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CO-SPONSORED PUBLIC WORKSHOP – BIOLECTRIC IMPLANTS AND PUBLIC HEALTH IMPACT

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University of Pittsburgh

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M E E T I N G

(8:30 a.m.)

MS. NGUYEN: Good morning and welcome to our public workshop on expediting innovation of bioelectronic implants for vision restoration. This effort today is cosponsored by FDA and the University of Pittsburgh.

My name is Tieuvi Nguyen, and I am the Director of the Division of Ophthalmic Devices at FDA. And thank you to all of you that have participated today and have joined the webcast for what we believe will be a really remarkable workshop. The purpose of the next two days will be to provide a forum for all stakeholders, including clinicians, researchers, regulators, and patients, to show their perspective on important topics that will help expedite the development of bioelectronic implants so that more effective treatment options can soon be made available to patients. We look forward to an exciting program that promises to bring unique and diverse perspectives on this topic.

So before we begin, one housekeeping note, at anytime during today's webcast, you may email us your questions by clicking the ask a question icon which looks like a little thought bubble on the bottom right side of your screen. We'll try to get to as many of these questions as possible. Also recordings of our webcast will be made available on the FDA website following the conclusion of the workshop.

So to get us started today, I'm delighted to introduce Dr. Malvina Eydelman. Dr. Eydelman is the Director of the Office of Health Technology One, or OHT1, at the Center for Devices in Radiological Health at FDA. In addition to ophthalmic devices, OHT1 is responsible for the regulatory oversight of dental, ENT, respiratory, anesthesia and sleep

disorder devices. Welcome, Malvina.

DR. EYDELMAN: Good morning. My name is Malvina Eydelman. I am the Director of the Office of Ophthalmic, Anesthesia, Respiratory, ENT, and Dental Devices at FDA's Center for Devices and Radiological Health. Thank you for joining us at our two-day workshop cosponsored with University of Pittsburgh on expediting innovation of bioelectronic implants for vision restoration. I am privileged today to welcome all of our workshop speakers, moderators, and panelists, and our audience including clinicians, regulators, researches, industry representatives, and of course, the patients. Patients are at the heart of all we do.

CDRH vision is for all patients in the United States to have access to high quality, safe and effective medical devices of public health importance first in the world. This is the driving force behind our workshop today. We believe that no person should be left behind in healthcare. CDRH is committed to advancing the development of knowledge for safe and effective technologies to meet the needs of all patients.

We have identified health equity as one of our strategic priorities. Bioelectronic implants for vision restoration are medical devices implanted in or around the retina or visual cortex that use electrical stimulation to provide a level of vision restoration for patients with profound vision loss due to disease or trauma. For the purposes of today's workshop, the organizing committee agreed to the following definition of the profound visual loss, visual acuity of 2400 or worse.

This definition is consistent with categories four, five, and six of the World Health Organization's International Classification of Diseases Eleventh Revision. However there's

a slight difference in that we're also including a visual acuity of 2400, and we're not considering visual field in our definition. The number of diseases that lead to profound vision loss are rare diseases. In United States, rare diseases are defined differently by law for drugs and biologics versus devices. Overall, the vast majority of rare diseases lack FDA approved therapies.

The product that demonstrates promise for the diagnosis, treatment, or prevention of a rare disease or condition is considered an orphan product. Orphan products often experience special challenges for medical product development. Outcome measures and biomarkers are often lacking. There's complexity in identifying the appropriate endpoints. Many sponsors are academics or small companies with little regulatory experience.

Patients with profound vision loss have limited treatment options. As of today, there's only one FDA-approved bioelectronic implant for vision restoration in the U.S. Second Sight Argus Retinal Implant was approved in 2013 for patients with severe to profound retinitis pigmentosa. While there has been significant research in the area, no other device has obtained marketing authorization. Our 2013 investigational device exemption guidance for retinal prostheses outlines a number of considerations and will be discussed later in the program.

However, there are a number of key questions that need to be addressed in order to expedite innovations of these technologies. Putting patients first is an empty promise if it only applies to some and not all. No person should be left behind in healthcare. Not only do we need to make sure that patients with profound visual loss are given the same resources and opportunities as others, we must recognize that these patients have different

circumstances. We need to identify and allocate the appropriate resources and opportunities needed to reach an equal outcome.

During this workshop, we will focus on ensuring the conceptualization, design, and innovation of bioelectronic implants and address the population for which they are intended. I want to extend a special thank to the 15 patients who have agreed to participate in our program to assure that we can better understand their needs and the challenges they face in access to healthcare and health technologies. We believe that patient input is valuable throughout the total product lifecycle of a medical device, from discovery and ideation to clinical testing and on to post-market monitoring.

We look forward to hearing their points of view and incorporating their input into all aspects of regulating bioelectronic implants. In order to increase opportunities in evidence generation for patients with profound vision loss, in addition to traditional objective assessments, we need to consider clinical outcome assessments which provide subjective information about how a patient feels, functions or survives.

It is important to note that they differ by the reporter. There are clinician-reported outcome measures, observer-reported outcome measures, performance outcome measures, and patient-reported outcomes or PROs. You will hear much more about these later in the program and about their core underlying principle of structured data collection.

I want to thank our outstanding organizing committee for their contribution to this workshop aimed at facilitating innovation and technological advancements for the bioelectronic implants for vision restoration.

To achieve these objectives, we've fashioned a two-day agenda. Today we will be

begin with a session on public health impact of bioelectronic implants followed by a session on technology and regulation. And we will finish with a much-awaited session on patient perspectives.

Tomorrow, we will begin with a discussion of safety evaluation followed by clinical outcome assessments and patient preference. We will then move to a discussion of effectiveness and plus market consideration. We will conclude with a unique session on government agency opportunities for device innovation.

We recognize that utilization of novel approaches can be best achieved by working collaboratively with stakeholders. We know that we can achieve better outcomes in protecting public health when we integrate different perspectives, experiences, resources and expertise from each participant in the medical device ecosystem. We hope that by bringing together all stakeholders for this workshop, we will advance solutions that promote innovation of bioelectronic implants for vision restoration.

Thank you again for joining us today. I look forward to the discussion and to collaborating with all of you on our continued efforts together.

MS. NGUYEN: Thank you, Malvina, for that great introduction to the workshop.

We will now move on to our first session of the day. In this session, we have lined up an impressive group of speakers that will provide an overview of bioelectronic implants and discuss important health topics that need to be considered for these devices. We will first hear from Dr. Jose Sahel, Chair of the Department of Ophthalmology at the University of Pittsburgh School of Medicine and Director of the University of Pittsburgh Medical Center Eye Center. Dr. Sahel is a clinician scientist working on retinal degeneration and developing

novel vision restoration therapies. Welcome, Dr. Sahel.

DR. SAHEL: Good morning. Thank you for attending this workshop on bioelectronic implant therapy. I have been tasked to introduce the first session by discussing why we need bioelectronic implants, which should be an obvious answer, but in view of the recent past years, this question is an important one.

Full disclosure, I have been involved in this field of academic research but also the development of various products. And the most relevant interest is funding by the Department of Defense for (indiscernible) project and funding by Pixium Vision to complete a trial, and GenSight Biologics, as well as for a different implant camera Prophesee.

Why do we need implants? It's because the impact of blindness is still extremely strong. A couple of years ago in JAMA, there was a review of the main conditions that are considered by citizens as the worst, and blindness was coming first of all, even before cancer and Alzheimer's disease. So this is considered as a major cause of impairment, and the bad news is that there is an expectation that the number of blind people is going to double by 2050. And the person affected with low vision are expected to triple by the same time.

So there is not yet, despite all the important development in therapies that have been occurring over the past few years, any evidence that blindness is receding. And some of the reasons is the complexity of visual system. Some are access to care. But for the sake of today, I'll focus on the untreatable cause of loss of vision.

As a reminder, which obviously is not necessary, vision starts at the level of the retina and is processed from the retina to the lateral geniculate and more importantly to

the visual cortex. So it's a continuous processing of information that starts at the retina with various pathways dealing with movement, direction, contrast, color, and these are carried out from the retina to the brain.

The first steps of vision are recurring at the level of the retina and actually in the depth of the retina. As a reminder, also, human vision is complex research because there is not only dark -- and light -- vision, but even more importantly central vision which is directed by visual attention and ocular movement towards the center of the retina in the small area called the fovea or foveola with high visual acuity and extremely (indiscernible 00:14:05) details as emphasized by Renoir in his painting illustrated when he was depicting the Mrs. Renoir. The face is very crisp, the rest of her body is fuzzy. When we move our eyes, at each area of that is put into focus and align to the macula becomes high resolution which means that we need to restore not only central vision with high acuity vision, but also peripheral vision for mobility and a lot of the daily tasks.

Unfortunately there are many conditions that are affecting both central vision and peripheral vision. The most well known for central vision is age-related macular degeneration, but also conditions that are impairing peripheral vision. Initially dark -- vision and then peripheral vision -- and retinal pigmentosa and end up with -- vision and eventually loss of central vision. And there are conditions that are producing a mix of that like diabetes -- or glaucoma that are associating both central and peripheral defects.

Patients affected with this type of condition have a lot of issues and important to this symposium is going to be the interviews of patient affected with this condition and they are going to tell us what is impacting mostly their daily lives. From my own experience and

the experience of many people that have been published, there are different objectives when trying to restore vision. We tend to think about reading, and we'll see that this has been part of many trials. But actually even more important is face recognition, the ability to recognize faces, the ability to recognize objects, and in connection to face recognition, the ability to recognize emotions.

In parallel, Oriontation and independent locomotion are extremely important tasks of daily life that patients would like to get back or to protect. I tried to use -- in a review what could be the potential scope of therapies in, for example, degenerative conditions like age-related macular retina pigmentosa, potentially age-related macular degeneration. The ideal therapy would be to cure the disease by correcting the cause of the disease like the genetic cause in retina pis pigmentosa. This could -- gene replacement or gene editing, totally protect vision and prevent any loss of vision.

In determining stages of a disease, what you would like to do is to protect the remaining vision, and this is attempted by trophic factors. At length, the stages of the disease when there is a loss of most of the vision if not all, there are attempts to restore some level of vision by optogenetics or prosthetic therapies, and for the sake of today, prosthetics. But the amount of vision we can hope to restore is no longer a normal vision. You are aiming at restoring partially vision which would be some level of contrast detection, shapes, potentially Oriontation, and reading.

When you look at the spectrum of therapies, it turns out that the less advanced the stage of a disease, the smaller the size of the therapy molecules or antibodies or even vectors are quite small as compared to some therapy, and for the sake of today,

prosthetics, that present a pretty sizeable implantation which means that it can be pretty invasive.

Focusing on the prosthetic vision now. What prosthetics and for what condition? If we talk about retina degenerations where photoreceptors have disappeared as a consequence of various processes, the attempt is to restore photo detection. This can be attempted either by bypasses, if it's bypassing the photoreceptors and directly targeting the Ganglion cells that are forming the optic nerve, and this has been at the core of the -- of prostheses like Ar gus for example.Other approaches of trying to replace photoreceptors, and this is aimed and produced by implanting under the retina in the location of the photoreceptors is subretinal implant. That can be wired or wireless.

Other I've tried stimulate directly the optic nerve, and this has been done in a couple of centers. But because of the backing of the fibers, it's unlikely that you would get high resolution. All these approaches are assuming that the optic nerve function is still preserved, and that the inner retina is still able to function. But there are conditions where the optic nerve has been severed, has been degenerated, like glaucoma for example. And then the only possibility would be to put directly to the geniculate or to the cortex using cortical stimulation.

So there are already currently three types of approaches a epiretinal, subretinal, and cortical that are being developed. All of these started many years ago, thanks to the work of Mark -- who was able to demonstrate in patients with advanced stages of retinitis pigmentosa that these patients were able, despite the total degeneration of photoreceptors, to detect some light, some phosphenes and even some shapes, despite the

very important degeneration of the retina.

So you could possibly aim at reinducing some level of visual perception using prostheses. And we tried at that time, we -- in Geneva to determine what would be the ideal resolution that could help to read letters. And we found that by degrading the signal in healthy individuals, that until you get to the level of 800 pixel, possibly 300 pixel, it would be still the ability to recognize letters. And this was also attempted by looking at the reading strategies. Depending on the number of pixels, it's totally random or it can be pretty well aligned, and this corresponds to a level of vision that could be useful.

We also tried to determine how many training sessions would be necessary for that. And the team of focus have demonstrated that if you have a resolution of 300 pixels or less, you need many sessions, probably up to 60 sessions to get up to some level of recognition, a range of 60 to 70 percent. If you have more than 500,close to 600 pixels, you have the ability to read letters and words becomes much better after a far less number of resolution sessions.

Another question is do you need just more pixels or do you need also more contrast? And it turns out that if you degrade information and you look at what level of resolution you get, the gray level, the ability to have many gray levels are very important in terms of visual resolution. So this was done while many groups were first starting to develop prosthetics.

The first group was really Mark Humayan's group. He implanted six patients with 16 electrodes, and they were able to show that there was some detection, not really a good -- because you're stimulating many Ganglion cells at the same time. And some viability

among patients -- but still, this was paving the way, and Mark Humayan is going to speak later to really demonstrate a lot of this and just hinting that is a short review. The ability to produce a better resolution using 16 electrode, which was the Argus II, which was really paving the way to all the other prosthetics. And this Argus II using a camera, the stimulation through wire of an epiretinal prostheses that was placed at the surface of the retina on the macula, was able to -- in patients some level of reading, and this is the fondness of an implanted patient.

And I am not going to talk too much about the results because Mark will do so. But as you may know, many of the response of these trials, it was possible to demonstrate that patients could recognize squares, recognize lines, and the movement of light, some level of contrast, but also the ability to read some letters which led to a registration of Argus II. But unfortunately, a few years later, for lack of enough market or enough results, this product disappeared which is really one of the issues we are going to discuss later which is the follow-up of this patient.

Another group, two groups actually in Germany were working in -- and the group of -- was working on the subretinal implant with many more electrodes, close to 1600 electrodes, but with only one return electrode that was aiming at stimulating the subretinal space. So this is a prostheses that was developed after being in Germany many, many years but comprised partially of wired system but also a light activated system with a large panel of electrodes that could be activated in its original space.

And this led to a stimulation by various electrodes, photodiodes, and also wired electrodes. But this still required also because of the wires a very complex surgery to

connect it to the stimulator. And it was possible to implant this patient and to obtain a good location of the implanting in some of the patient with subretinal implant, and then they started to report similar outcomes. But interestingly, the level of resolution obtained despite the number of electrodes was not better than the one observed with the Argus II, at least to my knowledge.

Another group of Daniel Palanker, and we soon partnered with Daniel Palanker on this project, was working on the wireless original implant and Daniel is going to speak a bit later, but I'm not going to describe too much of the technology, but each electrode has its own return electrode, and we are close to 400 electrodes with our wireless activated by light, in bright light, for a camera. This led to a clinical trial in my center in Paris with several patient implanted, and this is implant in the macula, and this was targeting patients with age-related macular degeneration in contrast to the others that were targeting end-stage RP, and as you see the location of the implant is original at 65 --. Daniel will probably show you the visual outcomes in every patient and also the ability to combine central and peripheral vision, so I won't insist on that.

In parallel, groups have been working on cortical implants. So -- many years ago, also the -- group, and more recently, the Orion project which was using electrodes from the Argus project implanted at the surface of the retina in the -- and those are interesting paper, and you'll see hear from that by Daniel I'm sure, but you'll hear from that in the sessions. But stimulating the cortex and the ability through a very clever algorithm to be able to monitor letters.

A group of -- in the Netherlands was able in primates to obtain high resolution with

multi -- thousands of electrodes, and this led to temporary implantation in patient in Spain that was reported two years ago. All of these technologies are still in the making, but if you look at what happened, for most of them, the Argus II, as it appears the IMS has disappeared from the market, the subretinal implant by Daniel Palanker and Pixium Vision is currently in clinical trials, but this is the only one. Our groups in Australia and in Japan that are still developing prostheses and the cortical implants are in the making.

There are still many issues that need to be assessed, and this is what we are going to discuss about with the community today. One is the safety, how do you assess the safety in the trials? We have experienced surgeons and a very good team surrounding the implants, and you don't, when this is on the market, and this is used by many more surgeons in many other patients.

How do you assess if efficacy? We tend to think of efficacy by visual acuity, but you've heard many testimonies from the patient, visual acuity is not the main thing because there are many alternative technologies. So what is the most meaningful? How do you assess that using patient reported outcomes, performance based test, real-life assessment. All of this is going to be discussed, and there are going to be specific sessions dedicated to that. How do you perform this assessment? How do you determine that there is a real benefit to the patient? How are these technologies going to be accessible? What patients are going to benefit? What stage of the disease, currently it's for the end stage of the disease? Where are these patients going to be treated? You certainly need experienced surgeons. Could be neurosurgeon, retina surgeon, orbital surgeons, but also you need a really good rehabilitation team surrounding and a very good psychological environment.

When and what is the stage of the implantation is another question. What is the follow-up of the patient that has been treated, and we have to realize that this is currently developed by small, very weak companies is a very volatile industrial landscape which means that patients have to be aware that the follow-up of this technologies is sometimes difficult to obtain. But at the same time, it does produce some benefit to the patient that has to be assessed and produced.

And to go back to a demonstration of efficacy, we are going to discuss at length the different metrics, especially how do we determine what is beneficial to the patient. Is one line of visual acuity beneficial? Or should we think different? Should we think really about what the patient experience is about, and we have to get outside our comfort zone of reliable highly standardized, precisely measured clinical test, and we will see a lot of these tests as they're being developed including -- and real-life assessment into a very messy world, a world of patient-reported outcomes, questionnaires, subjective assessment, performance-based tests, and this is going to be at the core of the discussions in the coming days.

So I just tried to give an overview of the field why we need implants, and there is competition in the field as you will see. There are also new technologies emerging which is good news. Importantly, we need to make sure that these technologies that show some promise and have shown promise in other indications are going to become available to our patients, and they're well assessed very safe and long-term follow-up for the benefit of our patients. I thank you for your attention.

MS. NGYUEN: Thank you, Dr. Sahel, for that wonderful overview. Next we'll hear

from Dr. Thiran Jayasundera, Professor of Ophthalmic Genetics at the University of Michigan.

DR. JAYASUNDERA: Good morning. Thank you very much for this invitation to speak to you today about the psychological considerations in patients with inherited retinal diseases. I am located at the University of Michigan, and we have a clinic for patients with inherited retinal disease, and we have experience in implanting the Argus II visual prostheses some years back. These are my financial disclosures.

Emotional distress in patients with vision loss is very prevalent and this is particularly more prevalent in young and middle-aged adults. And as these conditions lead to ongoing visual loss, the distress that patients have may also worsen or be continuous.

So when we describe how a disease progresses, we do these types of studies where we document how the visual field would worsen the vision would worsen, and this is just an example of what we did for -- and mutation prudent patients with retina pis pigmentosa. But what we don't often ask is what are the difficulties and limitations and distress that these patients experience.

In order to answer those questions, we came up with two PROs, the MRDQ and the MVAQ. These were published in the American Journal of Ophthalmology in 2021. We used a theory called item response theory in which basically by asking a number of questions will affix you along a curve of having low disability or low anxiety or high disability or high anxiety. The MRDQ and the MVAQ were validated in patients with inherited retinal diseases. MRDQ has seven domains of visual function, and MVAQ has two domains of anxiety based on whether the anxiety symptoms are rod-photoreceptor based or cone-

photoreceptor based.

When we looked at our patients, what we found is that there's a striking correlation between disability and anxiety. The worse someone's disability is in their visual function or functional vision, the worse their anxiety is as well and vice versa. This is -- this correlation holds when you control for vision measurements such as visual acuity. So two people with the same level of visual acuity, the person who has worse anxiety will have worse central vision disability.

This is particularly true, this correlation, you can see the lines are steeper for patients with better vision. So patients with much worse vision, this correlation is less strong. When we look at night vision disability and rod-function anxiety, again we see this correlation. And this is when we control for the visual field area. And we can use different targets to measure the visual field area. And this is what's called a I-4e Isopter, and this is using the III-4e, typically used to determine driving eligibility. You can see that the anxiety correlates with the disability.

One of the questions we wanted to ask was whether the generation of having visual symptoms affected anxiety. And initially when we looked at the raw data, which is the blue line, you can see that the longer you wait or the longer you have the symptoms, the worse the anxiety might be. But when we control for a number of variables, you see that this correlation doesn't exist.

But what does exist is that the number of vision symptoms you have does affect anxiety patients with inherited retinal diseases have. This anxiety/disability correlation may be even stronger for patients who are African American. In Michigan, we have a small

group of African American patients with inherited retinal diseases, and so we have a wide confidence interval here. And it was a great joy to implant the Argus II back in 2014, and these are some images that were captured by photographers and media of the successes of this visual prostheses around the country.

And here you can see one of our patients using the Argus to help navigate. And so soon after we implanted a number of patients, we actually had a meeting of the providers, the physicians, and rehabilitation specialists from around the world in Michigan to really optimize how we can implant this visual prostheses. In terms of optimizing patient selection, the process that we took in Michigan and we highly recommend, two screening visits. The initial visit, what's important is really have your patient understand -- have realistic expectations of the outcomes, and you review the risks and benefits. And in visit two, what was really important for us was to have occupational therapists evaluate the patient for success of implantation and of the device after implantation.

And our conclusions were that the factor that correlated with a good outcome were having reasonable expectations, supportive family members, having familiarity with the technology, and having baseline functional abilities and cognition. Rehabilitation is very crucial for success and use of visual prostheses like the Argus, and you can do an in-clinic rehabilitation. But also what's really important is community rehabilitation at the patient's home.

So these are some of our patients have in-clinic rehabilitation. And a really strong recommendation for rehabilitation is that we use objects that the patients can use at home to improve functionality. Consultations at home have a very positive effect on the patients'

level of engagement and motivation. Teaching the patient to use Argus II particularly as a spotting tool and the rehabilitation specialist seeing the patient prior to the surgery and screening the patient is very important.

After we implanted our patients, we really wanted to understand the motivation that led to success post implantation. And we used a theory or applied a theory called the self-determination theory SDT model and to understand how a patient's experience and motivation led to success after the implantation. So the closest analogy to use of a visual prostheses is hearing aid adoption where motivation has been strongly shown to impact the success of hearing rehabilitation.

And our Argus II patients, some of them were frustrated and dissatisfied, and you know that often leads to the device not being used at all. And so this is very important to understand motivation factors in order to limit unhappy individuals. The SDT model really comes down to three types of motivation, amotivation or no motivation, extrinsic motivation, intrinsic motivation. Extrinsic motivation is further divided into identified regulation and external regulation where identified regulation is more positive and it's more intrinsic where there is -- where one sort of does something for the value for them, as opposed to extrinsic regulation which is more of a punishment or a direct reward.

So as I said, SDT has intrinsic motivation, and external regulation is when an individual experiences an obligation to behave in a specific way to satisfy people around them or to receive a reward. And identified regulation which is a form of intrinsic motivation is a more positive form of motivation where the person chooses something for themselves for the value that it has.

So what SDT proposes is that to have successful help behaviors such as the use of a visual prostheses, you have to have autonomy, competence and relatedness. And a person feels autonomous when they value the behavior and its importance. They feel competent when they know how to use it. And relatedness is really the positive relationship they have with their healthcare provider. And they're more likely to be successful if they have internalized the value of the activity.

So we found that our Argus users were influenced by both identified regulation and intrinsic motivation. And they found that engaging with the device was their own personal decision and was for their own good. We didn't see extrinsic regulation, external regulation or extrinsic motivation and amotivation, and people decided to opt to have the device to improve their quality of life. A reason that we had such positive feedback from our patients, which was definitely -- this was a formally conducted study, was perhaps because we had been very positive provider/patient relationship with a number of people including genetic counselors, physicians, surgeons, and rehabilitation specialists.

So in conclusion, in hearing aid technology, autonomous motivation also referred to as identified regulation has been shown to positively impact hearing aid adoption and satisfaction. And so when we look at visual prostheses and design the implementation of them, it's really important to consider the motivational factors of our patients. That will enable the successful usage of the visual prostheses after implantation.

Thank you very much. These are my coauthors in Michigan.

MS. NGUYEN: Thank you so much, Dr. Jayasundera. Now on to our next speaker. Our presenter is Dr. Nabin Paudel. He is a vision scientist currently working as a research

and innovation manager at Retina International. At Retina International, Dr. Paudel leads socioeconomic research studies that have implications for policy actions to ensure universal access to diagnosis, treatment, and care for people affected by inherited and age-related retinal degenerated disease. Dr. Paudel.

DR. PAUDEL: Thank you very much for this opportunity to present the socioeconomic considerations in this workshop. My talk will particularly focus on socioeconomic impacts of inherited and age-related retinal diseases because we think that these are the diseases that could benefit from the bioelectric implants which is the main focus of this workshop.

I am representing Retina International which is a global umbrella organization of patient-led foundations and charities that support research into rare inherited and age-related retinal diseases. And our offices are based in Dublin, Ireland.

These are the conflicts of interest. We see research grants from several industry partners, as well as not-for-profit organizations across the globe. Before we move on to the socioeconomic impacts, it is important to understand a little bit of introduction to inherited and age-related retinal diseases. In reference to the inherited retinal diseases, these are the group of heterogenous diseases that lead to partial or complete visual impairment or blindness due to progressive degeneration of photosensitive, mostly photosensitive, cells within the retina.

And the one on the left is of the commonest -- this is the list of the commonest forms of inherited retinal disorders, which are retina pigmentosa, Usher Syndrome, Stargardt's Disease, Leber congenital amaurosis, -- disease, cone dystrophy, cone-rod

dystrophy, Achromatopsia --.

And most of these conditions have degeneration in the photosensitive cells which is rods and cones, and in some cases there is degeneration of retinitis, retinal pigment epithelium, a special kind of cell there in the retina, as well as in some cases there is the degeneration of the choroid, which is a vascular nerve that supplies blood to the retina.

Now in relation to the age-related macular degeneration, it is the commonest form of age-related retinal disease, and again, as the name suggests, it is age-related. So in most of the cases, it is in a person, people above 55 years of age, but it can operate as early as 45 years. In this case was well, there's a progressive and gradual degeneration of the retina pigment epithelium as well as the photosynthesis cells which is rods and cones, which can lead to complete or partial blindness.

Now let's look into the prevalence of these diseases. If you look at the inherited retinal diseases, these are kind of rare diseases. And the prevalence in Europe and North America is approximately 1 in 3500 individuals, and the overall prevalence of the 10 areas that was listed in the earlier slide is 0.03%, so that means 3 out of 10,000 people are likely to have these conditions. It is in terms of the public health importance, it is a leading cause of -- IRDs are the leading causes of visual impairment and blindness among the working-age population.

Now let's look at AMD and the global prevalence of AMD is about a 8 percent, so 8 out of 100 individuals has some form of AMD, especially in populations between 45 to 85 years. And so the fact is AMD is more common in Europeans and whites, and in relation to public health importance, it's the fourth leading cause of blindness in people over 50 years

globally. So what this means is both of the conditions have a significant public health impact because they're the leading causes of blindness in the working-age population or people above 50 years of age.

Now let's look into the socioeconomic impact, and when we talk about the socioeconomic impact, we're talking about the cost incurred due to these conditions. And broadly categorizing, there are two types of costs that's incurred due to any sort of disease, that's individual cost and the societal cost, which I'll discuss a little later.

When you look at the individual cost, is the cost incurred due to diagnosis and treatment, and some of the individual costs are also included in individual costs which are costs that are incurred due to traveling to appointments, home modifications that are necessary due to the condition, nursing home care due to the disability, due to the condition, and hospital visits due to falls. As we all know that people with visual impairments have higher risks of falls, and also assistive technologies to navigate through their daily lives.

Now in relation to the societal costs, the costs are wellbeing costs and productivity costs. And I'll discuss about these costs in more detail in the next slide.

So now expanding on the earlier slide, I mentioned that they are broadly characterized into individual cost and societal cost. But if you further break it down, it can be categorized into four different cost categories which is direct cost, indirect cost, wellbeing cost, and productivity cost.

In relation to the direct costs, these are the costs that are incurred due to eye appointments, diagnosis, and treatment-related costs. Indirect costs are the costs that are

incurred due to travel, formal and informal care, hospitalizations due to falls, emergency visits due to falls, nutritional supplements which are common among AMD patients, and optical assistive technology which are common among AMD as well as ARD patients.

Now the other category is the wellbeing cost which is based on a non-financial approach where the pain, suffering, and the pre-mature mortality of the disease is monetized based on the global burden of disease study where they calculate the disability-adjusted life years and utilize this method to monetize the wellbeing cost. And the other one, other category, is the productivity cost category which is a calculated using a foregone income loss due to the early retirement or reduction in working hours.

A couple of things that I'd like to highlight in this slide are the differences in the cost categories. The direct costs and indirect costs are the tangible costs. As you can see, these are the cost amounts that are spent by the individuals. And in relation to wellbeing costs and productivity costs, there is an intangible costs. These are invisible costs that are not actual spent by the individuals, but it has a secondary effect in this society. It actually impacts the economy as a whole.

So these are the intangible costs. The wellbeing costs and productivity costs are intangible costs, whereas the direct costs and indirect costs which are visual costs are the tangible costs.

The other thing I'd like to highlight is that the impact of the disease, not only for the patients but also their caregivers. But the challenge here is that caregivers don't realize, caregivers are mostly friends and family members, and they don't realize that they are the caregivers. And there's an impact to the caregivers which is challenging to capture.

And in relation to the productivity costs, the caregivers might have to limit their working hours, and in some cases, take early retirement to take care of their loved ones. So there's a different -- there's not only the impact on the patient, but also to the caregivers, family members and friends as well.

Now we learned from the earlier slides that there are different cost categories, but if you really look into the literature in the previous published studies or grant literature, we don't really see the comprehensive approach of the costs incurred due to these conditions. There are a handful of studies that have reported the tangible costs, the direct costs, the indirect costs, and it's clear that AMD is an expensive disease. Also IRDs are expensive diseases, and they have a significant cost to the patients, but if you look at the intangible cost. There's questionable evidence. There's very limited evidence in the literature in relation to reporting the intangible costs. But we know that these costs have effects on the society and the economy as a whole.

So in this talk, I'm going to focus on key, a few studies that have actually reported the tangible costs as well as the intangible costs, and report the original results from those studies in this talk.

So as I mentioned earlier, there are only a very few studies, very few studies that have actually reported the comprehensive cost categories, comprehensive cost implications of these diseases in society and to these individuals. So my presentation will be based on these three studies that have reported the tangible as well as nontangible costs incurred due to inherited retinal diseases as well as the age-related macular degeneration.

Now looking at the socioeconomic impact, the results for the socioeconomic impact

of inherited retinal diseases, as you can see that in the countries they studied, the impact of the IRDs is ranging from 42.6 million euros to almost $32 billion depending on the country studied. So this means that there is a significant impact, a considerably substantial impact of these diseases on society which ranges from millions to billions of dollars per annual. This was a report that has come from Retina International in the year 2019.

Now similar to the impact of inherited retinal disorders, the impact, socioeconomic impact of advanced AMDs is also substantial. In this study in three countries, two in Europe and one in North America, the socioeconomic impact for, annual socioeconomic impact of advanced or late-stage AMD was a range from 449 million to 42 billion euros. And the socioeconomic impact of this disease in Bulgaria was 449 million, whereas the socioeconomic impact of this disease in the advanced form of AMD were $43 billion in the USA. So as you can see, these diseases have a substantial impact in the society and economy as a whole.

Now in the earlier slides, we saw that the economic burden of these diseases was significant but in this slide, I'm going to just try to demonstrate what is a cost per person for these conditions. And this is an example of the late-stage AMD where the cost per person varied from 19,685 euros to 43,000 almost 44,000 euros which was approximately $50,000. So in the European countries, it was approximately $22,500, whereas in the USA, it is almost $50,000. So this means that AMD is a very expensive disease. It incurs a significant -- a significant cost to individuals as well as to the society.

So in earlier slides, we learn that there's a significant socioeconomic burden of these diseases, but it's important to understand what is the driving -- of the socioeconomic cost.

And if you further break it down to different categories and look at the percentage contribution or percentage counted by that category in the overall cost, you see that the direct cost in the IRDs, the direct costs are only a fraction of the costs. The majority of the costs that are incurred to the society are the productivity and wellbeing costs in most of the countries we studied, which accounted for 62% to 66% of the total cost.

So if you look at the AMD as well, the direct and indirect cost was only a fraction of the total cost which ranged from 19% to 22% in these countries we studied, and approximately 74% to 77% to 84% of the total cost was incurred to productivity as wellbeing lost. So it seems that the major drivers are the -- the driving factor, driving category for the major socioeconomic cost is the productivity and wellbeing element which is very rarely reported in literature. And this is very important to understand that these are the elements that literature needs to be considered in the future clinical trials and therapy interventions and things like that.

The cost categories are better visualized using this graphic which is an iceberg analogy where the direct costs and indirect costs as you can see, are just the tip of the iceberg. They're only a fraction of the cost, total cost. And the majority of the cost, that's wellbeing cost and the productivity cost is the main body of the iceberg which is the main driver of the higher socioeconomic -- high socioeconomic impact of these diseases. So the costs that are incurred on day-to-day life, that's direct cost and indirect cost, that's just the tip of the iceberg. But what is really impacting the society is the wellbeing cost and the productivity cost, and these are the body of the iceberg.

Now in the earlier slide, I said that increased wellbeing and productivity impact was

the main driver of the socioeconomic costs. But what does that really mean? So in this slide, I'm just going to explain a little bit on the greater impact of wellbeing and productivity, what that means by having greater impact on wellbeing and productivity. That means that people with these conditions, have higher prevalence of wellbeing issues such as anxiety and depression. In these studies that I mentioned earlier, in patients with IRDs, anxiety was reported by 74% to 85% of the population, and depression was reported by 65% to 74% percent of the IRD population.

Similarly, the age-related macular degeneration population, anxiety was reported by 44% of the patients, whereas depression was reported by 41% of the patients. This is much higher than the -- supported by the general population. So that is what is meant by higher impact on wellbeing.

Similarly, what's meant by higher impact on productivity? It means that there is a reduced workforce participation among this population with these diseases. In the Republic of Ireland and the UK, it was found that people with IRDs were approximately 56% and 40% less likely to be in a paid employment than the general population. And in the -- from the AMD study, it was found that 26% of the patients labeled AMD reported job loss and 55% of them reported job reduction due to their condition, due to AMD.

So this is what's meant by -- and these numbers are significantly higher than the normal general population. This is what is meant by the greater impact on wellbeing and productivity in this population.

So from the earlier slides, I think it's now clear that the economic burden of IRDs and AMDs is substantial, but has there been any great investment in research in addressing

these conditions? This slide will just demonstrate the total economic burden versus investment in research across different conditions as compared to IRDs and AMD. In Ireland, there was a study in 2019 which demonstrated that the cancer costs, costs related to cancer treatment and diagnosis were 7802 in the year 2019. And in the same year, the cost for IRDs was 28,000 pounds, which is clearly higher than the cancer costs, cancer-related costs, costs related to cancer treatment. Similarly in the UK, the associated healthcare costs per person for stroke was 22,429 pounds, and in the same year, the cost for IRDs was 25,140, which is clearly higher than the stroke-related costs.

But if we look at the investment in cancer and stroke, there's clearly higher investment in cancer and stroke than in the IRDs and AMD areas. So this is an example of impact, the total economic burden versus investment in research, particularly in the USA. We say that this is a comparison between Parkinson's Disease and the inherited retinal disorders. We see that the economic impact of Parkinson's and IRD are close, although there is a slightly higher impact by Parkinson's Disease. But if you look at the funding attracted in the same year, it is more than 20 times higher than the IRDs. So given the fact that the economic impact is not that higher, the funding attracted is 20 times higher, which is -- which clearly indicates there is a more need for support or funding required for the treatment in IRDs.

Therefore the take-home messages from this talk is that inherited and age-related retinal disorders cause substantial burden to the society with costs ranging from millions to billions of dollars per year. As we saw in our slides, direct costs, the costs related to treatment, diagnosis, appointments for care, hospitalization, and assistive technologies are

only a fraction of the total costs incurred due to these conditions.

We see that wellbeing and productivity costs accounted for me that two-thirds of the impact in the countries studied. And given the fact that there's a similar cost burden to society similar to cancer, stroke, and Parkinson's disease, it clearly indicates that more investment in the field of IRDs and AMD research is required. And it is hoped that new treatment such as bioelectric implants, which is the focus of this workshop, will significantly reduce this society burden, particularly the wellbeing element as well as the productivity element of those who are affected by these conditions.

So with that, I'd like to conclude my presentation, and thank you very much for your attention. And if you have any questions or comments, please feel free to email me at nabinpaudel@retina-internation.org. So good luck. Thank you very much.

MS. NGUYEN: Thank you for your presentation, Dr. Paudel. It is now my pleasure to introduce Dr. Joseph Fins, Chief of the Division of Medical Ethics at Well Cornell Medicine. Dr. Fins will discuss important ethical considerations for these devices.

DR. FINS: Good morning. I'm delighted to be here to talk about ethical considerations related to bioelectric implants for vision restoration at the CDRH and the FDA. And I've entitled my talk Looking In because in a sense, I'm looking in from the outside of your space. My work has been in neuroprosthetics related to brain injury, but I think that there are a lot of common threads and common themes related to post-trial access that I think we can learn by the comparison and by analogic reasoning.

Of course we're all here to talk about the Second Site of abandonment of individuals who had retinal implants whose devices were basically abandoned by the manufacturers

ceasing to be in the marketplace. So these people who were able to see and have different kinds of live as articulated here in the IEEE spectrum article were left high and dry without any recourse. And I think this is an ethical imperative and really a tragedy in the face of success of neuroscience to be left by market forces that left them without visual abilities that they had hoped for and people had worked to achieve for many, many years and decades.

But as I said, I'm a neuro-ethics interloper. I don't work in the individual space, but for 25 years, I've been working as a physician ethicist and physician scientist helping to improve the diagnosis and treatment of patients with disorders of consciousness. Most notably though, in the minimally conscience state, and I worked as a co-investigator helping to frame the ethical use of deep-brain stimulation in the minimally-conscience state. And our results are published in *Nature* in 2007. More recently, I've been a collaborator on a DBS trial in moderate to severe brain injury as part of a brain initiative UH3, and I have my own RO1 to explore the experience of participants and their families related to that study.

And in that exploration of their narratives, I've learned a lot about how they think about post-trial obligations and responsibilities for another intervention that seemingly works. And I think there are lessons from neuroprosthetics in brain injury that can be applicable to implanted vision restoring devices.

So just to give you a little background in our work, our first use of deep-brain stimulation in a minimally conscience state was with a 38-year-old man who had had a very severe brain injury six years prior to enrolling in our study. He had initial Glasgow Coma scale of 3 which is as low as it can go without you actually not being alive. He progressed

over months to the minimally conscience state and had a stable baseline for years. He would sometimes respond to commands with his eyes. He couldn't speak. He couldn't eat. He was bed bound.

But with the deep-brain stimulator, he developed the ability to have improved cognitively mediated behaviors, limb control and oral feeding, in this double blind crossover study, and what was done was we put electrodes bilaterally into the interlaminar nucleus of the thalamus. You see here a CAT scan which shows the artifact of the metallic filaments. So this is a distortion into the thalamus. And he had approved abilities and functionality with DBS. So he could say six or seven word sentences. He could say the first 16 words of the pledge of allegiance. He could go shopping with his mother at Old Navy and voice a preference. He could tell his mother that he loved her for the first time in six years. He had improved limb control, and for the first time he was able to maintain his secretions and eat by mouth.

And this was, in a way, a restoration of his agency exmachina through the neuroprosthetics, through the DBS machine, he was able to participate in conversations. And it was the first evidence that DBS could promote late recovery from severe TBIs. Doing this work, I began to think about what do we owe these folks, and who -- who are in a trial? A trial works, at least for them, not yet if any treatment, and I came up with notion of non-abandonment at the neuro interphase. I believe it was the first time anyone talked about post-trial obligations for neuroprosthetics. And I articulated in this paper from 2009, the concerns that people who have these devices lack the community-based infrastructure to be maintained. They're dependent on specialty centers where they got their implant, and

they're dependent on battery replacement, stimulation parameter adjustments, hardware failures, things like ex-plantation, and the availability as a Second Site of the manufacturers to warranty and sustain these devices over time. And it's more challenging for devices that are still in a clinical trial, and you have to get a bedded (ph.) therapy. So it raised all these questions about post-trial access, ongoing care, fiscal responsibility, medical care for these individuals.

Now as we begin to think about the unique challenges of devices, I also think it's important to highlight the differences between devices and drugs. The FDA spends the vast majority of its time regulating drugs and not devices, we have the IB and the IMB. But if you think about, the realities are very different. You could have a drug that has a small effect for a lot of people, and it can be approvable and have a market space. Devices have to have a bigger effect for a smaller number of folks to have sustainability in the market, and the trials are smaller. In many ways, it's more like personalized medicine because you have to adapt to the anatomy of the individual. Whereas in drugs, there's a common biochemistry. These are indwelling devices that may need to be withdrawn versus a drug that's simply stopped. And there are longitudinal complications that may be different than drugs. So it makes phase four surveillance very different for devices and for drugs.

And then there's the clinical adaptation to the device, these positively disruptive devices that engender needs for specialized rehabilitation, psychosocial support. If you have somebody who had retinal implant and now have visual abilities, what kind of occupational therapy do they need to get back into the workforce in a different way? Do they want to go back in a different way? And then you have some biological changes.

These devices interact with the eye, with the brain, might engender neuroplasticity and changes that we really don't understand, and we need to learn how to manage. And this may lead to the need to recalibrate devices over time. So it's not just the implantation and the acute care, it's really a suite of interventions that are necessary over time to maintain this homeostasis, this symbiosis between the device and the participant.

So what is owed to these folks? And Henry Richardson, who was the son of Elliot Richardson, the Attorney General who would not fire Archibald Cox during the Watergate scandal, wrote this wonderful book published by Oxford University Press entitled *Moral Entanglements*. And what he talks about here is the presence of ancillary care obligations. He was mostly talking about medical researches who do research overseas and are precluded from providing any kind of medical care outside of the research intervention, and he began to question this dichotomy between research and practice. And I've written about how this argument is relevant to folks who have specialized neuro devices and our ongoing ancillary care obligation to provide interventions that are more like clinical care to support the research work that we're doing.

And Richardson has a nice typology that the degree of ancillary care obligation correlates with the novelty of the intervention, the uniqueness of that intervention, the depth of the relationship that is established with participants, and their degree of dependency on your expertise as an investigator to maintain, sustain, and support the device in this -- in you, the host. And he suggests a longitudinal moral entanglement and fiduciary obligation to people that I think is relevant to, especially so with folks with indwelling devices, whether patients or trial participants.

Now beyond the ethical obligations and the ethical ties here, I think there's also a scientific argument that is also overlooked when we talk about longitudinal responsibility for folks who have indwelling devices. And I think we can learn a lot by studying of these patients, these participants, over time. And I think you'd maximize the discovery and return on investment if the cost of the implantation of a deep-brain stimulator or a retinal device is really upfront, why don't we maximize that initial investment by studying people longitudinally? We can study the natural course of recovery with the device in place. Remember brains and eyes recover by biological mechanisms, not the length of trials which are often so very short, and it's dictated by market forces.

And if we have a long-term clinical trial over time, we can look at the effects positive and negative. The positive effects of elasticity, and the negative effects, gliosis, increased impedance at the neural interphase. And we can learn about basic mechanisms of sight and cognition, whatever the intervention is doing, and these become tools of discovery that I think we're short shrifting (ph.) the possibilities by having longitudinal trials. So it's not only the right thing to do ethically and morally, it's also the smart thing to do if you're doing clinical and translational research.

So what are some of the remedies that I'd like to propose? Well first and foremost, I think we have to adhere to the ethical principle of non-abandonment. Okay? We cannot have another Second Site scenario. You know, Second was one too many, okay, and this should never happen. We have to have respect for persons. We talk about respect for persons as a cornerstone of medical ethics, and we have to have a longitudinal fiduciary obligation to these people who are pioneering and helping us work at the vanguard of

scientific knowledge. We owe a lot to these folks who are volunteering to participate.

And I think there's a tri-part type set of obligations between the funders, okay, the government funders, industry sponsors and academic institutions who provide these clinical trials. Plus we have to think about insurance coverage that helps to fill the gaps. Fundamentally, I think there should be an enduring covenant articulated in clinical trials in consent of provisions and decisions by institutional review boards. So when an IRB looks at a clinical trial, they should say what is the post-trial access plan for this participant should it work? And I do think that the FDA should stipulate that at all future IB applications, IDE applications to the FDA, that they must stipulate aftercare plans and questions about post-trial obligations. I think that needs to be done in a regulatory space, and that would get a lot of attention, and it would also be a real catalyst to fulfilling the non-abandonment mandate.

Now this has to happen in a way that's sustainable, and you just can't mandate something that's unfunded. And I think we need to develop, also, public/private partnerships to fund this kind of support, this post-trial obligation, otherwise it would -- research development, and we don't want to do that either. And in this article written with Joe Pancrazio who was a program officer at the NINDS, and I and Gary Dorfman, we wrote about a pragmatic response to some of these ethical, fiscal, and regulatory concerns. And we suggested a public/private partnership and some modifications to the Bayh-Dole Act of 1980 which governs intellectual property, which is a space I don't have time to get into here, but I refer you to this paper.

Let me make some meta comments that I think transcend some of the pragmatic

concerns about the funding and the regulatory issues, and that is how this all relates to the civil rights and disability rights of individuals who have brain injury or visual impairment. And I wrote this essay in the Disability Common in the Op-Ed pages of the *New York Times* that's talking about injury and the civil right we don't think about. And I think that to deprive people with brain injury or visual impairment the ability to reengage with society through the miracle of these neuroprosthetics is to violate the Americans with Disabilities Act, and the mandate of the ADA and the UN convention on disability.

So this is an international question, it's not just a domestic concern. Both of these conventions and the law of the ADA, and I love this icon here from the lighthouse, from the lighthouse of San Francisco, is the right for people to be maximally integrated into society. And here you see an individual with visual impairment with a cane. Well we can do better than that. We have done better than that, and we should do better than that. And to deprive people of a retinal implant that we now know works and could be available to so many more who would want them, if they want them. We're not going to impose sight on people who don't want it. But should they want it, it should be available because that's how people can be maximally integrated into civil society which is the ethos of the Americans with Disabilities Act.

And to do anything less is not worthy of us as a country. This is not a red state, blue state kind of question. This is a purple state question. All of us should be able to rally around this mandate that here, these investments in science have produced these incredible interventions. And not to make them widely available is something that I just can't understand. I can't imagine. And we have to be aware that there are market forces,

but we shouldn't be constrained by market forces.

So I think the next chapter is moving from rights, the rights of people as articulated in the Americans with Disabilities Act, to capabilities. And here I'm thinking of the work of Martha Nussbaum and Amartya Sen, and they're talking about giving people the ability to flourish in human society. And I think we need to make the distinction between the ADA which accommodates the environment to the disability. So that's the cut on the sidewalk that allows somebody in the wheelchair to get from here to there, versus, and we recently wrote this article with my colleagues at Yale Law School, my students and fellows, proposing Americans with Abilities Act, that empowers individuals and adopts a capabilities approach.

So in summary, what should we do? We need to overcome -- we need to realize that the problem for retinal implants or DBS, there are specific challenges to brain injury and to blindness and visual impairment, but they're a common set of challenges. And we need to bring all of these spaces together, and I would suggest commissioning a National Academy of Science, Engineering, and Medicine rapport by the government to explore post-trial access. And I think that NASEM is the perfect place to do this because it speaks to the sciences, basic sciences, engineering, right, of course, these devices are the product of engineers, and medicine.

And this rapport should establish ethical norms for post-trial access for implanted devices that would enable legislative and policy remedies to adhere to the ethical principle of non-abandonment, which is a sine qua non, and also, that would affirm the rights of these individuals to have access to integrate in society by giving them the technological

capabilities that are now available but not widely disseminated to individuals who have visual impairment or cognitive impairment.

So let me stop here and just acknowledge my collaborators, my funder, and the families who've consented to participate in all of our studies and who've shared their insights with us in the broader clinical community. Thank you very much, and I wish I was there in person to answer your questions. But I hope this will spark some good conversation. Thank you. Good morning.

MS. NGUYEN: Thank you so much, Dr. Fins. Throughout FDA and the Center for Devices, patients are truly at the heart of all that we do. Hearing patients describe what it's like to live with a medical condition and be treated with the medical devices gives us greater insights as we consider new innovative medical devices and patient-centric designs and outcomes that are most important to patients. Throughout this workshop you will hear patients share what it's like to live with vision loss and the impact that it had on the quality of life and their family.

During these next two days, you will hear from patients with diverse perspectives. This includes patients without implants, patients with different types of implants, those that have just recently implanted, and others with more experience with their devices. A patient that has recently undergone implantation will have a long recovery and training period after surgery as the device is not immediately turned on. We believe it's important to hear from the different perspective from patients throughout their implant journey.

So with that, the next two videos are from Paige and Bill, two patients living with retinitis pigmentosa, who will share their individual experiences including how technology

has been integral in their lives.

PAIGE: My name is Paige, and I have retinitis pigmentosa. I have worked as a computer programmer and a director for a non-profit agency. I am now retired. I enjoy walking every day with my guide dog, listening to audiobooks, and doing genealogical research. I was diagnosed by RP when I was five years old by my family's ophthalmologist. I never had good light perception. My peripheral vision declined so much in my mid-20s that I chose to stop driving.

In my early 40s, my visual acuity was worse than 20/200, so I learned how to use screen-reading software for my computer, and I got my first guide dog. My vision declined to just my perception in my 50s. I had iridectomies in both eyes, and last year, I had cataract surgery in both eyes. I've been under the care of ophthalmologists for 55 years and retinal specialists for the past 25 years. I traced my RP back to my third grade grandmother who was born in Germany in the 1830s. I can remember going to family reunions as a child and thinking there are a lot of blind people here. I have seven nieces and nephews and two of them have RP. Vision loss has impacted my life choices. For example, when it was time to choose a career, I ruled out airline pilot and surgeon and photojournalist because I knew eventually I would lose my sight.

I grew up on a small farm with a close family. Unfortunately in my experience, rural settings tend to have little to no public transportation, so I'm quite dependent on family and friends. When I moved to an urban setting, I had many more options for transportation, and I felt more independent. But at times, my personal -- and I didn't get to visit family as much as I would have liked.

Vision loss impacts social gatherings like church and club meetings and parties. There's no find a friend command for a guide dog. I miss reading letters and picking blackberries and scuba diving and tutoring elementary-school-aged children in math. As I've lost vision, I've lost those activities.

BILL: Hi, my name is Bill, and I am a vision rehabilitation specialist for the United States Government. I've been doing this job for approximately eight years. I was born with a condition called retinitis pigmentosa. I was diagnosed within the first 18 months of my life, and RP has impacted my life in lots of ways, specifically to the way that I live my life every day. A lot of daily living activities such as reading, driving, and moving safely throughout my environment. Communicating was a challenge. It was helped out by the invention and the progression of technologists. People who have invented assistive technology have helped folks like myself in many ways, including being able to use a computer, being able to communicate with coworkers, customers, colleagues, anyone who I need to communicate with has -- I've been able to use assistive technology in order to make that happen.

As a child growing up, I was the type of kid that like to explore quite a bit. And I liked to explore my environment, move around through it, and see what's out there, and it brought up some challenges with respect to being able to do the types of things that other kids enjoyed doing. So throughout school, I was always pulled aside from physical activity such as physical education, and I had to very often push hard and fight for the ability to do the things that every other kid was doing. And as an adult, I've continued that process in pushing for the ability to be treated and viewed as any other human being even though I

have a tremendous amount of vision loss.

MS. NGUYEN: So this concludes our first session today. Thank you to all our speakers this morning. As you heard during our last session from Paige and Bill, vision loss can have psychosocial and physical impacts that affect not only how one functions daily, but also how they feel about their dreams and aspirations. It is important for us to remember that vision loss is multifaceted, impacting all aspects of a patient's life.

So with that, we will now take a short break for 10 minutes. Our next session will include overviews of different device types in this technology area and a discussion from FDA who will provide a regulatory overview. See you soon.

Welcome back everybody. We have an exciting lineup of speakers next who will provide different overview of different types of bioelectronic implants currently in development. Our first speaker is Dr. Daniel Palanker, Professor of Ophthalmology at Stanford University, who will provide an overview of subretinal implants. Dr. Palanker.

DR. PALANKER: Hello. My name is Daniel Palanker. I am professor of ophthalmology at Stanford University, and I will review the topic of subretinal prosthetics. Patents related to the technology I develop in this field are licensed to Pixium Vision from Sanford University, and I serve as a consultant to Pixium Vision.

Retinal signaling begins by conversion of light into changes in photoreceptor potential, namely hyperpolarization. Those photoreceptors with increasing light levels which decreases the rate of release of glutamate on the second order neurostimulator, primarily the bipolar cells. These cells integrate signals from multiple photoreceptors and perform spatial and temporal filtering. They're the non-spiking neurons that can be

motivated by amplitude or duration of the stimulus. And they transmit this information also as it changes in the rate of release of neurotransmitter onto Ganglion cells. Through the spiking neurons, they convey information into the rate of spikes action potential that propagate through optic nerve to the brain. And there are about two dozen types of Ganglion cells that represent different aspects of the projective images. On cells respond to increasing light. Off cells respond to decreasing light. And there are cells responding to motion, to various -- cells having different sizes of receptive fields, different properties of contra sensitivity and so on. Together they encode the image that then propagates to the brain and merges into the vision of the person.

In terms of acuity, normal vision corresponds to 20/20 visual acuity, which corresponds to 10 micrometer special frequency on the retina, and -- by pixels of 5 micrometers or smaller. 20/200 is the level of legal blindness, and corresponds to pixel zie of about 50 micrometers.

It is also important to keep in mind that a large number of pixels is required for object recognition even in a familiar environment. The studies with healthy volunteers have demonstrated that with complex background in 25 degrees of visual field, that requires about 8,600 pixels. And with a clean background of about 3,500 pixels which are for the recognition of familiar objects in -- environmental are shown here. And so a large number of pixels is required to provide meaningful vision.

In retinal degeneration, patients lose photoreceptors, either over the whole retina as in retinitis pigmentosa, or in the central macular as in atrophic macular degeneration. But in the retinal cells, bipolar and Ganglion cells and amacrine cells are preserved to a large

extent. Therefore reintroducing information by stimulating the second order neurostimulator and subretinal approach provides an opportunity to introduce visual information through the visual system to the retina and thereby restore sight.

The subretinal approach targets bipolar cells non-spiking neurons so the signal can be moderated by amplitude or duration of the stimulus. And then we rely on transmission of the signal through the retinal network through Ganglion cells for generating the actual potential to propagate through the brain. Therefore preservation of inter-retinal network is important in this approach, and it provides preservation of multiple features of the natural signal processing in the retina as we will see below.

The studies of prosthetic vision were conducted first ex viva using, for example, retina explanted onto multi-electrode arrays where we can measure spiking of Ganglion cells in the response to either natural or a light stimulation or stimulation with electronic implants. This way, for example, we have seen that antagonistic center surrounds the structure of normal receptor fields in the retina shown here for natural vision, is preserved through the electrical stimulation of normal retina and the electrical stimulation of the -- retina in RCS -- shown here. Antagonistic surround is important for a contrast enhancement in the retina.

Many other features are preserved such as flicker fusion. We see not only on but also off, and on and off responses which correspond -- which illustrate complexity of signal processing in the retinal network, even with simple excitatory stimuli by electrodes. The antagonistic center surround are preserved probably by the proper function of the remaining amacrine cell. A similar sublinear summation of subunits propagating through

different bipolar cells to Ganglion cells which enables much higher resolution than average size of receptor field. Contrast sensitivity of prosthetic vision is about six times lower in the retina than natural, and therefore it should be compensated as partial loss of contrast by image preprocessing before projection onto the implant.

And the dynamic range of prosthetic response received is lower than natural by a factor of three approximately, which should be kept in mind in designing the stimulation. Some implants have been placed in animals. Here, for example, you can see test of subretinal -- in rats, in RCS rats. You can see that the implant in subretinal space is very close to the inner-nuclear layers as they're bent where bipolar cells reside. And therefore, it provides sufficient stimulation of bipolar cells.

In viva, we perform different studies including acuity measurements and resulting gradings. And here you can see comparison of natural vision in rats which is about 20 micrometer on retina acuity limits and the measurements with pixels of 75 micrometer and 55 micrometer in size that match -- their acuity matches the pixel pitch. Several of the systems tested ex vivo, and in animals have been commercialized and tested clinically as we will view below.

So first system which in clinical trials was Alpha IMS/AMS retinal implant by Retinal Implant AG, a company operating in Germany, where the implant is basically a camera where every pixel converts light into electrical current with some electronics for image preprocessing. This camera is powered with a cable, flat cable, shown here, that propagates under the retina, from the implant, through the sclera, under the skin and behind the ear, where it gets its power. Initially it was through transdermal connector. And

later through RF power supply like a cochlear implant. These pixels are 70 micrometer in size. There are 1600 of them 40 by 40 array. Each of them has an electrode of 30 micrometer in diameter.

The Nyquist sampling limit for visual acuity and the -- pixels is 20/280. The system has been tested in patients. Out of 44 trial participants, visual acuity using Landolt C, shown here, was measurable in six patients, ranging from 20/2000 in acuity to 20/546 in two patients. None of the patients came close to the theoretical limit of acuity for the 70 micropixels 20/280. And unfortunately, implants were failing over time, over a few months, and therefore the company closed in March 2019.

Another implant was developed by a company called Nano Retina in Herzliya, Israel. It's called NR600. This is also a camera. It is photosensitive pixels about 26 by 26 ratio. In some electronics, to convert image into stimulating current to deliver to the electrodes which have this peeler (ph.) shape of 150 micrometer in height and 100 micrometer in pitch. And even though the implant was placed on top of the retina, the electrodes penetrate through the retina down to bipolar cells. That's why I included it in this review because in terms of stimulation, it is subretinal.

So far, about 9 patients have been tested in Belgium, Italy, and Israel. And they report perception of light but not really a full vision. Here is an example of a patient recently reported by Nano Retina. The patient shows grading acuity at and below .1 cycle per degree which is 300 lower than normal. 30 cycles per degree in humans corresponding to visual acuity of 20/6000. In grading period of 10 degrees, the 3mm is larger than the actual sensor array, so it's not really acuity, it is more a light sensitivity. However, using this

light sensitivity -- patients can use it for increased ambulation. Here is the patients walking along the white line. So it certainly helps Oriont the patient, the blind patient, in space.

Another system is called PRIMA. It is made by Pixium Vision. This is our technology licensed to Pixium Vision in Paris, France. This system has augmented reality glasses where the camera catches some image that is processed and projected into values using infrared light at 880mm. Each pixel converts photovoltaically into electric current to stimulate bipolar cells nearby. And traditional normal retina is not affected because this light is invisible. The first generation of the implant is 2 by 2 mm. It is 30 micrometers thick and has 100 micrometer pixels. And the visual field is about projected to be 18.5 degrees -- implant in subretinal space in AMD patient.

So the first tests were conducted on five patients, feasibility trial. Subretinal implantation was found to be feasible and safe. Now with three years follow-up, the chip and the retina and its performance are stable. No post-operative decrease in peripheral natural vision, which is very important benefit of the completely wireless design. All four patients with subretinal chip placement demonstrate monochromatic shaped visual perception in the former scotoma with letter acuity very close to single pixel size 1.72 pixels on average, and a pretty narrow spread was -.15. or in fractional acuity units from 20/438 to 20/564 or vertical limit of 1 pixel corresponds to 20/420.

What is also very important with central prosthetic vision and natural peripheral vision are perceived simultaneously even though we know that the retinal chord is this prosthetic vision is not exactly normal, but the brain can perceive those images simultaneously. The second trial with 37 patients is ongoing now in Europe and in U.S.

In another approach called suprachoroidal, a company called Bionic Vision of Australia developed an array designed to be placed in the sclera -- below the choroid, and it is deemed to be less invasive since it doesn't touch the retina. But because the larger distance between the implant and the target cells, the electrodes are large, about 1mm in size, and resolution is expected to be low, so it was designed for low resolution peripheral vision. It has been tested in three patients, and here's one example of one patient where electrodes can be seen here separated from the retina by a difference of about half a millimeter and then increasing over time up to a millimeter.

Patients can localize light in this system. And one patient could even see letter, very large letter acuity of 20/4450 to 20/21,000. Very low vision.

Regarding the future development, there is one company progressing towards clinical trial in Taiwan called Iridium Medical. This system is based upon flexible CMOS array. It includes 4096 light-sensitive pixels with differential amplifiers, and the system is powered by radiofrequency collected with this RF coil placed on the conjunctive in front of the eye. And the coil on the glasses can communicate to this implant and the coil. So this system has been tested successfully in pigs, and clinical trial is planned in Taiwan.

These PRIMA implants, since the clinical trial demonstrated that the prosthetic vision may just decrease pixel size very -- the question is how to decrease pixel size. Just scaling pixels down with bipolar electrodes where each pixel has an active and return electrode is very difficult because electric field is confined to small and small size and doesn't penetrate deep enough to activate bipolar cells in the nuclear layer. So address this challenge, we pursued two different paths. One of them is 3-dimensional electrodes, either peelers or

honeycomb shapes. Both are based on migration of the cells between these 3-dimensional features to improve proximity to target neurons and better confine electric field.

The other approach is based on optical current steering where neighboring electrodes are used to collect light, so they use -- not just -- illuminated pixels. In this way, the penetration depth or distance between neighboring electrodes is increased to one pixel pitch instead of about one-quarter of a pixel in the bipolar design, and this improves the stimulation. The smaller pixels, so we have demonstrated recently, that acuity in rats was 40 micrometer bipolar photovoltaic pixels, and this sort of current steering matches the pixel pitch. With 20 micrometer pixels, it reaches the natural resolution of 28 micrometers in rats.

And this 3 millimeter of the implant that we expect to have in human patients, it will include about 20,000 pixels at 20 micrometer sites. So the expected acuity was 20 micrometer photovoltaic pixels in AMD patients, ranges between 20/250 for flat implants to 20/100 with 3-dimentional electrodes. So that's kind of the expected future developments in the next generation implant of PRIMA.

This review is limited to commercial systems that have faced clinical trials. But it's important to add that several labs in the world study other approaches to subretinal stimulation, including various --, nanoparticles, and if these efforts succeed, we may see more technologies coming to clinical testing.

With that, I would like to conclude this review, and I will be happy to address any questions you might have.

MS. NGUYEN: Thank you, Dr. Palanker. Next with be a presentation from Dr. Mark

Humayun. Dr. Humayun is a professor of Ophthalmology and Biomedical Engineering at the University of Southern California. Over the past 30 years, he and his colleagues have pioneered the development of the only FDA approved, epiretinal prostheses, and he will be speaking on this topic today. Thank you, Dr. Humayun.

DR. HUMAYUN: Hello, this is Mark Humayun, and I will be presenting on epiretinal implants today. Unmet medical needs such as complex retinal diseases in the cases of retinal degeneration require a multifaceted approach, pharmacological, gene therapy, cell-base therapy, surgical therapy, and implants. Today I'll be speaking about implants.

It is not well known in the public, but certainly in the ophthalmic community it is well known that the eye receives many implants after cataract surgery. Once the cataract is removed, a lens implant is placed into the eye and is actually the world's most common implant. Approximately 3.3 million of these interocular lens are placed after the removal of cataract in the U.S. alone. Today we will be talking about implants in the back of the eye for the retina, how to really work in the area of the macula, which is the center part of the retina, and how to engineer and restore sight using devices that are placed either on top of the retina or underneath the retina.

So bioelectronic sight is an approach taken for retinal diseases, and I'll be speaking specifically about inherited retinal degenerations which lead to photoreceptor loss of rods and cones. These conditions are termed retinitis pigmentosa, have an incidence of 1 in 4,000, with many genetic mutations, and gene therapy, although has shown success, only addresses a very small fraction of these total retinal degenerations. Whereas bioelectronic solutions, should we be able to develop them, bypass damaged neurons and stimulate the

remaining cells of the retina. And by doing so, are indicated for all genetic defects. One device could effectively treat all genetic defects. And so there is a distinct advantage and enthusiasm for developing these devices.

In other talks, today you will be hearing about visual cortical implants, which are not in the eye obviously, but focused in the center of the brain. There are also some other research areas looking at lateral geniculate and optic nerve implants. And also in the retinal area in and around the eye, there are different places to put implants, and you'll be hearing about subretinal implants in another talk. And I'll be focusing primarily on epiretinal implants.

So epiretinal implant is shown here. It has a camera which is worn in the glasses which captures an image such as this letter E. Then the camera sends this information to a visual processing unit which is not shown in this animation, and then once processed, the information is sent into the implant wirelessly. Both power and data are sent in, and the implant, then, is able to use this information and here you see the wireless communication. The implant is able to use this information and using tiny controlled electrical impulses, stimulate the remaining cells in the retina. It's called epiretinal because it lays on top of the retina. You see here the Ganglion cell side and stimulates the inner-retina. And in spite of the fact that these photoreceptors are damaged.

So in doing so, this information is sent to the brain, and is implant effectively jumpstarts an otherwise blind eye. Here is a picture of the Argus II, one of these epiretinal implants. It was approved by the FDA as a humanitarian use device for patients with light perception vision from retinitis pigmentosa. It has a camera just as the animation showed.

Now you can see the transmitter coil also in the center. There's a video processing unit that we spoke about, and again this can be worn, the video processing unit can be worn as shown on this mannequin around the shoulder with a strap, around the waist, or even worn in the pocket of a shirt.

The implanted part is the receive which receives information and the electrode array that goes into the eye. And most of this device goes around the eye where there's lots of space, and only the electrode array goes into the eye. And here is a patient who's received the Argus II implant, and just to demonstrate that you cannot tell if a patient has the implant because this is well-positioned in and around the eye, underneath the conjunctiva tissue of the eye. So it's not visible to the naked eye. Only if we look in with an ophthalmoscope can we inside the eye and looking in, we can see the electrode array, and also using another imaging modality called OCT, optical clearance demography, we can actually evaluate the distance between the electrode array and the retina.

So the Argus II was not only approved in the FDA, but it was approved in Europe and many other countries as you can see on this world map. And it was implanted in many centers around the world. Initially, the type of vision you could see with these large letters with this device, this was in -- this was in 2008. This patient, again, has light perception vision only, but you can see with the Argus II, she was able to see these letters that are pretty large.

So then fast forward 10 years, in 2018, you will see in the next video, with software improvement, the Argus II device is being used in Korea, and the patient is able to see much smaller print as you can see in this next video. She can read simply Korean sentences. And

she can also write using this device. You can see that she's able to write very complex Korean characters and also write these characters in a straight line across which all this requires very good vision to be able to do this. But the Argus II was not necessarily or primarily for allow patients to read, it was more important for Oriontation and mobility effect and including activities of daily living.

So it enabled patients to stay within the crosswalk, you know, be able to sort different color clothing, be able to participate in various activities such as bowling, locate doors and windows, and do fun things such as watch fireworks or to even see Christmas tree lights. But since then, Second Sight no longer is manufacturing the Argus series implant. The Argus implant had excellent durability lasting 15 years in some cases, and in many cases, more than 10 years. And Second Sight announced that it's focused on the Orion visual cortical prostheses and therefore no longer is manufacturing the Argus series implant at this point.

However, a new device called IMIE 256 has been developed. It has 256 electrodes by another company. It's easier to implant; it's smaller, in spite of the fact that it has many more electrodes, and it has a more sophisticated camera input and software. Here's a picture comparing the Argus II implant to the IMIE 256. Each of the black dots are electrodes, and you can see that there are more than 400 percent more electrodes in the same area, roughly, of the Argus II. So much denser electrode pattern which should provide better visual acuity.

So here you can see that we will play the video showing the use of this device. The letter, actually, the subject is seeing is at the very center of the screen is so small that I

made the letter purposefully large in the corner so we can see it, but just remember that the letter that this patient is seeing is a very tiny letter in the center of the screen. And again, the magnified letter in the corner is just for us to be able to track what this subject is seeing in the center of the screen, and the subject does not see the magnified letter that we're seeing.

Here is a picture on -- dim light mobility. So actually, the patient is in this very dark room to the left. And once again, in order for us, the viewers, to see what he's doing, we have shown an infrared image to the right. Again, the patient does not see the infrared image. The patient is walking more in the dark environment, and you can see, and I'm going to play both so you can see how quickly he's able to follow this line and go to the door. I'll play both videos at the same time. You can barely see on the dark screen, but if you look at the infrared image which is just for us, you can see how quickly this patient is able to walk in a very, very otherwise dark environment and go right to the door.

So next I would like to talk about an area that has been of our interest for a while which is providing color vision, and why color vision? Well it provides important object recognition information. For example, if you were to see these two round objects, and even if I were to tell you they're fruits, it would be difficult to tell. But once we give some color to it, you can tell one is a green apple and one is an orange.

So color at lower resolution does have content information. And so, again, if you're walking on a road with some grass and trees, if you give it some color as you see here, you can tell the grass from the road, and it helps with mobility as well. And so one of the ways to do this is to actually use frequency encoding, which is changing the frequency of the

stimulation, and some of the motivation for this came from the Benham top phenomenon which spinning a top at different frequencies gives you different colors. So taking this motivation, we asked the question can we actually encode color with the electrical stimulation of the inner retina. And we remember we do have a video processing unit, so we can talk the information from the camera and take the video processor and then send information to different electrodes at different frequencies.

So for example, if some electrodes, we wanted that part of it to be blue, we could send that at different frequency. And other parts, if we want it to be yellow, we could send those electrodes different frequency. So this is work of that Lan Yue did with us. She's now at the FDA along with Javad and Professor Lazzi and myself. And what this shows is in the middle is probably the easiest way to understand this information is that as the Y axis is the number of electrodes, on the X axis is the frequency. But as we increase the frequency, we can see the change from yellow to purpose in most cases of these electrodes.

So again, increasing the frequency at higher frequency, you do get a change of the color going from yellow low frequencies to the purple or bluish color in the high frequency. And I provided the reference where this manuscript was published in *Scientific Reports*. Also, you can create two different colors like I was just mentioning on different electrodes simultaneously. So you can send different frequencies to different electrodes and get different colors at the same time.

So in conclusion, what I've shared with you is that epiretinal prostheses have provided some restoration of vision. The surgical technique and placement of these devices is critical to achieve the maximum functionality. There is training with device that is very

important after surgery to realize the best visual gains, and improvements in software and hardware are being implemented in the new generation of epiretinal prostheses and are showing improved restoration of vision.

So at this point, I'd like to acknowledge the Argus II team that helped with the data that led to the approval of this device. Also acknowledge the IMIE 256 device which is the new device, and again, that was published here. I'm providing the reference so those are you interested can look it up in this Translational Vision Science and Technology Volume 10 journal.

And lastly, I would like to acknowledge our funding sources, the National Eye Institute, National Science Foundation, Department of Energy, Department of Defense, and DARPA, and also the efforts of our volunteer subjects. Without them, this wouldn't be possible, and this is a wonderful picture. Actually on the day of the FDA panel review when patients with the Argus implants actually went with the devices and wore them and actually were part of the -- were there to answer questions and participated as observers in this panel review. Thank you for your attention.

MS. NGUYEN: Thank you so much, Dr. Humayun. Now we will hear from Dr. Nader Pouratian, Professor and Chair of the Department of Neurological Surgery at UT Southwestern Medical Center who will provide a background on cortical implants. Thank you.

DR. POURATIAN: Hello, I am Nader Pouratian with the UT Southwestern Department of Neurological Surgery. Thank you for this opportunity to speak to you about visual cortical prostheses.

I'm going to start with a review of my disclosures. I have consultancies with the following companies, the most relevant here is with Vivani which is part of Second Sight with whom I did much of the work here in epicortical stimulation. We also share a grant from the NIH, from the brain initiative to explore this as a therapeutic option. The outline of my talk includes an initial discussion of the need for cortical prostheses, the history of cortical implants for vision restoration, the current generation of epicortical prostheses, early experience with the intercortical prostheses, and finally future directions.

What I hope that we get from this discussion is common themes and challenges that have been seen historically and across different modalities that we need to tackle as we move forward with developing this therapy.

In terms of the need, we all know that there are many people who are legally blind, and at the beginning of our exploration of cortical stimulation, we noted that retinitis pigmentosa was the only therapy for which there was an FDA approved intervention. That left many untreatable causes, and part of the challenge with blindness is that blindness can arise from injury to many different parts of the optic system. And the promise of a cortical prostheses is that it bypasses much of the early visual system and can potentially be agnostic to the underlying cause.

Now the idea of cortical stimulation or cortical prostheses for vision is several decades old thanks to the work of Brinley and Lewis. This is a publication from 1979 but builds on work that they had been doing over a decade before that, initially in sighted patients but then in blind patients. And they came up with the device that's shown here that is an epicortical device in interhemispheric fissure over the visual cortices and is shown

here in the radiograph. And patients had glasses that had a camera and a processing unit that then connected directly into the externalized units.

Part of the challenge was that there was a direct connection. There was always a risk of exposure to the elements, and this was not necessarily a long term solution. That said, they did a lot of work that was critical to our understanding of the promise of this therapy. We got our initial look at spatial maps with this work. And one thing I want to highlight here is the challenge of the spatial map. On the left here, you'll see the electrode array as it say on the cortical surface, this being posterior, this being anterior. And you'll notice that there is no 1:1 mapping of the cortical surface stimulation map and what the visual field representation was.

We see that again here. The numbers go sequentially across the array, but there's no particular pattern in where the phosphines are located. They also did some initial work looking at the effect of stimulation patters on the threshold for phosphine perception, which really laid the groundwork for some subsequent work that we did and others have done as well. But highlighting that this has been a longstanding goal to understand how stimulation affects the visual cortex.

Now when we set out to do this in, let's say, the modern era, we wanted to develop a cortical prostheses for previously sited patients who had no or bare light perception. And as we went about designing a prostheses, as a surgeon and as a scientist, but more so for my clinical perspective, I thought that we needed to really think about patient safety. And as far as the safety goes, we wanted to have a solution that took advantage of established surgical techniques so that there could be widespread adoption. Also we wanted a

technique that would minimize unexpected surgical complications.

And finally we were thinking about what might be clinically useful. What are our goals of stimulation? Was it provide perceptions of what was going on in the outside world or shadows or edges? These are the types of questions that we started thinking about as we thought about how we move the prior work of Brinley and Lewis in to the current era and how we make this practically available for a larger population.

Before we got too far ahead of ourselves, we thought it would be useful to really understand firsthand how we could stimulate the cortex, how consistent the response would be. As we used an off-the-shelf device and a 30-year-old volunteer in which we implanted this device which is normally used for epilepsy over the visual cortex, we did chronic studies in this patient. This is what the array looked like. Four contacts over the media occipital lobe with -- shown there in yellow.

And what we see are the illustrated phosphines for this patient in month 8 and month 19, and you can see there's relative consistency of where that phosphine was perceived. And so we show consistent localization, and we show that stimulation at different parts of the visual cortices resulted in perceptions of different shapes and sizes.

We're also able to do much more biophysical work to look at the effects of stimulation and to look at how we might tailor the stimulation in order to alter the perception of brightness, what the minimum thresholds are. And we came up with some very interesting strength duration curves that mimic what we see at the cellular level, although we're obviously stimulating at the microcellular level. I won't go into the details except to say that these types of experiments to define stimulation parameters and what

patients perceive or don't perceive are absolutely critical to moving the field forward.

What we did conclude from this study using an off-the-shelf device which I think is a very robust and easy way to get additional information about the potential of this therapy, when the phosphines are reproduceable and consistent over time, the phosphine thresholds depend on charged density, and it's independent of frequency or the burse duration. But what we didn't know quite yet was how we could modulate these phosphines on a continuous basis. You know, how can we get patients to perceive shapes? How can we have them perceive different sizes? Our initial patient volunteer had some color sensation, although only in the very periphery of the stimulation areas.

What about the temporal factors? How often can we stimulate? When do we get a sustained perception of a light versus a flickering perception of a light? There were also questions about frame of reference. What happens when the patient turns their head in one direction or moves their eyes in one direction? That said, these studies gave us a lot fo confidence to go ahead that with a purpose-specific device. And this work in collaboration with Second Sight led to the development of Orion I. This is technology that really leveraged the existing retinal prostheses which has a video camera, a video processing unit, and what was a retinal array which we adapted for cortical use.

We were fortunate to get breakthrough device designation from the FDA, and we were able to move forward with our early feasibility study with NIH funding as well. With the adaptation, what we created was a triangular shaped array that was epicortical that slipped into the interhemispheric fissure. It's shaped to conform the occipital pole. There's a skull-mounted device with an RF coil which is used for communication as well as external

powering of the device. This is an image from the first patient that we had implanted with the epicortical array in the -- over the occipital pole in the interhemispheric fissure.

Ultimately as part of this early feasibility study, we implanted six patients, four of them at UCLA while I was there and two of them at Baylor, with varying durations of implants as shown there. What you will notice, again, is that there are many different causes for the visual loss. And so this type of technology is agnostic to the underlying cause of vision loss, as long as it's proximal to the primary visual cortex individual pathways.

Now I wanted to share a video of one of the patients using the device. This is someone who has no light perception and is doing a square localization task. And although not natural, you can see that he's able to use his head, move his head around, use the device, detect where the light is, and localize that box with quite a bit of accuracy as we'll see again in this next demonstration.

So if we look at the performance with square localization with this fully-implanted device now, distinct from Dobelle's device that had an externalized lead, we can look at one subject's performance with the device off in terms of square localization and where they pointed to. With the device on, you see much smaller error in terms of localization, which is quite impressive. This is across 6 subjects, and you'll see 5 out of 6 subjects performed significantly better on square localization with the device on than with the device off.

We also looked at direction of motion preference. And as you might guess, looking at lines moving in a certain direction, if you can't see anything, you're going to have a relatively even distribution across all different angles relative to the angle of direction. As opposed to when the device is on, you see a localization right around zero with some error

in direction of perception. I'm actually going to show you some work later on that might get us to understand this in a moment, but what you'll see is in all 6 subjects, all of them performed better with direction of motion performance, although it's questionable how much better and whether this is clinical useful. It's something that needs to be understood further.

Finally, ultimately what we're concerned about is not these tasks of square localization or direction of motion, but how these affect patients' function and their everyday life. And we use the flora, which is a functional low vision observer rated assessment. This is working with a vision therapist to rate the patients' use of the device. And what we see is that at six months, everybody who was using the device had at least a mild positive or a positive impression of the impact of the device on their function, and that persisted at 12 months as well.

Again, building up that idea that we can measure these objective outcomes, but sometimes it's important to look at the individual's specific experiences, I wanted to share some of these quotes that patients shared saying that they were able to find the cue ball without a problem on the table, able to see cars parked on the side of the street, openings in the sidewalk and up into driveways, able to correctly determine whether someone's moving from the left to the right or the right to the left, order patters on a small checker or a tablecloth. So what we saw was that patients were able to use this device on an everyday basis. If fact, I have stories of patients using it in everyday life, and it's quite astonishing to hear how they naturally are able to integrate it into some of their functions.

Now this is not to say that we don't have many challenges, and I think what this

work really showed us is that once you have an implant, you realize just how many more questions come up. One of the key things we started looking at was the affect of eye position on perception of phosphines. In this experiment, we tracked eye movements. We had patients look to the left, look to the right, look up or look down, and what we saw was that depending on which way they look, and you can see by the arrows there, they pointed to the phosphine being in a different location. Once we correct for eye motion, you get a very discreet localization of where that phosphine actually is in the spatial world.

Again, we can look at it here. If we stimulate two different contacts on the array, we might get a wide array of where they perceive those phosphines to be in space. But once we correct for eye position, they actually localize quite specifically. And two phosphines that seem like they're completely overlapping can actually separate in space once we account for eye positioning. And this lends towards the idea that eye position and head position really probably needs to be part of the algorithm as we think about employing these devices.

Now there is a big question about the spatial resolution of these devices and whether we need to have more electrodes, less electrodes, what is the effect of electrode count. This is work done with Dan Yoshor and Mike Beauchamp who are now at University of Pennsylvania in collaboration with our team and using the Orion device. But what they were able to show is that you could use differential patterns of stimulation to do current steering. So if you turn one electrode on by itself, you might see a certain area of phosphine. Turn another electrode on by itself, the phosphines in a different location. But if you turn them on with different relative amplitudes, you can actually find intermediate

areas of phosphine localization which increases the effective resolution of the device even though we have the highest channel count device available for an epicortical array.

Now they were able to use this to have patients actually draw out letters. And what they showed is that sequential stimulation with this current steering could actually result in perception of different letters, and patients were able to consistently reproduce patters of letters which can help us with decoding. This is in contrast to turning all of the electrodes on at once where it was hard for patients to interpret things.

Now I've started to allude to many of these challenges that we face, eye position, hand/eye coordination, what the effects of stimulation parameters are on perception, and what I'll say is is that although we have these beautiful visual cortical maps that map out eccentricity and polarity, it does not seem to map as cleanly as we'd expect. And so much of our work and much of the challenge that lays ahead is trying to detail these spatial maps in a more meaningful way.

I do want to highlight that there's been more recent work done with some penetrating arrays, and this was using a Utah array with an externalized pedestal only for six months over the occipital pole itself instead of in the interhemispheric fissure. And some common themes emerged. One is that, again, even though the electrodes are numbered in sequence, you'll see that there's not much of a pattern in the sequence of where the patient perceives the phosphines in the visual field.

So one would hope that it was sequential, 1, 2, 3, 4, 5, 6, and so on and so forth, but it's not. And so spatial maps remain a significant challenge. It is interesting, though, that despite what the maps would predict based on MRI studies, that there is quite a good

coverage of space with this microarray.

I will also highlight another consistent finding which is that these are very reproduceable phosphines. So if you stimulate contact 22, it's almost always in the same spot. 30 is in the same spot. 72 is mostly in the same spot, with one apparition there. One would predict that perhaps eye position or head position might have affected those results.

Now they have also done studies look at the biophysical stimulation and looking at the ability to -- the thresholds for eliciting phosphines, and very similar types of curves emerge even with intercortical stimulation. But the major difference here is that the thresholds for stimulation is around 70 microamps, whereas with epicortical stimulation, we're working in the range of 2 to 3 or 4 milliamps per contact.

They were able to show some functional differential between a big O and a little O with stimulation. But I'll say that patients are very smart about these devices, and whether or not they actually see what we think they're seeing or they learn to interpret it is a very important part of this prosthetic development as well. And it's made me realize that in many cases we are not trying to replace vision, but we're perhaps providing them with artificial vision, and rehab is a critical part of that process.

Still they were able to show some functional improvements with this device. It's important to know that there's other intercortical arrays, in particular work done by Phil Troyk to have a wireless microarray. And in this case, they've implanted a patient with several microarrays that are on the occipital pole, wirelessly communicating. And they haven't reported the results, although we know they have implanted a patient.

So I think what we conclude is that visual cortical prostheses can provide useful

artificial vision. The challenge of whether we can bring these phosphines together and make it something meaningful is all up to interpretation. I think in my opinion we are providing artificial vision. Reproducing vision as we know it is probably not in the near-term future. Phosphines are not equivalent to pixels of vision, and so we really need to understand many more things.

Some of the challenges and future directions, we need to define spatial maps and define methodologies for that. We need to define stimulation patters. We need to think about whether we're restoring vision or providing artificial vision, and how do we measure outcomes for people who have bare or no light perception. And is this really what we're aiming for, which was great in the Dobelle, where they were able to show someone driving a car in a parking lot? But maybe those aren't the goals that we want. We should think about how much improvement is necessary, and how much risk is acceptable.

With that, I'd like to acknowledge the extensive team that I've worked with to get much of this work done, as well as the other people that I've cited. It's an exciting field, and I'm glad to be here speaking to you about it. Thank you.

MS. NGUYEN: Thank you, Dr. Pouratian, for that great talk. Before we begin our last presentations of the session, let's hear from two patients that have received the same implant but who are very different stages of their journeys with their devices.

Larry is a patient with dry age-related macular degeneration who recently received an implant and has not received training on how to use the device. The next patient video will be from Jane who will -- who has had more experience and training with her implant. Please enjoy the videos.

LARRY: I'm Larry Randle, and I have dry age macular degeneration in my left eye. And it has impacted my vision quite severely. Of course here at this clinic now hoping to get some benefits from their expertise.

About five years ago, I had an appointment with my regular physician for a yearly check-up, and he said I believe you're getting dry macular degeneration. As time went along, I kept track of what was going on, and my son in law found this clinic here I'm currently involved with now. And I have had, since I've been here, an implant in my left eye in the part of the macular which is -- or did, degenerated, that won't affect any vision I had to begin with.

The implant that I have in my eye now has not been activated, so I don't really know what kind of benefits to expect other than I have some hope it's going to enhance my vision. And that's about all I know right now. I can no longer drive. I can't watch TV, and it just really changes your life. You have to watch where you step. Is there any inclines or stairs or anything like that? Everything -- you really can't see them, so you have to have somebody to help you or you have to be very, very careful.

So it has impacted my life very severely. And I'm so hopeful I can get some of that back.

JANE: My name is Jane. I've got dry macular, and I'm as a cashier. And I loved gardening and painting, and because of the dry macular, I couldn't continue. And I was diagnosed -- the reason I was diagnosed was when my husband my died and my sister-in-law died and my grandson died, all within a year, and I couldn't cry for any of them. And then I went to see my optician, and I explained, and he put weight on my bottom lid, my

eye, and he said I had dry eyes. And then he gave me a letter to my doctor, and then my doctor got in touch with Moorfields, and I was sent to Moorfields. And then a few years later, I had a phone call. I had the letter from Moorfields that said I had to go and see Mr. Moffit who has been very good. And he said I had perfect -- I was a perfect candidate for this operation.

And I have a Primavera implant, sorry I was trying to think of the word, so anyway, since then, I have been able -- in over nearly a year now since it was done. And I can see a little better, and I'm attending the hospital once a week. So now I can do my gardening, and I can read in little bits and pieces, but at least it's working out very well. And I'd like to thank the staff and the doctor for recommending that I come here. So thanks very much to everyone. Thanks.

MS. NGUYEN: Thank you so much, Larry and Jane, for sharing your stories with us. Our last speakers of the session will be from FDA. First up is Dr. Michelle Gabriel Sandrian, a senior staff fellow at FDA. She is a biomedical engineer and lead reviewer on the retinal and diagnostic devices team. She has also been the FDA lead in organizing today's workshop. And as you can see, has done a really tremendous job.

Her talk today will provide an overview of the FDA regulatory process. Take it away, Michelle.

DR. SANDRIAN: Good morning. My name is Michelle Gabriel Sandrian, and I'm a lead review on the retinal and diagnostic devices team. We are responsible for evaluating safety and effectiveness of bioelectronic implants for vision restoration. Today I am going to provide regulatory context for those developing these devices. I will be reviewing

bioelectronic implant device regulation over the total product life cycle, or TPLC. I will touch upon programs meant to support innovation, including the presubmission program, the breakthrough devices program, early feasibility studies program, premarket approval, and humanitarian device exemption.

The regulation of bioelectronic implants for vision restoration spans several regulator programs across the total product lifecycle. This presentation will highlight several of the premarket programs that can be used at various stages of development. There will be another FDA presentation on post-market programs tomorrow done by my colleague, Dr. Neilso Loyo-Barios. FDA includes six centers for responsible for protecting the public health by assuring the safety, effectiveness, quality and security of human and veterinary drugs, vaccines, and other biological products and medical devices.

The FDA is also responsible for the safety and security of most of the nation's food supply, all cosmetics, dietary supplements, and products that give off radiation. Medical devices are reviewed at the center for devices and radiological health or CDRE. Part of the mission of CDRH is to protect and promote public health by assuring that patients and providers have timely and continued access to safe, effective, and high-quality medical devices and to facilitate medical device innovation by advancing regulatory science, providing industry with predicable, consistent, transparent and efficient regulatory pathways, and assuring consumer confidence in devices marketed in the U.S.

So what exactly is a medical device? A product meets the statutory definition of a medical device if it diagnoses, cures, mitigates, treats, or prevents a disease or condition, or it affects the function or structure of the body, and it does not achieve its intended use

through chemical action, and it is not metabolized.

The three regulatory classes for devices are outlined in this slide, along with the requirements which apply to them. Class I are simpler devices with -- low risk and are mostly exempt from premarket submission. Class II devices are more complex and subject to premarket notification or 510k submission. Class III devices are those that are most complex and present the highest risk. Class III devices require a premarket approval or PMA submission.

Here's some examples of ophthalmic devices by classification, including some lower risk devices such as prescription glasses, and higher risk devices such as excimer lasers and endotamponades. The law gives us the flexibility to calibrate our regulatory approach to the level of potential risk posed by a product. For example, tonometers, which are used for measuring eye pressure are regulated differently from devices implanted in the body, such as interocular lenses.

As you have learned from earlier presentations in this workshop, the term bioelectronic implants for vision restoration is a general phrase to describe medical devices that are implanted in or around the retina and visual cortex that use electrical stimulation to provide a level of vision restoration for patients with profound vision loss due to disease or trauma. There's currently only one FDA approved device in this category, the Argus II retinal prostheses system.

The Argus system is intended to provide electrical stimulation to the retina to induce visual perception in adults ages 25 and older with severe to profound retinitis pigmentosa who have a previous history of useful form vision. We recognize that patients with

profound vision loss due to conditions such as retinitis pigmentosa, age-related macular degeneration, or from ocular trauma and other conditions, have very limited options. We also realize that bioelectronic implant devices are novel and complex with unique considerations that pose challenges to device developers, manufacturers, and to regulators. Given this, the remainder of my talk is focused on special programs available by the agency to help facilitate innovation in this device area.

The remainder of my presentation will cover various voluntary programs and program updates that may be advantageous for sponsors bringing implant low-vision restoration devices to market. This presentation is focused on the breakthrough devices program, early feasibility study, IDEs, PMAs, and HDAs, since these are the most relevant and hopefully most informative for this audience. While it does not cover every possible submission type, this slide demonstrates how the programs are interrelated. For example, sponsors may benefit from discussing the early feasibility study protocols in a pre-submission prior to submitting their IDE for approval. Information about each of these resources is available on the FDA website and links are included throughout this presentation.

I will begin this overview with a brief comment about the que submission program, in particular, one potentially very beneficial-type of que submission, the pre-submission. Because implants for vision restoration are innovative and present new technological challenges, we recommend that sponsors come in early and often to talk to us during the development process. One mechanism for doing this is through a pre-submission. Pre-submissions are a type of que submission. They're entirely voluntary, they're free, and

they're a way for you to get feedback on all aspects of your clinical and non-clinical test plan prior to initiation of those studies. They can also be submitted throughout the development of the device.

Examples of the types of questions that are appropriate for a pre-submission are provided in appendix 2 of the pre-submission guidance document. The agency will provide written feedback within 70 days of receiving a pre-submission, and sponsors have an option for a meeting with the review team as a chance to receive clarification on the written feedback.

The breakthrough devices program is another voluntary program for certain medical devices and device-led combination products that provide for more effective treatment or diagnosis of life threatening or irreversibly debilitating diseases or conditions. This program was initiated by the passage of a 21st Century Cures Act in 2016 and replaced the expedited access pathway. Certain criteria must be met to receive breakthrough device designation.

First, the device must provide for more effective treatment or diagnosis of a life threatening or irreversibly debilitating disease or condition. It must also meet one of the following: the device represents breakthrough technology, there are no approved or clear alternatives, the device offers significant advantages over existing or approved or cleared alternatives, or the availability of the device is in the best interest of patients. For example, the device addresses an unmet medical need.

The breakthrough devices program guidance document goes into additional detail regarding what is needed to meet these criteria. This slide provides an overview of the breakthrough devices program. A breakthrough device designation request is submitted as

a pre-submission, and interactions happen through the que submission program. If the criteria for breakthrough designation are met, then the designation tracks with the device through subsequent submissions. There is prioritized review and other benefits as described in the next slide.

However, even if criteria aren't met, traditional pathways are made available for obtaining the FDA feedback. For example, pre-submissions and marketing approval or clearance.

This slide outlines some of the benefits of the breakthrough devices program. For example, sponsors are awarded prioritized review and more interaction and timely communication during development. There's additional review team support and senior management engagement throughout the review. There's also possibility for more flexible clinical study design. For example, intermediate and surrogate endpoints could be used where there's evidence to support the endpoint as a reasonably -- to predict a clinical benefit of a device, or an adaptive study design may be used in certain circumstances.

In addition, there are opportunities for balancing pre- and post-market data collection for breakthrough devices. We may not have definitive answers to questions relating the benefits and risks of a device at the time of approval because a time and cost associated question would significantly delay the availability of a novel device. Generally, we weigh the benefits against the risks for breakthrough devices and we do for all devices, and may accept a great extent of uncertainty if information could be collected post-market.

Specifically, as part of FDA's benefit risk determination, the agency weighs a device's impact on patient health including the probable benefit of earlier access to the device

against the probable risk of harm from patients should the subsequent data collection demonstrate the device is ineffective or unsafe. FDA also intends to expedite review of manufacturing and quality systems compliance for the purposes of expediting the development and review of breakthrough devices. One additional important point is that breakthrough devices -- the breakthrough device program does not add new requirements or change the statutory standards for approval of a pre-market submission.

To date, there have been 17 ophthalmic devices that have been granted breakthrough designation. Three of these devices were for bioelectronic implants for vision restoration.

Next I will discuss the early feasibility studies or EFS program, which as been used by several sponsors developing bioelectronic implants for vision restoration. Investigational device exemptions regulation or IDE regulation 21 CFR Part 8-12 describes three types of device studies, significant risk, non-significant risk and exempt studies. The -- for bioelectronic implants are significant risk device studies and must follow all of the IDE regulations and have an IDE application approved by FDA prior to proceeding.

Their requirements for informed consent, labeling, monitoring, recording, reporting and more, and EFS requires IRB approval and approval by the FDA. In the FSID is the standard ID except there may be a greater level of uncertainty about how the device will perform. This includes devices generally early in development or an approved device that has a new intended use. There's a small number of subjects in the clinical investigation, and its goal is to provide an initial indication of safety and/or effectiveness or a proof of concept.

The goals of the program are to enhance patient access to beneficial technology and -- innovation. FDA acknowledges that completion of all non-clinical testing prior to initiation of an early feasibility study may not be necessary when relevant non-clinical testing methods are not available or are not adequate to provide necessary information needed to advance device development. Therefore it may be acceptable to defer some non-clinical testing until the device design has been finalized for use in a pivotal setting.

Here are some examples of areas where EFS may be used to obtain insights to further device development, ranging from human factors to device performance. As stated earlier, we encourage sponsors to discuss their planned IDEs, including EFS IDEs in a pre-submission prior to submitting a protocol for approval.

Multiple developers in the bioelectronic implant space have successfully utilized the EFS program to obtain early clinical experience with their devices and facilitate device development. Here are a few examples of publicly available information regarding early feasibility studies for implants intended for vision restoration, including subretinal and cortical implants.

As mentioned earlier in this presentation, pre-market approval is the FDA process of scientific and regulatory review to evaluate the safety and effectiveness of Class III medical devices that have the highest level of risk. PMA is the most stringent type of device marketing application because the devices support or sustain human life or are of substantial importance in preventing impairment of human health or present a potential unreasonable risk of illness or injury. To date there have been no PMA approved implants for vision restoration. The FDA PMA page provides a great resource for those preparing a

PMA marketing application.

Next I'm going to discuss the humanitarian device exemption program which way be more relevant to this audience than the traditional PMA authorization given the prevalence of the conditions meant to be treated. An HDE is a marketing application for a device classified as a humanitarian use device. It was established in 1990 to encourage the development of devices intended for rare diseases was updated by the 21st Century Cares Act of 2016. HDE approval authorizes the marketing of a humanitarian use device.

A humanitarian use device is a medical device intended to benefit patients and the treatment or diagnosis of a disease or condition that affects or is manifested in not more than 8,000 individuals in the U.S. per year. The 21st Century Cares Act changed the number of individuals from less than 4,000 to not more than 8,000 individuals in the U.S. per year.

In addition to receiving humanitarian use device designation, in order to be eligible for an HDE, there must be no comparable device currently legally marketed in the United States. The exception is that there can be more than one approved HDE for the same intended use. However if a PMA is ever approved for that particular intended use, those HDE approvals expire.

HDE approval is not the same as PMA approval but both can be used to bioelectronic implant devices. The similarities and differences between HDE and PMA approval are outlined in the HDE guidance document and summarized on this slide. If you're familiar with the traditional PMA pathway for Class III devices, you will notice that the biggest difference between HDE approval and PMA approval is that where PMA approval requires demonstration of reasonable assurance of safety and effectiveness, HDE approval is based

on reasonable assurance of safety and probable benefit. Appendixes B and C of the HDE guidance document provide more details regarding what FDA considers when determining whether probable benefit has been demonstrated.

FDA recognizes that rare diseases or conditions such as retinitis pigmentosa by definition occur in a small number of patients. This means it is especially challenging to gather enough clinical evidence to meet the FDA PMA standard of reasonable assurance of safety and effectiveness. An important aspect of HDE application for a humanitarian use device, therefore, is an exemption from the effectiveness requirements that are necessary for PMA devices. There must be sufficient information to show a probable benefit, however, and there are some limitations and other information that is needed for HDE approval.

As I referred to earlier, the only FDA-approved bioelectronic implant for vision restoration in the US is the Second Sight Argus II retinal implant which was approved as an HDE in 2013. This device is indicated for use in patients with severe to profound retinitis pigmentosa that meet specific criteria. We encourage those developing implants for vision restoration to read the publicly available summary of safety and probable benefit document. This outlines everything from the indications for use and device description to the -- animal and clinical study data that were used to support the probable benefit for this device.

My colleague, Dr. Lan Yue, will be going into more detail regarding this -- test in her presentation which follows this one.

In summary, FDA recognizes the challenges to the development of novel and

complex devices such as bioelectronic implants and the need to facilitate innovation for a particular population where patients have few options. My presentation today has highlighted a number of programs that manufacturers should consider when developing their bioelectronic implants. These programs offer unique opportunities to obtain testing recommendations early during development as well as early and frequent engagement with regulators to identify appropriate testing requirements.

I have included links to the FDA webpages that I encourage you to visit if you would like additional information on these topics. Thank you.

MS. NGUYEN: Thank you so much, Michelle. Next I will turn it over to Dr. Lan Yue. Dr. Yue is a staff fellow at FDA. She's a biomedical engineer and lead reviewer and is also on the retina and diagnostic devices team. Her talk will summarize FDA's current guidance document on retinal implants. Thank you, Lan.

MS. YUE: Good morning. My name is Lan Yue. I'm also a lead reviewer on the retinal and diagnostic devices team. The previous presentation from Michelle cover broad programs, and this presentation will go into more specifics with the respect to visual prostheses. I will provide an overview of the guidance documents and FDA recognized standards that should be used to guide the development of such devices. We will first go over general information of standards and FDA guidance documents and then focus on the specific guidance for investigational device exemption, IDE, application of retinal prostheses.

Standards provide a consensus approach to certain aspects of the evaluation of the device safety and effectiveness such as test methods and acceptance criteria. The term or

condition refers to the FDA's formal identification of a standard after determination that it is appropriate for device manufacturers to declare a conformance in order to meet regulatory requirements. If a manufacturer elects to conform to a recognized standard to meet a pre-market review requirement, they submit a declaration of conformity as part of their paperwork. FDA can decide to recognize all, part or none of a standard. The decisions and the rationale can be found in our recognized consensus standards database which is shown here on the right and is publicly available. Please note that the FDA recognition of a standard may change when revision occurs. Although the decision to utilize standard is completely voluntary, FDA strongly encourages its use since FDA has already put the work into evaluating the standard and determining that it is acceptable for use. Less documentations are needed from manufacturers who choose to declare conformity.

If the sponsor chooses to use alternative methods to address FDA data requirements, they would need to describe the basis for the use of those methods which require additional documentation. Since the FDA had not previously reviewed the method, it is also uncertain whether it would be adequate to satisfy regulatory requirements. Ultimately, the use of recognized consensus standard can result in both cost and time savings during device development. Later in my talk, I will be referring to a number of standards relevant in this area. FDA staff plays a large role in the development and recognition of standards to ensure that regulatory considerations are built into them.

Our standards program is overseen by the Standards and Conformity Assessment Program, SCAP. The key element of our standards management operation is our specialty task groups or STGs. They align with our regulated device areas from horizontal aspects

such as quality system and risk management. So you need a more vertical or device-specific area such as ophthalmics. Currently, we recognize more than 1400 standards with about 60 ophthalmic standards recognized.

Once standards are recognized, we need to put standards to work which leads to another important component, conformity assessment. A key priority of our conformity assessment work is to promote -- of declaration of conformity to those recognized standards in the regulatory submissions. We recently started our accreditation scheme for conformity assessment pilot program, ASCA, to help with this initiative. In this program, a manufacturer can work with an ASCA accredited lab to develop and finalize a test plan based on recognized consensus standards to evaluate specific aspects of essential performance of their device.

In addition to the consensus standards, we recommend sponsors use FDA guidance documents in the development and validation of their device. Guidance documents describe FDA's interpretation of our policy and regulatory issues. These documents usually discuss more specific products or issues that relate to the design, production, labeling, promotion, manufacturing and testing of regulated products. Use of the FDA guidance is voluntary, but it has similar benefits to the use of FDA recognized standards. Therefore it is highly encouraged. You can search for guidance documents on the FDA website as shown here. For example, when I searched for retinal prostheses, the search engine returns the IDE guidance that I'm about to present in the next slide.

Now that I have introduced the FDA recognized standards and the FDA guidance documents, let's circle back to this retinal prostheses specific IDE guidance which was

issued in 2013. The intended audience includes members of industry who intend to submit an IDE including an early feasibility study IDE to the FDA to conduct feasibility and/or pivotal human trials of their retinal prostheses in the United States, to support a pre-market approval, PMA, or a humanitarian device exemption, HDE. More detailed information on PMA and HDE has been discussed in Michelle's presentation. This document provides guidance about developing preclinical and clinical tests on retinal prosthetic devices. It describes preclinical tests that you should conduct to characterize device safety before initiating any clinical testing. This document was a -- guidance which is a form of guidance by the FDA designed to serve as a mechanism by which the agency can share initial thoughts regarding the content of pre-market submissions for emerging technologies very early in product development, generally, before the FDA has received any such submissions.

This guidance is limited to retinal prostheses, but many elements are still applicable to other types of visual prosthetic devices, for example, for cortical implants. Please note that pre-submission is strongly suggested if you like to obtain device-specific recommendations from FDA. Prostheses that incorporate drugs or biological products may be combination products. Combination products are outside of the scope of this guidance but the recommendations may still be applicable.

The IDE application should include the complete investigational plan or, where appropriate, a summary of the plan. This investigational plan should include a description of the prosthetic device and its functional components. We recommend that you include descriptions of both the implanted and external parts. If your device includes an image capturing component, we recommend that you describe the type of photosensor or video

input, resolution, and configuration of systems in the eye-tracking capabilities and the means of attaching any external components.

We also recommend you describe the effects of coil distance and eye movement on wireless transmission. We recommend that you describe all device accessories used for programming, clinical fitting, testing or home use of your device. You should provide a description of the manufacturing and inspection steps related to achieving critical specifications for the device including the final device acceptance criteria.

The investigational plan should include a description and analysis of all increased risks to which subjects will be exposed by the investigation, as well as the manner in which those risks will be minimized. To fulfill this risk analysis requirement, we recommend that you perform a failure -- risk analysis summary on the electronic components and circuity. Your failure mode and risk analysis summary should identify and assess the risks due to any potential electronic hazards, failures, the potential severity of these risks, and how to eliminate or reduce them. We recommend that you supply traceability matrix showing how you validated your risk and mitigation features. For more information on the current thinking of FDA on risk analysis in general, please refer to the ISO 14971 standard as noted here.

In the investigational plan, you should completely describe the material compositions used in your device for all implanted material or material contacting the subject. You should provide detailed speculations for the formulation or chemical composition. You should also provide material biocompatibility profiles for all subject to contacting device components as described in the FDA guidance in use of international

standard ISO 10993.

We recommend that you provide bacterial endotoxin test results and pyrogen test results. For those two tests, you may refer to the FDA guidance for more information. In leachable testing, we recommend you determine the stability of the material components in a saline environment through detection and quantification of possible degradation products and changes in physical appearance.

We recommend that you conduct animal testing on an active finished device to establish adequate safety before commencing a substantative human trial. We also recommend that you design a staged testing approach that includes evaluation on several animals which are implanted long term. Since implantation may induce failure modes not predicted by bench testing, we recommend that animal studies evaluate the ocular tissue biocompatibility compatibility of the implant.

The animal study reports should include the following items: study protocol and objective, study design, stimulation levels and rates, visually evoked response testing such as ERG and VEP, and histology of the eye and retina with particular attention to the regions of device implantation or attachment. We also recommend that you provide an analysis of the animal testing data and a description of any modifications made to the device as a result of this testing.

The first animal tests should include acute tests and long term tests. In the acute test, we recommend that you test electricals to stimulate the retina near their maximal limits in an animal model for a period of 24 hours. In the long term test, we recommend that you implant the final form of the fully functional device in the eye of an animal model

for at least six months and characterize the functionality of the implanted device. After explantation, we recommend you examine the eyes and its layers histologically for any pathology associated with the implant. We also recommend you evaluate the explanted device at magnifications sufficient to detect any failure of mechanisms such as corrosion or insulation degradation.

We recommend you report the stimulation testing range and limits for the electrodes in the array. For each electrode, we recommend that you describe stimulus parameters, electrode impedance, et cetera. We recommend you also briefly describe how the maxima of the stimulation parameters will overlap your subject test on single electrodes. For example, we recommend that you describe the maximal charge density, pulse frequency, and stimulus duration of the test.

For durability testing, we have the following recommendations. Report the design lifetimes for both the implanted and external device components. Design the implanted components of your device to withstand a minimum of 5 years simulated use or provide a rationale for a shorter duration. Conduct a series of accelerated lifetime tests to address the durability of the stimulation electrodes and the entire implant. Durability should also be assessed on the external visual processor electronics, optical sensors, and telemetry coils. We recommend that you relate the assessments of device lifetime to the results of the tests conducted, which may include hermeticity tests, coating durability tests, corrosion tests, welding and bonding patency tests, stress tests, fatigue test analysis, and any other test necessary to evaluate the potential device failure mode.

We recommend that you supply accurate specifications and fabrication data

supporting the design, thermal dissipation, electronic circuitry, ASIC, interconnects, cabling and transmission coils of the implant. When applicable, we also recommend you describe how the portable subject controller of your device addresses usability. Regardless of where the physician fitting software device programming, patient software controls, and protections against excessive stimulation levels should all be described. It is also important to describe how the software is configured for home use and user adjustment.

Naturally, essential preclinical testing also includes EMC and MRI compatibility and appropriate light hazard evaluations. You may refer to the listed guidance documents and standards for more information. Appropriate testing to demonstrate the implanted device is sterile and is functional throughout a labeled shelf life is also essential. The previous slides discussed the preclinical tests. Now I'm going to describe some specific recommendations regarding the clinical testing requirements for retinal implants as stated in our guidance document.

Before getting to the specifics, I'd like to note that surgery should be performed only to implant the test device and not simultaneously correct other ocular conditions to avoid compromising demonstrations of clinical safety or effectiveness in your IDE studies. Now I will recommended safety outcome measures. Sponsors should identify a primary safety endpoint in the protocol as well as capture rates of surgical complications and potential longer term adverse events. The choice of safety endpoint and list of potential adverse events will depend on the device design and the patient population for which the device will be indicated. A risk analysis should identify the most likely types of adverse events and also attempt to identify acceptable levels for the most probable and the most serious

adverse events.

The acceptable level of risk will depend upon the possible benefit and the level of visual function and health conditions of the enrolled eyes. A statistic plan should justify the sample size based upon the safety considerations in addition to providing justifications based on effectiveness. Primary effectiveness endpoints of visual performance should provide quantitative documentation of subjects performance in support of device effectiveness. Depending on the patient population and the nature of the underlying condition, the guidance recommends a list of effectiveness assessments to be performed as appropriate to your device.

We first recommend visual function assessments. For these types of assessments we recommend low vision letter acuity tests, grating acuity tests, assessment of visual field map, and assessment of form or pattern vision for which we recommend short-duration, timed, single letter or symbol recognition tests to avoid excessive use of compensatory hand, eye, or camera movement.

Assessments that evaluate the subject's functional vision may provide a better understanding of what users' visual capabilities are, real world situations. Real world assessments should at least be used in pivotal studies. We recommended the listed procedures as appropriate to your device. We recommend an orientation and mobility assessment of your subject's real world --. Your protocol should include an assessment of daily living. Additionally, a PRO, patient reported outcome questionnaire, should be administered to all subjects to assess the overall benefit of the device when used in the home and other settings outside the clinic.

We have a specific guidance on PRO as noted here. We will be discussing more on clinical outcome assessments including PROs in sessions 4 and 5 tomorrow.

Besides recommendations on preclinical and clinical testing, the retinal prostheses IDE guidance also includes recommendations on other elements that you should include in your investigational plan. Your IDE application must include a copy of all information to be provided to subjects to obtain informed consent. In addition to the common ICD requirements, we recommend that an ICD for retinal prosthesis also describes the frequency of subject tests, objections for explantation if the subject is not satisfied with the implant, and the need for periodic ocular health evaluations.

Your investigational plan must also include copies of all labeling for the device, including all cautionary statements.

In summary, we strongly encourage you to use the IDE guidance for retinal prosthesis and the referenced FDA guidance documents and consensus standards to develop preclinical and clinical testing of your visual prosthetic device to streamline your future IDE application. We also encourage you to take advantage of the pre-submission program if you seek to obtain device-specific recommendations. We acknowledge that this guidance was finalized almost a decade ago, and certain recommendations may need updating or revisions. One of the goals of this workshop is to discuss and collaborate on meaningful endpoints in this device area to expedite innovation. I look forward to hearing your feedback in future sessions. Thank you.

MS. NGUYEN: Great. Thank you to all our speakers for these wonderful presentations. These discussions provide a really great foundation for the topics that will

be addressed in the next two days, including discussions on the challenges regarding collection of bench and clinical data, and possible identification of novel safety and effectiveness clinical endpoints and assessments for these complex devices. We will now take a break for lunch. We're a bit ahead of schedule, so we'll see you back here at 1:15 p.m. Eastern Time. We have an exciting afternoon session ahead that will focus on hearing from the perspective of patients. See you again at 1:15. Thanks.

Welcome back everybody. I hope everyone had a great lunch. Our next session will provide a unique and exciting opportunity to hear directly from patients. Before we started our moderated panel session, each panelist will introduce themselves sharing their journey with vision loss and the impact it has had on their life and those closest to them. Thank you.

KEN: Hello, my name is Ken, and I spent more than 23 years on active duty as an Army officer, much of it legally blind. I retired in 2010. For many years, I simply felt like everyone else saw better than I did. But as time went by, it became clear that I had vision problems. When I would complain about not being able to see at night or loss of peripheral vision, I was sent to an optometrist who would give me a basic vision test which I passed with flying colors because my central vision had not yet been affected. When I was diagnosed with retinitis pigmentosa, I was simply told there was nothing that could be done. I had a horrible experience with the state resources, and one ophthalmologist told me to be prepared to be blind. So that's what I did.

I found the blinded veterans association and VA low vision clinics. I attended the clinic in Tucson, Arizona, and they taught me how to use my cane correctly, showed me

other options available to me as my vision deteriorated, and helped me apply for my guide dog. While I was aware I had a vision problem, I never felt disabled or handicapped until somebody told me that I was. I say this to highlight the loss of confidence that came with the label and the loss of freedom and dependence on others that comes with no longer being able to drive.

For someone who's used to being in positions of authority and holding great responsibility, vision loss is an incredibly humbling experience and often downright depressing. I'd fortunate to obtain some good but limited central vision. And my vision loss, albeit slow, hasn't been without notice. The frequency of accidents has increased along with the severity of those accidents.

Oklahoma has limited mass transportation, and not being able to drive is a significant and sometimes costly obstacle. Being visually impaired is very different from being blind. Whether you are or not, it's easy to feel judged when using your cane or guide dog and then reading a menu in a restaurant. Your mind often tricks you into believe you are more capable than you are, often leading to disastrous results. My totally blind friends are naturally far more careful than I am.

I don't like being told that I can't do something. Like many of my totally blind friends, I live for physical challenges such as skiing, snowboarding, white water kayaking, rock climbing and more. I often test my levels of independence by traveling alone or trying new challenges such as fixing an appliance, mowing my yard without missing huge swaths of grass or trimming limbs in my yard. These building into those small victories that often sustain me over time.

I have a strong network of blind veteran friends across the country. We keep each other upbeat, laugh at each other's mishaps, and commiserate on occasion. I was the first blind person that I ever knew, but now I know I'm not alone. An old Army commander of mine once said, "There's no such thing as problems; only challenges". Well this is my challenge. It could have been worse. I could have been born ugly.

CALAHAN: Hello, my name is Calahan Yanga. I am 27 years old. I'm originally from Pittsburgh, Pennsylvania, and I currently live in Fort Wayne, Indiana. I recently graduated with my masters in Healthcare Administration from George Mason University. I was diagnosed with my eye condition when I was around the age of 2, and I was diagnosed with the condition of retinitis pigmentosa which was passed on to me from my father. And this condition results in my retinas slowly degenerating as I get older, and this resulted in me having a pretty standard childhood growing up. I played sports from football, baseball, basketball, and as I got older, I wanted to continue on playing sports. And then I transitioned into a sport for the blind and visually impaired. It's called goal ball. It's the coolest sport you've ever heard of, and I'm the captain for the USA men's team, and we competed in the Tokyo 2020 games last summer.

And with all this said, my quality of life from my vision loss has been pretty severely impacted. I've had a lot of positives and a lot of negatives. Some positives are that I get to travel the world competing in a sport that I love and spreading disability awareness, trying to improve the quality of life for other people in the world, working for the Department of State and trying to provide opportunities for them. Whereas some of the negatives are that I have lost a lot of my ability to be independent. I try to use technology like Uber and

seeing AI and other devices to increase my independency and ability to navigate life on my own, but there's a lot of occasions like large venues and crowds that I really do struggle with navigating and being independent without having to depend on other people. And in implant to help improve my vision has never been something I've thought about but I would definitely be interested in, if something came along that would help improve my vision.

TERRY: Hello, my name is Terry -- I'm from Riverside, California. I'm 74 years old, and I have an eye disease known as RP or retinitis pigmentosa. I've been blind since the end of November of '93, and I'm married. I have a wife named Sue, 5 children, and 16 grandchildren. And blindness came on in a gradual sense from '86 to '93. '86 when I was diagnosed. '93 when I couldn't see anymore. And then it was very difficult to, especially the first year, to deal with the vision loss, and it takes you completely out of the world you're used to. But I managed to do it because I made a lot of good friends who were also blind. That really helped me a lot.

But then that went on for about 10 years, and then I was able to -- I found out about a clinical trial at the University of Southern California for people with RP. And I went down there, and they examined me and said that I would be a perfect candidate for it because my optic nerve and all that was okay. And I said great.

So we started testing within -- after I was operated on. It was about an 8-hour surgery. And a couple weeks later, we started to do the testing. And the very first thing I saw was 16 little pinpoints of light which represented the 16 electrodes. And when you're totally blind for all those years, to see anything like that is just unreal. It's kind of positive. It's a lot of good things. And then I did a lot of testing with the Argus I until 2011, and then

went on to the Argus II from 2015 until 2019. And that's where a lot of the intense testing took place and found out what I could see with the device and all of the hard work that went into it.

So what it did for me, it took away some of the negativity of blindness and put it into a positive mode for me and made it better for me and my family and so on.

JACOB: Hi there. My name's Jacob. I am from L.A., California. I was born with a really rare genetic disorder called Usher's Syndrome, specifically Type 1C. The disorder affects my hearing, balance, and vision. With the hearing, I was born completely, profoundly deaf. I have zero percent hearing in both sides. Luckily I was able to get a cochlear implant at a very early age, but it's been a process, a lot of successes and failures to make it happen. But I am here today being able to communicate and speak and hear and all that just because of the cochlear implant, and it definitely has a huge impact on my life and the people that I deal with.

So with the balance, I cannot walk in a straight line for the life of me, and that does have a little bit of something to do with the hearing loss. And with vision, it all started out when I was 7 years old, which is when I was diagnosed with Usher's Syndrome. And it started out with night blindness. And with night blindness, I cannot see the life of me at night time. It's definitely a struggle to move around. But not only with the blindness, it's also called retina pigmentosa which it's a deteriorating disorder where I lose my vision over time. And right now, I only have little bits of my -- vision, and I have no peripherals what so ever.

So because of that, I don't drive. It's very hard to move around at nighttime,

especially at movie theatres, bars, clubs, whatever, you can name it. And so it's a challenge to deal with, but I take it day to day, and it definitely takes -- it affects my life and what I do. But I try to not let that limit me. But I think it would make a huge impact being able to have a visual implant the same way a hearing implant has done for me. But that's just all of it about me.

JOHN: Hi, my name is John Cox (ph.). I'm 81 years old, and I have macular degeneration. It started when I was around 60. I was looking at some charts, and the lines became very wavy. I consulted several ophthalmologists, and they confirmed, yes, this is macular degeneration. So I've been under treatment for about 20 years, beginning with the PDT as we call it, which is a laser treatment which left scarring in the eye. But it worked so far as my left eye and contained the spread. The topography didn't get any larger.

But in my right eye, the fluid continued and eventually the treatments began with the various injections that are available. The appeal of the bioelectronic implants is very strong, and if I were not 81, I probably would consider it. But seldom do you get into your 80s without other health considerations as well, which I have. So it's sort of a cost benefit analysis for me, but I think it's wonderful for other people, particularly the younger ones who can adapt. I volunteer a lot although I am retired, and one of the things that I volunteer is to help with other blind people by forming support groups. In that capacity, we have had many contractors come in to talk about the advances in the technology for various wearable devices. But to be honest with you, have not had very many to come in and talk about the implants.

I keep up with that a little bit through various news reports that I get throughout the

internet, and the notices that I get from NIH where I have been going all these years now, so that I'm aware of some of them. And it is just astounding what the development of these new medical devices can do. And I absolutely totally support it and encourage younger people to get whatever is available now and not deliberately handicap themselves for the rest of their life and just get on with it, whether they can see only slightly or pretty good.

So I think it's a great thing, and I'm just delighted to be here to hear more about that.

CLEONE: Hello, my name is Cleone, and I live in Maryland. I was diagnosed with macular degeneration in 2009. Within 6 months of being diagnosed, the vision in my left eye went from 20/70 to 20/200 to 20/400. I heard about the implantable telescope on a short segment on the evening news. So I contacted my retina specialist, and I asked him if he thought that was something that I would qualify for. And he said absolutely. So he helped me fill out the forms. We mailed them in, and I was notified by CentraSight that I qualified in all categories but one. I was too young to have the surgery because the FDA had only approved it for persons over the age of 75 at the time. Meanwhile my macular degeneration kept keeping worse.

So I was scheduled and had a cataract surgery to try to help my vision. The surgery went fine, but it didn't really do much for my vision. I had to give up my drivers license. I had to retire from my job as elementary school teacher. And although I didn't like it, I accepted the fact that I was just going to be blind. Then in October of 2014, I received a letter from CentraSight telling me that the FDA had changed the age from 75 to 65, so I fell

into that category. I started going to see specialists, having tests done, and then when I got to the last doctor, he asked me what were my expectations if I was to have this surgery. And I told him first of all, I wanted to be able to see my grandchildren's faces again. I have always been an avid reader, and I would like to be able to read again and also, I love quilting, and I would like to be able to do one of those two things again.

He told me that my expectations were within reason, and so then I was approved for the surgery. I was scheduled and had my surgery on May 27th, 2015, but that just started my road to recovery. And it was a lot of hard work, a lot of therapy, a lot of -- but I wouldn't give up. I knew I wanted to go through with.

So it's truly a miracle of technology, and if by telling my story I can help someone else who has vision problems have the same results I have, then I will be very happy. Thank you.

DON: Hello, my name is Don. I sustained a bilateral penetrating ocular trauma while serving in the Unites States Army during combat operations in Iraq, and I currently serve as the Executive Director of Blinded Veterans Association. I was deployed with the 82nd Airborne Division during Operation Desert Shield and Desert Storm which took place during 1990 - '91 timeframe. While in -- Iraq, there was a detonation of an ordinance complex. I sustained a traumatic brain injury, bilateral penetrating ocular blasts which resulted in bilateral retinal detachments, traumatic bilateral lensectomies, trauma to the corneas. I was placed into a medically induced coma, medivac'd back to Walter Reed where surgeons from John Hopkins' Wilmer Eye Institute came in and helped to stabilize my ocular systems. I emerged from the medically induced coma several weeks later totally blind in the left eye

and legally blind in the right eye. Had scleral buckles to reattach each retina. They were not able to do anything with artificial lenses. I had Malteno implants to help regulate eye pressure and multiple corneal transplants.

As far as impact to quality of life, obviously it's traumatic to go through an experience such as that. It had tremendous adverse impacts on quality of life. You go from highly functioning. I was extremely athletic at that time and very active. So to lose a lot of those opportunities, I was very fortunate to be on the veteran side. The Department of Veterans' Affairs has phenomenal rehabilitative services, particularly for blind rehabilitative services, both in-patient and outpatient. So going in and learning how to adapt to my new abilities, being equipped with state of the art technologies that continue to be improved and expanded upon has given me the opportunity to not only pursue the athletic endeavors that I was active in prior to the injuries, but have afforded me the opportunity to be extremely successful in my professional life as well.

Still day-to-day challenges, but obviously to be in a sighted world with legal blindness, but again, with ongoing technologies and new approaches in the medical realm, the world continues to evolve and afford us great opportunities to continue to improve and enhance our qualities of life.

JASON: Hi, everyone, my name is Jason Esterhuizen. I went blind in 2011 due to a motor vehicle accident. I was diagnosed by a trauma surgeon at -- hospital in --. Before my accident, I was studying to become a pilot. I loved driving cars, driving motorcycles. So my blindness severely impacted my quality of life negatively. I came to the United States in 2018 where I received a brain implant at UCLA called the Orion visual cortical device. And

since receiving the brain implant, it's improved the quality of my life a lot in the sense that I now have the hope that technology will improve and is improving on a daily basis. And this is just the first steppingstone in the progression of vision restoration by method of brain implant or implant in general. And I am very hopeful and glad to be a part of this medical trial.

MS. NGUYEN: Thank you. I would like to welcome all of the panelists and thank each of you for participating in today's discussion. We will now begin our panel discussion. We have tried to create a panel to represent a variety of perspectives and experiences with implants, including different medical conditions and various implant types. I will now turn it over to our moderator, Dr. Eva Rorer. Dr. Rorer is Assistant Director for Patient Science and Engagement in the Office of Strategic Partnerships and Technology Innovation at FDA. She is a board certified ophthalmologist who has been with the agency for over 20 years, serving most of that time in her previous position as chief ophthalmic medical officer in the division of ophthalmic devices. Eva.

DR. RORER: I would like to welcome and thank the panelists whose introductions you just heard for joining us today. Unfortunately one of the patients who was planning to join us for the panel discussion, Calahan, is unable to make it. As you heard in their videos, all of the panelists have vision loss from various conditions, but not all panelists have had an implant, and of those who have, one has had a bioelectronic cochlear implant for hearing restoration, and one has had an implantable miniature telescope for vision restoration, but not a bioelectronic implant.

We have brought these panelists together because they all have experience and

perspectives that can provide valuable insights which are applicable to bioelectronic implants for vision restoration.

Now I would like to turn to the panelists with the first question. We saw in your introductory videos, but can you please elaborate on what it's like living with vision loss? Ken, I would like to start with you, please.

KEN: Well, I carry a small flashlight around my neck at home all the time. It's kind of comical. I use it in poorly lit spots, or if I drop something, I get down on the floor, and I use it to help cast a shadow on what I've dropped. I spend a lot of money on new lighting inside and out in areas that I'm in frequently or otherwise would be dangerous for me to see, like around my swimming pool. I have black countertops in my bathroom, so I have a white cloth that I lay next to my sink to put things like my black comb for contrast on. I have a guide dog who not only helps keep me safe but is much needed company during the day. I work part time from home and have a small gym in my house that I use to try to keep in shape and give me purpose for the day and help keep me from being too sedentary.

DR. RORER: Jacob, would you like to go next, please?

JACOB: Sure, absolutely. So with my vision loss, it has affected me in multiple different ways only because when I was four, and I had full range of vision, and with that loss, over time, every year starts to get harder. And so what I've noticed is that I easily trip over things. I easily run into people. And it really depends on if it's daytime or nighttime because with nighttime, I have night blindness, and that has affected me in ways where it's incredibly hard for me to move around on my own, especially without the help of another person or even a flashlight.

And sometimes the flashlight of our phones isn't bright enough to help me move around, so there's definitely a lot of struggles there. And it's just there's a whole lot of challenges in terms of being able to get around safely and efficiently without stress or the fear of hurting somebody else or yourself. But that is what I deal with on a daily basis. I do not have a cane or a guide dog right now because of where my vision is. I'm actually in the process of getting cane training so that way I can qualify for a guide dog.

DR. RORER: Thank you, Jacob. Terry, we'd like to turn to you next.

TERRY: Okay, thank you. Yeah, back in 1985, I started experiencing night vision problems, and in the summer of '86 I was diagnosed with retinitis pigmentosa from two different sources. And at that time, I was told that I had probably several years and maybe even 15 years of limited vision of how this things works. And then slowly but surely, the tunnel vision started happening, and so instead of lasting longer than they thought, by the time I was 45 in November of '93, I had lost it all. So it went from night vision to tunnel vision to no vision.

And then I was just going along like anybody else, just kind of loss and out of place, without a job, without a career. I had an understanding family, but even with all that, it was very difficult to go from losing -- from gaining some things and losing others. And so that continued on with me until 2004 when I met Dr. Mark Humayun and took part in a clinical trial called Argus I. And do you want me to go on any further?

DR. RORER: We'll talk some more, Terry, about your journey with your Argus devices later on in the panel discussion. So thank you very much for sharing your experience up to that point with us.

TERRY: You're welcome.

DR. RORER: Cleone, would you like to share your experience with vision loss?

CLEONE: Sure. Well, in addition to what I said in my intro, I think one of the hardest things was losing the independence of being able to drive. I have family and friends who were very willing to take me places, but I really sometimes don't want to ask anybody to do that. Other things, I have a hard time getting up and down steps, and I don't have the night blindness that other people have talked about. Because I was diagnosed with my macular degeneration at a later age, there are a lot of things that I had to give up. But after I got my implant, I have been very happy and would like to share that with anybody who would like to hear about it. Thank you.

DR. RORER: Thank you, Cleone. John, would you like to go next?

JOHN: I was more fortunate than most, I think. My macular degeneration came on when I was in my late 50s, and by then, I had already retired from the Air Force and was general counsel for a trade association. And I remember exactly when it happened. I was in an airport ready to go to a convention or a meeting, and I was trying to read some charts, and the lines became very wavy. So anyway, I continued as long as I could then couldn't drive anymore. And that's of course a big handicap. But with my wife driving and my introduction to Mr. Uber, and I learned the metro system. I live in Vienna, Virginia, just outside of Washington, D.C. And so I got another job, an old friend of mine had been elected to the U.S. Senate, and I just went by his office one day, and I said, well, you know, what's up? He said, what are you doing? I said, well, nothing. And he said, you know I've got a lot of young lawyers on my staff, but I don't have any old gray heads. And so for the

next five-and-a-half years, I worked in the Senate. And I knew my way around the Capital building from all the years that I'd been there anyway because as the in-house counsel, I was also a registered lobbyist for these -- we had 3,200 small manufacturing companies.

So I continued around the Capital. And then I became a guide for the U.S. Capital historical society. And now I've gotten -- I work on a volunteer basis for the Fairfax County library system. Make sure that our 21 libraries are accessible for the blind, low vision, and physically handicap. And that keeps me busy, as well as two, we call them the VIP, visually impaired persons. Support groups, one here in my town of Vienna about 10 miles outside of D.C. and then Restin, Virginia. So I'm active in both of those.

So I found out very quickly when I was diagnosed that the world did not stop because I did, but my wife told me early on, she said, well, I'll give you about 30. I said 30 what. She said seconds of self-pity, and then we got to get on with it. And so I have learned since I have been dealing with this, I've learned a lot of good things. I've learned patience. I've learned that if I drop something and can't immediately find it, leave it alone. It's still going to be where it is, and either I can find it during the day or somebody else can find it. I have learned to listen a lot better than I used to, and I have discovered that everybody has a story, and they just want to be heard. And listening is a great thing.

But I think the biggest adjustment though is really two things. It's already been mentioned by several is can't drive, so you can't get in the car. You can't go help your wife and say, oh, yeah, I'll go down to the store and get the milk or the bread or whatever it may be. You can no longer do that. It's very difficult to pick out anything to wear, so you're at the mercy of others on that. And you can't say, oh, that looks terrible because you can't

see it.

But things are coming along good. It could be worse. I do not have any implant. I've been going to the National Eye Institute. Like another couple of people, I first was diagnosed at Walter Reed. Received some treatment there and then they said, you know, you better go the National Eye Institute at NIH, and I've been going there. I don't know what else you want to hear, but that's my story.

DR. RORER: Thank you very much, John. Jason, can we hear from you now?

JASON: Good morning. Good afternoon, everyone. How are you? My name is Jason. I'm in California right now, but I'm originally from South Africa. I lost my vision in 2011 in a car accident. It affected my life in every aspect you can think of, going from being someone very independent, racing motorcycles, studying to become an airline pilot, to all of a sudden not knowing how to even put toothpaste on your toothbrush. It was a big change in life, obviously. Took me a while to adapt, to go through the stages of grief, if you want to call it that.

I think all of the speakers so far have touched on every single aspect of the things that you have to overcome once you've been sighted and then go blind, driving the car, not being able to hop around like the way you used to, getting dressed. My little boo boo this morning was technology. You think you've got everything under control and then, yeah, one click or one tap of a button and you send up being 20 minutes late. I did receive a brain implant for vision restoration in 2018. I was one of six people that were picked to be a part of this FDA feasibility study for the Orion cortical implant, and since receiving the implant, it's given so much more hope and excitement for the future because this is the first of its

kind.

And with the advancement of technology, everything is just so getting better and smaller and faster so quickly. Just look at like cell phones. You buy the best one today, tomorrow there's a better one. So that's given me a lot of hope. And, yeah. Like I said, I'm from South Africa. Now in America, and yeah, this has changed my life. I'm part of a blind baseball team now. I volunteer for a bunch of blind organizations where we help other people. So yeah, it's changed my life in a bad way, but also in a better, a good way. So that's my story for now.

DR. RORER: Well, Jason, we're so glad you could make it, and technology came through for you just in time.

JASON: Yeah, just in the nick of time. Thank you.

DR. RORER: Don, can you share your experience?

DON: Yeah, and I think -- I probably really be echoing the sentiments of my fellow panelists and thank you to them for sharing as well as they did. I think the greatest challenges are really that loss of independence, right? So being fully independent and capable of accomplishing really anything, being extremely active in sports and recreational activities to, you know, having to learn. A term that we like to use is being differently abled, right? Learning how to adapt. Really being able to put those types of skill sets in place to realize that you can still do the same things that you did before with vision loss, you just do it differently, everything from learning patience and learning how to work through that.

But that loss of independence, it really becomes a challenge and you become so

dependent upon others. I think a real awakening for me was when our youngest son, and we were off on a vacation one year, and I just found that he had really become a guide naturally. There was never any formal training, but he had become really, really good at looking at the environment around us and calling things out to me in advance to make sure that I was safe in whatever I was doing. And at that point in time for me, I really began to pay more and more attention to how much was I depending on my family members for my day-to-day travel, for my day-to-day activities.

And that was a motivator for me to put my life into perspective, begin to look at how could I play a more active role in the things that I did and challenge myself further to come to terms with vision loss. But we do this often with different events that we participate in at the natural level, then it's trying to help sensitize the world around us to what it is for somebody with vision loss. So whether that's dining in the dark events where we put individuals under blindfold and allow them to attempt to eat a meal. So trying to help sensitize folks to what the most basic daily functions are for a blinding individual, chasing peas around the plate, things along those lines.

But it's a very sighted world. It's a very visual world. As more and technology comes online, a lot of it is around vision and being able to tune into that. So the struggle's real. The challenges are real. But there are unique opportunities for us to adapt and assimilate into our communities, into our environment, to be very productive still in life. I think on the occupational side, we continue to break down barriers there as well. Technology helps us to do that. And for those out there in the scientific realm that are continually adapting new and emerging technologies to give us greater levels of independence but greater

opportunities, again, to fully reintegrate back into society, to be those active participants in our families. And so through venues such as this where we're able to have these shared dialogues, share our experiences and what things are like for us, and then also to continually learn from those that are in a realm trying to improve our quality of life and our outcome.

So we appreciate the opportunity and look forward to the continued discussion.

DR. RORER: Thank you so much, John, and thank you to all the panelists for elaborating on the challenges they face. So now I'd like to go on. This question is for Don as well as John and Ken. You've all not received an implant. Ideally, your vision could be completely restored without any complications. But short of this, what are two or three specific outcomes that would need to be achieved for you to consider treatment with a bioelectronic implant to be successful? Don, since we have you on camera, why don't you go first?

DON: Yeah, and so the challenge I think for those of us, I know for speaking from a trauma perspective, right, multiple surgical procedures and some pros and cons around those processes, we would still, I know myself personally, I would still be extremely open towards looking at these new and emerging technologies. For me, the ability to, I think, put away a backpack full of assistive technology. There was something that was capable of providing me that level of detail, allowing me to stay gainfully employed, to be able to travel independently, to be able to, perhaps, participate in those sports and recreationally activity that really drove my life for so many years.

So I think those are the things that would be the primary drivers for me. How many

devices could I eliminate from my daily arsenal of accessibility technologies, how well could I regain those levels of independence on the mobility sides of things, and then just the overall aspects of improvement in quality of life. But that this was something that wasn't going to have an adverse impact on the current level of remaining sight. Those would be a lot of the drivers for me I think.

DR. RORER: Thank you, Don. Ken, can we hear from you next? Ken, if you're speaking, you're on mute. Okay, while we're waiting for Ken --

KEN: I got it.

DR. RORER: There you go.

KEN: I was trying to -- I was watching some of the discussions earlier and listening to the things that are going on, and I'm a lot more encouraged than I had been before. But I'm still assuming at this point for me, I feel like I would have to get much worse before I would consider it. Probably completely blind even though mine's gone much faster than I had hoped over the years. I'm not there yet, but for me some of the things that I feel like I would need to have out of it is the ability to read or watch TV, even if it's with an assistive device, glasses or some wearable. And then any changes to my eye to accommodate a device wouldn't preclude me from a different device or an upgrade later, and that's because I see the advances that are being made and how rapid they're becoming. I wouldn't want to settle. I'm counting on you guys to make it awesome, and so that's me. And then the last thing is, and I know this sounds kind of tough, but minimal or no training on adapting to the device. And I say that because even though I might not seem like I'm very old, I'm getting to where I'm pretty technically challenged because I just don't even want to

learn some of that stuff anymore. Now I will tell you, I'm kind of the odd man out because most of my blind friends, especially in the veteran community, are very adept at everything from smart phones to other technology on the computers and stuff like that. But I think there's a lot of guys that are like me, and the older you get, the more you just hate technology. So that's me.

DR. RORER: Thank you very much. John, do you have anything you'd like to add to that?

JOHN: Well, just a couple things. I understand exactly what Ken is talking about. I'm in my 80s now, and so I tend to look at investments in terms of the cost benefit analysis, and I don't know which would last longer, me or the implant. But on the implant, I would like, if I were going to get one, and if it can meet these conditions, that if it went bad, I don't know the right terminology, but if it ceased to function properly, could it be replaced without damaging or permanently making me totally blind with no chance of recovery at all? The second thing would be whether that's covered under Tricare or Medicare that I receive. And the other thing is, and this could be misinformation on my part, as to whether I could even get one or not since I have had both of my cataracts removed. So with some of those qualifications satisfied, yeah, I'd be all for it. None of us know when we're going to go, but I don't think that's any, at least for me, I think I'd like to do the things I'm doing now, but be able to do them much more quickly and much more effectively than I am now. If I could see, one of the small pleasures in life is sitting on the back porch with a cup of coffee reading the Washington Post. If I could -- and drive a car again, that would be wonderful, and go to a movie. I don't remember the last theater I was in. I could hear the

sound all right. Nothing's wrong with my hearing. But visually, it doesn't pay me to go to the movies at all. So my computer has become my window to the world, and when that malfunctions, I'm really in a world of hurt.

DR. RORER: Well thank you so much for sharing those additional insights, John. I'd like to now turn it over to Jacob. Jacob, you had a cochlear implant, but you've not received a bioelectronic implant for vision. Can you elaborate on whether you've considered getting one, and if so, what factors you considered and what led you to not getting one?

JACOB: Yeah, absolutely. So with cochlear implant, I was fortunate enough to receive it an early age which has allowed me to be able to communicate and hear and speak to this extent. With that, the whole idea of the visual implant, you know, we are in a very visual, hyper-functioned world, and without that, it kind of makes us fall out of line and feel out of place in the world and feel missed out in those things.

And to just compare it with the hearing device is that we -- it was invented over 50 years ago, and now I'm in a place where you don't even actually see the hearing implant. You can't even tell that I was deaf, and I can have amazing cool things. I can connect it to my phone and be able to work with that. And so there's a lot of crazy, cool technology that has grown from there. And with the visual implant, I do hope that it has that same growth. With that, it's just that I am willing to accept that visual implant.

The only concerns is that with the little vision that I have left, it's just a matter of how big of a chance is it to take that in terms of losing the vision that I already have. But I do know it is most popular to test it when you're completely blind, but it won't be long before I do. So I'm very open minded and with the -- the only thing that would keep me

from it is just the financial aspect. If it's something that will be taken care of, or if it's something that comes out of pocket or insurance, whatever. But I don't have any true big concerns because at this point, when you have hearing loss or vision loss, you're kind of in a point of, you know, what do you have to lose? So you know, I'm very open, and I don't really feel limited to saying no to a visual implant.

DR. RORER: Thank you, Jacob. Don, do you want to share whether you've considered it and what went into your considerations?

DON: Yeah, so I haven't necessarily been put in a position for consideration. I look, and I've really been, I think that Ken's earlier point for me, embracing a lot of the assistive technologies that are out there that, from an external perspective, continue to evolve and emerge which allow me the level of functioning to be able to maintain my work performance. And I think as was shared by fellow panelists, you lose out on opportunities to do things like go to a movie or the theater and really be able to enjoy those things, sporting events.

So it's really kind of looking, and I think as we look at the assistive technologies that we're able to deploy right now and seeing where the limitations are with those technologies and understanding where we are right now with implantables and some of those approaches, those same limitations still exist. So I do want to say that the biggest driver I think for all of us is going to be we all want to hold on what we still have, and there's always inherent risk with any procedure. So when you look at that, you've got to weigh those options and those variables.

And so there's a lot that would go into making a decision such as proceeding with

any type of a procedure and an implantable. And we're going to have to weigh those cross benefit analysis again as one of my fellow panelists stated earlier. That's going to be the biggest driver, I think, for all of us.

DR. RORER: Thank you. John, you shared with us some of your considerations earlier. Is there anything you wanted to add?

JOHN: Well, no, I see more positives than negatives, and the negatives, it's been my experience that when you have to do something, you usually find a way to do it. I was addressing a group of visually impaired people at a retirement center last week, an auditorium full of people, and it occurred to me at that particular point, I asked myself the question, I didn't ask it to them, but I just felt so much at ease and at home helping them to do simple things that they hadn't learned to do yet. And I thought if you're walking in the valley of the shadow of death, it's impossible to have a shadow without a point of light. So I'm thinking, well, what is my point of light here? Losing my vision.

Well as I mentioned before, I have one visual impaired support group, and we meet once a month in the library here, and we built that up now from, I think there were about 10 of us to begin with, and now we have a mailing list of about 50. And over at Reston, It's the same story. Started with about 15, now we've got more than that. And if it had not been for me being in the particular gene pool that I am with macular degeneration, I would not have had the absolute total pleasure of meeting all of those people.

Many of those people are brilliant. They are smart as they can be. They are a pleasure to be around, and they are closer to me than many friends that I've known for years. We all came together because we were all imperfect in one way or another, and we

learned to love each other in spite of our imperfections because after all we were there to support each other and help each other. And you can't say that about too many groups. So I'm delighted to be a part of that group. Would I trade that to see better? I don't really look at it as an either or. If I got an implant and I could see well enough to drive, I would still go to those meetings and help as many people as I could and give them the benefit of my experience.

I have loved the speakers this morning, and as I listen to all of the speakers this morning, and I'm going to do the same this afternoon and tomorrow, I'm at the keyboard. I'm taking notes so that our next two meetings that I go to, I'll be able to share what I've learned here about progress that's being made and methods of coping with the limitations that we have.

DR. RORER: That's wonderful, John. Thank you so much for sharing. Ken, do you have anything that you wanted to add regarding the considerations that you already discussed with us?

KEN: Are you talking about those additional barriers in place?

DR. RORER: Well, let me clarify. Earlier you had talked about that you had thought about what bioelectronic implants for vision restoration could potentially do for you. Are there any other factors that you would consider that might lead you to not getting an implant?

KEN: I think everybody's pretty much hit on it. I think the only other thing that I would submit to you is I understand that there's a limited number of places in the United States that this can take place. And for me, some of it would be maybe geographically

challenged. My wife still works full time. She works six days a week. And it's been my experience you don't just make one trip to the doc and it's done. So a lot of it for me, also, may be follow-up exams, the travel involved with that, how far it is, costs, those kinds of things, but by and large, what I would have told you a few days ago, I would have absolutely never considered it. My mind was changed considerably after watching the previous three or four folks speaking before this panel.

DR. RORER: Thank you very much. So now I'd like to bring in our panelists that have received an implant for vision restoration. Terry, Jason, and Cleone, you have received an implant for vision restoration. Are you currently using the implant, and if so, can you elaborate on how you use it? Terry, you've had a retinal chip. Can we start with you?

TERRY: Yes. I do have what they call the Argus II right now, and I've had that since 2015. But before that in 2004, I was implanted with the Argus I. And it was 16 electrodes biodevice, and it helped me distinguish between light and dark in some ways, which I didn't have before. And so before all this happened, I was -- I lost all my sight in '93. The following you, I was very lucky to hook up with the -- group and a couple of social support organizations for the blind where I live, and that made a tremendous difference to me because I knew I wasn't the only blind person out there. But it was very difficult to go from working to not working. And that support that I had from those groups still carries on today.

But getting back to the Argus I, I found out about it through a family friend, that at the University of Southern California, they were looking for one last person to be part of a clinical trial. And so I met with Dr. Mark Humayun there, and he explained to me they were

looking to implant one more device in me if I passed all the tests. And luckily I did. And that really gave me a new lease on life thinking that maybe one day I could see more than I could now which was nothing. That was a really beautiful thing to be a part of. And I was with that device for eight years.

And then in 2015, I was told I could have the Argus II, and that really opened up other avenues for me and gave me opportunity to see more with that device than I did with the first one. So with that in mind, I was part of that for four years actively, going back and forth and laboratory testing and different things like that. So I use the equipment here at home, and what it does for me, I was able to see with the help of natural and artificial light used in different ways. You have to -- it's not just a matter of turning on a lamp. You have to have light directed at a certain area to help you. The same way when you're outside, you have to experiment with it and see is the light better behind me, next to me, in front of me. How does it work?

And I had to go through a lot of self-analysis with that to find out how best to use the device and how best it could help me.

DR. RORER: Thank you very much, Terry. Jason, can we hear from you about your cortical implant?

JASON: Yeah, so like I said in the beginning, I'm one of, originally, one of five people that had the opportunity of receiving this experimental brain implant. I traveled all the way from a different country because it was like a big -- it was a big decision to actually come to America from a different country, say goodbye to your family, your friends, everything that you know, to take this risk. But at the end of the day, for me, it's been 100% improvement.

Going from being totally blind, not seeing anything, to now being able to see -- identify light sources. I can literally, while I'm walking on the sidewalk, tell when there is a tree next to me because it's casting a shadow on the sidewalk. It's blocking the sun.

It was, for me, almost like learning a new language in the beginning. It was confusing. Didn't really know what these flashes of light mean the device creates in your brain. But over time, you learn to interpret the movements, the patterns, how to perceive them. It's not vision as someone that is sighted would think of vision. I can't see faces or facial expressions or silhouettes or shapes, but it helps me. It's that extra layer when I'm navigating the world, right?

So first and foremost, I rely on my orientation mobility skills to get around. I have to know how to get to the corner store to go and buy milk. But now with the device, it's that added layer of now I can see these dumb bird scooters on the sidewalk. Or if there's a car parked in front of me, I'll be able to identify it. I was in a bar wearing the device, and I could see the bartender walk to me and walk away from me because it was just like the previous speaker said. The perfect lighting condition, the person had a very bright shirt on, so it was just all in my favor, and that was amazing. I've been to Dodgers baseball game where I could see the fireworks. Not fireworks like someone would remember it when they were sighted, but I could see some flashes of light which was amazing to me. I saw my birthday candles on my birthday cake, little flickers of light.

Small little things like that that it's really like just giving me that extra little bit of joy in life again that I miss for almost 10 years. So yeah, for me, receiving the brain implant has been a total game changer. And I know it's going to develop. Like the previous speaker had

the Argus I and then the Argus II, I have Orion, the first version, and the next version is obviously going to be better. And it's just going to improve from there on. So yeah, that's what I have to offer right now.

DR. RORER: Thank you very much. Cleone, you've gotten a miniature telescope. Do you want to add to what you've already discussed about how you use your miniature telescope?

CLEONE: Yes, and like you said, I have -- mine is a different type. It's not a bioelectrical. Mine was actually implanted into my eye, into my retina, and it gives me -- I had no sight in my left eye at all. I still do have sight in my right eye. It's not good, but I still do. And what mine has enabled me to do is I can now see the faces of my grandchildren. I can read. True, I have to use larger print, but I love to read, and I can now read. One of the things that I'm really, really happy with is I used to be a quilter before I lost my vision, and I am now quilting again. It might not be as tiny of stiches or as straight as stiches as I used to do, but I am quilting. Last year I made a Christmas gift for all of my family from quilting. This year, I'm working on individual quilts for each of them.

So I am very happy to be able to do that. I have limitation with it. I have no peripheral vision, and I have no depth perception. But I went through extensive occupational therapy after I had my surgery, and I had a wonderful therapist. And she helped me, giving me hints and things that I should do to help me with my vision. And I use those. Sometimes I forget if I get into a hurry, and someone else had mentioned about walking into people. I have done that several times, too. Quite embarrassing, but I just have to -- I deal with it, and I've dealt with it well, and I'm very pleased with the outcome.

And I wish more people knew about it. I would love to help people learn that they can have this, too. I mean, mine was macular degeneration, and I know some people have things that are more involved than I what I do. But with my implant, I have just -- when I was first diagnosed, I was very upset, and I just thought that I would just be blind, and I'm not. And I'm so happy and so fortunate that I was able to do this.

DR. RORER: Thank you, Cleone. So now I'd like to turn briefly back to Jason and Terry to just hear from them since you've both received bioelectronic implants for your vision. We heard about some of the considerations that -- what benefits you might be able to obtain from your implants before you made your decision. Can you elaborate a little more on any risk considerations or any other considerations that were unrelated to the actual visual benefits of your devices? Jason, let's start with you.

JASON: Okay, so knowing that I was receiving a brain implant; I was going to have brain surgery, which was very scary to think of that they're going to cut open your head and place something in your brain and all the risks involved with that. The doctors and all of the people that I was working with in the beginning, clearly laid out the risks and what could happen, the potential dangers. But I've had so many surgeries my life after my accident that caused my blindness that I knew that you could have a tooth removed and you could potentially die. The risk is always there every time that you're put under, you might not wake up.

So I did factor that in. It's going to be a brain surgery. Some complications could happen, and thank goodness, nothing did. I'm perfectly fine. Like I said, they did explain to me exactly what the adverse effects could be, what the potential dangers are. So I was fully

aware of the risks involved in the beginning. And then after the implant itself, there was the fact that we were the first people in the world to -- that would be going through this FDA trial. There had been brain implants, excuse me.

DR. RORER: Keep going, keep going.

JASON: There had been brain implants for vision restoration done in the past, so we're not the pioneers, but this was the first FDA monitored brain implant study that would have been done. So we had to do a bunch of testing afterwards. We had to figure out the parameters like what was the safe amplitudes and voltage or whatever your brain could withstand before going into a seizure or it causing some damage or a side effect. Yeah, I mean we went through all of that knowing that, in the case of that, something might happen, and now we know. We know the limits, we know the parameters, so the next batch of people that are going to receive these brain implants potentially don't have to do all of this because it's been done. It's been four years of going to the university almost weekly for testing or refining of the device. The scientists, the doctors, have put in decades of their blood, sweat, and tears for us as visually impaired or blind people to see something again one day.

So I think it's amazing that they are giving up their lives in the pursuit of helping us in the future. And I mean, like I said, we've basically identified the risks, the dangers. We've pushed those rocks out of the way for the next batch of candidates that wish to have a brain implant. So I think every time someone gets an implant, it paves the way for the next person and makes it more easy for them, less risks, less risks. So that's my personal opinion.

DR. RORER: Thank you, Jason, for being a pioneer patient in this journey.

JASON: Sorry for the rambling.

DR. RORER: Terry, do you want to share what risks you considered before you got your Argus II retinal implant?

TERRY: Well one of the things that Jason was saying about being a pioneer of an experimental clinical trial is you don't always know exactly what you're going to see and when you're going to see it, but you do realize that you're opening up the door for somebody in the future because of all the work between the surgeons, myself, the technicians, scientists, engineers.

I was never really worried about much of anything post-surgery wise because everything was explained to me, what they were going to do, why they were going to do it. And they were always involved with my safety, whether it was any pain in the eye or anything else. So there is a -- with the Argus II, if I could be allowed to just mention a couple things it helped me with. I was told that the device worked best when you have contrast, dark and light, to work with. In other words, if you're looking at a building that's all one color, you're not going to get anything out of it. It has to have some other color there to point you in the right direction.

So I learned how to use the device with artificial and sunlight to my advantage. And one of the things that was really tremendous was in 2017, I was outside and had the device on. And I'm looking around, and the sun, which was facing me when I walked into the building in the morning, was behind me now. So I was looking around, and there was a friend of mine standing about, oh, 10 feet away, and she was there to let people know

when the busses were ready to pick people up to go home.

So I was looking her direction, and I could see -- the further you are away, obviously, the more you can see of something. And I was able to see her waving her arm, pointing towards where the busses were. And I could see her head movement and her arm movement, all the way down to maybe mid-chest level on her. And I thought, oh my god, this is great. This is really great. And there was a lot of successes with the Argus II, but to be able to see that all at one time, really was a big thing for me, and of course telling the people at USC and also at Second Sight, what I was able to see with it and what I was doing to try to make things better between me and the device.

So it's -- all these years have been tremendous for me. Like Jason was talking about, you know, you're in a world where you're going from darkness to a little bit of vision to more, and where you never thought before 2004 that I would ever be able to see anything again. So the technology really was a big, big boost for me, physically and emotionally.

DR. RORER: Well, thank you for sharing that, Terry.

CLEONE: Excuse me.

DR. RORER: Yes.

CLEONE: This is Cleone, and I am going to have to leave. They knew I have to leave. I have a doctor's appointment. But I just wanted to say thank you.

DR. RORER: Thank you, Cleone, for staying.

CLEONE: And thank you to all the other panelists because it's an insight, definitely, to get everybody else's experiences. And, Jason, like you, I was one of the first ones to have this implant, too. So it's -- we're still finding out things more every day. So good luck to all

of you. Thank you.

DR. RORER: Thank you so much, Cleone, for joining us today. We really appreciate your insights.

CLEONE: You're welcome. Thank you.

DR. RORER: Turning back to Jacob, can you describe your experience with your bioelectronic implant? What was your journey like?

JACOB: Yeah, so with my cochlear implant, which is the only implant that I have received for both sides, there was definitely a lot of trial and error at first. As you know, everything comes with a risk. So at the age of 3 years old, I was able to receive my first implant. And with that, I had to do the surgery a couple times, but mainly that's just because I was a growing child and there's complications of your body accepting it or rejecting it. But now I recently actually just three years ago received a new implant because after 20 years, it stopped working, which was expected. And so now I just had my implant, and right now, about this week, I'm actually going to be able to test it and see if the implant is working. So that way I can be able to hear from both sides of my hearing.

With the experiences, honestly, they always have been extremely positive, way more positive than negative, even with the surgery aspects because everybody stresses about pain or functionality or anything after the surgery. Because of how long this has been developed and how crazy technology has grown for me, I was completely painless. They had to cut my head open completely and put the implant and stitch it back up, along with fixing the muscles and everything, and after the surgery, I only had to deal with discomfort for a week. And after that, I was pretty much back to normal. So there was a lot of

positives with time growing from it.

But it definitely has helped me in terms of how I function in today's society. And vision is a big aspect but so is hearing, and without hearing, I wouldn't have gone to public school, I wouldn't have graduated high school let alone college, and with extremely high GPA. Luckily the hearing didn't limit me from my ability to achieve success in what I wanted to obtain. But with vision, driving is such a huge factor in terms of how we function, and it does affect my access to food, friends and family, and let alone how I decide what kind of job I can do because I do depend on Uber, and it does get expensive over time.

But there's a whole lot of factors that do play into my decisions today, and along with the hearing implant, it has removed those obstacles for me. And that's what I'm hoping that the vision will do for most people.

DR. RORER: Thank you so much. Jason, can you please describe the training that you received and what were some of the biggest hurdles that you had to overcome to use your implant? I know you touched upon that before, but is there anything you'd like to elaborate on?

JASON: So like I mentioned earlier, in the beginning, the first couple of years was going to the university almost weekly to do training sessions where we would figure out how we could refine the device, how to map the phosphines that the implant creates in your brain. Phosphines for those that don't know are little dots of white light, flashes of light, that your brain creates when it gets electrically stimulated, your visual cortex. So we had to figure out when they pressed the button on the computer, and I see a flash of light, I had to map it out on the screen for them and tell them, okay, I see it over there. I see

something over there. I'm pointing with my finger for those who can't see, just randomly.

But that took a while to figure out the layout of my vision. And then from thereon, we could create maps where eventually I could -- they would project something on a touchscreen for me, and I would use the device to scan the screen, and I would straight, like within a second or two, touch it, identify where it was. They call it square localization. That was one of the experiments that now is, for me thinking back, it was the freakiest thing. I can see something, and I can point at it, touch it, without fumbling or rubbing my hands all over the table trying to find it or whatever.

So it took a while in the beginning.

DR. RORER: Jason, how long did that process take until you got to where you felt like you didn't have to fumble around?

JASON: Okay, so after the implant, it was about a month of recover, then they started switching my phosphines one at a time. That took about two months, and then after that, probably another four months. So in total, six to eight months from receiving the implant to being able to actually use it quite well.

DR. RORER: And does your training continue now?

JASON: Yes, I don't go in that regularly. I was actually supposed to go in today, but obviously, I'm here. But yeah, we still go in. We still do experiments. All of the scientists and the study team are like I said earlier, constantly trying to refine and develop and make it better. Even if it's the tiniest little tweak of changing a current, changing an amplitude, seeing what it would do better, is it brighter, is it dimmer, does the phosphines last longer? They're doing everything they can to make this thing the Cadillac of brain implants. So

yeah, I think also, again, because we were the first people to do this, they're trying to figure out a way to, when someone else gets the brain implant, it's going to be a plug-n-play, short little training session, and then they're out; they're gone, so that you don't have to spend months at a time to try and figure out what you're learning.

So I think that was one of the patients or one of the panelists things that they mentioned, that they wouldn't want to deal with the intense training to get to use the device. So, yeah.

DR. RORER: Terry, was there the same intensity of your training, and how was your training different for your retinal implant than it was for Jason?

TERRY: For me? Well, in my case, it was explained to me that when a person goes blind, there's a part of the brain called the visual cortex, and it goes dormant because it hasn't been working for years. So when the implant was put in there, in my left eye, what it did, over time, it started stimulating electrically the connection between the visual cortex and the retina where the implant was. So that part was slowly coming around, and at the same time, my part of it with the mobility training and so on that I was given, and also the training I got at Second Sight were different things of my equipment.

I was able to slowly make sense of what I was seeing, either a movement or the contrast between light and dark. For instance, walking down the sidewalk and scanning back and forth, I could see the sidewalk was white and the grass on either side turned out to be dark. So I could tell that with my cane and I could tell that with my device, so it was a matter of coordinating the two together.

And fast-forwarding a year later, I was in the building one day, and it was explained

to me they were going to try something new. So they took me in to this big part of the building, and they said, now, we got a door that's cut our of some kind of wood or something, and it's probably about 30 feet away, a regular sized door, three feet wide, and we want you to scan back and forth with your device and let us know if you can see it. And if you can see it, then walk up there and try to touch it.

Well, I'm scanning back and forth, and finally I see some light at the end there, about 30, 40 feet away. And I took a couple steps. The closer I got, the more I could see the light became brighter. And scanning with the camera back and forth, I could tell where the edges of the door were. So to make a long story short, a half a dozen times, I walk up there and put the cane right in the middle of the door. And I don't mind telling you that that was very, very emotional for me to go from seeing nothing to be able to do that with my cane and the great technology that really has helped me so much. That was the first really breakthrough with the Argus I.

And then Argus II came along years later, and it really opened up even more visual avenues for me.

DR. RORER: Thank you so much, Terry, for sharing your really personal story with us. So now I'd like to wrap things up. I'd like to just hear, Jason, we can start with you. What is the most important lesson you would like to share with us about the management of your condition or your implant?

JASON: If there's something that I would like to share with other people, it's just don't lose hope. I think that's my main thing that I always want to tell other people that are going through the stages of vision loss, either newly blind or going blind. Just don't lose

hope. I myself struggled to accept in the beginning that there's nothing they can do. The doctor said that I'll be blind for the rest of my life; deal with it, and then this brain implant came along and it totally changed my life. Mentally, for my mental health, you know, I was suffering from depression and anxiety and stuff before, and now after the device, it's like a veil's been lifted and there's just hope for the future that it's going to get better and better and better and better.

So yeah my main thing is don't lose hope, and I just wanted to add one thing. People think, oh, you have a brain implant, you're probably like a proceilan doll now. You're scared to do things. And completely the opposite. Like I said, I play on a blind baseball team. We're diving around, running into each other. It has not changed my life in any way where I have to be more cautious. I can still do whatever I want, go be adventurous. And so, I just wanted to point that out to the people that are thinking of receiving or thinking of getting a brain implant. So don't lose hope. That's all.

DR. RORER: Thank you. Jacob, how about you?

JACOB: Yeah, with what I've learned throughout life is that with losing your senses, but, not only if you -- you kind of gain a little sense of loss. And with seeing all this new technology happening, it definitely does give us hope. But the biggest lesson that I have definitely learned is that because once you go blind, once you go deaf, you kind of lose a little bit of sense of independency. And with that in mind, it makes us incredibly stubborn. It makes us want to constantly prove to other people that we can be independent, even if we're missing a few things. But just receiving implants and stuff, it definitely has taught me to learn how to accept help and to ask for help.

And that's one of the biggest challenges that we do face, even if we're tripping or running people over, having a scene being caused because of our limitations, that's just us being fixated on trying to prove to be independent. And you know sometimes, you can -- there is a possibility that you can be independent, but there is a possibility that -- there is also certain situations that we do need help. And it's just a matter of accepting that and allowing ourselves to ask for that.

But with technology, ever since I was diagnosed at the age of 7 with going blind, especially being told I was being to be blind in my early 20s, it definitely has affected my choices. But with the hearing loss alongside with receiving those implants and the positives that has, with that alone, it's definitely gave me a lot of hope for the technology that we do have. And if we can restore hearing then we definitely can restore vision. And so that's kind of the hope that I carry with me with --

DR. RORER: Don, do you have anything you want to add?

DON: No, I think they did a tremendous job in really back that through. The greatest challenge, and I think just probably to reiterate and reaffirm is we're all in this unique journey, coming at it from different perspectives, and there's competing interests out there. Obviously, again, there's those assistive and adaptive technologies that we openly embrace. It's much easier to integrate those into our lives than to look at that additional potential medical procedure and what that would entail and the potential for complications.

So there's a lot that goes into those considerations. But when you can overcome. Again, if you can overcome the volume of technology that somebody such as myself, I've seen it on a daily basis, coupled with the medication management to maintain the current

health of my eyes. We were able to overcome some of those medication uses. How many different pieces of technology are required to do the most basic thing each day which is be able to travel on public transportation, get to a place of employment, do the basic things like go out to lunch with a colleague or do those. It's something that would really improve that level, that quality of life with very minimal impact, then I think it would be openly embraced.

And so we look forward to the future. We'll definitely stay apprised of emerging technologies and we're all, I think, extremely hopefully for any level of restoration that we could experience.

DR. RORER: Thank you. John, do you have any final lesson for us that you would like to share about the management of your condition?

JOHN: Well I think it's been covered, but whoever said never give up hope, I think is correct. When you give up hope, you give up life. And we have to make the best of what we have to work with. And I think that the fulfillment of that is doing all you can. If you do less than that, then you're giving in to something that you don't have to do that; you don't have to be that way. And I learned that lesson. My wife was instrumental in teaching me that.

So it can be very rewarding.

DR. RORER: Thank you, John.

JOHN: One more little thing. I've learned that people have a story to tell, and most people just want to be heard. And even if you can't see them well, you can hear them. And listening is not a hard thing to do, and you'll find out that you learn from everybody you

meet. And I have learned that if I hadn't had a visual problem, I don't think I would have had the patience to do that. So it's been very valuable to me.

DR. RORER: Thank you, John, for the lessons that you've shared with us today. We appreciate it. So, Ken, do you have anything you would like to add?

KEN: The only thing I would add besides from everybody else, while we all have common challenges, the driving freedom and things of that nature, one thing I like to remind all the doctors and scientists, everybody's challenge is a little bit different. And while I may have RP, and my buddy may have it, his conditions may be different. I'm rural; he lives in the city. So all those things that are external to it sometimes, affect our decision making. And that really matters at the end of the day. And sometimes it's family oriented or whatever, but I just want to thank all of them that are involved in this, for their research, and their hard effort, and their work that's going into it. Thank you.

DR. RORER: Thank you. Terry, do you have any important lessons that you would like to share with us?

TERRY: Yes, over the years, I learned a very important lesson. It's not so much what it does for me, which has been a lot, but also with the addition of extra electrodes along the way, above and beyond what I have, that will open up even more visual avenues for other people. And to know that I could be part in a pioneer sort of way to bring that about, it really gives me a good feeling knowing that someday, people younger than ourselves will be able to get these additional electrodes and additional implants and be able to go even further than we have.

So it's not just about me, it's about helping them to get information to help other

people down the road.

DR. RORER: Thank you. So, Terry, you've had the final word. This ends our patient panel discussion for today. So I'd like to thank all of our panelists for the generosity of your time and sharing your personal stories and your perspectives. We have so much to learn from you. We've gained so much knowledge from you sharing your experiences, and we really appreciate it, and we look forward to making advances in this field. Thank you.

MS. NGUYEN: Thank you to all our panel participants for that amazing discussion. That's a great way to wrap up the first day of our workshop. A big thank you to all of today's speakers, moderators, and participants, and of course, a big thank you to all of you in the audience for joining us today.

Today we were provided a great overview of the bioelectronic implant's landscape. We also heard from the FDA who summarized some important regulatory considerations when evaluating these devices, and we heard from groups of diverse stakeholders about important public health topics that need to be considered for those living with the variety of vision loss conditions.

And lastly, we had the unique opportunity of hearing directly from patients about their individual experiences and what they consider to be important when it comes to deciding on treatment options. We really look forward to seeing you all again tomorrow for day 2 where we will focus on topics that can hopefully help expedite innovation in this device space. This will include discussions on the evaluation of safety and effectiveness of bioelectronic implants, different funding opportunities, and post-market considerations after a device is approved.

Thank you so much again for joining us today, and we look forward to seeing you all again tomorrow. See you then.

(Whereupon, the meeting was adjourned at 2:54 p.m. until October 25, 2022.)

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 – BIOELECTRONIC IMPLANTS AND PUBLIC HEALTH IMPACT

October 24, 2022

Virtual/Yorkcast

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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