

**Food and Drug Administration - Ophthalmic Digital Health Workshop
10/23/2017**

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FOOD AND DRUG ADMINISTRATION

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OPHTHALMIC DIGITAL HEALTH WORKSHOP

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October 23, 2017

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7:55 AM - 4:12 PM

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2 Montgomery Village Avenue

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Gaithersburg, Maryland

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21 Reported by: KeVon Congo,

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Capital Reporting Company

1 C O N T E N T S

2 AGENDA ITEM:

3 FDA Welcome

4 Malvina B. Eydelman, MD

5 CDRH Efforts in the Digital Health Space

6 Jeffrey Shuren, MD, JD

7 Welcome from Cosponsoring Organizations

8 American Academy of Ophthalmology (AAO)

9 Michael Xavier Repka, MD

10 American Academy of Pediatrics (AAP)

11 Ken Nischal, MD

12 American Association for Pediatric

13 Ophthalmology and Strabismus (AAPOS)

14 Derek T. Sprunger, MD

15 American Society of Cataract and

16 Refractive Surgery (ASCRS)

17 Natalie A. Afshari, MD

18 American Society of Retina Specialists

19 (ASRS)

20 Mark S. Humayun, MD, PhD

21 Stanford Medicine Byers Eye Institute

22 David Myung, MD, PhD

1 C O N T E N T S

2 (Continued)

3 AGENDA ITEM:

4 Accelerating Innovation To Encourage
5 New Frontiers in Ophthalmic Digital
6 Health

7 Zach Bodnar, MD

8 The Regulation of Digital Health

9 Bakul Patel

10 FDA Perspectives on Ophthalmic

11 Mobile Medical Applications and
12 Telemedicine

13 Ronald Schuchard, Ph.D.

14 Medical Device Data Systems

15 Krishna Yeshwant, MD, MBA

16 Telemedicine in Ophthalmology

17 Paul P. Lee, MD, JD

18 Telemedicine Diagnostic Challenges for

19 Diabetic Retinopathy:

20 Ingrid E. Zimmer-Galler, MD

21 Advanced Analytics in Ophthalmology:

22 Michael Chiang, MD

1 C O N T E N T S

2 (Continued)

3 AGENDA ITEM:

4 Machine Learning in Ophthalmic

5 Diagnostics

6 Linda M. Zangwill, PhD

7 The Patient Interface with Digital

8 Health

9 John Reites

10 Question/Answer

11 BREAK

12 PANEL 1: Safety and effectiveness concerns when a

13 digital health device provides information as an

14 aid for diagnosis and the assets, threats, and

15 vulnerabilities to be considered and identified

16 (Questions 1 & 4)

17 MODERATORS: Natalie A. Afshari, MD

18 and Mike T. Trese, MD

19 PANELISTS: Dimitri Azar, MD; Leslie Bottorff;

20 David Morrison, MD; Darius M. Moshfeghi, MD;

21 Maria A. Woodward, MD, MS;

22 Ingrid E. Zimmer-Galler, MD

1 C O N T E N T S

2 (Continued)

3 AGENDA ITEM:

4 LUNCH

5 PANEL 2: Safety and effectiveness concerns for an
6 ophthalmic digital health device used in a
7 clinical or non-clinical environment and the
8 assets, threats, and vulnerabilities to be
9 considered and identified (Questions 2 & 4)

10 MODERATORS: Mark S. Blumenkranz, MD;

11 Ken Nischal, MD

12 PANELISTS: Michael Abramoff, MD, PhD;

13 Michael Chiang, MD; Pravin U. Dugel, MD;

14 Michael H. Goldbaum, MD; Quinton Oswald;

15 Linda M. Zangwill, PhD

16 BREAK

17 PANEL 3: Effective safeguards and methods for
18 mitigating the risks for an ophthalmic digital
19 health device and the assets, threats, and
20 vulnerabilities to be considered and identified
21 (Questions 3 & 4)

22

1 MODERATORS: Mark S. Humayun, MD, PhD;

2 C O N T E N T S

3 (Continued)

4 AGENDA ITEM:

5 PANEL 3 (continued)"

6 MODERATORS: Mark S. Humayun, MD, PhD;

7 Derek T. Sprunger, MD

8 PANELISTS: Lama Al-Aswad, MD, MPH; Nitin

9 Karandikar, MD, PhD; David Myung, MD, PhD;

10 John Reites; Eitan Sharon, PhD

11 MODERATOR SUMMARIES FOR PANEL 1, 2, AND 3

12 Moderators from each Panel

13 CONCLUDING REMARKS

14 ADJOURN

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1 P R O C E E D I N G S

2 DR. EYDELMAN: I m the Director of FDA's
3 Division of Ophthalmic and ENT Devices. I am
4 honored to welcome all of you to today's first
5 Ophthalmic Digital Health Workshop.

6 Digital technology has been revolutionizing
7 all of healthcare. Ophthalmology, with its ease
8 of obtaining anatomical images digitally, has been
9 inundated with opportunities to improve patient
10 care via digital health technology. My staff and
11 I are driven by our vision of bringing U.S.
12 patients safe and effective medical devices in a
13 timely fashion. Today's workshop, by fostering
14 innovation in ophthalmic digital health will help
15 us bring our vision to reality.

16 Before we start, I want to take this
17 opportunity to thank all of our six co-sponsoring
18 organizations for their hard work during a whole
19 year to make today's event possible. And now I'm
20 truly honored to introduce an individual who has
21 reinvented FDA's oversight of digital health
22 technologies. Dr. Jeffrey, our Center Director of

1 Devices and Radiological Health will now share his
2 vision about ophthalmic -- about digital health
3 innovation plan. Thank you.

4 (Applause.)

5 DR. SHUREN: Thank you, Malvina. It's a
6 pleasure to welcome everyone to today's
7 conference. I also have to apologize and send
8 regrets on behalf of Dr. Gottlieb, our
9 Commissioner. So I was supposed to open up the
10 conference and he was supposed to end it.
11 Unfortunately, he is tied up in hearing prep all
12 day. I think he is testifying twice this week
13 before Congress starting tomorrow so, again, sends
14 his regrets, but this is an area of deep
15 importance to him and to myself.

16 As you heard from Malvina, there are
17 tremendous innovation that's going on and
18 opportunity for greater innovation due to digital
19 health technologies, I mean all the way from
20 enhancing existing functionalities, like the
21 opportunity to provide more precise placement of
22 ophthalmic implants to entirely new

1 functionalities with learning systems and decision
2 support to greater connectivity, connecting
3 technologies so they can share information but
4 also impact each other's function, and then to
5 provide care remotely through telemedicine.

6 Now the north star for the Center for Devices
7 and Radiological Health at the FDA is our vision,
8 that patients in the U.S. have access to high-
9 quality, safe and effective medical devices of
10 public health importance first in the world. And
11 it's not about a competition between countries.
12 It's a recognition that we want medical devices to
13 provide benefit to patients but is of limited
14 value to patients unless they have timely access.
15 And first in the world is simply a good metric for
16 that.

17 Now we at the FDA face some challenges in
18 achieving that vision when it comes to digital
19 health technologies because the regulatory
20 paradigm, while risk-based, is also very product-
21 focused, and it was designed around hardware
22 technologies. And even as they evolved to have

1 software, it was more as a component because
2 digital health technologies are different. And
3 when we talk about these technologies in the
4 international arena, the term we use for "medical
5 devices" is "software as a medical device" where
6 the technology truly is the software. So software
7 as a medical device, SaMD; and when it's in the
8 device as a component, it's Sims. So we think
9 about very different.

10 So hardware technologies; well, they have
11 rapid innovation but it's more around the order of
12 months to sometimes years and in very competitive
13 spaces, we'll see next generation technology about
14 every 18 months. You can learn a lot about
15 hardware technologies by looking at them, taking
16 them apart, kicking the tires, if you will. And
17 their impact on patients tends to be very direct
18 and observable. You can see changes to the
19 structure or the function or measurable biological
20 or physiological parameters. And the knowledge
21 that's generated about one device is often
22 transferrable to other devices within that

1 category.

2 But when we deal with software, it's very
3 different. The innovation cycles are much faster.
4 There are new challenges, like cybersecurity. You
5 can't just look at software and have a good
6 understanding of what it's going to do. And when
7 you go ahead and test it, the impact may not be so
8 direct on patient health. These may be impacts on
9 cognitive and behavioral aspects of the patient or
10 the clinician. And what you understand for one
11 software program isn't necessarily transferable
12 for other technologies even when they have similar
13 functionality.

14 So it's a very, very different kind of beast
15 and we started to revisit our approach on these
16 technologies around 2010 when we started to
17 receive inquiries from software developers, many
18 of them not in the healthcare space but looking to
19 enter it or just having entered it and wanting
20 clarification regarding the FDA approach. And so
21 we started to revisit how we think about these
22 technologies. And at the time, we had already

1 cleared over 100 mobile applications over a period
2 of 15 years but often for very traditional kinds
3 of functionalities.

4 So based upon this deeper dive, we put out
5 draft policy and guidance back in 2011 that we
6 finalized in 2013 on mobile medical applications.
7 And there were three key principles that came out
8 of it; first, a recognition that we should not
9 regulate unless it's truly value-added. So we
10 were seeing lots of technologies being developed,
11 very low-risk, functionalities we'd seen before in
12 hardware but not lots of innovation going on. and
13 we said we might better serve patient care if we
14 backed away from it. So we engaged in the largest
15 deregulatory effort we had as a sector in over a
16 generation.

17 The second was recognizing that what really
18 matters to look at is the functionality, that we
19 would be platform agnostic. So if you made a
20 software application and you put it on a
21 ubiquitous platform like an iPad, we don't
22 regulate the iPad. We'll regulate that software

1 and then the software developer is responsible for
2 the whole system.

3 But the third thing is we recognized we need a
4 new paradigm, we need a new way of thinking about
5 these kinds of products, the old model that had
6 been put in place simply didn't work. And then we
7 started to further expand on that idea of got to
8 be value-added, so you saw policies come out on
9 what we call medical device data systems,
10 essentially the technologies to receive and send,
11 store and display information from medical devices
12 and then applied that same approach on general
13 wellness principles and general wellness claims.

14 Now you're going to hear from Bakul Patel in
15 just a few minutes about our current thinking
16 regarding our approach to digital technologies.
17 You'll hear about our digital health innovation
18 action plan, our pilot on pre-certification that
19 we just launched in July. You'll hear about our
20 efforts in interoperability as well as our efforts
21 to expand this approach in the international arena
22 and drive international harmonization. And you'll

1 hear in particular about a different way of
2 thinking, not focused so much on the product but
3 much more about the firms and the idea that if
4 firms can demonstrate that they conform with
5 excellence principles, let's say they're very good
6 at software and testing, then we may be able to
7 rely on that in lieu or some of all the kinds of
8 evidence we might see pre-market, particularly for
9 lower risk claims, allow those products out there.
10 Then we'll gather that information in the post-
11 market setting, feed that back on a levels of
12 evidence approach that as we learn more, the
13 applications for those technologies can expand.

14 Let me leave you with one thought -- that not
15 only do we need to think about a different
16 paradigm for digital health technologies, but we
17 need a different way to approach it. The
18 traditional model of government acting in a
19 command and control fashion does not work well
20 here. We have to do this collaboratively and
21 today's conference is just a great example. We
22 need to establish a forum or multiple forums where

1 we can bring together the interested stakeholders
2 to work collaboratively and proactively to address
3 common challenges and even unique challenges of
4 the various stakeholder groups through a
5 collective responsibility approach, what we call a
6 "collaborative community," something that we are
7 in the nascent stages of setting up in a variety
8 of areas. But if there's any place where there's
9 truly a need to problem solve in this
10 collaborative community approach, it's here in the
11 digital health technology space.

12 So with that, let me turn it over to Mike
13 Repka to speak on behalf of the American Academy
14 of Ophthalmology. Thank you.

15 (Applause.)

16 DR. REPKA: Thank you, Dr. Shuren, for coming
17 out this morning and everybody else for traveling
18 either far or wide for this platform. It's my
19 pleasure to welcome you as one of the first of the
20 stakeholder organizations that assisted the FDA in
21 sponsoring this, the American Academy of
22 Ophthalmology, who also recognizes the importance,

1 the mission, if you will, of innovation to improve
2 patient care. So our 24,000 members congratulate
3 the FDA on their willingness to be open.

4 We have -- the other sponsoring organizations
5 will come up and if you guys can see who's next, I
6 think it's Derek and then Ken. Thank you, Mike.

7 DR. SPRUNGER: Thank you, Mike. I'm from --
8 President of AAPOS, which is the American
9 Association for Pediatric Ophthalmology and
10 Strabismus. We feel this is a very important
11 meeting so children can be represented as well in
12 all this. It's -- it's pretty timely for us as we
13 have a lot of interest in screening for ROP via
14 telemedicine vision screening, so we have a lot of
15 interest. Like to thank the FDA for allowing this
16 to happen and also for the people, the organizing
17 people. It's been a great group to work with. We
18 look forward to a great meeting. Thanks for being
19 here.

20 DR. REPKA: Thanks, Derek. Ken?

21 DR. NISCHAL: Thank you very much for allowing
22 a representative of the American Academy of

1 Pediatrics. I'm Ken Nischal. I'm on the Section
2 of Ophthalmology. The American Academy of
3 Pediatrics has 66,000 members. One of the things
4 that the Section of Ophthalmology's been very keen
5 on doing is working on the interface between the
6 primary care physician or pediatrician and the
7 specialist. And we've been very interested in
8 some of the new digital health applications for
9 screening for amblyopia, which is one of the
10 commonest causes of visual loss in children under
11 the age of eight. So we think that the importance
12 of digital health in getting to these children
13 can't be underestimated. And again, thank you
14 very much for arranging this.

15 DR. REPKA: Thank you, Ken. Dr. Afshari.

16 DR. AFSHARI: Natalie Afshari representing
17 American Society of Cataract and Refractive
18 Surgery and a warm welcome to you all. The
19 mission of ASCRS is to promote deliver of cutting
20 edge surgeries as well as promoting delivery of
21 care by working with patients, medical agencies,
22 medical communities as well as government. So

1 that delivery of care will be much more possible
2 with the explosion of digital health. So a
3 special thanks goes to Dr. Malvina Eydelman as
4 well as the FDA for spearheading this effort. We
5 look forward to a great meeting and a warm welcome
6 to all of you. Thank you.

7 DR. REPKA: Thanks, Natalie. Mark?

8 DR. HUMAYUN: Okay. Good morning and it's
9 great to be here. My name is Mark Humayun. I'm a
10 Professor of ophthalmology at University of
11 Southern California. I've worked for a long time
12 with the DA medical Device Division, developed
13 many products and perhaps you know me best for
14 working with the Second Sight Argus II retinal
15 implant, which is the only FDA-improved implant to
16 restore sight to the blind.

17 But I'm here today as the President of the
18 American Society of Retina Specialists, which is
19 the largest retina society in the U.S. The
20 mission of the American Society of Retina
21 Specialists is to provide a collegial open forum
22 for education to advance the understanding and

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1 treatment of vitreoretinal diseases and to enhance
2 the ability of our members to provide the highest
3 quality of patient care. So this is a very
4 important conference for us and a workshop. I
5 look forward to working on the panel and sharing
6 that. I'm looking forward to learning a lot from
7 this and thank you Malvina, very timely to have
8 this workshop.

9 DR. REPKA: Thank you, Mark. And finally,
10 from Stanford, Dr. David Myung.

11 DR. MYUNG: Good morning, everyone. Thank you
12 so much for having us here. We're honored as
13 representing here -- representing Stanford here
14 and the Byers Eye Institute at this really
15 wonderful and important event. My name is David
16 Myung. I'm a member of the faculty at the Byers
17 Eye Institute. Also, Co-Director of the new
18 Ophthalmic Innovation Program.

19 So Stanford has a number of collaborative
20 educational and research programs in place with
21 the FDA's Center for Device and Radiological
22 Health. One of them is this educational one-year

1 year-long fellowship in ophthalmic innovation
2 directly collaborating with CDRH. It's a project-
3 based didactic, hands-on fellowship that teaches
4 fellows the -- in a step-wise some often
5 sequential or sometimes parallel stages in
6 development needed for successful
7 commercialization of new medical technologies.
8 The fellows get to collaborate with members of our
9 Department, other Stanford Departments, like
10 Department of engineering, other Silicon Valley
11 innovators and colleagues at the FDA. It's
12 affiliated and, in many ways, inspired by the
13 Stanford Byers Center for Biodesign, which teaches
14 courses like biodesign for mobile health and
15 biodesign innovation. So the fellows get to work
16 with faculty members in our Department who've led
17 the way in a number of new technologies, taking it
18 from bench to bedside.

19 And digital health has been an important
20 recent focus of our -- members of our Department.
21 We've been trying to pioneer devices such as, you
22 know, Smartphone-based visual acuity testing,

1 ophthalmic cameras, new ways of doing visual field
2 testing, new applications in virtual reality
3 headsets, machine learning and artificial
4 intelligence and novel ways of doing ophthalmology
5 telemedicine.

6 One of the things I'd like to do here is
7 actually introduce our next speaker. Our first
8 speaker of the speakers we have today is actually
9 our inaugural innovation fellow, Dr. Zack Bodnar.
10 Zack completed an innovation fellowship in June of
11 this year, is currently one of the surgical
12 vitreoretinal fellows at Stanford.

13 He has a very unique background and perfectly
14 suited for this workshop. He graduated with a
15 bachelor's and a master's degree from MIT in
16 computer science. Then he worked in the tech
17 industry for a number of years before going off to
18 medical school at Dartmouth, then doing his
19 ophthalmology residency at St. Louis University.

20 As the first ophthalmic fellow, he
21 accomplished quite a bit; for instance,
22 successfully drafting a mock pre-submission

1 package for an app that he developed as a resident
2 that measures the degree of ptosis in affected
3 patients using a Smartphone. He then -- he also
4 coauthored an editorial in *JAMA Ophthalmology* on
5 the very subject of this workshop along with
6 Doctors Malvina Eydelman and Dr. Michelle Tarver
7 from the FDA, so in my opinion, a true expert now
8 in the emerging field of digital health in
9 ophthalmology.

10 Please welcome Dr. Zach Bodnar to the stage to
11 tell us about accelerating innovation to encourage
12 new frontiers in ophthalmic digital health.

13 DR. BODNAR: Thank you.

14 DR. REPKA: One thing, Zach, before you start,
15 just for minor -- you can come on up -- for the
16 audience. We are on an extremely aggressive
17 timeline today. There are many, many talks and
18 I'm going to ask the speakers to adhere as
19 carefully as you can to times, because we do have
20 these introductory lectures, talks this morning
21 followed by perhaps the most important part of the
22 session which are the panels, the dialogue in

1 which CDRH, the Agency, is looking for guidance
2 from the community on how best to handle the very
3 difficult issues that are going to be presented.
4 So Zach, go ahead.

5 DR. BODNAR: Thanks. Do I have a clicker
6 or --

7 UNIDENTIFIED MALE: Well, you could --

8 DR. REPKA: -- which means I'm going to have
9 to cut speakers off, I guess.

10 DR. BODNAR: Okay. Well, I'll try not to be
11 the first. It's a pleasure to be here, everybody.
12 I have one financial disclosure to make which is
13 that I've done consulting work for DigiSight
14 Technologies over the past year. And it's my
15 pleasure to talk to you about mobile medical
16 devices and digital health.

17 So there really have only been three
18 technologies invented in the modern era that human
19 beings are willing to carry on their person at all
20 times, and that is the wristwatch, the credit
21 card, and the mobile phone. Since the iPhone was
22 introduced in 2007, the number -- the percentage

1 of Americans who have Smartphones has increased up
2 to 77 percent, so they're pretty much ubiquitous
3 devices now. And they're great platforms for the
4 development of mobile medical devices and just
5 medical devices in general. They have graphics
6 processors, which are excellent for hardware
7 acceleration of graphics, and they have high
8 resolution cameras for the capture of photo and
9 video. They have biometric sensors as well and
10 they have very flexible dynamic user interfaces.
11 The touch screen is very intuitive and can be
12 customized in a myriad of ways that make it
13 possible for medical devices to be customized. In
14 addition, developing for a Smartphone or a tablet
15 is a rapid process, which increases the rate of
16 innovation and deployment of these devices.

17 Now, of course, digital health doesn't just
18 encompass mobile medical devices and Smartphones.
19 It's things that we're also familiar with that are
20 becoming integrated into part of the internet of
21 things as computational power is added to things
22 that are traditionally what you could consider as

1 analog devices. So now we have digital phoropters
2 and all kinds of things that are integrated with
3 Bluetooth and wireless and other technologies that
4 enable additional computational power.

5 Now that raises a question of what exactly is
6 a medical device in this context now. So the FDA,
7 based on the Federal Food and Drug Cosmetic Act,
8 defines a medical device as anything that's not a
9 drug but is intended for diagnosis, management or
10 prevention of disease. And as was mentioned
11 earlier, software in and of itself can meet that
12 definition. In addition, a consumer medical
13 device like a Smartphone can be transformed into a
14 medical device either by adding software or by
15 adding hardware extensions that enable those
16 capabilities.

17 So there's great potential for this. We're
18 already mentioned telemedicine as one application
19 and you can see from the right side of the slide,
20 there is already a pretty rich ecosystem of
21 applications and devices that have been developed
22 on these platforms. These allow patients to

1 personalize their health data collection. They
2 enable home health care, disease monitoring, and
3 will create innovations for screening, diagnosis
4 and new management of ophthalmology diseases.

5 But the create challenges for device
6 developers; namely, as was mentioned earlier, many
7 of the companies and organizations that are
8 developing these devices are not traditional
9 medical device developers. They're software
10 developers that are entering the space for the
11 first time, and so they may not understand the
12 rules and regulations regarding regulation of
13 medical devices and whether or not their
14 application even meets these criteria. Things
15 like unmodified hardware change their risk profile
16 when they become a medical device so while the
17 torch on a Smartphone camera is perfectly safe in
18 the hands of somebody taking their family photos,
19 it becomes a different risk hazard and different
20 profile when that same torch is used to take
21 camera -- take pictures of the back of the eye.
22 In addition, this all depends on the setting in

1 which the devices are used. For example, within
2 the operating room, these devices have to be able
3 to coexist wirelessly with all of the other
4 technology that's available. And it depends on
5 the intended use and the user that is trying to
6 use the device. A patient is going to use a
7 device much differently and understand its
8 operation much differently than a physician.

9 Of course, all engineers -- experienced
10 engineers know that small changes in these complex
11 systems can have a cascade of consequences. They
12 have robust quality assurance frameworks to ensure
13 that the catch errors early but they need to think
14 about these things in terms of safety and also the
15 usage profile for patients. Small changes in the
16 user interface, like the size of a button or the
17 label or its color can profoundly change the way
18 in which a patient may use it, and that can
19 potentially impact its safety.

20 These are data-driven devices, which means
21 that HIPAA considerations are important as well.
22 It goes without saying that personal private

1 health information should be encrypted on these
2 devices but it's also important to recognize that
3 not everything about this is completely within the
4 control of the developer. For example, the
5 operating system and the hardware itself is
6 developed by a third party. That means that when
7 operating system updates come out, which are often
8 done in order to address security flaws, there --
9 it's the responsibility of the developer to notify
10 the end user who is then responsible for
11 installing the device -- the update. But the
12 ultimate responsibility for safety and security
13 rests on the developer itself.

14 There are questions related to telemedicine as
15 well. Because these devices are mobile, it puts
16 them in the hands of non-physician users in
17 different settings which raises the questions of
18 when is physician oversight necessary, is there a
19 need for realtime synchronous communication.

20 And when patients are the users, that changes
21 the risk profile as well because there, the errors
22 and patterns of misuse that patient has are going

1 to be different than those of an expert user.

2 As I said, most technology enterprises have a
3 robust system, development cycle beginning with
4 design, development, quality assurance including
5 integration and unit testing that is pretty well-
6 established and they can leverage that as long as
7 they recognize that they are also testing for
8 safety and effectiveness of devices. One
9 particular issue is that because these are
10 consumer devices, it's not possible to test every
11 possible software and hardware configuration that
12 might be deployed.

13 So one way to mitigate that risk is to limit
14 the possibility of installing your application
15 onto only tested configurations. Of course, as I
16 mentioned, it's important to recognize human
17 factors in the testing of these devices which
18 involves robust testing of the user interface and
19 documentation and making errors very clear to the
20 user, to the patient so that they understand White
21 House en there are safety issues.

22 But with all that, there's great promise for

1 this technology. It has many advantages. It
2 brings the technology to the point of care. That
3 can be the Third World, it can be the E.D., it
4 could be a school. It improves the efficiency and
5 automation of many routine tasks that physicians
6 do. It streamlines communication between patients
7 and their providers.

8 The other thing is because these are mobile
9 devices, you have the opportunity to gain insight
10 into disease states outside of the clinical in the
11 interval in between visits, so for example,
12 tracking intraocular pressure while a patient is
13 at home or at different times of day. The network
14 connectivity of these devices provides information
15 into their actual operation while they're deployed
16 in the real world which means that safety signals
17 can rapidly be recognized and quickly acted upon.

18 The FDA has developed some guidance as was
19 mentioned. The pre-submission program which I had
20 the opportunity to be involved in is a great way
21 to -- for device developers to submit a plan
22 submission to the FDA and learn about how they can

1 improve their development plan and their testing
2 for safety and efficacy. Initially, there's a
3 digital health mailbox that device developers are
4 willing to -- are able to send emails to you.

5 I just want to thank Mark Blumenkranz, Stephen
6 Young, Malvina Eydelman, Michelle Tarver, and Ron
7 Shuchard, who were my mentors over the past year.
8 They did a great job in helping me to develop some
9 of these ideas and really enriching my educational
10 experience. And with that, I pass it on.

11 DR. REPKA: Thanks, Zach. We do have a
12 question period at the end of this session,
13 assuming we have any time at the end of this
14 session. So our next speaker will be Mr. Bakul
15 Patel, who is coming to speak about the regulation
16 of digital health. Mr. Patel is Associate Center
17 Director for Digital Health at FDA and has a
18 longtime interest in sort of this area in business
19 development improvement.

20 MR. PATEL: Thank you -- thank you so much.
21 Thank you, everybody, and this cannot be even an
22 under -- it cannot be said enough but this

1 collaboration and the need for collaboration in
2 digital health is exemplar here in this room. And
3 the more peoples trying to connect the dots is
4 actually even more important as time goes n.

5 What I wanted to do today is just give you a
6 perspective, sort of how we got here, things we
7 have done, how we are sort of getting to a place
8 where we can now all sort of starting to rely --
9 start to rely on these technologies that are
10 becoming part of our lives.

11 And Zach, as he rightfully mentioned, there --
12 there -- enough convergence is happening in the
13 space that's taking, really, healthcare -- or
14 healthcare to all walks of life.

15 And this is really a slide that talks about
16 how digitization and sensors and software is now
17 moving to every part of life and it's becoming
18 something so ubiquitous that computing power
19 sensors, connectivity and software has become the
20 leverage -- the data that we are generating and
21 then converting that into -- for -- converting
22 that into -- for health purposes.

1 So two years or three years ago, I think the
2 conversation was just about variables. The
3 conversation was just about actively tracking but
4 now, I mean today we are talking about how can we
5 use that technology in true healthcare purposes,
6 and how can we use that connectivity that exists
7 and the ability for people to have this technology
8 at a much lower cost and how can that be sort of
9 brought together and make it meaningful.

10 As Jeff mentioned this morning, we truly care
11 about how to get these products to be patient-
12 centered; how can care be delivered in a patient-
13 centered way. At the end of the day, we all look
14 for these technologies to be high-quality and safe
15 and effective but more importantly, for us, as
16 FDA, as -- for us as a community, how can we
17 partner together to sort of create an ecosystem
18 lean forward, you know, 23:23:45 that can get us
19 ready for the digital health future. And that's
20 really what's required at this point in time. I
21 think we'll stop talking about being ready in the
22 next five years but today, I think we need to be

1 ready. And how does FDA do that? So the talk I'm
2 going to give today is about how we got here.

3 When we first looked at what kinds of
4 technology and software exists in the world of,
5 you know, medical devices and we chunked it into
6 these three buckets; software that is simply a
7 real medical device but on its own; software that
8 it's inside a medical device; and then software
9 that is used to make medical device, and they're
10 all becoming important as we move forward. I have
11 an anecdote. You know, a few years back, or
12 actually, I would say 10 years back, there used to
13 be, you know, one software engineer and 10
14 hardware engineers, and I think today if you ask
15 anybody, any organization, it's the opposite.
16 It's nine software engineers and one hardware
17 engineer that is employed in any of those
18 companies. And the reason is you can do many
19 things very easily. The hardware has become so
20 malleable that you can change it and change things
21 that it's intended for by just changing software.
22 And that has been sort of the trend as we move

1 forward.

2 How do you sort of take that and sort of bring
3 the two to this place of healthcare and what does
4 that mean? So you take those three things that I
5 talked about, software that can show up as, and it
6 raises a lot of issues and a lot of sort of topics
7 for us to connect, to think about. And it's all
8 driving by connectivity, driven by technology,
9 driven by sensors so it brings up, you know, can
10 it be used for diagnostics, too; can it be used
11 for simple telemedicine. And in a way, that may
12 actually touch -- cut across care giving to care
13 managing across the spectrum.

14 And then you have sort of advances in
15 technology in terms of artificial intelligence,
16 machine learning, algorithms are continuously sort
17 of evolving over time and what does that mean in
18 terms of regulations. And as we talk -- and I'm
19 hoping today we'll have -- get some ideas about
20 how we sort of move forward in those spaces.

21 But one thing I would say, that connectivity
22 also has raised many, many, many different issues;

1 cybersecurity and interoperability. There's a
2 need for interoperability and then the need to
3 protect that interoperability solution through --
4 and being careful about cybersecurity.

5 We do have policies that we started off in
6 2013 with mobile medical apps but just scratched
7 the surface that really talks about, you know, how
8 do we sort of move forward and focus on things
9 that are really important and that can be value-
10 added. We have, over the last five years, we have
11 published many, many documents and it's really
12 about how do we focus on the high risk
13 functionality and really allow the low risk
14 functionality to flourish and give a pathway for
15 people that can create technologies in the high
16 risk phase. And that's really how we've sort of
17 been approaching this area altogether.

18 What does that mean? It does not mean that we
19 can only do this locally here. Digital health, by
20 definition, is global. Software, by definition,
21 is global. That means that connectivity and
22 operability of those products can be -- does not

1 know the boundaries of the geography, right. So
2 we work together with our international partners
3 and regulators to figure out what should that
4 starting principal look like and how should we
5 even think about going forward.

6 Over the last -- in the last five years, we've
7 been -- or four years we've been sort looking at
8 how do we sort of take the concept of software as
9 a medical device and have a framework that can
10 actually help people understand and get off on the
11 same page. As Jeff mentioned, we can't touch and
12 feel software when you look at it and the concept
13 of, you know, not knowing what it looks like, what
14 impact does it have starts off with a very
15 fundamental thing called definition of what the
16 product does. And it seems pretty commonsense but
17 what we found over time is that description was
18 not standardized so we ended up defining -- if you
19 define it in a certain way, you will actually know
20 where the software sort of falls into and what
21 markets.

22 Now again, this is a principle level that

1 crosses the globe, that regulators across the
2 globe have agreed upon and we just published, just
3 a few weeks back, the final document in the series
4 of our documents on software as a medical device
5 that lays out a starting point for us to start
6 considering in each jurisdiction what -- what's --
7 how should we approach it, how should the
8 community approach it. And this was meant to be a
9 guidance, a technical document for regulators as
10 well as industry as we start moving in this area.
11 So that's the second stage. So we have a bunch of
12 documents that we have released that define --
13 that showed how you would focus on and where we
14 would focus on in terms of regulation.

15 Internationally, we worked on coming up with
16 the framework that led us to, most recently or
17 last year, the 21st Century Cures Act, which took
18 our policies that we had so far on where core
19 focus should be and codified it. There are a few
20 things in that 21st Century Cures Act which talks
21 about certain types of functionality would not
22 necessarily be regulated by FDA and gave that

1 clarity based on some of the things that we said
2 we are not focused in our guidances, for example,
3 mobile medical apps, general wellness, medical
4 device data systems, that have become so
5 ubiquitous and become such -- at a low risk that
6 it did not warrant FDA to oversee it actively.
7 Congress took that and codified that into law.

8 So moving forward, we will provide -- we'll be
9 providing more clarity on how those policies are
10 affected in the coming months and that's part of
11 the innovation action plan we published a couple
12 months back.

13 And then let me bring back to like the
14 challenges Zack was talking about of why software
15 is unique. We talked about -- and Jeff mentioned
16 this morning -- is the pre-market timeline from a
17 regulatory Perspective were best-suited for
18 hardware. On the flip side, software development
19 timelines can be continuous. Some of you may have
20 heard about DevOps which basically happens all the
21 time where things develop, created, tested and
22 delivered to the customer on a realtime basis.

1 That is an extreme case of how software can be
2 delivered to patients or users at the end of the
3 day.

4 So just an example of how we have been
5 thinking about the challenges and unique
6 opportunities -- so challenges about developing
7 software and delivering fast is one aspect. The
8 other aspect is things change in software so
9 quickly and we -- our approach to those changes
10 with software, if it doesn't change, I think it
11 may actually cause risk to patients because change
12 is absolutely necessary. So how do you sort of
13 take those unique aspects and turn them into
14 public health benefit is something that we've been
15 looking at.

16 The other point is how does -- how do we take
17 that -- take the unique opportunities that
18 software avails us because you can connect to the
19 patients and the user directly and have that
20 information be collected? How do you leverage
21 that real world experience a user has with
22 software and turn that into something that's

1 useful for patient benefits and for public health?
2 So we've been thinking about those and that led us
3 to this concept that we are going forward, is
4 bringing those four things together and going to a
5 paradigm that really talks about focusing on high
6 risk products or high risk functionality that's
7 aligned software development timelines and aligned
8 with industry best practices but -- and on top of
9 that, being consistent and aligned with the global
10 regulators. That will -- that, we think, will
11 yield better products to market that are safe and
12 have high quality to all patients.

13 So this leads to, you know, what we are
14 going -- what we are doing and what we are
15 going -- how we are going forward with this. The
16 concept emerged of how will you change the
17 paradigm to not focus on product-by-product but
18 rather than product-by-product, take it to a
19 company level, we then trust the companies making
20 these products, we -- based on their
21 organization's excellence and culture of quality,
22 we could imagine a streamlined regulatory pathway.

1 And what would that look like? The pathway looks
2 like if you're -- if you know what kind of
3 products you're making in terms of risk, with the
4 framework that we use in the IMDRF, and you know
5 what excellence looks like, you could afford a
6 straight to market pathway for certain low risk
7 products or changes that could happen over time.

8 Or the flip side is if you're not as
9 excellent, are you building products that are at a
10 high risk. We would come up with a paradigm
11 that's different than what we have today in terms
12 of how we review it. Imagining a software review
13 done by a paper submission is just simply not
14 cognitively, you know, connecting for me or for
15 many others. So how do you change how we review,
16 how we change what we review is something also
17 we'll be looking at this -- during this
18 development. It's all predicated on how we
19 leverage the unique abilities of software that can
20 collect post-market information, real world
21 information, and then feed it back to the product
22 itself.

1 We don't stop there. We don't want to stop
2 there with the development of this program. What
3 we want to do is we want to learn, as a regulator,
4 that this program does not become static. We want
5 to keep this program self-learning as well. So
6 how do you take the evidence that's been created,
7 how do you take the learnings that have been
8 learned by the companies, and how do you aggregate
9 that and bring it back to us to see whether we can
10 make the right -- whether we have made the right
11 choices, can we tweak and can we learn and grow
12 and be scalable for -- as products and
13 technologies grow, because we know this will
14 change over time as we have seen already.

15 One other concept in the IMDRF document which
16 we are adopting in our thinking for the new
17 paradigm is how do you sort of take the continuous
18 learning that can happen, allow for the right
19 clinical evaluation to sort of take place so that
20 there is a wide path for people to start with the
21 small claims that they can make or small
22 functionality claims they can make and learn with

1 product being existence in the marketplace and
2 being used by users and prospectively collect that
3 information that is -- that can supplement your
4 next level of substantiation of claims. So how do
5 you sort of do that more (inaudible)? So in
6 essence, we are creating -- we are taking a
7 chapter out of the book "Agile," that developers
8 use today and applying it to regulatory paradigm
9 and saying how can we be more agile, how can we be
10 learning, how can we sort of allow -- how can the
11 regulatory system allow for products to be safe,
12 at the same time effective, not changing the bar
13 on that safety and effectiveness but being more
14 nimble and more iterative as far as products can
15 get in the market. We feel that will help us get
16 there.

17 How do you sort of get there? So many
18 unanswered questions in this paradigm. This is
19 exactly where we have started when we talked about
20 what an excellence looks like. So I'm going to
21 touch upon this really briefly. We will probably
22 not have time to go over all of these, but this is

1 really what we thought the starting point for what
2 excellence should look like. When we think about
3 patient safety, we all agree that there are many
4 things packed in that word "patient safety," which
5 means people need to make choices for patients all
6 along and throughout the entire product life
7 cycle. What's -- commitment to product quality;
8 commitment to clinical -- be clinically
9 responsible, matching claims, understanding and
10 doing the right evaluation, etcetera; what does
11 that look like? Cybersecurity is one of the top
12 topics right now and at the end of the day, we
13 still want people to be proactive.

14 How do you have these five fundamental
15 principles that we all care about embedded in
16 every organization and if they achieve that, how
17 do we give that credit back to those companies
18 that can then be afforded a path to market in a
19 more trusted way. So this, we believe, is the
20 starting point. This will evolve over time.

21 I know next year at this time, I will be
22 thinking about how these things refined over the

1 last year but really, what -- in the pilot, what
2 we're doing is we're developing -- taking this
3 concept and taking it to the next level and
4 developing a program that will sort of refine this
5 further, get people to include these principles in
6 their own balance scorecard so they're monitoring,
7 and we are able to just sort of observe and not
8 have inefficiencies because somebody has to start
9 reporting something to us or creating something
10 special for us We are trying to leverage what
11 exists in the -- by existing in the practices
12 today in these organizations. And that's why we
13 announced the nine participants to take what they
14 do best, learn from them and create a program that
15 is best suited for the community.

16 We want other input along the way so I would
17 encourage every one of you to be -- stay engaged,
18 pay attention to what we are putting out. We are
19 going to do the nine participants but we'll share
20 what we're doing with them publicly as well. So
21 any input from that perspective we very much
22 appreciate it.

1 So the concept here is taking the five
2 principles, looking at it from five different --
3 four different lenses. If you allow people the
4 process flexibility and we have allowed people for
5 measurement flexibility but still anchoring on
6 those five principles, can we determine trust; can
7 we prove trust, not just by up front but also
8 after the product's been in the marketplace.

9 So I'm packing a lot of this information that
10 I spent an hour-and-a-half talking to the pilot
11 participants, but this is where we are going and
12 I'm happy to talk a little bit afterwards as well.
13 But as we move through the program, we are
14 iterating as well, we are learning as well. We
15 are also taking what we're hearing from folks,
16 building it in the program. But the way we are
17 approaching to build those three big components is
18 we are focusing the first few months on the
19 excellence principles and how do we identify
20 organization excellence.

21 The next phase we'll focus on -- and not to be
22 very serial on this but we will focus on the what

1 should a review look like and we'll practice what
2 a post-market observation looks like, what -- how
3 do you get access to that data, perhaps change the
4 word from "reporting" to "access" or supplementing
5 the word "reporting" to "access," how do you do
6 that. So we are going to look at different ways
7 of one, informing the agency; two, informing
8 public health; and three, sort of how -- keep us
9 sort of current and learning along the way.

10 I think that was the end of my slides but I
11 want to close with saying if we're -- it's high
12 time we need to look at a paradigm that is best-
13 suited for high risk technologies that are
14 emerging, are collaborating. As you heard,
15 players at med tech companies are not -- they're
16 not previously considered to be part of digital
17 health are now partnering with people that you
18 have not imagined. I mean you -- if you think
19 about the folks like Google and Omada Health and
20 others who have not really been in this space and
21 purely in general wellness are now moving quickly
22 into medical device space, and how do you sort of

1 provide a path for them so they can actually
2 deliver products, bring that innovation to
3 healthcare that we all see for. Thank you very
4 much.

5 (Applause.)

6 DR. REPKA: Thank you, Mr. Patel. So our next
7 speaker is Dr. Ronal Schuchard who is a lead
8 reviewer for Ophthalmology Division, Medical
9 Devices at FDA. His talk will be on FDA
10 Perspectives on Ophthalmic Mobile Medical
11 Applications and Telemedicine.

12 DR. SCHUCHARD: Good morning. Thank you very
13 much for attending and giving me the opportunity
14 to share with you. From the point of view of the
15 ophthalmology review teams that are looking at
16 this area, the ophthalmic digital health area is a
17 broad area.

18 There is a variety of topics that must be
19 looked at when a device comes in for evaluation.
20 You've heard many of these already from previous
21 speakers, Bakul and others, that -- so today we'll
22 look at primarily, because there's not enough time

1 to cover all of these, is software as a medical
2 device, interoperability, and mobile medical
3 applications and last, artificial intelligence or
4 deep learning. Some of you, I think, are aware
5 that, for example, the commercial applications of
6 deep learning is driving this in a big way but
7 obviously, it is overlapping into the digital
8 health. There's a 100 percent investment, Tesla,
9 et al, with autonomous college, if nothing else,
10 in this area.

11 So the types, as already been talked about a
12 couple of times, but just to reiterate; software
13 in a medical device that we see; you're going to
14 hear in a few minutes how perimeters have software
15 that evaluates the results coming out. This is a
16 prime example of software in a medical device
17 where abnormal or normal results are part of the
18 perimetry system. And also, we're seeing more and
19 more and more OCT images where color-coding is an
20 aspect of what is reported or what is put out by
21 the device to enable better reading of these
22 devices.

1 But software as a medical device is where the
2 innovation and where the prime areas that are
3 challenging us in terms of digital health are.
4 And so the top right shows you one example of a
5 cleared device that is using a Smartphone to do
6 at-home testing of vision and, of course, you'll
7 hear many times this morning about how cameras and
8 other things within Smartphones are being
9 utilized.

10 So it is a rapidly-evolving landscape. Many
11 ophthalmic devices we already have and will
12 continue to expand in terms of the digital
13 technology. Software diagnostics, CADX, computer
14 assisted diagnosis, and advanced analytics, which
15 is the computer assisted detection are rapidly
16 emerging. The greater connectivity and the
17 interoperability is going to introduce new but it
18 has greater aspects of the things that we must
19 consider.

20 And so all of these areas are rapidly -- and I
21 put a little slide there that shows *Moore's law* --
22 and yes, this is an expanding field that is only

1 going to increase.

2 So telemedicine in ophthalmology is here
3 already. We are seeing that telemedicine is
4 practiced in ophthalmology but to note that it is
5 not regulated, the practice of telemedicine is not
6 regulated by the FDA. There's many devices within
7 the telemedicine or the tele-ophthalmology --
8 the -- there are many devices within the
9 telemedicine world that are regulated but the
10 practice. You'll find that there's a lot of what
11 we refer to as medical device data systems, that
12 is systems that transfer, store, display the
13 medical device data but they don't control or
14 alter the function of the device. And these
15 devices in themselves are also as part -- as Bakul
16 has mentioned, the 21st Century Cures has changed
17 how we do things and functionality is no long part
18 of the definition of a medical device.

19 So telemedicine systems, the devices within
20 the telemedicine that you'll typically see are
21 like ophthalmic cameras. Many of the cameras that
22 produce the images, they are regulated and at-home

1 vision testers can be regulated although they can
2 be class I devices; therefore, they would be
3 510(k) exempt, so we are seeing visual acuity, an
4 Amsler grid and a variety of visual function
5 tests. So the distinction, again, is that class
6 one or class II 510(k) exempt devices within this
7 world allows one to have perimeters with databases
8 so that their class I. They can be part of a
9 telemedicine program and there's not a distinction
10 between class I and class II with group one light
11 sources for ophthalmic cameras and group two light
12 sources, and you'll hear a little bit more about
13 this in the panel discussion.

14 In all of these things, people will come to
15 the digital health world thinking that they can
16 compare their devices with what's ongoing in
17 telemedicine. But as I've already shared with
18 you, since telemedicine is not regulated by the
19 FDA. Oftentimes we have difficulty with the
20 claims that are made by the telemedicine systems
21 in terms -- especially in terms of the sensitivity
22 and the specificity of the systems. And so,

1 therefore, a comparison to an unregulated or to a
2 practice of medicine is difficult and one should
3 be careful about comparing your digital health
4 devices and especially in the ophthalmology world
5 in terms of these sensitivities and specificities
6 let alone the application to a particular patient
7 which we would be looking at the positive
8 predictive value or the negative predictive value
9 of these systems or devices.

10 I'm having a devil of a time with -- so the
11 categories of health IT is another category that
12 is found within ophthalmic realm. There is
13 administrative functionality. There are the
14 health IT which it talks about admissions,
15 billings, and a variety of those kinds of things,
16 and there is the health management functionality,
17 those aspects of things with managing a patient.
18 But it's not until you get into medical device
19 functionality that we see primarily that the FDA
20 would start providing oversight in terms of those
21 types of things.

22 then in terms of clinical decision support

1 software, which is also an area that is part of or
2 allied with health IT, we see that, again, the
3 health management functionality in terms of
4 clinical health records and drug dosing or
5 reminders of preventive care and those types of
6 things are distinct from a medical device
7 functionality where we start seeing computer-aided
8 detection or computer-aided diagnosis and
9 refraction treatment planning for your laser
10 refractive systems or robotic surgery -- surgical
11 planning may be coming, let along
12 electrophysiology.

13 So the FDA perspective of review challenges is
14 that we lack - there's often a lack of experience
15 for the established device, that is that we
16 really -- this is an innovative world. This is a
17 world that we're seeing for the first time in
18 terms of many devices so there's no clear complete
19 description of the technology or device or there's
20 no experience that we have on how one should
21 describe these types of devices. There is often
22 unclear indications for use and intended us

1 because it explores new areas. We consider things
2 for eyecare clinical environment versus non-
3 eyecare clinical environment or even non-clinical
4 for devices that are going into the home or going
5 into a school, for example. Those are completely
6 different environments and, therefore, the
7 indications and the intended use would be
8 completely distinct and would need to be clearly
9 specified. But there is often a lack of clearly
10 appropriate predicate so this is, being the
11 innovative field, not devices that are already
12 there. And the risk analysis is inadequate given
13 the risk of the device used and again, the
14 environment where it's -- what population, the
15 environment where it's going to be used is
16 critical to be able to do this risk analysis, and
17 here's -- the limited information is not allowing
18 the evaluation. And this is -- this risk
19 assessment is key to what's, as Bakul has already
20 mentioned, is key to what we need to be doing in
21 terms of looking at devices.

22 So for lower risk functionality, we find that

1 the device may not always be enforced in terms of
2 regulatory requirements. These are lower risks
3 and oftentimes are compared to the -- exceeding
4 the limits of exemption but the higher risk, and
5 this is not in other fields like mortality we
6 often don't deal with. But we do risk -- we do
7 deal with risk like permanent vision loss or other
8 aspects of things that are risk functionality and
9 that we need to assess whether or not the safety
10 of the patient... And because of the innovation
11 technology, we're going to find that many of our
12 applications are going to be *de novos* because
13 there's no appropriate -- and once they start
14 coming in as *de novos*, then they get shifted to
15 510(k)s.

16 And it is unlikely that we'll see a lot of PMA
17 applications, at least at first, but you may
18 challenge us, those of you in the field developing
19 the devices. You -- we may start seeing some of
20 the future that we're just not foreseeing yet what
21 would be a class III PMA device.

22 So again, the risk assessment is key and the

1 premarket assessments are to be able to fully
2 define what are the key functions of the device,
3 what are the aspects that are unique and actually
4 key to this device, what aspects make the device
5 vulnerable, what is the impact of that
6 vulnerability and what protections are in place.
7 And you'll hear panels discuss those protections
8 that should be in place to be able to protect the
9 safety of the patient.

10 The methods of mitigating the risk are also
11 part -- a response to this, the safeguards built
12 into the software or the hardware, for example,
13 inherent in the digital health device, methods to
14 limit the intended users so that's another
15 approach to be able to say that we'll mitigate the
16 risk by limiting the intended users or labeling
17 provided for patient use. And finally, training
18 modules and tutorials may be relied upon to be
19 able to mitigate these risks.

20 The medical mobile apps is the area where
21 probably we're going to see the largest expansion,
22 as already mentioned. We don't see a lot in the

1 ophthalmology world the medical mobile apps that
2 are not considered medical devices. You have your
3 Smartwatches that tell you how many steps you've
4 taken today or the variety of things that help you
5 stay fit. We don't have that kind of equivalent
6 in the ophthalmology world, although some but
7 there's not a lot of them. Rather we see a lot of
8 mobile apps that are lower risk mobile apps that
9 meet the device definition. So what we're seeing
10 a lot of these days are people that take Amsler
11 grids and put them on a Smartphone or people that
12 take visual acuity testing and put them on a
13 Smartphone or a tablet. Those types of devices
14 may -- or other types of devices may border that
15 whether or not they are lower risk mobile apps
16 that meet the device definition. But we don't
17 intend to enforce requirements or that they're
18 510(k) exempt.

19 Today what we are trying to focus on is the
20 mobile medical apps, the ones that really truly
21 challenge and innovate and provide us new
22 functionality in the digital health world, and

1 those types of things you're going to hear about
2 today.

3 So to give you an example of the types of
4 things that we have seen in the mobile medical app
5 or the software as a medical device world, we've
6 seen diagnostic mobile apps such as the DI or the
7 Paxiscope. We are starting to hear about R&D in
8 tablet video field assessment where you take what
9 is done with a perimeter and you put it on a table
10 and you go to India and/or rural areas of the
11 United States and you do your visual field
12 screening with a tablet instead of a perimeter
13 device.

14 We're hearing at ARVO there was a symposium on
15 computer assisted detection for diabetic
16 retinopathy and at that ARVO symposium, there were
17 several companies that identified themselves as
18 talking with the FDA already to be able to submit
19 an application. So soon you may see devices that
20 are already CE-marked but they are soon to be on
21 the U.S. market as well for computer assisted
22 diagnosis of diabetic retinopathy.

1 Then in terms of therapy, we are seeing R&D
2 for dichoptic treatment of amblyopia; people that
3 are developing red-green glasses or virtual
4 reality glasses with mobile displays, you see
5 these in the press, you see these in publications,
6 that this is being developed. These are virtual
7 reality with tablet-type of technology.

8 There's R&D for wave-finding and object
9 detection and assistive technology for devices for
10 visually impaired.

11 So to give you a couple examples of disease
12 progression aids and diagnosis, there's the
13 myVisionTrack™ which I showed you before, is the
14 Amsler grid on a Smartphone using circles.

15 There's a Saccadometer Plus which which is an eye
16 movement monitor, EYE-SYNC, which is a
17 nystagmograph looking at abnormal eye movements;
18 ophthalmic imaging systems, there is a large
19 number of them that have come in with the cameras
20 that put their images into an imaging system that
21 then uses software to be able to do additional
22 analysis but these PACS systems are, if they do

1 not do advanced analytics or other types of
2 digital health, they, too, may be just class I or
3 devices that do not need a 510(k), but that is the
4 trigger that you will need to evaluate.

5 So the last topic I'd like to talk about is
6 the interoperability. So we have a picture
7 here -- I've tried -- I've stolen, I admit, a
8 picture that doesn't truly represent the types of
9 things that we see in an ophthalmology, but I
10 would ask you to bear with me and think that this
11 could be a laser refractive surgery system, for
12 example. And that little picture of a guy
13 standing -- or sitting at a workstation, let alone
14 all of the devices that are interplaying with
15 laser refractive surgery, are soon to be changed.
16 So we have devices within a company, if they are
17 all talking, it's very easy for that company to be
18 able to interchange information between these
19 different devices.

20 If, on the other hand, these devices are
21 produced by different companies, then the
22 challenges start increasing in terms of making

1 sure that all of the interoperability aspects are
2 maintained because of different companies and that
3 workstation is now becoming a tablet. People are
4 walking around with a tablet instead of sitting at
5 a workstation. So these are starting to get into
6 the digital health world.

7 The interoperability standards are there.
8 There's -- FDA has recognized 14 standards for
9 interoperability. There is -- I'm sorry for the
10 small print but the standards are there to be able
11 to help with the guidance in terms of the
12 standards that would help you evaluate this
13 interoperability . Of course, the standards alone
14 by themselves do not provide all of the
15 information that you should be thinking about, so
16 the standards alone will not answer all questions.
17 And as the innovation increases, the challenges
18 with making sure that all of the information in
19 terms of HIPAA, in terms of safety, in terms of
20 good effective information exchange is maintained
21 is critical.

22 So in conclusion, ophthalmic digital health is

1 going to lead to many new innovative devices that
2 will provide diagnostic and therapeutic
3 healthcare. We hope today's workshop will foster
4 this type of new innovation in the ophthalmic
5 digital health. You're starting to see, I hope, a
6 phrase that is used by many people in the digital
7 health world. We believe that this digital health
8 will be able to help the right cure for the right
9 patient at the right time be an appropriate
10 phrase. Thank you for your participation.

11 (Applause.)

12 DR. REPKA: Thank you, Dr. Schuchard. So our
13 next speaker will be Ms. -- Dr. Krishna Yeshwant,
14 who is a physician programmer and entrepreneur
15 working with GV. Prior to Google, he worked on
16 electronic data interchange. His background is
17 both Stanford and Harvard. Good morning.

18 DR. YESHWANT: Hey guys. Look at this. All
19 right. So thank you guys for letting me spend a
20 little bit of time this morning talking about some
21 of the things we're doing at Google Ventures. And
22 I'll talk through some of things that I find

1 interesting, exciting about data systems more
2 broadly and we'll find some particular
3 applications in the ophthalmology universe.

4 Just by background, I'm a physician, as you
5 kindly noted. I was a computer scientist before.
6 Had started two software companies, sold one to
7 HP, one to Symantec but am a primary care doctor
8 over at Brigham and Women's now, and I spend most
9 of my time looking at the intersection between
10 technology and healthcare. At Google Ventures, we
11 invest in companies across the space and so if I
12 went through all of my disclosures, I'd spend the
13 entire time here doing that, probably investor a
14 few hundred companies across the space.

15 But I couldn't be more excited about the
16 moment in time that we're at right now. We have
17 Scott's, we have Jeff, we have Malvina, we have
18 Bakul; it's just a tremendous array of insight and
19 forward-looking thought processes around the
20 regulatory sphere here. So I thought I'd just
21 call out a couple of areas that I think are
22 interesting and I'll actually get my timer here

1 started so I don't go too far over.

2 I know that there are some people talking
3 later on around machine learning so I probably
4 won't spend as much time on that today but I'll
5 spend most of the time really on this area that
6 we're seeing a lot of activity in called "real
7 world evidence." And I know there's been a lot of
8 interaction with the FDA over the last few years,
9 really, but increasingly around how we can use
10 real world evidence to help in various parts of
11 the clinical universe. And then I'll kind of
12 interweave some lessons from some of our
13 experiences there.

14 So real world evidence, this is a graphic that
15 many of you have probably seen before, if you can
16 see it in the back, and perhaps some of you may
17 even have helped create. So it's from a report
18 that was released in 2012 from the Institute of
19 Medicine around the learning health system. And I
20 find -- being somebody who's interested at this
21 intersection between clinical medicine and
22 technology, I find this to be at least one of my,

1 you know, goals on life so to speak. This is I
2 think at the dream state of what we can achieve in
3 our healthcare system. And today I'll just walk
4 through it briefly.

5 You know, at the top, you have kind of
6 care delivery and, at least in today's world,
7 thanks to a lot of progress that's happened
8 because of work from the government, we have
9 actually reasonably EMR penetration in the
10 universe. So there is data produced just as
11 clinicians see patients day to day. In an optimal
12 world, that data would be fed into our scientific
13 discovery process, the data coming out of clinical
14 trials, and the process of discovering new
15 therapeutics and diagnostics would be used to
16 fluidly generate evidence that we could then use
17 to rapidly expand clinical limitation of new
18 opportunities and new things that we see

19 And, of course, also from that same report,
20 we're kind of still in a world where a lot of data
21 is kind of lost. In particular, data from the
22 day-to-day work that we do as clinicians, in that

1 array, we see a variety of natural experiments
2 that happen every day that we don't really take
3 advantage of in today's universe. And that's for
4 all sorts of reasons that I think most people in
5 the room are probably familiar with. But that's
6 perhaps what I find most interesting, exciting is
7 other ways in whatever format, whatever vehicles
8 possible to kind of close the loop around the
9 subtle data, that we're producing every day that
10 we're paying for every day as a society, as a
11 system, that we don't really bring back to bear on
12 other parts of the healthcare system.

13 So, to me at least, I think ophthalmology sits
14 in a unique place in being able to reconnect and
15 bring some of that data back to bear in many of
16 the different pieces of the healthcare system.
17 And I think that for a few different reasons.
18 First off, it's unlike, - you know, my practice in
19 primary care. Data in ophthalmology tend to be
20 much more structured. I think part of it is that
21 ophthalmologists are just very smart. They can
22 organize their notes in this really organized way.

1 I'm always jealous when I see the referrals come
2 in and it's all just, you know, this nice tightly
3 compacted note but on the technical side, it
4 allows for a computer to be able to pull the data
5 out far more easily than what we see out of places
6 like general internal medicine. Also, of course,
7 as we've heard already, there's huge amounts of
8 imaging data in ophthalmology and as we'll, I'm
9 sure, talk about later and I'll certainly allude
10 to, some of the techniques that we're seeing in
11 machine learning, deep learning naturally allow
12 for better analysis of these sorts of graphical
13 and the sort of data that comes out and is
14 fundamental to ophthalmology.

15 That naturally leads to, I think, another
16 exciting area on pragmatic clinical trials so --
17 and I think this ties also back into the entire
18 context of there's data being produced, can we use
19 it and more sophisticated ways to give us a better
20 sense of how new therapeutics and diagnostics
21 might be useful across not just the group of
22 people who we might study as we're looking for

1 efficacy but how it might actually work as we
2 deploy these products and services into the rest
3 of the clinical environment, which is obviously a
4 lot more complicated.

5 There are a couple of use cases that just over
6 the last few months that I think we've all seen
7 come through the ophthalmology world where once
8 again, I think if we'd had a unified dataset that
9 is tied into the clinical universe could have
10 been, I think, transformative in our thinking.
11 And I kind of went through with that experiment
12 when I heard each of these pieces of news, you
13 know, so certainly the Lucentis versus Avastin,
14 you know, sort of thought process; you know, each
15 of these medications we'd -- I think are all
16 alike, one had the suspicion that they might be
17 similar in use, and it took a long time for us to
18 be able to put together the clinical trial to
19 raise the funds to get the coordination amongst
20 the investigators to ask this questions. And with
21 that experiment, you know, I often go through when
22 we see these sorts of questions is, you know, if

1 we had this dataset, couldn't we have asked this
2 question. It wouldn't have necessarily be the
3 definitive answer but could we have gotten an
4 earlier read as to whether there's a equivalents
5 and where in our practice do we see other
6 opportunities like this that we're not really able
7 to take advantage of today because of the friction
8 of putting these sorts of studies together.

9 On the opposite -- and I think -- and I
10 just -- I go back to it and say, you know, I think
11 ophthalmology is well-suited because there are
12 large populations of patients out there we can ask
13 these questions of. And again, day-to-day, we are
14 seeing these patients in clinic, we're taking care
15 of them, we're actually running these trials in
16 kind of a natural experiment sort of way but we're
17 not really yet tooled up as an infrastructure to
18 be able to take advantage of all that.

19 A look in the opposite end of the spectrum is
20 kind of small cohorts, which, to me, I think are
21 particularly interesting as we're entering a world
22 of gene therapy. You know, clearly, there are

1 exciting things afoot, even recently with Spark
2 Therapeutics and a variety of other companies. I
3 think we'll see a lot more in ophthalmology just
4 given that the delivery modality into the eye
5 being, you know, perhaps more clear as to how one
6 might do that. But these tend to be small rare
7 disease cohorts and, you know, how do we think
8 about regulating these sorts of drugs when they're
9 small patient populations and can we enable, you
10 know, post-market approval surveillance. And I
11 think once again, this sort of data infrastructure
12 would enable that.

13 So going back to it, I think, you know, I find
14 this to be kind of my guiding principle as we look
15 at various opportunities in this space. And
16 unlike many other specialty areas, I think
17 ophthalmology is, again, particularly well-suited
18 because there's been some work that the societies
19 in this space have already done in starting to
20 pull these pieces together. You know, in
21 particular, there's the iris database that the
22 American Academy of Ophthalmology has pulled

1 together. And it can clearly be applied in a lot
2 of different areas. Whenever and however that
3 happens, I think one of the learnings I've had
4 from the technology universe is to rather than try
5 to, you know, take the whole system on at once,
6 you know, it's always better to try and start in
7 one arena.

8 We spent a lot of time in a company called
9 Flatiron Health, which is a company based in New
10 York working in oncology looking at some of these
11 real world evidence opportunities. And a couple
12 of the learnings that we've seen there as it's
13 applied to the regulatory framework is the deep
14 need for clarity and transparency around what the
15 data is and what the outcomes are. And that
16 sounds obvious but in the end, when we're making
17 these sorts of inclusions around any of these
18 sorts of decisions, one wants to be able to go all
19 the way back to the raw clinical data and any sort
20 of transforms that are done on top of that to be
21 able to understand what is it that's guiding some
22 of this decision-making process. And so -- and

1 the infrastructure here needs to account for that.

2 There's a deep need for careful cohort
3 selection. Thinking back to the -- some of the
4 examples we were talking about earlier. It's one
5 thing to compare it to drugs but you have to be
6 very certain that you're talking to similar
7 patient populations. And leading into -- kind of
8 following out of that or as a corollary to that,
9 there's a real necessity for a pre-specified
10 analytic plan. As a computational person, you can
11 sometimes fall into the trap of asking a whole
12 bunch of "what ifs" just to get to the answer that
13 you want and not necessarily to the ground truth,
14 and I think we've all seen some of the flaw with
15 that.

16 And then, of course, culture incentives are
17 crucial in this whole thing.

18 I'll spend a couple of minutes just talking
19 about machine learning and I know that there are a
20 few people talking about it in the -- you know, in
21 the subsequent sessions but I guess the the main
22 point I want to make just as someone speaking from

1 the perspective of Google is that it's been a
2 transformative set of things that have happened
3 over the last few years, and it's certainly been
4 transformative internal to our company. And I
5 think that we're starting to see how some of these
6 areas are affecting healthcare.

7 You know, the broad painting of it here is
8 that, you know, we historically used "if then"
9 statements to write a lot of our software and over
10 the last few decades, we have seen the
11 opportunities to actually write software that
12 figures out based on exposure to datasets how to
13 classify different inputs.

14 And fundamentally, the structure of what's
15 happening in deep learning, which is kind of this
16 term that I think we all hear a lot, is not that
17 different than what's happened before, you know,
18 is fundamentally the same sort of neural network
19 architecture that's possible today that was
20 possible 30 years ago.

21 But what's different is that the
22 infrastructures that we're running these sorts of

1 analyses on are far larger and far more robust.
2 So when I was a computer science student, we maybe
3 were able to make neural networks that were, you
4 know, single digit sort of layers, so 5, 6, 7, you
5 know, layers in depth. And then you kind of run
6 up against the limitations of what was possible
7 and today we're seeing far deeper sort of
8 structures which will offer far more sophisticated
9 classifications. And clearly, we're seeing that
10 touch on some of the areas. I think we've seen
11 the paper in *JAMA* around diabetic retinopathy
12 project.

13 But I kind of wanted to call out this
14 interesting effect that's kind of well-known in
15 the artificial intelligence and machine learning
16 world called "the AI effect." And it's a little
17 tongue-in-cheek but I figured I'd bring it up here
18 because we talk about it a lot inside of Google.
19 And it's one of these funny things where, you
20 know, there's this quote, "intelligence is
21 whatever machines haven't done yet." And, you
22 know, when we see kind of some of these sorts of

1 advances, it's sometimes easy to kind of look at
2 them and say, well, like the world's going to move
3 forward in this particular way and machines are
4 going to take over and all this stuff, and we hear
5 various venture capitalists saying that we don't
6 need doctors anymore and, to me, I think that's --
7 you know, that's certainly one of the ways that
8 people can characterize it.

9 But I think what tends to happen far more
10 often in these fields --and there are several
11 examples, you know, that we can go through, but
12 usually what happens when an AI application works
13 is it kind of gets subsumed into the field that
14 it's working in. You know, so to that extent, I
15 think as I look at what's happening in the world
16 of machine learning meets ophthalmology in
17 particular, you know, nothing but excited because
18 I think ultimately, it will mean that we're able
19 to do better diagnoses for our patients and get to
20 the sorts of care that they need. And I think the
21 way the world will look at it ultimately is not
22 machine learning taking over some of these areas

1 but rather these areas finally kind of getting
2 some of these benefits of computer science applied
3 in these areas and getting to some of those
4 efficiencies.

5 So just in the interest of time, I'll close
6 the comments there but I'll be around the
7 conference very excited to engage with this
8 audience and thank you very much.

9 (Applause.)

10 DR. REPKA: Thanks for those comments. A
11 couple announcements -- just they were asked. In
12 the interest of interconnectivity, there is a wifi
13 pass code for this room. It's an upper case "W-A-
14 S-R-V." Don't know the source of that but that's
15 great. And the slides will be available to
16 attendees subsequent to this meeting.

17 Our next speaker -- and thank you, Dr. Paul
18 Lee for joining us at the podium. He's the
19 Professor and Chair of the Department of
20 Ophthalmology and Visual Sciences at the
21 University of Michigan and has to direct the WK
22 Kellogg Eye Center and all of its people. Thanks,

1 Paul, for joining us.

2 DR. LEE: Thank you and the organizers for the
3 opportunity to be here. I was asked to speak
4 about an introduction to the area of telemedicine
5 in ophthalmology and we have a terrific program
6 that's put together today.

7 In terms of the rationale for why
8 teleophthalmology is so prevalent and so important
9 today is that we are in the midst, as our last
10 speaker talked about, about a transformation in
11 health and healthcare.

12 And so you can see the pressures on the left
13 that are forcing us to look at the changes and all
14 the new attributes on the right that, as Eric
15 Topol put very nicely, is leading to a new way of
16 looking at medicine and healthcare. And our
17 earlier speakers have already talked about a key
18 part of this movement is to take what we do out of
19 our traditional offices and clinics and de-
20 marketizing it and moving it into the hands of
21 patients where they live as well as other
22 distributive networks.

1 In terms of the level of usage that we have
2 right now, Kaiser is a leader in the
3 implementation of e-health. There are many others
4 but Kaiser last year had over 50 percent of their
5 patient interactions done through remote
6 mechanisms. And so if you look at some of the
7 things that they were doing in ophthalmology; for
8 example, they're using glaucoma suspects being
9 followed only by OCTs after initial examination.
10 There are a lot I interesting things going on out
11 there right now.

12 And the other piece is all the experts we
13 talked to tell us that at least 25 percent of our
14 visits that we do in the office today, within the
15 next few years, will be done by e-health or remote
16 mechanisms.

17 Patients are interested. That's helping
18 driving the market and why this is growing and
19 there are a lot of folks that look at how we can
20 do this. And we all recognize that there are
21 various ways we can interact, storing forward,
22 live motion. There's going to be some good talk

1 about that today.

2 Across the disease areas we have in
3 ophthalmology, there are a lot of different use
4 cases across a lot of different diseases. Pretty
5 much everything that's out there that we do is
6 being investigated and in many aspects, especially
7 in the back of the eye, there's solid evidence for
8 why it works well.

9 So in today's presentations, you've already
10 heard from our colleagues at the FDA and at Google
11 about all the different things that we need to
12 look at as we're interested in moving these into
13 the hands of real patients. Going forward, we've
14 got some great talks about some key examples where
15 there's rich data about what we do and the issues
16 related to understanding their usage. And you've
17 heard about the deep analytics and the deep
18 learning.

19 And the meat of today's presentations,
20 obviously, are going to be the panel discussions.
21 The panel discussions will focus on digital health
22 devices as an aid for diagnosis, safety and

1 effectiveness and the risk mitigation strategies
2 that are out there.

3 Just a few additional thoughts for us as we
4 move forward in today's agenda; a really important
5 question is "what is the gold standard?" Is it
6 what a group of doctors or an individual doctor
7 thinks? Is it a reading center or is it a
8 machine? If we go back to the original ETDRS
9 papers, there was that beautiful grid or table
10 that had the reading center on one axis, the
11 physicians on the other axis, and the diagonal
12 fortunately matched very nicely. But there were
13 differences and discrepancies across there. And
14 so what's truth? What are we going to use to say
15 this is accurate and this is the way we should go?
16 Is it the machine learning? Is it the physician?
17 That's something that we have yet to resolve.

18 A second along the lines of validity is how
19 well does this device or software perform relative
20 to whatever we determine to be the gold standard.
21 And then the reliability piece is very important.
22 If we do repeated measurements, do we get the same

1 result? Within an image, if it's software, do we
2 get the same analysis at different spots with the
3 same characteristics? And also, if it's
4 appropriate, do we get the same result if
5 different people use the equipment? Now this is
6 something that we apply to all the new devices but
7 have we applied it to clinical care as we
8 understand it today?

9 So let's look at some of that information that
10 we have in the literature because I think this
11 will help frame the standards and the context by
12 which we evaluate the new technologies.

13 So the ATA has some nice guidance on diabetic
14 retinopathy in terms of the relative ways we can
15 look at standard comparison, but in real -- the
16 real world -- this study is almost 25 years old.
17 It looked at how ophthalmologists compared live
18 examinations for patients with diabetic
19 retinopathy compared to photographs, single site
20 study but you can see that the performance
21 specifications of various technology elements can
22 rival that of ophthalmologists and that there are,

1 were and potentially still are opportunities for
2 improvement.

3 This is a paper from the Oats Reading Center
4 (ph) out of Miami that reviewed the literature for
5 the simple vertical cup to disc ratio performance
6 in the literature of ophthalmologists relative to
7 other means of analysis.

8 And this is a meta analysis just published
9 recently looking at teleglaucoma and looking at
10 the sensitivity and specificity of performance in
11 the literature and those studies that compared
12 teleophthalmology, teleglaucoma to in-person
13 examinations.

14 In terms of the implementation issues, a key
15 factor is to recall where in the care spectrum are
16 we using this. Is it a new patient or established
17 patient and what's the level of autonomy we expect
18 the system to be able to deliver.

19 Patients do want to use this. There's good
20 data from the public opinion polling that suggests
21 that patients are very receptive to using these.
22 And the National Academy of Medicine has made it

1 clear that the communications aspect of what we
2 find is as important as the diagnostic accuracy
3 for what's considered diagnostic error. We know
4 that the implementation of diabetic retinopathy
5 programs -- this one in LA -- greatly increases
6 the screening rates of use of retina, but there's
7 still a problem in terms of getting people into
8 care even after they've been screened. So to
9 close the loop, we have to keep that in mind.

10 And, of course, there are various legal issues
11 and payment coverage issues, so some questions on
12 the legal liability side on the left for providers
13 and physicians relative to malpractice coverage,
14 to actually use it. On the system side, we were
15 having dinner last night, conversation with Mike
16 Change and Mike Abramoff about if there's an error
17 in a system, who's responsible; is it the system;
18 is it the physician, and it probably varies based
19 on the purpose of the system. Is it an aid in
20 which case the physician's probably going to be
21 responsible. Or is it meant to substitute for a
22 physician in which case it's probably the system.

1 And then there are a whole host of issues we
2 run into that the FDA Centers have a lot of
3 precedence on in terms of radiological monitoring
4 devices and teleradiology in terms of display
5 characteristics.

6 Lots of different state laws that need to be
7 navigated relative to the actual implementation as
8 well as reimbursement issues that are for another
9 time.

10 And just a couple of final thoughts. The
11 first is what's the implication of all this? We
12 saw the reference to the Institute of Medicine
13 National Academies report on a learning health
14 system. As we look at the impact of all of this
15 technology on how we interact with patients, we'll
16 be able to do a lot better. But the essence so
17 far that the system can't quite replace is that
18 human interaction. And so in a way, this has a
19 promise of restoring traditional physician-patient
20 functionality that current regulatory and work
21 pressures keep us from doing as well as we want.

22 The second you've seen is that there are a lot

1 of new entrants and so the world's going to be a
2 really exciting place in the next five years. I
3 see many of our pioneers out here in the audience
4 and participating in a panel, and so I'm looking
5 forward to a terrific day. Thank you very much.

6 (Applause.)

7 DR. REPKA: Thank you, Dr. Lee. So our next
8 speaker will be Dr. Paul Chan, Professor of
9 Ophthalmology and Visual Sciences at Illinois Eye
10 and Ear Infirmary at UIC and Vice Chair for Global
11 Ophthalmology there with a great deal of interest
12 in telemedicine for ROP. So, Paul?

13 DR. CHAN: Great. Thanks, Mike and thank you
14 to the organizers for having me speak here today.
15 Wonderful series of talks which I think leads into
16 what I'm going to talk about, which is where did
17 we go wrong, right. So in terms of diagnostic
18 accuracy and things that we don't necessarily do
19 well, what are we having trouble with and also,
20 how do we do better and what are strategies to
21 make that improved.

22 Here are my financial disclosures. I am a

1 consultant for Visionex Medical Systems, which
2 does make some of these ophthalmic cameras. And
3 I'd first like to acknowledge the collaborators
4 that I work with, especially Mike Chang, the i-ROP
5 Group and the Gen-Rop Group that focuses on
6 education for ROP. So what do we know? I think
7 historically, there are a lot of retrospective and
8 prospective studies looking at whether or not
9 telemedicine and image-based diagnosis for ROP
10 works well. And I think that we've shown that
11 its' very good for identifying something called
12 referral warranted ROP. We've shown that it's
13 reliable, accurate, cost effect. In terms of
14 physician time, it's definitely more time
15 efficient.

16 And there are a lot of active clinical ROP
17 programs outside of the context of the study. For
18 example, SUNDROP -- Darius is here -- is going to
19 be part of the panel with Mike Trese and the focus
20 ROP and also, in a development world, which is a
21 specific interest of mine, many, many ROP programs
22 actively in use and they design their own

1 telemedicine reading centers, so it's going on in
2 the real world.

3 What I'm going to talk about mostly is, well,
4 okay, it's going on but who's really qualified to
5 do these image readings. And this is sort of a
6 personal experience but, you know, are we good
7 enough? And as I mentioned before, a lot of the
8 systems that we look at today, a lot of the
9 programs that we're focusing on focus on this
10 definition of referral warranted ROP, which
11 basically is what we call "type 2 ROP," so things
12 that need to be referred immediately, something
13 that may progress to treatment sooner than later
14 and needs to be examined very quickly by an
15 ophthalmologist.

16 One of the potential diagnostic challenges --
17 I'm not really going to go into image quality,
18 field of view, or go too much into the hardware
19 issue; going to go mostly into how do physicians
20 perform in terms of making the correct diagnosis.
21 We know that experience matters. We also know
22 that potentially, experts have some challenges in

1 identifying pluses use. That's been well-
2 documented. We know that there is a lot of
3 controversy and a lot of variability in how expert
4 graders examine pluses use and make that
5 diagnosis.

6 And in terms of training, so how do we certify
7 graders. That's been a particular interest of
8 mine and there's a lot of variability in, you
9 know, I call it sort of telecertification or how
10 do we certify people to actually read telemedicine
11 images.

12 Many years ago, we started doing studies
13 looking at whether or not board eligible
14 ophthalmologists so these are really general
15 ophthalmologists who finish their residency
16 training, they're going into fellowship; how do
17 they do in terms of compared to an expert grader
18 reading a telemedicine image? They don't do that
19 well, okay, so what's interesting is that they
20 actually misdiagnose type 2 ROP more frequently
21 than not and these are retina fellows who are
22 going into retina practice and when they're done.

1 And we also looked at pediatric ophthalmology
2 fellows.

3 Again, in the general community, sometimes
4 general ophthalmologists are screening for ROP so
5 this has some relevance. And in pediatric
6 ophthalmology fellowships in the community, a lot
7 of times the pediatric ophthalmologist is doing
8 the screening. They're making a diagnosis and
9 then they're calling the retina specialist to do
10 the treatment. Pediatric ophthalmology fellows
11 also don't do very well, right, so the type 2 ROP
12 and also even treatment of treatment required ROP
13 were challenges.

14 So what do we do? Well, we found that there
15 were issues so we created a tele-education system
16 using the system that Michael has with the i-ROP
17 system. And what -- we recruited about 250
18 ophthalmology trainees from around the world, U.S.
19 and international. And it wasn't just to
20 education them to make them better. We also used
21 the system to evaluate their performance and see
22 what they were doing wrong or incorrectly. And we

1 presented them with RP case presentations, very
2 much in the same way that someone would read a
3 telemedicine image; give a case, read the image,
4 how do you do, what's your answer.

5 What did we find? Well, similarly, there are
6 struggles with type 2 ROP, so this referral
7 warranted ROP that we focus on, right; this
8 critical period, this threshold and they're not
9 diagnosing this correctly. Almost 50 percent of
10 the time, they're incorrectly diagnosing this.
11 And why? Well, there are struggles in zone of
12 disease in the diagnosis and there are struggles
13 in terms of pluses used diagnosis. So these are
14 specific categories that they're struggling with
15 that make this difficult to do well.

16 In the international arena, we talked about
17 global. This isn't just about domestic policy.
18 We have to look at the international role and I do
19 a lot of this. And they're also finding similar
20 error rates, right. So type-2 ROP is difficult to
21 examine if you're not experienced. So looking at
22 inadequacies in diagnostic accuracy for ROP, the

1 U.S. international cohort, all of them across the
2 board find difficulties. They misdiagnosis almost
3 50 percent of the time.

4 What does this mean? Well, we need to improve
5 our diagnostic accuracy. We have to find ways to
6 improve the ability to diagnose referral warranted
7 disease to get these kids to an ophthalmologist,
8 to get get kids examined so they don't go blind.
9 And in terms of just the real world, why is this
10 important? Well, general ophthalmologists, you
11 know, we talk about non-physician readers and so
12 forth and so on, well, are they good enough,
13 right? Well, we have over 250 physicians,
14 ophthalmologists in training who just didn't seem
15 to do very well. Okay. Then that's problematic
16 if we're going to implement these systems in the
17 real world.

18 So how do we do better? Well, let's first go
19 to experts and what they might do well with. And
20 when looking at the clinical diagnosis and the
21 image-based diagnosis, we started doing some exams
22 about stage four, retinal detachment. What we

1 found is that retinal detachment seen on a two-
2 dimensional image may be difficult to pick up even
3 among expert graders compared to indirect
4 ophthalmoscopy.

5 Here's an example. Well, so this patient
6 here, you can see the subtle changes here, some
7 traction and some elevation of sub-retinal fluid.
8 Examiner one, stage 4-a, so diagnosed this
9 correctly, but examiner two actually said that no
10 treatment was required. And if that were the case
11 in a telemedicine scenario, this child may have
12 gone blind and didn't receive a vitrectomy.

13 What about aggressive posterior ROP; we
14 published some data looking at this and there are
15 some difficulties in identifying this type of
16 disease. Now we could say that ancillary images
17 in other modalities can help improve diagnosis for
18 AP-ROP or other conditions that may be subtle but
19 again, there are certain things that we may not be
20 doing very well.

21 How can we do better? Okay. So we mentioned
22 the tele-education system. How do we certify

1 readers. This potentially can improve diagnostic
2 accuracy, definitely has implication for training
3 and we think that it has implications for ROP
4 telemedicine as well. Can we add ancillary
5 imaging, so fluorescein angiography, OCT
6 angiography, OCTs into our paradigm and our
7 algorithm? Can that pick up retinal detachment
8 and subtle changes that improve diagnostic
9 accuracy?

10 We've show that, actually, FA improves
11 diagnostic accuracy for identifying this referral
12 warranted disease. We've shown that digital
13 mosaic images may improve inter-grader liability
14 and agreeing among graders, which is important,
15 and also improve diagnostic accuracy for certain
16 conditions.

17 Here's just the data showing that the tele-
18 education system improves performance from U.S.
19 and international trainees for every category of
20 disease.

21 And in summary, we have challenges, right. So
22 I say this all the time to people who say that

1 they want to set up a telemedicine system. Well,
2 it's just about reading an image, right. There
3 are all sorts of logistical issues. It's
4 challenging in terms of diagnostic accuracy. You
5 have to be good at this, right. There's a certain
6 level of quality that we have to look at. How do
7 we do better? Tele-education, standardized
8 certification programs to certify readers,
9 investing in potentially improved imaging in
10 multi-modal imaging, and computer-based image
11 analysis and deep learning that was mentioned.
12 And I think that this is really exciting in terms
13 of the future

14 Now what it comes down to is who should be
15 responsible for ROP telemedicine programs. Now,
16 you know, I sort of a little opinion with some
17 data but in my opinion, I think we're still at a
18 point where skilled ophthalmologists should and
19 need to be responsible for the oversight and the
20 diagnosis and management for decisions regarding
21 ROP care and telemedicine. Thank you.

22 (Applause.)

1 DR. REPKA: Thank you, Dr. Chan. So our next
2 speaker is my colleague, Dr. Ingrid Zimmer-Galler
3 from the Wilmer Institute who's going to speak
4 about the diagnostic challenges for diabetic
5 retinopathy.

6 DR. ZIMMER-GALLER: Thank you very much for
7 allowing me to be a part of this very exciting day
8 today. I do not have an financial disclosures to
9 report.

10 So just to clarify, telemedicine is certainly
11 used in a number of different ways for diabetic
12 retinopathy screening, but we are talking about
13 here is doing the telemedicine screening in the
14 primary care setting. Remember that the big
15 problem we have with diabetic retinopathy is that
16 so many patients with diabetes do not have their
17 recommended eye evaluation but they do go to see
18 their primary care physician. So this is the
19 perfect place where we can capture patients that
20 are not compliant with the recommendations for a
21 diabetic retinopathy evaluation. Traditionally,
22 this is done with a nonmidriatic fundus camera but

1 it can be certainly done with a number of
2 different imaging devices.

3 Traditionally, those images are transmitted to
4 a remote reading center and at least in the United
5 States, typically, the images are then reviewed by
6 a licensed eyecare provider and a report is sent
7 back to the primary care physician generally
8 within one to three business days including
9 whether or not referral to an ophthalmologist or
10 to a retina specialist is warranted for further
11 evaluation. What's exciting is the possibility of
12 using automated image analysis to do this image
13 reading at the point of care at the time when the
14 patient is actually in the primary care
15 physician's office. The algorithms will allow
16 that report to immediately come out and the
17 patient will know whether a referral is needed
18 before they leave the primary care physician.

19 Some of the diagnostic challenges with
20 telemedicine diabetic retinopathy surveillance
21 that I'm going to touch on include ungradable
22 images, diabetic macular edema, the use of wide

1 field imaging, and then the concept of other
2 pathology.

3 So what is an ungradable image? Would this be
4 considered an ungradable image? Or what about
5 this image? Would you call this an ungradable
6 image or is this considered advance diabetic
7 retinopathy with a vitreous hemorrhage. Or would
8 you say "does it really matter if an ungradable
9 image results in a referral as well. So there are
10 a lot of questions that come about with ungradable
11 images. Certainly, image quality depends on a lot
12 of factors, many of which you really can't
13 control, some that you can control include the
14 imaging device. The resolution of most fundus
15 cameras that are available today really is
16 adequate to pick up even the tiniest micro
17 aneurysms, but the field of view comes into play
18 as well. And then we will hear more and more
19 about the use of various handheld and Smartphone
20 adapters to allow fundus imaging with handheld
21 devices.

22 Keep in mind one of the problems with

1 Smartphones is that I'm not sure we really have
2 good enough validation yet and also, an issue is
3 that Smartphone platforms keep being upgraded and
4 by the time you have a validation study done for
5 one Smartphone platform, that Smartphone may be
6 one or two generations further along. The
7 acquisition procedures play a role here, too.
8 This is mydriasis dilating the pupils or not
9 dilating the pupils, the number of images, the
10 number of fields that are obtained. The operator
11 experience clearly still makes a difference,
12 someone who is well-trained on an imaging device
13 is going to more consistently get good images than
14 someone who does this once in a while.

15 And then, of course, patient variables come
16 into play as well; the age of the patient, whether
17 or not they have media opacities, whether or not
18 they are able to be positioned adequately at the
19 imaging device.

20 So ungradable images really need to be
21 discussed in the context of validation, and Dr.
22 Lee already mentioned the American Telemedicine

1 Association has different categories of
2 validation. The American Academy of Ophthalmology
3 also stresses the importance of validation.

4 When we talk about traditional telemedicine
5 diabetic retinopathy systems, the reference
6 standard that we are comparing that telemedicine
7 system to, the "gold standard" is considered ETDRS
8 7-field stereo photographs. When we talk about
9 validating automated systems, what we are talking
10 about is looking at large datasets that have been
11 annotated, that have been looked at by experts or
12 groups of experts and you're comparing how the
13 machine is reading that to the group of experts.

14 The problem with have with validation studies
15 is that the validation really needs to be targeted
16 to the clinical outcome that the program is trying
17 to achieve. So the targeted outcome may be
18 presence of absence of any diabetic retinopathy;
19 it may be presence or absence of vision-
20 threatening diabetic retinopathy; it may be
21 presence or absence of specific diabetic lesions
22 so you can't really compare the validation studies

1 across the board. The measures that we use for
2 validation, of course, include sensitivity,
3 specificity, false-positives, false-negatives and
4 positive and negative predictive values. We need
5 good sensitivity so that we can make sure we pick
6 up all the disease, that we don't miss someone who
7 has significant disease, but we also want high
8 specificity because we want to limit the number of
9 patients that are referred who don't actually need
10 to be referred. This, of course, will increase
11 the cost of the whole screening process and it'll
12 decrease the efficiency.

13 We draw a lot of information from our
14 colleagues in the United Kingdom who have done an
15 admirable job of setting up a national
16 telemedicine diabetic retinopathy screening
17 program and together with traditional
18 examinations, they have now screened more than 90
19 percent of their patients with diabetes, and they
20 have been able to, for the first time in five
21 decades, show that diabetic retinopathy is not
22 longer the leading cause of vision loss in the UK

1 among working-age adults. They first came up with
2 the numbers of a target sensitivity of 80 percent
3 and a specificity of 90 percent, and those are
4 numbers that are often tossed out but we don't
5 really even know if these are the best target
6 number that we should be using.

7 Coming back to the ungradable images, a
8 validation really is not useful if we don't
9 include the ungradable images. For the
10 traditional telemedicine systems, a lot of the
11 validation studies did not include ungradable
12 images. Having the ungradable images included
13 will certainly likely result in a change in the
14 specificity because you're probably referring
15 patients that don't necessarily need to be
16 referred.

17 Again, drawing upon the experience from the
18 UK, they give a target ungradable rate of five
19 percent. That's a pretty specific -- that's a
20 pretty high target to have. And again, it will
21 depend very much on what the outcomes are that the
22 particular telemedicine screening program is

1 looking for. So again, this is not necessarily
2 the best number to be using.

3 With automated systems, one of the things that
4 we can do is adjust the target, the
5 set -- you can have a set point at a different
6 level so that you can minimize the false-negatives
7 but also have a manageable level of false-
8 positives.

9 In the interest of time, we can't really talk
10 about QA, about quality assurance but it's very
11 important to keep in mind that the relevance of a
12 program's validation really can only -- you can
13 only keep that relevance if you have a robust QA
14 program in place as well.

15 A couple of quick words on diabetic macular
16 edema. So clinically, this requires
17 identification of retinal thickening, and this, of
18 course, can be done with stereo viewing or with
19 OCT. And most diabetic retinopathy screening
20 programs don't include stereo images or,
21 obviously, OCT. And without an assessment of
22 retinal thickening, we are traditionally using

1 surrogate markers, so we use hard exudates, micro
2 aneurysms, and hemorrhages in the macula as
3 surrogate markers. But that clearly doesn't
4 identify the extent of the macular edema and you
5 can have surrogate markers present even in the
6 absence of macular edema. So this is an area
7 where we still have work that needs to be done.

8 I also want to just point out some of the new
9 information that we have with ultra-wide field
10 imaging. This, of course, gives us a much larger
11 of the retina that is imaged. And studies have
12 shown that for telemedicine purposes, this can
13 significantly reduce the ungradable image rate and
14 it also reduces the imaging time but keep in mind
15 that these imaging devices are very large and
16 usually, they're too expensive to be used in a
17 screening environment in every primary care
18 setting.

19 What's interesting, though, is that wide field
20 imaging has been shown to, in approximately 10
21 percent of cases, result in a more severe -- a
22 higher level of severity of diabetic retinopathy

1 compared to that same image if you look at only
2 the ETDRS field of view. And this, of course,
3 brings up the question again, what is the gold
4 standard; what is the reference standard if we
5 have information that potentially gives us more
6 information than the reference standard does. And
7 also, for diabetic retinopathy, that brings into
8 question how is this relevant with all of our
9 clinical trials that are based on the ETDRS
10 photographs.

11 Other posterior segment pathology also needs
12 to be considered. This is where perhaps there is
13 a greater question that comes up with a human
14 versus a machine interpreting the images. If
15 there are other abnormalities on that image, how
16 are we looking at that with the machine or do we
17 even need to be concerned about that if the
18 purpose of the imaging is specifically for
19 diabetic retinopathy.

20 And then I'm just going to end with this
21 question that isn't so much a diagnostic challenge
22 but what about the culture change; what will it

1 take; will physicians and will patients accept
2 what a black box spits out and says is the result;
3 will they accept that result. So thank you very
4 much.

5 (Applause.)

6 DR. REPKA: Thank you, Dr. Zimmer-Galler. Our
7 next speaker, Dr. Michael Chiang, is Professor of
8 Ophthalmology and Medical Informatics at the Organ
9 Health and Science University in Portland, who's
10 been active in ROP and comes to speak today about
11 advanced analytics in ophthalmology or, I guess,
12 how to get the doctors to trust the box.

13 DR. CHIANG: Okay, Mike. Thanks. So I'm going
14 to focus on this interface between clinical
15 diagnosis and analytics and artificial
16 intelligence. So I -- a couple of disclosures
17 here; one of them is that I manage a group called
18 Imaging and Informatics in ROP and we get some
19 funding from NIH and a staff and have a couple of
20 financial relationships here. But -- and I also
21 have a couple of relationships through AOO. I'm
22 on the iris registry executive committee. I'm on

1 the board of trustees and manage the -- a data
2 analytics committee but I'm not speaking here on
3 behalf of the AOO. But I think it's a relevant
4 disclosure.

5 I want to highlight that I've worked with Paul
6 Chan and a couple of others here for years on this
7 and'll be presenting some data from those
8 projects.

9 So the disease I will focus on here is
10 retinopathy of prematurity, and, you know, one of
11 the reasons I'm talking about that is because it's
12 the work that I do and it's the work that I'm most
13 familiar with and several people in this room have
14 done a lot of work in this area. But more
15 importantly, I think that I'm going to try to
16 highlight some generalizable principles out of
17 this work that I think are going to be relevant
18 for this topic. Okay. So that's what I hope we
19 can focus on, sort of the generalizable principles
20 that come out of this data.

21 So the topic here is going to be "gold
22 standards." Paul Lee and several others alluded

1 to this, like how do we classify a disease in ROP
2 and diabetic retinopathy but really not a whole
3 lot of other diseases in ophthalmology. There are
4 very clear classification standards that have been
5 develop din the case of ROP over 30 years ago with
6 what's called the international classification of
7 disease, a standard terminology that, really,
8 everybody else in the world uses. And it happens
9 for ROP that these terms are things like the zone,
10 stage, clock hour extent and something called
11 "plus disease."

12 And so because of these standards, we can do
13 clinical trials. And because of the clinical
14 trials, we know that presence of something that's
15 called "plus disease" is the most critical thing
16 that determines whether or not a baby needs to be
17 treated. So if you have plus disease, you are at
18 risk for going blind; you need treatment. Okay.
19 So we really need to be good about identifying
20 plus disease in ROP.

21 So what's plus disease? It means that you've
22 got tortuous arteries and dilated veins in the

1 posterior pole of the retina. Okay. so remember
2 those terms tortuous arteries, dilated veins in
3 the posterior pole. Okay. and if you've got
4 that, that's bad. So one of the problems is that
5 we're not very good at identifying plus disease.

6 Okay. About 10 years ago, we worked on a
7 project where we presented the same images to
8 experts around the world. Now these are not
9 trainees These are legitimate world experts
10 who've led clinical trials in the area. And so
11 here's an example where there's a little bit of
12 tortuosity, a little bit of dilation in the
13 retina. And 15 percent of experts called this
14 "plus disease," 85 percent called this "not plus."
15 And the image on the right side, it's split 50/50,
16 half called it "plus," half called it "not plus."
17 And so we've got a situation where, you know, the
18 world -- you know, this is so important that it
19 determines whether or not you to treat a baby, yet
20 the world's experts are splitting 50/50 or 60/40.
21 So intuitively, that's not good.

22 And so I want to talk a little bit about the

1 science and the art as medicine, because I think
2 that's going to be relevant to this panel here.
3 So seven or eight years ago, I'm on a panel about
4 ROP and one of the experts on the panel used the
5 analogy that there was a U.S. Supreme Court
6 Justice, Potter Stewart, in the 1980's and so the
7 analogy was that plus disease is like what Potter
8 Stewart -- how Potter Stewart described
9 pornography: You can't define it but you know it
10 when you see it, because it just looks bad. Okay.
11 And, you know, that's what I would call the art of
12 medicine, clinical judgment. And yet that comment
13 bothered me for a few months because I thought if
14 we want to be scientific about it, how can we just
15 be saying that things look bad, okay, but you just
16 get a gestalt about it.

17 And so the thing that it made, really, us
18 wonder is that -- you know, we see this all the
19 time in clinical medicine, that the experienced
20 doctor will say, I just don't like the way this
21 looks. And so we got interested in this fact.
22 Well, if everybody is looking at different things,

1 could that explain some of the variability that
2 we're seeing and are these definitions that we
3 come up with post hoc; arterial tortuosity, venous
4 dilation in the posterior pole, is that an over
5 simplification?

6 Okay. And so what we did is we got who we
7 considered the seven most prominent experts in ROP
8 diagnosis in the world. They were people who, in
9 many cases, had come up with the original
10 definition of plus disease and came up with that
11 original classification scheme and, you know, we
12 got them individually into a room and we collected
13 standardized images and we had them, you know, sit
14 there and you diagnose this image, you annotate
15 the images, we'll videotape when you do it, take
16 us through your thought process.

17 Okay. And so there were house of videotape
18 record, you know, hundreds of transcript pages
19 here. And so we analyzed them with a cognitive
20 psychologist. And it turns out that there's a
21 disagreement in the process of diagnosis, that
22 you've got one image diagnosed with expert number

1 one as plus; expert number two as pre-plus, okay,
2 an intermediate state; expert number three is
3 normal; okay, same image and they're all looking
4 at different parts of the retina when they make a
5 diagnosis.

6 Okay. So not only is the diagnosis different
7 but the process of diagnosis is different. And in
8 fact, if you go through and analyze those hours of
9 transcript, it turns out that it's not just those
10 three terms, arterial tortuosity, venous dilation
11 in the posterior pole that they're looking at,
12 it's all sorts of different stuff. Okay. So
13 these terms that we use in ophthalmology are, in a
14 lot of ways, oversimplifications. And so I think
15 that Krishna made a really good point about the
16 ophthalmic exam being structured, you know. But
17 opinion the other hand, what we do as
18 ophthalmologists is we look at images and the
19 counterpoint is that those images are inherently
20 unstructured. And with these classifications
21 (inaudible), we try to create structure out of
22 that but it's not perfect. Okay. In fact, in a

1 lot of ways, its' far from perfect.

2 And that's one of the reasons that, you know,
3 we've gotten interested in things like computer-
4 aided diagnosis. Can you, you know, use machines
5 to, you know, try to quantify these areas and make
6 it more objective and quantitative instead of
7 subject? And so, yeah, we've done some work in
8 this area. There have been a couple others, some
9 in this room, like Mike Trese has done some
10 beautiful work in this area with a guy, David
11 Wallace at Duke University.

12 And, you know, for our team, the data that
13 I'll be talking about represents the work of, you
14 know, us together with Paul and several computer
15 scientists, Jayashree Kalpathy-Cramer from
16 Harvard, (Inaudible) and Deniz Erdogmus from
17 Northeastern University and we've got a team with
18 two post docs, four PhD students and two master's
19 students who've worked on this for about six
20 years.

21 But anyway, we found -- you know, come up with
22 -- you know, we've looked at two different

1 approaches and the ones that Paul and, you know,
2 others have talked about; you know, number one's a
3 classic machine learning approach, and number two
4 is a deep learning approach with convolution on
5 neural networks.

6 And, you know, Paul mentioned the idea of
7 reference standard and I think that's a huge
8 challenge. And the way that we've dealt with
9 reference standards where is that we've captured -
10 - a clinical exam did; in other words, what did
11 the real ophthalmologist diagnose at the bedside.
12 We've taken photographs of every retina and we've
13 had a series of several experts look at each
14 photographs and come up with consensus reference
15 standards that blend, in this case, four different
16 evaluations into a consensus reference standard.
17 Okay. So that's how we evaluate these systems.

18 And I just want to present some data about
19 what we're -- you know, what we're getting here
20 because again, I think the generalizable thing is,
21 you know, what's our concept of how you evaluate
22 these systems and, you know, how you validate

1 them. And Paul, we used terminology. So this
2 happens to be a system that classifies images
3 using machine learning approaches. And so there
4 are 73 images and we're comparing diagnostic
5 accuracy of how well do you classify plus versus
6 pre-plus versus normal, okay, compared to that
7 reference standard diagnosis. And you've got
8 eight experts and a computer system and the eight
9 experts here are between 79 and 99 percent
10 accurate; on the average, 87 percent accurate.
11 And the computer system is 95 percent accurate,
12 okay, for classifying plus versus pre-plus versus
13 normal.

14 Okay. Second approach here is a deep learning
15 approach and, you know, this has gotten a lot of
16 press recently. In our case, we've trained a
17 convolution neural network on a series of about
18 6,000 RP images. Again, every image has a
19 reference standard diagnosis. Okay, so very
20 painful to come up with that for 6,000 images in a
21 consensus way, but "a" under the arc, "c" curves
22 her about***98 for diagnosing plus disease. And

1 so really, really high. If you divided them on
2 independent data sets, the system outperforms most
3 experts. Okay. So in this case, 91 percent
4 accurate compared to between 77 and 94 percent
5 accurate.

6 And I just want to make one point about this
7 black box concept because I think Ingrid made a
8 really good point about, you know, do people trust
9 these systems as black boxes. You know, one of
10 the things that we've looked at is occlusion
11 analysis; in other words, you feed the systems
12 into these deep neural networks and based on what
13 part of the image you don't feed into the network,
14 it can highlight areas here shown in purple that
15 the machine thinks where most important for
16 clinical diagnosis. So in other words, it's a
17 process of working backwards. Okay. What can the
18 machine tell us what the doctor might have been
19 thinking; you know, because if you take that piece
20 of information out, the diagnosis changes. Okay.
21 So I do think that there's potential for these
22 systems to work backwards and tell us what we were

1 thinking in a way that doctors are actually not
2 always able to articulate, because we've done the
3 cognitive psychology studies. So maybe some
4 potential for that.

5 And I want to close just with a couple
6 examples looking at variability because again, I
7 think this is going to be generalizable. So here
8 what we've got is data, in this case, from eight
9 different experts looking at 100 different images.
10 Okay. SO here's one, two, three, four, all the
11 way up to 100 and if the box is "red," that expert
12 diagnosed it as plus disease; if it's "yellow,"
13 that expert diagnosed that image as pre-plus; if
14 it's "green," that expert diagnosed it as normal.
15 Okay. So point number one is that experts seven
16 and eight diagnosed plus disease six times more
17 frequently than expert number one. Okay. So
18 that's not good. And if you go to a different
19 dataset, it's that same six to one ratio. Okay.
20 So this phenomenon of under-callers and over-
21 callers is a real thing. Okay. We all know this
22 clinically but, you know, I think this presents it

1 graphically.

2 The second thing is that for every image, if
3 you give it a score, one point for a "green," two
4 for "yellow," three for "red," and if you average
5 that score for each image, convert it to a color,
6 you've got a continuous spectrum. You've got the
7 very abnormal over here and the very normal and
8 then every color in between. Okay. So that's
9 that graphical represent -- what we do in
10 ophthalmology is a continuous spectrum and what we
11 do when we treat disease and diagnose it is that
12 we draw those lines; okay, are you plus or pre-
13 plus; are you pre-plus or normal.

14 And as ophthalmologists, we've got data that I
15 haven't shown here that ophthalmologists are very
16 good at comparing; okay, what's better, number one
17 or number two, you know, very consistent. But we
18 are not consistent at drawing those lines and I
19 think that's a huge problem. And I think that's
20 where these systems can really help us make better
21 decisions.

22 And so, yeah, we've done some work here

1 choosing sets of standardized images where this is
2 very, very abnormal. And how do we know it's
3 abnormal? Eight experts called it plus, nobody
4 called it pre-plus, nobody called it normal. And
5 this one's very, very normal. Everybody called it
6 normal, nobody called it plus, nobody called it
7 pre-plus, everything in between. And in fact, if
8 you feed these images into that computer-based
9 system and give it a score, it falls on a straight
10 line. Okay. So I think, again, that's where
11 computer diagnosis can really help us as
12 clinicians.

13 And so my -- this is my last slide and these
14 are some points that I think are useful for
15 discussion later. Number one is that I think that
16 ophthalmic diagnosis is innately subjective and
17 qualitative and, you know, we've seen that in
18 diabetes, you know, with Ingrid's story and Paul
19 Lee's story. We see it ROP and they're
20 significant inconsistencies, even among experts, in
21 terms of drawing these lines. And my suspicion is
22 that in the real world, the variability is even

1 more than what we're seeing here. I do think
2 there's a role for expert systems and improving
3 that consistency. I think the bar for these
4 systems should be that they're human-like and that
5 they're not going to be perfect but, you know,
6 they should be as good as humans.

7 And I do think that validation requires
8 transparency. I don't think it's enough to use a
9 single expert as a reference standard like Paul
10 was saying. And, you know, we've tried to use
11 consensus panels, maybe there's a better approach.
12 I think this is a rapidly changing field and, you
13 know, this point was made before. You know, these
14 systems inherently learn from their mistakes, you
15 know, with this concept of the learning health
16 system.

17 And so I hope that in coming up with these
18 rules, you know, we can take that into account
19 where, you know, the cycle time for updating these
20 systems, you know, whatever we can do to try to
21 decrease that I think is going to help the field.

22 And I do think that the intended use of these

1 systems matters. You know, do they a), give
2 advice to physicians in a decision support manner
3 or b), are they closed-loop systems, you know,
4 like (inaudible) for primary care where there's no
5 ophthalmologist involved? And I hope that the
6 FDA's going to consider variable levels of
7 regulation based on the intended use. So thank
8 you very much.

9 (Applause.)

10 DR. REPKA: Thank you, Dr. Chiang. Our next
11 speaker is Dr. Linda Zangwill, Professor of
12 Ophthalmology at UC San Diego and serves as
13 Director of Clinical Research in the Glaucoma
14 Center and Director of Imaging Data Evaluation and
15 Analysis. Good morning.

16 DR. ZANGWILL: I want to thank the organizers
17 for inviting me here today and I want to
18 acknowledge my financial disclosures. And I'll be
19 talking about machine learning in general and,
20 obviously, the applications in ophthalmic
21 diagnostics.

22 Machine learning, obviously, is changing our

1 lives on a daily basis with recommendation
2 engineers, with autonomous driving, and we've
3 heard a lot about it in ophthalmology. And
4 there's terminology that we've already heard about
5 but I just want to emphasize the difference
6 between machine learning and deep learning where
7 the deep learning can really -- the instrument,
8 the machine, the algorithm learns from deep layers
9 and sees the patterns within the layers.

10 There are different types of machine learning
11 tasks, most of what we heard about is supervised
12 learning where you have data and a label. In this
13 case, for example, glaucoma or not from visual
14 fields, the processor looks at the data and the
15 label. You have an outcome, glaucoma or not, and
16 the accuracy is compared to the expert or the
17 label data. Unsupervised learning, you just have
18 data and the machine looks at that data and sees
19 patterns; in this case example, visual field
20 patterns. Sometimes these patterns are very
21 similar that a clinician might identify as a nasal
22 step or paracentral scotoma and sometimes they are

1 not.

2 In terms of machine learning applications,
3 we've heard a lot about today software as a
4 medical device and there are different categories
5 of software as a medical device. And machine
6 learning applications are relevant for informing
7 clinical management, driving clinical management,
8 and treating or making a diagnosis or referral.

9 So there's a long history of machine learning
10 in ophthalmology and it started, really, with the
11 supervised learning and the most applications have
12 been in retinal disease and in glaucoma. Here's
13 an example from my colleagues, Mike Goldbaum in
14 the early 1990s, from UCSD before I arrived,
15 looking at visual fields, and the conclusion was a
16 neural network can be taught to be as proficient
17 as a trained reader interpreting visual fields for
18 glaucoma. So that was, you know, many years ago,
19 over 30 years ago almost.

20 There's lots of work in this area looking at
21 visual fields, looking at fundus photographs,
22 really early with the machine learning, with the

1 neural networks, for glaucoma damage and detection
2 and progression. Similarly, with retinal disease,
3 detection of retinal lesions started very early.
4 Later came detection of diabetic retinopathy.
5 There are numerous challenges to the community for
6 automated detection. And there's -- in diabetic
7 retinopathy, we've heard that's really the most
8 mature, I'd say, in the ophthalmic diagnostics.
9 And once again, there are differences between
10 strategies that wanted a design to detect micro
11 aneurysms, hemorrhages -- this is an excellent
12 review article from 2013 -- and also detection of
13 diabetic retinopathy.

14 Also, there's, as I mentioned, unsupervised
15 learning in ophthalmic diagnostics. Here are some
16 examples where -- mostly in visual fields in
17 glaucoma, some of our work and others where you
18 put the visual fields points in the machine
19 learning algorithm and these patterns are quite
20 remarkably like some of the patterns the clinician
21 identifies and others are not. And we can even
22 see the progression of these patterns that really,

1 the diagnostic accuracy is similar to more
2 standard progression algorithms that we are using.

3 There's been tremendous progress in the last
4 three to five years due to deep learning, due to
5 the computational resources that are now available
6 and also due to available data sets for these
7 algorithms. This is a slide about deep learning
8 and health informatics, the tremendous growth of
9 published articles through 2015. I think if you
10 went to 2017, they graphs would be off the chart
11 but look at where imaging is in here. And in
12 ophthalmology, we use imaging on a day-to-day
13 basis.

14 So can -- deep learning can be supervised or
15 unsupervised and here's an image and it uses the
16 patterns of the image to recognize a face, recall
17 this particular photograph, identify the specific
18 person. Once again, deep learning with
19 convolution neural networks, we can identify
20 specific lesions, micro aneurysms, etcetera as
21 well as diabetic retinopathy or different diseases
22 classifying the severity of the disease, as we've

1 heard, from different speakers to date.

2 I want to highlight three -- oh, here's an OCT
3 for segmentation deep learning that's trying to
4 target some of the more challenging aspects of
5 segmentation with macular edema, exudates, and
6 detecting and measuring the fluid in these
7 lesions. Competitions have spurred machine
8 learning progress in general and in ophthalmology
9 in particular, in 2015, there was the Kaggle
10 competition where they classified five levels of
11 diabetic retinopathy using 100,000 images from
12 50,000 patients with the EyePACS database from
13 California. There were over 661 contestants. The
14 winner, as we've heard, did better than the
15 experts and this was a professor -- or I think an
16 assistant professor from the UK with absolutely no
17 ophthalmology experience.

18 I want to highlight three recent -- very
19 recent papers of deep learning for diabetic
20 retinopathy detection. I apologize for these
21 slides, the legibility, but I want to highlight
22 these because they were done with deep learning

1 with very large data sets with independent
2 validation datasets. We heard a lot about
3 validation and the importance of validation using
4 more than one grader, etcetera.

5 And what's unique about these three studies,
6 and there are others, is that all used, at least
7 for one of their independent validation sets, this
8 method or a dataset from France that had over
9 1,700 images that were graded by numerous experts
10 as one of their validation sets. The first paper
11 used with a lesion-based approach -- this is
12 Michael Abramoff as the lead author
13 here -- and a lesion-based approach with lots of
14 images, and the area under the ROC curve for --
15 curve for referable diabetic retinopathy, was
16 quite high at .98.

17 The second, Gulshan and colleagues at Google
18 used EyePACS database and an Indian database and
19 they also used "transfer learning" where they
20 trained the system on non-ophthalmic images at
21 first, and this tends to boost the performance of
22 deep learning algorithms. They had an area in the

1 ROC curve of .99 for referable diabetic
2 retinopathy. As we've heard, it depends on the
3 target, the objective. The last study was
4 detecting diabetic retinopathy "yes" or "no" with
5 also a very high diagnostic accuracy.

6 We heard about opening the black box and I
7 think this is really where there's' going to be a
8 lot of work in the near future. We heard about it
9 in the last presentation. Here's another example
10 where the automated generated heat maps identify
11 the regions for closer examination by the
12 clinician. This is -- these are the areas where
13 the deep learning algorithm was focusing, at least
14 in part, to detect the disease in these particular
15 cases.

16 Also, other areas that haven't been yet
17 touched upon here; pediatric cataracts; these are
18 very high diagnostic accuracy for not only
19 detecting the lesion, measuring the density, the
20 ilea, etcetera.

21 So where are we today? Well, Google DeepMind,
22 as many of you know, is working with Moorfield's

1 Eye Hospital using OCT images in the macula, and
2 their work is, I think, being submitted very soon.
3 It's going to be detecting not only diabetic
4 retinopathy is my understanding but other retinal
5 diseases.

6 Using fundus photographs, IBM Watson is
7 working with IDX and colleagues at University of
8 Iowa and they're algorithm has been approved in
9 the Europe economic area and Google Brand and Eye
10 Research Group is using their work to put their
11 algorithm in India. So that's where we are today.

12 Obviously, there are many advantages and
13 limitations to AI. We've heard a lot about the
14 advantages, objective reproducibility, tends to do
15 better than the experts; you can modify the
16 sensitivity and specificity to the specific
17 application, and you can -- the model can be
18 trained and it can be relatively inexpensively
19 deployed.

20 Many limitations; large datasets are needed;
21 Gulshan and colleagues did a post hoc analysis and
22 found that 60,000 images were optimal with 17,000

1 images for referable diabetic retinopathy. We
2 need well-labeled datasets that we're going to be
3 -- there's also weak labeling is possible.
4 There's -- the black box, I think, is being opened
5 and obviously, there's a lot of regulatory, legal
6 and other issues that I'm really looking forward
7 to discussing today.

8 There's also unintended consequences in
9 machine learning. One of them is the context.
10 There's a well-known example where a machine
11 learning-based decision support system determined
12 by patients with pneumonia and asthma were at a
13 lower risk of death than patients with pneumonia
14 and without asthma. Well, how did this machine
15 learning algorithm come to that conclusion? Well,
16 what happened was it was trained on a dataset
17 where patients with asthma and pneumonia were
18 immediately sent to the ICE so they had better
19 outcomes. So the machine was accurately learned
20 but the treating set was flawed, so the context
21 matters. And these are things that we have to be
22 area of when we're applying and testing our

1 systems.

2 Other unresolved issues that others have
3 mentioned, the patient and physician acceptance of
4 these models; and analogous to the pneumonia
5 example, are these classification systems for
6 diabetic retinopathy that are doing so well, are
7 some of them, because these -- they're detecting
8 eyes with a small pupil in cataract, which is also
9 more prevalent in eyes with diabetic retinopathy,
10 and how much does that matter if this person will
11 be referred, if the objection is referral diabetic
12 retinopathy, does it matter?

13 So I think with the future with AI and deep
14 learning, there's going to be a general algorithm
15 for diagnosing some retinal diseases. There's
16 going to be new clinical and scientific insights.
17 We're going to be really reinventing the eye exam
18 and possibly allowing more time for that patient
19 interaction where there's going to be seamless
20 integration perhaps with EMR, with instruments,
21 with cameras. The black box is already beginning
22 to be opened and is going to be the eye as a

1 window into the body. There's already deep
2 learning algorithms for predicting cardiovascular
3 risk factors from fundus photographs.

4 I look forward to discussing the constraints
5 and unresolved issues in the panel discussion.

6 Thank you.

7 (Applause.)

8 DR. REPKA: Thank you, Dr. Zangwill. Our
9 final speaker of this session will be Mr. John
10 Reites, a partner and Chief Product Officer at
11 Thread where highly involved in digital health
12 platforms to enable patient research. Thanks.

13 MR. REITES: Great, thanks. And while he gets
14 that loaded up, thanks for having me today. I'm
15 going to shift gears a little bit and we're going
16 to talk about this really big topic called the
17 patient interface in digital health. And we're
18 going to try and do it in like nine minutes, so
19 I'm just going to warn you we're going to blaze
20 through this. And we're not going to capture
21 everything, but one of the things I've really
22 learned -- I've connected a few hundred digital

1 programs with patients all over the world and one
2 of the things that we continue to find is that the
3 interface, the engagement, the interaction that
4 people have with these technologies is just as
5 critical as the scientific validated measure we're
6 trying to get out of them.

7 And so one of the key components that we have
8 to keep in mind when we're looking at digital
9 health technicians is what is that interface, how
10 does it work, and how does it produce value for
11 patients. So let me give you an example. So I
12 just bought a new TV and I put it in my living
13 room and my four-year-old walked up to it -- so
14 just imagine with me for one second, this is the
15 new TV on the wall and she walks up and I said,
16 "What'd you think?" And she said, (off
17 mic/nonverbal gesturing).

18 (Laughter.)

19 MR. REITES: So I think we'd admit that the
20 world's changed, right? We're all carrying these.
21 I'm sitting in the back of the row, I'm seeing
22 everybody on iPhones, iPads, computers, we're

1 typing, we're engaging but it really has changed.
2 And one of the perspectives I want to do is I want
3 to kind of step back from the science, from all
4 the work we're trying to do and I want us to just
5 take a patient, a consumer's perspective for a few
6 minutes and maybe take some takeaways home from
7 this to apply to all this really innovative
8 scientific work we're doing.

9 So let's talk about these evolutions happening
10 really quickly. So remember that this digital
11 evolution is not just happening to us. It's
12 actually happening because patients and consumers
13 are pushing it forward in the market. And so
14 let's not think that we're all smart creating all
15 these great devices. It's actually that the
16 devices out there are helping people, patients,
17 consumers to see that there's more out there that
18 can be done with digital technologies. And so if
19 you look at this evolution we've been under,
20 there's really four key areas we're in. First is
21 we've been digitizing stuff, right; we've been
22 taking everything we've been doing on paper for a

1 long time and putting it in digital, right. And
2 everybody kind of knows that's happening but I got
3 to tell you I was at a research site a couple
4 weeks ago, and there were still paper forms being
5 collected outside of an EMR.

6 So the reality is we all know that we're still
7 in this movement. But the second piece of this
8 movement is really important and it's this made up
9 word called "remotidization" (ph). Remotidization
10 is where we start taking digital things and we
11 make them remote, right. We let patients do them
12 in their homes. We let patients do this as they
13 live their lives.

14 This third movement though that's really
15 happening, and one that's taking place, is
16 contextualization. Contextualization is not just
17 in the data we collect. Contextualization is
18 actually when I'm a patient and I'm on my phone
19 and I've got something digital and I'm doing it
20 outside of a clinic, and then I'm in the altitudes
21 of Denver, Colorado, the barometric pressure where
22 I'm at may impact data that I'm providing. So

1 understanding the context of when, how, and why it
2 was collected is really important and that's
3 becoming a variable, actually, in the interface
4 that we're collecting this research data with.

5 And then last but not last, we've talking a
6 lot about the automation today, right. We look at
7 deep learning, machine learning, AI. These start
8 to take the data, the interface we're collecting
9 and starting to give back insights and information
10 to people. And so remember that evolution; this
11 is what consumers are actually seeing in many
12 other consumer engagements they're having. We're
13 just finally getting to it in our industry.

14 So let me give you an example. Anybody ever
15 spent your life savings at Disney World by chance,
16 Walt Disney World. Okay. So I have three kids,
17 10, 7 and 4 and like 25 percent of my salary in
18 QuickBooks is like Disney and Disney products.
19 But one of the opportunities I got because I'm a
20 tech nerd and because I've been involved in a lot
21 of these sort of technology innovations was I got
22 a chance early on to try this thing called a

1 "MagicBand." You guys ever heard of MagicBand?
2 So I'm wearing one today. I won't tell you how
3 many of these paid for but I have one today, and
4 this MagicBand is essentially what Disney was
5 trying to create as a digital health device. Now
6 it's not the digital health devices we're creating
7 but I want you to just take this example and think
8 about it in your perspective and know that really
9 what patients want is not another device. They
10 don't really care about the data you capture.
11 They care about the experience you're giving them
12 and they know that if you take something from
13 them, you should give something in return.

14 And so what Disney figured over a long stretch
15 of working through this problem that they had was
16 that their parks were expensive, that actually
17 survey results showed that some of the most
18 stressful situations beside a hospital setting
19 were going to Disney World with your kids. There
20 are a lot of similarities, actually, to the work
21 we live in that when you look at that, they were
22 trying to alleviate and provide a support and

1 structure for people to make this experience
2 easier but also to collect data along the way.

3 And so what you need to understand is that
4 Disney is actually having an impact on the work
5 we're doing in digital health. There are two
6 impacts you need to be aware of. One is they've
7 introduced an omnichannel experience and we'll
8 talk about that in a minute. But the second thing
9 they've done is they've actually raised the bar in
10 what consumers and people see as a good experience
11 in digital health.

12 So it used to be when I did an early sort of
13 mobile app like eight years ago, I built it and it
14 was the ugliest thing you've ever seen. It was
15 ugly and it worked and it could be validated but
16 it wasn't very engaging. It really just took a
17 lot of data from patients but the reality is, is
18 because it came out of a research institute,
19 nobody even gave it an issue. Actually, the
20 patients are like, okay, great. They kind of said
21 oh, I expected this to look like this because it
22 came out of a -- out of your practice.

1 And fast forward to today though, because
2 patients have been engaging, consumers are
3 engaging in all these experiences, they're bar is
4 raised So they see thee apps, and they go "that
5 is an ugly app," close it. Wow, this app's asked
6 me for nine reminders today and not given me any
7 value; close it. So that same thing, I'll just
8 tell you, from all the data I see every day with
9 tens of thousands of patients across the U.S.
10 shows that patients do the exact same thing even
11 when there's altruism involved, even when there's
12 a medical device involved. So we have to be
13 cognizant of this omnichannel experience.

14 So what's an omnichannel experience? It's
15 just a key word that I could leave you with one
16 word today to think about. An omnichannel
17 experience is using multiple channels that
18 integrate together to provide one seamless
19 experience for a user. So what that means is we -
20 - tend to focus on the point solution, right; you
21 focus on the digital health device or what it does
22 but remember from a patient's perspective, that's

1 just one of a lot of things that they're
2 experienced with, right. So if we go back to that
3 slide before and we think about Disney, they don't
4 just have a wearable, they have a mobile app.
5 They have a web experience. There's a location
6 they're going to. There's all these different
7 sort of locations and places they're experiencing
8 with and all of them are coming to the same value
9 and to the same goal. And so this omnichannel
10 experience means that whatever you do in digital
11 health, make sure that it's connected to all the
12 other things that a patient is experience. IT
13 should be linked to the location therapy go to.
14 It should be linked to the mobile app and the web
15 experience and to the medical device.

16 So don't just think about the point solution
17 you have or you've made. Think about how it
18 integrates into overarching experience because
19 that's actually what patients want. That's
20 actually what patients are being trained to do in
21 the consumer world.

22 So on this little slide that I know you guys

1 just all want to punch and make bigger, right; am
2 I experience receptive? I want to leave you with
3 just a couple points to keep in mind. So I know
4 that we're really training to come up with these
5 digital health solutions and to really focus on
6 the data collection and the validation in those
7 pieces. But one of the things that, frankly,
8 really hit me really hard about six years ago was
9 I got this chance to enroll in a clinical trial
10 myself. And I won't belabor the story because I
11 don't have time but I'll just cut to the chase. I
12 dropped out of a clinical trial and I've been
13 running clinical trials for 15 years. And I
14 dropped out because the experience was not great
15 and one of the things that I really took away from
16 that learning was that even though I'd been doing
17 clinical trials for so long and then I was a
18 patient myself and experienced it, the same issues
19 were coming up whether I workshop surveying
20 patients or whether I was the patient.

21 And these four issues I think we can really
22 dial into this area. When we think about a

1 digital health interface, there are four key areas
2 I'd like for you to keep in mind. The first is --
3 first and foremost is value. So if you're going
4 to do something in digital health, don't just
5 think about the value we get out of it from the
6 data, think about the value that the patient gets
7 out of it making sure we instruct them that when
8 you do this, we get this data, this data does "x."
9 I can't tell you how many apps I've seen this year
10 that don't do that. They just say do this,
11 collect this data. They don't take advantage of
12 the opportunity to help apt understand the
13 positivity of what we're doing.

14 The second piece is the experience, like I
15 talked about this omnichannel experience, bringing
16 together your solution into a mix of other things
17 that a patient engages with.

18 The third piece is what we call balance.
19 Balance in digital health is really important
20 because a lot of the things we've been building
21 have been very active, right, very activity-based.
22 Please click here, do this, touch that but

1 remember that there are a number of different
2 passive sensors, clock alarms, all kinds of things
3 that are interrupting our day, and we need to make
4 sure that we have a good balance of active versus
5 passive things we're having patients to do.

6 And then last but not least, again, is the
7 channel. And when you think about the channel,
8 we're not just thinking about -- this is not a TV
9 channel; this is what channels are you using to
10 get people to engage with the digital platform you
11 have or see the results. And remember that most
12 patients are using, just as a basics, a mobile app
13 and a web experience. So if you're not -- if you
14 don't have at least those base minimums, you're
15 not reaching the majority of the population that
16 would want to engage with your digital health
17 solution. So again, try to rapid through a lot on
18 a patient interface, we're going to talk more
19 about it on a panel later today.

20 But hope that gives you some thoughts to think
21 about. We take the patient's perspective whenever
22 we're implementing and starting to coordinate our

1 health efforts. Thanks so much for having me. I
2 really appreciate it.

3 (Applause.)

4 DR. REPKA: Thanks, Mr. Reites. Thanks to all
5 of the speakers for their engaging comments. It's
6 10:20 so we are going to go to break. We do
7 reconvene at 10:35 so just 15 minutes. If the
8 panelists for the first panel could just stop up
9 real quickly so we can make sure that they have a
10 plan, that would be great. Thanks.

11 (Whereupon, off the record at 10:23 a.m., and
12 back on the record at 10:42 a.m.)

13 DR. REPKA: You can start with --

14 MALE SPEAKER: Michael, microphone.

15 DR. REPKA: Oh, sorry. Is that better?

16 MALE SPEAKER: Yes.

17 DR. REPKA: Okay. Dimitri, please just say a
18 few things about yourself and we'll go around the
19 table.

20 DR. AZAR: Hello, everyone. My name is
21 Dimitri Azar and and I think there are -- I
22 apologize that the conflicts of interest go beyond

1 what is listed there. We have to add Verb
2 Surgical and Novartis. I'm on their board, so I
3 apologize for that.

4 I am currently the Dean of the Medical School
5 at the University of Illinois. in a very unusual
6 arrangement where I'm spending only a day a week
7 as a Dean. We hired an Acting Dean, the Chief of
8 Radiology,, and I spend the balance of ht time at
9 Google as the Verily Life Sciences Senior Director
10 for Ophthalmic Innovations. So nice to be here.
11 Thank you so much for including me.

12 DR. ZIMMER-GALLER: Ingrid Zimmer-Galler. I
13 think you already heard a little bit about me. I
14 have a long history in the past being involved
15 with diabetic retinopathy screening and currently,
16 I split my time half between Wilmer in the Retina
17 Division and the other half is running the Office
18 of Telemedicine for all of the Johns Hopkins
19 tele -- all of the Johns Hopkins health system so
20 not just tele ophthalmology but all of
21 telemedicine.

22 DR. MOSHFEGHI: Thank you for having me here

1 today, Darius Moshfeghi. I'm at Stanford
2 University. My areas in telemedicine surround
3 pediatric retina, specifically retinopathy of
4 prematurity and also universal newborn screening.
5 I have numerous conflicts with Visionex, which is
6 a camera company. I am involved in a screening
7 company, an artificial intelligence company, and I
8 serve on the board for 1-800-contacts where I work
9 on their telemedicine outreach.

10 DR. WOODWARD: Hi. My name is Mia Woodward. I
11 am cornea specialist from the University of
12 Michigan and I co-direct the Kellogg Eye Center
13 for eHealth. I also serve on the Academy of
14 ophthalmology's Telemedicine Task Force and have
15 an NIH grant to study telemedicine for anterior
16 eye diseases.

17 DR. TRESE: I'm Mike Trese. I'm a pediatric
18 retina surgeon in Michigan and have done quite a
19 bit of work, as Darius has, in ROP telemedicine
20 type things. And I'd like to introduce my co-
21 moderator.

22 DR. AFSHARI: Natalie Afshari, talked earlier,

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1 Professor of ophthalmology from the University of
2 California San Diego. It's a pleasure to be here
3 and I also wanted to let you all know that the
4 audience can ask questions once the panel
5 discusses a question. So question one and four
6 will be our charge and please feel free to ask
7 questions once questions one is done. Thank you.

8 MS. BOTTORFF: And I'm Leslie Bottorff. I'm
9 with GE Ventures. I've been in the venture
10 capitalists about -- capital business about 20
11 years, the last four with GE and we're invested in
12 a number of portfolio companies across digital
13 health as well as some other areas and pleased to
14 be here.

15 DR. MORRISON: Good morning. My name is David
16 Morrison. I'm a pediatric ophthalmology and I'm
17 the director of the Telemedicine Screening Program
18 for Retinopathy of Prematurity at Vanderbilt
19 University.

20 MR. PATEL: Hi everybody. This is Bakul
21 Patel. I'm the Associate Center Director for
22 Digital Health at CDRH and I lead sort of the

1 efforts on digital and various aspects of how
2 emerging technologies are coming together in this
3 space and how they're cutting across every aspect
4 that we have regulated in the past and what those
5 connections really mean. So I am also leading the
6 pre-certification program, as you heard me talk
7 this morning. So happy to be here. Thank you.

8 DR. TRESE: Well, we have a very exciting
9 thing. We have some new technology that was not
10 discussed this morning and won't be this
11 afternoon. And it's basically made for people my
12 age that are getting into the digital age, and
13 that is this is Mahmud, who is your personal
14 digital health advisor. So you may want some of
15 these as you go along.

16 So what we're going to do is discuss two of
17 the questions that the committee came up with.
18 And the first question is one that deals with
19 safety concerns. I think we had a really nice
20 discussion this morning relative to control of
21 risk and benefit of efficacy and what gold
22 standards are and what they may become and things

1 like that.

2 And I think these -- this first question has
3 some interesting implications and let's just read
4 it together. A digital health device provides a
5 diagnosis, a computer-assisted diagnosis for
6 screening diabetic retinopathy by adding on
7 software to a fundus camera image in comparison to
8 a digital device that provides information as an
9 aid for diagnosis to the healthcare provider. I
10 think you have an answer, perhaps, Mr. Patel, but
11 why don't we start with the Dr. Azar and give us
12 your opinion on that.

13 DR. AZAR: I think that we want to advance on
14 both areas and here the question is about safety
15 and effectiveness. Questions at the early stage
16 are going to be where do we draw the line along
17 this continuum that we've all heard about;
18 referable versus not referable in areas where
19 you're trying to -- let's take diabetic
20 retinopathy as a good example; that's at least a
21 group I'm involved in is focusing on and there
22 it's relatively easy to go ahead and let the

1 machine learning algorithm, for example, the
2 machine make the diagnosis because it's a low
3 level impact. You can always increase the
4 sensitivity at the cost of effectiveness and at
5 specificity as a result of which there will be
6 more costs but greater safety. There's always
7 this balance to draw.

8 Now if you want to go into various subgroup
9 diagnoses, it's going to be very difficult to do
10 that. The gold standard approach has become much
11 more difficult. We know that today's gold
12 standards are -- need some alchemy, but you can't
13 do that today. You have to look, I think, at the
14 end at outcomes meaning whatever has come out of
15 the early studies were based on the different
16 subgroups and the machine learning algorithms of
17 today have to simulate that. But at some point,
18 new categorization has to come out looking at
19 long-term outcomes of patients who have been
20 diagnosed and we're really far from doing that.

21 And from an FDA perspective, I think
22 categorizing some of these rapidly-evolving

1 systems is -- may slow down the pace to improve
2 safety but at the same time may, if the pace is
3 not very slow, we may have new developments but
4 then there's a potential downside of having
5 potential serious unintended consequences that may
6 end up stopping many of these processes, and
7 that's where the FDA has to draw these lines.

8 DR. TRESE: So Ingrid, how do you feel about
9 those things?

10 DR. ZIMMER-GALLER: So I basically agree with
11 everything that's been said here. Diabetic
12 retinopathy is certainly a great place to start
13 with automated image analysis or computer-aided
14 diagnosis, because unlike, as we heard earlier
15 with retinopathy of prematurity, there is much
16 more variability in how experts read those images,
17 and we really have very good consensus on diabetic
18 retinopathy. It's a much better or much more
19 easily-defined disease state.

20 I want to step back for one second and just
21 also remind everyone why this is something that is
22 going to become more and more market participant.

1 Obviously, the diabetes epidemic globally is --
2 that's going to continue to get worse. We clearly
3 need to do a better job of evaluating patients
4 with diabetes 4 retinopathy because we have
5 fantastic ways to treat the disease, and we
6 can't -- we cannot afford to continue to have
7 patients come into our practices that have
8 traction retinal detachments and, you know, come
9 in at a point where we really can't do anything to
10 help preserve their or maintain normal vision.

11 And I'm sure everyone has heard some of the
12 numbers that have been tossed out but I think, for
13 example, if every patient with diabetes in the
14 world were to have the recommended eye
15 examination, we would have to do one every seven
16 seconds and, you know, we clearly don't have the
17 workload either to examine all those patients in
18 person but we also don't have the workload if we
19 have millions of images -- we don't have the
20 workforce if we have millions of images that need
21 to be evaluated. So I think this is something
22 that very much we need to continue to work on in

1 advance. I think it's certainly, for a disease
2 like diabetes, imperative.

3 DR. TRESE: So I know that I'm in Washington,
4 DC now because the question really deals with risk
5 analysis between the risk of a device that gives
6 you a diagnosis and something that gives the
7 doctor an aid. So what would the two o you -- how
8 would you -- would you grade one of those as more
9 risky than the other and if so, why?

10 DR. AZAR: I think there is a happy solution
11 by thinking about the context in which the machine
12 is providing either help or diagnoses. For the
13 screening, I think especially in diabetic
14 retinopathy, the referable versus non-referable, I
15 wrote down what the ROP people use -- referral
16 warranted, it's the same idea. The referral -- I
17 mean there, as I said earlier, you can increase
18 the sensitivity but what you could do for aiding a
19 doctor in instances where there are potentially
20 more difficulty where you're trying to make a
21 diagnosis, etcetera, I think at this stage, we
22 would need to go into a technology that's easily

1 available but that's inside the black box which is
2 the heat map assistance, meaning the reasons
3 sometimes these programs do better than the
4 experts is that they can focus on 50 notes in one
5 image whereas an expert, given their limited time,
6 even under time when they're given time, can focus
7 on four or five different areas. So by
8 identifying heat maps, you can assist the
9 healthcare provider, the ophthalmologist most
10 often, to actually make a diagnosis. We leave it
11 up to the ophthalmologist and the higher the risk
12 in missing a diagnosis, the more likely there will
13 be a need to assist the physician rather than
14 replace the physician.

15 DR. TRESE: I agree with that. I think that's
16 a very good point. Ingrid, what is your opinion
17 on risk assessment.

18 DR. ZIMMER-GALLER: So I think it basically
19 does boil down to validation and the validation
20 has to be appropriate for what you're trying to
21 accomplish with that -- with the program. You
22 know, it's interesting we talk about validation

1 but we don't validate physicians and, you know, so
2 you can -- you know, clearly there are physicians
3 that do a not very good job of diagnosing any of
4 these diseases. But I think with proper
5 validation, I think you can very definitely keep
6 the safety issue -- you can control that very
7 well.

8 DR. TRESE: Darius?

9 DR. ZIMMER-GALLER: And that also includes you
10 need to have ongoing QA.

11 DR. TRESE: Yeah.

12 DR. ZIMMER-GALLER: You need to be
13 continuously monitoring all of these programs to
14 make sure that things don't change over time.

15 DR. TRESE: Go ahead, Darius. What's your
16 opinion on this? You may take the ROP point of
17 view.

18 DR. MOSHFEGHI: So when we look at the safety
19 of diagnostic-based systems versus diagnostics-
20 assisted systems, it really comes down to what
21 Michael Chiang was referring to earlier, is what
22 is the intent of the system, because at the system

1 level, the difference between them is really kind
2 of arbitrary. It's what are you trying to do.

3 For example, when we were looking at a
4 diagnostic system that's going to work independent
5 of a physician, that may be appropriate for
6 certain low risk situations where the rapidity of
7 which the disease onset can occur and the
8 magnitude of the bad thing that can happen from
9 the disease are not very large. And so an example
10 of this may be glaucoma screening in a general
11 population. You're not going to go blind
12 immediately and if you -- you know your risk of
13 vision loss is very slow over a long period of
14 time on one missed examination and so I would feel
15 quite comfortable using an independent diagnostic
16 system in that sort of situation.

17 When we go into the opposite, which is
18 retinopathy of prematurity, both the disease
19 severity, you can end up bilaterally blind and the
20 speed at which that can happen can be within 24 or
21 48 hours. And there I'm more comfortable using an
22 ROP-assisted sort of diagnostic system.

1 Then you get into these intermediate areas of
2 where things can go wrong which is such as
3 diabetic retinopathy where the disease, obviously,
4 you could end up with bad macular edema,
5 proliferic diabetic retinopathy, tractional
6 retinal detachment but clearly, the screening
7 burden is very large and we can tolerate a lot of
8 macular edema and a lot of diabetic retinopathy
9 for a long time and still come in and end up with
10 good visual acuity outcomes. So the overall risk
11 is low but it's higher than what we see in the
12 glaucoma situation so I would be more inclined to
13 go towards using a -- I'd be a little bit happier
14 using that, a diagnosis-only system in that sort
15 of situation than I would where the rapidity and
16 the magnitude end p being a lot worse.

17 DR. TRESE: So your risk analysis really is
18 based on rapidity of disease progression and
19 severity of outcome --

20 DR. MOSHFEGHI: Sure.

21 DR. TRESE: -- and that time. And I think
22 that's what Dimitri said first of all was that the

1 time feature with diabetic retinopathy is a lot
2 less than ROP. Mia, what is your opinion?

3 DR. WOODWARD: Well, I'm very happy to follow
4 those comments. So as an anterior segment
5 specialist, you know, the diseases in the front of
6 the eye that are population health level diseases
7 that we really should be focused on here today are
8 ones that are urgent and, you know, ones that
9 don't have a really known underlying condition.

10 You know, we don't know the patient has diabetes;
11 we don't know they were born prematurely; we don't
12 know they have macular degeneration. So that's
13 our problem with the anterior segment diseases.

14 You know, people come in because they have
15 symptoms, they have eye pain, their hurts, and
16 where they show up is also very different. So,
17 you know, the problem is is about two million
18 people come to the ER per year for eye complaints
19 and half of those eye complaints are nothing,
20 they're -- well, they're not nothing but they're
21 not things that need me that day, right; so
22 they're dry eye; they're --

1 DR. AZAR: They do not need a retinal
2 consultation?

3 DR. WOODWARD: Correct.
4 (Laughter.)

5 DR. WOODWARD: Nor anterior segment
6 consultation urgently. You know, they're dry eye,
7 they're a floater so they're -- but not a retinal
8 detachment so -- but what we worry about is any
9 one of those people, are they angle closure
10 glaucoma; are they a corneal ulcer; you know, are
11 they diseases that could be very severe and could
12 progress very rapidly. And for anterior segment
13 diseases, you know, I think -- so time is very
14 important for us and humans.

15 So I interpret this question to say like
16 what's the value of humans and, you know, when are
17 we useful. And I really enjoyed Dr. Yeshwant's
18 comments to that effect, you know, because I hope
19 that machine learning will help us not have the
20 burden of things that we don't understand and be
21 useful as human beings. And I think that my added
22 value as a human from a rapid standpoint is I can

1 tell if -- you know, cornea patients and people in
2 the ER walk out the door and then you tell them to
3 come back in one or two days. And so I can tell
4 if that person's not going to come back in one or
5 two days versus a, you know, a diagnostic
6 independent device, right. So I can tell if
7 there's alcohol on their breath; I can tell if
8 they don't have a ride to come back the next day
9 and so I think that's the value added of a human.

10 And I also think geography is very important
11 for your anterior segment diseases, like these
12 people have symptoms in their home. The young
13 people are going to go online first to maybe
14 triage their symptoms. They're not going to --
15 you know, they're not even going to think about
16 going to the ER unless it really, really hurts
17 and -- but then they're going to go to an ER or a
18 primary care doctor. They're not going to come to
19 an eye provider. They're not going to be in a
20 hospital getting ROP screening because they're a
21 young baby. And so, you know, there's a huge role
22 of devices.

1 I think, you know, what's better in an ER
2 setting is also interesting. You know, only one-
3 fifth of medical schools now teach any
4 ophthalmology training whatsoever, so the primary
5 providers, whether they're in an ER or an ED do
6 not know ophthalmology. So these devices that can
7 say this is a bad eye thing, please find an eye
8 provider really does have huge value and has huge
9 opportunity to triage patients appropriately to
10 get the right ones to us.

11 And I also wanted to bring up one separate
12 point. You know, I do think that -- my concern --
13 and I like that we talked a lot about trust of
14 systems earlier in the morning. I have a concern
15 about how devices are being built around young
16 versus old patients.

17 You know, the statistics were thrown out but
18 77 percent of people have Smartphones but all of
19 those people are -- like they're not the older
20 patients and they're not the poor patients, and
21 those are the people who are the sickest and, you
22 know, old people get sick and so if you're 65 and

1 older, you're more at risk of having diseases.

2 And so applications that are Smartphone only

3 and not -- no, don't panic if that's you --

4 because I mean ultimately, it's all of us, right.

5 You know, I'm going to be 65 someday and I will

6 get sick and I hope that the device that's built

7 and, you know, it's about the sort of patient

8 experience, the omni -- what was it -- I know I

9 learned a new term this morning -- omnichannel,

10 like that's fantastic, right. You know, it is

11 about that experience that anyone can relate to.

12 I mean we all went to the airport and half the

13 people still have paper tickets because they don't

14 trust, you know, that they can do it on their

15 device. And so we have to do that -- you know, we

16 have -- whatever we do, we have to design it for

17 all patients.

18 DR. TRESE: You know, I've often thought that

19 90 percent of that slide that shows the percent of

20 people that have cell phones are in the East and

21 West Coast and not in Michigan, that --

22 (Laughter.)

1 DR. TRESE: And then in addition to that, you
2 not only have to own a Smartphone, you have to be
3 able to turn it on.

4 DR. WOODWARD: Right.

5 DR. TRESE: And that can be challenging.
6 Darius has trouble with that sometimes. So
7 Natalie, do you have an opinion there?

8 DR. AFSHARI: Well, I think one of the most
9 important things that was brought up by Mike
10 Chiang was -- and also Paul Lee -- it's what is
11 the gold standard, you know, if you're going to
12 have this safety and efficacy that is high and
13 that is our charge, to really decrease our error
14 rate and increase our efficacy and safety over
15 time. You know, when experts don't agree, then
16 what? So, you know, while we have started a great
17 road, in some fields, we're not quite there and
18 while it's great in anterior segment, that many of
19 our patients otherwise wouldn't get diagnosed or
20 wouldn't -- you know, in the ER, they show up and
21 that's the best thing that we have, we still have
22 some roads to really decrease our error rate and

1 our safety and efficacy.

2 And there is so much more in retina, as Dr.
3 Azar said. It's not all about referring to the
4 retina doctor, so what about these anterior
5 segment diagnoses. And many of them can be really
6 crucial right there and then; you know, is it just
7 a regular red eye or is it a corneal ulcer as Dr.
8 Woodward said. And that could have devastating
9 visual consequences. So we have a little work to
10 do but we are, as I think Dr. Bakul (sic) said, we
11 are in high road right now, so.

12 DR. TRESE: So Leslie, you bring a little
13 different perspective to us and for those of you
14 that may not be aware, Leslie has done a lot of
15 work in radiology. And so I would think there'd
16 be some of the same type of concerns in terms of
17 radiologic diagnoses being made by machine as
18 opposed to the doctor. Can you address some of
19 that?

20 MS. BOTTORFF: There are absolutely the same
21 types of concerns and radiology may be even a
22 little bit ahead of this in terms of the

1 proliferation of the number of companies that are
2 doing various types of image analytics and
3 combining that with other analytics. And what's
4 happening in that field is that initially what
5 we're seeing is the adoption is about automation
6 and efficiency. And, you know, that because these
7 radiologists are getting so many more scans per
8 study and so many more patients and volume that
9 they just can't do a good job, just like what you
10 were talking about in looking at these images.
11 They just can't do a good job in terms of the time
12 and money allowed for this. And so they're using
13 these tools to help them scale basically and to
14 have greater efficiency but yet they're still
15 making the diagnosis in the end.

16 And what the physicians have suggested here I
17 think is exactly right, that depending upon what
18 that information is going to be used for and,
19 therefore, what safety risks and what kind of time
20 scale do you have to work with with that patient
21 should be the factors in determining what level of
22 sensitivity and specificity that these devices

1 have because they -- you know, the other
2 constituencies here are these people who wouldn't
3 normally even get any care.

4 I mean, you know, scale and access and reach
5 is what these new technologies will do for you,
6 the amount of patients that you can see before,
7 you know, like let's say that are - that haven't -
8 - are going to have a diabetic retinopathy
9 problem, that you can see them while you can still
10 do something with it, they are your constituency
11 also in terms of safety and thinking about those.

12 And so I think that the direction you're going
13 here is exactly right. And the other thing I
14 would say is that all of these technologies are
15 great but you have to get them paid for. The
16 economics here are key because the fact is is
17 that, you know, it doesn't get adopted
18 commercially if you can't get reimbursed for it
19 and if it doesn't make sense on time and money
20 allowed.

21 And so I think that it's fantastic to see the
22 FDA and the physician groups and the industry

1 groups all working together, you know, in this
2 ophthalmology area. And in fact, it's one of the
3 specialties that can really take the ball and run
4 with it on digital health because of the
5 ambulatory nature generally of the practice and
6 also because these digital technologies lend
7 themselves very well to people with eye problems.

8 So your group, really, in this room could be
9 the leaders in this but you have to bring along
10 the economics of this, the reimbursement parties
11 and not that any of these -- any of you, you know,
12 of those -- these groups control that but have to
13 make them part of the conversation and also make
14 efficiency and resources allowed part of the
15 consideration in terms of, you know, how are we
16 going to use these devices and what can we really
17 use them for.

18 And then later on, you're going to be able to
19 out of the efficiency and automation level and
20 into the multi data source diagnostic predictive
21 value of this, and that's going to be incredible
22 also. And the data that you're going to collect

1 as these things progress are going to really help
2 you to get to a higher level of diagnostic power
3 as well.

4 DR. TRESE: David, do you have some comments?

5 DR. MORRISON: Yeah. I'd like -- actually
6 like to put on my pediatric ophthalmologist hat to
7 answer this because I think it emphasizes a couple
8 of different things that we've touched on so far.
9 I think vision screening is really the original
10 telemedicine in ophthalmology. We've been doing
11 it for years and years and it was initially
12 software in a medical device and as we move
13 forward, it is not software as a medical device.

14 And I'll kind of hit on a few points of how
15 this could be positive or negative. I think the
16 benefit of making a diagnosis with a machine is
17 that you can absolutely improve care and improve
18 the finances of care. In addition to that, I
19 think that you run the risk of excluding the
20 physician completely in certain circumstances.

21 And so let me give some examples. About 20
22 percent of kids will have amblyopia risk factors,

1 so refractive error, anisometropia, different
2 things like that; about two to three percent of
3 the population will have amblyopia and if not
4 discovered and treated, then you can have
5 permanent visual loss, and so that's obviously a
6 significant problem. We do have a large window to
7 treat but it's there.

8 So with vision screening, initially, we were
9 taking photographs of the eye and were looking at
10 the red reflex and on a film-based camera, someone
11 was looking at the photograph and determining
12 whether that's normal or abnormal. As we moved
13 forward, now we autorefractors and different
14 levels of technology that can absolutely diagnose
15 relatively accurately the refractor error itself
16 and not just say "yea" or "nay" but this is your
17 diagnosis.

18 Further, as we develop this technology in
19 apps, there is an app that you get on your phone
20 called "go check kids" and that's the red reflex
21 test that basically says "positive" or "negative"
22 and there are multiple other apps. I wrote them

1 down. I Googled it while we were watching so
2 there's one called "the eyes can" app, Blink
3 Netra. MIT has an app that they've developed that
4 can actually diagnose refractive error on your
5 Smartphone in an autorefractor-type setting.

6 So the pros; if you have this technology, you
7 can reach a bunch of people at once. In
8 Tennessee, with our outreach program, we've
9 screened over a half a million children that
10 likely would never have been screened or had their
11 amblyopia diagnosed. We also went back and looked
12 at kids who had normal exams that ended up getting
13 glasses and it was shocking.

14 So if a child had a normal exam defined as the
15 absence of a post-amblyopia risk factors, if a
16 child had a normal exam and they saw a pediatric
17 ophthalmologist, about two percent of the time,
18 they got glasses. If they saw a comprehensive
19 ophthalmologist, about 12 percent of the time,
20 they got glasses. And if they saw an optometrist,
21 about 35 percent of the time, they got glasses.
22 I'm not going to comment as to why that may be.

1 I certainly am not going to imply anything by
2 it. I will say that there's obviously a wide
3 variance in how we treat these kids. But if a
4 child has a normal exam and 30 percent of the time
5 in a state-mandated program, every child in that
6 state is getting glasses when they don't need
7 them, that's poor care and it's poor use of
8 healthcare dollars. So the technology does have
9 the ability to improve care and certainly improve
10 finances.

11 But let's look at the other side of that coin
12 now. Say we have a parent who screens their child
13 with one of these app screeners, finds amblyopia,
14 goes to an autorefractor, diagnoses the
15 prescription that they think the child needs and
16 then they go to Zenni Optical or one of the other
17 online stores, enter in those numbers, they can
18 theoretically diagnose and treat their child's own
19 disease without ever having seen a physician. and
20 I don't think that's good care. I think it's the
21 opposite of good care.

22 And so I think that as we move into this new

1 realm, there's definitely positives or negatives
2 but I think that this specific example shows us
3 kind of the extremes of what it can be on either
4 side. I think in the end, big data and the
5 ability to improve care will win but there are
6 some pitfalls.

7 DR. TRESE: I think you bring up a dilemma
8 that's common to probably everything we're talking
9 about today and that is that I notice as I'm
10 dealing with residents that as soon as I say
11 anything, they take their Smartphone and they get
12 on Google. And so I think we've talked about
13 artificial intelligence. We've talked about deep
14 learning. What we need to do is try and structure
15 what Paul Lee so nicely showed as the new
16 medicine. How do we use these things to our
17 patients' advantage? I'm very happy about the
18 program so far because it's clear that the message
19 is to try and develop better care for patients,
20 that the FDA is delivering and that I think that
21 all the speakers have.

22 And I wanted to ask Mr. Patel this question

1 because you're a little closer than Malvina.

2 That's the only reason I'm asking you. Has any of
3 this helped you that you've heard so far?

4 MR. PATEL: I would say "yes" and a
5 resoundingly "yes."

6 DR. TRESE: Because you're a nice person?

7 (Laughter.)

8 MR. PATEL: That could be one of the reasons
9 but I just wanted to make a couple of comments and
10 just hearing people's opinions here, I think what
11 we are seeing is just not about them in the
12 questions phase as raised is about what are the
13 concerns, right? So I think every conversation
14 that I've heard so far is about benefits and
15 risks. It's not about concerns only but there are
16 some benefits that come with that. And it comes
17 from the aspect about can it deliver care at the
18 right point, at the right time, to the right
19 patients in the right way. It sounds very "right"
20 but let's just leave it at that for the moment.

21 But how do we think about those new benefits
22 that are sort of coming into play with the new

1 risks that are coming into play as well? And
2 there are some social risks with it; there's a
3 provider risk to it; there's actually some
4 transforming that's happening because what if
5 those gold standards that were are all accustomed
6 to is different today. I think that's really what
7 we are asking in terms of, in my mind -- for me,
8 it is fascinating to see that we are talking -- we
9 are having a conversation about gold standards.
10 And I think fundamentally, in my mind, gold
11 standards are being changed with this technology.
12 And it happened in the imaging world. The gold
13 standard was changed. Radiologists were the gold
14 standards and then they had aids to help them spot
15 things that they couldn't spot when they had the
16 volume come across.

17 So that's how I think about these worlds. So
18 we can lose the sight -- lose sight of the fact
19 that there are benefits and there are some new
20 risks that we are not quite there in terms of
21 understanding how big or small a risk they are.

22 One quick thought I think from a positive

1 perspective and a negative perspective is when I
2 heard and I was sort of putting notes down,
3 there's this opportunity to sort of detect early,
4 so early that interventions can be extremely
5 small. So that's a big opportunity I see with
6 this technology.

7 And then on the risk side I see as negative is
8 we are not being trained to recognize when things
9 are not what we expect it to be. So how do we
10 change that equation from, you know, from med
11 schools to engineering schools to delivery and
12 etcetera to -- even for FDA for that matter, like
13 how do you start recognizing that detectability of
14 error, which we all know is really easy when we
15 know a fundus camera with whatever it puts out, it
16 puts out, and we know what those readings mean,
17 right, and that this technology, when it's in the
18 hands of patients, how do you sort of allow the
19 detectability to be there that's ubiquitously and
20 doesn't require, you know, eight years of college
21 to go to -- so I'll leave it at that.

22 DR. TRESE: So I -- when I first looked at

1 this question one, I said this is so trivial, I
2 can't believe it's actually a question and how in
3 the name of God are we going to spend 30 minutes
4 talking about this. But -- and originally, I
5 thought well, it's simple. If you're aiding the
6 doctor, that has to be less risk than if a machine
7 is making the diagnosis. That would be my initial
8 opinion.

9 But then I agree exactly with what Ingrid said
10 earlier about validating the physicians. And so
11 we have an ROP software program called "FocusROP"
12 and in it, we have an education module. And if
13 you're OMIC insured ophthalmologist, you have to
14 take a test and you have to pass it with an 80
15 percent and you get three tries. Okay. So we
16 first launched that maybe 2.5-3 years ago,
17 something like that. I think one out of 19 people
18 got an 80 percent the first time. And obviously,
19 ROP is the worst thing that OMIC insures.

20 So I think that the education component -- the
21 gold standard thing I agree is changing but I
22 think the education component is really very, very

1 important. And to get the doctor that just what
2 Paul was talking about earlier -- to get the
3 doctor to be educated in terms of either diabetic
4 retinopathy or retinopathy of prematurity or
5 anterior segment disease or any other -- glaucoma,
6 any other thing that lends itself to telemedicine
7 is still extremely important.

8 So I can cross off my list here payment,
9 Leslie. Thank you. That was on my list to do.
10 And the gold standard, I think we've discussed
11 pretty aptly. And I think that we can probably
12 switch now to question four. Natalie, you're
13 going to do question four.

14 DR. AFSHARI: Are there questions from the
15 audience?

16 DR. TRESE: Yes. Do we have any questions
17 from the audience? Yes.

18 MALE SPEAKER: (Off mic.)

19 DR. TRESE: Oh, there's a microphone there if
20 you wouldn't mind.

21 MALE SPEAKER: (Off mic). (Inaudible)
22 something about computer systems (inaudible) and I

1 remember being (inaudible) New England Journal
2 (inaudible) screening program, and it showed docs
3 assisted by a computer in their work in
4 (inaudible) actions and then (inaudible)
5 regular(inaudible) alone. And (inaudible/off mic)
6 rather than computer-assisted so I'm just
7 wondering what (inaudible).

8 DR. ZIMMER-GALLER: I can just -- I'll make
9 one comment. As -- just from my past experience,
10 I can say that for diabetic retinopathy, having --
11 and I haven't -- I have no experience with
12 computer-assisted reading but the reading center
13 that we had, when I read images when I was doing
14 over-reads, no question; when somebody pointed out
15 already -- had already circled the lesions that
16 were there, it was infinitely easier. Literally,
17 you take a quick look and you immediately say,
18 yes, I agree, that's a hemorrhage, or yes, I agree
19 that's NBD or yes, I agree, you know, whatever the
20 lesion is and it clearly, as far as reading
21 diabetic retinopathy, from my standpoint, having
22 something already pre-read that image made it much

1 quicker for me. So I do think that that can be
2 very helpful but I also think that for diabetic
3 retinopathy, I think that we are at a point where
4 if it's properly controlled and validated and has
5 QA, I think very clearly, it's an area -- and I
6 strongly believe that we are at a point where we
7 can use automated analysis.

8 DR. MOSHFEGHI: I think those are very
9 excellent points. One area that I would like to
10 differentiate a little bit is that there's a
11 difference between doing a screening one off for,
12 let's say, glaucoma or diabetic retinopathy and
13 then monitoring an active disease like retinopathy
14 of prematurity. And so I'm a little more happy
15 using diagnostic-based systems for one off
16 screenings and a little bit more concerned with
17 the rate of progression in diseases that we're
18 actively monitoring.

19 MS. BOTTORFF: Yeah. I just wanted to point
20 out one difference in the CAD, like the R-2, when
21 that came out, that was CAD design. You know,
22 they were like 80 percent or something like that

1 sensitivity specificity and they never got any
2 better. It didn't get any better no matter what.
3 It was not a learning technology. And I think
4 that's' one of the big differences in what's
5 happening with the new technology wave that's
6 happening today is that it does get better with --
7 as it learns, you know, because it gets compared
8 with the outcomes and they get to add that
9 knowledge back in.

10 And then the other thing that's really
11 different is that with these new digital
12 technologies like "Mobility," then you get to
13 continue to collect and monitor that same data and
14 so you get a lot more data streaming in, you know,
15 than what they ever got with the R-2s of the
16 world. And that technology is still used to help
17 mammography, for instance, but the radiologists
18 complained that it took them actually more time
19 because they had to go through there; whereas --
20 so that was an efficiency problem but it helped
21 the sensitivity and specificity.

22 And so with the new technologies, I think that

1 some of those problems, you know, are -- go away.
2 And the numbers you saw presented earlier were
3 much higher in terms of what kind of sensitivity
4 and specificity that these are able to get.

5 DR. WOODWARD: Can I add one comment? I think
6 it also very much depends on the user, right. So
7 it's all about Bayes' theorem and, you know,
8 what's the user's pre-test probability; what does
9 the device add; does the user understand how good
10 that device is in terms of sensitivity? And I
11 just wanted to tell an anecdote.

12 When I was pregnant with my second son, I
13 developed my second kidney stone and when you're
14 pregnant, they can't do the same imaging. And so
15 I got an ultrasound to detect my kidney stone,
16 right. And then the resident comes into this
17 pregnant kidney -- active kidney stone me and
18 says, "We don't think you have a kidney stone; the
19 ultrasound is negative." And I was like, "You've
20 got to be kidding me, right?" You know, so I was
21 like Bayes' theorem says I have a kidney stone.
22 My pre-test probability is like 90 percent. This

1 diagnostic test is very inaccurate. I have a
2 kidney stone, you know.

3 So I mean I think that like this is the point,
4 you know. If you don't know that the accuracy is,
5 you know, 80 percent sensitivity specificity and
6 you are confident in that test and you're not a
7 knowledgeable user, like you're -- it's a higher risk
8 situation.

9 DR. ZIMMER-GALLER: But I think we can also
10 add to that and think of what we can potentially
11 do in the future. I know -- I don't think we're
12 there yet but at some point, if we can plug all of
13 the -- looking at analytics, if we can plug all
14 the data in, if we can add how long the patient
15 has had diabetes or when it was diagnosed, if we
16 can add what their A1C is, if we can add all of
17 those things in and include that in the analysis I
18 mean the -- you know, from a safety and
19 effectiveness standpoint, you know, in the future,
20 these are things that will be tremendously
21 valuable.

22 DR. AFSHARI: Mike.

1 DR. CHIANG: Good afternoon. Like I was --
2 (inaudible) panel. I think that there are two
3 issues within the culture of medicine that are
4 relevant to telemedicine and sort of computer
5 (inaudible) -- you know, number of (inaudible) by
6 virtue of being board certified, I'm considered
7 competent to make diagnoses and manage things that
8 I'm probably not competing. And I think that
9 applies to everybody.

10 And then the second is that we've got a
11 culture in medicine where when we make mistakes,
12 we get punished for them, and I think that it
13 could be argued that both of those are barriers to
14 quality improvements that really could be
15 addressed, you know, with these sort of
16 technologies that we're talking about.

17 And so my question to the panel is what do
18 you -- how do you think we can address these
19 issues in terms of the culture of medicine and is
20 there anything that we can do from a regulatory
21 standpoint that can sort of promote that
22 gradual -- that cultural shift?

1 DR. TRESE: So I have a comment. I think
2 that's a great question but I think maybe Dr.
3 Repka could answer it better than most any of us,
4 because I think it deals more with legislation; it
5 deals with the doctors of the world wanting their
6 licensure to be so broad that I can go home and do
7 a breast biopsy or an appendix. Are you kidding
8 me? And I meant that's a licensure issue. the
9 licensure issue, I think, needs to be broadened
10 relative to telemedicine but you're absolutely
11 right. To be board-certified -- I don't want to
12 put a tube shunt in either so, you know, it's --
13 I think it's a very, very good question. I don't
14 know an answer.

15 DR. AFSHARI: Other panelists?

16 DR. MOSHFEGHI: I actually like that question
17 a lot because it kind of goes towards the whole
18 problem that we deal with in retinopathy of
19 prematurity and a lot of this stuff that you
20 brought up with experienced physicians having a
21 lot of change there.

22 Roughly, we have four million live births a

1 year; 400,000 are premature; 80,000 are eligible
2 for screening which comes out to be about 10,500
3 week. And you could have 15 highly trained
4 individuals using telemedicine with cameras
5 distributed over 1,000 different NICUs around the
6 country doing three days a week, you know, eight
7 hours a day of reading, and then if you have
8 assisted device using ROP plus algorithm,
9 evaluators and, you know, trying to -- you could
10 really eliminate a lot of the people who shouldn't
11 be screening and take it from referral warranted
12 ROP up to treatment warranted ROP up to the
13 really, this is the one that needs to be treated
14 in an hour kind of ROP.

15 And you can avoid putting people into
16 positions where they shouldn't necessarily be. We
17 have general ophthalmologists doing screening for
18 retinopathy of prematurity; we have other people
19 screening in other areas that they're not
20 necessarily experienced in. And I think this is
21 an area where telemedicine could actually enhance
22 what our safety network is overall by bringing the

1 very best trained people to the diseases that need
2 them.

3 DR. AFSHARI: Great point and an excellent
4 question. Other comments? I think Bakul --

5 MR. PATEL: I was just going to make an
6 observation and perhaps this is more to the
7 combination of the first question and the second,
8 I think what we are seeing and witnessing is a
9 need for sort of one technology aiding to the
10 right points or clinicians who got validated once
11 in their life and got their license. And to your
12 point about being continuously validated, so as
13 humans, we get validated once, get licensed to go
14 practice and then we rely on something that's
15 validated continuously. How can those two things
16 come together? I think that's really what the
17 question comes down to is when we talk about
18 aiding and making people make choices that are
19 right in terms of patients at the end of the day,
20 I think that's really where it comes down to.

21 So my observation was more about I don't think
22 it has to be one or the other. I think it has to

1 be n combination of like how can technology,
2 schools, licensing boards, and other things can
3 come together to figure out what the right, you
4 know, in machine learning terms, what the right
5 minimum or the right maximum can be reached. So
6 we need to maximize this and I think what
7 technology is sort of enabling or getting us there
8 to think about is like how do you maximize those,
9 you know, positives and negatives.

10 DR. AFSHARI: Great. So --

11 DR. TRESE: Can I have one more comment?

12 DR. AFSHARI: Oh, yes.

13 DR. AZAR: I think this came up before and
14 this follow-up on the issue of trust that today I
15 think any of us asked the question, and it was
16 asked in previous sessions, do people, do the
17 patients, the doctors even, trust that black box.
18 And it seems where asking the question, the
19 implication is "not yet" but I can see a day when
20 we combine this with the question that will just
21 ask -- that we'll be asking -- we trust the black
22 box now, can we trust the doctor, because -- and

1 that's going to be the status of affairs of the
2 future and we have to prepare ourselves for it at
3 all levels, technology, medical student education,
4 and residency and fellowship education.

5 There's going to be a lack period between the
6 two but I think that's a question to have to be
7 prepared at the educational level as well.

8 DR. AFSHARI: Great point. So we'll move on
9 to question number four and this focuses on
10 patient privacy and there are three prongs to
11 this; one regarding electronic medical records;
12 second, about storage; and third is about patient
13 behavior and locations. So let's read the
14 question together. What are the assets, traits
15 and vulnerabilities that should be considered and
16 identified as a threat to the privacy of a patient
17 by ophthalmic digital health device developers.
18 And there are three sub-questions; transmission of
19 information to electronic medical records or other
20 databases; b) storage of information on the
21 personal device or cloud devices; and c)
22 monitoring patient behavior and locations.

1 So let's start by -- from Dimitri.

2 DR. AZAR: Well, I don't think I'm highly
3 qualified to answer this so I'm looking at it from
4 perspective of this similar to the HIPAA
5 compliance days of the late 1990s. There's going
6 to be two issues I think; one is the intentional
7 misuse of information whether it's because of
8 sloppiness or because of malice; and the other is
9 unintentional, meaning despite all the safeguards
10 that are applied, there could still be some
11 unanticipated problems that hackers can go into
12 the systems and work on them. So that's a
13 potential difficulty because then whoever develops
14 the databases or the analyses or the way to guard
15 against the issues have to be knowledgeable
16 enough. And you would think you can do it.

17 I remember -- I'll give you an anecdote here.
18 At the university level -- and I'm not judging
19 universities versus private business -- I thought
20 we had a good enough, very secure IT system
21 because the number of hackings that, as a Dean of
22 a medical school, I was aware of was very small.

1 But I think it's because nobody was interested in
2 hacking us. Move to a private company on which
3 I'm on the board, most of the discussions at the
4 board level are about how do we avoid this from
5 happening and it's a fear that they have that --

6 (Leaf blower noise interruption.)

7 DR. AZAR: -- is this a hacking?

8 (Laughter.)

9 DR. AZAR: And you can tell it's in
10 transition; the systems are there. The expenses
11 are numerous but it's a problem that these
12 companies are dealing with. Now you move to the
13 new place where I'm now spending most of time, at
14 Google, and I wondered about how do we use these
15 videoconferencing between multiple offices. You
16 feel you're in the same room whether in you're in
17 two neighboring buildings or I'm in Chicago and
18 somebody else in San Francisco are conversing.
19 And I was told there are 600 people who are on the
20 payroll who are hacking the system on a regular
21 basis. Whether that's a rumor or not, I don't
22 know but that's what I was told by an outsider --

1 to make sure that these systems are secure. And
2 this is just for conversations over the phone.

3 Imagine the level of security that's needed
4 and the risk that many beginning companies trying
5 to get in this field would be facing if you didn't
6 have that infrastructure of IT security that's
7 needed. That's a fear, a big vulnerability but
8 that comes from the unintentional component.

9 I don't want to talk about manners and
10 sloppiness but those are other issues also that
11 you can have one company that's really advanced,
12 they do everything in a good way and some others
13 collect data and there's fear that that data can
14 be used for other purposes for secondary gain,
15 etcetera and again, you can -- in a way that may
16 inadvertently lead to loss of protected
17 information.

18 DR. AFSHARI: And I will give an example. I'm
19 at the University of California San Diego and
20 there is a system that you could access any
21 medical record from another University of
22 California campus by just going to the electronic

1 medical record. Well, so the broader the access,
2 the possibility of threat is larger. So how do we
3 dealt with that over time as the access would be
4 anywhere, anytime for any patient, any place in
5 the country or the world that we would have this
6 systematic access? So Leslie.

7 DR. ZIMMER-GALLER: So I'm certainly not an
8 expert in this area either. Going back to, again
9 with diabetic retinopathy, I think certainly the
10 programs are -- that are in place, really, by and
11 large, images are being transferred in a HIPAA-
12 compliant manner. They're being transferred
13 securely and, you know, the technology is there
14 that if you are using a Smartphone, you can take
15 images and they can be transmitted to an
16 electronic medical record and instantly be deleted
17 from the imaging device. So there's a lot of
18 technology out there. An evil-intended --
19 intended (ph) person probably can hack just about
20 anything but I think the technology is there to
21 keep medical records, to keep personal information
22 relatively secure but I don't think it's 100

1 percent guarantee no matter what you do so.

2 DR. AFSHARI: Dimitri.

3 DR. AZAR: I was going to add before the
4 blower came and --

5 (Laughter.)

6 DR. AZAR: -- a point about --

7 FEMALE SPEAKER: Before the hackers.

8 DR. AZAR: -- before the potential hackers --
9 it just made me forget a second important point
10 and I don't know how to -- this whole group will
11 address this. At some point, the retina becomes
12 an identifier of a patient so if we're dealing
13 with retinal images, we may be -- again, this is
14 inadvertently but as a group, it has to be
15 decided; it's different than a radiological image.
16 It's -- whether it's a pathologic or normal
17 retina, this is going to be a very difficult
18 aspect to be dealt with and the stricter the
19 regulation, the greater the impedance on the
20 advancement of the technology. So I think the FDA
21 is probably spending a lot of time thinking about
22 this and the guidance about it is going to be a

1 major determinant of where these technologies will
2 be going.

3 DR. AFSHARI: And then ethically, are we
4 responsible somehow if there is pathology in the
5 retina to diagnose it, to do something about it
6 when it's being saved in some company for some
7 security detection? Darius.

8 DR. MOSHFEGHI: So Dimitri brought up the area
9 that I was thinking about which is biometric
10 identifiers and it's not just the retina, it's the
11 iris. I have cleared. I go to the airport. They
12 have me scan my iris. It gets me through. I go
13 to the front of the line. It's really fun but it
14 used to be that we worried about hacks where
15 people are going in to get your information just
16 to expose a big healthcare corporation or
17 something like that.

18 But really, now we we have two areas with
19 these informations. For ROP, we get the iris
20 photograph and we get the retina photographs. My
21 database is very valuable, particularly when
22 you're going to use facial recognition, eye

1 recognition, retina recognition to get into this
2 and increasingly into your ATM account or anywhere
3 else.

4 And there are two ways to go after it. One is
5 the kind of like pickpocket approach which
6 patients, customers, people out there, the 77
7 percent who have their phone, they're easily
8 hackable. We don't all have robust software. But
9 then that's kind of like the small bear approach
10 if you want.

11 If you really want to go for robbing the
12 Brink's trucks, you're going to go for these
13 database systems because you can download
14 incredible amounts of data which can then be
15 deployed across that person's entire financial
16 life. So that's where the concern is on my part,
17 less on a patient privacy issue. I'm fully
18 cognizant of privacy issues and a big advocate of
19 them but more on the potential for mischief in
20 other areas.

21 DR. AFSHARI: Okay, Mia.

22 DR. WOODWARD: I think this is a really

1 interesting discussion. Again, you know, I think
2 that as an anterior segment specialist and again,
3 looking at this from an urgency, you know,
4 emergency room perspective, it think that privacy
5 is often compromised when we're trying to deal
6 with something fast. And so, you know, either
7 because of privacy, we can't get the information
8 as quickly as we needed it.

9 You know, a lot of solutions right now are we
10 get a PDF dumped into our media tab of our EMR and
11 that has the most up-to-date information and
12 that's really not accessible for the doctor who's
13 trying to use it, right; or a separate app that I
14 then have to download if I want to get the
15 information from this emergency visit. So I think
16 the how privacy interplays with interoperability
17 is very important. I don't have a solution for
18 that. That's your job.

19 And I guess the other thing is again, about
20 older populations and really giving away privacy
21 and not recognizing it, I can guarantee you that,
22 you know, a lot of older patients are on Facebook;

1 you know, they have their kids, they want to see
2 their grandkids on Facebook and so they don't --
3 probably aren't aware of the privacy settings that
4 they are giving away. And, you know, again, I'm
5 not immune to that. I will not be immune to that
6 n the future as well.

7 So those are my main concerns when I think
8 about privacy is we're -- you know, are the older
9 populations giving things away and not realizing
10 it and that the burden's on us to make it private
11 for them.

12 DR. ZIMMER-GALLER: But it's not just the
13 older patients. Nowadays young patients have a
14 rash and they "I don't want to see a doctor for
15 this, let me just send a picture to my doctor,"
16 and they'll even send it through email or, you
17 know, any other way that they can. So patients
18 really aren't aware of it either or don't think
19 about it I should say.

20 DR. AFSHARI: And then there are some patients
21 who ask their primary care doctor for certain
22 things not to be written in the electronic medical

1 record because of the fear of the privacy, so we
2 have that opposite aspect. There are patients who
3 email us all of their medical records and all of
4 us, I think, have some patients records in our
5 iPhones; even though they are protected by some
6 password, is that enough? So Mike

7 DR. TRESE: Well, that actually raises an
8 interesting point because the rules -- one of the
9 things that I thought was interesting this morning
10 was that there is an international device group
11 that's going to set standards, but I get a lot of
12 both in-country and out-of-country requests like
13 that. And the out-of-country requests I handle
14 pretty easily because I don't know the rules. The
15 in-country requests, I handle by saying, you know,
16 you're an American citizen --

17 DR. AFSHARI: You are on the watch list of
18 many countries and you don't know it.

19 (Laughter.)

20 DR. TRESE: That may be true -- but I ask -- I
21 think the -- I handle it the way I'm supposed to
22 for the United States but it is definitely -- it's

1 an important feature when we think about global
2 telemedicine for at least rare diseases, you know.

3 The other thing that I wanted to bring up -- I
4 share the concerns about the patient privacy and
5 the idea that you could be hacked from almost any
6 position. But I think one of the things that's a
7 big deal in a lot of places is where you're data
8 is stored; is it local server stored; is it cloud
9 stored.

10 The iris registry, which was mentioned
11 earlier -- I think you said you're on the board of
12 the iris registry, is that right -- so that data
13 is cloud is my understanding and it's -- I mean
14 it's carefully cloud stored; its' cloud stored
15 with the same security level that is like high
16 security military, just one below that is what I
17 was told. So -- but that type of consideration is
18 a limitation for moving telemedicine some places,
19 because people insist, universities, hospitals,
20 sometimes insist that their data only be stored in
21 their server.

22 And you lose the capability of secure access

1 wherever you are to patient data, like you were
2 referencing for the people in your hospital
3 system. So -- and that can be a big advantage for
4 patients that you can deal with from here that
5 have problems wherever your home practice is. So
6 I think that's an important issue.

7 I don't know are any FDA regulations on
8 storage. Is that correct or no?

9 DR. AZAR: Don't give them ideas.

10 (Laughter.)

11 DR. TRESE: Try Denmark.

12 DR. AFSHARI: Leslie.

13 MS. BOTTORFF: Yep. So of course, GE and also
14 a bunch of our portfolio companies are doing
15 things that are cloud-based and we have
16 discussions every day with, you know, integrated
17 delivery network big systems as well as smaller
18 entities about this very issue, because everyone's
19 quite concerned about moving to the cloud and
20 having it off premise. But, you know, that
21 presumes one thing, that their on-premise security
22 is better than Amazon web services. Really?

1 Probably not, you know. Not even for, you know, a
2 big IDN necessarily but certainly not for an
3 individual practice person. Their security is
4 probably not nearly as good as the cloud. So, you
5 know, everyone's working through that issue, of
6 course.

7 And you're right that the big sources of data
8 storage are a bigger target but nevertheless, if
9 it's an easier target, then the people who are
10 trying to get at this information are going to go
11 for smaller -- a lot of smaller sources. So I
12 think that's still an issue.

13 Some of the things that -- even though the FDA
14 does not regulate this, there certainly regulatory
15 entities that are regulating cybersecurity. And
16 some of the advent of things that are coming about
17 is there are some guidelines like the NEST
18 guidelines, but they're pretty big-level
19 guidelines. And one of the things that I think
20 could be helpful, especially to small companies
21 who, you know, I invest in and represent, is, you
22 know, what are some of the ways that we can meet

1 the requirements of these guidelines in a more
2 specific way.

3 And some of the things that I know are coming
4 up are there's a number of companies working on
5 some metrics for cybersecurity, both inside-out
6 and outside-in type metrics. So there's a lot of
7 activity, companies like FICO, RedSeal Happens to
8 be one that my husband, you know, is involved
9 with. He's a cybersecurity expert. There's a
10 number of them though that are working on these
11 concepts and that could the regulatory bodies that
12 are working with this sort of come to some kind of
13 agreement or guidelines just like they do for
14 medical ways to monitor people; here are some ways
15 that you could report this metric, and it's not
16 perfect.

17 It doesn't, you know, cover everything but at
18 least ways that companies that are manufacturers
19 that are trying to produce these medical devices
20 and services and systems can, you know, have
21 something to go to and say, okay, we did that test
22 and here is our metric so that you have some way

1 that they can tell you, you know, that they're
2 cyber secure. I mean I know, like for instance,
3 the MACRA guidelines which are not the FDA's but
4 are CMS guidelines, have a component upon which
5 bonuses, incentive bonuses are based for providing
6 you have a certain level of cybersecurity. But
7 they're not very specific about like what -- how
8 do I report that to you and how do I prove that to
9 you.

10 And so -- but I think we're getting there and
11 that's something maybe that the FDA can think
12 about in terms of working with the other
13 regulatory bodies on your piece of, you know,
14 those privacy concerns about how can we provide
15 some really clear and specific guidelines or goals
16 to the big companies and small companies alike out
17 there of here's the kind of level you have to
18 reach. I don't know.

19 DR. AFSHARI: David.

20 DR. MORRISON: I think that my perspective is
21 going to be a little different, mainly because
22 things have been covered, to a large degree, and I

1 can't actually define what the cloud is so I can't
2 think I can be of much help there But I think
3 "c," monitoring patient behavior and location is a
4 very interesting and concerning topic. So as we
5 move forward with telemedicine, there's a
6 significant chance that patients can be monitored
7 in a way that they've never been monitored, or at
8 least that data could be collected, continuous
9 blood sugar monitoring, IOP with glaucoma may have
10 some ability to locate the patient to a specific
11 geographic area to a specific behavior that could
12 then, in some way, represent a breach of their
13 privacy if it were disclosed to insurers or anyone
14 else.

15 Physicians certainly have been led into the
16 concept of pay for performance in addition to
17 outcomes measures; is it possible that insurance
18 companies would be interested in trying to obtain
19 any of this data to change premiums based on
20 patient behavior and risk of having higher cost of
21 healthcare So I think that we haven't touched on
22 that as much but it certainly a potential for the

1 technology moving forward and something that I
2 think would have to be regular and would be very
3 challenging to deal with.

4 DR. AFSHARI: Bakul.

5 MR. PATEL: I think we should ask the patients
6 what they care about. I think that's really the
7 question right here. I think this question is not
8 the role that, you know, this community played at
9 one point in time about, you know, privacy and
10 privacy of -- or it's preferences that people had
11 for privacy. I think that's fundamentally
12 challenged with this technology.

13 I could argue one hand that we can secure the
14 data that people have in hospitals all the time
15 but then you allow them to download from and to
16 their "MyPatient portal" and they put it on a disc
17 somewhere or a paper somewhere and just they'll
18 forget about it.

19 So I think that's sort of the realities of
20 where we are today, the realities of being able to
21 glean into retina images and identify a patient as
22 things are becoming more and more ubiquitous and

1 sort o almost common. But so is being on Facebook
2 at the same time. So I think the fundamental
3 question in my mind -- I wondered about this -- is
4 it may not be just one of us where you're able to
5 take the fully responsibility of what we consider
6 privacy or patient preference for that matter. I
7 think previously in our -- even in this space,
8 there is (inaudible) of civil rights that does
9 HIPAA, FTC, the Federal Trade Commission talks
10 about security as well from a commerce
11 perspective. And just to take the example to the
12 international front for a second and the EU,
13 pretty much every state has their own security
14 requirements and they're' all different.

15 So I don't think one universal answer sort of
16 serves in these purposes. I think we had a
17 tolerance at some level before I think that
18 tolerance is changing rapidly because people are
19 just donating. I don't know if some of you guys
20 have heard about the non-profit organization,
21 Tidepool. They're actually one of the pilot
22 participants, they just advertised to help

1 patients who are collecting their CGM data,
2 continuous glucose monitor data, to be donated to
3 their website. And if you just go to their
4 website, you will see tons of people just
5 willingly give that data away to that website for
6 the greater good.

7 So I think the concept about protecting
8 patient data and, you know, clinicians have the
9 responsibility, healthcare institutions have the
10 responsibility to do so, it's being sort of
11 questioned at this time. So that's how I would
12 start thinking about it.

13 DR. AFSHARI: And the patient's desire,
14 depending on the data point, may be different and
15 each patient may be different, or there are ways
16 to study the identified data like dbGaP we have
17 for -- from an NIH, that whole genetics database.

18 So are there comments or questions from the
19 audience? I know we are getting very close --
20 yes.

21 MALE SPEAKER: (Off mic) ophthalmologist (off
22 mic). So thank you for this conversation. This

1 is actually what I believed for the last five
2 years trying to get a single device (inaudible/off
3 mic) -- so when I deal with the vendors, the
4 vendors put their hands up and say, "It's your
5 problem, it's not our problem" and I think we, as
6 a community, have to recognize that it is our
7 problem, for ophthalmology in general. In fact,
8 radiology is much better at governing and pressing
9 on the vendors to improve their (inaudible)
10 posture. In ophthalmology, we know the vendors
11 have (inaudible) whenever they want.

12 So a couple comments about the cloud. So
13 there is an accreditation-certification process.
14 It's (Inaudible/office mic). Now it's government
15 accreditation. I think there are (inaudible) out
16 there that are a part of that, Microsoft, Amazon
17 and I think Google and that's it. So Amazon has
18 one part (off mic) so have to make sure when
19 you're talking to your vendors or you (inaudible)
20 "yes," which is part of the design. And I
21 (inaudible/off mic) who use the cloud services are
22 not (Inaudible) certified.

1 So if you're going to place (inaudible/off
2 mic) on a system or (inaudible/off mic) on a
3 system that's not (Inaudible) certified, just
4 understand that there's risks there. (Inaudible)
5 startups themselves who work with the (Inaudible)
6 rule (inaudible) or PHI so if you're going to leak
7 a data, that is (inaudible). So if you're not
8 going to use a (Inaudible) certified system, you
9 lose data. There's potential risk (inaudible/off
10 mic).

11 I could use the help from the DoD because I
12 can't use any of these new emerging technologies
13 unless it's accredited. I can't get it accredited
14 if we won't have (inaudible) efforts (inaudible).
15 So I just want to thank everyone for talking about
16 this.

17 DR. AFSHARI: Great point. Comments from the
18 panel or from the audience? Now I believe
19 everybody is ready -- yes, please.

20 MALE SPEAKER: (Off mic) question back to the
21 first one (off mic.) My name is (Inaudible/off)
22 mic, very small startup so this is very

1 appropriate for us (inaudible) discussions.
2 (Inaudible) I've heard a lot this morning about
3 physicians really (inaudible) the gold standard.
4 And if you looked at gold standards as
5 (inaudible), gold standard seems like it's the
6 physician. And then I heard -- we went all the
7 way back through well, our physicians, most of us,
8 is a black box. And so we're back to this
9 question of well, how do we then -- you know, what
10 is the standard or how do we test or, you know,
11 what is enough data for us to have, you know, a
12 clearance for a medical device? So I don't know
13 if the panel could help address that in terms of,
14 you know, how much data do we need in -- you know,
15 in order to get our clearances for a screening
16 device in particular, something that is going to
17 be an adjunct to the physician, not to replace,
18 not to be viewed as a diagnosis but just an
19 adjunct? Any thoughts on that?

20 DR. AFSHARI: Thoughts on that -- and of
21 course, it depends on the device. I'm sure we are
22 going to hear that. Michael.

1 DR. TRESE: I think we're really close to the
2 end of time. I know that Mike made a big point
3 about that. I'd be happy to talk to you about
4 that afterwards because there is a lot of info --
5 or was that Mike to go ahead and answer it?

6 DR. CHIANG: I think we should answer his
7 question.

8 DR. TRESE: Okay. The -- I think that there
9 is no real gold standard of to what a gold
10 standard is. It comes in terms of physician
11 acceptance. In my mind, someone that does a
12 drawing of a retina for retinopathy of prematurity
13 might as well hand me a cartoon about peanuts or
14 something like that, because I can take a picture
15 and get an exact image, okay. That's not the
16 mentality of everybody that does ROP. And some
17 people think that there may be reasons to draw
18 something that may be wider even though you can
19 image really from aura to aura with some of the
20 cameras now. So -- but I think it is -- in all
21 parts of medicine, it seems to me it takes to me
22 it takes a really long time to get to -- things to

1 change and a gold standard to emerge.

2 So years ago, Bill Rich (ph) told me that
3 there was some data that suggested -- this was
4 maybe five-six years ago -- that it took almost 20
5 years for clinicians to accept randomized
6 controlled prospective data. And so I think it's
7 hard to determine. I think the black box is
8 opening. I think the gold standard is evolving
9 Bureau you could get arguments on both sides, I
10 think, of diabetes and ROP for sure.

11 DR. AFSHARI: Michael Goldbaum and Bakul.

12 MR. PATEL: Oh, I'll just make a point. I
13 think it all depends on the device -- the device
14 that we're looking at specifically but I think it
15 really -- and this is the way I think about it.
16 It is what you really want it to be and it's not
17 about what we want as an FDA review product,
18 right. So it has to match the claim that the
19 evidence is there for. So it's not about what it
20 is. It is about where you want to be as a product
21 and we can talk in detail about that and Malvina
22 and the team is there to think about -- think

1 through that but it's about matching that. In my
2 mind, that's really where we need to sort of get
3 to and not -- it's not about you need 50 patients
4 or 500. That's really not the discussion.

5 DR. AFSHARI: Mike Goldbaum.

6 MR. GOLDBAUM: Yeah. So I'd like to pretend
7 that the physician is not a black box. So the AI
8 is a (inaudible) -- you have to come up with some
9 techniques to try to figure out how it got to
10 where it. And there's a bunch of (off mic) inside
11 this device, and you can't really figure it out.
12 They're all (inaudible). You can talk to a
13 physician. You can get the reason. You may not
14 agree with it. And there's (inaudible) if the
15 reasoning is wrong. You can teach them the
16 correct reason. So there is -- I think you -- to
17 say the physician is a black box is more than
18 (inaudible/off mic).

19 The other thing is that the seclusion is one
20 of the methods to try to (inaudible/off mic)
21 machine learning classifier got to where it got
22 and got to -- and it's a variant factor of

1 elimination. I mean it's an old technique. These
2 are a lot of techniques to try to figure out
3 what's going on inside a machine unclassified and
4 in factor of elimination is one -- it's -- and
5 it's --actually, it's quite effective. And as you
6 can see, (inaudible/off mic).

7 DR. TRESE: One more.

8 DR. AFSHARI: Comments? Dimitri.

9 DR. AZAR: Can I comment about this because
10 the black box issue was raised by me. I was
11 actually agreeing with you that the worry that
12 people have now is about the black box not being
13 trusted but in fact, we need to be focusing for
14 the future that the question should not be about
15 physicians. We need to establish the trust in
16 physicians and that requires recognition of that
17 potential risk and preparing our doctors today to
18 be -- for that future that if we don't, they will
19 be questioned. Trust in the machine, I dread the
20 day if the trust in a machine is greater than
21 trust in your physician.

22 MR. GOLDBAUM: As an example, the testing for

1 colleges, the scores went up when (inaudible).
2 The scores went up as we went on the in years and
3 the reason why the scores went up is that the
4 young people were using the internet to teach
5 themselves a lot more than people of previous
6 generations were able to do so that -- so my point
7 is that all of these tools can help us to become
8 better at what we do so that we don't need to be
9 abandoned and replaced by AI.

10 (Laughter.)

11 DR. AFSHARI: So Leslie, the last comment.

12 MS. BOTTORFF: I just had one more comment
13 because I just want to say to the folks of the FDA
14 that the pre-certification process and the
15 collaborative, you know, things that you suggested
16 are really the way to go to make this thing go
17 fast. And I just congratulate you on that and
18 say, you know, that needs to speed ahead. And it
19 might not be perfect the first time around. Just
20 get it going because the data is going to help it.
21 And so congratulations on that. It's a fantastic
22 concept.

1 DR. AFSHARI: So on that topic of the black
2 box, we have boxed lunches outside. Please come
3 and join us so we can talk about privacy or less
4 of it this day and age. Thank you to all of the
5 panelists, Dr. Trese. Thank you for a great
6 morning and session.

7 (Chorus of thank yous.)

8 (Applause.)

9 DR. BLUMENKRANZ: Afternoon. Hopefully,
10 everyone had a good lunch and you didn't
11 carbohydrate load so much that we'll all be sleepy
12 here. But we're already a few minutes behind so
13 we'll try to catch up, and we're going to be doing
14 a panel two. This is safety and efficacy concerns
15 for ophthalmology digital devices in differing
16 settings and there's an emphasis on differing use
17 settings, and there's an emphasis on differing use
18 settings. The same tool might be more or less
19 useful in the clinic versus in a primary care
20 setting or in the workplace.

21 And I thought we ask the -- I'm Mark
22 Blumenkranz, and I'm the immediate past Chairman

1 of the Department of Ophthalmology at Stanford,
2 and I've co-founded the Optomic Innovation program
3 with David Myung, and I am a a practicing
4 vitreoretinal surgeon, and I have worked in
5 technology development in Silicon Valley.

6 I'll ask everyone to introduce themselves and
7 then we'll move on to the presentations and
8 questions and so forth, and this is my co-
9 moderator.

10 DR. NISCHAL: Thank you. I'm Ken Nischal.
11 I'm representing the American Academy of
12 Pediatrics and Section of Ophthalmology. I'm
13 Professor of Pediatric Ophthalmology at
14 Pittsburgh. We've been involved with a lot of
15 global health in terms of telemedicine, not just
16 for ophthalmology but also for cardiology and
17 hepatology, and we provide real time ICU
18 surveillance for several centers in South America,
19 and it's sort of a pivotal role of what we do in
20 terms of tele medicine.

21 MR. OSWALD: Good afternoon. My name is
22 Quinton Oswald. I traveled a long route in

1 ophthalmology. Currently, I'm the the CEO of a
2 company called Notal Vision, which is a device-
3 based platform which we'll talk about briefly in a
4 second.

5 Right from the the existence of vision died
6 through the launch of Lucentis were experiences I
7 had, and now I moved to the light side. Dealing
8 with the side of the business has been a
9 fascinating change in my life and certainly the
10 way that I think about measurement of the
11 patients.

12 DR. BODNAR: Good afternoon. I'm Zach Bodnar.
13 I am originally a software engineer and I
14 transitioned to become a physician. I've
15 completed my residency in ophthalmology at St.
16 Louis University and over the past year, I did the
17 ophthalmology innovation fellowship under the
18 tutelage of Dr. Blumenkranz and David Myung, and
19 I'm currently a vitreoretinal surgery fellow at
20 Stanford.

21 MR. PATEL: Bakul Patel. I'm Associate Center
22 Director for Digital Health at CDRH.

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1 DR. ZANGWILL: Linda Zangwill at UCSD. I'm an
2 epidemiologist by training and Director of the
3 Diagnostic Imaging Laboratory and the Hamilton
4 Glaucoma Center.

5 DR. GOLDBAUM: I'm Michael Goldbaum. I'm also
6 at the University of California San Diego, and I
7 do -- I practice in retina but my research, a lot
8 of it, is also in glaucoma. And I've had an
9 interest as far back as 1987 in imaging and
10 machine learning. So that's where the original
11 work came from.

12 DR. ABRAMOFF: Yeah, I think we're the oldies.
13 I'm Michael Abramoff. I'm -- I was trained in the
14 Netherlands as a vitreoretinal surgeon, came to
15 the U.S. 15 years ago. I'm a Professor of
16 Ophthalmology at Iowa. I'm also the founder and
17 president of IDx which is getting ready to put its
18 first submission for an automated diabetic
19 retinopathy detection device for primary care into
20 the FDA.

21 DR. CHIANG: I'm Michael Chang. I'm a
22 pediatric ophthalmologist by background and also

1 board certified in clinical informatics. And I
2 run a research group at Oregon Health and Science
3 University that deals with various aspects of
4 applying information technologies to eyecare.

5 (Off record comments.)

6 DR. BLUMENKRANZ: Good. So this is our
7 listing. So I thought by way of introduction, it
8 might be worth just talking a little bit about the
9 fact that this is an area that benefits all
10 constituencies. Digital health is -- has a value
11 proposition for patients in terms of engagement,
12 better care, and convenience for physicians in
13 terms of workflow, expanded reach, engagement and
14 research for payers, in terms of, hopefully -- I
15 won't say reducing costs but appropriating cost
16 and better outcomes, and finally, for industry and
17 pharma and the device industry for data-based
18 insights and value based analysis.

19 I think our -- there we go -- it's
20 interesting, I think, to get to look at the
21 evolution of the Smartphone and as you saw earlier
22 today, although 75 to 80 percent of Americans have

1 Smartphones, it's true even in the 65 and plus
2 category, in which it's now approaching 30 percent
3 in 2016, so it's -- they are becoming ubiquitous
4 across all segments of society although maybe a
5 little more prevalent on the coasts.

6 Smartphone capabilities are increasing at a
7 similarly rapid rate if you compare the original
8 Mac in 1984 to existing iPhone or Android, you can
9 see the -- whether it's the pitch or the DP,
10 whether it's the degree of memory in terms of
11 images, in terms of the speed, and in terms of
12 overall memory, they're all dramatically greater
13 for small Smartphones now than they were for the
14 very best Macs that were available at that time.
15 And we can expect that in keeping with Moore's
16 laws to continue.

17 Smart devices are now being used across all of
18 all of medicine, not just ophthalmology but
19 whether it's asthma, cardiovascular, ENT,
20 oncology, diabetic management, they are becoming
21 an accepted standard of practice and I think this
22 workshop today, it just goes a long way in terms

1 of bringing ophthalmology into the forefront of
2 this area.

3 These are just a few of the companies that I
4 am aware of as of last year that are already
5 offering products, some approved some not, that
6 are being used by inpatients are being put through
7 clinical trials to be able to seek approval. If
8 you look at it just in terms of cameras alone,
9 there are more than seven cameras that are either
10 approved or in the process of being approved to
11 take advantage of the degree of the high
12 resolution camera found in Android platforms and
13 in iOS devices that, coupled with some sort of an
14 optical device, can produce very high quality
15 images.

16 The FDA has cleared -- as of 2014, the FDA had
17 already cleared more than 100 mobile health apps
18 for medical use and that's been increasing at an
19 increasingly rapid rate. If you look at it from
20 the total market perspective, although the amount
21 spent in the last few years is still significant,
22 it's expected to grow by more than 6x, according

1 to market research, between 2015 and 2020. So
2 it's certainly a very important area of the
3 medical economy as well as the value-based
4 creation for patients and for physicians and for
5 the industry as a whole.

6 With that I'd like to go on to our questions.
7 Now our questions really revolve around safety and
8 effectiveness and in specific situations. So the
9 first question is for Quinton Oswald and that is,
10 What are the important safety and effectiveness
11 concerns for an ophthalmic digital health device
12 for the screening or monitoring of progression of
13 macular diseases?

14 MR. OSWALD: Thank you, Mark. I'd like to
15 handle the effectiveness piece first because
16 safety, I think, is a relative issue in the device
17 space. But in reality, I think insufficient focus
18 has been put on the effectiveness and the clinical
19 utility of these devices as we go forward.

20 And for example, before we're able to get
21 reimbursement at Notal Vision for our device, we
22 had to involve ourselves in quite an extensive

1 clinical study to prove the relevance of our
2 device in terms of a reimbursement environment.
3 So, therefore, we think that that clinical utility
4 and the evidence based of that clinical utility is
5 a critical element in the development of the
6 device situation.

7 So I think that the bar for approval of a
8 device is relatively simple today. We think that
9 maybe we need to expand that from a point of view
10 of the clinical evidence that supports that, and
11 being, you know, well-controlled clinical trials
12 as we would thought of in the drug space. As I
13 said, with regard to safety in particular area,
14 it's benign by virtue of the fact we have no real
15 impact on the eye, so that's not something we
16 certainly think about.

17 DR. BLUMENKRANZ: Linda, perhaps you could
18 address that with regard to glaucoma to the extent
19 that there are similarities or differences between
20 macular disease and glaucoma relating to the
21 particular type of pathogenesis of those diseases.

22 DR. ZANGWILL: Well, I think there are a lot

1 of similarities and it's really the attended --
2 intended use is what's critical here. And in
3 terms of, for example, screening for glaucoma, I
4 think detecting the earliest disease is not going
5 to be effective or efficacious, but treating --
6 detecting moderate disease that we can do well --
7 with early disease, there is -- the clinicians
8 disagree and the machine learning will disagree,
9 but for moderate disease, we are fortunate that
10 glaucoma is, as mentioned earlier, slow
11 progressing. So if we can detect moderate
12 disease, that would be -- and I think we have
13 tools that we can do that -- is -- would be a
14 target for specifically screening or advanced
15 disease. Lots of advanced disease is undetected.

16 And in terms of the safety as well, if you're
17 thinking about the safety of the visual field test
18 or a photograph or something, the safety issues
19 are not that difficult to deal with in terms of
20 safety in a similar way to to the macular disease.

21 MR OSWALD: (Inaudible.)

22 MR. OSWALD: I think it does fundamentally

1 different medical diseases versus glaucoma
2 relative to the time of onset, because we know
3 that the earlier you get a patient in a switch
4 from dry to wet, the more -- the better the
5 outcome is going to be for the patient in terms of
6 treatment. If you can get them with a relatively
7 good vision and small lesion or fibrosis, the
8 outcome for the patient is going to be superior.
9 So, yeah, different from glaucoma, we think that's
10 a really critical element.

11 DR. GOLDBAUM: If I may add something? As
12 well as diagnosis for glaucoma, diagnosis is
13 important but what the glaucoma clinician needs
14 day-to-day is to determine whether the disease is
15 stable or progressing. And we have found that
16 that machine learning classifiers or a hybrid
17 system using machine learning classification is
18 quite good at picking up and detecting
19 progression.

20 DR. BLUMENKRANZ: I just want to remind the
21 fact that the panelists that -- and the audience
22 as well, please, before -- if I haven't called on

1 you, if you could just state your name so the
2 transcriptionist will be able to do their jobs in
3 terms of having the proceedings of this
4 publishable.

5 DR. BODNAR: I have something to add to that.
6 This is Zach Bodnar. I think one of the
7 differences with glaucoma and macular disease,
8 glaucoma, it depends on the type of testing you're
9 doing but if you're talking about visual field
10 testing, one of the big issues is the reliability
11 and the reproducibility of the test. And there
12 are some questions about an increase in the
13 variability if a patient is testing their visual
14 field at home. Are they going to do it in the
15 same setting where there's the same background
16 luminance each time or even across different
17 patient populations?

18 So some of those things need to be validated.
19 And I think there's a risk that in some of these
20 initial projects, we'll see kind of a negative
21 result where we find they're not useful, but that
22 may just be because there's a lot of noise and we

1 haven't taken into account the amount of
2 variability that's in these other environments.

3 DR. NISCHAL: Before we go on to the next
4 question, Linda, I wanted to ask you when we talk
5 about safety with glaucoma, you know, there's the
6 issue of self-monitoring with some of the
7 companies that give you the self-monitoring
8 equipment, and there's the issue of implanting a
9 device in the eye that gives you constant
10 monitoring. You know, if there is that kind of.
11 implantation of a device, that must have some
12 safety issues.

13 DR. ZANGWILL: Yes. You know, that that's a
14 good point and I was not addressing -- I was
15 focusing more on the screening but that's a good
16 point. I believe the -- one of the implants, IOP
17 monitoring, has just been approved by the FDA for
18 continuous monitoring. So that is absolutely a
19 safety issue and my understanding is it went
20 through the proper -- the -- it has been approved
21 but there are safety concerns. It really depends
22 on the intended use, if it's screening, if it's

1 monitoring pressure, etcetera, that is but that
2 is -- that's a very good point.

3 DR. BLUMENKRANZ: Just for point of
4 clarification, Bakul, was it -- I know there was
5 an external device, the SENSIMED or -- but I don't
6 -- was there an internal implant as well or --

7 DR. ZANGWILL: Oh, go ahead. My terminology --

8 MALE SPEAKER: Yes. Actually, I'm going to
9 see if Ron is in the room to answer that. He's
10 probably better-suited because his branch and his
11 division sort of looks at that.

12 DR. SCHUCHARD: This is Ron. As far as I
13 know, the SENSIMED is what's being referred to,
14 and that is a device that is monitoring relative
15 change rather than absolute IOP.

16 DR. BLUMENKRANZ: I think also the point being
17 the risk-benefit ratio. I think that the physical
18 risk that is there -- we'll set aside the risk of
19 getting the numbers wrong or things being
20 imprecise or not reproducible. But there is there
21 is a fundamental difference between a surgical
22 procedure to implant a device in the eye and one

1 to monitor externally in terms of the risk
2 profile. And I think that was the only reason I
3 asked the question, was because I think you might
4 value them -- evaluate those in a different way
5 fundamentally related to the risk-benefit ratio,
6 not to the accuracy or reproducibility per se.

7 DR. ABRAMOFF: Mike Abramoff. I wanted to say
8 something about diabetic retinopathy where the
9 presence of preferred practice patterns. For
10 example the American Telemedicine Association's
11 guidelines for DR detection have been invaluable,
12 so if you have these guidelines to align with, and
13 we prefer a practice plans to align with, that
14 makes it much easier. All these debates about
15 which level of diabetic retinopathy to detect, you
16 know, what to do what the different levels, that
17 has sort of been decided already by a professional
18 society. So -- and, you know, if we're looking at
19 glaucoma, it's a little bit more tricky just
20 because the guidelines are a bit more vague so,
21 you know, professional societies can really help
22 by making, you know, the guidelines as specific as

1 they can be.

2 DR. NISCHAL: Okay. So we're going to move on
3 now and one of the other questions that we have to
4 cover is alluding to what Zach was saying, you
5 know, do the use of these digital applications
6 change depending on the environment that you're
7 using them in. So we're going to start off with
8 the use in an eyecare clinical environment.

9 And the first question, really, I want to
10 discuss is the fact that if you -- do we need to
11 specifically train somebody in the office to have
12 the responsibility to look after the data that
13 comes in? This is a real live, practical problem
14 at Children's Hospital of Pittsburgh. We have a
15 portal for patients to be able to contact us, and
16 I sometimes find it difficult to return emails on
17 the same day within a couple of hours rather than
18 having a number of patients go home and then send
19 me a message. So we've actually trained somebody
20 who is -- was an ophthalmic tech, to take the
21 responsibility to look at the portal messages of
22 all the attendings. That's one question and the -

1 - the one thing to discuss.

2 And the other thing that's quite important is
3 that in my role with Telehealth in helping develop
4 surveillance for pretty sick children in another
5 part of the world, if something goes wrong with
6 the data that you're getting, you need someone to
7 recognize that it's a data acquisition problem and
8 not a problem with the data itself. And so I'm
9 becoming more and more concerned that rather than
10 having somebody who's just an ophthalmologist or
11 an eye healthcare person who we may give the
12 responsibility to do this, that you need someone
13 who has adequate training in IT and software so
14 that they can then assess whether the data they're
15 guessing is wrong or indicating that there's a
16 problem with the patient or whether there's a
17 problem with the acquisition.

18 DR. BLUMENKRANZ: So I'd be interested to see
19 what the panel says about that. Michael, you've
20 done a lot of work with Telehealth. What do you
21 think about the specific roles?

22 DR. CHIANG: Can I have a comment about the

1 first thing that you mentioned in terms of that
2 monitoring? So this is in response to your
3 comment, not an answer to your question. I think
4 that we have a fundamental model in clinical
5 medicine which is that we will see a patient every
6 "x" number of months; you know, every three months
7 we'll see them and we'll say, you know, take your
8 eye drops, take your blood pressure medicine.
9 We'll come back three months later and then they
10 either have done it or haven't done it, and we'll
11 repeat that cycle like every three to six months/
12 With a lot of these Telehealth things that we're
13 talking about in this panel. we're sort of
14 fundamentally changing that model where the idea
15 is that instead of every three months, you go do
16 this at home and you'll do it every day or every
17 week, and you tell us or, you know, somehow we've
18 got to figure out when there's a problem with
19 that.

20 And so I think that number one, I think one of
21 our challenges, as a community, is to demonstrate
22 that that second Telehealth model provides added

1 value over doing it every three months. And I'm
2 not convinced that we've answered that question,
3 but I hope that's something that we can all kind
4 of go back and tackle, you know a little bit more,
5 because you know, Ken, for the reason that you're
6 mentioning, you gave an example, I think, of how
7 that might hurt us because you can get bad data
8 and we may make the wrong decisions based on
9 something that came up. And so I hope that's
10 something that we can, you know, address a little
11 bit as a community.

12 In terms of -- Ken, in terms of the question
13 that you asked me, I think that the way that I
14 sort of put these technologies together is sort of
15 who is responsible for interpreting the data and
16 who is going to be that decision maker. And it
17 seems like there are three options; one of them is
18 that the managing ophthalmologist takes that data
19 and then they make a decision on it, which in that
20 case, it's a decision support tool and so that
21 seems easy.

22 Number two is that like it's basically a --

1 some sort of remote reading center where, you
2 know, some expert remotely, you know, makes that
3 diagnosis and you've got to have faith that that
4 was done correctly; in other words, it's a black
5 box kind of approach and I think that there are
6 some safety issues with that. Who is doing the
7 readings; what's the validation?

8 And and I think the third issue is that the
9 system does it automatically, which I think is a
10 whole 'nother level of of oversight that that
11 requires. So I think that in a lot of cases, how
12 we deal with them is got to depend a little bit on
13 how those systems are architected and what that
14 sort of model is.

15 DR. BLUMENKRANZ: Let me let me push back to
16 you a little bit, Michael. It came up in the
17 course of we did some work on home monitoring for
18 macular degeneration with patients generating
19 visual plots and data that are then able to be
20 shared with in a secure and private way the
21 physician. But when -- in talking to other
22 physicians, they say we're already horribly

1 burdened by information overload. I'm getting
2 emails, questions from patients through a portal.
3 All of a sudden somebody sends me an alert that
4 says that maybe a vision is dropped; I'm not
5 checking that every day amongst all of my other
6 email accounts, my other correspondence, and so
7 forth.

8 Question comes up; does it put a burden on
9 physicians if they don't have some procedural
10 process that -- so that somebody actually is
11 looking at these results every day, even if it's
12 not a physician, if it's a paramedical personnel
13 and so forth? I mean what are your thoughts about
14 that.

15 DR. CHIANG: Mark, my first thought is that I
16 think that's a really good point, you know, that
17 you made. You know, I think that doctors feel
18 pushed to do more in less time, you know, often
19 with fewer resources than ever before and I think
20 that's an example of that. And so I guess my
21 first thought is that if the data is going to be
22 generated, there has to be somebody who is

1 available to interpret that data and ideally, it
2 would mean that there's somebody who can get paid
3 or whose job it is to interpret that data and, you
4 know, get paid for doing it.

5 You know, I think one of the challenges is
6 that if we get patients who are generating more
7 and more data and you've got 2,000 patients in
8 your panel, that's an enormous amount of data
9 that's going to be coming back, and I don't think
10 any human can do that. And to me, the natural
11 extension of that is that we need to develop
12 automated systems to do exactly what you're
13 saying, which is to screen at what point does a
14 doctor need to get involved. And so I think with
15 those issues, the challenge is going to be number
16 one, how good are those systems and how good can
17 we make them at distinguishing the sort of normal
18 from the not normal.

19 And the second is what is our threshold as
20 healthcare providers for being bothered by the
21 system. In other words, do you set your threshold
22 here or here or here, you know, to get bothered a

1 lot versus a little based on your tolerance for
2 potential errors. And so those are sort of the
3 frontiers that I see that we'll need to address to
4 try to deal with this question of basically what I
5 would call data overload.

6 MR. PATEL: So can --

7 MALE SPEAKER: Yes, please.

8 MR. PATEL: I was just going to make a point.
9 I think this discussion is fascinating for me
10 because I think we're really talking about data
11 prominences, like what -- where is the data coming
12 from, right? So -- and this is the cross-walk of
13 interoperability where things can -- things --
14 devices and other products would have to sort of
15 declare itself the performance, not just put it in
16 a label someplace but actually be that -- the data
17 performance and the validity of it should travel
18 with the data stream itself. So that's one issue.

19 I think then we talked about the data volume
20 itself, like how do we sort of take care of data
21 volume. And that's where -- so in the discussion
22 we had earlier, thought comes into play where

1 automation is probably the only solution that sort
2 of exists in terms of taking in -- taking data
3 volume into insights. And that data insight is
4 really where we are talking about does it really
5 mean meet the screening threshold. Does it really
6 meet our sensitivity-specificity sort of
7 threshold? And how does it actually aid?

8 So if we take this string of requirements, so
9 to speak, you start with what generating; how
10 transparent it is; how does it report back so
11 people -- either it's man or machine interpreting
12 the data, knows what kind of data they're
13 interpreting. And then you walk down to the next
14 step of how do you take that and turn that into
15 insights or information that can be used in
16 practice. I think that scale will be something
17 that we need to evolve.

18 FDA just put out or are in the process of
19 putting out the interoperability guidance which
20 talked exactly about that. It's about how do we
21 sort of get people who are generating this
22 information and data streams to be very

1 transparent. So it doesn't really matter whether
2 man or a machine sort of uses that data. They
3 know how much to trust it, what -- how much to
4 rely on it. So we should think about that even in
5 this space.

6 DR. NISCHAL: So now that we've sort of
7 discussed that, you know, we either have somebody
8 who has a a specific role where you go for
9 automation, the question really is if, Mike --
10 Michael -- going back to what Michael was saying,
11 if you're going to have a physician look at this
12 data, how do we reimburse them, because I can tell
13 you right now if we do a tele ROP screen for
14 Inaudible), the middle of Pennsylvania from
15 Pittsburgh, it's been a real struggle for my doc
16 to get the appropriate reimbursement either from
17 the insurance or from the hospital that wants to
18 do it. So the question, really, that I wanted
19 Quinton Oswald to track is how do we -- should we
20 tackle that question now and, you know, how do we
21 do it.

22 MR. OSWALD: Thanks, Ken. In 1974, the

1 *Harvard Business Review* published a one-page
2 article entitled, "The folly of incenting x whilst
3 was expecting a y." and really, we have to think
4 about the alignment of incentives through this
5 process. And you think about the ophthalmic
6 space, the reimbursement environment and the rapid
7 change of telemedicine/telehealth are traveling to
8 different paths. And today we're having
9 difficulty aligning those incentives. And we
10 really need to set up a platform and a process
11 where we think about how to do this so we're not
12 expecting x whilst incenting y.

13 DR. GOLDBAUM: So I think what we're hoping is
14 that computers will help physicians or healthcare
15 providers to be able to do more with less time.
16 And so if I understand Michael Chiang correctly,
17 then his answer to nagware is triageware and that
18 may be the answer actually, because then the
19 physician is presented with what's important and
20 can concentrate on either the patient or other
21 parts of the patient care.

22 DR. BLUMENKRANZ: Okay. Can you turn the

1 slide back on? We're going to move from the
2 ophthalmology office or the optometric office to
3 another side of medical service; in this case,
4 let's just say hypothetically either a primary
5 care center or the emergency room where we're
6 using telehealth and digital tools to try to
7 expand the reach and improve efficiency and
8 outcomes.

9 What experiences do we have now for
10 interfacing between eye health professionals and
11 primary and urgent care providers? Michael, I'm
12 going to start this off with you, and then I'm
13 going to move to -- I'm sorry -- Michael Goldbaum.
14 We have three Michaels on this panel. I don't
15 know what that means.

16 DR. GOLDBAUM: And we're all right next to
17 each other.

18 DR. BLUMENKRANZ: It must mean something. I
19 think we need to do deep learning to figure out.

20 DR. GOLDBAUM: So this is the Michael cluster
21 over here.

22 DR. BLUMENKRANZ: Yeah. Well, some names are

1 in vogue like Ambrose at the turn of the century
2 but is -- you don't hear much anymore. So we'll
3 start with Mike Goldbaum since you've got the mic,
4 and then we want to move to Michael.

5 DR. GOLDBAUM: So we can go to the --

6 DR. BLUMENKRANZ: Yeah.

7 DR. GOLDBAUM: -- communication or --
8 communication slides.

9 DR. BLUMENKRANZ: And while you're doing that,
10 would each of the kindly brought along some visual
11 materials and so please feel free to bring those
12 up when I -- when we ask you to be able to answer
13 the questions. And we'll -- if we have to work
14 through them a little, hopefully, that'll be worth
15 it.

16 DR. GOLDBAUM: I think we're starting at 46?

17 MALE SPEAKER: Yeah. Mike's at -- Mike starts
18 at --

19 MALE SPEAKER: (Inaudible) --

20 DR. BLUMENKRANZ: Why don't you hoof it while
21 he's looking for it here.

22 DR. GOLDBAUM: Well, anyway, I can start by

1 saying --

2 (Off record comments/adjusting slides.)

3 DR. GOLDBAUM: It's labeled. It says "FDA
4 workshop" and it says "interface" on the --
5 "interface between eyecare."

6 And anyway, so the goal of interface is to
7 overcome incommunicable silos in medical records
8 and I think what you're talking about is, really,
9 peer-to-peer communication, not necessarily
10 eyecare to non-eyecare and it's a generalized
11 problem. And there are methods of communication
12 or hard copy with letters and -- or a patient can
13 carry information in either paper or a thumb
14 drive, and that helps to overcome the HIPAA
15 because you don't have to get permission, the
16 patient's already got the data with them in
17 hospital consult and -- and one of the things
18 that's good about a hard copy is that you can --
19 if it's in another language, you can use something
20 like "Google Translate" to translate for you.

21 Phone calls requires that somebody be there to
22 take the phone call but its benefit is that it's

1 interactive and you have proof of receipt that you
2 know that the person getting that information --
3 who needs to get the information has gotten it.
4 And you can send messages by phone which is
5 invariant to time, place, or geography and that --
6 but it can be interactive if you get somebody
7 who's responsive at the time.

8 DR. ABRAMOFF: So it's encrypted or secure?

9 DR. GOLDBAUM: Yes. Well, I think if you're
10 using cell phones, it's -- well, I don't know how
11 the digital -- I think that's person-to-person and
12 not -- and reasonably secure. But if you send a
13 message, there's no proof of receipt. Email also
14 invariant to time, place, and geography. You need
15 to use a secure system for that. Electronic
16 medical records, you have professional-to-
17 professional notes within the electronic medical
18 record system with -- or you can autopopulate a
19 report which take -- which is not as time
20 consuming. I mean you make your report and it
21 automatically populates the report for you so you
22 don't have to spend the time doing it. And with

1 the EMR, you have a holistic view of the patient.
2 And the social networks, not very good for
3 communication about a patient but a good way to
4 communicate to distribute knowledge.

5 So in summary, we have hard copy, cell phone,
6 email, EMR, and social networks as ways that peers
7 can communicate.

8 DR. BLUMENKRANZ: Thank you. I'm going to
9 move it over to Michael Abramoff now and just --
10 he's starting at slide 25. Okay, thanks.

11 DR. ABRAMOFF: Since I made the slide, I want
12 to show at least one. And the rest we'll just
13 forget about it. But as I mentioned, we finished
14 this -- sorry -- I will show only one, this one
15 because it sort of sets the context. And so
16 remember, we just finished the clinical trial for
17 automated detection of diabetic retinopathy, not
18 FDA cleared; we don't know where it will go but
19 I'm just saying.

20 And so one of the sights for the trial was in
21 New Mexico, close to the Mexican border where
22 there's no ophthalmologists and, in only four

1 hours, we install a DRAI system there. And then
2 the question is, you know, the family physicians
3 don't have experience with EDT arrests or ICDR,
4 and so, you know, the question is should it be
5 actionable for this primary care physician because
6 they don't have any experience or context of
7 knowledge of what to do with a patient with a
8 certain level of diabetic retinopathy. So I think
9 it should be you know very much dependent on the
10 context, but at least in primary care, it needs to
11 be, you know, very actionable rather than some
12 abstract disease level that they need to look up.

13 DR. GOLDBAUM: Presumably, if you use a
14 dichotomous system, either refer or not refer, or
15 refer with urgency, then you can cover that. I
16 mean that -- I guess the question is how do you
17 set up the workflow? What have you done? What
18 have you seen done that works to sort of simplify
19 that so that they don't have to make a judgment
20 about whether level 35 or 43 retinopathy is or
21 isn't?

22 DR. ABRAMOFF: Well, other slides will show it

1 but we won't show it because it takes too long,
2 but, you know, the preferred practice patter from
3 the American Academy of Ophthalmology has very
4 clear levels of which is actionable by, you know,
5 maybe see earlier, which needs treatment, which
6 needs close management, like you know follow-up
7 much sooner. And so you try to stick with those
8 preferred practice patterns if they exist. If
9 they don't exist, you know, it's much harder to
10 automate any of this

11 DR. GOLDBAUM: But in other words -- but in
12 terms of producing that report so that a busy
13 primary care physician or any other physician
14 knows what to do, I mean isn't -- shouldn't we be
15 making that part of the workflow and --

16 DR. ABRAMOFF: So that's my answer. So, yeah,
17 you have, you know, for example, the output is
18 more than mild diabetic retinopathy and/or macular
19 edema, refer patient and --

20 DR. GOLDBAUM: Right.

21 DR. ABRAMOFF: -- that's the output.

22 DR. GOLDBAUM: Right, perfect.

1 DR. ABRAMOFF: But again, not clear.

2 DR. NISCHAL: So there will be time for
3 questions once we finish the environment section.
4 We got one more environment section to go to, but
5 it seems to me what you're saying is that
6 protocolization is actually the first step, that
7 the more protocolized we are in medicine, the
8 easier it's going to be for AI devices to follow
9 those algorithms that our professional bodies have
10 created.

11 DR. ABRAMOFF: Absolutely. It's so much more
12 difficult for glaucoma screening let alone AMD
13 screening where we -- you know, there are so many
14 rules for when you should screen and not, it needs
15 to be a treatment, it needs to be efficacy, it
16 needs to be equitable; there's so many, you know,
17 rules for when you should screen and when not.
18 But it definitely helps for someone making an
19 automated system or an algorithm or a black box or
20 whatever it is, an AI system that there is
21 something that you can guide yourself by. And
22 gold standards, we have been discussing this at

1 length this morning, are really important. The
2 more (inaudible) on a gold standard, the easier it
3 is because then you know what to choose. And
4 similarly for what the output should be like and
5 how it should fit in our healthcare system, it's
6 so much easier.

7 DR. BLUMENKRANZ: So, Michael Goldbaum and
8 then we go to Michael Chiang.

9 DR. GOLDBAUM: So we're talking about gold
10 standards and we're talking about a lot. Is gold
11 standards where the physician or the expert is the
12 gold standard and you're trying to make the
13 classifier approach what the physician is doing,
14 but it can never be better than what the physician
15 is doing if you use that. So another gold
16 standard -- so that's expert-driven.

17 Another way of having it would be outcomes-
18 driven, so you can follow patients and see if they
19 had a certain outcome over time that says that
20 that patient needed to be referred and you use
21 that. That doesn't require physician or expert
22 input. What you're doing is you're looking at the

1 outcome and then you're teaching based on the
2 outcome.

3 And so the machine learning classifier may
4 become better than the expert at determining which
5 ones need to be referred.

6 DR. BLUMENKRANZ: Michael Chiang.

7 DR. CHIANG: Ken, I wanted to comment on the
8 idea of protocols that you and Michael Abramoff
9 talked about, because I think that they're really
10 important and I'm a big -- part of my career is
11 based on developing and implementing, you know,
12 protocols.

13 But I wanted to talk about the limitations of
14 protocols, because I just want to get that on the
15 record here. In ROP, we had done some studies --
16 and I want to use an example -- where they're
17 very, very clear protocols based on tens of
18 millions of dollars of NIH money about who gets
19 treated and who doesn't. You know, we studied who
20 gets treated and who doesn't and about 10 percent
21 of the time, the kids who got treated were treated
22 outside the protocols, and it was not because the

1 treating doctors were not aware of the protocols.
2 Something made them nervous that didn't fall
3 within the protocols.

4 And that's where I would consider the art of
5 medicine. So you've got the science which is the
6 protocols, and the art which is sort of clinical
7 judgment and what makes someone nervous. And so I
8 wanted to say that, you know, just because we've
9 got a protocol and we've got a machine that can do
10 that doesn't necessarily mean that there's no role
11 for the doctor. And I hope that that's something
12 that we can consider as a community, that there
13 still is a doctor to interpret what we're seeing
14 and make their own individual sort of a clinical
15 judgment, and the systems are tools to help the
16 doctors do that.

17 DR. NISCHAL: Michael, I totally agree with
18 you but I think what's really important is that if
19 you have protocols, when you look at the protocol
20 deviations, you then look at the outcomes that
21 Michael was talking -- Michael One -- One, Two and
22 Three, okay -- Michael One was talking about. And

1 and I think those protocol deviations actually may
2 give us more information than the actual people,
3 the ones where you followed the protocol.

4 And -- but the reason why I'm raising this is
5 I'm glad that you're you're invested in protocols,
6 because having come from Europe six years ago, it
7 was a real mountain to climb to convince my
8 attending colleagues to put together protocols,
9 because they felt it was taking away their
10 autonomy, and I don't think it does. I think it
11 actually protects you. It still allows you
12 deviations but you can now quantify and qualify
13 those deviations to look at outcomes.

14 DR. CHIANG: Ken, I completely agree. And
15 just a couple follow-ups to that. One of them is
16 that this particular study that we did was looking
17 at real, you know, investigators who were really
18 intimately familiar with those protocols. And so
19 I think that's different from the population of
20 real world ophthalmologists who the protocols are
21 intended to target, you know, to standardize to
22 standardized care.

1 You know, the second thing is that earlier
2 this morning, Krishna made a great comment about
3 the learning healthcare system. and I hope that
4 this is something that -- and, you know, I think
5 that that's relevant, Ken, to your comment -- that
6 hopefully, you know, we're going to have a
7 situation where the, I'll call them errors or
8 protocol deviations or something, can maybe feed
9 back into the protocols to say well, what was
10 different about this that made the expert nervous
11 and how can we develop a better protocol based on
12 that constant feedback.

13 And where this ties into the regulatory thing
14 is that I hope that in developing the rules for
15 this that we don't have a system where it takes
16 like a year to refine the algorithm if somebody
17 comes up with something new, because some of these
18 data may be generated in real time. And, you
19 know, hopefully we can come up with a rule that
20 lets these systems get better as they learn more
21 from the data, because I think, in a way, that was
22 the whole point of the National academy of

1 Medicine Report, the learning healthcare system.

2 DR. GOLDBAUM: Well, this is the point where
3 regulation steps in because now you've come up
4 with something that looks like it makes the system
5 better and you have to retest it for so many
6 millions of dollars or can you just make an
7 adjustment. And so that's a question for the FDA
8 to answer

9 DR. ABRAMOFF: I think Ingrid Zimmer-Galler --
10 I don't see her right now but she (inaudible) this
11 morning, right, that even after approval, you need
12 some form of continuous monitoring or, you know,
13 whatever, post-market surveillance, to make sure
14 your system, a, is indeed doing what it should do,
15 and if there is are exceptions like Michael said,
16 find them and try to improve your algorithm. I've
17 done the regulatory. You would then go back to
18 the FDA say, hey, you know, we approved it because
19 you need to prove that but yeah, definitely that
20 will be very important for these systems.

21 DR. BLUMENKRANZ: Could you go back to slide
22 14 for me, please? I'm going to go back to

1 Michael Chiang for this next question which is
2 we're going to talk about the non-clinical
3 environment. We spoke about the ophthalmology
4 office. We've spoken about other primary care and
5 urgent care settings. Now we're going to talk
6 about testing in the home and what unique sorts of
7 concerns and considerations we might have in that
8 environment.

9 So I'm going to start with you and ask is
10 symptom diagnosis and triage analysis safely left
11 to the potential patient, or does it rest with
12 someone else? In other words, where is the
13 responsibility, both ethically and also legally?

14 DR. CHIANG: Yeah. Mark, it's -- I -- you
15 know, one of the things I do is I teach user
16 interfaces to grad students in Oregon. One of the
17 things that we sort of use is, you know, could
18 your grandmother use this system. And, you know,
19 I think that, for example, in glaucoma, since that
20 was the example, we've got evidence that patients
21 cannot put eye drops in their own eyes let alone
22 use the system. So I don't know how they're going

1 to perform when they're asked to do -- you know,
2 Bakul, the point that you made -- doing home
3 visual field testing. And I think this is a huge
4 problem. You know, it's what the engineers will
5 call, you know, quote, "garbage in, garbage out."

6 And, you know, I think, Bakul, your point was
7 some method for assigning quality of data. And,
8 you know, we do this for visual fields where there
9 are metrics to assign the quality of that field.
10 And I hope that we can come up with something to
11 assess the quality of data that are obtained
12 outside the clinical environment, because I think
13 that ties into the issue of, you know, as the
14 doctor or, you know, somebody is going to have to
15 review all these data and then figure out is this
16 going to be my trigger point for taking some
17 action.

18 And the whole purpose of these systems is to
19 save us -- you know, to lead to better outcomes,
20 to save money for the healthcare system. And I
21 can think of some scenarios where, you know, where
22 these systems could have an unintended consequence

1 of bringing more patients to the office because of
2 bad tests and there's going to be a way of
3 distinguishing. We've got to have some way of
4 distinguishing, I think, good versus bad. And I
5 think it's completely solvable, you know, just as
6 long as we think about that and, you know, figure
7 out in advance.

8 DR. GOLDBAUM: On the other hand, I think one
9 of the things that the Kaggle competition showed
10 is how these systems work with bad data, because a
11 lot of the images in the Kaggle competition were
12 atrocious and some of them were very good. And
13 your system had to learn on the whole complex, the
14 whole cloud of data, and they managed to learn
15 pretty well. So I think these systems can look
16 past some of the bad data and still learn how to
17 classify as we need it. So, yes, good data are
18 important but at times, the real world doesn't
19 have a lot of good data and so it's nice to have a
20 system that can survive in that environment, too.

21 MR. PATEL: Just one comment. I was --

22 DR. BLUMENKRANZ: Identify, Bakul, just for

1 the transcriptionist.

2 MR. PATEL: Bakul -- going with Michael Three
3 with your (inaudible) train here. I can also see
4 we're all, I think which is a unique opportunity
5 for us in the digital health is to tailor
6 solutions for other population types, right. So,
7 you know, in the hardware world, there's one thing
8 about, you know, you need to make a product that
9 sort of spans across the populations you're
10 intending to use. But in the digital health
11 world, I think with software especially and when
12 you're looking at screens, easily malleable to
13 make it to the population
14 data -- population set that we really intend to so
15 it can evolve, it can be personalized.

16 So when you think about personalization, and I
17 think we need to think about those population
18 types that can provide the same experience that we
19 talked about earlier, right, because without that,
20 you know, the efficacy or effectiveness of the
21 products will be diminished or sort you'll be
22 leaving stuff on the table that we shouldn't so.

1 MR. BRITTON: I'm going to move to
2 the second part of this question which is, are
3 there digital pharma innovations that could be
4 applied in these circumstances such as tailoring
5 of return visits or modifying treatments based on
6 this information that's gained in the home? And
7 I'm going to direct that to Quinton because you
8 have some personal experience with this.

9 MR. OSWALD: Thank you, Mark. Can we go to
10 slide 19, please? So Notal Vision introduced a
11 device that monitors the switch from dry to wet
12 AMD and was faced with a number of issues by
13 virtue of the fact that dry AMD can be anything
14 and the switch to wet can be anything from a 3 to
15 10-year journey which required frequent patient
16 monitoring. And we realized that it was important
17 to create an ecosystem that interfaced the patient
18 with a doctor. And this is a real challenge going
19 forward and we certainly have learned a lot from
20 this process.

21 So on the left, you see -- on the top left is
22 the ForeseeHome device which is a little difficult

1 to see, and I'll talk about the next device as I
2 go through my presentation. But basically, what
3 happens is a patient tests on a daily basis or
4 every second day, and we're finding very good
5 compliance because patients are really scared
6 about losing their eyesight so we don't have
7 compliance as an issue, although we have a
8 compliance loop built into the process. This data
9 is then fed to a cloud-based platform which sits
10 in our independent diagnostic testing facility in
11 Manassas, Virginia, tied to the cloud. And
12 basically, it's reviewed by ophthalmologists and
13 ophthalmic techs.

14 If the patient is not compliant, there's a
15 feedback loop, as I indicated.

16 And on a monthly basis, we supply reports to
17 the physician which we're learning need to be a
18 lot more decision-based. Yeah, we used to supply
19 a lot of data and we need to turn this a lot more
20 into information, and we went through the process
21 that we've started to do that more efficiently.

22 Should the patient or when the patient

1 switches from dry to wet AMD, an alert then is
2 sent by our ophthalmologist, both digitally as
3 well as a telephone call, to the treating
4 physician to say the patient has switched from dry
5 to wet AMD. That's really important because we
6 find that in the study we did to support the
7 reimbursement of this product, we were getting
8 patients on average of 20/40 or better. And as
9 Michael will tell you out of the iris registry,
10 650,000 patients that switched from dry to wet
11 AMD, the mean presentation of patients at first
12 treatment was 20/80 or worse. Think about it. So
13 you've got a functionally blind person arriving
14 for treatment on an expensive AMD drug so
15 obviously, treating earlier is going to be far
16 better. So that's the mission that we have
17 embarked upon.

18 The second is we're developing a home-based
19 OCT because we think this is critical for the next
20 phase of the treatment of wet AMD, because if a
21 patient comes in even on a monthly basis, you have
22 no idea what happened to the patient between day 1

1 and day 30. As we know, that treatment interval
2 is extending to two and three months and we really
3 don't know what is happening to the patient.

4 So basically, on top of the platform we've
5 built with ForeseeHome, which is we've just
6 completed our 3 millionth test, so it's a pretty
7 validated platform, we're introducing -- we're in
8 early clinical trial on a home-based OCT. Now the
9 three components about a home-based OCT; first of
10 all, what's it going to cost; how reliable is the
11 machine; and how do we present the data?

12 So basically, we're busy developing it but
13 probably the most important element goes to the
14 next slide. Now we basically developed an
15 algorithm that basically automates the outputs
16 from an OCT, and we conducted a study with 142
17 eyes, and the top left-hand side is we identified
18 fluid and lesion activity of the 128 scans -- RP
19 scans from the machine. The algorithm then
20 categorized, as you get into point two, and
21 unfortunately, the slide is compacted a little bit
22 but basically, it prioritizes (ph) from 1 to 10 the

1 likelihood of fluid being present. So really, it
2 becomes a decision support platform for the
3 ophthalmologist or the retinal specialist. So we
4 have this device that categorizes where the
5 patient is.

6 We then validate that test against two groups,
7 compared (Inaudible) to a reading center and we
8 compared (Inaudible) to three individual retinal
9 specialists. And you can see on specificity,
10 accuracy, we pretty much were comparable to that
11 reading center and the three independent retinal
12 specialists. Why is that important? Now
13 obviously, Krishna talked this morning about
14 machine learning and basically, we've run this
15 device
16 through -- this algorithm through about 100,000
17 scans. We're looking to push that a million so
18 that we continue to learn and improve the accuracy
19 of the algorithm.

20 So in summary, coming back to the question
21 that Mark asked me, I think it's important to
22 create an ecosystem with not only just the device.

1 It's how you interface with the patient, how you
2 monitor and you also enthuse the patient or
3 encourage the patient to comply and then having a
4 backend process that provides decision outputs for
5 the physicians that are valuable and are
6 actionable, and it's the three-way system we think
7 is critical to the future of this particular
8 product of telemedicine in the ophthalmic space.

9 DR. BLUMENKRANZ: Thank you, Quinton. Pravin
10 Dugel was supposed to be here and unfortunately,
11 due to a family illness, he wasn't but he sent me
12 a few slides. I'll just -- if you could turn to
13 slide 22? I think the idea of processing all this
14 information and having it be actionable is an
15 interesting one. And it turns out that aside from
16 using AI and DL and so forth, it's possible to use
17 different ways of looking at data. For instance,
18 in the office, we're used to looking at individual
19 hand-written reports or typed reports or tabular
20 data.

21 This is just actually a page from Epic here.
22 And you can -- it's hard to read but that's --

1 they typically are hard to read even if you're not
2 in the back of the room here. But you can see
3 that data there. This is the same patient. This
4 is tabular data. Can anyone pick out a pattern
5 there? Is anyone quick enough to figure out
6 what's going on? Maybe two, three, four minutes
7 you'd be able to. How about that pattern there?
8 Those are individual data points taken of a
9 patient at home. Anybody starting to see anything
10 going on?

11 What if you connect the dots, does it get more
12 interesting? And what if you used a smoothing
13 algorithm to interpolate between the points?
14 Well, that's all home data. That's a real patient
15 and Drug A is a drug that was given for treatment
16 of exudative AMD, patient seemed to be doing
17 poorly, switched to Drug B. I'm purposely hiding
18 the names of the manufacturers so as to not be
19 unfairly accused of favoring one over the other.
20 And this -- that's the data, the patient was
21 switched to Drug B and you can see immediately
22 upon doing so, the visual acuity went up.

1 And this is the office data. This is the two
2 points, they connect the dots and the smoothing
3 and then finally, in the "light blue," you can see
4 the actual office data. So it points out that
5 there are lots of different ways, first of all, to
6 acquire data, and there are also lots of different
7 ways to look at data. And we may be still living
8 in an era where we're used to looking at numbers,
9 but I think if you think about the whole field of
10 infographics and how to analyze large datasets,
11 our minds are really based on pattern recognition
12 and, I guess, Gestalt or however -- whatever the
13 nontechnical terms are. And I think there is an
14 opportunity for all of us to be able to use
15 different ways of looking at the same data and
16 acquiring more data but more of the same. Even
17 simple numbers like vision and being able to
18 acquire information. I'll stop at that point.

19 MR. OSWALD: Question, Mark.

20 DR. BLUMENKRANZ: Yeah.

21 MR. OSWALD What is the interval between the
22 tests?

1 DR. BLUMENKRANZ: The interval, those are
2 taken, on average, between three and five times a
3 week.

4 MR. OSWALD: Okay.

5 DR. BLUMENKRANZ: And it's just a -- it's a
6 visual acuity taken on a Smartphone.

7 MR. OSWALD: Okay.

8 DR. BLUMENKRANZ: Yeah.

9 DR. NISCHAL: Okay. So we're going to stop
10 just for a few minutes for questions from the
11 floor. Are there any questions for any of the
12 panel? If you can just say who you are for the --

13 FEMALE SPEAKER: (Inaudible) from Columbia
14 University. I have a quick question. We're
15 generating all this data, offices are generating
16 the data, hospitals are generating the the data,
17 these data are required by imaging companies and
18 AI companies to build these algorithms. Who owns
19 the data? This is one. Second, in an era in the
20 future, retinal images, iris images are going to
21 become protected health information. What is
22 going to happen then so?

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1 DR. BLUMENKRANZ: Who wants to take that?

2 DR. NISCHAL: Not me.

3 DR. BLUMENKRANZ: Michael, do you want to --

4 DR. ABRAMOFF: I have strong opinions.

5 MALE SPEAKER: Yes, go ahead.

6 DR. BLUMENKRANZ: Why don't we have the two
7 end Michaels talk about that. Between you, you
8 have (inaudible) --

9 DR. ABRAMOFF: -- but I took (inaudible) --

10 DR. BLUMENKRANZ: -- perspectives.

11 DR. ABRAMOFF: -- okay, well, we'll see. So I
12 think the patient owns the data or should own the
13 data. I mean I would want to own my data. I do
14 not want it to be sold by some hospital where I
15 don't even see what they got for it. So -- but
16 then I am a proponent of using data that is
17 acquired for training algorithms, right, if we're
18 testing algorithms, that is acquired fairly, you
19 know, in a controlled fashion like for clinical
20 trials and not just, you know, buy it from some
21 hospital where patients don't even know that their
22 data's being bought. So I would say I have a very

1 strong opinion and competitors will think very
2 differently, so I will leave it at that. So now
3 you talk for the competitor.

4 DR. CHIANG: No, no. I -- it's (inaudible)
5 that I am -- you know, we can talk about opinions
6 and we can talk about sort of -- you know, sort of
7 legalities of it and I think that, you know --
8 Lemma, I think my answer to that is that it's
9 contextual. And, you know, if we see a patient
10 sort of, you know, we own the data, from the
11 hospital perspective, you know, the patient owns
12 the data because it's their data, you know.

13 And if it's home-generated data, I'm not sure
14 we have a clear precedent for, you know, for what
15 happens with that. You know, presumably, that
16 home data may be uploaded to the electronic health
17 record in which case it may fall under, you know,
18 the auspices of both of those. I know that's
19 something that we've got to, you know, we've got
20 to work out.

21 And, you know, as an aside to that, you know,
22 I think as a medical community, I've personally

1 seen a few situations where there's a little bit
2 of ambiguity in that where patients get access to
3 their own medical record and will say things like,
4 you know, what are you talking about, I'm not a
5 drug addict or I'm not an alcoholic; you know, can
6 you change that from my medical record. And so I
7 think there are things with oversight and
8 patients, you know, sharing to this that I think
9 are questioning some of the assumptions that we've
10 had all along in terms of medicine. So I think
11 it's an important question.

12 DR. NISCHAL: Can I just say I think that
13 owning data and exposure to data are two different
14 things, and I'll give you an example of what
15 happened. And so the adolescent diabetics at our
16 children's hospital were given monitors to monitor
17 their blood pressure, and some of them were put on
18 a beta blocker and some weren't. And the ones
19 were put on a beta blocker, their traces at home
20 actually were higher than the patients who were
21 not a beta blocker. And it turned out that these
22 children had access to what their blood pressure

1 was. They could see it and that some of them were
2 getting anxious about the blood pressure, and as
3 they became anxious, the blood pressure went up.
4 So it's really important that while the patient
5 owns the data, it's not necessarily best for the
6 patient's health to be exposed to that data, which
7 comes back to the question of who analyzes that
8 data.

9 DR. BLUMENKRANZ: So the Heisenberg
10 uncertainty principle?

11 MALE SPEAKER: Right.

12 DR. BLUMENKRANZ: Okay, please.

13 DR. ORR: Hi. Susan Orr with Notal Vision and
14 I have a comment about the amount of data as well.
15 Going back to the physician, there was a slide at
16 the beginning saying, I think, 100-plus apps have
17 been approved by the FDA, which is an
18 unprecedented amount of data that's inundating the
19 physician who's trying to treat that patient. And
20 in our experience, which Quinton has spoken to,
21 the doctors are very limited in how much time they
22 can spend looking at this data.

1 So I'm interested in a comment on the level of
2 robustness and validation of the benefit of these
3 apps in order to drive adoption across the
4 physicians. Now just the example with home OCTs,
5 since we've spent a lot of time interrogating it,
6 doctors are not going to look at every scan on
7 every OCT for every patient. So in order to
8 extend the visits or have better outcomes, at some
9 point, there has to be a reliance on that. And
10 many of the apps don't have that level one
11 evidence to support modifying the practice of
12 medicine for a given indication.

13 DR. BLUMENKRANZ: Anybody? I can comment. I
14 think you're absolutely correct. I think
15 everything that's used in clinical practice needs
16 to be very rigorously validated and I think
17 efforts are now under way. And I think that's
18 really part of this -- the whole idea behind this
19 workshop is to both expose people to the potential
20 benefits of this and also the pitfalls and the
21 need for rigor and validation of anything that's
22 going to be used. So I I certainly completely

1 agree.

2 I think in speaking to the issue of data
3 overload, that was kind of what I was alluding to
4 before. I think that's really where automation-
5 augmented intelligence and deep learning can
6 really play a role. I think if it was left -- if
7 we generate -- you know, if you look at the number
8 of terabytes of data that are being produced every
9 second in the world today and who's going to look
10 at that, who's going to do something based on
11 that, it's -- it would be impossible without using
12 some sort of, you know, very augmented kind of
13 computing power. I think -- and I think that's
14 where it all fits together. That's worthy -- in
15 my view at least, that's where the AI solves the
16 problem of the data load and also the learning and
17 making actual -- making real use of that data, not
18 having it be just a botherance and then finally
19 validation of that.

20 I'll just make one point because I've been --
21 everybody's been -- I think it was Paul Lee
22 initially that talked about the issue of what's

1 the gold standard. Fifteen years ago we published
2 in the American Journal of Ophthalmology a study
3 in which we were looking at whether or not a
4 single mydriatic non -- a nonmydriatic
5 monochromatic fundus image was as good as seven
6 standard fields.

7 And we also got physicians at the Kaiser
8 health system -- or it doesn't matter which one --
9 who were were -- who practiced in the art of
10 ophthalmoscopy and diabetic retinopathy detection
11 to grade those same patients at a separate
12 sitting. And the first interesting part was that
13 the digital nonmydriatic monochromatic images
14 on -- in general were about 87 percent as
15 sensitive as 7 standard fields. And we happened
16 to be using that as the gold standard.

17 We then checked the ophthalmoscopy results
18 and it was a 34 percent concurrence of the data.
19 And so the interesting problem was that we had
20 shown that digital was pretty good but that
21 ophthalmoscopy, which was the gold standard in
22 previous years, was no longer as good as either

1 the new innovation or even the one that was
2 existing.

3 And so it raises real questions as to what
4 is -- you know, what are gold standards. I was
5 interviewed by Ken Mills, who was the President of
6 the American Academy in commentary on that, and he
7 was not only bright but but wise and he said the
8 problem with all of this is that when you
9 introduce these new technologies in that case,
10 those images were read not by physicians -- and we
11 didn't have AI at that time -- they were read by
12 graders at the Wisconsin Reading Center, so we
13 know they were very good. And in fact, the
14 nonphysicians graded retinopathy better than
15 ophthalmologists.

16 Now it's were they better at really seeing it?
17 No. I mean they had as many hours -- minutes or
18 hours as they wanted to stare at a high resolution
19 image on a screen whereas an ophthalmologist is
20 seeing perhaps 30 patients in a half-day, the
21 pupils not optimally dilated, no one's giving them
22 the very best photo.

1 So in the real world, you know, situations are
2 quite different than they are in clinical studies,
3 and I think it's an important point that you
4 raise, is how do you how do you get to the best
5 data; what is the best data? I don't know that
6 home data might not be better, worse or the same
7 than clinical data obtained in the office, but
8 that's what we have to do and that's the critical
9 role that the FDA plays working hand-in-hand and
10 collaborating with the people that are trying to
11 develop this technology so everybody buys into
12 whatever those results are. That's what they are
13 and we know whether something's better, worse or
14 the same than what we're currently doing. At
15 least that's just a personal opinion

16 DR. NISCHAL: I'm going to have to move us
17 along I'm afraid because we still have some really
18 important questions to answer.

19 So, hopefully -- I'm sorry, Michael, we'll
20 come back to you.

21 So we're going to move on to artificial
22 intelligence which we've been discussing, and one

1 of the first questions that we wanted to tackle
2 was, how will I affect the use of our family
3 digital tools in the future, which we've covered
4 to an extent. And, Michael One, I wonder if you
5 could -- slide 15, please.

6 DR. GOLDBAUM: If we can get back. Is --
7 which is One.

8 DR. NISCHAL: That's you.

9 DR. GOLDBAUM: Okay.

10 MALE SPEAKER: We figured it out.

11 DR. GOLDBAUM: I wanted -- I just wanted to
12 make sure that -- so somewhere past 46, there's a
13 slide that says "AI in medicine." But -- so the
14 thing -- there are a number -- this has been
15 studied. AI can break down into a number of
16 different groups and it's something like 12
17 different subtopics. But the three that most
18 interest us would be natural language, management
19 of uncertainty, machine learning data mine and
20 data mining, and image processing.

21 And the natural language, I guess, best would
22 be for translation though it's also been used to

1 to -- for other questions in medicine.

2 Management of uncertainty; in the past, we
3 were doing things like expert systems, and that
4 was labor intensive, and so it never got adopted.

5 With the deep learning, it learns from the
6 data. You don't have to guide it and it does
7 everything, and that really helps for us to be
8 able to build these systems. And so we're using
9 it for image processing and I think we'll continue
10 to use it for image processing. We'll use it for
11 image classification or interpretation and also
12 for the component parts like image segmentation to
13 find the various structures of importance in an
14 image. And I think that will be -- it will be
15 basically physician assistance in the beginning.
16 Maybe eventually, we'll be able to learn from
17 these systems but I think initially, it will be
18 physician assistance in managing large amounts of
19 data and learning, helping us to learn from the
20 data.

21 DR. ABRAMOFF: Me? I need to see the slides
22 (inaudible).

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1 DR. NISCHAL: So thank you, Michael. We'll go
2 on to the next part. Are there specific AI
3 examples that help us negotiate these issues?
4 Now, for example, interpretation of fundus photos
5 for retinal disease screening and Michael Abramoff
6 is going to tackle that question for us. While
7 we're waiting for Michael --

8 DR. ABRAMOFF: I will just stand here and
9 control my slides.

10 DR. NISCHAL: Okay. All right.

11 DR. ABRAMOFF: So two things --

12 MALE SPEAKER: Take the microphone --

13 DR. ABRAMOFF: This is good, this is good.
14 So, Michael Abramoff. Shameless plug. I am
15 briefing Congress, both the Senate and the House,
16 on AI in medicine on Wednesday and I will be
17 speaking about this meeting and that we had it and
18 that FDA was involved, just so you know that we'll
19 be speaking with Congress about this.

20 So now to AI. So, you know, Mike G., you're
21 Mike One now, you know, did an excellent
22 introduction. And so I just wanted to talk about

1 algorithms for image analysis and specifically for
2 retinal images where on the top you see sort of,
3 you know, the way we do it where it's lesion-based
4 so you have an image. You look at the image
5 quality which is a big issue. We got many of the
6 images coming from especially not so well-trained
7 photographers will be insufficient and you need to
8 know that so in real time you can tell them, hey,
9 take it again. So that's an important aspect.

10 And then what we do, our algorithms do, is
11 have specific deep learning modules that detect
12 micro aneurysms and exudates or an abnormal disk,
13 etcetera. And then that combines with anatomy,
14 where the disc is, where the fovea is, etcetera,
15 and that determines the outputs of the system.

16 And then Mike One and me, so Michael G. --
17 sorry, I get us confused all the time -- so we
18 probably disagree about goal or role of black
19 boxes, which is the bottom line, where essentially
20 you have an image and you actually share it with
21 an output and you don't really know what's going
22 on. So instead of having an explicit exudate and

1 explicit micro aneurysm, you say, well, I want you
2 to associate this type of image with diabetic
3 retinopathy or with glaucoma and this without.

4 So, you know, next slide. One thing I worry
5 about is this, which is -- we showed this at
6 (Inaudible) and hopefully, that publication will
7 be accepted once. So --

8 (Whereupon, off comments/adjusting lighting.)

9 DR. ABRAMOFF: Oh, yeah, it's hard. You won't
10 see it. So on the left is an image with diabetic
11 retinopathy. Just believe from me that it's very
12 obvious full of exudates, and Mark can probably
13 confirm that it's DR, right, on the left. Yeah,
14 there you go. And so there's exudates and
15 hemorrhages and --

16 DR. BLUMENKRANZ: Probably.

17 DR. ABRAMOFF: Pardon me?

18 DR. BLUMENKRANZ: Probably. No, I'm just
19 kidding.

20 DR. ABRAMOFF: Not probably.

21 (Laughter.)

22 DR. ABRAMOFF: Okay. It's the most obvious.

1 And so if you change a few pixels on the right,
2 it's only minimally changed. And, you know. it
3 still looks to me and you and Mark, hopefully,
4 like DR. And then if you have algorithms that 99
5 so these are minimal changes and you have
6 algorithms that are very sensitive to this and you
7 don't know that, like black boxes, and we test
8 this on a number of a black box, you know, CNNs,
9 meaning convolution of neural networks, and they
10 all started to see this image as normal. And
11 so -- and experts would never do that.

12 So there's a sort of risk that it trains on
13 things you don't really know about, and so I worry
14 about black boxes in general. So I just wanted to
15 bring that up because it's an interesting debate,
16 and I'm sure you have something to say against it.

17 DR. GOLDBAUM: No. Actually I don't have
18 anything to say against it, but what you can do is
19 put your adversarial images in there, too, and
20 label them correctly, and then it will learn how
21 to get less than optimal images.

22 DR. ABRAMOFF: Yeah. So then -- but you don't

1 know what the perturbation will be, right? So it
2 can be compression or some noise and so you would
3 have to train for all these different relatives.

4 DR. GOLDBAUM: You made this up but
5 photographers will have various qualities of
6 images. That's the real world. This one is not.
7 So you can use -- you can train on the adversarial
8 images created in the real world and the system
9 will learn how to look beyond those adversarial
10 elements

11 MALE SPEAKER: I think we're learning about
12 adversarial communications here.

13 (Laughter.)

14 DR. NISCHAL: Can I --

15 MALE SPEAKER: -- (Inaudible).

16 DR. NISCHAL: -- can I just ask -- so, you
17 know, with the question of poor image quality, I
18 mean does anybody on the panel, anybody in the
19 audience have experience with fractal analysis,
20 because this seems to be one way of picking up
21 retinal diseases looking at the the actual
22 branching of the vessels? Does anybody have any

1 experience, either on the panel or in the
2 audience, of fractal analysis for analysis of
3 these images?

4 MALE SPEAKER: Yeah, I do but --

5 MALE SPEAKER: Yeah.

6 MALE SPEAKER: -- yeah. You want to say
7 something?

8 DR. CHIANG: We've done it --

9 MALE SPEAKER: Yeah, we've done it.

10 DR. CHIANG: -- and it works but it doesn't --
11 we have -- it doesn't work as well as the other
12 things that we've done.

13 DR. ABRAMOFF: It doesn't add to the
14 performance for DR or glaucoma --

15 DR. NISCHAL: Okay. We're going to keep
16 moving. Could we go to slide 16, please? This is
17 more about AI. This AI-enabled image analysis
18 questions. So this is for you, Linda, because
19 you've been very quiet and polite. And so are we
20 ready for a fully automated interpretation?

21 DR. ZANGWILL: I think in some --

22 DR. BLUMENKRANZ: Slide 16, please, 1-6?

1 DR. ZANGWILL: -- I think there's good
2 evidence in some cases. I think diabetic
3 retinopathy is the closest to that. And as a non-
4 clinician, I tend to defer to clinicians on this,
5 but I really do think that the algorithms are
6 close enough, and the -- it's compelling enough
7 for diabetic retinopathy when the lack of access
8 ophthalmic care, etcetera.

9 And I just want to also say that in terms of
10 fully automated interpretation, I would take AI.
11 We're talking about poor quality training at home.
12 I think another avenue for AI would be to help
13 train the people at home develop algorithms and
14 training schemes to identify poor quality images
15 or identify poor quality visual fields and bring
16 that back to the patient to -- and improve the
17 quality of those questionable data points.

18 DR. BLUMENKRANZ: Okay. Thank you. Michael
19 A., this is for you. Does the AI DR algorithm
20 give the patient or a doctor a diagnosis or a
21 plan? We're going to go sequentially here just so
22 you can see. Or does the patient's MD make the

1 reading? Or does a third party doctor get to do
2 it? So we're giving you the first crack at that.
3 Does the -- does it go right to the patient or the
4 doctor from the AI?

5 DR. ABRAMOFF: I think I've already spoken to
6 them about this one.

7 DR. BLUMENKRANZ: Sort of covered that.

8 DR. ABRAMOFF: Yeah. So I think, you know,
9 alignment with preferred practice patters really
10 helps. I think again, it totally depends on the
11 context. We're talking about normal eyecare
12 professionals, primary care, it really needs to be
13 (inaudible) and patients, you know, probably the
14 same. I don't have experience with home
15 monitoring but -- so, yeah, it should probably
16 more -- be more of a diagnosis and a plan than,
17 you know, probability of developing, you know, PDR
18 two years from now. That is not something they
19 can work with. We've thought about that.

20 DR. BLUMENKRANZ: And Michael C. -- or does
21 the patient's MD make the reading enabled by IA?
22 Is something that the personal physician should

1 use and this is a tool available to them? Or does
2 it go through a neutral vendor, if you will, or
3 alternative source?

4 And then Michael G., we'll go to you next.

5 DR. CHIANG: Yeah. Mark, I think this is an
6 opinion issue as much -- I mean is more so than a
7 fact issue, and I guess I would say that my
8 opinion is that machines are very good at --
9 machines can be very good at making diagnoses or
10 by analyzing data. But I personally believe that
11 doctors make plans; in other words, doctors make
12 diagnoses and doctors make management plans.

13 And I guess what I mean by that is that I
14 personally hope that we, as a society, will use
15 these machines as decision aids the same way that
16 I'll use my ophthalmoscope as a decision aide, or
17 a cardiologist will use a stethoscope as a
18 decision aid or an echocardiogram as a decision
19 aid. In other words, they're all pieces of
20 information that we use to piece together and make
21 that diagnosis. And so I would think of these AI
22 systems, you know, in the same way that it's

1 another piece of information that I use that
2 contributes to my overall clinical judgment and
3 management of the patient.

4 And, you know. I think that one of the
5 reasons, just just for the record, is that I think
6 that as doctors, we do two things; one of them is
7 that we diagnose and the second, we manage. In
8 other words, you've got this diagnosis. What do
9 you do now and how do you weigh the risk-benefit
10 tradeoffs of one alternative versus another
11 alternative.

12 And I think machines are, you know -- can be
13 very good at diagnosing but I don't think they're
14 very good at understanding patient preferences or
15 understanding the context that we're going to
16 apply those things in. And I think that all of
17 that, you know, we have to consider in terms of
18 developing and applying these systems and, you
19 know, basically how to use them for patient care.

20 DR. GOLDBAUM: Okay. So if we can go to the
21 slides 46 beyond --

22 MR. OSWALD: So just one comment --

1 DR. GOLDBAUM: -- who does the interpretation?

2 MR. OSWALD: Sorry, Michael.

3 MALE SPEAKER: Okay, go ahead.

4 MR. OSWALD: Yeah. Just one point

5 It's interesting in the last two months, we've
6 had three different inquiries at Notal Vision
7 about AI. We've had one from China. We read one
8 from the UK and we've had one from a health system
9 in the U.S.

10 DR. GOLDBAUM: Who does the interpretations?

11 MR. OSWALD: And I think the answer --

12 DR. GOLDBAUM: Who?

13 MR. OSWALD: -- to the question depends on
14 what problem you're trying to solve for and I
15 think will change by virtue of what you have
16 available to you and what degree of trained
17 personnel you have to deal with the issue. So
18 rather than taking a U.S.-only context, I think
19 there's a global context to this discussion.

20 DR. NISCHAL: Michael.

21 DR. GOLDBAUM: So there's one called, "who
22 does the interpretation," but I'll read -- it's a

1 single slide after that.

2 So if the machine does the interpretation,
3 it's available 24/7; it's consistent; it doesn't
4 get tired. It's a black box mostly; maybe we'll
5 learn in the future how to get information out of
6 it. And it should assist the physician at this
7 point. And deep learning has allowed us to do a
8 lot more with classifiers than in the past. The
9 patient's regular doctor reads it. If the
10 patient's regular doctor reads it, the data or the
11 interpretation, that doctor has an interface
12 between the -- that -- there's an interface
13 between the physician and the patient and that's
14 where the doctor still fits in.

15 That person is not available 24/7 and that
16 person can be inconsistent, can be sleepy, can be
17 wired, could be all sorts of things affecting him.

18 A third party doctor reads the results; no
19 interface to the patient's radiologist, for
20 example; no interface to the patient, but that
21 person has the domain expertise that the regular
22 doctor may not have; also not available 24/7 and

1 also may be inconsistent. So those are the
2 variables that fit with each of the three types of
3 interpretation.

4 DR. ABRAMOFF: I want to go back to what
5 Michael Chiang just said, which is I think it
6 depends on the level. So, you know, we have been
7 developing guidelines for autonomous devices for
8 diabetic retinopathy with the American
9 Telemedicine Association. So we go back and forth
10 a lot with a group of authors, and one is this
11 level. So that's a -- for the primary care
12 physician, if you have a DR screening automated
13 device, that's an assistive device; right? I mean
14 --

15 MALE SPEAKER: Yeah.

16 DR. ABRAMOFF: -- they just hear, hey this
17 patient is likely to have DR, manage this patient
18 so maybe, you know, regulate better and also maybe
19 refer. But it totally depends on the primary care
20 physicians, so it's assistive. However, me, as a
21 retinal specialist, I'm not having any influence
22 of the results. So, for me now, as a retinal

1 specialist, it's automated, so it's -- you know,
2 it's terminology or semantics almost. So you have
3 to be careful I think.

4 DR. NISCHAL: So we're going to move on to the
5 last slide. Slide 18, please; 1-8. And I'd
6 really like to give the whole panel an opportunity
7 just to give a short answer to these two
8 questions.

9 Firstly, how do -- and their safety of privacy
10 concerns, you know -- h how do we address these
11 concerns regarding the storage of information on
12 personal devices in the era of common cloud backup
13 for other data on personal phones and for
14 technicians and patients? And how does monitoring
15 of patient behavior and location relate to safety
16 and efficacy concerns?

17 So if we'd like -- we're going to start with
18 you, Michael Chiang, and then just work around and
19 see what everybody has to say, and then we'll open
20 the questions up to the floor.

21 DR. CHIANG: Yeah. Ken, I'm thinking about --
22 I think there was a really good discussion this

1 morning about that that Natalie Afshari and Mike
2 Trese did. And the one thing that I thought
3 was -- that I would add to that discussion is
4 that, you know, a couple of months ago, my 15-
5 year-old daughter played in her first soccer game
6 of the season. She came back cursing, you know,
7 because she played 18 out of 80 minutes, and she
8 felt undervalued as a player by the coach. And
9 so, you know, I said, Erica (ph), you've just got
10 to control what you can control, which is your
11 attitude and your effort.

12 And I see an analogy with this, that we're
13 sort of cursing about the hackers from China and
14 India yet what we can control is the single most
15 common security breach that, you know, I think is
16 out there which is passwords that are either
17 shared among people, or posted up on sticky notes,
18 and -- or, you know, people use the same password
19 for every system.

20 And, you know, I actually think that that's
21 something that, you know, that, you know, to some
22 extent that's sort of our low-hanging fruit in

1 terms of these personal devices, sort of, you know
2 people -- I think there are HIPAA rules are
3 actually pretty good, you know, for protecting
4 information. But the problem is that we don't
5 apply them consistently and we're not very good --
6 so I think that if we could pay more attention to
7 that, we'd go a long way toward solving, you know,
8 this problem.

9 DR. NISCHAL: Michael A.

10 DR. ABRAMOFF: Well, I would just say that --
11 okay, the reason AI and deep learning is so
12 popular right now is because of the enormous gains
13 in computer power, and those are most achievable
14 in the cloud or at least remote service because
15 it's just more cost effective that way. And so
16 there's a sort of push to do that because it saves
17 you a lot of hardware and GPU costs that can be
18 enormous. And at the same time, you know, because
19 of doing that, you have traffic that otherwise you
20 wouldn't have, because it would be processed
21 locally. So it's sort adding a risk for a
22 benefit, you know, making this AI technology even

1 possible.

2 So there's a sort of -- you know, you need to
3 find a balance there between security and even
4 being able to do it. But it's -- you know, we're
5 trying to solve it, all of us, but not fully
6 solved.

7 DR. GOLDBAUM: Okay. So just move on to where
8 it says "cloud." There. So I'm going to leave
9 the cloud for now and just talk about security.
10 So I think it's three slides beyond that. So if
11 you just move three slides. Yeah.

12 So first of all, there is the -- in Europe,
13 there's the European Union General Data Protection
14 Regulation which is addressing a lot of these
15 issues of patient data security. And I haven't
16 found something comparable in the U.S. and there
17 may be something comparable. If there isn't, it
18 would be good for us to be looking at the same
19 thing. And you can read about it at the website,
20 eugdpr.org.

21 So there are ways to control -- ways of
22 security. One is access; only authorized users;

1 you can have a password but even better would be a
2 two-factor system where you put in this password
3 and then it has to make a contact with your
4 Smartphone and an app on the Smartphone says,
5 "Yes, it's okay." So that's one of the methods
6 that our institute is using right now.

7 Now transmission, there are various hypertext
8 transfer protocol and various transfer methods
9 that are more secure. And there's VPN which is
10 just you and the direct communication to where
11 wherever you are trying to communicate to.

12 The one thing that has not been addressed, and
13 I don't know the answer to this one yet because --
14 it's the person going rogue. So the person who
15 has access to the data and then decides that
16 they're going to make it available to the entire
17 world because of some feeling that they have. And
18 so if anybody has an answer to that one, I'd like
19 to hear it.

20 DR. NISCHAL: Linda.

21 DR. ZANGWILL: Yeah. I want to touch on, I
22 think, the conversation this morning and my

1 panelists. The human factor is really critical.
2 I just want to remind everyone that Eric Snowden
3 did not hack into the system. He took the data
4 just like the person going rogue on the USB port,
5 and that's something that's really challenging.
6 And it could be -- that was obviously
7 intentional -- it could be inadvertent that
8 somebody wants to do more work at home and take
9 something home, and then their laptop is, you
10 know, lost, etcetera, etcetera. So I think the
11 human factor in all these different systems and
12 taking patients, monitoring -- home monitoring,
13 etcetera is really going to be the challenge and
14 the make or break of these systems really going
15 forward.

16 MR. PATEL: So I'll just touch upon on a
17 couple of points. I think one is, in my mind, is
18 about trust. I think when we -- when FDA put out
19 the guidance on cybersecurity, I think the
20 fundamental principle in the guidance was about,
21 you know, can the data be trusted and the person
22 be trusted. So it's authorization and

1 authentication about the data and the person
2 accessing that data. So if you keep those
3 principles, I think that concept needs to be sort
4 of expanded in training and education as well as
5 in use, and it can be one time and be done. I
6 think it has to be -- or at a periodic basis to be
7 reminded to people. So once we sort of think
8 about those aspects, we get to a different spot
9 and to maybe even address or identify or catch
10 things that may be slipping away from us.

11 So I think thinking about not just cloud but
12 just having data, sort of where the data resides;
13 what it means; who do you trust it with and where
14 do you get that information back, and who is
15 accessing it is something that needs to be sort of
16 -- that as an education level, should be up there
17 and also awareness. So that's how I would think
18 about it.

19 DR. NISCHAL: Thank you. So we're just going
20 to wrap up with Zach and then Quinton.

21 DR. BODNAR: Sure. I think we had a good
22 discussion in the earlier panel about the fact

1 that it's very hard to secure these things from a
2 technological point of view. If there are
3 malicious actors out there, they're going to find
4 a way to get in.

5 But this panel brought up something that I
6 wanted to just continue on, which is that there is
7 a human factors aspect to this as well and a lot
8 of it is just not adherence to protocols. So to
9 go back to like a classic example, the Enigma
10 machine would have been an uncrackable device if
11 the -- if they hadn't -- if they had used it
12 correctly and that -- you know that's true to this
13 day as well.

14 One of the ways that we could potentially
15 mitigate this, but it's a little bit at odds with
16 the principle of using that information to get as
17 much from it as you can is, to compartmentalize it
18 somewhat. So in the current practice of medicine,
19 when you log into an EMR, you have access to every
20 patient and everything about that patient. Should
21 it really be that way? And when we go to a
22 telemedicine-type environment where not everybody

1 who has access to the system is even a physician,
2 then I don't think that that's necessarily the
3 right way to go. I think that you should have
4 access to the information that's pertinent to you
5 and what you need to do to use your job, and we
6 have to do a better part -- a better job of
7 compartmentalizing it that way

8 DR. NISCHAL: Quinton, last but not least.

9 MR. OSWALD: Two quick points. First of all,
10 I think it's important, as a company, for us to
11 maintain an external evaluation of our systems and
12 processes. We do that with HIPAA on an annual
13 basis.

14 The comment that the gentleman from the DoD
15 made -- called me to ask a question to my CEO --
16 we use Amazon Cloud but we're not at the level
17 that he indicated. And, you know, the question is
18 what do we need to do to get there. So I think
19 it's thinking about these elements is going to be
20 important as we go forward.

21 DR. BLUMENKRANZ: Well, that brings us to a
22 close. You -- some of you may have questions and

1 I would encourage you during the break that
2 follows to sort of seek out the panel members.

3 I do want to thank all of you, all the
4 Michaels and Linda and Bakul. And Quinton, you're
5 thinking of changing your name, I know, to Michael
6 and Zach. And so we will see -- we'll see you at,
7 I guess --

8 DR. NISCHAL: 2:45.

9 DR. BLUMENKRANZ: -- 2:45. Thank you very
10 much, everyone.

11 (Applause.)

12 (Whereupon, off the record at 2:27 p.m., and
13 back on the record at 2:48 p.m.)

14 DR. HUMAYUN: (Off mic) a seat, would
15 appreciate it. Thank you. So we'll get started
16 with Panel 3 now and our panelists are listed up
17 here. Lama will be going first followed by John,
18 Nitin, David, and Eitan. If we go the next slide?

19 So the -- panel three was tasked to look at
20 the effective safeguards and methods for
21 mitigating the risks for an update on a digital
22 health device and the assets threats and

1 vulnerability to be considered and identified.

2 Mark Humayun, the the moderator and my co-
3 moderator, Derek Sprunger.

4 If we go to the next slide? So we'll be
5 addressing these items. What are the most
6 effective methods of mitigating risk for
7 ophthalmic digital health devices, safeguards
8 built in the software and in the hardware, and
9 methods to limit the intended users labeling for
10 patient use training modules and tutorials?

11 The way we've organized this panel is we're
12 going to have each panelist present a talk and try
13 to address these questions during their talk, and
14 then we'll open it up to the group.

15 Next question that we're going to answer is
16 what are the assets, threats, and vulnerabilities
17 that should be considered and identified as threat
18 to the privacy of the patient for ophthalmic
19 digital health device developers? Again, this is
20 a topic that has been discussed previously, but I
21 would like to ask the panelists to please focus in
22 particular on how their device or how their

1 technology has addressed some of these issues of
2 transmission of information, storage of
3 information, and monitoring patient behavior and
4 location.

5 So with that, Derek, would you like to make a
6 few comments.

7 DR. SPRUNGER: No. Just we're ready to go.

8 DR. HUMAYUN: Okay. So we're ready and we'll
9 have Lama go first. So if you can go ahead and
10 please make your presentation?

11 If you have any questions after the talk,
12 please feel free to ask it at that time but again,
13 we'll have a lot of discussion time to follow. So
14 we have Lama's slide first?

15 DR. AL-ASWAD: So my name is Lama Al-Aswad.
16 I'm the Director of the Tele-ophthalmology
17 Initiative at Columbia University, and I started
18 this effort because we launched a tele-
19 ophthalmology project for identifying early
20 disease in the community for diabetes, diabetic
21 retinopathy, macular degeneration, glaucoma, and
22 cataract. And this was based on a work that I did

1 for seven years screening for glaucoma in the
2 community, and we screened 8500 people.

3 But naively, when I started this project, I
4 thought that I could set up this whole project
5 within a year, launch it have it running. And I
6 had timelines for every step of it, acquiring the
7 system, acquiring the equipment, acquiring the --
8 you know, hiring people. And then IT security, I
9 gave it for a months. And wrongfully thinking
10 that IT security would take four months, it took a
11 year. The server to be approved took three months
12 at Columbia. The IT security to be approved took
13 eight months and for multiple reasons. We were
14 the first in a lot of them.

15 The electronic signature for consent was the
16 first, so we had to tackle that. Having a mobile
17 unit move around transmitting data to the
18 institution, we had to tackle that. The question
19 is can we mix it with the electronic medical
20 record or not mix it with the electronic medical
21 record; we had to tackle that.

22 But thankfully, it's launched and we've

1 been -- we've had a pilot and we've screened over
2 300 individuals with results but that's not the
3 place for -- to talk about it. But in reality,
4 this mobile unit goes into high-risk communities
5 screening them for, as we said, for ophthalmic
6 disease in addition to diabetes through hemoglobin
7 A1C, blood pressure and BMI. And in this system,
8 we created tunnels to maintain the data inside a
9 closed system so there will be no leaks of the
10 information that's being transmitted. It goes to
11 its own server and it's protected in that server
12 and there will be no leaks anywhere in the system.

13 And our system is as secure as the ambulances
14 in New York or even more secure, some people told
15 us, than that through the way we created the
16 security in it.

17 But I was asked to answer some of the
18 questions. The first one was what are the most
19 effective methods for mitigating risk for
20 ophthalmic digital health device. And from that
21 question, I was asked the methods to tell -- to
22 limit intended and users. So all our users have

1 individual-issued IDs and passwords for the
2 application, for the network, for the server, and
3 they're not the same password FYI. And they're
4 issued by the administrator. In addition, all the
5 users have to change their password every 90 days.
6 So we maintain that, we update that, and we
7 continuously monitor that.

8 Labeling for information our individuals or
9 participants in the study, they usually have to
10 enter their information on an iPad. This is their
11 regular information, protected health information
12 in addition to answering a questionnaire about
13 their health and their habits. So we -- those
14 individuals don't require a password because their
15 privileges are limited. They only have two
16 screens. One is to enter their information, the
17 second is to answer the health questionnaire.
18 They cannot surf this iPad. They cannot look at
19 anything else, and they cannot go back. And we
20 have somebody assisting them during this process,
21 so no alteration after they enter it.

22 But the challenging part which I learned, too,

1 is training and tutorial modules. We developed a
2 comprehensive system that requires PDF instruction
3 guides to references; video recording tutorials;
4 onsite training, scheduled or nonscheduled;
5 screenshots that's everywhere for them to use the
6 system without any identifiers; Retraining when we
7 notice that they require retraining; and every now
8 and then, we keep updating the system so we
9 retrain and retrain, and we do do report cards.

10 And as Ken said from the prior panel,
11 actually, I do audit the data that's being entered
12 into the system. And I learned that after having
13 the first month happen and I went back into the
14 data, and I notice you do need to audit it every
15 now and then. And according to my audit, I decide
16 if that individual who was doing the reading,
17 because this data is being transmitted real time
18 to a reading center; there's a doctor,
19 ophthalmologist, or optometrist there giving the
20 instruction to the individual where to follow up.
21 And based on those audits, we retrain the
22 individual and based on that report card, we

1 retrain the individual more to to better serve and
2 either image or give instruction to the
3 individuals or comments or recommendations for
4 follow up. And we keep updating our system based
5 on what we notice in that system to develop better
6 tutorials for those individuals.

7 The other question I was asked was to assist
8 threats and vulnerabilities that should be
9 considered and identified as a threat to the
10 privacy of a patient by a digital health device
11 developers. So in our system, we transmit to a
12 server and we have our own independent server that
13 is not mixed with the electronic medical record of
14 the institution. And that made everybody happy in
15 the institution for IT security. The data-
16 capturing system that we built actually is offline
17 when it's not in use. The server is always online
18 but the data-capturing system is offline, and that
19 protects any vulnerability or anybody trying to
20 open it or hack it.

21 The other tricky part is monitoring patient
22 behavior and location. As a lot of you know,

1 there are there are few states that have tele-
2 ophthalmology licensure, like Maine has a tele-
3 ophthalmology licensure but not all states. So as
4 a physician practicing, let's say, in New York, I
5 cannot -- if I don't have a license in New Jersey,
6 I actually cannot practice telehealth in New
7 Jersey.

8 So with our mobile unit, we go to areas where
9 the reader has a license. So we have some people
10 are licensed in New Jersey so when the mobile unit
11 goes to New Jersey, the reader is licensed and can
12 practice. But personally, I'm not licensed in New
13 Jersey. I cannot be a reader when that happens
14 why.

15 NYP, or New York Presbyterian Hospital, has
16 telemedicine initiative and they have urgent care
17 visits. They have virtual visits. And in those
18 visits, they actually enter a contract with the
19 patient, legal contract that gives them -- they
20 sign that they are presiding in a state that the
21 doctor that they are working with has license in
22 and the legality behind that. But right now

1 they're developing a geolocation into their app.
2 So basically, if that patient, although resides in
3 New York and the doctor has a license in New York,
4 they go to, let's say, Wisconsin, the geolocator
5 will notify the institution that this patient is
6 not in New York. And if the doctor does not a
7 license in Wisconsin, then the app is turned off
8 and there's no virtual visit with that individual
9 at all. So that's a different way of dealing with
10 that.

11 Sorry, I forgot to do this.

12 So in general, these are things that we do to
13 protect against the hacking, to protect IT
14 security, and to train individuals for
15 telemedicine. Thank you.

16 DR. SPRUNGER: Lama, thank you for presenting
17 that, your experience. I think a lot of what
18 we've discussed today is balancing safety yet
19 convenience. And you're storing on a separate
20 server. If that person then becomes a patient in
21 your hospital, I would assume there's no crosstalk
22 there. So do you have to start all over? And

1 does that cause an inconvenience as opposed to
2 being secure?

3 DR. AL-ASWAD: So a couple of things. With
4 this initiative, we're not always working in the
5 area the hospital is, and we've learned from our
6 project before that you need to create systems
7 where it's convenient for the patient to follow
8 up. So we've contracted with safety net hospitals
9 in the area that the mobile unit is, and those
10 patients are sent to them and they, the patient,
11 is given all their records and they can go with
12 their records to that institution.

13 At Columbia, right now, we're working to merge
14 -- create a different system that we can merge our
15 information. Once the patient comes to our
16 hospital, we merge it with our hospital so the
17 data is available, but once they come. We can't
18 guarantee every patient is going to come there.

19 DR. HUMAYUN: Okay, great. So I think next is
20 John. If you could --

21 MR. REITES: Okay. I'm going to build on from
22 what I was talking about earlier this morning just

1 to give you some perspective of our project, what
2 our company was doing. I mean my story is really
3 quick. You heard blurbs of it, but I spent all
4 this time in clinical research specifically and
5 just realized that there were all these different
6 stakeholders that needed to see patient-generated
7 health data; right? Everybody needed to see it
8 but they had a very different reason and purpose
9 to see that data. The patients wanted to see
10 feedback on the data so that they could feel
11 engaged and know what was going on. A researcher
12 or a provider wanted to see that data so they can
13 make a decision maybe at the next telehealth visit
14 or what have you. A sponsor of a study wanted to
15 see that data at a macro view to make sure their
16 investment was being triggered and that the
17 patients were being enrolled as planned.

18 And so there's all these different
19 stakeholders involved, and we kind of saw this
20 ability to have this omnichannel experience as
21 something that not just the patient needed but
22 also the site, so the researcher needed but also

1 the sponsor needed. And in doing that, one of the
2 things that really came to fruition is the need to
3 sort of make interoperability happen but not
4 interoperability at sort of this high level that
5 we talk about with maybe EMRs or other big assets.
6 But if we were to come in and we were to collect
7 data from a patient, remember that all-- there's a
8 lot of different ways we can collect data from
9 people, and they can be a medical device; they can
10 be a consumer wearable; it could be, you know,
11 scraping data off their phone; it could be
12 authenticating them through KBA or some other
13 technology. There are literally 37 ways of --
14 ways two ways you can collect data from a person
15 through their phone.

16 And we realized that there were a few people
17 that were nailing this piece or nailing that piece
18 but really, we felt like the industry need to put
19 all that together. So that's what we did. We put
20 together a system that would help us to roll out
21 and in one omnichannel patient experience, collect
22 all the different data they need.

1 And the reason we did it is we did a ton of
2 patient-focused insight work. So we went out and
3 talked to patients and providers and actually got
4 people's insights. And one of the things we heard
5 over and over again is, especially in our world,
6 that we had patients downloading three apps and
7 two websites to do telehealth, provide an e-Pro,
8 and connect a medical device.

9 And so it wasn't that the patient wasn't
10 altruistic or wanted to contribute data or be
11 involved. It was like they couldn't figure out
12 all the tech. And so we're talking about like
13 usability; you know, it's this button in the right
14 place when really, we're not even -- we weren't
15 even giving patients like the ease of just having
16 everything in one app. And I know that sounds
17 really simple and a lot of people that aren't
18 tech, too, will say, oh, just put it all in one
19 app. It's not simple. It took me like nine years
20 to figure out and break and make a lot of
21 successful mistakes in pilots and studies to
22 figure out how to make this work. And so that's

1 really the -- sort of the framework in which we
2 see things.

3 And so I know it's hard to see on this visual
4 but one of the questions that I'm tackling for the
5 panel today is really, you know, when we're
6 looking at these risks, how do we start to tackle
7 training and helping people, helping our patients
8 to actually do something we give them to do. And
9 there's a lot of ways, there's a lot of tactics to
10 that, but one way that I want to throw out to you,
11 because we've really found some some really early
12 progress and success with this method, is
13 instituting what we call eDROs. These are
14 electronic device reported outcomes. And
15 essentially, what these are is another acronym
16 because you know in our industry, we like acronyms
17 so we just made one up. But the reality is is the
18 acronym's important because what this thing does,
19 what this eDROs is it takes an activity that a
20 patient needs to do and it combines all those
21 things together. So for instance -- let me give
22 an example of what an eDROs is and it's a really

1 simple one; actually, it workshop an app, an
2 active task in Apple's research kit, but it will
3 give you a framework for this to start.

4 So what this task looks like is we've been
5 able to do instructional videos and tap training
6 for a patient, and then before they -- so let me
7 back up. Let me give you a for instance. So
8 we've got a mobile spirometry and this mobile
9 spirometry in the study requires the patient to do
10 an e-pro, so they've got to do a survey. They've
11 got to be trained on it. They have to make sure
12 they do the reading exactly like they need to do
13 at home. And then when they're done, we need to
14 confirm that they completed that task correctly.

15 So think about all those different things they
16 need to happen. And what we did is we combined
17 all that into one activity. So patient gets on
18 their phone, gets a notification or reminder and
19 says, hey, it's now time for you to do your
20 spirometry; they click button; button opens up
21 activity; activity says, okay, John, let's walk
22 you through the steps you need to do to do this.

1 And so it starts by training the patient, making
2 sure they understand. You can put a quiz in there
3 if you need to. And then it says, okay, now you
4 have to do the activity, let's connect a Bluetooth
5 device.

6 And so what it does is it takes something that
7 could potentially be really complex and tries to
8 make it as simple as possible so that any user can
9 do it. And what I'll tell you is that -- what we
10 found that's also exciting is that this doesn't
11 have any limits in age and demographic in that we
12 have patients of all different ages and different
13 therapeutic areas using these app tasks with
14 success. Doesn't mean they're all perfect but it
15 does mean that we're seeing early success in the
16 way that we're combining the effect. Does that
17 make sense? So combining this is really a way
18 that we're tackling the training.

19 And then the last piece is I wanted to also
20 make a few statements about sort of these threats
21 and vulnerabilities and data privacy, because
22 obviously this is a really huge thing that

1 we're -- that we have to be careful for. And
2 there are a couple of resources that I direct you
3 to. One is recently, with FDA and Duke-Margolis,
4 we actually went through a process and released an
5 in-health action plan. And in this health action
6 plan, we didn't just describe the types of data
7 you can collect on these devices. We didn't just
8 give you a bunch of use cases, but we actually
9 talked about some some practical things you can do
10 to secure data privacy for patients. And so if
11 you're interested in that after, we can give you
12 that link to that information.

13 But one of the things that comes throughout
14 sort of that plan and, frankly, in all the work we
15 do every day is that we think about these
16 different modes of dealing with patient data -- I
17 want to start by saying the biggest sort of
18 question people have is how do we data transfer;
19 how do we use APIs; and we move data around.
20 aren't we impacting patient's, you know, privacy;
21 aren't we moving their data around? And what I
22 would tell you is that one of the ways we've

1 accomplished keeping that data private and secure
2 is by doing tokenization.

3 And so if you're not aware of what
4 tokenization is, tokenization is if I'm John
5 Reites and I come into a study, when I come in
6 that study and I enroll, my name is then turned
7 into a hash, is turned into a really complex
8 token, and then that token has data assessed with
9 it and it separates my data from PIII to PHI to
10 clinical data. And and it takes that data and
11 parses it into completely different cloud servers.
12 And so what you're doing is you're losing the
13 ability to re-identify a patient, but you're
14 really taking the most extreme stance on securing
15 someone's privacy. And in a clinical trial, this
16 is really what we've seen to be valuable.

17 And so when you go through that tokenization
18 service, even though the patient and the app knows
19 it's talking to me, John, in the data and
20 everything else that we see, I'm just patient
21 00123 and all my data is completely separated.
22 And so when you do that, your ability to do data

1 transfers and API integrations from EMRs to other
2 assets really opens up, because the data security
3 and privacy of the data becoming public becomes a
4 lot less of a risk.

5 Real quick I just want to touch on two other
6 items. I know we've talked enough about local
7 versus cloud storage. And I mean my two cents is
8 that you should be using cloud. There's too many
9 reasons to use cloud. And what I will tell you,
10 even when I'm working with academic and healthcare
11 centers, I would tell you two years ago, I
12 definitely saw sort of this push for On-Prem.
13 We're seeing huge advances in that in our own
14 work. And what we're seeing is that the academic
15 and healthcare institutions are learning more
16 about other compliances for ISOs and SOC-2 to and
17 other sort of data security and privacy things
18 that you need in your cloud. And so if you're not
19 aware what those are those, those -- there's a
20 good educational component to know how cloud is
21 actually providing, in a lot of sense, more secure
22 storage than even your local Prem.

1 And then the last piece I want to touch on is
2 this patient authentication. So I want to flip
3 this discussion a little bit and throw out just
4 one new piece, is we're talking a lot about how to
5 how to keep a patient's data private and that's
6 appropriate. But on the flip side, remember when
7 we're working in today's digital health world, 99
8 percent of the data I'm getting in the studies is
9 from a patient not in a clinic. They're at home.
10 And so the question I would actually reverse is
11 privacy aside, how do I make sure the person doing
12 the data is the person I signed up in the study or
13 is the person I'm actually treating. How do I
14 know? You know, you've seen this old classic
15 image of how you know the dog's not on the
16 computer typing away or how you know the Fitbit
17 didn't get put on a dog. Have you guys seen these
18 things? There are a lot of different ways to
19 actually authenticate a patient.

20 And so I would actually tell you that in this
21 data privacy world, the other piece to keep in
22 mind is how do we authenticate; how do we make

1 sure people are who they say they are as they
2 actively contribute and provide remote data. So
3 lots more we'll talk about in the rest but that's
4 it for now.

5 DR. HUMAYUN: That's very good. Again, the
6 way we've structured this, each panelist will give
7 a brief talk, and feel free to ask any questions
8 during their or after their talk.

9 I had a question for you about tokenization.
10 I mean I think that's good to take a name and
11 turn it into this token, but as we heard earlier,
12 you know, for us, a fundus image or iris image may
13 be an identifier. Have you thought on it and, you
14 know, have you guys thought about how to tokenize
15 something that's very characteristic like an iris
16 structure or a retinal structure when you're
17 actually looking at findings in that structure so
18 you do have to display it? Do you -- you know, do
19 you somehow just decode the information, blur
20 their -- I mean how do you -- how would how would
21 you think about doing that? So John or Nitin.

22 DR. KARANDIKAR: Yeah, hi. So we actually

1 have thought about this quite a bit.
2 Interestingly, we actually asked DHS, the
3 Department of Health and Human Services, if
4 retinal images are by themselves considered PHI
5 for HIPAA reasons. And frankly, the answer was
6 kind of unknown. They didn't -- there's no real
7 ruling on whether an image by itself, even a
8 retinal image, is considered PHI purely. And this
9 Kaggle competition, for example, has these
10 hundreds of thousands of images, right. If that
11 was PHI data, then you can imagine that's almost a
12 HIPAA breach. But I don't think by itself it is.

13 But the challenge comes when you're -- and as
14 we do, when you're combining the image with a
15 patient's demographic information. Then it's
16 clearly HIPAA information. And so what we are
17 doing is that -- where tokenization comes in --
18 this is a great point John brought up -- if you
19 separate the demographic information from the
20 image storage and you're keeping the images in a
21 secure location with -- essentially "hash it"
22 identifying the image and you keep the hash back

1 in with the patient demographics, you can still
2 match those up for the purposes of analytics. But
3 by themselves, then, you know, that makes it a lot
4 more secure. So that's kind of how we are
5 addressing it right now.

6 DR. SPRUNGER; So our next panelist will be
7 Mike. No. We've had all our Mikes in the last
8 session so we'll move on to Nitin Karandikar who
9 is Vice President of Engineering for DigiSight
10 Technologies. There he leads all software
11 development activities and architects new
12 functionality at the -- for the company's mobile
13 cloud-based technologies. He's been doing this
14 for 25 years.

15 DR. KARANDIKAR: Thank you, but you can call
16 me "Mike."

17 (Laughter.)

18 DR. KARANDIKAR: All right. So like let's see
19 here. Okay. Dr. Sprunger already talked a little
20 bit about background. I've been doing this for a
21 long time, been doing health technology from
22 different aspects of it for many years as well

1 across a variety of companies including security,
2 HIPAA compliance, essentially enterprise
3 integration, all of those things, within a variety
4 of different solutions in health care, created or
5 had teams build provider mobile apps, built in the
6 HR for a while and then patient portal, home
7 health, so a lot of texture and different things
8 there.

9 One point about that about my background -- so
10 my background and focus is on software really.
11 I'm not a device guy so I was a little bit
12 concerned about coming here, but it looks like the
13 worlds are colliding, right, and digital health is
14 going towards software increasingly.

15 A little bit about DigiSight Technologies; so
16 we -- very easy to use technology solutions for
17 ophthalmology providers at the point of care, so
18 a lot of you here directly. It's composed of an
19 iPhone-based app with a hardware imaging adapter
20 that's a class 2 510 exempt device. And then on
21 the backend, we have servers in the cloud, the
22 ubiquitous cloud. We can certainly talk more

1 about that. And we have integration, so we have
2 HS7 and Diacom integrations for EHR impact
3 systems.

4 What we do is we provide -- essentially
5 streamline the workflow for providers to capture
6 images and patient data, collaborate among the --
7 among providers and provider networks, and then
8 document that information with the EHR in the back
9 system. Obviously, we are HIPAA compliant. Our
10 security is a core requirement, a core value for
11 us. And then my role, as Dr. Sprunger said, is to
12 lead the software development.

13 So mitigating risks; so if you were to design
14 a new digital health software systems (sic) from
15 scratch, what are the kinds of things you need to
16 think about from a security perspective? So first
17 of all, security is kind of a complex and evolving
18 issue and frankly, you're never done. It's a
19 process that you're continuously, you know, trying
20 to improve security over time. It's a little bit
21 like securing your house and, you know, you can
22 lock the doors, lock the windows, but, you know,

1 somebody could come through the walls. You
2 continuously keep working on that.

3 Today's software systems are composed of
4 multiple tiers. There are many different points
5 of vulnerabilities and so you want to think
6 holistically about the system security as a whole
7 and basically build the security in layers so that
8 an attacker gets, you know, progressive walls that
9 they have to break through to get the data.

10 In terms of safeguards, there's a ton of stuff
11 we do but I just want to talk about the top three
12 things that I focus on certainly. One is
13 encryption. You know, encryption, encryption,
14 encryption, those plus three. But encryption,
15 really, at every point where data is stored and
16 during transmission, both over the internet and
17 also within your network, that really helps you
18 even if an attacker gets access to the system. If
19 the data's encrypted, it's a lot harder for them
20 to access it.

21 Second is employee training and comprehensive
22 training for employees about policies and

1 procedures. HIPAA actually mandates that so it's
2 kind of part of HIPAA compliance. This really
3 goes to -- you know, the previous panel was
4 talking about internal, you know, people doing
5 things inadvertently inside the organization.
6 This also targets like social engineering where
7 somebody compromises a valid user's activity. So
8 all of those things, the more trained your users
9 are and also if your (inaudible) on what each
10 employee's role will be if there is a breach and
11 getting ready for that, that really helps to put
12 you in a good position, because with healthcare
13 labor, it's really at some level a question of
14 "if" -- I mean "when not if" there's going to be
15 an attack. And so you want to be ready for that.

16 And finally, login and access control is
17 pretty self-evident. Everybody, you know, you
18 want to have the appropriate access at the web EPI
19 level, at the -- for web apps, mobile apps, at
20 different stages in the system.

21 So data storage is one of the questions we
22 want to talk about. One approach we take is we

1 try to get the data from the mobile app to the
2 server as soon as possible and delete it from the
3 mobile. So as soon as the app connects,
4 essentially move the data to the server if -- so
5 if a user wants to look at on the mobile, we re-
6 download it and we interpret it, of course, so
7 that at any point, there's less data accessible on
8 the mobile and this also mitigates -- you know,
9 device device loss is a real issue. People lose
10 their phones and so you want to have the reader
11 back on the server.

12 And one interesting thing we've seen
13 repeatedly with customers, there's a lot of
14 connectivity issues at the point of care in larger
15 systems and practices. And this makes it
16 extremely challenging to get the data to the
17 server and it makes a difficult problem, you know.
18 for for making sure that you are making the data
19 not just secure but available and you have to make
20 it reliable And so solutions we looked are
21 caching and synchronization. We looked at like
22 adding two-faced (inaudible) -- for the computers

1 science folks among you. So there's different
2 ways we can do to mitigate that but it's it's a
3 serious issue for us.

4 Storing it in the cloud, I know there's this
5 sense that the cloud is less secure and there was
6 -- I think one of the panelists here talked about,
7 you know, the Brink's truck versus the, you know,
8 let's -- to pick on somebody -- 7-Eleven, you
9 know, getting -- you know, there's a robbery
10 there. And actually, the Brink's has a lot more
11 security. And so in some ways, you could imagine
12 that on the data cloud providers, if you go to a
13 large reputable provider, they actually do a
14 better job of securing the servers. And no
15 offense to the ID things, right, but this is what
16 these folks do like, Amazon Web Services or Google
17 Cloud and they live or die by that. And so that
18 is -- you know, as long as you have a BA with the
19 provider and the provider is a well-funded, you
20 know, reputable service, you might actually be in
21 a better position to do that.

22 And we had some real challenges in the past

1 when we were in with with a smaller cloud
2 provider, and since we moved to a bigger, more
3 serious kind of provider, life has become a lot
4 easier.

5 And then there was a question about the data
6 transmission. Seemed to have lost the slide
7 there. Go up one further. Oh, yeah. And then in
8 terms of data transmission through EHR and PACS
9 systems, what you're trying to do is you're trying
10 to get the data from your system to the remote
11 system. You want to get it there securely. You
12 want to get it complete and accurate, and you want
13 to fit it within the provider's workflow. So you
14 want to meet all of these criteria for it to work
15 well.

16 So one of the key challenges with health
17 system integrations, and I have suffered through
18 this for many years -- one of the key challenges
19 is matching patient records matching or matching
20 MRNs or patient IDs across systems, and you can
21 lose a patient demographic vector, and depending
22 on what the partner has, to match those records.

1 And interestingly, what we are seeing is
2 multipoint integration, so you are matching your
3 health data with multiple systems within a given
4 partner. So they might have an HER system for
5 patient data, a back system for images, SSO system
6 for single sign-on, and so you have to really
7 orchestrate the order of the calls across all the
8 systems at the partner site to make that workflow
9 work. And that gets pretty hairy sometimes.

10 So that -- and you still have to do all of the
11 other stuff like patient matching, you know,
12 across all of the systems at the partner site.
13 There are many different organizations or some
14 organizations within the partner site and you're
15 to make it all kind of work together.

16 And then there's the usual kind of IT things
17 like transmission endpoint security; we can always
18 go a lot more into that; completeness, accuracy,
19 downtime. There's a lot of challenges to the
20 system with system integrations. They're all
21 solvable but it takes a lot of work and you have
22 to kind of plan for -- around a lot of these.

1 So I could go on for a while but I know that
2 we have time limit so I'll stop here. I'm
3 looking forward to the discussion going forward.

4 DR. HUMAYUN: Any questions for Nitin? Thank
5 you. So far we've covered a lot of the server and
6 also software approaches, but now we're going to
7 switch to David, and he's going to talk a little
8 bit more of about hardware so please introduce
9 yourself as well.

10 DR. MYUNG: So, hello, again. David Myung. I
11 spoke briefly earlier and I'm Assistant Professor
12 Byers Eye Institute and Co-direct the Ophthalmic
13 Innovation Program with Mark Blumenkranz, but
14 also, recently, Darius Moshfeghi passed the baton
15 to me to lead the ophthalmology telemedicine --
16 the ophthalmology effort at Stanford and at the
17 VA, so some interesting perspectives there, and a
18 lot of learning today about that.

19 So my talk is, again, switching gears to
20 hardware and Bakul mentioned earlier in this -- in
21 the day today that now, you know, these medical
22 device companies are, you know, out of 10 people

1 only 1 is a hardware person and 9 are software
2 people, and so I kind of feel like this one's for
3 you, the 1 in 10. This -- you know, this is for
4 the hardware -- hardcore hardware device engineer.
5 It's also actually a lot of other shout-outs
6 during this one because it's a bit of my own
7 personal journey through this process of learning
8 this process of mitigating risks in ophthalmic
9 digital health devices through safeguarding in
10 hardware, specifically on light hazards and the
11 light hazards safety and electrical and EMC
12 standards, EMC being electromagnetic
13 compatibility.

14 So we're doing it through a kind of a case
15 study and first of all, as a we have disclosure, I
16 am a co-inventor on this ophthalmic camera system
17 called Paxos that was actually licensed by
18 DigiSight Technologies, which I'm now consulting
19 and helped developing it and as a design
20 consultant.

21 But this is really a kind of a story over of
22 an aspiring and somewhat confused entrepreneur and

1 inventor -- would be inventor and with an idea
2 that many of the people actually had as well on
3 using Smartphones. This is almost six years ago
4 now. Some of these images are from about six
5 years ago and a lot of people are looking at
6 trying to take pictures of the eye with the iPhone
7 which had just gotten to the resolution and camera
8 quality to take pictures as an ophthalmic camera.

9 So we were -- I was coupling -- we were
10 coupling and ophthalmoscopy lens to the iPhone
11 through, first of all, some plastic parts that I
12 ordered on Amazon. Then we started printing them
13 in my friend's bedroom. He had a 3-D printer in
14 his room. He had a bed and a 3-D printer and we
15 would just -- said, "Make this" and he would make
16 it, and then I'd attach the lens and we would take
17 pictures like this.

18 DR. HUMAYUN: Did he print his bed, too?

19 (Laughter.)

20 DR. MYUNG: Yeah, maybe his friend. So,
21 actually, actually that's him right there,
22 Alexander, and he gave me permission to use his

1 PHI there. But it's -- you know, he helped drive
2 this. But what I was was -- we were stuck. My
3 co-developers told me we were stuck. They're
4 like, "What do we now? We can take these pictures
5 and -- but how do we get it to the next level.
6 How do we get it in people's hands?" And all --
7 life all changed when I -- a mentor of mine many
8 of you know, Dr. Emmett Cunningham, actually put
9 me in touch with Dr. Eydelman who then introduced
10 me to Brad Cunningham. I thought they were
11 related but they're actually not.

12 He -- and (inaudible). He is actually not
13 here. I think he's leading a relief team in
14 Puerto Rico right now which is one of his many
15 hats that he wears, amazing guy. But it was a
16 conversation I had; I was in a parking lot of the
17 county hospital and I was talking to him and I was
18 telling him exactly what we were doing, and he
19 said -- and just like, "Can you help me; what's the
20 next step?"

21 And he said, "Well, the next step for the FDA
22 is we want to know, you know, what are you doing,

1 the what." What is the -- what is -- and what is
2 -- what are you're doing? You're -- -- this is an
3 ophthalmic camera; you're putting light into the
4 eye. You know, FDA cares about things that go
5 into the patient's body whether it's a drug, a
6 device or a device (inaudible), so we want to know
7 what is that light source; what exactly -- what's
8 the source of the light; is it an LED, is it
9 halogen, is it a xenon light source, is it --
10 what's the intensity; what's the spectral of
11 characteristics.

12 And for me, I mean literally, it was like the
13 light bulb going off. Said, oh, okay, so that's
14 taking it step-by-step. That's the next frontier
15 to tackle. Characterizing that -- there's a
16 (inaudible) another set of standards, very
17 (inaudible) of standards that he turned me to.

18 And the other one was, you know, what is the,
19 you know, electrical characteristics of it; you
20 know, how is powered; is it plugged in; is it
21 battery; is it plugging into the phone; does it
22 use -- is it drawing power from the phone itself?

1 Those are really the two key things and so
2 this is that story, a little bit of the process of
3 getting eventually as a class two 510(k)-exempt
4 device. And so we had a choice. At the time, we
5 were using the light -- I was using the light
6 source, (inaudible), of an iPhone light. But by
7 the time I talked to Brad, two generation the
8 iPhone had already passed. So I was like I don't
9 even know which light source (inaudible). And in
10 fact, there were many other Samsung devices and so
11 on and so forth. So for me, it was -- well, for
12 anyone developing these things, they're faced with
13 a choice, like do you use the light drawing from
14 the phone itself, or do you develop your own light
15 source and you characterize that. And there's
16 pros and cons to both.

17 The choice that we -- the pivot we made was to
18 just develop our own, characterize it once and for
19 all, and then let it work with other phones.
20 Other people have taken other paths but that's the
21 path we just had to take. We got some funding for
22 the biodesign program at Stanford and then

1 developed -- worked with a (Inaudible). You then
2 do that kind of the nuts and bolts stuff of
3 getting it sort of certified under these
4 safeguards.

5 So this is the product code. Well, first of
6 all, ophthalmic chemistry used to be regulated
7 under product code HKI for almost all cameras and
8 Ron Schuchard had mentioned this new code, PJZ.
9 That was a huge turning point because actually,
10 Jeff Shuren mentioned today, too, that there was
11 an effort to sort of down regulate as much as
12 possible these devices, because realizing there
13 was such a huge volume of innovation coming
14 through to really help, like this workshop's
15 trying to, accelerate innovation. I think this
16 was part of that.

17 So in April 2015, there was an announcement
18 that new code had been announced and if you fall
19 under their group one designation -- group one or
20 group two, but if you get group one, then you
21 follow under the PJZ and then you become -- you
22 qualify as an exempt, 510(k) exempt device. So

1 that was April of 2015.

2 And with that, talking about accelerating
3 innovation, I'd been working on it for three
4 years. Seven months later, we were on the market.
5 We're registered as a 510(k) class 2 exempt
6 device.

7 And so there is an algorithm for optical
8 radiation safety, the ISO 15004 at the time, and
9 now in 2016, it's actually the ANSI, the American
10 National Standards Institute, Z8036 standard, very
11 similar but there are differences. There's
12 actually a flow chart that helps you navigate
13 where you fall as a group one or group two.
14 There's also electrical safety standards, the
15 60601 standard. I'll touch briefly on that in the
16 next couple of slides.

17 But then also important are actually quality
18 systems, having a 1345 ISO certification, and
19 working with the group, we worked with a dive shop
20 that did that. Basically, to me, that says don't
21 print this device in your friend's dorm room, make
22 it in their garage, work with someone who knows

1 how to manufacture these devices and let it be
2 safe for the public.

3 The second one is actually risk management.
4 So, you know, what are the -- you know, we declare
5 what the risks are. Does the device have sharp
6 edges that can cut the user; is -- if it has to be
7 unfolded, does it unfold, you know, properly
8 without breaking down or wearing out; are there
9 small pieces? Actually, I was looking through the
10 49-page document that we have on this and, you
11 know, there was a part about are there small
12 pieces that a child could swallow. These are all
13 things that are important because these are
14 potential hazards and what strategy that can
15 mitigate those things. So they all kind of work
16 together -- sorry -- so those four things.

17 And then just -- can you go to the next slide,
18 please? If you comply with those thing as a
19 general package, then you can fall under product
20 code PJZ. The next slide, if we can advance it --
21 I'm trying to remember what the next slide was --
22 oh, the electrical safety standards so it's

1 really --

2 MALE SPEAKER: (Inaudible).

3 DR. MYUNG: Yeah. The main thing is that for
4 electrical safety, it comes down to two things. I
5 like to boil things down. I like to boil things
6 down. It's immunity and emissions. So one is is
7 your device emitting some kind of energy or
8 radiation and what are the implications of that.
9 And number two, what -- is it immune to
10 electrostatic discharge. So there's actually a
11 test where you take a device and you give it
12 electrostatic discharge in different places and
13 you sort of record its performance. And then in
14 terms of emissions, is it interfering with an
15 antenna that you placed in a device. So it's a
16 pretty well-subscribed set of performance
17 criteria.

18 Just as a way of conclusion, so as we all
19 know, no mobile device technologies have continued
20 to evolve quickly. So since then, we're on iPhone
21 X or 8 right now. The FDA has put in a place a
22 set of straightforward guidelines for building

1 safeguards in new devices anticipating all this
2 change. Two of the main (inaudible) related
3 safety issues are inherent to what you're doing
4 so, so what is a camera. A camera needs light and
5 the light needs energy. So you need light source
6 characterization and hazard protection and then
7 also electrical safety. But along those lines,
8 two quality systems and risk assessments are
9 critical. You need to have those in place.

10 And the other sort of comment that I'd like to
11 make is that much like the theme of this workshop,
12 I think what I learned from this sort of personal
13 experience is just how approachable and accessible
14 the FDA really is and talking to -- I've been
15 talking to Brad Cunningham and then Michelle
16 Tarver, Malvina Eydelman, and Ron Schuchard as
17 well -- just how approachable they are, because
18 they really do want to help us would be inventors,
19 would be startups, companies accelerate their
20 ideas into market just do -- so in a -- through a
21 process and a safe fashion so thanks.

22 DR. SPRUNGER: David, this may be a very

1 simple question but for someone who is starting or
2 someone wants to start something now using a
3 phone, did you measure the actual light intensity
4 or did you assume that the product specifications
5 from the manufacturer were accurate?

6 DR. MYUNG: Oh, no -- yeah, you have to
7 measure them. So there's -- with the 150040 and
8 now the ANSI standard, there's a clear -- it's a,
9 I don't know, 15-page document that goes through
10 under different types of conditions. There's a --
11 first of all, I was going to show you -- there was
12 actually a test set up where you put the device,
13 shine the light. There's a radiometer and a bunch
14 of other things, one in UV spectrum, one in the
15 yellow light spectrum, and you measure the
16 intensities at at certain wavelengths and under
17 certain conditions at different working distances.
18 And you have to record all those and you have to
19 say in that test certificate whether you've met,
20 you're below that threshold or not. And if you're
21 not, then you bump up to the next level. So it's
22 pretty -- it's very much a test and it's not

1 something that's that easy to do as an individual.
2 So we use a test house. So we use -- we outsource
3 it to a group that -- a third party that can say,
4 yes, you you've passed all these tests.

5 DR. HUMAYUN: So, yeah, Dave, I mean I'm
6 always for not inventing anything that I don't
7 have to --

8 DR. MYUNG: Yeah.

9 DR. HUMAYUN: -- or building anything that I
10 don't have to, but I've learned with these bulbs
11 that -- or light sources, the -- depends on how
12 long you've used it or what --

13 DR. MYUNG: Yeah.

14 DR. HUMAYUN: -- period, there is a
15 degradation.

16 DR. MYUNG: Yep.

17 DR. HUMAYUN: And, you know, I did some work
18 and currently, you're doing some work in
19 spectroscopy and there, it really does matter very
20 much so. Can you comment on -- you know, we're
21 using -- we're taking these devices and saying
22 they'll have good light and, you know, the

1 illumination will stay pretty steady. Is there
2 any work done on the iPhone or the Droid, you
3 know, how well those those light sources work and
4 flashes, I mean after how many uses and so forth?

5 DR. MYUNG: Yeah. You have -- you do -- I
6 think you just have to do the work, the
7 characterization. I mean they -- it's not that
8 they think one source is better than the other,
9 but -- the agency, but they just know what you're
10 using and how it works. So with ours, when we
11 went to the external light source, we -- first we
12 had to pick the battery, what kind of battery to
13 use, a D battery or a little calculator battery.
14 And it turns out not every battery is the same.

15 I just -- it was this whole new world for me.
16 It turned out two of these CR2032 batteries
17 sitting side-by-side and wired a certain way gave
18 the longest life. And even then, it was a little
19 bit of degradation over time but it -- compared to
20 the other configurations where they pooped out in,
21 you know, several hours, this one lasted some 18
22 hours.

1 But then, you know, prior to that, I was
2 working with an iPhone 4S or 5 and first of all,
3 if you're using that, the iPhone battery just
4 drains very quickly so, you know, in two hours,
5 you know, we were using it in a clinic and it
6 would drain and the phone would get hot.

7 So that's when we were kind of like well, we
8 want to use this in the developing world for
9 instance and, you know, I don't know how that's
10 going to work, so I might as well send them with a
11 bunch of batteries, these are coin batteries. So
12 I think every -- that's why every phone is so
13 different. Some phones might have a brilliant
14 light source that just lasts forever and ever but
15 it's not touted as a major feature. Even if it
16 was, you have to still do -- go do the work,
17 because the moment you use it as an ophthalmic
18 camera, it becomes a medical device so you have to
19 -- you know, you as the developer, it's on you to
20 demonstrate that it fits all the criteria

21 DR. HUMAYUN: Yeah. And please feel free to
22 ask questions. I have one more for you.

1 DR. MYUNG: Yes.

2 DR. HUMAYUN: You know, clearly, you're
3 looking at the ANSI light standards and
4 electrostatic discharges. What about human
5 factors? I mean I think we talked --

6 DR. MYUNG: Yes.

7 DR. HUMAYUN: -- a little bit about it. I
8 could imagine somebody doing something at home,
9 scratching their heads and so forth.

10 DR. MYUNG: Yeah.

11 DR. HUMAYUN: How do you deal with human
12 factors issues, and how do you control for that
13 somebody with a tremor in their hand, you know 75
14 year old lady who's trying to get a picture of her
15 retina?

16 DR. MYUNG: Yeah.

17 DR. HUMAYUN: How do you address the human
18 factors aspect of it? I mean, again, a lot of the
19 devices I've built, I've spent a lot of time on
20 the human factor. It always is the thing that I
21 don't want to deal with but eventually forces me
22 to deal with it. So any thoughts along those

1 lines?

2 DR. MYUNG: Yeah. Really glad you brought
3 that up because I feel like human factors is a
4 huge area, important area that I think maybe in
5 the next digital health workshop, will be of a
6 major topic. But yeah, I think this is important
7 issue. First of all, for this camera or any
8 system, you kind of describe an indication of use.
9 Is it to be used at home; is it to be prescribed
10 by a physician; is it to be used only in the
11 clinic? So that's, first of all, prescribed, I
12 think, for this device, but there are other
13 devices under development that are intended to be
14 used at home, and that's where the human factors
15 comes into play.

16 I think the FDA -- and maybe the FDA, maybe
17 Ron May want to speak about this is there's a
18 whole human factors testing that's sort of like a
19 subset of a clinical trial where people can take
20 the device home or actually patients are to take a
21 device home and describe their experience. And
22 all that is supposed to be recorded because then

1 there's certain feedback, you know, and like a
2 device -- for instance, if you're trying to
3 measure your own IOP, I think there was a device
4 approved recently that does that. I'm sure there
5 was a lot there that -- about hazards to the
6 patient's eye, you know, causing harm to your own
7 eye, all those ergonomics and things like that
8 that are important. So Ron actually just stood up.

9 DR. SCHUCHARD: So real quickly. There is a
10 guidance document, a human factors guidance
11 document and I would point you towards that but in
12 terms of human factors testing, it falls back to
13 what you've heard Bakul and I say. It's all based
14 on the risk. So indeed if there is risk, you got
15 a device at home and there is a risk for safety or
16 risk associated, it all plays into how much of a
17 risk. And that's part of the human factors
18 testing, is to assess the usability risk.

19 DR. MYUNG: Right. So go ahead.

20 DR. SPRUNGER: Thank you. Our next panelist
21 will be Eitan Sharon who is a founder and CEO of
22 Mode AI, which has developed artificial

1 intelligence-powered visual chatbot. He's co-
2 founder and CTO VideoSurf which will acquired by
3 Xbox, so that means probably all our kids know
4 your name very well.

5 (Laughter.)

6 DR. SHARON: At least I'm in the box. So I'm
7 going to to take you to a little bit of a
8 different perspective. If we moved from software
9 to hardware, I'm going to go back all the way into
10 algorithms, so all the way back to AI. My
11 background is academic in math, computer science,
12 computation, vision and learning, been teaching in
13 Brown University and other places and then moving
14 into the world of startups, entrepreneurialship,
15 and building machines and code that can see in
16 real time and analyze visual things and provide
17 things like, you know, intelligence on the Xbox or
18 even more AI power, what we call -- and I'll break
19 that down for you to see the relevance -- AI
20 visual bot for conversational shopping.

21 So it sounds colorful but let's break it down.

22 So AI, we've talked about it so many times here.

1 That's what we actually do, deep learning AI,
2 visual. We do that's for images for visual things
3 which is very much relevant for medical imaging as
4 well as other images.

5 Bot is the aspect of actually talking to some
6 machine, which many of us could be confused as to
7 whether they're talking to a person or not. Our
8 conversation is just the, again, back and forth so
9 we didn't talk about that a lot, but AI --
10 conversational AI is becoming a thing quickly
11 because it's back and forth with the AI, not only
12 on one off provided image. So you've been
13 asked -- you are being asked questions and
14 according to the responses, there's a
15 conversation.

16 And shopping, well, it's not not a medical but
17 many of the aspects that we care about in terms of
18 safeguards apply to the financial information,
19 other shopping patterns that you do. For
20 instance, the GDPR European standard -- it was
21 just mentioned -- we're heavily into that and
22 reviewing that with legal all the time is forcing

1 some compliance with the information that is very
2 much relevant to the privacy that you would want
3 in your medical record, because that would be what
4 you shop and how you pay and what you're
5 interested in, so very much relevant for that.

6 I'll about three of the questions that were
7 raised for our focus. I'll do it pretty quickly
8 and then we can move to the discussion. One is
9 the safeguarding software, so machine learning can
10 be helpful very much in that; for instance, things
11 that we've been doing for many years, unit testing
12 and holistic testing of the software. We can make
13 that dynamic. Yeah, that would be -- they
14 actually --thank you very much -- we're already
15 there. Thanks.

16 So machine learning could be applied to
17 testing units and (inaudible) in whole, and it's a
18 dynamic thing. And again, talking about risk, it
19 basically looks forward and it behaves in a way
20 that we have expected it to behave but not in a
21 rigid but rather in a dynamic learning way. So as
22 the unit progresses, the checks progresses as

1 well.

2 Abnormalities is just another manifestation of
3 that. So just things that deep learning, I've
4 learned that our standard behavior, once you
5 exceed, they raise a situation which we need to
6 intervene.

7 And the human factor that was discussed
8 before -- so I don't know if you're aware but
9 currently in companies, the office sales of
10 security are for social are running many tricks,
11 like, you know, they put in front of you an email
12 with a screen that you should be familiar with but
13 it's not the real screen and you would enter your
14 password and your information and you'll just give
15 access to anyone. Or I can go right outside here
16 and set up a wifi that says digital health, you
17 know, conference and you go on your phone you
18 would see that wifi, no one would check anything,
19 would just go on it and put your passwords, and
20 everything on that network is exposed.

21 So the human factor, in terms of adversary and
22 how to monitor all those things is very much an

1 relevant in order to, you know, protect the
2 information that we care about.

3 The other point of patient behavior, again, an
4 interesting point of view. Any one of these
5 machines may not be able to know exactly where it
6 is right now, but it does an accelerometer. So it
7 can to the millimeters know where it's moving,
8 which means that actually, it can start from a
9 place and know exactly where it is. So if it's in
10 your pocket in your home and you allow, as a
11 patient and you're interested in, we could know
12 actually quite accurately the pattern of movement
13 of your day, the locations, like the kitchen, you
14 know, or the bathroom or your living room or other
15 places, a walk, and monitor movement, location,
16 and functional behavior, like where you would
17 spend your time; in this regard, also be alert for
18 problems. I know of people who actually watched
19 the Nest machine on their parent's house, and it
20 has some sense of motion and, you know, when they
21 don't see a motion for a day where there should be
22 one, they'll get concerned and they call their

1 parents. That's something that is of service if
2 we are able to monitor some behavior.

3 Things -- and the last point to talk to is
4 just safeguards in storage of information, so it
5 was mentioned here before as well. We have the
6 cloud. We have the two-factor. We have the
7 instrument that we're actually holding, so once I
8 approach the cloud, I can get pinged for
9 validation that it's me through the hardware, and
10 then I can choose which information stays on the
11 cloud and which stays on that phone. Actually.
12 there's a debate where is it better off, to be on
13 the cloud more exposed or actually on this machine
14 in which case we need to retrieve data if I use
15 the machine, but it may be, in some situations,
16 actually safer, believe it or not, to be on the
17 machine than on the cloud. But in any case, the
18 two factor helps us in the end-to-end encryption
19 that we see these days, you know, with things as
20 simple as "what's up" and other conversational all
21 things that I've mentioned before is also very
22 critical. We talked about that before but there

1 are protocols in which me and the other end are
2 the only ones to be -- you know, have knowledge of
3 the conversation and no interference in the middle
4 can know what was sent.

5 This was a brief brush-up on the three points
6 and then we'll, I guess, move to the discussion.
7 Thank you.

8 DR. HUMAYUN: Great. Thank you. Could you
9 talk a little bit about, you know, what your
10 experience with AI is and managing some of these
11 areas, you know, your personal experiences. Has
12 it been something that's been, you know, easy; has
13 been -- taken, you know, a million reiterations to
14 train? I mean where is it in terms of your
15 experience with AI?

16 DR. SHARON: That's a good point. I'll use to
17 talk a little bit to AI. It was mentioned before
18 that the main -- you know, main things we are
19 aware of may be aware of are the data. Data is in
20 abundance or there's a lot of training data these
21 days, and machines have become very powerful;
22 right, it was mentioned before, so graphical

1 designers and GPUs. But also, there was a kind of
2 a mini revolution in the space of deep learning
3 and machine learning in the last couple of years,
4 that deep entered deep; basically, mean
5 (inaudible) hierarchy entered into the system and
6 currently, the results have surprisingly good. So
7 if before we had to worry about these types the
8 things that I've been seeing, your features or
9 reasoning or things that we pay attention to, the
10 beauty in this AI is that oftentimes the holistic
11 view of the samples does not easily expose what
12 those features are, which could be considered as a
13 black box but is also something good because
14 oftentimes they are not breakable to a few simple
15 things.

16 Having said that, there is a walk around
17 localization, identification of the features that
18 matter to a system that has exerted successful
19 behavior. So generative -- adversary networks,
20 for instance, a network that works against unit
21 can provide samples to -- again, was mentioned
22 before -- to train against and then two networks

1 encrypting and decrypting the same thing in order
2 to improve. It's not -- it does not require many
3 iterations, actually surprisingly efficient. If
4 you have grunt trust data to a sufficient degree
5 and you use -- and, you know, you use a good
6 system, results are surprisingly good and they are
7 not relying on features, and I think there's a
8 breakthrough.

9 Are we close to machine awareness? Not
10 anywhere more than flying with our hands, but it's
11 also impressively better and and allows us to do
12 many more things and training is straightforward
13 if you have someone who is sharply focused, you
14 know, about what they're doing and feeding the
15 machine.

16 DR. KARANDIKAR: So I did want to add to that
17 briefly or give a different perspective on AI if I
18 can.

19 MALE SPEAKER: Please.

20 DR. KARANDIKAR: So, I mean the previous panel
21 there was a lot of discussion, the Michaels were
22 arguing, right, which is -- you know, there's this

1 concept that, you know, AI is certainly magical
2 and, you know, were are like solving everything.
3 And there's no question that machine learning
4 specifically, especially supervised learning but
5 also a deep learning, has produced some amazing
6 results. There's no question about that.

7 But at the same time, there's two major
8 issues, right, that are solvable that I need to --
9 think we need to look at. Dr. Yeshwant mentioned
10 this morning with the advances in computer science
11 now and hardware technology especially, you know,
12 you're going to have these neural networks that
13 have hundreds of thousands of layers. And if you
14 do that -- and it is going to be a black box for
15 the foreseeable future -- understanding, you know,
16 in these hundred thousand layers how the AI
17 algorithm arrived at the conclusion it did is
18 going to be essentially unknowable for the
19 foreseeable future, because there's just too many
20 layers to be able to go back and look at it
21 arrived where it did. That's one thing.

22 Second, when the algorithm looks at a certain

1 set of data -- and I think Eitan kind of alluded
2 to this -- it doesn't have any of the context, so
3 it might look at an image, and it does a really
4 good job, as the Kaggle competition showed us,
5 about specifically doing deep learning and it --
6 deep learning especially good for image analytics.
7 But, you know, a typical physician would say, oh,
8 but I happen to know that this patient is older
9 and, you know, of a certain ethnicity and maybe,
10 you know, whatever else. And so they use that
11 information to qualify what they get from the
12 images. And so that's a second thing.

13 And Dr. Woodward, I think this morning,
14 mentioned Bayesian learning, right? I mean the
15 thing is, right, you want to take priors into
16 account as well and really, if you just have a
17 deep learning algorithm focusing on a very
18 specific, although very, you know, wide data set,
19 it still can go wrong because there's no sense of
20 what's happened before. And so, you know, if
21 you -- if we can think about how to combine
22 multiple AI approaches to get to a better, you

1 know, sort of intelligence, right.

2 So imagine that you have, you know, the expert
3 systems of the past have been discredited but use
4 some aspect of that, use certainly machine
5 learning and deep learning or both, you know, two
6 sides of the coin we need to look at, but also
7 look at probabilities where instead of the famous
8 Google algorithm that says is this a cat or dog,
9 what if instead you could say it's a "yes" or
10 "no", it could say we think there's a 70 percent
11 probability it's a dog, 20 percent it's a cat, and
12 5 percent maybe it's a mouse, right? And that's a
13 -- that may be a more accurate representation of
14 how a physician thinks about an image. I -- and
15 I'm not a physician, right, but I don't -- I
16 imagine that, you know, people think "I think it's
17 this but let's get some more data and find out."
18 And you could imagine that AI algorithms in the
19 future could, at some level, formulate the
20 premise, design some experiments, get additional
21 information to validate the results you get from
22 the previous AI.

1 So sorry -- I mean, you know, that's a long
2 spiel but, you know, I think we should consider
3 multiple approaches coming test procedure a larger
4 AI conclusion. So that's sort of a thought
5 process.

6 DR. MYUNG: I have a question for Eitan and --
7 or anyone else who wants to answer this, but I
8 think chatbots are amazing. I think that's sort
9 of the -- we talked a lot about AI in terms of
10 image analysis. With chatbots, it's really you
11 can have a conversation with this -- with the
12 machine basically. And, you know, for instance, I
13 voted last -- I registered to vote last year
14 through a chatbot. I thought, oh, this is cool.
15 So I texted this number and then they asked me my
16 name; then it asked me my -- where I was born; and
17 then it asked me all these really personal
18 questions. But then at the end of this,
19 "congratulations, you're registered to vote" and I
20 just see there's so much power that could be used,
21 because I mean compared -- I think most people
22 would say -- maybe not now but soon -- that they'd

1 rather text, almost prefer to text than talk to
2 someone on the phone maybe in some cases. It's
3 faster in some; you know, maybe the younger
4 generation. It seems that way.

5 And so I don't know if you want to mention
6 like what's the future of chatbot in medicine as
7 far as communicating, maybe talking to a device, a
8 chatbot device nurse, that type of thing. I
9 personally think it's really powerful but what's
10 the horizon there?

11 DR. SHARON: Yeah, I fully agree. I -- you
12 know, if you talk to some of the leadership in the
13 big companies, some is real, some is not. They'll
14 you basically it's already happened. If you just
15 look at the East in which are the nine billion
16 billion of people are just doing that, and they
17 voted with their fingers, not their legs this
18 case, that are shopping and other sensitive
19 information, will be conversation or that will
20 talk to the machine, and it's a very powerful
21 thing. And if you experience any of those like
22 you did, the first time you get some kind of

1 flowing experience, you just see it's natural.
2 There's no buttons to know. It's not an app.
3 It's not site.

4 DR. MYUNG: No forms to fill out, right?

5 DR. SHARON: And look, look, thing forward
6 like next year, you know, all the big companies,
7 you put some glasses on our heads. They're
8 already there, all of the companies, and they'll
9 give us some augmented reality. And now, you
10 know, these things are connected inherently to the
11 chat platforms, right; Facebooks will be connected
12 to the Messenger and Google to the Arlow (ph) and
13 whatnot, and Microsoft will be connected to the
14 Skype with (inaudible). And can you imagine a
15 website or one app on your glasses to talk to? I
16 mean this would be inherently a conversational,
17 social the bot thing, so it's just unavoidable and
18 people love it, and it's natural and I think we're
19 going in many of the cases, and it's better to be
20 ahead of the curve with these things.

21 DR. MYUNG: Yeah.

22 DR. SHARON: It will be taking us further

1 (inaudible) AI just to -- we'd like to meet in,
2 you know, one world as well. I think you're right
3 to think -- but I think AI is acknowledging and
4 getting there. For instance, in a bot, as I said,
5 it's not a one off so it's not "what's this
6 image." It's like are we talking now; what did
7 you say before to talk to a question of a buyer;
8 are we in a conversation; what was said, typed,
9 which is NLP versus visual AI; and which image
10 will click to interact with or the machine has
11 seen? We're doing all that. And the way to go
12 about it is math and vision and whatnot. You just
13 take the vectors from the deep learning and you
14 have a bunch of PhDs and you build upon the
15 probabilities of the AI interweaved with NLP and
16 other priors. So that's something we know how to
17 do. You're and not limited and I think so many
18 resources are going there that there is a lot of
19 activity, and there will be innovation. It's just
20 the beginning of something so certainly getting
21 there within the framework.

22 DR. HUMAYUN: John --

1 DR. KARANDIKAR: Absolutely.

2 DR. HUMAYUN: -- I have a question --

3 DR. KARANDIKAR: I'm excited about the future.

4 DR. HUMAYUN: I had a question for John and,
5 Nitin, since you're out there, you know, for a
6 device you verify and validate and you put it
7 through stresses so you get device failures. In
8 this case -- I mean I heard Dimitri talk about
9 this. I think maybe -- you know, I don't know
10 who's doing it outside Google but people are
11 actively trying to hack in. So, you know, small
12 companies can do this. I mean how do you tell
13 somebody that your system is safe when you haven't
14 had somebody for -- put it through that rigorous
15 testing or some sort of testing where somebody is
16 trying to hack into it? Have you guys thought
17 thought about it? I mean, you know, is it -- is
18 that how you test a system and its proprietary and
19 safeguard nature of it, by hiring, you know, 10
20 people to hack into it? I mean I -- you know,
21 could you comment on that?

22 DR. KARANDIKAR: Absolutely. And so there's a

1 couple of different things that we are combining
2 here; right? One is -- I think Dr. Humayun
3 actually alluded to testing and making sure the
4 app works the way it's supposed to. And
5 separately, there's a security aspect of it. And
6 thirdly, I think, you know, I want to talk a
7 little bit about penetration testing which is kind
8 of what Dr. Humayun alluded to as well.

9 So first of all, for verifying the quality of
10 the system in terms of one of the challenges --
11 and it was really refreshing for the FDA to sort
12 of talk about agile software development, and it's
13 impressive, right. I mean this is where software
14 is and it's amazing to see the device industry and
15 the health technology industry getting you know at
16 the same level. So for software quality, you can
17 actually have a -- you know, we have a fairly
18 comprehensive QA process that looks -- and this is
19 fairly well understood in software; you know,
20 there's aggression testing, unit testing; you know
21 what should I say, action testing, all of those
22 things, There's a whole bunch of QA activities

1 that happen for every release. So that's one part
2 and I can go into that in more depth.

3 Second, I think you kind of eluded to security
4 and so security is (inaudible) each release to do
5 some quality testing or security, you can actually
6 design your security architecture, and you can
7 design the software so that you have a higher
8 level of security regardless of those -- you know,
9 those individual releases don't necessarily have a
10 huge impact on the overall architecture and
11 security framework. And so, you know, you can you
12 can kind of manage that more longer term. As an
13 example, you know, you think of the idea
14 architecture and you have firewalls, you have a
15 DMZ interface where all of that stuff is set up,
16 and that does not change release to release. So
17 you can actually test it very, very thoroughly,
18 although for each release, you still need more
19 testing.

20 But, third, I think, you know, in terms of
21 hacking into the system, there are these software
22 consulting firms that essentially offer services

1 called "penetration testing pen test," and so you
2 can actually get these folks to come in as a tiger
3 team and try to hack into your software. And I
4 worked with them at -- you know, these folks are
5 really, really good. No matter how well we kind
6 of protect our app, they find a way to get in.
7 And -- but that actually gives us really valuable
8 information to figure out how to address some of
9 the security issues. One thing I learned is that
10 security is never done, right, so no matter how
11 much you protect it, there are always ways to get
12 in, but the challenge is to make it progressively
13 harder so that at the commercial level, it's too
14 much work for the attacker to come in. So, you
15 know, in other words, you know, they -- you rather
16 have them, you know, burgle a different house
17 because yours is too hard to break into. That's
18 not a really good analogy but that kind of is how
19 it works in security so that's -- I don't know if
20 that answered your question but that's the
21 different parts.

22 DR. SPRUNGER: So this being a very up-to-date

1 technologic meeting, we have someone who sent a
2 question from the webcast as a webcast attendee.

3 DR. HUMAYUN: We have a number of those but --
4 so it is being well-attended.

5 DR. SPRUNGER: So this question comes from Ron
6 Cummings Kralik, who is a principal network
7 engineer, surgical equipment at Bausch & Lomb.
8 His question is, "What are the FDA's and doctors'
9 thoughts on storing non-patient, in other words,
10 machine data, on public cloud space?" Who would
11 like to address that?

12 MALE SPEAKER: So that's maybe --

13 DR. KARANDIKAR: So (inaudible) the question
14 is what are the FDA's thoughts on that
15 so --

16 (Laughter.)

17 DR. BIN-NUN: So this is a GDPR; the European
18 standard for information, requires that the
19 information of the users will stay local to their
20 activity or their country, but this local, to
21 their regulations, could be Amazon's, be public,
22 could be any company's, could be Microsoft so as

1 long as they keep it local, for instance, the
2 regulations require that but do not require it
3 will belong to the company with (inaudible). It
4 will require -- it requires that it be protected,
5 deletable, sent back to you upon request and many
6 other things but not that it will be off of a
7 public cloud, just under some regulations. So
8 that's a cue from there (inaudible).

9 DR. SPRUNGER: I think these questions are
10 probably exclusive to this panel so if anybody has
11 any answers. Second one from the same person is,
12 "Would the doctors find value in being able to
13 merge anonymized treatment results from their EMR
14 back into the public cloud space to allow
15 analytics to rate treatment effectiveness? Any
16 takers on that.

17 UNIDENTIFIED MALE: I mean I do have an
18 opinion here but -- so I do have an opinion which
19 is if it's -- if the question is for de-identified
20 data, then by definition, that is de-identified,
21 there's no HIPAA concerns about putting it in the
22 public cloud. Sorry (inaudible).

1 DR. SPRUNGER: I think Michael has a comment.
2 Please.

3 DR. CHIANG: Derek, just in response to that
4 question, I think in a lot of ways, that's the
5 premise of -- this is Michael Chiang from
6 Portland, Oregon -- I think that's what the
7 premise of iris registry is really meant to do,
8 from that big data paradigm, the data gets out
9 there and everybody sort of benefits from the
10 knowledge discovery that can occur from that`.
11 And I think the challenges are, you know, getting
12 the doctors to buy into that, getting doctors to
13 send the data, and then finding people to do that
14 analytics and, you know, perform that knowledge
15 discovery.

16 DR. EYDELMAN: And we at the FDA are very
17 interested in utilizing all of the data in the
18 registries for -- as post-market data, as data
19 that we can, hopefully, utilize to expedite
20 getting new treatments and new devices to market.
21 And we are exploring collaborations Iris in a
22 number of venues.

1 DR. SPRUNGER: So while you're there, please
2 don't move. That led to question number three,
3 Would the FDA allow this sort of sharing, which I
4 think you just said yes.

5 DR. EYDELMAN: We actually would like to
6 propose that more of that occurs as that really is
7 a way to move forward and that is one of our
8 strategic priorities, as a matter of fact.

9 DR. AL-ASWAD: Can I --

10 DR. SPRUNGER: If you don't mind staying there
11 for number four. Oh, we --

12 DR. EYDELMAN: Okay.

13 DR. AL-ASWAD: -- can I make a comment? I
14 don't know if you know, there is a big study.
15 It's called "all of us." It's five big centers.
16 One of them is Columbia University in New York.
17 And basically it's a genetic study that patients
18 register in it and they get their blood tests and
19 urine tests in addition to their health
20 information. And it's the start of the part of
21 President Obama's initiative to collect
22 information to use it for precision medicine in

1 the future. And this is currently happening, so
2 it's collected somewhere. The -- well, not
3 identified fully because you have the patients'
4 health information with it, and you can actually
5 do a lot of studies as a participant. You can
6 have an idea for a research project and you could
7 utilize that data, and it's called "all of us" and
8 it's different -- five centers

9 DR. HUMAYUN: Okay. Well, thank you. The
10 panel has been very interactive. Hopefully, you
11 got something out of it and we're moving on to the
12 next part of that program. Thank you.

13 (Applause.)

14 DR. REPKA: So we just have a very short
15 remaining portion of the program, and there will
16 be the three summaries from each of the panel
17 chairs or co-chairs and then some concluding
18 remarks.

19 Those of you that weren't here at the
20 beginning, Dr. Shuren mentioned that the
21 Commissioner would be unable to attend this
22 afternoon, so that's an unfortunate but realistic

1 outcome.

2 So the first panel, I think when Natalie's
3 ready, she'll start.

4 DR. AFSHARI: Well, great. We had a great day
5 with lots of discussions and exchanges.

6 So we had the panel one, Mike Trese and I, and
7 the panel was for Dr. Dimitri Azar, Leslie
8 Bottorff, David Morrison, Darius Moshfeghi, Mia
9 Woodward, Ingrid Zimmer-Galler. And the main
10 question and discussion was safety and
11 effectiveness concerns when a digital health
12 device provides information as an aid for
13 diagnosis and the assets, threats, and
14 vulnerabilities to be considered and to be
15 identified.

16 So we talked and touch base on several items
17 but one was the tempo of the disease may reflect
18 on how important the device contribution is to the
19 diagnosis, and a physician and user may be able to
20 override any machine inconsistencies. It also
21 came out that some of the safety factors depend on
22 the end user, that there should be some assurance

1 that the doctors are up-to-date in the management
2 of that disease, and it came up that some of the
3 diabetic retinopathy patients may read the images
4 even better than some doctors because they're
5 focusing so much this day and age on their images.

6 Also, regarding privacy, we have come a long
7 way in privacy but have some ways to go in digital
8 health. It came that there is evidence that local
9 storage and cloud-based storage have similar
10 security profiles and industries are being created
11 to assess the level of cyber security.

12 And that was the summary of our panel. Thanks
13 again, everyone, for a great day. I'll say
14 goodbye from here, so we won't come back and take
15 a minute to save a minute at the end. Thanks
16 again to all of the organizing organizations and
17 as well as FDA.

18 (Applause.)

19 DR. NISCHAL: So this is a synopsis for the
20 second panel. What I found really interesting was
21 that there was a real variety within the
22 panelists. You know, we had known physicians who

1 were scientists and epidemiologists, physicians
2 who were retina guys, and pediatric
3 ophthalmologists, and also somebody from the FDA,
4 Bakul, in particular, of course. And it was a
5 very global represent -- if you listen to the
6 accents, you know, we went from South African to
7 the UK, Europe and the U.S. So I think that gives
8 you an idea of the backgrounds coming into the
9 panel.

10 You know, what I took away from Mark
11 Blumenkranz's introductory slides was that digital
12 healthcare actually is a response to the increased
13 connectivity that the Smartphone has brought to us
14 and our society. It's a societal response that
15 we're gaining from entrepreneurs and the relevance
16 of the clinical utility of the digital digital
17 healthcare applications requires large data
18 analyses, which Quinton Oswald was was talking
19 about.

20 It appears that whatever the environment that
21 the digital application is being used, in we need
22 to identify a workflow that designates who reads

1 the data, who acts on the data, and who's
2 responsible for that data and the actions that you
3 have to take on that data. I think we don't want
4 to be in a situation where the data ends up in the
5 physician's office, we don't act on it, and a
6 patient comes to harm, because I think we then are
7 in an enormous amount of legal problems.

8 The development, therefore, of specific roles
9 within the health care environment is probably
10 essential and whether those health care roles have
11 an IT background or a software background, you
12 know, I leave the audience to ponder and to think
13 about.

14 I think that -- I got the overall sense that
15 the safety of data storage didn't seem to be so
16 much of a problem, that HIPAA compliance with
17 these storage was there; if somebody wants to hack
18 into it, they're going to hack into it no matter
19 how hard you try but that there is this issue of
20 the human engagement or the human abuse of the
21 data that might be more of something that we have
22 to look into.

1 As big data and volume increases the data that
2 we get, it seems to me that artificial
3 intelligence is almost inevitable. And I was
4 really interested that there was no question that
5 AI had to be involved amongst all the panelists.
6 In order to get it to be effective, however, I
7 think that needs to be a culture change. That's
8 what I got the impression of where protocolization
9 becomes part of the medical culture more than it
10 perhaps is now and that the deviations of -- from
11 the from the protocols are important because they
12 may act as an echo or a feedback so that we can
13 look at the protocols again and see how we can
14 make them better so that there's reduced
15 deviations.

16 I think as we move to digital health
17 applications more and more, defining who owns that
18 data is also going to be an extremely important
19 point of reference, because is it the patient; is
20 the institution; is it the doctor; or is it the
21 company that's made the application? And I think
22 that these areas perhaps today have given us food

1 for thought because they're gray areas; they're
2 not black and white. And the arguments that were
3 made amongst the panelists in the second group, in
4 our panel, I think, just highlight that it's
5 exciting but there are a lot of issues and
6 questions that we still have to answer.

7 Thank you very much to the FDA and everybody
8 else who was involved. Thank you.

9 (Applause.)

10 DR. SPRUNGER: So I think Ken and Natalie went
11 over most of the major points, don't have a lot to
12 add. Couple of things that Mark and I wanted to
13 pass on. The importance of software as far as the
14 password protection, employee training, and
15 encryption, I think we need to emphasize all
16 those things.

17 As far as hardware, we heard about the light
18 standards, the ANSI and the electrical standards,
19 the ISO, again, being very important.

20 And lastly, I think, for me, personally, I got
21 out of this more than anything is the human factor
22 again, and that was mentioned by Ken. That's very

1 important. I think a lot of us tend to overlook
2 that and I think it's very important.

3 So with that, panel three, was happy to be
4 here today and thank you to the FDA for allowing
5 us to participate.

6 (Applause.)

7 DR. EYDELMAN: Well, apparently I get the last
8 word. Thank you all so much for coming, spending
9 the day, and sharing with us your thoughts, your
10 knowledge, and your, most importantly, your
11 enthusiasm for helping us expedite ophthalmic
12 digital health.

13 All of the slides from all of the participants
14 today will be available at FDA's website pretty
15 soon as will be the complete transcript of today's
16 proceedings.

17 The a goal is for us to write a manuscript
18 summarizing highlights of today's meeting, and I
19 believe that just sharing the knowledge that we
20 accrued today with the general public will help us
21 in our goal of expediting ophthalmic digital
22 health. Thanks to all.

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1 (Applause.)

2 (Whereupon, at 5:12 p.m., for above-entitled

3 meeting was concluded.)

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