR. HAMMER: So I think it's important to match the tool to the application, and a lot of that is built into the context of use that Hilda talked about. We're talking about three tools. There's other tools in terms of registries and other things. But, you know, if you want to validate, verify and validate your system for multisite studies, clinical studies, maybe you'd choose a phantom. If you're looking at a new method, a new method where transgenic mice or other types of animal models can be used, then you apply that tool. So I think there are roles for all of these tools in the work we do, and choosing the right tool for validation is important. And I think we also want to open up the discussion a little bit and not just have us talk up here, so if anybody has any points, please go up to the microphone, and let's open up the discussion.

DR. ASHFARI: Any colleagues in the audience that want to make a comment about what role the nonclinical sources such as animal models, phantoms, any of them -- Dr. Abramoff.

DR. ABRAMOFF: You recognized me, wow.

DR. ASHFARI: Even a cornea person.

(Laughter.)

DR. ABRAMOFF: Yeah, Mike Abramoff.

About synthetic images, I mean, I'm still not concerned about them. We use them to test tools which are actually validated, and I think it's more risky. I think, in reality, it's not normally distributed, and with synthetic images you make a lot of assumptions about the variance that you put in there rather than the real variance that can have long tails, if that means something statistically. So I'm a bit concerned to go into more detail about the statistics, but we have to careful, I think.

DR. ASHFARI: Okay.

Alfredo.

DR. DUBRA: I think I wouldn't be offending anybody in the AO retinal imaging community if I say that in answer to the question, what role do these items play in device development, validation, the answer is, at the moment, I think none. And I think there's a lot of room for improvement, and it's particularly important in our community because, as opposed to maybe OCT or other instrumentation that is more developed where you might have dozens or hundreds of instruments made at least by the same manufacturer, hopefully with the same quality assurance testing, most of the AO instruments that you see publications from are different. So maybe the need for us to be able to perform multicenter studies is a really important need that we need to address.

DR. HAMMER: Yeah, we might be talking about this a little bit later, but I mean, standardization is something that's antithetical to what companies do and what a lot of researchers do because they have to do something that distinguishes themselves from other people. So that's where, you know, a collaborative community in a precompetitive space can come up with ways where their own, you know, special sauce that they apply to their imaging datasets can be sort of determined where there's, you know, traceability in terms of the post-processing and you don't have the scenario where only one group can

produce a certain type of image and it doesn't propagate to the rest of the community. So I think that's something where some of these tools can be applied. The comment about the synthetic images I agree with, they have to be very carefully used, and maybe, again, for a very focused application or idea, then they can be verified.

DR. CARROLL: If I could follow up on that. You know, I was one that always said it's great when we can cure retinal diseases in mice, but that doesn't do much for the patients that are suffering from those diseases. And I think the same goes for phantoms and synthetic images. It's great if you can show that your device images a phantom that may be stationary or may be, you know, designed in a certain way, and it's great if you can show that your software works a certain way in a synthetic image, but it's completely different, speaking back to Vas's point in the morning, to demonstrate that in a real-world situation that your algorithm is reproducible and repeatable and that your operators can use the device to collect images in a reproducible and reliable way from patients. So while those may be informative for standardization across, say, centers and sites and trials, I think it's a big step to suggest that that says anything about how those devices can be used clinically.

DR. ASHFARI: So on that note then, let's think about it this way. So this part of the question: As the researchers move -- (microphone cuts out) -- towards functional analyses and biomarkers such as angiography, now we have oximetry, cell motility simulation, all of those, can nonclinical sources aid image interpretation and clinical translation? I know we started to touch base on that.

DR. SRINIVASAN: Yeah. So let me highlight some of these vascular techniques. I'm talking about angiography and oximetry. And I think there's a real question even in OCTA, you know, what exactly is OCTA measuring; is it flow or velocity or hematocrit or some combination of these? I think it's possible to make phantoms that are well controlled. The problem is that flow in vivo is very complex, particularly in capillaries at single file the

hematocrit is variable, there's interactions between the cells and the endothelium.

So I think there's a real space here for animal models that have realistic vascular networks. Of course, a mouse is not the same as a human, but it's certainly closer than a phantom to actually validate what some of these techniques are telling us. And I highlighted in the morning, particularly with OCT oximetry, it's possible to apply well-defined modulations of oxygen or CO_2 or blood gases, validate those measurements using gold standard techniques that are perhaps more invasive and can't be applied in humans to really understand what are these vascular hemodynamic measurements actually telling us, and some of that would hopefully carry on into the clinical measurements.

Thanks.

DR. HAMMER: And so phantoms in this case are kind of a starting point. We, in OSEL, have a phantom that's used in our photoacoustic work that is used to extract oximetry, and it's got -- it's, you know, got the pumps and it has -- it's very complicated and so -- but that's sort of the starting point and then moving towards clinical work, and that really gives us a lot of foreknowledge about what we expect to see in the clinical cases. So I would say phantoms are a very useful starting point during device development and validation.

DR. ASHFARI: And it sounded like, Alfredo, you certainly agreed with that from your earlier comment. And so does Joe Carroll. Great. So any comments from the audience? So let's think about some -- oh, yes.

DR. BUCKLAND: Yeah, we're starting from a very funny point with OCT to begin with, which is most OCT systems present a linear length on the retina when we're doing an angular scan. And so it seems like every ophthalmic fellow has gotten through their program by writing a paper comparing OCTA to OCTB, and they're close, but they're just not the same, and it seems, from a regulatory perspective, a simple thing of kind of getting the

right specification for what we are actually reporting in OCT. It would be nice if we went backwards and said we're going to report an angle instead of a distance. That would be one.

But then, also, we have to get the distance, and it's dependent upon some assessment of what the average refractive index is. So I'm sure people are reading the same papers and trying to use the same numbers, but again, I would just say, from a regulatory perspective, these very simple questions that affect every single instrument that's out there, if we could just get some commonality on that before we start talking about advanced phantoms, I think we would probably make a lot of progress.

DR. DUBRA: I think you made a great point, and one of the things I'm learning as part of these -- I'm trying to put together is that this is maybe more of a question for somebody like NIST. So there's really different players that we need to get involved, because if we want a standard, we need to talk to -- to get ANSI involved. If we want it to be approved for clinical use, we need to talk to the FDA. But if we want something that is traceable, then we really need to reach out to NIST. So that you know it's a recovery, cost recovery, whatever agency, so you actually need to hire them, you need to set up a contract to get them involved.

DR. ASHFARI: Go ahead.

DR. SRINIVASAN: Yeah. So getting back again to the animal studies. So we saw a lot of great work in the morning sessions highlighted by several people on measuring phototransduction functional OCT in the photoreceptors. So even here there's opportunities. If the claim is that these techniques actually measure phototransduction, why not take a mouse and knock out phototransduction?

So Ed Pugh and Robert Zawadzki and Min Zhao at UC Davis have actually shown unequivocally that these functional OCT measurements, in particular the swelling, is

associated with phototransduction.

Other opportunities for ganglion cell imaging where you can actually label subtypes of ganglion cells in the mice, you can conclusively say, not just comparing the histology but in a living animal model, what types of cells are visualized by these OCT techniques.

DR. ASHFARI: Go ahead.

DR. HAMMER: Especially for the -- you know, the question on functional imaging, I think the animal work has to happen and it can -- looking at, for example, what we're doing in our lab, looking at RPE motility, you know, if we did animal studies to learn about the specific organelles that are causing the different time constants, that would shed a lot of light in terms of the mechanisms of where these signals are coming from. So, again, going back to my point earlier about matching the tool to what you're trying to get out of it, that's something I think the functional work has to be driven by in the preclinical space by animal work.

DR. ASHFARI: Great. It seems everyone agrees about the functional studies. We still have some ways to go with these phantoms, but a great start. Sorry, Alfredo, did you want to --

DR. DUBRA: Yeah, I just wanted to add that -- to make a broader statement about Vivek's statement, we tend to think of a phantom as in a piece of metal and a lens or some other physical device, but I think the animals combined with genetic manipulation tools or techniques that might, for example -- (microphone cuts out) -- blood cells, we might have some sort of living phantom that we can customize. So we should think broader than just a physical device such as a phantom.

DR. ASHFARI: Great. So let's tackle this question a little different. Can we attain traceability of processing through standardized post-processing algorithms for rigor and reproducibility? And that would be particularly for quantitative analysis. What do you all

think of that?

Dan.

DR. HAMMER: We touched on that a little bit earlier. I think I can say, for the FDA, we're interested in regulatory robustness. So I guess we get to see the secret sauce that manufacturers have, and that's what -- we want to see what goes into that in order to make the determination but really without cutting down the ability of companies to separate themselves in the competitive space. In terms of regulatory review, I think we need to see that kind of traceability so there's not any sort of unknowns about where -- how the images are acquired and what post-processing occurs.

DR. CARROLL: If I could follow up on that. I think that's especially problematic within the OCT space, for a second, to get off of the depth of optics, in that much of the post-processing that's done on commercial systems is in a black box with respect to the user, and while its intended use of measuring thickness and maybe sizes of lesions and whatnot are probably okay, you now find people who are trying to make measurements of the intensity of the OCT image or a specific layer of the OCT image, completely unaware that even within a volume that one B-scan may have been modified differently than other B-scans in that very same volume for that same patient. And I think it's -- you know, it borders on irresponsibility for some of the companies to allow that to continue to be done without providing it, you know, fairly transparent to the extent that can without giving away their competitive edges, but transparency to say, you know, full disclosure, this is not real raw data, it's been manipulated, and I think that's critical. If we're really going to maximize these imaging modalities, we've got to know what's being done to the images.

DR. HAMMER: Boiling it down to a simple image quality number is maybe overly simplistic.

DR. ASHFARI: Alfredo, you were -- you were nodding your head. What do you think?

DR. DUBRA: I completely agree with Joe. And Dan. I think that it's a really difficult thing where on one hand we want to have transparency or understand what happens to the data, but on the other hand, that is what might make your company unique or your product unique. So I think that maybe what Joe was hinting at is that there's nothing wrong, we still have the black box software come with your instrument or the black box software be your product, but maybe allow access to the raw data so that you can process in any way you want. I think that that might be a reasonable compromise, that you're not disclosing or jeopardizing the unique technical aspect of your software. Is that fair?

DR. HAMMER: Do you want to talk about registries a little bit, as a tool? I suppose those are -- I guess those aren't -- those are clinical sources in a way, but the question of whether one might use -- and I guess synthetic images could be -- there could be a registry of synthetic images that's shareable. All of these tools, whether it's a phantom, a synthetic image, or a registry of human images being available for different manufacturers and different researchers, I think, is critical. So, you know, we take the stance that, you know, sharing of images is probably pretty critical to the successful development of and validation of these devices.

DR. CARROLL: Yeah, especially for researchers who don't maybe have the resources to get an AO system and build up the learning curve that you need to be able to build an AO instrument, having access to a registry, AO registry, could give them a tool to develop new methods.

DR. ASHFARI: We have a couple of comments from the audience.

DR. AL-QAISI: Yes. So just to go back to the point Dr. Eric raised and coming back to the thing and you've got five Gerkins from the suppliers and manufacturers. It seems, I mean, even if you get -- there are many different ways of reconstructing an OCT image and taking the data and looking at it. But it seems the more obvious way to deal with this is to

have standard measurements on axial motion, it could be phantoms, it could be model eyes, and it's not clear if -- at least to me, it's not clear if it's FDA's responsibility to do that or someone else's.

But like you were saying, we see all these comparative papers between technologies that are very similar, but the final outcome isn't good, and that isn't necessarily working for the benefit of us, as manufacturers, because our device works different than the other manufacturer's device. We want them all to be similar, but we'll only expand over all fields. But today there's just no standard for intensity or resolution. Every manufacturer ends up picking his own method and goes with it. So having someone developing a standard to use is actually in the benefit of the manufacturers, not something that manufacturers don't want to do.

DR. ASHFARI: A great point.

DR. ABRAMOFF: Yeah, Mike Abramoff.

I want to make a comment about transparency or traceability of the algorithms. There's many levels to transparency. You can copyright, you can patent, you can give to the FDA your materials and then delete out, if there is a Freedom of Information Act, the things that we should disclose, like what are the properties of the training and validation set, who was in it, who was not in it, inclusion and exclusion criteria. So there's a lot of transparency levels that are appropriate at different groups of stakeholders.

DR. DENNISTON: Hello. Yeah, so I just really wanted to pick up on Joe's comments about the intensity measurements and kind of when he was trying to apply researchers working actively in an area which the technology is not really designed and validated to do. So speaking as a researcher who's also worked in this area as well, I can absolutely reiterate the need to go back to the raw signal, and obviously, to do that, you need to be working actually with the manufacturers, and that is not often done, but it requires that kind of

openness between the manufacturers and the researchers. Yeah, so --

DR. ASHFARI: So thank you for that comment. And hopefully during the break, we get to, with our colleagues in the panel, to discuss that because our time is up and we are trying to catch up in time. So a special thanks to all of our colleagues in the panel, Dr. Dan Hammer, Dr. Alfredo Dubra, Dr. Joseph Carroll, Dr. Vivek Srinivasan, and FDA, as well as Dr. Malvina Eydelman for putting this workshop together. Thank you. We look forward to talking with you during the break.

(Applause.)

(Off the record at 3:05 p.m.)

(On the record at 3:20 p.m.)

DR. REPKA: Okay, I think we'll go ahead and start this session, this closing session on reimbursement. I'm Michael Repka. I'm part of the program planning group from the American Academy of Ophthalmology's group, of course, of the 10 societies that were involved.

We're going to talk about reimbursement, and as Dr. Eydelman mentioned in the beginning, this has not been typically a part of these forums, in fact, how one has a margin out of doing all of this wonderful science. So this session will be reimbursement considerations, coding coverage. We have a terrific panel, sort of a world's expert panel in how we manage these problems.

I have no personal financial interests or relationships to disclose.

Now, the physicians know this stuff, but we have to at least go back to basics. So who pays for a physician's services in the United States? Well, we have government or public payers. The CMS will represent many of those through either Medicare or Medicaid. There are commercial plans which, of course, most of us know is employer-provided coverage, and that may be what you have in the commercial space for Medicare Advantage,

so Medicare beneficiaries, non-Medicare, the bulk of the U.S. population, and then about 10 million people in ACA insurance exchange products. But we can't forget the self. There are anywhere from 10 to 20% of the population that have no insurance or have high deductible plans, which means for many of the services you're building products for, they really are effectively self-insured because it falls under their deductible.

Medicare coverage does not mean any service a doctor writes for is covered. The statute requires that the service be reasonable and necessary for the diagnosis or treatment of illness or injury or to improve the functioning of a malformed body member, in our case, the eye.

There are some pathways for research coverage, but they'll be very thin in this space. That would be a pathway for a patient to participate in a clinical trial might allow them to get their routine coverage paid for. Yet, the manufacturer of a new device would be able to pay for that study, but this is pretty thin in this area. So there is an NCD, or a national coverage determination, that if you're doing a study within that area, there could be coverage with evidence development where your technique is the add-on. There might be a clinical trial policy that allows your device to be an add-on and the routine costs are covered by Medicare, but the intervention or the test itself would not be covered, or an IDE study which, of course, would not be particularly relevant to this group.

Medicaid. Physician payment levels are determined at the individual state level. Actual dollar amounts vary widely when examined as a percentage of Medicare, but they are generally less, as much as 40% of Medicare or even less. Not all the fees are RVU based, and though we're going to talk about RVUs today, Medicaid does its own thing some of the time. And, in general, Medicaid fees are not going up because Medicaid costs are going up, and there isn't as much money for those programs as there was.

Commercial carrier coverage. Each of these large companies, and we have a

coalescence today of major insurance carriers, do their own literature review and coverage pathway determinations, which means that there are fewer places to go to but still many places to get a positive determination for coverage with each of those companies. Each of them typically is doing an annual review or update of their coverage, and so it is complicated and involves knowing what's going on in that space. And, in general, I would argue that their coverage policies are more stringent than what Medicare Part B or Part C carriers will do. And they almost never cover investigational work or new services, and as we'll learn, new services are typically coded under a Category III system.

The first part of a path to coverage involves a CPT code. Without a CPT code, there is almost no way for you to have your physicians report the service and obtain reimbursement, and it's not a simple pathway.

Category I CPT codes, which many, many companies, many physicians feel is, you know, the highest level -- it's heaven, if you will, if you have a service or a device. They must be FDA approved to get that. So without FDA approval, you're not going to get Category I. It also must be performed by many physicians in the United States. It's frequency has to be consistent with intended clinical use. For example, if you wanted to have a procedure that was for glaucoma, it ought to be used in a lot or a high proportion of glaucoma patients, and the threshold for peer-reviewed literature is difficult. You need to have U.S. papers, they have to be U.S. populations, at least two of them, and they can't be overlapping groups. And we often have a problem in eye care because we don't have a plethora of groups within the United States doing procedures in some of our areas.

When a Category I code is granted coverage and payment, it's usually covered by CMS in Part B Medicare. We'll get to how it's valued, but CMS sets the value, and commercial carriers typically follow coverage but often with a delay of 1 year or 5 years; it often takes time. If you're doing a device that is an add-on, particularly if it's done in a

facility, so think the imaging that we saw earlier in the day, simultaneous OCT done in the operating room under the microscope, that add-on process is not usually covered, and we could talk more about that in the panel. And that creates a great deal of discomfort in the industry.

Lastly, new codes. When we get a new -- if we were to get a new OCT code, what would happen? Well, the whole family, anterior segment, posterior segment, would get open for revaluation, and as we'll see, revaluation is synonymous today with devaluation.

Category III CPT codes. Often, this is the first step before getting to Category I. It's a necessary pathway. It is by far the easiest. The requirements are that it must be performed in humans, that is, the tests; that it is supported by one CPT or HCPC advisor, which is really easy; or you have a clinical trial going, which I hope is really easy; or IRB approval. Category III codes expire after 5 years and then may be renewed at 5-year intervals or applying for a Category I. Why go this route? Because it's easy to get a number, and in general, it's easier to get a promotion from Category III to Category I than to get Category I de novo.

Now, Category III has its hazards. Commercial carriers often see the number and say, forget it, we're not paying. There are no prescribed rules for coverage or for physician payment for the carriers, for the Medicare carriers. And it does, at least in some facility side, if you're doing a procedure in the facility, may add into the APC that the facility gets paid, but the doctors don't get anything extra.

What about valuation? Valuation is not quite a black box, although it is sometimes equally mysterious. Physicians in the United States are paid on what's called resource-based relative value scale. This all came out in the late 1980s and early '90s when we switched from UCR. That was sort of nirvana to physician payment; payments were good, they went up year over year, and industry was able to introduce new equipment, new tests, and those were generally paid for on a charge basis.

Well, 25 years ago we changed, and we went to a new system based upon relative value units in which doctors were assessed for how much work, companies and physicians were assessed for how much effort was in the practice expense. You added in a little bit of insurance for the service, and you came up with a dollar amount which was based upon whatever, the annual inversion factor. Think of that simply as the *k* that converted work units to dollars.

But who determines RVUs? So the RVUs start with the RUC, and many of you in industry know the RUC, not because it always gets what you want but because it's how we get to dollars. It is a committee made up of representatives from the American Board of Medical Specialties, 28 voting positions, values based upon a two-thirds super majority. Can you imagine they actually get that enough times to actually get a value? And then RVU recommendations are passed on to CMS, which they can accept or reject. In the past, CMS has been highly accepting of the RUC valuations. About 90% or so have been accepted.

But I wanted to call your attention to the last bullet, and that comment was made to a number of us years ago by a CMD, a CMS medical director, who basically said Medicare does not pay cost. We have a formula, we have other parts of the calculation, but you don't necessarily assure you're going to get cost out of it. Doctors really never like hearing that.

One of the things the RUC works under, and CMS works under, is the concept of relativity, and that means that your service is compared to other services that have been valued to come up with a dollar amount. And so, basically, different values for similar timed codes, the only time that changes is when the doctor work has either more or less intensity. That can be a modifying factor. In general, though, doctor intensity in the imaging space is not very variable.

And if we look at a number of codes here, so these are physician work values, and you can see that the doctor work there for remote retinal imaging, fundus photography,

posterior segment OCT, and then I have a comparator as a complete EKG and three-view chest x-rays, and IST stands for how much time the doctor is doing the service, and you can see that remote retinal imaging happens to be the non-doctor code, so I chose that as zero. Fundus photography has 10 minutes of work in it, posterior segment OCT similarly, and EKG and chest x-ray have far fewer minutes. But if you look at the fee, you can see that doctor work is highly correlated to the amount of dollars you get out of the procedure. Why? Well, we'll get to why in a moment. So doctor work calculates, and it's about 40% of the codes in general.

The bigger part of imaging or testing is based upon practice expense RVUs, which aren't going to count clinical staff time, so the tech time, the chair, the place where the patient's done, disposables. But the key concept here is that non-disposable instruments, capital equipment, pretty much everything you're building, is not broken into some number of dollars per visit or a thing like that, but rather it's amortized over 5 or more years by CMS based upon invoice pricing, not based on list pricing, and then it's assumed, in general, that its utilization is about 50% of the time. There are different utilizations for different instruments, but we'll make that sort of a starting point. So if you think about five or more years, 50% utilization, you can see that the dollars per patient go down pretty low.

The determination is also formulaic. CMS takes these costs and does whatever it does. But if we look at the example 92134, you can see that there is 0.45 work RVUs in it and just 0.69 RVUs for practice expense. If you think about it, there's probably a lot of dollars in that practice expense side that may not be calculated or that are included, and the practice -- the professional liability insurance portion, therefore our services, is generally quite low. And that's because ophthalmology and optometry have very low medical liability premiums, so it drives that portion of the fee down.

Now, why are codes revalued? A number of you have lived the visual field reduction.

Others have lived the OCT reduction and the ERG reduction most recently. Why? Because the Congress says we have to. Protecting Access to Medicare Act of 2014 basically said that we need to reallocate $1 billion per year through 2020 by reducing misvalued codes. And then, of course -- sorry, then the ABLE Act accelerated the implementation of the PAMA Act so that the Congress was trying to move money around within Medicare.

Why does it happen? So to be able to reallocate that money, people bring codes up for review to figure out who's misvalued, if you will. So the RUC can do that, CMS can do that, and even you can write to the system and have that suggested code fixed.

What about the CMS and RUC screens? This is where most of the code revaluations occur. The public doesn't really write in; CMS will write in. But the RUC is tasked with doing this for physicians, and the biggest factor is rapid growth in volume. So any new service automatically has a growth in volume, and that triggers the code or at least triggers the review frequently.

There may be other causes if the practice expense goes up or down a lot. You know, if there's a sale on the instrument, I suppose it would go down. Valuation anomalies within a family, those are statistical things that look at the codes for that. And then recently, the one ophthalmology has been getting in trouble with are codes billed together on the same day can trigger those screens.

So if we look at what happens after revaluation, and this is where I commented that revaluation was synonymous with devaluation of the reviews that have been done by the RUC, in purple, 41% of those have gone down. Only 9% have gone up, and you can see the 9% there in one of the gray shades. So we fear revaluation, but also it's the nature of a successful product that is going to be subject to that process. Oh, and then the revaluation, so far, has moved $4.5 billion around, so it's a pretty successful program as that goes.

Coverage policies. Commercial carriers typically use a similar fee schedule. They

have a formal process, this was would be Anthem's, and they usually give you about 6 weeks to respond, and they are fairly vigorous.

Coverage in Medicare. Remember that we're really talking here about physician and outpatient services, so Part B. Those are paid for from premiums from beneficiaries plus the taxpayers, or Part C, which is a commercial plan providing those services.

Now, those of you that successfully get a Category I code, Medicare coverage is administered by nine contractors known as the MACs. They're located around the country. We'll hear more from one of the carrier medical directors in a moment on that.

Medicare has several policies. Few of those affecting the eye care space are national coverage determinations. For instance, we have one about photodynamic therapy, not obviously a high-volume procedure at the moment, but they're out there, and you need to be aware of where they impact. More often we have local coverage determinations, or LCDs, which are contractor polices, and although they're often harmonious across the contractors, they're not always. And we have those for cataract surgery, but here we have them for OCT going by its somewhat older name, SCODI, which was the original CPT descriptor.

And where do you find these? The easiest way to find these is at cms.gov. Novitas are listed here, one of the contractors. But you can find them for every local or region that you're looking at addressing.

So thanks for letting me do those intro comments. We're going to have our next speaker, Dr. Rochelle Fink, who's joining us from CDRH to talk about a program that perhaps lets the FDA and the CMS coverage polices be more harmonized.

DR. FINK: Good. Thank you very much for having me here today. I appreciate it. You know, when I was first asked to talk about the payer program and given 10 minutes, I thought this was an impossible task; what am I going to do? And then I recently was asked

to talk about FDA and CMS's regulatory and reimbursement authority in 10 minutes, and I thought this is going to be a breeze, so thank you.

All right. So we're here to talk about the CDRH Payer Program. So there are a few points in these 10 minutes that I'm hoping you will gain from this. First of all, FDA and CMS have different statutory authorities, so sometimes a sponsor will come, especially they'll come to CMS, and they'll say I conducted the trial, you know, I got these endpoints, this is what FDA wanted, here you go, and CMS will look at it and they will say, you know, possibly we're looking for different endpoints. So we're going to discuss that. We're going to talk about Medicare's beneficiary population, Medicare's benefit categories, informal parallel review options, local contractors, private payers, hospitals, physician groups, etc., all in 10 minutes.

Okay, first of all, Medicare and the FDA have different statutory authorities, so the reason they're looking at different endpoints is not because anybody's trying to be mean or cruel or anything else, and it's Congress who decided that they need to look at different things according to the law, so let's take a look at the law.

Okay. This is just a quick blurb from the Medical Device Amendments law. You can tell, it looks old, and you'll see there, highlighted in yellow, it says the safety and effectiveness of medical devices. Okay, so FDA and CDRH, the Center for Devices, is going to look at the safety and effectiveness of medical devices. Now if you go to CDER, the Center for Drugs, then it will look at safety and efficacy, okay?

Now, CMS, by contrast -- and Dr. Repka, you already stole my thunder. I think that's the right saying. But, anyhow, they look at reasonable and necessary, okay? So they look at items and services that are reasonable and necessary for the diagnosis or treatment, etc. All of you can read. So you can see that reasonable and necessary is different than safety and effectiveness or safety and efficacy, and because of that difference, the two agencies

must look at different endpoints.

So why does this affect you? It affects you because if you want to bring a device to market or even if you want to bring a drug to market, you need to get both the input of CMS and FDA. Now, do you get this input once you've already developed everything and done your clinical trials, etc.? No, it's best to get it in the beginning so that you only have to run one clinical trial, and during that one clinical trial, you'll get endpoints that satisfies everybody.

Now, Medicare beneficiaries. This is also really important because FDA, when FDA looks at endpoints, right, it can look at endpoints for a pediatric population or it can look at endpoints for an adult population, and an adult population, and all the reviewers in here can correct me because I'm not a reviewer, but my understanding, we're looking at like 18 or above, okay? But Medicare is looking at endpoints for its beneficiaries. Who are the beneficiaries? Sixty-five and older, end-stage renal disease, or the long-term disabled. So yes, there can be some Medicare beneficiaries that fall into the younger groups. I gave a talk once, and this was before I came up with these slides. These are like the highlight slides, all-important slides. If you leave, like listening to me not at all, just look at the slides. But, anyhow, I got done with this talk, and somebody came up to me and they said I've got this great pregnancy test. What do you think Medicare will think of it? So that's why I wanted to go back and give my talk again because clearly it didn't go anywhere. So, yes, Medicare does have some women who are pregnant, clearly, because they could be end-stage renal disease or disabled, but the vast majority of the Medicare beneficiaries are 65 plus. I'll tell you another story because I didn't get some laughs at that one.

I was sitting in a sponsor meeting at CMS once, and somebody came in with their device, and they're telling us how great it works in NFL players. Clearly, we all found that very, very interesting. But your NFL player, I guess unless they have end-stage renal

disease, is probably not the beneficiary population. So please, please, please, when you want to get Medicare coverage coding or payment, make sure that you're doing your studies in the Medicare beneficiary population.

Benefit categories. And thank goodness I was talking to Dr. Clark over there a little bit earlier, yes, and he is going to talk about benefit categories, so thank God, I don't really have to because you can see here, this is my one picture with Snuffleupagus. My kids don't know who Snuffleupagus is, but hopefully a few people in here do and remember you never can find Snuffleupagus. But the idea is it's really, really hard to get a list of these benefit categories, but if you want your device to be covered and paid for by Medicare, it needs to be in one of the benefit categories, okay? And what that means is that it either needs to be not excluded by statute, so I always give the example of my eyeglasses, and if you come with like awesome eyeglasses, you know, they can be so cool or whatever, it doesn't matter because Congress has written into the statute that Medicare cannot pay for eyeglasses. The same thing with hearing aids, okay?

Or I guess, some things, if the agency issued you a 1A, it can be included by statute. So we look at diagnosis and treatment, right, but I don't know how many of you know people who have gotten a screening mammogram, right? Well, that's not diagnosis or treatment, but that has been specifically added to the statute, and it needs to have a benefit category. Your device must have a benefit category to be separately payable by Medicare, so what does that mean? That means basically that if you have a DRG or some kind of a bundled payment, if you don't have a benefit category, it's just going to be paid for in part of the bundle and it's not going to be parsed out.

Okay, so what is the parallel review program? First of all, this is only one way, and I should say, you know, of all the interactions I have with FDA and CMS, this is only a very small portion of them because I'm about to tell you what the big way is. This is one way.

And the idea is, with parallel reviews, we're going to decrease the time from FDA regulatory decision to a national coverage determination. Now, no, I said national coverage determination, and as we heard from Dr. Repka earlier, and I'm about to show you a map, most decisions are made by the local contractors.

So sometimes I'll go to meetings, and they'll think that like, you know, the person speaking on behalf of CMS is the important person. No, no, no. It's Dr. Clark over there in the back part of the room, the local contractor who makes most of the coverage coding and payment decisions for the country, okay?

And the idea of the parallel review goal is that the idea is you'll have both agencies will give -- and will talk about the endpoints early on in the trial, and this will assist the manufacturer, so the manufacturer will only have to do one trial. All of the evidence collection will happen at once, okay?

What's great about these *Federal Register* notices is that they're all about one or two pages, so there's no 200 pages here. So please feel free to pull up the *Federal Register* notices. If you do happen to ever talk to me again, tell me how much you liked the last one because I helped write it. But they're all really, really easy to understand, okay?

Now, the thing about the program candidates, and this is so important, okay, is that your device either needs to have a PMA or a de novo review. Okay, please don't say that it's going to have a PMA or a de novo review when it really needs a 510(k), because I do a lot of phone calls and I'll find out probably if it needs a 510(k). So please just tell us what's going on. And then, again, and I can't say it enough, it has to fall within a defined benefit category because probably the vast majority of the rejections we give is because the device doesn't have a defined benefit category.

Now, as I said earlier -- oh, wait, I guess I didn't have my informal part here. No. Okay, so that's the part that I really want to talk about is what is this informal parallel

review, because that we do a ton of. And what informal parallel review is let's say that you have a sponsor that's coming in to FDA for a pre-sub meeting, right? What the sponsor needs to do is you need to put it in writing. You can even send an email to the reviewer; you can put it in a formal letter. It just needs to be in some kind of writing, and what you do is you say I would like CMS to be present at the meeting, okay, because CDRH or CDER, all of FDA, you will never come to a meeting and there will be a surprise that somebody is there that you didn't invite because we truly respect your confidentiality. But if you put it in writing and your device has a benefit category, then there's a really good chance that CMS will either send somebody to your meeting or at least they'll be available by phone.

Another way you can do this, and I've seen it done both ways, is you can go to FDA for your pre-sub meeting, and then you can also ask to meet separately with the coverage group or the payment group or whoever you want at CMS. So that's another way. They're only about 30, 45 minutes apart on 29, so it's up to you if you want to do one meeting and have them both there or you want to visit them separately. There are pros and cons to both, but I highly recommend it's totally worth your time that you do reach out to both of them, especially CMS, because you're going to have to reach out to FDA; it's the CMS that you need to reach out to and talk to them about your pivotal clinical trial design. They'll be happy to talk to you and to give you comments on the endpoints.

Again, you want this information before you start your trial. I had to recently talk to a sponsor that had already started enrolling in their trial, and now they want to know their CMS endpoints, and what we said to them, we said we can give you the endpoints, but then you're going to have to decide do you want to continue with the trial or not. So that's really what we're trying to avoid; we really want to avoid that and have everybody just do one.

Okay, local contractors. Again, Dr. Clark is our local contractor here today, and you can see that the country is brought -- is broken up into different regions where you have

local contractors. So this is totally different than the FDA paradigm where you have FDA as the only game in town. In the CMS world, you do have the national level, but you also have these MACs, which Dr. Repka had mentioned before, and I would highly recommend that you also reach out to your MAC in addition to, if you decide wanting to reach out to the national level.

FDA has many, many private payer opportunities, and again, I think that a lot of sponsors, often they're so focused on getting Medicare coverage payment and coding that they don't think about the wonderful private payer opportunities that are out there. For instance, this woman who came up to me to ask about her company's pregnancy test, I mean, the private payers might be more of a market, or hopefully they are, than Medicare, right? So the private payer opportunities, if you're interested, here's the email. Also, if you just like Google private payer and CDRH or something like that, it pops up; it's a great webpage. And you can see there are a lot of current participants, Blue Cross Blue Shield, Cigna, Equi. So I highly recommend, when you're thinking about your reimbursement strategy, please, please also think about the private payers.

So thank you very, very much for your time.

(Applause.)

DR. REPKA: Let me have the panelists come on up. Thank you. Rochelle, thank you for those comments.

The program planning committee recognized that there might be questions about reimbursement, so we've allotted a substantial question period for that. We have pretty much, as I mentioned at the outset, an excellent panel with expertise that is tremendous.

Sitting soon next to me, Allison Shuren, who's a partner at Arnold & Porter and co-chairs the Life Science and Healthcare Group.

Larry Clark, Dr. Larry Clark, an internist, is a carrier medical director for Novitas.

David Glasser, an ophthalmologist who serves on the RUC as the ophthalmology advisor and is involved in pretty much all the deliberations that go into pricing our services.

To his right, Dr. Christopher Quinn, who is a past president of the American Optometric Association and has also spent a lot of time in the payment arena as well as dealing with whether or not a technology can be incorporated into a practice when it can.

To his right, Dr. Pierre Yong, CMS, so we're talking now about CMS in Baltimore, was in the quality group but now is in payment or coverage, depending upon how you view that.

And to his right, Dr. Cindy Mattox, a glaucoma expert also with a lot of experience in trying to price procedures for the glaucoma space and generally a lot of knowledge in how to run a practice.

So great; thank you, guys, for joining. Those of you that spent the day, I hope it was interesting. We certainly had some pessimistic comments, perhaps, but I'm going to start a series of questions. We have one, but it's pretty global. And so the first question is going to be -- and I'll direct this primarily to Allison with the others to chime in. In your experience of regulatory clearance, CPT process or insurance coverage, what's been the most difficult to achieve?

MS. SHUREN: I guess, initially, I probably would've said the CPT process since there was, in the past, so much more unpredictability to it, but I think even though it's predictability, it's not great predictability. Now, just about every new technology that comes out winds up in a service that's a Category III code. That's at least predictable. But once you have the Category III code, then, really, it's fair game in terms of whether or not you're going to get either a private payer and/or Medicare at a MAC level to pay for the technology. I honestly think, at this point, FDA is probably the more predictable pathway. And so I tell all my clients, plan early for reimbursement at the same time you're -- before you're even thinking about your FDA pathway, understand what your reimbursement

pathway might be.

DR. REPKA: And I assume you must ask about -- or you provide comparative experience to those companies.

MS. SHUREN: Yes, the successes and then the -- usually the ones, the non-successes are the most important so they can learn from others' mistakes.

DR. REPKA: Okay, great. Does anyone want to add anything to that? Dr. Clark, push your button. There we go. Thanks.

DR. CLARK: I sort of wish this cup would pass, but I think it's going to fall with me to be part of the difficulty. I think coverage and the criteria for coverage are efforts to standardize coverage at the local level across the country, and the newer initiatives in the 21st century to standardize the threshold by which we cover, you know, I just have to say, I think we're it, and you know, I would appreciate hearing what the others have to say.

DR. REPKA: So you can't toss that to Dr. Yong?

DR. CLARK: No, I don't think so.

DR. REPKA: Okay, great. David, as a -- or actually to David, Chris, and then Cindy. How about for, you know, in your sort of roles in the process before, where have you seen companies fail? Or not do as well as they hoped.

DR. GLASSER: So one of the issues is getting coverage and showing that, you know, a new technology actually has something to offer us. We have to convince these guys that, you know, being able to take the picture actually gives you some actionable information that can improve outcomes. But once you get the coverage decision, then the issue is how much are you going to get paid, and that's where oftentimes surprises come.

So Category III codes, you've heard Michael say they're very easy to obtain, there's a pretty low bar, but the coverage determination and the pricing is set by individual carriers. So you've got to go to the individual carrier and convince them. Category I is done on a

more formal basis with surveys of physician time and work.

And the problem with a lot of the technology that's being discussed here, when you're asking for valuation, is that there isn't a lot of physician work. Most of the work is done by the staff in acquiring the image. You guys build a great machine, you make it really easy to take the picture, it's a snap and it spits out information that's easy for the physician to interpret in just a couple of minutes, and then I have to go in front of 30 people who don't want to give us any money, and I'll tell them why they've got to give us a lot of money for something that takes the physician only 2 minutes to do. So that's a big barrier.

And if you've got something that has artificial intelligence built in, then the physician work goes to zero because the artificial intelligence does all of the work. So if you're going to bill it under the fundus photo code, you'll only be able to bill the technical component because the physician component is done by the machine. So I think a lot of companies aren't aware of how difficult it is to get a "reasonable" reimbursement level even if you get coverage.

DR. REPKA: Yeah, Cindy and then Chris.

DR. MATTOX: Yeah. I think, you know, in my experience over the last few years, I'd say, given that the glaucoma companies, a lot of them have been through this process or watched their peer companies going through the process, they're being a little more proactive, a little more prepared, perhaps a little more realistic, just from hearing panels like this talk about it and consultants talk about the pitfalls. So that's good, and preparation is key, and now there's these other pathways to prepare earlier.

I think, from the physician side and your user, your customer side, there's frustration because there is variation from state to state, Medicare region to Medicare region, commercial payer to Medicare, and that causes confusion and difficulties, and we continue to see problems where policies are made by some of these entities with very unusual

criteria. They may even vary from state to state as to who can have your test, and then even worse, they may go back to your pivotal trial and extract the inclusion and exclusion criteria and create a policy with those kinds of restrictions, which makes no sense for a clinical use purpose.

So there is a lot of challenges, and we, as advocates for the technologies and our patients, don't oftentimes have input early enough in the process, I would say, to effectively counsel the payers as to what's valuable.

DR. REPKA: Chris.

DR. QUINN: Yeah, and I would add that the challenge is greater on the commercial side than it is on the federal side because there is really very little transparency in the process for accepting a new device or a new code, and it can take years and years for a device or a procedure to be deemed not investigational on the commercial side, and that's a particularly big challenge because that's a large population.

DR. REPKA: Yeah. Pierre, I have a question that is sort of for your agency, how they're thinking about the eye portion of chronic disease, either age-related macular degeneration or diabetic retinopathy, and whether the agency is really trying to figure out how to best serve those patients on a proactive way or is it generally reactive.

DR. YONG: Thanks. Hi. So, yes, certainly chronic illness is a particularly important area for our population of Medicare; Medicare beneficiaries often having multiple chronic conditions. Certainly, as we've been looking across the conditions, we sort of look -- we have tons of claims data, for example, so we know the prevalence of different conditions which are billed for, for the Medicare population. Certainly, we have looked at the different organ systems as well.

When it comes to payment issues, we are often looking in terms of like if a new code comes through, we're looking for a payment and seeing if there are similar procedures

already within the payment, Medicare payment system, that we can then sort of match and sort of potentially match payment rates to it, if the procedures are similar, on that basis. So if they are new procedures, for example, they'll come in relative to eye diseases, that's sort of the process we begin to go through. There are also separate processes particularly that are available to new technologies that we may also consider they're available to technology developers.

DR. REPKA: Great. One of the panels today was on adaptive optics, which as the speaker said, this is an add-on to whatever imaging procedure that one is doing. So is there a feasible way to get extra credit for that technology in the fee schedule? And I'll throw that -- that's a softball. Maybe that's a hardball to somebody. But that is a true problem. So if we took OCT as an example, is there a way to get adaptive optics OCT paid for differently?

DR. GLASSER: So the two places where you can get more money, at least in Medicare, are from practice expense and from physician work. So if it doesn't require any more physician work, the machine does all the work, you're not going to get any more money for physician work. In fact, it might even be said that it makes more sense to use an existing code if essentially the work is the same and you're just processing the data a little differently.

On the practice expense side, unless there's a dramatic increase in the amount of time your staff spends, the clinical staff spends acquiring the image, you're probably going to not get very much on practice expense either, because the formula Michael described earlier of how CMS amortizes the cost of the machine over 5 or 7 years and assumes it's in use 50% of the time, a thousand hours a year, means that you're going to get pennies on the dollar for the cost of the machine. So your machine may cost five times as much as the old technology, but you're not going to get paid five times as much, as a clinician, to use it.

DR. REPKA: So how do I get paid?

Larry.

DR. CLARK: While pessimistic, he hit the nail on the head, and that's where you challenged me to look into benefit categories and other things, but the problem is, Mr. Glasser just said there is not extra physician work, and so we're looking at the pricing of the technology and the difficulties therein. The add-on service is not a physician service, and, you know, I'm struggling in my head, and I'll talk about it a little later, but I don't really see what benefit category that service added.

DR. REPKA: Service. So what if I said let's get CPT, Allison, Robbie's CPT and get some new CPT code, OCT with adaptive optics, won't it turn out well?

MS. SHUREN: The practice expense should go up. Now, I don't want to be completely pessimistic here because --

DR. REPKA: That's her job.

MS. SHUREN: -- you know, CAD faced this with mammography a number of years ago. So computer-assisted, you know, diagnostic software came out, and we had the same conversation. Somehow they managed to penetrate into the market and be successful. So there seems to be at least enough money in the system, if there's a real need for additional technologies, to find a way to make sure that it gets to patients. And at the end of the day, you know, there's always Congress, too, right? That's how we've had other things added to the benefit category list, because we convinced Congress that it's good for patients.

So, you know, we are early enough in this conversation, and kudos to everyone in this room for spending the day here. We're already identifying shortcomings to try to get this technology to our patients once we figure out what our patients need. I heard a lot of medical necessity. You know, conversations today are not convincing me that at this point we know what that is, but maybe there needs to be more, you know, grander thoughts here

in terms of changes to the Social Security Act.

DR. REPKA: Always good to think.

So Chris.

DR. QUINN: One other thought is that there's always the possibility that, as an add-on, it could be considered a non-covered service. Now, providers sometimes like a non-covered service because they can set the fee and they can collect directly from the patient. Obviously, the disadvantage is that, you know, it's a form of rationing based on ability to pay.

DR. REPKA: Yeah. And, of course, it changes office patterns.

Cindy, do you want to talk about -- anything more about advance beneficiary notices of use of a non-covered --

DR. MATTOX: Not really. I think it's a big concern for the Medicare population to start to have that as a payment avenue.

DR. REPKA: Thanks.

Just so everyone knows, because, of course, many Medicare beneficiaries are limited in their income resources, and so, you know, the doctors don't universally like it and there may be times where it's okay.

One of the questions that was raised to me earlier this afternoon was some tests take longer to do, and we do visual fields, we have three levels of visual fields in our space. Why can't we do that for these imaging modalities and get a tiered payment? I'll toss that one up. Nobody wants to take that one. So I guess --

DR. GLASSER: The answer is if it does take longer, then there's more work, and you should be able to get a different code and survey it to show that it takes more time, but you have to really know that it takes more time. And, you know, it's tough when you read these things online about how great the newest gadget is and how you can get the information in

1½ minutes and then have to take data from a survey of 30 or 40 or 50 people who respond, let's say, it takes 20 minutes. So, you know, if there's a real difference, you can get a new code and you can get a higher valuation.

DR. REPKA: But I think it can't be, you know, a few percent. It has to be, you know, 25 --

DR. GLASSER: It has to be significant.

DR. REPKA: Yeah. All right, great.

(Off microphone comment.)

DR. CLARK: -- practice expense, if you're not -- if you're talking about your staff doing it and not talking about, again, the physician service, so there you have to think about who is doing the extra service.

DR. REPKA: Yeah.

DR. CLARK: So agreed, again.

DR. REPKA: Right. So the three levels of visual fields, incidentally, predates any of this resource-based relative fee schedule. I'm not sure we would've ever gotten three levels in the current era. In fact, I'm pretty certain we wouldn't. One of the things about imaging is how to expand and reach the patient where they are, and one of the things, Dr. Clark, has been how do we get a beneficiary at home to do, say, glaucoma testing or retinal testing as an early warning or monitoring system? And so I'll first go to see what the carrier discretion is and then perhaps to Pierre for sort of what he knows for the overall CMS policy.

DR. CLARK: This is the super secret list, but physician services, dialysis-related therapy services, physical therapy, the compendium of services that are defined and the frustration is that they are enumerated in different places so you have to be able to go to all of them. But the point is that is this service at home something that is immediately acted

on in terms of therapy for the patient? You know, is it general monitoring where there's some difficulties in terms of Medicare coverage? You know, monitoring is not, per se, a benefit. If you stick your finger and you have a service paid under Part B DME, well, you're going to inject directly in response to that service. However, if it is just general monitoring and you are not going to respond, well, then, that may be outside of the benefit category. And I know this stuff seems arcane and difficult --

DR. REPKA: Because it is.

DR. CLARK: -- but I think we're really -- it is, and we're really down to a granular is it really part of a benefit category, but that's sort of the way it would be looked at.

DR. REPKA: So if I sent my patient home with a glaucoma test to measure their pressure every day and they called when there was a signal somehow and the pressure was over 30, whatever we made the marker.

DR. CLARK: Well, that's a tough one in the sense that what are all the other services, or is that service really integral to the evaluation and management that you're going to perform when that patient comes in for you to treat? And I think, again, we have the physician service component, and I know I'm not giving you a good answer because there isn't a really good answer. I think that is really the issue, what is being done in response to each individual incremental measurement?

DR. REPKA: So probably for Larry and/or Pierre. So what's the discretion the MAC has versus what CMS would interpret on that issue, because those, at least to my knowledge, can differ.

DR. YONG: Just on that comment --

DR. REPKA: Yeah.

DR. YONG: -- about sending a patient home with a glaucoma test. So there are some -- for example, last year we finalized a code for what we call virtual check-ins where a

patient could contact their provider and then the provider could have some interaction with the patient and assess whether or not that patient needs to come in for a visit. If they do need to, then they could bill that virtual check-in code. It's not specific to glaucoma testing per se in this example, but it is applicable to this general, I think, sort of clinical scenario where you have a person -- a patient sort of following up with you and providing information and that there's some exchange and some sort of clinical assessment that happens. You know, if that patient does need to come in, then that sort of consultation piece of this from the home monitoring would then get rolled into an E&M decision, and that's where you're billing for that patient.

DR. REPKA: So that means my device that I sent home is not covered?

DR. YONG: It typically is about sort of covering the physician time relative to the assessment of that patient, so it's not specific to the device per se or the --

DR. REPKA: Cindy.

DR. MATTOX: So I think this is something that is definitely ripe for reevaluation by the whole system, right? We have to move to some sort of a different system for patient care in the future, and almost certainly that's going to involve some sort of home monitoring system, some sort of reimbursement model for that, and I think that there would be a lot of interest in that. And, yes, maybe statutes have to be changed or Congress has to be approached about this and authority given to the agencies involved, but it certainly seems to me like this is coming, and I think that's reasonable to expect.

DR. REPKA: Yeah, go ahead, Allison.

DR. CLARK: I think you were talking about the G code now for the virtual check-in, and I think, you know, this is where we are having legitimate expansion. I think we're dealing with the telehealth services. They are not your equipment, but they are a concept in patient interaction that goes away from the traditional face-to-face interaction. But in

answer, that's still not the device; that's the interaction.

DR. REPKA: Yeah. So, right, the interaction gets paid for; it's a very low-paying service taking 5 to 10 minutes, and it would never pay for the home testing.

Allison.

MS. SHUREN: Yeah, I was just going to say, you know, there's some precedent out there in remote cardiac monitoring to sort of start thinking about what a model might look for ophthalmology, depending on what we're monitoring and, again, what Dr. Clark had to say about in terms of what the response is. That moved it out of the physician office, so at least then it wasn't the physician office expense. Worrying about it moved it into independent diagnostic testing facilities. That feedback comes back to the IDTF, that then reports to physicians, but -- so that's there. It's not as if Medicare has, you know, never had a remote monitoring process, probably not ideal, from ophthalmology, but I think we can at least build off of it as a concept.

DR. REPKA: Great. So I have a company and I have got CDRH to approve the instrument and I have a Category III CPT code. Is there a way to approach the MACs? What's the best way to do that, if there is a single best way? And it's in the agent, so we will -- Dr. Fink's issue, we have the right population for the right test. So, Larry, how do we go about calling you up?

DR. CLARK: In the 21st century, you're not going to get through. I think the --

(Laughter.)

DR. REPKA: Well, that says it all, doesn't it?

DR. CLARK: Right, don't call me. You know, I walked in today, and I saw the first slide said, oh, we're not FDA approved yet. And then the next slide said, oh, you know, we're not FDA cleared, and I was like this is going to be a tough audience.

You know, the way that gets our attention, and Allison and I were -- or Rochelle and I

were talking about this, is to submit claims and you go through that sort of crossing the bridge that, you know, there's no established reimbursement and you're taking a chance on your company's product. You know, hopefully your institution may be backing you or some fellow faculty or something and they're going to try this product and we're going to be stuck with these claims that we don't know what to do with, but that legitimately begins the process.

Now I would suggest that by the time you got there, you already had the conversation with the FDA, that you already had looked at the slides that I'm going to let you distribute on, perhaps, investigational devices, that you are actually amassing the data.

And I'm going to conclude with a little homework assignment, but it was something that was written by my fellow CMD, Craig Haug, on a policy on corneal hysteresis, which I understand -- I mean, I love eye meetings, if you allow me to say this, because you have great gizmos, but the thing is can we cover them? And the conclusion on his policy and the rationale for determination is something that I think you all need to take away from here as a lesson on how to progress forward in your company. Actually, I'll tell you right now so you don't have to go back, go to the Medicare coverage database DL38014 and read the rationale for determination, and you will see what we are looking for, for coverage.

DR. REPKA: Thank you.

Allison.

MS. SHUREN: So, Dr. Clark, you and I were talking about this, and I view this as a chicken and the egg. And commercial payers are even, I think, a deeper black hole, but a client comes to me and says, Allison, I'm being told that I need to -- there need to be claims in the system for my device. Okay, I understand, why bother wasting resources trying to determine coverage and payment for something that might be up-taken might not be something physicians want to use. But then they say, but why would a provider want to

buy my device on the chance that they may or may not get paid for it? Because there's no predictability in the system, and you haven't even considered coverage because there's no claims.

So we have this chicken and egg. So then they want to know, well, can I guarantee reimbursement to the provider if they don't get paid? What does that do? So then I have to put, you know, my fraud and abuse hat on and say, well, we can't give free devices, right, we can't guarantee reimbursement. So I guess, from my perspective, it's one of the frustrations in terms of is there another way to trigger it earlier other than there's got to be claims in the system.

DR. REPKA: So we have open microphones as well, that are available, both corners. So, Larry, so we have to come in with our homework done.

David.

DR. GLASSER: Chris mentioned earlier that, you know, the commercial carriers are often an even bigger black box than the MACs, but we in the academy actually work with the commercial -- get requests for evaluation of coverage determinations, and over time we've learned what they tend to respond to and what they tend to respond to is clinical data showing that whatever new gadget it is works. So, you know, if you can get your data published, that helps.

DR. REPKA: Great.

Alan.

DR. ROBIN: Yeah, hi. Alan Robin, no financial disclosures.

I have come from three points of view. First, I am a Medicare beneficiary, and thank you for paying for my healthcare.

DR. REPKA: Well, yeah.

DR. ROBIN: Two. I, up until recently, was a practicing clinician. And three, in 1990

we got one of the first confocal scanning laser ophthalmoscopes in the country or in the world, and the manufacturer at that time, who shall remain nameless, but a major brand, decided not to pursue it because they never thought there would be adequate reimbursement to cover their fully burdened cost of the device.

My concern to Larry and then to Pierre is how is your reimbursement scheme, for lack of a better word, inhibiting the development of better diagnostic techniques? AO really seems like a wonderful technology, perhaps, that may impact my healthcare, so when I get older and may need this, that it will not be available to me because of poor reimbursement.

DR. REPKA: Do you guys want to do that before we blame the Congress?

DR. CLARK: Whenever he's speaking, I'm going, because it's not really Medicare's job, and I think that's the problem is we are in some ways bound by a budget and, you know, that budget neutrality. I do think that after distribution of the slides, which were developed by Dr. Rosemarie Hakim, there are three major pathways by which Medicare covers clinical research trials. I suggest you look at that, and that would be my suggestion to you who are in that mode and in that mindset, look at those three opportunities and actually come to us first with the trial going on. I think you're going to get a lot more attention if you are participating in some type of IDE trial. So, you know, again, I can't go beyond what the boundaries are around, and I'll pass it on to Pierre.

DR. REPKA: So Pierre.

DR. YONG: I totally agree with what Dr. Clark just said. I mean, we often look -- we do look to the -- like, to the recommendations of like the RUC committee as we assess -- you know, I forget how many codes we have this year, but we've looked at all of them, looked at them in comparison to, you know, their valuations in comparison to other similar codes within a family and how they're currently valued within the CMS payment scheme.

But then, ultimately, they are all budget neutralized.

DR. REPKA: Yeah, budget neutral, just so everyone knows, is the -- CMS is only allowed to spend a certain number of dollars calculated based upon the past and with a slower rate of growth than the medical marketplace has done. And so that's our ultimate black box. Go ahead.

DR. BUCKLAND: So I'm a little confused about the RUC. It seems if we have an imaging device that reduces the burden on the clinician, the reimbursement cost goes down. The reimbursement --

DR. REPKA: Got it.

DR. BUCKLAND: -- goes down.

DR. REPKA: David --

DR. BUCKLAND: So you don't have to answer that, so I have a hypothetical for you. So Luxturna is reimbursed, the gene therapy, at $850,000. So let's say the adaptive optics improves patient selection to double the successful outcomes. So what would be the reimbursement path, just hypothetically, then, for an AO system in that application?

DR. REPKA: Go ahead.

DR. GLASSER: I mean, it's a completely different payment system, and that's part of the problem.

DR. REPKA: Yeah, I mean --

(Off microphone comment.)

DR. REPKA: No, I think that that's the key issue with that answer. I mean, unfortunately, that's different outcomes for two different types of medical interventions.

Yeah, Cindy.

DR. MATTOX: I would just say that that's a whole other potential model, right? You start to look at things that can be -- I hate to use the word bundled but, you know, brought

together to make an impact on patients, and if you identify a patient with a retinal ganglion cell that's about to die and you give them something based on that information and then prove that you have restored that function, there could be something set up around that. It doesn't exist right now, but you would hope that it could get to that point.

DR. GLASSER: Yeah, Cindy's telling -- I'm telling you why it can't be done under the way the system is currently configured, and Cindy's telling you how the system needs to be reconfigured so it can be done.

DR. REPKA: Allison.

DR. BUCKLAND: We don't really have the power, right, so we don't have the power to change the system, I think.

DR. REPKA: Well, you're a voter. I mean, as comical as that may seem, it's without people getting worked up over the issue and figuring out ways to change the Medicare policy. Now, clearly, the Medicare policy is like the third rail, as is always said, but change does happen. Part D happened.

MS. SHUREN: And I would say those kinds of conversations are easier to have and more likely to happen on the commercial side where they are further along on the value-based medicine spectrum than Medicare is. They just have more flexibility, and Medicare is bound by statute, and I think that's where companies are starting to think out of the box in terms of where does my modality fit along this, how can I actually impact it, how can I impact cost, and you might be able to come up with some kind of agreement with a commercial payer to use some kind of value-based payment system at least for a period of time, you know, while you try to prove your point in terms of the health economics around your product and clinical outcomes.

DR. REPKA: Allison, would you target one of the companies, or how would you develop a strategy for, you know, the commercial approach?

MS. SHUREN: And I don't do commercial pay stuff, so I'm going to say I would work with consultants who have good contacts because the hardest part in the commercial payers is getting in the door and finding the right people to talk to. Medicare is wonderfully transparent that way, and you can find the right people to talk to. You may not always like the answer, but you at least can find them. And then also look at the payers who are doing more interesting value-based, you know, payment systems now and work with, you know, ophthalmologists who are out in the community, who are potentially working with payers who have different models and have different agreements out there and target them first.

DR. REPKA: Great. Any closing comments from the panel? Other comments?

(No response.)

DR. REPKA: Larry, I was going to ask you one closing question, and that's you guys have long had flexibility on an LCD level at the individual payer -- the payer level. Now, with the change in the carrier advisory process to going more national, is that going to make it harder in vision or easier to get a device covered?

DR. CLARK: That's a great question. I think one of the aspects, and I don't want to leave on a pessimistic note in something that was trying to be good, but one of the aspects of the 21st Century Cures is that when coverage is expanded on the local level, we have to go back through the process, something that we did not do before, and we have to give an explanation of why we did that. So I asked you to look at rationale for determination of corneal hysteresis, think about that if we add a new skin substitute, so I'll keep it out of this audience, we have to explain why we added that particular product. Now, the problem is going -- you know, I understand that we're headed towards complete transparency and that's good, but then the maker of X gel versus Y paste or whatever product is going to want to know why we decided this other product was included in our policy. And then there is a pressure, which I think is a good one, to standardize our coverage across the country.

But you put those two dynamics together, and I see that every time we expand, we have to go at least through the open meeting and say we added X gel because we found that it created more fibroblastic activity in burn patients, and we have to explain that's our thinking, we did it on the basis of this article, and that's going to slow things down, and the maker of this OCT might not like this OCT with the add-on that you had. And I see that transparency is good, but we may have a little bit of an unwieldy product.

DR. REPKA: Thank you.

I'd like to thank the panel for participating this afternoon, and I'd like to ask Dr. Eydelman to come back up for some closing remarks. And maybe she'll tell us that she got none of her questions answered.

(Applause.)

DR. EYDELMAN: I would like to start out by thanking the planning committee, who took about a year of really hard work and education, many, many countless Wednesday night phone calls to put together today's agenda. I want to extend special thanks for all the speakers for coming and sharing their thoughts and being so well prepared in their talks, and all the moderators and panelists for sharing their thoughts and answering difficult questions. We truly broke new ground today on many fronts. We asked difficult questions, and I think we identified a number of areas that can only be addressed if we continue to work collaboratively.

I would like to hope that each one of you thinks of today as a beginning, not a one-day forum that was nice to attend, but it has to be the beginning. It has to be beginning of everybody in this room who took their time to attend, the professional organizations, academia, industry, patients, groups on reimbursement, to come together in a sustained format and continue these conversations, continue identifying the areas that were just touched upon today and trying to find solutions. And we at FDA will be happy to

continue to work with all of you. With all of your help, I'm sure we can continue to improve regulatory science in ophthalmic imaging devices. Thank you.

(Applause.)

(Whereupon, at 4:33 p.m., the meeting was adjourned.)

C E R T I F I C A T E

This is to certify that the attached proceedings in the matter of:

PUBLIC WORKSHOP - FORUM ON LASER-BASED IMAGING

April 8, 2019

Silver Spring, Maryland

were held as herein appears, and that this is the original transcription thereof for the files of the Food and Drug Administration, Center for Devices and Radiological Health.

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Official Reporter

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