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5 ADVANCING THE DEVELOPMENT OF
6 BIOMARKERS IN TRAUMATIC BRAIN INJURY WORKSHOP
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1 C O N T E N T S

2 AGENDA ITEM/SPEAKER:
3 Welcome Remarks
Robert Califf, MD, MACC,
4 Commissioner of Food and Drugs, FDA
5 Keynote Address: History and Lessons Learned from Clinical Trials in TBI
6 Col. Todd E. Rasmussen, MD, FACS
Director of DoD Combat Casualty Care
7 Research Program, US Air Force Medical Corps.
8 Workshop Overview
Lakshmi Kannan, PhD
9 Commissioner's Fellow, Emergency
Preparedness and Medical
10 Countermeasures, Office of Center
Director, CDRH/FDA
11
Theme 1: Potential and Emerging Biomarkers-
12 Challenges and Opportunities Advances in TBI Biomarkers
13 Geoff Manley, MD, PhD
Principal Investigator of TED/TRACK-TBI
14 and Chief of Neurosurgery, University of
California, San Francisco
15
Neuroimaging Biomarkers
16 Esther Yuh, MD, PhD
Associate Professor,
17 Radiology and Biomedical Imaging
University of California, San Francisco
18
Neuroimaging Biomarkers
19 Luca Marinelli, PhD
Program Manager, Healthcare Commercial
20 Partnerships, GE Global Research Center
21 Bio-fluid Biomarkers
Kevin Wang, PhD
22

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(continued)

2 AGENDA ITEM/SPEAKER:
3 Executive Director, Center for Neuroproteomics and Biomarkers
4 Kevin Wang, PhD (continued)
Research and Chief of Translational
5 Research, University of Florida, Gainesville
6 Bio-fluid Biomarkers
Ronald Hayes, PhD
7 Director, Banyan Laboratories and
Founder/President, Banyan Biomarkers, Inc.
8
Emerging Biomarkers
9 Cristin Welle, PhD
Assistant Professor, Department of
10 Neurosurgery, University of Colorado, Aurora
11 Correlation of biomarkers with Clinical Outcome Assessments
12 Harvey Levin, PhD
Scientific Director of Neurorehabilitation
13 Neurons to Networks TBI Center of Excellence,
VA Medical Center and Professor of Physical
14 Medicine and Rehabilitation at
Baylor College of Medicine, Houston
15
Q&A
16
BREAK
17
Theme 2: Regulatory Considerations for Biomarker
18 Development
19 Overview- Pathways at FDA to integrate Biomarkers into Medical Product Development
20 Allison Kumar
Senior Program Manager, Emergency Preparedness and
21 Medical Countermeasures, Office of Center Director, CDRH/FDA
22

1 C O N T E N T S
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2 AGENDA ITEM/SPEAKER:
3 Drug Development Tool-Biomarker Qualification Pathway
4 Shashi Amur, PhD
Scientific Coordinator, Program, Office of
5 Translational Sciences, CDER/FDA
Medical Device Development Tool
6
Kathryn O'Callaghan
7 Health Scientist, Office of Center Director, CDRH/FDA
8
Neuroimaging Biomarkers: Analytical &
9 Clinical Validation
Daniel Krainak, PhD
10 Biomedical Engineer, Division of Radiological Health, Office of In Vitro Diagnostics, CDRH/FDA
11
In Vitro Diagnostics: Analytical & Clinical
12 Validation
Kellie Kelm, PhD
13 Supervisory Biologist, Division of Chemical and Toxicology Devices, Office of In Vitro
14 Diagnostics, CDRH/FDA Clinical Trial Design Considerations
15
Peter Como, PhD
16 Health Scientist, Division of Neurological and Physical Medicine Devices, Office of Device
17 Evaluation, CDRH/FDA
Statistical Issues and Considerations
18 Bipasa Biswas, PhD
Mathematical Statistician, (Team Leader), Division
19 of Biostatistics, Office of Surveillance and Biometrics, CDRH/FDA
20
Critical Path Public-Private Partnerships
21 Diane Stephenson, PhD
Executive Director, Coalition Against Major
22 Diseases, Critical Path Institute

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2 AGENDA ITEM/SPEAKER:
3 Q&A
4 PANEL DISCUSSION
5 Moderator:
6 Allison Kumar
Senior Program Manager, Emergency Preparedness and
7 Medical Countermeasures, Office of Center
Director, CDRH/FDA
8
Panelists:
9
Ramon Diaz-Arrastia, MD PhD Director of Clinical
10 Research Center for Neuro and Regenerative
Medicine Uniformed Services University of the
11 Health Sciences, Walter Reed
12 Christine Mac Donald, PhD
Assistant Professor in the Department of
13 Neurological Surgery, University of Washington
14 Jamshid Ghajar, MD, PhD, FACS
Director of Stanford Concussion and Brain
15 Performance Center, Stanford School of Medicine
and President of Brain Trauma Foundation in New
16 York City and Palo Alto
17 Hao Wang, PhD
Program Director, Office of Translational
18 Research, National Institute of Neurological
Disorders and Stroke, NIH
19
Stuart Hoffman, PhD
20 Scientific Program Manager, Brain Injury
& Stroke Programs, US Department of Veteran
21 Affairs
22

1 C O N T E N T S
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2 AGENDA ITEM/SPEAKER:
3 Panelists (Continued):
4 Shashi Amur, PhD
Scientific Coordinator, Biomarker Qualification
5 Program, Office of Translational Sciences,
CDER/FDA
6
Theme 3: Advance Knowledge from Patients
7 Experience
8 Patient Perspective
Johnny Cebak, PhD
9 Iraq War Veteran, Medical student
at Lincoln Memorial University
10
Patient Perspective
11 Rebecca Lorraine, Col (Ret.), MS-FNP
Ex-Chief of the US Special Operations
12 Command
13 Clinic, MacDill Air Force Base
Patient-Centered Perspective
14 Ben Heywood, MS
Co-Founder, President
15 PatientsLikeMe
16 Suzanne Schrandt, JD
Deputy Director, Patient Engagement
17 Patient-Centered Outcomes Research
Institute (PCORI)
18
Theme 4: Strategies for improving data
19 standardization, sharing, and application of big
data analytics
20
Data Standardization-Quantitative Imaging
21 Biomarkers Alliance (QIBA)
Daniel Sullivan, MD
22 Professor Emeritus Department of Radiology,
Duke University, Founder and Chair, QIBA

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2 AGENDA ITEM/SPEAKER:
3 Theme 4: Strategies for improving data standardization, sharing, and application of
4 big data analytics (continued)
5 Data Standardization
Patrick Bellgowan, PhD
6 Program Director, Repair and Plasticity, National Institute of Neurological Disease and Stroke, NIH
7
TED Metadataset
8
Geoff Manley, MD, PhD
9 Principal Investigator of TED/TRACK-TBI & Chief of Neurosurgery, University of California, San
10 Francisco
11 TBI Registries
Tammy Crowder, PhD
12 Neurotrauma Research Portfolio Manager, DoD-Combat Casualty Care Research Program
13
BREAK
14
Big data analytics - Plantir Platforms
15 Chloe Coughlin-Schulte
Business Development Team
16 Palantir Technologies
Big data analytics - TBI Big data and IBM platform
17
Paul Vespa, MD
18 Director of Neurocritical Care,
Professor of Neurosurgery and Neurology, UCLA
19 School of Medicine
Big data analytics- In-silico approach
20
Yelizaveta Torosyan, PhD
21 Health Scientist, Division of Epidemiology, Office of Surveillance and Biometrics, CDRH/FDA
22

1 C O N T E N T S
(continued)

2 AGENDA ITEM/SPEAKER:
3 PANEL DISCUSSION
4 Moderator & Panelist:
Danica Marinac-Dabic, MD, PhD, MMSc
5 Director, Division of Epidemiology Office of
Surveillance and Biometrics, CDRH/FDA
6
Panelists:
7 Patrick Bellgowan, PhD
Program Director, Repair and Plasticity, National
8 Institute of Neurological Disease and Stroke, NIH
9 Geoff Manley, MD, PhD
Principal Investigator of TED/TRACK-TBI & Chief of
10 Neurosurgery, University of California, San
Francisco
11
Kevin Crutchfield, MD
12 Director of the Comprehensive Sports Concussion
Program at Brain & Spine Institute at LifeBridge
13 Health Care
14 Col. Dallas C. Hack (Ret.), MD, MPH
Medical Leader, One Mind
15
Tammy Crowder, PhD Neurotrauma Research Portfolio
16 Manager, DoD-Combat Casualty Care Research Program
17 Daniel Sullivan, MD
Professor and Vice Chair for Research,
18 Department of Radiology, Duke University,
Founder and Chair, QIBA
19
Lakshmi Kannan, PhD
20 Commissioner's Fellow, Emergency Preparedness and
Medical Countermeasures, Office of Center
21 Director, CDRH/FDA
22

1 C O N T E N T S
(continued)

2 AGENDA ITEM/SPEAKER:
3 Allison Kumar
Senior Program Manager, Emergency
4 Preparedness and Medical Countermeasures,
Office of Center Director, CDRH/FDA
5
Summary and Next Steps
6 Lakshmi Kannan, PhD
Commissioner's Fellow, Emergency Preparedness
7 and Medical Countermeasures, Office of Center
Director, CDRH/FDA
8
Closing Remarks
9 Allison Kumar
Senior Program Manager,
10 Emergency Preparedness and Medical
Countermeasures, Office of Center Director,
11 CDRH/FDA
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1 P R O C E E D I N G S

2 DR. KANNAN: Good morning, again. My

3 name is Lakshmi Kannan. I'm a Commissioner's Fellow

4 at Emergency Preparedness/Operations and Medical

5 Countermeasures Program in the Office of Center

6 Director at CDRH. On behalf of CDRH, and TBI

7 workgroup team I welcome you all to this public

8 workshop on advancing the development of biomarkers in

9 traumatic brain injury. And thank you, everyone, for

10 the webcast. coming in person as well as to those who have joined us on

11 FEMALE SPEAKER: Sorry about this.

12 DR. KANNAN: 00(inaudible).

13 FEMALE SPEAKER: -- (inaudible) issues.

14 DR. KANNAN: So it's my honor to

15 introduce our new Commissioner, Dr. Robert Califf,

16 who will give the welcoming remarks, and let's all

17 congratulate Dr. Califf on his recent

18 confirmation.

19 (Applause.)

20 DR. CALIFF: Good morning, everybody,

21 and it's great to be here with you. I'm sort of

22 experiencing the ecstasy of victory and the agony

of defeat in the same week here. You know, it was great to get through the confirmation proceedings last week and now being in this job that has such awesome responsibility, to work with such great people. On the other hand, I had three days this week that were mapped out to spend at meetings like this where I could actually sit and take it in and listen and learn but suddenly, my life has changed so I'm now in the speak and run routine that is not quite so satisfying. But I was glad to be able to give some opening remarks here because it's important to emphasize how critical this field is.

I don't need to talk to you about the importance of traumatic brain injury, whether we're talking about high school athletes or our soldiers and also don't need to remind you of how critical it is to understand how we might intervene early and also in a preventive manner where that would be helpful. What I would like to emphasize is that I think a lot of people have gotten accustomed to talking about biomarkers sort

of glibly, as if you look and find some association and some data set and then you're off and running with a treatment that's going to work because it affects a biomarker. Just a little story about this and it's something that I would urge you to pay close attention to as you work through the specifics in this field which are so important.

We have an entity called the FDA-NIH Joint Leadership Council, or as I like to say, if you're at NIH, you call it the NIH FDA Joint Leadership Council. And the idea, started by Dr. Hamburg, my predecessor, and Francis Collins, was the realization that because translation of discoveries into practice is so critical that it will be important for the FDA and NIH leadership to meet on a regular basis, identify critical topics, and then work on those priorities between the two federal agencies. And in my very first meeting with the group when I arrived here about a year ago was about two weeks into my tenure at the FDA, the topic was biomarkers. I

1 was pretty fired up because I've done a lot of
2 work in the field in cardiovascular disease.
3 We're well into the multi-marker, multi-
4 dimensional biomarker measurement way of thinking
5 with well-defined outcomes in the field. And I
6 was pretty excited about the high level of science
7 that we're going to do together with the NIH.
8 And right there in the first meeting, as
9 we were discussing it, Janet Woodcock from FDA and
10 Harold Varmus from NIH got into a bit of a feud
11 because they disagreed on the definition of
12 surrogate endpoint. And this is pretty
13 fundamental when the most esteemed leaders of two
14 major organizations that are funding and judging
15 medical evidence don't have agreement on the very
16 definition of one of the most important terms in
17 the field. And then as we all talked about it, we
18 realized that many of us had disagreements about
19 definitions and so we retreated to a very
20 different position.
21 While multi-dimensional high-end
22 biomarker work is absolutely critical to every

1 field right now, we decided that what we needed to
2 do was go back to the basics and see if we could
3 reach agreement between NIH and FDA on the
4 definitions that underpin the things that we're
5 measuring, the multiple types of biomarkers, what
6 constitutes a surrogate endpoint, and clinical
7 outcome assessments. And without that entire
8 spectrum, without a common nomenclature, we
9 realize that many people were getting lost.
10 People were getting major NIH grants based on
11 promises for translation that couldn't possibly be
12 met because of a fundamental understanding of what
13 surrogacy means, companies being formed and
14 bringing their wares to the FDA without a hope of
15 actually getting the product on the market because
16 the development pathway was misunderstood. And in
17 the end, and increasingly important now because of
18 the cost of drugs, which is a very hot topic,
19 people finishing their development programs and
20 not having the clinical outcome assessments that
21 CMS and the payers need in order to pay for the
22 treatment, they might even have some clinical

1 benefit.
2 And so it was amazing. It took us about
3 six months of head-to-head meetings, home and
4 home. I had to host several dinners so that the
5 disputes could be resolved peacefully over dinner
6 as opposed to in a pressured meeting. But we now
7 have come up with a set of definitions. They're
8 published in a living textbook hosted by the
9 National Library of Medicine. I'd urge you to go
10 look at as you go about your work. And the idea
11 here is we're starting out with a pretty simple
12 set of definitions. You might wonder why it would
13 take national leaders six months to come to
14 agreement but if you could see the tracked changes
15 in the documents, you'd have a complete
16 understanding. Part of it is that the same term
17 does mean something different depending on the
18 context in which it's used; for example,
19 regulatory approval versus biological expiration.
20 And so we had to come up with definitions that
21 covered the spectrum. And then in the next layer,
22 we're going to give a lot of context about the

1 multiple uses of biomarker surrogates, clinical
2 outcome assessment.
3 And then finally, our plan is to open it
4 up much like a Wiki document where people can send
5 in what they've learned as they've evaluated
6 specific biomarkers, because another really
7 noticeable thing is we worked through this is
8 every field of science is working on this but
9 there's a lot of misunderstanding even about the
10 specifics and it's very hard to find all the
11 information in one place that you might need. In
12 this field, it's simply not good right now to
13 repeat somebody else's mistake when you could have
14 just read about it had you had ready access to the
15 information. So this is going to be a document
16 that we hope the global ecosystem will help to
17 edit as it evolves. It'll be hosted by the NIH
18 but with sort of an editorial team which is co-led
19 by NIH and FDA but very much involving the
20 external community because we don't, obviously,
21 have the wisdom and knowledge and we're not doing
22 most of the research on the inside, and we need to

1 involve everyone in this.
2 So with that, I'll just also point out
3 something that you all know but has very much been
4 my experience. It's obvious that it's very hard
5 to make progress in a field unless you can measure
6 things, and I know that you have a particularly
7 difficult area. In my previous work at Duke, I
8 did not work directly in this field but I worked
9 with people who did and I would urge you, as you
10 think about what you're doing today, to think very
11 broadly about all the sources of information that
12 you can take advantage of, because we're now in
13 this amazing time where computation and storage is
14 no longer the limiting factor. And this means
15 that in every field, what used to be something
16 that you would hold onto in your own domain
17 because it was so hard just to get the data, now,
18 to really make the advances that we need to make,
19 we need to break down the silos and share the
20 data. And in fact, I was at a meeting last night
21 with a GW School of Public Health and Francis
22 Collins played a song -- as you know, he likes to

take out his guitar and sing at the end of meetings --is really totally focused on breaking down the data silos is the key to the progress that we need to make.

So I'll close just by saying I'm aware that there's a lot at stake for many people for you to have success. I hope you'll come up with some great ideas but above all else, given our ability to measure things now, I hope you'll talk about how in this field, it's going to be vital that you share information across people that used to work sort of in a cloister by themselves. That's the way we're really going to make progress. So, while I can't stay for the day; I've got to go downtown now, I will carefully read and look at your slides because we really do want to back this effort and we wish you great success. Thank you.

(Applause.)

DR. KANNAN: Thank you, Dr. Califf, for sharing with us your prospective on this topic and the Agency's broader efforts to improve biomarker

1 development and regulatory use. To deliver the
2 keynote address today, we have Colonel Todd
3 Rasmussen from the U.S. Air Force Medical Corps
4 and also, he's the Director of the Department of
5 Defense Combat Casualty Care Program and also the
6 Professor of Surgery at Uniform Services
7 University.
8 COL. RASMUSSEN: Thank you very much,
9 Lakshmi, for the opportunity to briefly address
10 this group. Thank you to Allison, to the
11 Commissioner and others who have made this great
12 venue possible. I'd like to just spend 5 or 10
13 minutes giving the perspective of the Department
14 of Defense, the military's Combat Casualty Care
15 Research Program and specifically some of our
16 efforts in TBI which many, or most, in the room
17 are aware of or have certainly helped start or
18 initiate.
19 As I thank Allison and the FDA team, I,
20 like the Commissioner, want to give you some
21 homework to look up a couple of articles that we
22 won't have the opportunity to go into in the 10

1 minutes that I have but this is one of them. This
2 was an article that Allison and Suzanne Schwartz
3 commissioned. It was in the Journal of Trauma
4 late last calendar year and I think it aptly
5 discusses for the trauma and injury community a
6 strategically aligned FDA. And I think this is an
7 article that I would refer to you and in here,
8 just briefly, Allison and Suzanne emphasize
9 strengthening clinical trial expertise, many of
10 the things we'll talk about today, balance of pre-
11 and post-market data collection and then providing
12 excellent customer service which I think we're all
13 a beneficiary of this morning and throughout the
14 day. So thank you again, Allison, for hosting
15 this event and for those in the audience, I would
16 refer you to this article.
17 Now I have -- these are the old slides.
18 I've loaded a new one I think and I wanted to -- I
19 think it was in the -- and it matters because I
20 told Lakshmi I felt like a fellow last night
21 because I emailed Lakshmi my slides at 11 p.m. and
22 then I brought a new set of slides. I felt like I

1 was presenting for a visiting professor. As a
2 fellow, we'd always finish our case about midnight
3 and then the visiting professor came at seven and
4 you had to go round and tweak your slides before
5 the visiting professor came, and so that's sort of
6 what I felt like this morning.
7 So the overview today, and I think it's
8 relevant, is I have been asked to go over the
9 past, the present, and the future of TBI clinical
10 trials and biomarkers, lessons learned, and I've
11 been given 10 minutes. So for those of you who
12 are parents of teenage kids, you realize that this
13 is easy, right. Ten minutes is a luxury to go over
14 such a comprehensive topic in ten minutes. With
15 my two teenage boys, I usually get about three to
16 discuss their past, present, and future plans.
17 And so ten minutes will be just a piece of cake,
18 so
19 The past -- but I do want to give a little
20 perspective about military leadership in clinical
21 research and I take the history part of this
22 seriously. And I wanted to give you one anecdote

1 and I think it's a significantly important story
2 of military leadership in clinical research, and
3 it's the story of Champ Lyons who was at Harvard
4 Medical School and at the Massachusetts General
5 Hospital as a surgical trainee in the late '30s
6 and early '40s, and he was, of no coincidence, a
7 surgical trainee of Dr. Edward Churchill who was
8 another great translational researcher in shock at
9 Mass General in the early part of World War II.
10 And so Champ Lyons was one of his understudies at
11 that time, and he developed a particular interest
12 in microbiology. And at that time -- again, for
13 those of you have read Malcolm Gladwell's book,
14 Outliers, you talk about timing, everything is
15 timing -- and Champ Lyons happened to be at Mass
16 General with an interest in microbiology working
17 with Churchill, the great World War II sort of
18 translational researcher at the time of the
19 Cocoanut Grove fire in Boston.
20 And so his interest in microbiology and
21 his involvement in the treatment of those patients
22 in 1942 and the early availability of penicillin

1 led to the clinical research and study of
2 penicillin, really which was forward -- which was
3 pushed, in large part, certainly by the Cocoanut
4 Grove fire but then by the Army who, at the time,
5 was experiencing a large burden of wartime injury.
6 So Army Surgeon General then, James McGee,
7 authorized experimentation in the treatment of
8 soldiers with this new drug. That started when
9 Champ Lyons was commissioned as a major and led
10 this new unit for penicillin study at Bushnell
11 General Hospital in Brigham City, Utah. This is a
12 photograph of that hospital.
13 And so what we had here was a
14 combination of a large burden of injury, a supply
15 of a recognized new drug and technology to advance
16 the knowledge, in this case, of wound management
17 and infection. And we detail this -- this is the
18 second paper that I'm assigning to this group; I
19 had to do my homework; you have to do yours. This
20 is an article that was led by Basil Pruett who
21 really is, in many ways, one of contemporary
22 fathers of burn sepsis care, and this was

1 published in the last year's Journal of Trauma
2 Supplement where he outlines the studies that were
3 performed under the direction of Lyons where he
4 really established penicillin dosages and
5 schedules and indications that was really pushed
6 by the military. And I tried to find the article
7 that was in 1943 JAMA and I couldn't do that in
8 the early hours of the morning but I do want to
9 find that because I suspect that's an interesting
10 historical paper by Champ Lyons to read.
11 Champ Lyons was awarded the Legion of
12 Merit in 1944 for his management of combat injured
13 advances he made and this is a photograph of him.
14 And when I first saw this, I had -- I thought of
15 my mentor and friend, Colonel Dallas Hack because
16 this looks like Dr. Hack -- Colonel Hack. And I
17 thought, boy, Colonel Hack has been in the
18 military -- he had been in the military a long
19 time but I didn't realize he had gotten the Legion
20 of Merit in 1944, so I'm glad Colonel Hack's here
21 and But this is the story of Champ Lyons.
22 So that's past. I needed to talk to you

a little bit about past and what they found and what Champ Lyons talks about, I think, is the formula for successful clinical research is a significant clinical problem, a burden of injury, available patients, integration of clinical and laboratory scientists, and that really, even in those early descriptions of penicillin study resulted in improved outcomes and decreased mortality. And, of course, that sounds familiar to us today as we consider the study of traumatic brain injury, the use of biomarkers in clinical study.

So here is the modern-day burden of injury. So this is present. This is the modern-day of wartime injury that has propelled our interest in study of TBI; again, led by and started by many in this room. The -- what we learned during this year, we've learned the value of the Defense Centers of Excellence, the clinical bedside. We've got to be linked to the bedside of combat casualty care. Science that's not linked to the bedside in real clinical problems is often

1 adrift. We've learned the value of a dedicated
2 requirements-driven top- down medical research
3 program. And then I think we've learned the value
4 of the Uniform Services University, America's
5 medical school is the academic foundation for the
6 military, at least as our military university.
7 So this is -- I was with a different
8 group of professionals a week ago and they were
9 lamenting the failure of clinical trials and this
10 was not TBI but I'll ask you to make a guess as to
11 who this might be. They showed this exact slide.
12 They were lamenting that out of 72 multi-center
13 RCTs in this topic area, only 10 had reported some
14 sort of positive signal or impact on mortality, 7
15 reported a detrimental effect, but 55 showed no
16 effect and they were lamenting the failure of
17 clinical studies in this area. So I'm not sure if
18 you could guess what this might be but in this
19 case, it was intensive care. And they were
20 talking about the multi-center RCTs that existed
21 in ICU care for sepsis, for management of
22 pulmonary failure, organ failure, and infection in

1 the ICU, and they were lamenting the challenges of
2 conducting clinical research in a heterogeneous
3 population. And I would refer this article by
4 Jean-Louis Vincent in Critical Care Medicine is
5 talking about the challenges with controlled
6 trials in the ICU setting.
7 So why do they fail? Well, in this
8 article and this audience knows, maybe ineffective
9 interventions; the wrong time interventions
10 including dosing maybe with medications or
11 biologics; lack of power or they're powered
12 incorrectly; the diversity of heterogeneity of the
13 injury and condition certainly applies to
14 traumatic brain injury; less than appropriate
15 endpoints, and I think we'll talk about that
16 throughout the day; what are the most appropriate
17 endpoints and then as I mentioned, a heterogeneous
18 population.
19 So the current or recent past, you know,
20 this audience has been involved with and certainly
21 is aware of the challenges of the protect --
22 series of protect trials and the endpoint of the

extended Glasgow outcome scale at six months and the challenges that affords to determining and clarifying the effects, in this case, of progesterone, the synapse trial and the series of work that went into this. Similarly, the endpoint was a clinical outcome scale at six months; again, limiting the ability for us to identify effects, in this case, of progesterone but these endpoints are also very difficult for other modes of clinical study, be they biologics or resuscitation maneuvers or others.

So how do we overcome the pitfalls? We need better endpoints. We need realistic endpoints. We need ideal goals, ones that set us up for future success. We need to consider, I believe, implementation of theragnostics and I think the definition of theragnostics is well-known by this group but I think important in the coming lectures; identify the sweet spot of the study population; maybe alternatives to RCTs. This -- so maybe a pragmatic comparative effectiveness study may have a role in this and I

1 think that that is something for us to consider.
2 I think that forums like this are very
3 important. Today, what we'll be able to do is to
4 leverage, really, the power of the community. I
5 think we can, hopefully, make inroads into the
6 power of community over individual efforts or ego
7 and bring this together. I think this is how we
8 overcome pitfalls.
9 And then lastly, I had actually
10 rearranged these bullets because I think all of
11 those four or five things need to b done before we
12 increase maybe the volume of studies. We need to
13 understand those top four or five points before we
14 increase, just launch into the higher volume of
15 studies.
16 So this is an article that does talk
17 about targeted biological therapy. This is
18 theragnostics and we'll spend most of the day
19 defining what this is in respect to biomarkers,
20 biologically targeted therapies. The Euphrates
21 trial, a little more homework for you, to look at
22 this trial in sepsis that is using circulating

biomarkers for the study of management and treatment of sepsis. Really, the Euphrates trial is the first biomarker-based clinical study in sepsis. It's halfway through enrolling right now and I would encourage us to become familiar with the Euphrates trial if we're not. Again, I have been referred to this and have been reading and learning about this but really, it's the first sepsis trial designed for the use of a biomarker -- circulating biomarker for enrollment and then therapy effectiveness. It's a theragnostics approach and really, as this group knows, and we'll talk today, circulating biomarkers provide us an opportunity to move beyond, really, a syndrome-based definition and inclusion.

So again, the power of community. I appreciate the opportunity to be here, Allison and the Commissioner and those others in the room who've organized this venue, and our program is appreciative and we look forward to a great day here. So thank you very much.

(Applause.)

DR. KANNAN: Thank you, Colonel, for walking us through the history and lessons learned from clinical trials in TBI and also sharing your perspective in overcoming some of the pitfalls in this field.

So now I just want to give a brief overview on the workshop topics. So to give you a quick flavor and walk you through some different themes of today's workshops, FDA recognizes the value of supporting biomarker development in TBIs. So we have actually designed this workshop into four themes and in the morning session, we will cover Theme 1 and 2. Theme 1 is on examining the potential biomarkers such as neuroimaging or the blood-based biomarkers as well as the emerging techniques such as the EEG, etcetera, and address the evidentiary gaps, challenges and some recommendations associated with the clinical and analytical validation.

And in Theme 2, it's the regulatory considerations for biomarker development and we have some FDA and C-Path folks talking about this.

1 And after lunch, we will cover 3 and 4
2 and Theme 3 is how we can advance the knowledge
3 from patients' experience focusing on
4 incorporating patients' input into research and
5 the mechanisms available for doing so.
6 And the last part of the workshop, we
7 will address strategies for improving data
8 standardization sharing and application of big
9 data analytics. One of the key challenges in the
10 field of biomarker development is the issue of
11 data sharing and this session. The last session
12 will provide an opportunity to discuss what these
13 barriers are and identify strategies to possibly
14 address these barriers.
15 And so I just wanted you all to know
16 there is no Q and A after each talk. Instead,
17 after a set of talks, we have a separate Q and A
18 session where audience can pose questions to the
19 speakers or make comments. And panel sessions
20 will be moderated and the formatis an
21 interactive dialogue fashion and each panelist and
22 commentator should identify themselves before

speaking. And we have a set of questions directed to the panelists and if time permits, members of the audience can pose questions or make comments.

Given we have close to 300 attendees, it's possible that we may not be able to hear everyone's thoughts, questions, comments so I highly recommend them to submit their input in the public docket which will be available for the next two months until May 3rd.

And I also want to mention that at FDA-sponsored or organized programs, presentations are not endorsements or recommendations for a specific product or service. Participation in an FDA workshop by an individual or an organization does not imply any endorsement by the FDA.

And just a few housekeeping items. This meeting is being webcast live to the registered public so a recording transcript and slides of the workshop will be published on the workshop website after a few weeks. And there is a concession kiosk at the registration lobby where you can purchase food and beverages, items including

during the break or at the lunchtime and a guest wifi access is available in the guestroom area and the code is "public access."

And any questions, I'm right here. Find me and I'll be happy to answer. And with this, I would like to invite our next speaker, Dr. Geoff Manley, who is the Principal Investigator of the TED/TRACK-TBI and also the Chief of Neurosurgery at
UCSF.

DR. MANLEY: Great. Thanks, Lakshmi. So I think this is really a momentous occasion. I think this is a turning point for the field. Many of us have been in this field for many, many years now and I think there's a sense of opportunity and, really, this idea that we really can possibly make a difference. So we're going to hear quite a bit about TBI biomarkers from some of the other speakers in the session this morning. And I just wanted to take us through just a little bit of an introduction and really a call to why we need to make a difference here.

As Colonel Rasmussen just pointed out, traumatic brain injury has been one of the signature injuries of the conflicts in Iraq and Afghanistan and these continue. With the unstable world that we live in, there are no signs of this letting up so this is an area that we need to stay focused on.

In addition, anybody who's watched the news in the last six months, we've been inundated with what is the impact of concussions which, in my opinion, is on the spectrum of mild TBI. We don't even know what the estimates are. The coding for this is poor but the CDC estimates between 1.6 and 3.6 million concussions every year. We have at least 2.5 million people coming to our emergency departments very year that are being coded with traumatic brain injury as a diagnosis code and we know from several studies that we're probably missing a substantial portion of these patients because we don't really screen adequately for mild TBI and concussion.

And finally, even though the news has

1 really been dominated by our younger men and women
2 in the service and our athletes who tend to be
3 younger folks, really, one of the biggest things
4 that we've seen in the community is a rapid
5 increase in the number of folks over the age of 65
6 with trauma. In fact, in many hospitals, this is
7 their most rapidly growing population that we
8 have, often referred to as the "silver tsunami."
9 They have the greatest rate of hospitalization.
10 TBI-related fatality is twice as high for those
11 over 65 and research is sorely lacking. If you
12 look in the literature, less than one percent of
13 the patients have been -- papers that have been
14 written cover this population and we really don't
15 have any idea what to do and this is a big issue.
16 So when we look at traumatic brain
17 injury in 2016, this is a complex and
18 heterogeneous disease, as Colonel Rasmussen just
19 discussed. We've used a classification system or
20 a way to stratify these patients using the Glasgow
21 Coma Scale which was developed over 40 years ago
22 now. And we use terms like mild, severe concussion

1 and we use an equally crude outcome measured
2 called the "GOS." And we talk about things like
3 death and vegetative state and good recovery, and
4 we take what's an eight point scale and we
5 dichotomize it to make it even more crude than
6 what it already is. And clearly, I think a lot of
7 us believe that we can do a better job.
8 For those of you who aren't so familiar,
9 we use this coma score and we break it down into
10 three different groups. So if you've got a GCS of
11 13 to 15, you're mild; 3 to 8, you're severe. We
12 look at things like alteration of consciousness,
13 loss of consciousness, etcetera. So there's a
14 spectrum in mild being concussion at that one end
15 and severe really being comatose patients.
16 So if we look at an area of medicine
17 that I think has been very successful and is used
18 -- data sharing is used, very granular methods to
19 look at this. When we look at cancer today, this
20 classification employs multiple biomarkers whether
21 they're anatomic, physiologic, metabolic,
22 immunologic, genetic; you know, breast cancer is a

1 great example and that many of these cancers now
2 we've become so precise with our diagnosis that we
3 whittle this down to where we have a very targeted
4 treatment.
5 And yet today, with traumatic brain
6 injury in 2016, we take one of the most
7 complicated injuries and the most complicated
8 organ in the body and we basically dumb this down
9 to mild, moderate, and severe. Can you imagine us
10 trying to develop a treatment for cancer with
11 mild, moderate, or severe? No, we would not and
12 that's one of the reasons why I think that we're
13 failing and we have to do a better job at
14 stratifying these patients, enriching them for
15 subgroups that are going to be likely to benefit
16 from the treatments that we're looking at.
17 I show you this just to show you six
18 different examples of severe TBI. You don't have
19 to be a neuroradiologist to look at this picture
20 and to see that all six of these scans are
21 actually quite different. So to think of a
22 treatment or a drug or an approach that's going to

1 cover all of these patients I think is really
2 naive. Now certainly, TBI biomarkers hold great
3 promise for refining this. I just showed you an
4 imaging biomarker and you're going to hear more
5 about some of the advanced imaging biomarkers, not
6 only with CT scans but also with MRI where this
7 technology has greatly advanced over the last 10
8 years. Lots of opportunities with bio-fluids.
9 We've seen the role of troponin in the treatment
10 of cardiovascular disease, and I believe that
11 we'll probably find other brain-specific proteins
12 that will help us along not only with our
13 diagnosis but with our prognostic abilities and in
14 many neurophysiologic approaches. And I just
15 showed this -- I mean an EEG approach but
16 obviously, there are ways to look at blood flow,
17 etcetera. So there are many other
18 neurophysiologic approaches to this.
19 Now, as we just talked about, we have
20 really had a trail of tears, if you will, the
21 valley of death, whatever term you want to use for
22 clinical trials in traumatic brain injury and at

1 present, there are no effective drug treatments
2 for acute traumatic brain injury. Really, the
3 only effective treatment that we have is
4 essentially surgery. You know, we have some
5 hyperosmolar fluids which were introduced by Weed
6 and McKibben in 1917, so it's been almost 100
7 years since we've come up with a new drug. One of
8 our most valuable drugs is probably normal saline
9 to help people with their blood pressure. So
10 we've got a long way to go.
11 And I think that a lot of people have
12 looked at things like the GCS as being too crude
13 to stratify but also, I think that we need to look
14 at the GOSE as also being a crude measure that we
15 can probably improve upon.
16 So Colonel Rasmussen the ProtecT study
17 and this was a study that many of the people that
18 I'm looking at in the room today were involved
19 with, and there was a lot of hope for the
20 progesterone study. There had been discussions
21 that we couldn't run a clinical trial because our
22 care was too variable. And I was head of the

clinical standardization team, was on the phone, really, almost every day, emails every day really trying to make sure that we were standardized and we followed every transgression. We did a very good job with this and yet this study was halted for futility. There had been over 200 pre-clinical studies in multiple animal models showing that this drug had multiple effects in improvement of outcome.

But let's look at this a little bit more carefully and maybe learn from this as to what happened with our lost in translation here. We were using rodents in many of these studies. They were litter mates. We had a very precise injury that we were making with a controlled cortical impact device and yet when we went to the human study, we looked at the study, there were patients between 17 and 94 years old. We had a GCS of 4 to 12. We had DAI in this study. We had diffuse swelling in this study. We had contusions and hematoma; again, that same smattering of injuries that I showed you in the six- panel slide. And,

1 you know, we don't do a GCS in rodents, okay; so
2 there's no translation between this model and the
3 rodents and how we're looking at the outcome in
4 the patients.
5 Furthermore, one of the primary outcome
6 measures that was being used with this is the
7 Morris water maze and this is a test of memory and
8 learning. This is an example of some of the date
9 from one of the progesterone studies, the Morris
10 water maze. What you can see here is there's
11 actually 10 serial measurements being done with
12 the Morris water maze to look at the effects of
13 progesterone. But what did we do in the
14 progesterone study? We looked at a GOSE at six
15 months, a single measure as opposed to serial
16 measures that were done with memory and learning,
17 and we used the GOSE.
18 So for those of you who aren't familiar
19 with the GOSE, and I know many of you are but for
20 those that aren't, this is a question that's
21 administered in the GOSE. This is question 3(a).
22 This can be asked either of the individual or by

1 the surrogate, say, for example, the significant
2 other. And the question is, "Are they able to shop
3 without assistance?" And this includes being able
4 to plan what to buy, take care of money
5 themselves, behave appropriately in public. How
6 does this relate to a Morris water maze? And I
7 always like to joke that I probably would fail
8 this if you talked to my wife.
9 I think I can shop independently but I
10 haven't been allowed in Costco by myself for at
11 least five years so, you know, maybe I'm not able
12 to shop without assistance. And I say this
13 jokingly because again, how do you go from a
14 Morris water maze to, you know, this sort of
15 disability measure which basically is not brain
16 specific. And we'll hear a little bit more about
17 that from Harvey Levin, that there are other
18 things that feed into this: your physical
19 disabilities, etcetera, so this is not a brain-
20 specific measure.
21 So I'll close by saying that I think
22 this is an inflection point in the field. We

1 started this, and I'll talk a little bit this
2 afternoon, really back in 2007 when we began to
3 question mild, moderate, and severe as a way to
4 stratify these patients. We've morphed through
5 several studies into the TBI endpoints development
6 grant where we're beginning to look at this
7 endpoints not only in terms of the biomarkers but
8 also the clinical outcome assessment tools and I
9 think that actually, the glass is half full here.
10 We have plenty of tools at our disposal.
11 We can borrow from cardiovascular. We can borrow
12 from cancer. There are many things. There are
13 informatics tools that are out there and I think
14 really what this is going to require is for the
15 field to come together, for us to work together in
16 large teams not only because we need to make some
17 progress but most importantly, our patients are
18 desperate for this. For those of you who take
19 care of patients like I do, not a day goes by that
20 I get an email from somebody somewhere that's
21 suffering from traumatic brain injury. And
22 there's a lot of disability. There's a lot --

1 over five million people in this country are
2 disabled by this; estimates of over $70 billion a
3 year. There is clearly a need for us to make a
4 difference and I think that, you know, we're not
5 going to fix this overnight. We need to take baby
6 steps but with these very small steps over time, I
7 think we will make a difference.
8 So thank you very much and I look
9 forward to speaking with you today.
10 (Applause.)
11 DR. KANNAN: Thank you, Dr. Manley, for
12 the very nice perspective and the overview and
13 also leading the efforts in the TED/TRACK team.
14 And we are very thrilled to have this partnership
15 with the TED and TRACK-TBI.
16 And now we have Dr. Esther Yuh, who is
17 the Associate Professor in the Department of
18 Radiology and Biomedical Imaging from University
19 of California.
20 DR. YUH: Thank you, Lakshmi. Good
21 morning. Today I'm here to talk to you about
22 neuroimaging biomarkers. So first, a quick case

1 study. This was a 27-year-old woman seen in our
2 county hospital. She had been found down near her
3 bike with a Glasgow Coma Scale of 13 on emergency
4 department arrival. So her non-contrast head CT
5 showed just some trace blood products over the top
6 of the brain, on top of the brain, not actually in
7 the brain substance so the final read was that
8 there was some trace blood outside the brain but
9 not actual brain parenchymal injury. She actually
10 didn't do well after discharge. She had
11 persistent memory problems, sleep difficulty. She
12 couldn't return to work.
13 So she underwent brain MRI after about
14 two weeks after injury that showed a spectrum of
15 injuries. Here in the lower left corner, there
16 was a hemorrhagic contusion of the hippocampal
17 head. She also had multiple foci of white matter
18 injury, both hemorrhagic as shown here as well as
19 non- hemorrhagic in the brain stem, so many
20 unsuspected injuries in the actual brain substance
21 that were not seen on the clinical head CT.
22 So this is a quick outline of what I'll

1 be talking about today: the need for biomarkers
2 in TBI and in particular, I'll be talking about
3 imaging biomarkers. So first, I'll discuss
4 quickly what structural neuroimaging is. So what
5 is structural neuroimaging? So that's basically
6 imaging studies that you can see macroscopic
7 findings on, so a neuroradiologist or radiologist
8 or any trained clinician who sees these studies a
9 lot can actually identify by eye the actual
10 abnormal findings. That's opposed to some of the
11 more advanced MRI imaging techniques that you will
12 hear about in the next talk by Dr. Marinelli where
13 you need some extensive post-processing offline or
14 a quantitative analysis. These are things that
15 you can actually just look at and see by eye.
16 So currently, CT is the current standard
17 of care for clinical neuroimaging. MRI is much
18 more sensitive as I'll show later in the talk but
19 is done less commonly clinically and more often in
20 a sub- acute timeframe after injury.
21 So structural neuroimaging is actually -
22 - so the findings on structural neuroimaging,

1 there was a multi-agency working group that
2 convened most recently in 2012 and established a
3 set of common data elements for these different
4 types of structural injuries that you would see on
5 imaging. And the CDEs were very strictly-defined
6 distinct pathological entities. So it was
7 actually 25 common data elements that described
8 all of the range of pathological findings that you
9 might see. There's actually only about 10 or so
10 that you would see commonly of the 25. The others
11 are quite rare. These are the most common, in
12 particular, that we see, these entities that I'm
13 showing on this slide.
14 And to give you a flavor of what some of
15 these might look like, this is epidural hematoma.
16 This is a subdural hematoma and midline shift,
17 hemorrhagic contusions, subarachnoid hemorrhage,
18 and traumatic axonal injury. So as you saw in Dr.
19 Manley's talk just recently -- previously, these
20 actually look different. They're very distinct
21 pathological entities. And then similarly on MRI,
22 you have different imaging appearances of these

1 different entities, so traumatic axonal injury,
2 hemorrhagic axonal injury, and hemorrhagic
3 contusions are all different pathological CDEs.
4 So how often do you see these actual
5 CDEs in clinical practice? If you look at a
6 civilian TBI population, which is what we did with
7 Dr. Manley's TRACK-TBI pilot study a few years
8 back, these are actually very common, some of
9 these common data elements. So this shows the
10 spectrum of CT common data elements in a civilian
11 TBI population and shows in "blue" here that
12 they're actually quite common some of these
13 entities, particularly, subarachnoid, subdural
14 hemorrhage contusion. And if you do MRI, you see
15 that there is even a larger number of
16 abnormalities that are seen, particularly shear
17 injury in the white matter but many of the other
18 entities also are seen more commonly on MRI.
19 So these CDEs actually -- practically,
20 you do see them quite commonly in a TBI population
21 and this is just in mild TBI, so these findings
22 were actually -- these are only the mild TBI

1 component of the population so quite common even
2 within mild TBI and would be even more common in
3 moderate or severe
4 TBI.
5 In summary, CT is the standard of care
6 and MRI is much more sensitive but is done less
7 commonly clinically.
8 Second point I'll talk about today is
9 that neuroimaging biomarkers have been formally
10 qualified by the FDA for use is TBI clinical
11 trials. So as a second quick example, this is a
12 24-year-old female bicyclist who was hit by a car.
13 Her head CT was actually read as completely
14 negative. However, in the hospital, she was
15 admitted and she was actually combative and had
16 some -- she actually ended up having a seizure.
17 She was combative with the staff and because of
18 that reason, after about a day-and-a- half, she
19 underwent brain MRI in the hospital. And the
20 brain MRI showed multiple foci of white matter
21 injury on her diffusion-ordered images and her
22 susceptibility-rated images, so unsuspected brain

1 substance injury.
2 So these two examples that I showed, in
3 summary, according to the current FDA standard,
4 CT. So no imaging biomarker has been qualified
5 formally but CT positive and negative has been
6 accepted based on its widespread use clinically
7 for many years. So by the FDA standard, the only
8 -- these two different patients would be
9 classified by imaging as simply CT-positive and
10 CT-negative despite the wide range of injuries
11 that they actually demonstrated on their imaging
12 studies.
13 So the third and last point I'll talk
14 about is I'll show some of the data that we have
15 that substantiates our pursuit of imaging
16 biomarkers for FDA qualification. So the first
17 step in this process, inter-reader reliability of
18 the imaging CTs. So we need to actually demonstrate
19 that different people looking at the studies,
20 trained eyes, actually identify the same findings
21 and classify them in the same way. So we did this
22 by using special software to -- and we had three

1 different neuroradiologists from different
2 institutions rate a set of about 20 CT and MRI
3 scans from TBI patients across the spectrum of
4 injury and actually demarcate on each scan the
5 abnormal finding and what they would actually call
6 it using the CDE classification system. Then we
7 can incorporate all the different
8 neuroradiologists' findings into the same scan and
9 use different colors to show what each different
10 radiologist marked to compare their results.
11 And so here, this is an example of a
12 hemorrhagic contusion, this bright white focus in
13 the right orbital frontal brain. And different
14 radiologists used different techniques to
15 demarcate the lesion but you can see there's
16 pretty good inter-reader liability in terms of the
17 location and the actually pathology. There is
18 some slight variation in the terminology but the
19 lesion was denoted similarly by all the
20 radiologists.
21 This was almost a perfect match,
22 different radiologists demarcating here in

1 different colors multiple foci of hemorrhagic
2 axonal injury in the subcortical white matter.
3 And then finally, midline shift, which
4 is another important CDE measured by the three
5 different neuroradiologists and you can see that
6 the measurements correlated very well.
7 For CT, similarly, this is traumatic
8 hemorrhagic axonal injury in the subcortical white
9 matter in the left frontal lobe demarcated in the
10 same way by the different neuroradiologists;
11 hemorrhagic contusion on head CT also demarcated
12 similarly; and finally, severe downward cerebral
13 herniations, another important CDE in severe TBI,
14 and that was demarcated very similarly by the
15 three different readers.
16 So if you take all of these ratings by
17 the different readers and calculate a capped
18 coefficient which is the measure of inter-rater
19 reliability, it actually turns out quite well.
20 This is only on a set of about 20 head CT exams
21 but so far we have excellent reliability that
22 we've seen for some of the findings. There are

1 some that don't perform as well and this is the
2 basis for some feedback that we'll be giving back
3 to the next meeting of the imaging CDE working
4 group. But for the most part, many of these CDEs
5 do very well in terms of their inter-rater
6 reliability. So a cap of .8 and above is
7 considered excellent reliability.
8 For MRIs, similarly, many -- most of the
9 pathoanatomic findings, the CDEs demonstrate very
10 high inter-rater reliability.
11 So this is just preliminary data given
12 that it's been performed only on about 20 scans
13 each, CT and MRI, but we think that this is strong
14 preliminary data showing that these are very
15 promising in terms of the ability of radiologists
16 to actually find the same findings on these TBI
17 scans.
18 So the second step and the second set of
19 (inaudible) data I'd like to show is regarding the
20 prognostic significance of these imaging CTs. So
21 what happens if you actually use these imaging CDs
22 and try to predict outcome in TBI patients? So

1 this shows the ROC curves for -- so random
2 guessing is shown here in "blue" with an area into
3 the curve of a .5. And this is what happens, in
4 "green," when you use clinical and demographic and
5 socio-economic data to try to predict outcome in
6 mild TBI patients. This is also from the TRACK-TBI
7 pilot study, Dr. Manley's study from several years
8 ago, and shows that if you use clinical and
9 demographic predictors alone and socio-economic
10 data, then you get a significantly better
11 prediction than random guessing. And keeping in
12 mind here that the outcome measure isn't perfect
13 so there's going to be some variability that's
14 associated with just the outcome measure itself,
15 the GOSE which I think Dr. Manley alluded to
16 earlier.
17 So then if you add CT structural
18 biomarkers on top of that, so not instead of but
19 on top of these demographic predictors, you get
20 another boost there into the curve. And then
21 finally, if you add MRI, a two-week MRI on top of
22 all of these other predictors, you get an

1 additional boost within a final area into the
2 curve of about .71. So we think this is very
3 promising, particularly given that there's going
4 to be inter-rater -- there's going to be some
5 variability that's associated with the outcome
6 measure itself which isn't perfect.
7 And odds ratios, you can calculate for
8 these and show that some of the imaging CDEs are
9 very strong predictors for three-month outcome in
10 particular brain contusion axonal injury and
11 subarachnoid hemorrhage.
12 So we think that this shows, for the
13 second step, strong preliminary data that I very
14 suggestive that MRI and CT structural imaging
15 biomarkers have prognostic validity for outcome at
16 three months.
17 So we've done this on the order of 10s
18 to 100 patients and the next step is to validate
19 these steps, these same steps in a much larger
20 population and that's the plan with the TED
21 metadata set in our upcoming work. Instead of 10s
22 of patients to 100 patients we'll be performing

1 these same types of analyses on over 1,000
2 patients across the TED metadata set which
3 consists of multiple component studies, some of
4 the major TBI clinical studies over the past
5 decade.
6 //
7 So in summary, talked about structural
8 neuroimaging, what is that, and some of the
9 definitions of the CDE biomarkers, neuroimaging
10 biomarkers, the fact that no neuroimaging
11 biomarker has yet been formally qualified by the
12 FDA although CT-positive and negative are
13 accepted, they've been grandfathered in based on
14 their widespread clinical use; and then finally
15 showed some preliminary data establishing inter-
16 relater reliability of the CT and MRI CDEs and
17 also showing promise for the prognostics
18 significance of these biomarkers. Thank you very
19 much.
20 (Applause.)
21 DR. KANNAN: Thank you, Dr. Yuh. That
22 was a very nice talk. And our next speaker is Dr.

Luca Marinelli. He is a Program Manger in the Healthcare Commercial Partnership at GE Global Research Center.

DR. MARINELLI: Good morning. Thank you, Lakshmi, for the introduction and for inviting me to speak here.

I would like to present today on a clinical research study that we are running as part of a partnership between GE and the NFL in mild traumatic brain injury.

These are my disclaimers. I guess the only thing relevant to the discussion today is that nothing that I present here is FDA-cleared or available commercially for sale. This is entirely investigational.

The idea behind the clinical research study that we set out to accomplish is to basically look at advanced MR Imaging biomarkers that could be useful for acute and subacute TBI patient management. In particular, we're interested in establishing correlations between imaging features and clinical measures of the

1 disease, including measures of (inaudible) and
2 symptoms. Ultimately, we hope to be able to
3 develop obligations that are going to be helpful
4 in the clinical management of mild traumatic brain
5 injury. But again, at this stage, it's really at
6 the level of figuring out what we can tell beyond
7 the structural imaging features that we've seen in
8 Dr. Yuh's presentation.
9 //
10 The way the study is organized is a longitudinal
11 study. We recruit subjects at -- this was the
12 first phase of the study where we're recruiting
13 subjects at three sites, three clinical sites,
14 Hospital for Special Surgery in New York City,
15 UCSF in San Francisco, and Houston Methodist. The
16 subjects, when they come in, they undergo an MR
17 scan. It's a comprehensive -- I'll describe this
18 in detail, but it's a very comprehensive brain
19 scan. The scan is reviewed by a radiologist for
20 structural imaging features, abnormalities that
21 may be present as well as then post processed
22 through a number of quantitative analysis

1 paradigms. We also collect clinical data both as
2 far as symptoms are concerned as well as some
3 memory and cognitive tests. This component has
4 changed significantly between phase one and phase
5 two of the study and I'll show basically what we
6 used initially and what we're planning to do with
7 the data from the second phase.
8 The data is collected at four time
9 points. We recruit subjects either within the
10 first 72 hours from injury or within the first
11 week and then people are scanned again at about
12 three weeks and at about three months out. The
13 inclusion criteria are basically what Dr. Manley
14 showed for mild traumatic brain injury. We
15 focused on an age range of 15 to 50 years old and
16 depending on -- different sites had different
17 recruitment strategies so the population are
18 slightly different between the sites but at the
19 end of the day, we're looking at the very mild
20 spectrum of mild traumatic brain injury. So every
21 subject we enrolled has GCS 14 or 15, and you can
22 see here on the chart on the left, the

1 distribution of symptom severity.
2 For symptoms, we used -- so for -- as an
3 outcome measure in phase one, we focused on the
4 sport concussion assessment tool and in
5 particular, we noticed that if we look at the
6 SCAT2 overall score and the symptom component, the
7 symptom component really dominates the variability
8 of the score, so we decided to use that as an
9 outcome measure to correlate imaging features to.
10 We can look at the maximum score over
11 the four encounters and that's the y axis on the
12 chart here on the left. And then here we're
13 looking at the slope, so how fast these scores
14 change. And you can see in the "spaghetti chart"
15 here that these people do get better although they
16 are still quite - - many of them are still quite
17 symptomatic even at three months out.
18 The imaging protocol that we use is --
19 has a structural imaging component. That's
20 basically what Dr. Yuh showed in the MR imaging
21 part of her talk with T1-T2 flare and
22 susceptibility weight at imaging. We also include

1 -- some of these images are looking a little funny
2 -- but we also include profusion imaging with
3 (inaudible) labeling and we include connectivity
4 mapping through both (inaudible) MRI for
5 functional connectivity as well as diffusion
6 imaging for structural connectivity. For both
7 these sequences, we have made significant changes
8 in what is available, again, commercially.
9 And in particular, two big changes that
10 are relevant to the presentation are the fact that
11 for both of them, we're using a simultaneous
12 multi- slice acquisition sequence that basically
13 allows us to collect multiple slices of the brain
14 simultaneously. This impacts fMRI and diffusion
15 imaging in different ways. For diffusion imaging,
16 it just shorted the scan time so that effects, for
17 example, motion artifacts or in our case, allows
18 us to collect more information in the same amount
19 of time that you would a conventional DTI kind of
20 scan. For fMRI, it has a different impact. fMRI,
21 the point is that we're reducing the amount of
22 time that it takes to collect a single brain

volume from roughly three seconds to roughly one second, so your temporal resolution increases by a factor of three seconds to roughly one second. So your temporal resolution increases by a factor of three and I will show you an example how that's relevant.

For diffusion, as I said, we're using the additional time that we have at our disposal to collect more than -- typically data in diffusion sensor imaging is collected on a single shell in diffusion and coding space. We're collecting data here on three concentric shells at different b- values. This allows us not only to have much more accurate tractography but also to start having access to higher order measures of diffusion beyond the conventional (inaudible) that we're used to from diffusion tensor imaging. So, for example, we're able to access diffusional kurtosis as well as then be able to model the diffusion process and extract quantities like neurodensity, free water, isotropic and anisotropic components of diffusion. We're also

1 collecting spectroscopy data in -- for the sake of
2 keeping scan under check, we focused on single-
3 voxel of spectroscopy and we collect two voxels in
4 the anterior and parietal white matter.
5 And finally, we're using also -- this
6 image, it doesn't look right -- but we're using a
7 variation on a magnetization transfer technique
8 from Dave Alsip's (ph) group at Beth Israel that
9 basically is extremely specific to myelin. So
10 instead of highlighting water that's bound to any
11 kind of macromolecule, it really focuses on water
12 that's bound to sheath-type molecules, and it's an
13 incredibly specific marker for myelin so it allows
14 us to start looking at quantification of myelin.
15 We also process the susceptibility data
16 through quantitative susceptibility mapping
17 algorithm to, again, get access to quantitative
18 information of changes in susceptibility and not
19 just qualitative data from susceptibility imaging.
20 One important point that I should make
21 is that our entire population -- and as you saw
22 before, we have -- in phase one, we recruited 111

1 subjects - - only a handful, less than five
2 subjects showed any kind of pathoanatomic
3 abnormalities. All the other subjects are like
4 this woman -- I mean there are incidental
5 findings, there are normal variations, there are
6 congenital things that we find but at the end of
7 the day, injuries that we can associate -- changes
8 in the brain that we can associate with the injury
9 in this population are just not very prevalent.
10 it is, as I said, the mild spectrum of the
11 disease. It is not mild if we look at symptoms.
12 It is not mild if we look at how long these
13 subjects are affected by the disease. But it is
14 mild in the sense that if we look at conventional
15 radiological findings as were described by Dr. Yuh
16 before, we don't see any. These people, for
17 example, we look at this woman, 19-year-old female
18 who was extremely symptomatic. You can see the
19 symptom severity school here. Again, out of a
20 scale of zero to 132, this person was extremely
21 symptomatic, had to withdraw from her studies for
22 a semester, only at the end of the study really

was starting to improve in her symptoms and her scans were clean from the first day. There was nothing that we could find in conventional radiological examination that would point to the injury. So these are the kind of people that we're really focusing on and we're trying to see what we can learn from these additional contrasts that we bring to the table.

I will focus specifically here on two examples from (inaudible) fMRI for the sake of time just to show the kind of analysis that we can carry out and the kind of information that we are extracting and learning in the study. So with functional-MRI, we're focusing on measuring functional connectivity of the brain and changes in functional connectivity of the brain.

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So here we can see that, for example, in this population, we are able to correlate the average correlation coefficient, so how the brain overall is functionally connected and this correlates pretty significantly with the symptom severity.

1 You can see in "red" here where our healthy
2 controls are and how this average correlation
3 changes with symptom burden.
4 The next step in this analysis was to
5 start looking more specifically at individual
6 networks and in particular, the question that we
7 wanted to ask was if we look at, say, 14 major
8 networks that we consider in the brain and look at
9 not only how the individual network connectivity
10 changes but also how the connectivity between
11 networks changes, so looking really at TBI as a
12 disconnection or a changes in connectivity
13 syndrome between systems in the brain, if we could
14 identify networks that are particularly affected
15 by and correlated to some of the clinical symptoms
16 -- and we find, for example, -- so in order to do
17 this, we basically set up a machine-learning kind
18 of framework that allows us to identify out of --
19 basically, if you have 14 networks, you have 105
20 features, so we throw all these MRI scans in; it's
21 like 200,000 voxels per subject, 111 subjects,
22 overall 274 MR scans, throw it all in and see how

1 basically which networks are and which network
2 correlations are best predictors of the clinical
3 symptoms. And you can see that several between --
4 first of all, the main result is that between
5 network connectivity is more predictive than
6 within network connectivity. So the fact that
7 different systems, again, talk to each other and
8 how that talk in between systems is affected by
9 the disease is a better predictor than the
10 behavior of the individual systems and systems
11 that we find that are particularly affected in how
12 they talk to each other, for example, executive
13 control and visual processing, primary visual and
14 higher visual networks.
15 Interestingly, we find that even though
16 most of these changes decrease, the connectivity
17 decreases with how -- with clinical symptoms, we
18 also find a few where that connectivity actually
19 increases; in this case, for example, with the
20 default mode network which, again, kind of makes
21 sense because you expect that to take over when
22 other things are not working.

1 Just to show very quickly another
2 example, here we're looking at the time course of
3 the bold signal itself. This is the fMRI signal
4 that we then process to extract these connectivity
5 measures, but if we look at it just as a time
6 course and look at changes in the frequency
7 content of this time series between traumatic
8 brain injury and controls, we find that there is
9 quite a significant change in the fraction of
10 frequency content in the low frequency regime
11 that's usually considered for normal functional
12 connectivity. That's basically between 100th of a
13 hertz and a 10th of a hertz versus the entire
14 frequency spectrum. And we find that basically
15 there's lower power in the low frequency bands in
16 TBI patients. Not only that, we can find that if
17 we separate out the contribution in gray matter to
18 white matter, we say that this change is specific
19 to gray matter so it's not just a motion artifact.
20 We find in particular that it's not homogeneous
21 across the brains. And again, it highlights
22 particular networks that are more affected than

1 others by this change in frequency content and,
2 again, we're finding visual networks being
3 particularly affected as well as sensory motor and
4 salience network.
5 As I said, this is just an example in
6 functional-MRI. We find in diffusion imaging, for
7 example, that kurtosis seems to be a particularly
8 efficient indicator of change in the brain. In
9 profusion, we have seen effects that we reported
10 in the literature before of reduction in cerebral
11 blood flow in the acute and sub-acute period that
12 does not follow clinical symptoms. Basically,
13 clinical symptoms go away first and then cerebral
14 blood flow comes back as well as some results in
15 volumetric changes in subcortical gray matter
16 structures.
17 Very quickly, just to close, for the
18 phase two study, as I mentioned, we're planning to
19 recruit 300 subjects and 150 controls. The
20 subjects will be recruited now at six sites beyond
21 the first three ones. University of Miami,
22 University of Pittsburgh Medical Center, and

1 Medical College at Wisconsin have also joined in
2 this effort and the clinical assessment will be
3 much more extensive that will basically give us
4 access to clinical outcome measures that are more
5 specific to individual systems that will improve
6 the overall analysis. Thank you.
7 (Applause.)
8 DR. KANNAN: Thank you, Dr. Marinelli.
9 And our next speaker is Dr. Kevin Wang, the
10 Executive Director of Center for Neuroproteomics
11 and Biomarkers Research, and he's also the Chief
12 of Translational Research at University of
13 Florida, Gainesville.
14 DR. WANG: Thank you. Good to be here.
15 So what I wanted to talk to you a little bit about
16 is translation from the imaging to the bio-fluid-
17 based biomarker. So let me just start by saying
18 there are different types of bio-fluid-based
19 biomarkers, you know, ranging from protein to
20 microRNA, metabolomic and lipidomic (ph), so I don't
21 want to leave any one out. And -- but the most
22 advanced ones are currently being (inaudible) are

1 the protein biomarkers. And there are no less
2 than a dozen of them so some of those that are
3 more -- with more data are highlighted in "blue,"
4 you know, GFAP, S100 Beta, UCH-L1, Tau and then
5 there are number of other ones.
6 So the table at the bottom kind of just
7 to try and point out to you that the level of
8 evidence of the four top marker, TfAP, is from
9 glial cells and S1G Beta, also from glial cell
10 usage, (inaudible) from neurons and Tau and pTau
11 from the axons of neurons. And so it shows you
12 basically the evidence -- I don't know whether
13 this pointer works; yeah, that's okay -- that you
14 have animal data that -- from severe, the
15 different types of animal models, the evidence
16 exists that we can measure this biomarker in the
17 bio-fluid. As far as in human study, both
18 moderate and severe GCS of 3 to 12 and then as
19 well as the more mild TBI. So the evidence is
20 very strong but obviously, this is a more
21 generalized figure in terms of the detectability
22 of the elevation. And mostly, they are measured

1 either in CSF and/or blood by the way.
2 So this is just a pictorial why we need
3 so many different markers. The brain is complex,
4 right?. There are different cell types, neuron
5 astrocytes and (inaudible) dendrocytes. We heard
6 about that from the myelin and as well as some of
7 the structures, like axons and dendrites and also
8 synapses, so these are structures that are
9 potentially vulnerable and they could be
10 individually giving you a signal from a bio-fluid-
11 based biomarker standpoint.
12 UCH-L1 has been one that we work on with
13 (inaudible) one of those that we actually
14 contribute the original discovery as a good TBI
15 biomarker. It's mainly in the cell body so as it's
16 an attractive as it's relative specific to the
17 brain, and it's a small protein so we think it
18 actually has sort of a property of a biomarker.
19 So here, (inaudible). So how do we particularly -
20 - kind of our criteria of a good marker? So we
21 are looking at mRNA level, you know, because the
22 data is available in human, in rat, and other

1 species, so we can see the "blue" curve, the one
2 that are highly -- in the brain or CNS tissue.
3 And you can also look at protein expression, so in
4 different tissue types, so that's important.
5 And lastly, from the proteomic and mass
6 spectrometry, they are now from the human proteome
7 map organization. Now they put out tryptic
8 peptide mapping, so that can also give you
9 validation that the, you know, the (inaudible)
10 biomarker is brain- specific or not. So in this
11 case, it looks pretty good. And then GFAP, many
12 of you have heard about it, that it's been around
13 for a while but we kind of re-discovered is it's a
14 really robust marker for TBI. And they go for a
15 very complex -- I don't have time to go talk about
16 how it can go from the brain compartment to the
17 blood and flip over, you know, (inaudible) as well
18 as the lymphatic systems. So it's a very exciting
19 and potentially also in other neurological injury,
20 like stroke and spinal cord injury and again, very
21 highly specific and highly expressed in the brain
22 and from mRNA protein and also from mass

1 spectrometric peptide mapping.
2 Then the third marker I'd like to touch
3 on is Tau. You heard a lot of interest in chronic
4 traumatic encephalopathy, so this is one of the
5 potential major culprits in the formation from
6 both TBI-induced CTE. And, you know, there are a
7 lot of parallels with Alzheimer's disease and this
8 protein is supposed to be regulating microtubule
9 assembly but if it's hyperphosphorylated (inaudible), they
10 tend to fall off and maybe it forms aggregate.
11 And what we're hoping to do -- just so you know,
12 some of this measures level at different time on
13 post injury to see whether we can track the
14 potential formation of CTE or who are more
15 susceptible to formation of CTE. And this is, you
16 know, obviously, a very complex protein. There
17 are at least 10 different isoform, different
18 sizes, but this protein is actually pretty darn
19 brain-specific as well as highly expressed, so
20 that's very encouraging; again, from mRNA, tryptic
21 peptide and Western blot analysis.
22 And so my colleague, Dr. Hayes, will

1 speak next about in vitro diagnostic potential of
2 some of these markers, so I kind of just want to
3 skip over that so I can talk to you about the
4 newer parallel path, which is what we call the
5 biomarker qualification for the so-called context
6 of use biomarker and to assist therapeutic
7 development, s that kind of goes back to Colonel
8 Rasmussen's point about the theranostics.
9 So I'll just give you some examples. So
10 this is, again, the concept of combining of
11 therapeutic diagnostics. I think it's a very rich
12 area and, you know, in fact TBI is one of the
13 lading fields that we are doing this. So, for
14 example, this is a DoD-funded project, Operation
15 Brain Trauma Therapy, OBTT, and you can see Dr.
16 Kochanek and a number of other people I am
17 privileged to be involved in this study with.
18 So what this study does is they look at
19 three different animal models: CCI, a very high
20 focal injury; penetrating brain injury model, PBI,
21 and also, fluid percussion injury as well as some
22 micro pig fluid percussion injury. And then they

1 measure biomarker level, histopathology, as well
2 as functional outcome to formulate a score to
3 assess the -- so a low-hanging fruit, if you like,
4 of therapy that's been tried by a number of other
5 researchers that look promising to see whether we
6 can attenuate this outcome.
7 So this is an example showing in two
8 different models. First of all, you see that
9 after injury, there is an elevation of GFAP so
10 that's a good thing, in 24 hours and in 2
11 different models. But more importantly is in each
12 of these cases, nicotinamide is one of the drugs
13 we tried and also Keppra, another drug. There is
14 an attenuation of the level of the marker at 24
15 hours compared to just the TBI alone. So this
16 gives us -- this is exactly where wanted to go.
17 By the way, we didn't see this in every single
18 drug but this is another, you know, component of
19 the scoring metric, so this is very exciting. And
20 obviously, this study is still ongoing.
21 And then, of course, as Dr. Manley is
22 mentioning, there are also clinical trials in

1 parallel, and I want to highlight two studies.
2 One is interpret the 256 (inaudible) a neuron drug
3 that is in trial for severe TBI as well as you
4 heard about the progesterone trial. So both of
5 these are a biomarker assay component. So in
6 order to see whether -- again, in human now with
7 the therapy, you can reduce the biomarker level.
8 So one of the studies, the bio
9 progesterone study is completed or ended and so we
10 are very anxiously waiting for sort of a detailed
11 analysis. So they are -- I know they will be
12 talking to you -- elaborating on this but just to
13 point out, they are truly a different application
14 for just the sort of therapeutic development, two
15 components of biomarkers including diagnostic,
16 prognostic, predictive, pharmacodynamic, as well
17 as efficacy response.
18 So we'd like to kind of focus a little
19 bit on the low-hanging fruit, if you'd like. It's
20 the diagnostic and prognostic. So this is just to
21 show you CT we know is a really good marker for
22 indicating whether there's pathology. And what

1 this show you is that with GFAP, we are seeing a
2 very good correlation to CT abnormality; in fact,
3 a number of CT lesions so we're kind of exploring
4 that and we are working with assays and others to
5 see whether MRI-visible liver pathology also can
6 be correlated. So this is from two independent
7 studies. We're excited about that.
8 And then GFAP also seems to prognostic,
9 not as good as in, you know, CT correlation so in
10 terms of you can see that where it says TOSC, you
11 know, the higher of the GFAP level so we can, with
12 poor outcome, we reach an ROC of .74; you know,
13 you can push forward but I like the idea of
14 combining, you know, other components, maybe CT
15 and additional clinical data into the mix and
16 really try to improve it.
17 And so this is very new. I want to just
18 share with you -- and this is in collaboration
19 with Dr. Richard Rubenstein of SUNY Downstate and
20 we were able to assay very sensitively Tau which
21 is, you know, the CTE potential marker as well as
22 pTau and what we want to do is -- what we're

1 trying to look at is, again, the CT correlation.
2 And this one actually -- oh, sorry, this is with
3 severity, so severity we can see correlation is
4 very good in terms of identifying. Even with the
5 mild TBI GCS 13 to 15, we can distinguish that
6 from control so that's very exciting so -- because
7 we want to see, you know, whether we can pull out
8 those potential mild injuries.
9 And then in addition, CT -- and you can
10 now see particular pTau, the ROC is very good.
11 It's like .92 now, all right, so there's a clear
12 separation and a little bit less over total Tau.
13 And then in addition, just like GFAP or
14 GOSE, we look at both poor outcome, GOSE 7, we look
15 at GOSE less than -- 4 or less versus 5 to 8 and
16 again, we get a -- we can get a correlation for
17 pTau around .77. That's very good so this is very
18 brand new data, a little bit less -- so if you're
19 trying to look at the good outcomes, so 7 to 8
20 versus 6 or less. So -- but what we like to think
21 of is that, you know, if we can -- so remember,
22 these assays are done within the first 24 hours.

1 So if you can find patients that potentially --
2 and which patients that were poor outcome so you
3 can potentially stratify those patients into a
4 clinical study for a drug trial.
5 So that's sort of the direction we'd
6 like to take. So I think this is a very exciting
7 opportunity because, you know, you have biomarker
8 discovery validation, you know, coming from
9 academia, from consortium study, but we see
10 partnership from industry. So there are a number
11 of companies represented here that I personally
12 know if and both representing device development,
13 assay development, you know, be able to have an
14 assay system either for the qualification as well
15 as for a diagnostic and, of course, with our
16 funding agency partner, DoD, with NIH and now FDA.
17 And so I think this is really an opportunity to
18 really move the needle, using Dr. Manley's term,
19 for a TBI biomarker and supporting therapy
20 development and hopefully beyond so, thank you.
21 (Applause.)
22 DR. KANNAN: Thank you, Dr. Wang. And

1 our next speaker is Dr. Ronald Hayes, the Director
2 and Founder/President of Banyan Biomarkers.
3 DR. HAYES: So this is a unique humbling
4 opportunity for me today to go over, from almost
5 four decades of research in traumatic brain
6 injury, where we are today. And as I look across
7 the audience, I would not have anticipated the
8 structure and the progress that we have in front
9 of us.
10 So no disclosures of note and what I'd
11 like to do today actually is cover, as some of the
12 previous speakers, including Colonel Rasmussen, to
13 go over the history, at least as I've experienced
14 it, some of the clinical and regulatory science
15 and commercial considerations that are often
16 unattended to early on in the process of biomarker
17 discovery and validation as well as to point to
18 the future with new indications.
19 And I am able to point to my very early
20 career, actually, at NIH and then I moved in 1979
21 to Virginia Commonwealth University to establish
22 the first basic science lab looking at traumatic

1 brain injury. And at that time, we were very much
2 focused on severe TBI. The mustached person in
3 the center is me for those of you who may not
4 recognize him. And we really -- when I came there,
5 there were, in fact, no rodent models of traumatic
6 brain injury. It spoke to the very nascent field
7 at that time so we had to go at the task of
8 establishing rodent models of TBI, the first ones,
9 the cortical impact injury device, a fluid
10 percussion injury device, and variants of that are
11 now in use today.
12 As I moved on to the University of
13 Texas, I began working for the first time with
14 Kevin Wang starting to establish more deeply an
15 understanding in the biochemical events that
16 underlie trauma which at that point, were really
17 largely unknown. We were very much focused on
18 edema and physiological measurements. And that
19 collaboration and our interest in proteolytic
20 mechanisms underlying that led to Kevin and I
21 being at the University of Florida where our
22 collective interest in brain biomarkers

1 flourished. And it was at this time, actually,
2 that I was privileged enough to make contact with
3 Geoff Manley and Mona Hicks and much of the vision
4 that ended up as TRACK and TED TBI was a product
5 of those very early discussions.
6 And of course, after leaving the
7 University of Florida, Center for Traumatic
8 Brain Injuries, I moved onto Banyan with a growing
9 understanding that the academic exercises alone
10 would not be sufficient to change patient care.
11 So this is an important slide to me personally and
12 I think to the field. Here, of course, is 9/11
13 and as Dallas Hack has taken note, in fact, a
14 study of brain injury biomarkers was born that
15 morning. In a meeting with Frank Tortella and me,
16 it became apparent to us that the world had
17 changed and that this was going to affect our
18 management not only of combatants but civilians as
19 well and OEF and OIF, move the military to commit
20 almost three-quarters of a billion funding to this
21 effort and study of TBI. And much of what we will
22 review today is a product of that effort.

1 I wanted to take the opportunity to
2 share with you my experiences as a laboratory and
3 a clinical scientist who moved into this field
4 very much motivated to change patient care and to
5 make a difference at the bedside. And this
6 process and the attendant requirements to achieve
7 this was at that time, really, unknown to me but
8 if you can follow this, obviously, you need to get
9 a target biomarker. At that time, our
10 identification of the pathology -- this cascades -
11 - was relatively unknown. We focused initially on
12 proteolytic mechanisms but then you have to build
13 a prototype assay development and collect samples.
14 This is an immensely challenging and
15 time- consuming and expensive process. And then
16 you have to move down the line to where you
17 ultimately get to regulatory applications which
18 I'll go through some today, and move us to sales
19 which, in effect, is changing patient care. And
20 the industry costs are about $100 to $200 million
21 to bring a biomarker through FDA approval. So you
22 cannot be promiscuous and non-selective in the

1 biomarkers that you choose to commit to this
2 process, so it becomes a very iterative process
3 and, frankly, quite challenging.
4 Now Banyan spring off from the
5 University of Florida, I think, as a rather unique
6 biotech entity. It was created with deep research
7 roots that, in many ways, are maintained even
8 today and we chose to build our program on a
9 pyramid of strong science and Banyan along has
10 generated greater than publications. We've done
11 it in humans. We've done pre-clinical studies,
12 all of these leading to our severe TBI studies,
13 mild TBI studies and more recently our FDA trial
14 that I'll talk a little bit about as well. But
15 the point here is that absent a strong basic
16 science program and clinical science program
17 integrated into the processes, the complex
18 commercial and regulatory processes to change
19 practice are going to either die, whither or
20 simply churn.
21 And here are some of the publications
22 that Banyan has produced since 2004, more than 70

1 and growing and we are, the people at Banyan,
2 researchers like myself and others, very wisely
3 appropriating the clinical expertise of many, many
4 others in the field. And having spent more than
5 20 years in a neurosurgery department as a PhD, I
6 learned very early that you need strong clinical
7 champions to ensure that what you hope to
8 accomplish will change the practice of medicine,
9 and that's really where we're quite focused.
10 Now this all led to a recent publication
11 in the Journal of Neurotrauma that is a template
12 for our Alert TBI. I encourage you to look at the
13 paper online but the conclusion was that ubiquitin
14 C- terminal hydrolase L-1 in combination with GFAP
15 and you see along could provide the objective
16 evidence clinicians desire to reduce the CT scans
17 with mild TBI. Many centers now routinely, if you
18 shoe up, reporting and history of a CT; a TBI,
19 they routinely give a CT. What our data showed,
20 that UCH L-1 and GFAP, with these cutoffs, can
21 provide a very, very strong sensitivity and at the
22 same time, eliminate 40 percent of unnecessary CTs

1 and significantly reduce exposure of patients to
2 ionizing radiation which, of course, is not
3 desirable and especially in the younger patients.
4 So our current -- all of this led now to
5 our ALERT-TBI pivotal study, because you have
6 prospective clinical evaluation of biomarkers of
7 traumatic brain injury. We call it the ALERT-TBI.
8 This is for head injury subjects with a Glasgow
9 Coma Scale of 9 to 15, our mild-to-moderate TBI.
10 They're 18 years of age or over. The CT scan is a
11 part of standard of care, the blood drawn within
12 12 hours, a neuroimaging review committee to score
13 the CT scan and classify them, the laboratory
14 assay testing was conducted independently and
15 blind. We had 24 centers in the U.S. and the EU
16 and the data analysis and ultimately the FDA
17 submission was done in close collaboration with
18 the FDA, so we're very delighted with the FDA
19 support that we've received from that.
20 Marketing strategy and platform partners
21 are another largely invisible area of this but if
22 you're going to get this information to the

1 patient, you need to have ultimately a point of
2 care device, and we've partnered with both Abbott
3 and with Philip to provide that. And our vision
4 is that we'll have very rapid 20-minute feedback
5 on biomarker values available in the E.D. or the
6 ICU. We're also looking at a general laboratory
7 opportunity as well.
8 So one other point that I think is
9 largely overlooked in many of the investigators is
10 the reimbursement pathway, which is a lengthy and
11 costly process. You have to create a
12 reimbursement team, generate the pharmaco-economic
13 evidence, engage key opinion leaders, and
14 ultimately work with CMS to generate the ICD-9/10
15 codes that will allow proper reimbursement.
16 So in closing, I just simply wanted to
17 go over, as I alluded to, the future. What's
18 terribly exciting about this predicate test in
19 mild and moderate TBI is the template and
20 infrastructure that it provides for rapid
21 expansion into toner critical indications. And
22 the ones that we're currently focusing on are

1 pediatric hypoxic ischemic encephalopathy. It's a
2 devastating and a disease, actually, for which
3 there is therapy, hypothermic intervention. It's
4 very difficult to identify the patients who would
5 respond.
6 We know very much about stroke. We
7 alluded earlier to the potential for GFAP and
8 others for early diagnosis and discrimination
9 between hemorrhagic and ischemic stroke as well as
10 stroke mimics. And in another very important area
11 I think that will allow a rapid rate of return is
12 to use these same biomarkers as non-invasive
13 markers of the clinical course of patients and
14 their monitoring ICUs for stroke, cardiac arrest,
15 epilepsy, even sepsis where post ICU delirium and
16 sepsis is a significant problem.
17 So I think the meeting here is a
18 testament to where we are and where we could be,
19 I'm optimistic to believe, in a relatively short
20 period of time. So I want to thank everyone here
21 for your time and look forward to questions at the
22 break.

(Applause.)

DR. KANNAN: Thank you, Dr. Hayes. Our next speaker is Dr. Cristin Welle. She was with us until a few months ago in the Office of Science and Engineering Lab at CDRH and now she's an Assistant Professor in the Department of Neurosurgery at the University of Colorado.

DR. WELLE: Thank you, Lakshmi. I'm really honored to be invited to speak here today. We've heard a lot of very compelling evidence towards the development of neuroimaging and bio-fluid biomarkers. Today, my talk is going to cover some of the evidence for devices that rely on physiological biomarkers of brain injury. And as Lakshmi mentioned, I, up until very recently, led a research group here within the Office of Science and Engineering Laboratories in the Center for Devices and Radiological Health.

So why do we need physiological biomarkers? Clearly, there are some exciting advances going on in other areas of biomarkers. I think that the primary answer is because of the

1 need for rapid point of care diagnostics. There
2 are situations where it's very important to
3 rapidly be able to diagnose and triage patients
4 who've experienced traumatic brain injury. And
5 currently, those types of triage decisions are
6 based on preliminary clinical exam. And I'd like
7 to also point out that the need for rapid point of
8 care diagnostics is important because patients may
9 not always be able to be transferred to a clinical
10 situation to undergo neuroimaging or other
11 analyses, situations such as the side of a sports
12 field or on the battlefield or in other emergency
13 care situations require on-site evaluation. And
14 clinical evaluations that rely on patient report
15 have been demonstrated to underreport the
16 incidence of particularly mild traumatic brain
17 injury.
18 In addition, for mild traumatic brain
19 injury, again, other biomarkers may not have
20 sufficient sensitivity. We saw it demonstrated
21 this morning that CT scans may not be able to
22 identify accurately patients who have experienced

1 mild TBI. And bio-fluid biomarkers don't
2 necessarily have their full -- their best
3 diagnostic potential immediately following the
4 injury whereas physiological indicators can
5 normally be measured and show disturbances
6 immediately following injury.
7 And of course, it's important to be able
8 to ascertain whether a patient has experienced a
9 brain injury in order to remove them from a
10 situation which might allow them to experience a
11 repeated brain injury which can lead to worse
12 outcomes. Also, patients, even those with a
13 Glasgow Coma Score of 15 and a negative CT
14 finding, are still at risk for the development of
15 post concussive syndromes and should be monitored
16 as such.
17 So in my talk, I'm first going to cover
18 devices that are currently on the market to aid in
19 the diagnosis of TBI. I'll then mention some
20 investigational efforts that are looking at new
21 types of physiological biomarkers. I'll briefly
22 touch on some non-medical devices that are used to

1 inform decisions about whether a TBI has been
2 experienced. and then I will mention FDA's
3 regulatory research science efforts on TBI
4 diagnostic development.
5 So to begin with, devices that are
6 currently being marketed, these devices are not
7 marketed as diagnostics per se but as assessment
8 aids so they can inform clinician thinking about
9 the patient's diagnosis. The first one I'll
10 mention is the AnthroTronix DANA device. This is
11 an app for the iPhone or tablet that measures
12 reaction time and a recent concussion guideline
13 that was published by Dr. Ghajar and colleagues
14 showed that reaction time is one of the four key
15 elements that can be sued to identify patients
16 with a concussion.
17 I also want to touch on the use of
18 quantitative EEG that is used by the BrainScope
19 device and they're ahead 100 -- ahead 200 devices.
20 Here they use quantitative EEG algorithms that are
21 combined to make a discriminate index that has a
22 reported sensitivity of around 90 percent compared

to a positive CT finding and a specificity of around 60 percent.

Another device on the market is the InfraScanner which uses optical techniques; in this case, near infrared spectroscopy to detect hematoma. And hematomas of a certain size can be detected with a sensitivity reported around 80 percent and specificity reported around 90 percent.

All three of these devices, I should mention, have been the recipient of considerable funding from the DoD.

So shifting focus to different approaches that are under investigation for other physiological biomarkers, the first is eye tracking. And in these -- this approach utilizes measurements of eye movement including those such as movements during visual tracking, saccade amplitude, peak velocity acceleration among other measurements and shows that there are differences in patients who've experienced a brain injury. On the left, I'm showing a research grade eye-

1 tracking device that's used in some of these
2 studies and I want to mention the company,
3 Oculogica, which is apparently in the process of
4 developing algorithms to be used for eye-tracking
5 in patients with brain injury.
6 Another area of investigation is the use
7 of brain-evoked potentials. So this approach
8 relies on EEG again but time averages those EEG
9 responses in response to the presentation of a
10 stimuli, be it visual or auditory, somatosensory,
11 and sometimes in the context of a behavioral task
12 or paradigm. And a recent meta-analysis by Rapp
13 and colleagues showed that brain-evoked potentials
14 do, in fact, seem to have some diagnostic utility.
15 Some other approaches include other uses
16 of quantitative EEG measures and also MEG magneto
17 encephalography. On the left, I'm showing a
18 picture of the CEO of a company, Cerora, which is
19 developing a headset-based device for Q-EEG
20 measurements for brain injury among other
21 indications and it's being demoed by the former
22 FDA Commissioner, Dr. Margaret Hamburg, in this

1 picture. And on the right is an example of a
2 functional connectivity network that was
3 identified in a recent MEG study shown to be
4 altered in patients with brain injury.
5 And finally, this is another device --
6 or approach that relies on optical measurements;
7 in this case, transcranial ultrasound, a Doppler
8 ultrasound to monitor blood flow.
9 So that's a really quick overview of
10 some of the approaches that are under
11 investigation. What are some of the drawbacks to
12 potential physiological biomarkers? The first,
13 and this applies to all of the approaches I've
14 shown except those including blood flow, is the
15 response magnitude is, in some way, dependent on
16 the attentional state of the patient. So it's
17 important to be able to, in some way, monitor or
18 control patient engagement in the task.
19 And like other biomarkers including, I
20 believe, bio-fluid and neuroimaging, it can also
21 be important to have a set of normative values for
22 which to compare TBI patients. So it's important

1 to have a collection of baseline measurements to
2 accurately interpret results.
3 Finally, some of these approaches may
4 not be specific to traumatic brain injury but
5 instead may be indicative of general neurological
6 dysfunction. This does not necessarily prevent
7 them from being used as a diagnostic for TBI but
8 it is an important consideration for the
9 interpretation of the results.
10 Briefly, I want to mention that there
11 are non-medical sensors that use accelerometers
12 and other types of moments to measure impact.
13 These, I believe, are being used to provide some
14 additional information when evaluating patients.
15 And so, you know, finally, to sort of
16 shift gears, I want to show you this quote from
17 the FDA draft strategic priorities from 2014 to
18 2018, and it says that, "Although the FDA's
19 primary responsibility is to review safety and
20 effectiveness of new medical products developed by
21 industry, the agency is also committed to
22 assisting product developers and translating

1 discoveries in basic science into new therapies
2 that will save lives and improve healthcare." And
3 so that's sort of the rationale behind the FDA's
4 regulatory science efforts which are efforts to
5 develop test platforms and new methods and
6 measurements to answer questions involved in
7 regulatory decision-making processes. And we do a
8 lot of regulatory science here in the labs at FDA
9 and the work I'm going to be talking about today
10 that's involved in TBI diagnostics has been funded
11 by the FDA's Medical Countermeasures Initiative,
12 which is a very important source of support for
13 these efforts.
14 So within the Center for Devices and
15 Radiological Health, there are some regulatory
16 science efforts. I'm listing two here that I've
17 been involved with although there are some other
18 efforts that are involved in -- that relate to
19 traumatic brain injury. the ones that I've been
20 involved with are first, looking at Q-EEG and
21 evoked potentials as measurements of brain injury,
22 trying to understand some of the fundamental

1 questions in those studies and also, phantom test
2 method development for calibrating near infrared
3 spectroscopy moments for the detection of
4 hematoma. So today I'm actually going to show you
5 data from the first of those but both of these
6 efforts are ongoing.
7 To look at quantitative EEG and also
8 evoked potentials, we first utilized a novel
9 method of brain injury and this was to allow us to
10 have a non-invasive calibrated and spatially
11 localized injury and we apply this injury using
12 high-intensity focused ultrasound. We then record
13 -- this allows us to record EEG from animal model
14 before, during, and after the injury application,
15 and what we have found is some significant changes
16 in low-frequency EEG activity in the animal that
17 actually persists weeks to months after injury.
18 And this, what I'm showing here, is a plot of the
19 delta to gamma frequency band ratio showing again
20 the persistence of changes following injury in our
21 animal model.
22 Another type of EEG measurement that

1 we're making is the somatosensory evoked
2 potential. This is a slightly different
3 experimental paradigm. Here we're looking at
4 acute injury as opposed to chronic, and we are
5 providing a sensory input in the form of
6 stimulating the median nerve and then time
7 averaging the EEG responses to create the evoked
8 potential that you can see there. So at the top
9 is the pre-injury evoked potential. Immediately
10 following the application of injury, you can see
11 that that potential is basically obliterated and
12 it does show a recovery trajectory over the course
13 of the next hour.
14 We are embarking on some very
15 preliminary pilot experiments with our
16 collaborators at the Uniformed Services University
17 and Walter Reed to measure somatosensory evoked
18 potentials in soldiers who have experienced TBI
19 and also healthy control.
20 And finally, with collaborators at the
21 University of California, San Diego, we're also
22 evaluating the ability to measure somatosensory

evoked potentials using a novel sensor type and these are flexible electrodes that are disposable and easily applied to the skin. And we have shown in animals thus far that we can, in fact, measure a comparable somatosensory evoked potential using this novel sensor technology.

So I would like to acknowledge all the people on the team who've worked on these projects both within FDA and also our external collaborators. I'd also like to thank both the FDA Medical Countermeasures Initiative and also Dr. Victor Krauthamer, Dr. Dan Hammer, who are the Directors of the Division of Biomedical Physics within OSEL. Thank you.

(Applause.)

DR. KANNAN: Thank you, Cristin. And our next speaker is Dr. Harvey Levin. He is the Scientific Director of Neurorehabilitation, the TBI Center of Excellence at VA Medical Center and also the Professor of Physical Medicine and Rehabilitation at Baylor College of Medicine.

DR. LEVIN: Thank you, Lakshmi. This

1 morning I will address clinical outcome
2 assessments and specifically the use of global
3 outcome assessments and then turn to cognitive
4 neurobehavioral and symptom domains of
5 assessments.
6 You've heard this morning from the
7 previous speakers beginning with Dr. Manley of the
8 timeliness to improve our outcome assessments. I
9 will begin with presenting some of the evidence
10 that was used to validate the Glasgow outcome
11 scale including the extended version based on
12 macroscopic pathology seen on imaging. Then I
13 will proceed to point out some of the limitations
14 which have already been mentioned, if you heard,
15 by Dr. Manley and other speakers this morning, and
16 propose that there are existing clinical outcome
17 assessments that are more specific to cognitive
18 neurobehavioral and symptom domains.
19 Here we see on the x axis the three
20 broad categories of outcome from the Glasgow
21 outcome scale. These were evaluated by Dr.
22 Jeannette (ph) and his co-investigators in 150 --

1 sorry, I'm skipping ahead. This is from my work
2 in which we classified, that is our
3 neuroradiologists classified the depth of focal
4 lesions in patients who had sustained a broad
5 spectrum of injury severity. So the different
6 colors are explained on the right. So there were
7 some patients who had no findings on MRI, then a
8 subgroup who had extraparenchymal lesions, those
9 with cortical lesions, subcortical, and deep
10 central gray lesions.
11 The rationale for this approach was
12 based in a infrahuman primate model that was
13 studied by Drs. Ommaya and Gennarelli. This was
14 back in the early '80s, late '70s, and they were
15 able to show that the deeper the brain lesion, the
16 more severe the impairment of consciousness.
17 So we did this using MRI findings and
18 what we could see on the y axis the percent of
19 patients in each of those subgroups defined by the
20 depth of lesion. So if we look at those patients
21 that had no lesion or had lesions no deeper than
22 cortical, they're well-represented in the good

1 recovery and some of them are also in the moderate
2 disability groups. However, if we look at the
3 deep central gray brain stem lesion subgroup,
4 they're overrepresented in the severe disability
5 group and to some extent in moderate disability.
6 And these evaluations of outcome were completely
7 independent of knowledge about the depth of
8 lesion.
9 //
10 Here are some examples. The top left was a
11 patient who had a GCS score of 14. There was a
12 depressed skull fracture and intracerebral
13 hematoma; impaired consciousness was only 15
14 minutes. On the top right, a patient with a GCS
15 score of 13 was struck by a cable and there was
16 involvement of the subcortical white matter,
17 impaired consciousness of 30 minutes. Both of
18 those patients at the top had good outcomes.
19 In contrast, the lower two images are
20 from the same patient who had a GCS score of 4 and
21 we could see that there's increased intensity at
22 the level of the medulla and as well as atrophy of

1 the mesencephalon. There was, of course, diffuse
2 atrophy but it extended deep into the brain. This
3 patient had about a month of impaired
4 consciousness and severe disability. So in a
5 relatively basic level, the GOS is supported by
6 different severities of pathology.
7 More recently, my colleague, Lisa Wild,
8 and our group used volumetric MRI to study
9 patients who ha pediatric TBI -- this was moderate
10 to severe -- at one year after injury. On the x
11 axis, again, you could see the different
12 categories from the Glasgow outcome scale and in
13 addition, we had a comparison group of children
14 who had no TBI. They had orthopedic injuries.
15 On the left side, on the y axis is the
16 percent of frontal temporal white matter that was
17 preserved. So we looked at the other side.
18 Instead of calculating the size of a lesion, we
19 looked at what was preserved. And you could see
20 that the percent of preserved frontal temporal
21 white matter had a strong relationship to these
22 general outcome categories from the Glasgow scale.

1 On the right, in contrast, when we
2 looked at the percent of posterior white matter
3 that was preserved, we didn't find much of a
4 relationship. I would suggest this could also
5 reflect a limitation of the GOS because perhaps
6 with other measures, we would have been able to
7 demonstrate but as you are aware, frontal temporal
8 white matter is involved in higher level cognitive
9 functions and a some neurobehavioral sequelae so
10 it's probably easier to measure the
11 neurobehavioral effects.
12 You saw this earlier from Dr. Yuh's
13 presentation and the point here is that this is a
14 much more advanced application of MRI and using
15 these common data elements, such as hemorrhagic
16 axonal injury, as Dr. Yuh presented earlier this
17 morning, this also was related to a dichotomized
18 GOSE at three months in mild TBI.
19 This is, in my view, a classic study.
20 This was by Dr. Jeannette and a very distinguished
21 panel of co-investigators; Dr. Snook (ph) is a
22 neurologist; Michael Bond was a psychiatrist but

1 originally he was trained as a neurosurgeon; and
2 Neil Brooks (ph) was, at that time, a leading
3 neuropsychological investigator. And on the left
4 -- this is based on 150 patients from the
5 International Coma Data Bank who were studied
6 intensively at one year after injury. And we
7 could see on the left side that there were
8 different domains that were affected by these
9 injuries. And these domains were through some
10 process that was performed mainly by Dr. Snook,
11 the neurologist, these were integrated into some
12 sort of a composite to arrive of the GOS. But
13 there was heterogeneity in these outcomes. If you
14 look at the right, over half of the patients had
15 cognitive or behavioral problems at one year that
16 dominated the clinical picture and influenced the
17 GOS category; whereas there was about 28 percent
18 who were disabled primarily by focal neurologic,
19 i.e., motor deficits or they had seizures or they
20 had aphasia. So this was quite heterogeneous and
21 this is lost when you only look at the global
22 outcome.

1 This slide made by Drs. McRae (ph),
2 Giacino (ph), Dickman, and Dr. Manley takes this a
3 step further because you can see that there are
4 multiple dimensions of outcome that are aggregated
5 by some process that may not be entirely
6 straightforward to arrive at the GOSE. And as
7 pointed out by Dr. Manley earlier, pre-clinical
8 research which is used to develop some of the
9 drugs under investigation or other kinds of
10 interventions use a task such as the Morris water
11 maze. What is that? It's a measure of episodic
12 memory.
13 If you look at the right, this doesn't
14 translate to the GOSE. The GOSE, as I've just
15 pointed out, is an aggregate of these major
16 domains including health-related quality of life
17 and Dr. Manley mentioned going shopping or return
18 to work. What does that have to do with episodic
19 memory? This is taken from the TRACK-TBI. Just to
20 point out, if we look at the lower right, that's a
21 block plot, the GOSE categories are on the x axis.
22 Y axis is the severity of anxiety. Well, there is

1 some relationship but I'll point to the box plot
2 for a GOSE of three. This is the worst level of
3 conscious survival and this subgroup had -- did
4 not have elevated anxiety. I would suggest that
5 this subgroup had problems perhaps with insight
6 and awareness of the severity of their deficits so
7 they didn't exhibit apparent anxiety as a result.
8 So it's an uncoupling of that type of outcome
9 measure versus a very global outcome.
10 So we would advocate the use of specific
11 measures for various cognitive domains and such as
12 memory, attention, processing speed, executive
13 function; in addition, specific clinical outcome
14 assessments for behavioral and symptom outcomes.
15 In the more severe injuries, behavioral
16 disturbance is quite common and if you interview
17 the family, it actually poses more of a burden to
18 them than even the cognitive outcomes. In the
19 post-concussion symptoms, as you've heard from Dr.
20 Marinelli and others, the symptoms are the primary
21 outcome, especially during the first 7 to 10 days.
22 And there are clinical outcome assessments that

are appropriate to measure symptoms. Especially in a prospective longitudinal study with retrospective kinds of studies or treatment studies for chronic patients, it's different because there could be comorbidities; for example, PTSD in veterans, which make it more difficult to rely heavily on symptom measures. Mood disorder is quite common throughout the spectrum of severity and there are clinical outcome assessments that are available for that domain.

So just to sum up, we've seen that yes, there is solid pathological validation of the GOS/GOSE. However, this is used primarily for the more severely injured patients and as we've seen, as a global measure, it can obscure specific areas of marked impairment as well as specific areas of preservation. And if there is a drug being tested which has a specific mechanism such as perhaps preserving hippocampal function and preserving memory, it may not even be measurable using such a global measure.

And as we've concluded, there are

clinical outcome assessments that are available that have good psychometric features which can be used for the cognitive, the symptom in the neurobehavioral domains. And I've mentioned here some of the context of use and this is focusing on adults. Thank you.

(Applause.)

DR. KANNAN: Thank you, Dr. Levin. So now I'd request all the speakers to come forward and have a seat here and open the floor to the audience for question and answer sessions. And I apologize; we may have to shorten the Q and A session for only 10 minutes given that we are running a little late but again, I want to remind you all that, you know, any thoughts, questions, you can always submit your comments and questions to the public docket to have the conversation going. And for those of you with any questions or comments, please come forward to the microphone and identify yourself first.

DR. JANIGRO: Yeah. This is -- my name is Damir Janigro and I work for a company called

1 Flocel and I have a question for Dr. Yuh about
2 your comparing radiological readouts across
3 radiologists. Did they know what you were asking
4 them to see; were they aware of the pathology, why
5 the scans were taken; and did you show them any
6 normal scans to see how many normals would be read
7 as abnormal?
8 DR. YUH: Yes. So they did not know the
9 pathology beforehand, so these were scans that
10 were taken from -- these particular scans were
11 taken from the ongoing TRACK-TBI study. So the
12 positive rate has been, for CT, probably around 20
13 percent and for MRI, probably 30 or 40 percent.
14 So that's the proportion of positive exams for CT
15 and MRI roughly, and they were given a random
16 selection of 20 studies -- 20 clinical trials, 20
17 MRIs without knowing ahead of time whether they'd
18 be normal or abnormal or what type of pathology.
19 And they didn't even have clinical history, so
20 symptoms or GCS score. These were just purely
21 based on the imaging, so --
22 DR. JANIGRO: And some subjects were

1 non- TBI; they were just controls?
2 DR. YUH: Oh, no. They all had been
3 enrolled for --
4 DR. JANIGRO: A TBI.
5 DR. YUH: -- clinical suspicion for TBI
6 but some of the scans were normal.
7 DR. JANIGRO: Okay.
8 DR. YUH: Thank you.
9 DR. KANNAN: Any other questions?
10 DR. HAMILTON: Hello. I'm Robert
11 Hamilton from Neural Analytics. I had a question
12 in general about the clinical utility of
13 biomarkers and clinicians when we've seen through
14 several studies, whether it's imaging or fluid
15 biomarkers, the resolution symptoms prior to the
16 resolution of these physiological biomarkers. And
17 so what is the next step? Maybe it's a little
18 cart before the horse but how do doctors then
19 utilize that information for clinical care?
20 DR. MANLEY: Everyone's looking over
21 here. So I think that we should look at examples
22 of other diseases. For example, if I have chest

1 pain today and they take me to the hospital,
2 they're going to do multiple tests; they're going
3 to run a troponin which we've all seen the
4 evolution of that biomarker over time; they're
5 going to do an EKG. There are a number of things
6 that they're going to do.
7 So I don't -- I think one of the
8 problems that I've seen in the field is the
9 thought that with something as complicated as the
10 brain, we're going to have one marker to use. I
11 think this is going to be a multivariate approach
12 and as you saw today even with the biomarkers, if
13 you use a couple of different biomarkers, they
14 work better than one proteomic biomarker. So I
15 think just like with the heart, which is a much
16 more simple organ than the brain, we're going to
17 have a number of things that we're going to look
18 at to refine this. I don't see this as a single
19 sort of silver bullet if you will.
20 DR. HAMILTON: Okay. Thanks.
21 MALE SPEAKER: My question is primarily
22 for Dr. Marinelli. It pertains to people with

1 mild injury and the question is how -- do you see
2 any abnormalities in patients where the symptoms
3 have actually disappeared? So the question really
4 comes back to if the symptoms have gone away, is
5 everything okay or do you still have some
6 underlying problems?
7 DR. MARINELLI: Yeah. So again, it goes
8 back to what Dr. Manley was saying. It really
9 depends on the imaging feature that you focus on.
10 Some track very well with symptoms; others are
11 less tracked with symptoms. For example, cerebral
12 blood flow seems to be an interesting indicator
13 because even after symptoms have disappeared, we
14 find that the physiological recovery timeline of
15 the brain happened at a different scale. It takes
16 more time for cerebral blood flow to come back to
17 normal values than it takes for symptoms to
18 disappear.
19 Resting-state fMRI seems to track
20 symptoms much better and so as the symptoms
21 recover, we find that resting-state fMRI tends to
22 go back to more normal values. And that's the

1 point where, in my opinion and I think most people
2 agree, that as we try to go from the kind of
3 population studies that most studies today are
4 focused on, to try to really figure out how to get
5 that information to be relevant for an individual
6 patient, this multivariate and multi-contrast
7 approach is going to be critical.
8 MALE SPEAKER: Hi. There was a comment
9 you made, Dr. Manley, earlier that we should try
10 to classify TBI along the lines of cancer and
11 cardiovascular disease have done. And then Dr.
12 Ron Hayes, your talk was very nice about
13 biomarkers. I've worked in the (inaudible) cancer
14 biomarkers for now and so -- and we recently had
15 someone in the family go through a TBI so this is
16 very personal. But I'm struggling to understand --
17 in the case of cancer where you knew a lot about
18 the cell cycle, the cell processes, the kinases
19 and the protease and pathways involved and there
20 the perturbations are literally biological, then
21 lead to physiological conclusions.
22 In this case, from what little I know of

1 what happened in our family or even my
2 understanding of it, it's a very physical
3 dislocation incidental and in some cases can also
4 be combined with potential exposure in the case of
5 the war veterans coming back, exposure to agents
6 that we don't know.
7 So I'd like some comments from Dr.
8 Manley and Dr. Hayes -- is how do you foresee
9 classification of TBI, because certainly the
10 person I'm thinking about in my family is still
11 undergoing some mild aphasia and a slide from Dr.
12 Levin where us aid there are these -- Dr. Snook
13 studied several different factors you can call
14 severe, moderate based on functionality? How can
15 we do this, I'm struggling to figure out, because
16 as a biomarker person, I'd love to dive into this
17 data but I can't seem to get a handle on this.
18 DR. MANLEY: So first of all, you can't
19 boil the ocean here. I think one of the ideas is
20 that you've got to take out subsets of folks. So
21 we didn't figure out how to treat all kinds of
22 cancer on day one. We started with, you know,

very crude agents and then started to refine. So the molecular things that we see today were really after decades of evolution. So you don't think that I think this is -- that there's no possibilities at all, we already have a couple of pathoanatomical entities that we know very well. So the epidural hematoma which was shown several times today -- there are several neurosurgeons in the room and any medical student knows I you see an epidural hematoma with a declining mental exam that you go take the epidural hematoma out, and if there's no underlying brain contusion, the patients do well. We know what a chronic subdural hematoma is and we know how to treat that.

So I think the goal is not to try to capture everything in your classification but to find subsets that are very homogeneous that we can then target. So it may very well be that some of these people that we're identifying with Dr. Yuh's work that have axonal injury, that that might be something we can target in a molecular fashion if we understand what the outcome measure is. You

1 saw that even though the GOSE does perform, it's
2 probably not to the level of sensitivity that we
3 need, so maybe a processing speed or a verbal
4 learning task is what we need with this. And then
5 we can develop a clinical trial where rather than
6 taking all patients with the ACRM definition of
7 mild TBI, we're only going to look for patients
8 that have MRI findings, and then those will be the
9 enriched population which we'll target with this
10 drug for that particular mechanism and we'll have
11 a more refined outcome measure. So that's the way
12 I would see that evolving.
13 DR. CRUTCHFIELD: Dr. Crutchfield here.
14 Dr. Marinelli, I have --
15 DR. WANG: Excuse me, if I may just --
16 DR. CRUTCHFIELD: Sorry.
17 DR. WANG: -- to continue that
18 point. You know, so to give you an example, today
19 there are no FDA-approved drugs for TBI. However,
20 you know, if the biomarker, for instance, I
21 mentioned, you know, there are markers that are
22 looking at axonal track on myelination, so you

1 could foresee that you can, in the future, target
2 medicine and then also a marker for neuronal
3 apoptosis versus necrosis. So those are the
4 potential pharmacodynamic biomarkers that can be
5 used to assist therapy development in the future.
6 So we're not quite there in terms of, you know,
7 the cancer. We'd love to get there but I think we
8 can potentially go down that path, so
9 DR. CRUTCHFIELD: Dr. Crutchfield. I
10 work in Baltimore. I take care of patients with
11 traumatic brain injury and I have a vexing
12 question that I've not gotten a satisfactory
13 answer to yet. Functional MRI is based on old
14 signal acquisition which is based on blood flow.
15 We know that traumatic brain injury alters the way
16 the brain regulates blood flow. How are you
17 accounting for alterations in hemodynamic
18 regulation when you're studying a population post
19 injury? We know that those bold signals may
20 correlate in a healthy brain with increased brain
21 activity, but how do we know we're looking at
22 changes in brain activity versus an alteration of

1 blood flow regulation
2 post trauma?
3 DR. MARINELLI: So that's a great
4 question. In many of these image contrasts for
5 MRI, we need to think about these kind of
6 confounders. For conventional fMRI, you're
7 basically stuck with the confounding effect of
8 blood flow and changes in connectivity. I mean
9 you cannot separate the two. There are techniques
10 that we are exploring and that we are starting to
11 use, particularly in the case of brain tumors,
12 where neurovascular decoupling is extremely high,
13 to push fMRI in a space where it is able to
14 separate out components that are primarily due to
15 blood flow and primarily due to changes in
16 neuronal response basically. We are not using
17 that in this study.
18 The other thing that we can do and that
19 we're planning to do is because we have both
20 profusion data as well as fMRI data, we do have
21 two independent measures; one that is exquisitely
22 related to flow and to how the gray matter is

1 served basically by blood and the other, that kind
2 of mixes that flow with neuronal contribution.
3 And so we're hoping to be able to point exactly to
4 the direction that you are asking about by
5 combining several biomarkers; in this case, it
6 would be perfusion and fMRI.
7 DR. KANNAN: I apologize to interject
8 but I just wanted you to know that this is the
9 last question that we can take because of the time
10 constraint reasons. I really apologize but like I
11 said, you know, you all are welcome to submit your
12 questions, comments and again, all the speakers
13 are going to be here so you can always approach
14 them later. Thank you.
15 DR. DeGRABA: Thank you. Tom DeGraba
16 from National Intrepid Center of Excellence at
17 Walter Reed. Tremendous session this morning.
18 Dr. Levin, I'd actually direct this to you
19 although others have said the same types of
20 things. You were talking about looking at domain-
21 specific cognitive functions and I think we're
22 right on target and we need to look at what

outcome measures in the brain are disrupted. Many of our patients, however, will say, gosh, I'm having problems at work. I'm high- functioning and I can't do what I do and yet the tests that are done in quiet, well-lit rooms puts me on the upper end of the cognitive scales. Can you make a comment about what we could look for in the future to try to standardize perhaps some stressors that might simulate White House at patients really experience in real-world activity when they look at their cognitive function?

DR. LEVIN: Excellent question and it speaks to the issue of ecologic validity in the outcome assessments we use. And I think it also implies that when we transition to greater emphasis on specific clinical outcome assessments, we could use a panel of specific measures. So to address he example you gave and this is someone who is experiencing stress on return to work but may have some cognitive problems, so perhaps a panel that would include a measure of processing speed which has been established to be quite

1 sensitive in the spectrum of TBI severity
2 In addition to that, it would be important to have
3 a measure of general emotional functioning and I
4 showed one example of such a measure. There are
5 others and perhaps there'd be a third measure that
6 might have something to do with coping with
7 stresses. That's just a hypothetical case but the
8 point is that a single measure is unlikely to be
9 satisfactory given the heterogeneity of TBI even
10 when we use specific subtypes of TBI defined by
11 imaging, as you've heard from Dr. Yuh and Dr.
12 Manley. There will still be some heterogeneity
13 because these individuals also differ in their
14 vulnerabilities, their pre-injury functioning. So
15 we'll need to use a panel and I think it's an
16 empirical question how many measures might suffice
17 and for which particular context of use and -- but
18 I think we have the tools that we need to arrive
19 at the solution to the question that you pose.
20 DR. KANNAN: All right. Great questions
21 and very insightful answers. Thanks to all the
22 speakers again for sharing their interesting data

with us. Let's give them a big round of applause.

(Applause.)

DR. KANNAN: And I request everyone to -- we're going to take a short break now, a really short break and I request everyone to be back by 10:35. Thank you.

(Whereupon, off the record at 10:27 a.m., and back on the record at 10:35 a.m.)

DR. KUMAR: So before we continue on the remainder of the morning, I want to give a brief overview of the FDA pathways to integrating biomarkers into medical product development, but first I wanted to tell you a little bit about how this meeting came about. This past August, we had a leader in the field of TBI here at FDA to give a talk about the work that's being done to advance this science and really learn in the clinical environment how we can better help patients. And while they were here, we had the opportunity to have what I would call a very frank discussion and we asked how can we, as the FDA, help in

1 translating the research and clinical evidence
2 being gathered to really advance products, to get
3 them on the market.
4 And what we heard in response to that
5 was that there's a noticeable disconnect between
6 FDA and the academic and clinical research
7 community in terms of White House at evidentiary
8 standards and science should be pursued to advance
9 products, to diagnose and treat TBI and to improve
10 the lives of our patients.
11 So FDA, we thought to ourselves, and we
12 said how can we better work with the TBI community
13 to evaluate this perceived disconnect and we
14 decided to do two things. The first was to listen
15 and to learn from the expert opinion in the field
16 what is the current clinical science and evidence
17 in brain injury. And then two, communicate to
18 those doing medical product development efforts
19 what regulatory pathways are available to them and
20 what standards of evidence FDA would like to see
21 in those pathways, so here we are today.
22 Again, thank you to this morning's

1 speakers that provided us with an overview of that
2 science. And now we're going to hear from my FDA
3 colleagues on the regulatory considerations for
4 biomarkers. And as you heard Dr. Califf mention
5 this morning and you will hear more about in Dr.
6 O'Callaghan's talk subsequently, the BEST
7 resource. The BEST stands for biomarkers,
8 endpoints, and other tools -- is a resource that
9 was just recently published in 2016, and it's from
10 this resource that the FDA recognizes the
11 regulatory definition of a biomarker. And I
12 think it's really important that we all start at
13 this fundamental definition, especially today as
14 this is the focus of our workshop.
15 And a biomarker is defined as a
16 characteristic that is measured as an indicator of
17 the normal biologic processes, pathogenic
18 processes, or responses to an exposure or
19 intervention including therapeutic interventions.
20 And then it goes on to further describe what a
21 biomarker can be and how they can be used because
22 as you can see, there are multiple pathways that

1 the FDA has made available for the development of
2 biomarkers. These pathways differ for drug
3 development and for medical device development.
4 They include qualifications of biomarkers through
5 drug development tools and use of biomarkers in
6 therapeutic applications, in vitro diagnostic
7 methods and assays, biomarker tests through the
8 medical device development tool, and diagnostic
9 and therapeutic devices.
10 We recognize that navigating these
11 pathways are daunting and can be confusing and we
12 hope to communicate our thinking to you today to
13 help you in your work that you're doing through
14 each of our presentations this morning, because we
15 feel as strongly as you do that advances in this
16 field have a great potential in addressing the
17 unmet needs of patients suffering from traumatic
18 brain injury.
19 So I would first like to introduce Dr.
20 Shashi Amur with the Center for Devices and
21 Radiological Health.
22 DR. AMUR: Thank you, Allison, and I

1 would like to thank the organizers for inviting me
2 to this meeting and thank you for that great
3 segue. I'd like to give you an idea about the
4 biomarker qualification program at CDER FDA. I'll
5 also talk about acceptance of biomarkers through
6 the IND and the (inaudible) process.
7 So here's a quick overview. I'd like to
8 start with a very brief introduction, talk to you
9 a little bit about biomarker qualification and the
10 strategy and the process. And then I want to give
11 you an example of a recently qualified biomarker,
12 total kidney volume in autosomal dominant
13 polycystic kidney disease and then end with some
14 take home points.
15 First of all, I think it's good to
16 define what drug development tools are.
17 Oftentimes DDT is mistaken for a pesticide so I'd
18 like to say drug development tools, which we call
19 DDTs here, are methods, materials, or measures
20 that aid drug development. Currently, we have
21 three qualification programs at CDER for drug
22 development tools. Those are clinical outcome

1 assessment qualifications, animal models under
2 Animal Rule qualification, and biomarker
3 qualification. The draft guidance for
4 qualification process for drug development tools
5 was issued in 2010. It was finalized in 2014. We
6 also have a lot of information on the webpage.
7 The information is given there.
8 Since Allison already covered the
9 definition and types, I'm not going to. I just
10 wanted to show some examples of biomarkers, some
11 that you're very familiar with, serum creatinine,
12 c-reactive protein, HIV viral load, BRCA1
13 mutations, blood pressure, tumor volume by
14 imaging, and FEV1 which is functional measure just
15 to give you some examples.
16 I am also part of the NIH/FDA or the
17 FDA/NIH Joint Biomarker team and proud to be part
18 of it -- and the BEST glossary and the webpage,
19 you will get a lot of information on some of the
20 details.
21 Biomarkers have been used in drug
22 development for a very long time. This is not a

1 new concept. Biomarkers have been used to
2 understand molecular pathways that underpin
3 disease. They've been used to understand
4 mechanism of action of therapeutics. They've been
5 used in pre-clinical and clinical safety
6 assessments, in dose selection and also in
7 modifying the clinical trial design through
8 stratification, patient selection or enrichment,
9 and sometimes as surrogate endpoints. They've
10 also been used as companion diagnostics to select
11 the right patients for increased efficacy or
12 safety.
13 Here are the two pathways to integrate
14 biomarkers in drug development at FDA, so this
15 will give you the CDER perspective. There are two
16 pathways and oftentimes the question is which
17 pathway do I use. I'll say it depends on the
18 objective. If the objective is to use the
19 biomarker in a single-drug development program,
20 then for you the best path would be acceptance
21 though IND, NDA and BLA submissions. Here a
22 sponsor contacts the appropriate review division,

1 provides the rationale for the use of the
2 biomarker, preliminary data, and then the
3 biomarker gets accepted into the drug development
4 program. And you might see the biomarker
5 information in drug labels; depending on the type
6 of biomarker, you will see it in different
7 sections of the drug labels. Sometimes this
8 information may be buried in the reviews and
9 strict protocols if it's just as an inclusion or
10 exclusion criterion.
11 However, if your objective is to
12 establish the biomarker for use in multiple drug
13 development programs, then your path of choice
14 should be biomarker qualification. Any individual
15 or group can send in a submission for biomarker
16 qualification but oftentimes we see consortia are
17 the ones who send us submissions. Here the risk
18 and resources are shared among the consortium
19 members so it becomes an easier process. Once
20 qualified, the biomarker information is announced
21 as draft guidance and then we finalize it and so
22 that is publicly available.

1 Here is a definition of biomarker
2 qualification. We define it as a conclusion that
3 within a carefully and specifically-stated of use,
4 the biomarker has been demonstrated to reliably
5 support a specified manner of interpretation and
6 application in drug development.
7 Since we talk about the context of use a
8 lot, I thought I'd define that, too. It's a
9 comprehensive statement that basically describes
10 the manner and purpose of use for the biomarker in
11 drug development. So in biomarker development
12 itself, if it's going to be used for -- in drug
13 development, let's say, you have to have some idea
14 of how it's going to be used so that's where the
15 context of use comes in. As data accumulates,
16 your context of use might change because it's
17 always the data that support the hypothesis that
18 makes the hypothesis. You cannot change the data
19 to fit the hypothesis. It always has to be change
20 the hypothesis to fit the data.
21 So the context of use is a very
22 important consideration in biomarker development

1 and in biomarker qualification. This in turn
2 drives the level of evidence needed which then
3 drives the qualification process. It would be
4 wonderful to have evidentiary standards for
5 different types of biomarkers for different
6 context of use. We are not there right now but we
7 are working towards that.
8 I'd like to point you to the bullet on
9 FDA co-sponsored workshop with M-CERCI and Critical
10 Path Institute that we held in August of 2015. We
11 discussed evidentiary considerations for
12 enrichment biomarkers and safety biomarkers. And
13 the last bullet tells you something about the
14 upcoming meeting the FDA and FNIH biomarker
15 consortium workshop that's planned for April and
16 we'll be discussing evidentiary criteria for
17 safety biomarkers which is the next step after
18 considerations.
19 In the meantime, here are some
20 considerations for those of you who are thinking
21 of taking your biomarkers towards qualification.
22 It's a great thing to know what your biomarker is

1 right, going into and what's the type of biomarker
2 and what the context of use of the biomarker for
3 use in drug development should be. And then you
4 need to have an understanding of how they
5 correlate. That was something that the previous
6 speakers brought up, how is the biomarker
7 correlated with the clinical outcome, for example,
8 or the treatment when applicable. That would be
9 needed for the proposed context of use.
10 Next comes assay considerations. It's
11 good to have an analytically-validated method
12 going into biomarker qualification. Even though
13 we don't qualify the tester, the device, it's we
14 do need an analytically-validated method to be
15 sure to be believe in your data that's coming out
16 of the assay. It's a good thing to have the
17 biological rationale for use of the biomarker but
18 we do understand in gene expression, you know,
19 signatures or proteomic signatures, mRNA, it may
20 be difficult to have a clearly-defined biological
21 rationale.
22 Next, you want to see what type of data

is already available and it might be retrospective or prospective data, registry data, etcetera. And then you need to remember that we need to see some reproducibility of data. For example, an enrichment biomarker, you might need a test data set to identify your biomarkers and the cutoffs and whatnot. And then you have a confirmatory data set to show that the biomarkers behave the way they are expected to behave. It's also important to remember that even if retrospective data is okay, we do need pre-specified statistical analysis plans. So in the end, it's the strength of evidence that decides whether a biomarker can be qualified or not.

In the process itself, we have three stages. These are initiation, consultation and advice and review. Because of time constraints, I don't want to delve into the details but in the initiation stage, basically you come to us with a letter of intent. Then we make a decision whether to accept it into the program or not. And then once it's accepted, we ask for additional details

1 in the consultation and advice stage.
2 This is a very collaborative process.
3 We work with you in helping you develop the
4 biomarkers and once the biomarker development is
5 complete, it goes to the review stage. And once
6 it's decided to qualify the biomarker, then an
7 internal FDA development process ensues.
8 These are not drawn to scale so please
9 don't think that it takes us internally as much
10 time as it takes you guys to develop the
11 biomarkers and for qualification. But we do have
12 to come up with a draft guidance. We have to
13 publish the FR notice and the draft guidance is
14 published. And then after the public comment
15 period, we finalize this guidance.
16 So far, we have qualified 13 biomarkers
17 and 6 submissions have been successful. Three of
18 them are for non-clinical safety biomarkers.
19 Those are 10 biomarkers in total and three
20 clinical biomarkers have been qualified fairly
21 recently. Currently, we have 25 submissions in-
22 house; 4 in the initiation stage; 18 in the

consultation and advice stage; and 3 in the review stage.

Another question that's often asked is what kind of biomarkers do you see in your submissions. So about 50 percent of them are for safety biomarkers and 33 percent for patient selection, 17 percent for response and recently one for monitoring our patient adherence biomarker.

I was asked to provide an example of one of the qualified biomarkers so here is one. This is the total kidney volume in autosomal dominant polycystic kidney disease. We got this submission form the Polycystic Kidney Disease Outcomes Consortium which is in the umbrella of Critical Path Institute. And I just wanted to mention that just to develop these data elements and to combine the data, it took them two to three years. So please plan in advance to have the right data elements that allow you to combine data if there would be a need to do that. And then they developed their disease progression model using

1 total kidney volume as the biomarker. So this
2 gives you the objective, their state of drug
3 development, where it would be used, and their
4 proposed context of use. I don't want to go into
5 the details here but they did want to use the
6 biomarker in all clinical stages of drug
7 development that included proof of concept dose
8 ranging as well as confirmatory clinical trials.
9 What I wanted to point out is that we
10 have a biomarker qualification review team which
11 is specific for each submission. We have the
12 people with the right expertise on this team and
13 they conducted additional analysis. They even
14 perform model development and cross-validation and
15 they limited their analysis to patient population
16 that represents the population that's likely to be
17 enrolled in clinical trials.
18 And modalities -- imaging modalities
19 were another, you know, part of the submission.
20 Some of the data was MRI data, some CT data, and
21 some ultrasound data.
22 And we suggested that patient age and

1 EGFR be considered as co-variants so that's
2 another thing to remember, to provide the best fit
3 model and we found that the total kidney volume
4 did provide a modest improvement in predicting the
5 risk of a confirmed 30 percent decline in EGFR.
6 And this was confirmed through cross-validation
7 and also validation with a separate internal data
8 set which we call external validation, little bit
9 of an oxymoron there.
10 And a draft guidance was published and
11 that provides you -- I just wanted to give you an
12 example. So there's a "you statement."
13 Basically, it says what's the biomarker, how is it
14 measured, and what's it qualified for, and then it
15 provides you with some conditions for qualified
16 use as to what patient population, etcetera should
17 be use and how it should be measured. Please go
18 to the webpage to get the details because of the
19 time constraints again.
20 And here are some take home points. So
21 biomarkers can be integrated into drug development
22 through one of the two pathways, the regulatory

1 submissions for drug approval in the context of a
2 single drug or biomarker qualification. I would
3 like to say that you don't have to qualify a
4 biomarker to us if it’s in drug development. Biomarker
5 qualification is a voluntary process intended for
6 biomarkers to be used in multiple drug development
7 programs and the advantage is that once qualified,
8 the biomarker can be used for the specific context
9 of use in regulatory submissions without having to
10 reconsider and reconfirm its suitability.
11 Please talk to us early. There are
12 other programs that I didn't talk to you about.
13 They are called the Critical Path Innovation
14 Meeting where you can discuss early biomarker
15 development. We also have a letter of support
16 initiative which is meant to give visibility to
17 promising biomarkers. So please feel free to
18 contact me and I'd like to thank Drs. Janet
19 Woodcock, Charlie Buckman-Garner, Suzie McCune,
20 Chris Leptak, Marianne Noone, Sarmistha Sanyal and
21 Katie Haskins. Thank you.
22 (Applause.)

DR. KUMAR: Thank you. I'd next like to invite Katie O'Callaghan, who is with the Center for Devices and Radiological Health, to discuss the MDDT program.

DR. O'CALLAGHAN: Good morning.

(Chorus of good mornings.)

DR. O'CALLAGHAN: Thank you, Allison, and to the organizers for the kind invitation to speak to you all today. I don't know if you can see behind that slide. It's a little dim here but it's -- I put Russian stacking dolls up there because as I've been involved with the biomarker efforts at FDA, I've come to realize that the medical product development and evaluation process is oftentimes a little opaque from the outside. And so part of what I'm going to try to accomplish with today's talk is to unpack that a bit for all of you.

So for those of you who may not be familiar with the Center for Devices and Radiologic Health, we are an organization of about 1,700 scientists and other public health

1 officials, and we are responsible for ensuring the
2 safety, effectiveness, and quality of over 5,000
3 different types of medical devices. So it's quite
4 a wide range of technologies that we have to stay
5 on top of the scientific and technical advances in
6 those fields. And this includes treatment devices
7 like coronary stents; it includes diagnostic
8 devices, imaging, MRI machines, lab tests, a wide
9 range of products from very low-risk things like a
10 blood pressure cuff to permanently surgically
11 implanted heart valves, so it's quite a range of
12 risk profiles, technologies and so on.
13 And so it's really critical for us to
14 maintain our focus on the patient at the center of
15 everything that we do and so our vision at CDRH is
16 that patients in the U.S. will have access to
17 high- quality, safe and effective medical devices
18 of public health importance first in the world.
19 We recently released our strategic
20 priorities for the next two-year period. One of
21 those three priorities is to partner more closely
22 with patients, and this priority reflects a

1 recognition that patients, while we do much of our
2 work on behalf of patients, we can do much more to
3 partner with them in our work to advance public
4 health safety and as well as innovation.
5 This schematic is one that we use to
6 depict the product development evaluation and
7 access continuum for medical devices. One of the
8 unique features that I think makes working in the
9 device realm particularly exciting is that we're
10 not so much dealing with discovery as with
11 invention and building and designing, and so there
12 are a lot of opportunities there to use patient
13 inputs to better inform design and improvement of
14 available devices. And our work at FDA includes
15 not just oversight of the products going through
16 this continuum, but we also seek to promote the
17 public health and promote innovation by a variety
18 of initiatives that will make this process more
19 predictable and more efficient so that promising
20 technologies get to patients as quickly as
21 possible.
22 When we evaluate medical devices, we

1 look at scientific evidence from a variety of
2 domains. Roughly speaking, they can be lumped into
3 human clinical, computational, animal and bench
4 top, and biomarkers, of course, play a key role in
5 our evaluation of many device types.
6 As Allison alluded to in her opening
7 remarks, when Dr. Califf arrived at the Agency, he
8 recognized that there was a lot of confusion that
9 was perhaps contributing to some of the delays in
10 the development of new medical products that had
11 to do with fundamental confusion about the use of
12 terminology and how the terms and concepts were
13 related to each other and how they feed into the
14 medical product development and evaluation
15 process. And so he elevated this issue as one of
16 the priorities for the FDA/NIH Joint Leadership
17 Counsel in 2015.
18 And so a group of scientists from both
19 agencies has been feverishly working together over
20 the past year to put together the best resource
21 that Allison spotlighted in her opening remarks.
22 So this is up on the website on the National

1 Library of Medicine. It's meant to be a living
2 resource. It includes definitions of some key
3 terms about biomarkers and other potential
4 endpoints and outcome measurements, and we
5 certainly welcome feedback and have plans to build
6 upon this resource over time. And the vision is
7 that this consistent use of terminology and
8 clarification of how the concepts tie into each
9 other will help accelerate development and
10 refinement of medical products which will lead to
11 improvements in health outcomes.
12 So here's the unpacking. So how do we
13 evaluate medical advances? These are some of the
14 terms that you can go and take a look at the best
15 resource for the definitions of. But here I'm
16 going to try to stick to plain language about the
17 concepts. So the clinical benefit is the thing we
18 care about and the effect we want to see in a
19 population or in a patient.
20 When we unpack that a little bit more,
21 what are we talking about? We're talking about
22 outcomes or more specifically endpoints, so what

1 affect do we want to see in patients, how is that
2 effect assessed in a clinical study. These
3 endpoints can be clinical. They can be patient-
4 reported. They could be biomarkers and oftentimes
5 it's a combination of aspects from each of these
6 domains. And endpoints are more specific than
7 outcomes. They include very specific definitions
8 of how the outcome will be measured, at what time
9 point, etcetera. And we sometimes look at
10 endpoint measurements -- you'll hear a lot of talk
11 about surrogate endpoints -- these are ones where
12 the actual measurement doesn't in itself have
13 inherent value but we believe it may have value
14 because of its correlation and relationship with
15 health outcomes that do have value.
16 So if we unpack that even further, what
17 are we looking at? We're looking at biomarkers,
18 analytes, or potentially concepts. This is the
19 reductive core thing that we want to measure as an
20 indication of change in the outcome or endpoint.
21 And there should be a clear or hypothetical
22 connection to the clinical benefit at the top

level. And the way that we measure that thing, that core reductive thing is through the use of a test or tool or instrument, and it may include a variety of components. There may be assays. There may be instruments, technical protocols, materials, and so on.

So to illustrate this with an example, if we take a look at heart attack treatment and prevention, the clinical benefit we seek to achieve with this treatment is reduction and myocardial infarction, or heart attacks. So the outcome or the endpoint we may look at in a clinical study would be MI at nine months after the intervention or treatment. And this would be assessed through a combination of cardiac biomarkers like troponin plus symptoms of ischemia; we may have imaging biomarkers like changes in the EKG and other imaging endpoints listed here.

And so the concept or the biomarker that we're looking at, you know, the troponin itself, the wavelength changes, the presence of

1 intracoronary thrombus and so on. And so the
2 test, the troponin test, the EKG evaluation, the
3 angiography, that is the instrument or the tool.
4 And so these tools are really critical to how we
5 evaluate medical products.
6 And this is a slide that one of the
7 people on my team put together. I think it's a
8 great analogy of why we're putting attention and
9 effort into qualifying biomarkers and other tools.
10 This picture was taken from a trip he took to
11 Africa where they got stuck in this long line of
12 trucks waiting to get across a river. And the
13 line had backed up because the ferry could only
14 carry one truck at a time, and so this is
15 essentially what we're doing now with biomarkers
16 through the routine case-by-case evaluation. But
17 the idea is that if we qualify a biomarker for a
18 given context of use that we're building a highway
19 across which a variety of trucks can come across
20 more quickly and more efficiently.
21 So I also just wanted to touch on the
22 point that endpoints are not the only use for

1 biomarkers and other tools. As Shashi listed,
2 quite a few options that these tools can be used
3 for in medical product evaluation, clinical study
4 endpoints, patient selection, diagnosis, non-
5 clinical roles like substituting for animal or
6 human studies or minimizing the use of animals or
7 reducing the duration or sample size that's
8 needed.
9 So now to pack it back up. How do we
10 evaluate the evidence around the moments that are
11 taken to evaluate a promising therapy? We take
12 the measurements from the test or the tool. We
13 want to assess the validity of that tool, how do
14 we know that the measurements its making are
15 reliable; what's the clinical validation or
16 content validation; how do we know the thing it's
17 measuring means something. And then fit for
18 purpose reflects the idea that the amount of
19 evidence and the strength of evidence that we need
20 depends a lot upon how the tool is meant to be
21 used, what's the context of use, what are the
22 advantages and disadvantages. And then, of course,

clinical utility is the conclusion that a use will lead to net improvements in health outcomes and what have you.

So, you know, use of biomarkers and other tools in early development and clinical and regulatory evaluation are things that we see through either individual applications or through the qualification program and the strength of evidence depends on that context of use.

So in summary, I think it's clear to all of us here that advances in diagnosis, treatment, and monitoring of patients with TBI and many other conditions is hindered by gaps in communication an also in measurement science. And so some of the activities that FDA is doing that you've heard about are aiming to bridge these gaps. This workshop, I think, is a great step forward in that arena as well, and collaborative science is really needed to improve outcomes for these patients. Thanks for your attention.

(Applause.)

DR. KUMAR: Thank you, Katie. So now

I'd like to introduce Dr. Daniel Krainak from the Office of In Vitro Diagnostics and Radiological Health in CDRH.

DR. KRAINAK: Hello. Hi. My name is Dan Krainak. I am with the Office of In Vitro Diagnostics in Radiological Health, the Division of Radiological Health. And I'd like to just re-emphasize FDA's support of the development of TBI biomarkers. I'm going to talk about imaging assessments and quantitative imaging biomarkers in particular.

So I'd like to distinguish a little bit imaging assessments form quantitative imaging biomarkers. So the imaging system includes the patient, the imaging system, the physician, often radiologist and their assessment of the concept of interest. This imaging system itself would include the equipment you're using; that's the scanner, acquisition protocols, reconstruction methods and any post processing. So something that I would consider an imaging assessment and

1 maybe one mentioned earlier today, would be like a
2 region of hypo or hyperintensity on a T2 MR
3 system. And I'd like to also note that there are
4 many semi- quantitative or quantitative parametric
5 maps that are used in imaging assessments but I
6 would kind of distinguish them from being
7 specifically biomarkers.
8 So in the regulation of imaging devices,
9 one of the key factors we have are intended use.
10 Most imaging devices have very in general intended
11 uses. For example, they're intended to produce
12 cross-sectional images of the body. Ultrasound
13 systems and analysis, they provide processing and
14 display capabilities for a variety of clinical
15 applications. Images might show cross-sectional
16 images of the body that display anatomical
17 structures. And often they'll include a statement
18 that says something along the lines of "these
19 images and/or spectra, when interpreted by a
20 trained physician, yield information that may
21 assist in diagnosis." One thing to note is for
22 all the imaging devices with intended uses like

1 this, I would wager that almost all of them or
2 most of them have some type of quantitative
3 feature. They're all used by physicians when
4 they're assessing a variety of diseases but very
5 few of them have any specific claims about that.
6 So in contrast, we have quantitative
7 imaging biomarkers, so it's a very similar system
8 but here we have the patient, the imaging system,
9 the measurement which translates into the
10 quantitative imaging biomarker and that
11 quantitative imaging biomarker, or QIB, is what we
12 look at in terms of the concept of interest. So
13 an example of QIB might be something like
14 fractional anisotropy in the corpus callosum,
15 assessed in a region of interest, drawn on the
16 midline sagittal slice, so it has to be specific.
17 It's a measurement.
18 So in terms of devices, and this applies
19 also to biomarkers, what evidence do we require?
20 Well, the evidence depends highly on the intended
21 use. As I mentioned, most imaging devices have
22 very general intended uses. So a device that is

1 intended to provide tools for measuring volume
2 does not require the same evidence as a device
3 that's used to measure changes in micro lesions
4 from CT images in patients suspected of mild TBI.
5 So the evidentiary standard here is very, very
6 different. So often, as mentioned previously, as
7 the intended use gets more specific, the
8 expectation for the evidence increases. So there
9 is a high level of evidence required for more
10 specific intended uses. It's more directed toward
11 the particular QIV.
12 So, as I was just mentioning, validation
13 depends of the claims and this applies to both
14 development tools, as Shashi and Katie were
15 mentioning, and the context of use for biomarker
16 qualification and it also depends for medical
17 device regulation and the intended use.
18 So I'd like to talk about a couple key
19 ideas about validation and these are from the BEST
20 glossary, as mentioned many times today. So
21 there's analytical validation. This is
22 establishing that the performance characteristics

1 of the test or instrument are acceptable in terms
2 of things such as sensitivity, specificity,
3 accuracy, precision, and other relevant
4 performance characteristics. So this is a
5 validation of the test or tools' or instruments'
6 technical performance, but it's not validation of
7 whether it's useful or not.
8 Then we have clinical validation and
9 this is establishing that the tool, test or
10 instrument acceptably identifies measure or
11 predicts some concept of interest. And so the
12 concept is the aspect of an individual's clinical,
13 biological, physical or functional state that the
14 assessment is intended to capture. So -- and
15 often those two things interact, analytic
16 validation is necessary for clinical validation in
17 most cases but the types of study designs,
18 etcetera that you might use to examine both can be
19 quite, quite different.
20 So in terms of assessing a QIV, we have
21 many sources of variability at all stages.
22 There's variability in the patient population,

from physiology to pathology, variability in the imaging acquisition system, protocol, slice thickness, manufacturer, make, model, vendor, software version. All these things can influence variability, increase it. There's variability in the measurement whether it's automated or semi-automated, which algorithm you choose, etcetera.

So here's a brief outline of what we would expect in terms of looking at a QIB analysis plan. So step one, define the QIB and its relationship to the quantity being measured; define the question to be addressed in the form of a hypothesis or bounds on performance; look at the experimental level; is this something on a per lesion basis, per patient basis? Define the statistical measures of performance. There are many different metrics you can look at in terms of analytical performance. Specify the elements of the statistical design; what are you using as your reference truth, around truth; what are the reproducibility conditions? Determine the data requirements; is some type of power analysis;

1 what's the patient population; what types of
2 images. And then collect the data and perform the
3 statistical analysis.
4 So I'd like to mention Dan Sullivan's
5 here and he'll be speaking later this afternoon
6 about the Quantitative Imaging Biomarker Alliance.
7 It's a division of the Radiological Society of
8 North America. And two years ago roughly, they
9 published some -- a series of papers and
10 statistical methods in medical research, and these
11 provide a common framework for researchers to
12 assess technical performance. So today I've moved
13 a little into analytical validation but it's often
14 also called technical performance in terms of
15 imaging analysis. And the goal of these is to
16 ensure reliability of image measurement. This
17 series of papers was drafted with collaboration
18 between physicians, regulators, statisticians,
19 imaging scientists, etcetera. I think they're a
20 very, very good resource for those interested in
21 how you might do this type of assessment.
22 So some take home messages. For

1 neuroimaging biomarkers, the validation depends on
2 the claims. These are often laid out in the
3 context of use or in the indications for use in
4 terms of pre-market submissions. Two components
5 of validation are needed, both analytical
6 validation and clinical validation. The first
7 step that you need to determine the appropriate
8 validation is to determine the claim. If you
9 change the claim, you'll probably change your
10 study design, change the analytical requirements
11 that you might have, change what your patient
12 population might be.
13 And then lastly, please come discuss
14 your potential biomarkers with FDA early and
15 often. There are many, many forums to talk to
16 regulators, especially at the FDA, whether it's
17 through drugs or devices, the MDDTprogram, or the
18 DDT program. I think we're very interested in
19 collaborating early and early feedback can be
20 very, very beneficial to sponsors so thanks and
21 here's a link to the BEST resource as well as the
22 QIBA metrology papers. I think these will be

1 available Later.
2 (Applause.)
3 DR. KUMAR: Thank you, Dan. And now I'd
4 like to introduce Dr. Kellie Kelm who is with the
5 Office of In Vitro Diagnostics in CDRH.
6 DR. KELM: Good morning. Thank you. As
7 Allison said, I'm Kellie Kelm. I'm the Branch
8 Chief for Cardio-Renal Diagnostic Devices in the
9 Division of Chemistry and Toxicology Devices,
10 NOIR. And today I'm going to talk to you about
11 analytical and clinical validation of in vitro
12 diagnostic tests. And a lot of what I'm going to
13 talk about, although it's what I do day-to-day
14 when people want to market their devices for
15 clinical use, a lot of this can also pertain to
16 what we would look for drug development for
17 example.
18 So first, for those of you who may not
19 know what is an IVD, and this is taken from the
20 Code of Federal Regulations, the definition is
21 "reagents, instruments, and systems intended for
22 use in the diagnosis of disease or other

1 conditions including a determination of the state
2 of health in order to cure, mitigate, treat, or
3 prevent disease or its sequelae. Such are
4 intended for use in the collection, preparation,
5 and examination of specimens taken from the human
6 body." So we have a number of things that we
7 regulate from your collection devices, your
8 instruments, your software, the reagents
9 themselves, etcetera. It's from sample collection
10 all the way through test report.
11 And IVDs are very interesting. We have
12 also a very wide range of where these are. So
13 these can be the tests that are offered in the
14 clinical labs but they're also the near patient
15 tests and then they're the ones that go home, so
16 they're pregnancy tests or other tests that are
17 used at home. We regulate all of those and those
18 drive -- you know, where you want these things to
19 be used will drive how your study should be done
20 and how we review them.
21 So IVDs are used for many things, for
22 diagnosis, for screening, prediction, prognosis,

1 surveillance, first response but we don't regulate
2 devices for environmental screening or forensic
3 use. Those are not considered medical devices.
4 So similar to what Daniel said, the way
5 we really look at how we review a device is what
6 you want it to be used for. So our review is
7 driving by the intended use and I'll have a slide
8 that sort of has an example for you. And the
9 other thing is we have to also determine what the
10 risk of the use of the device is. In that case,
11 we sort of take your intended use and then
12 consider what are the risks, what are the
13 consequences of a false result, both a false
14 positive or a false negative and in certain cases,
15 one or the other may be more important for us to
16 consider.
17 So the type of review -- so that is a
18 510(k) for moderate risk devices; a PMA for high-
19 risk devices and the types of validation studies
20 that are needed depend on what you say your device
21 is going to be sued for. So here's an example of
22 a product that actually was what we considered de

1 novo so we created a new regulation for this
2 product. And this is the NephroCheck Test system
3 and you can see here -- and I won't read it -- but
4 it's an example. It specifies how it's going to
5 be used and the clinical indication so
6 specifically the population and what it's to be
7 used for. The NephroCheck is actually a risk
8 score and it uses the measurement of two proteins
9 in a score that's provided to the physician in
10 order to make, as it says, the risk assessment for
11 kidney injury.
12 So when we actually have a pre-market
13 submission, we look at analytical performance and
14 clinical performance similar to what Daniel talked
15 about. So first of all, how accurately does your
16 test measure the analyte that you say that it's
17 measuring; how reliability. So we're looking at
18 precision over time. If you have the same sample
19 tested over 20 days, do you get the same result
20 when you test it every day? We're looking at the
21 limit of detection, potential interferences from
22 both endogenous and exogenous substances, cross-

1 reactivity. Is your assay linear over its
2 measuring range? That's a very important quality
3 of an assay. Is there carryover in your test
4 system from one sample to another or from other
5 assays to another?
6 And the analytical performance should
7 also be performed how you intend it to be used.
8 So if you want this to be a point of care test,
9 then we actually want to see precision studies and
10 your accuracy studies at three point of care sites
11 by your point of contact users. If you want it to
12 be offered at home, then we actually need home
13 users to do it and show that they can follow the
14 instructions for us without any guidance from your
15 staff or anybody. They should read the
16 instructions and they should perform the test and
17 then you should evaluate the accuracy of how well
18 they do and how informative the instructions are.
19 So those are a lot of the kinds of things that we
20 look at and that should be evaluated if you want
21 your test to be, for example, offered at home or
22 at point of contact.

1 Clinical performance: How reliably does
2 the test measure the clinical condition and that
3 can be done in a number of ways, either what we
4 call a method of comparison or actually a clinical
5 study.
6 IVDs have their own labeling regulation,
7 21 CRF 809.10. It is listed here. So in addition
8 to adequate instructions for use for the
9 populations using the test, once again, your
10 instructions for a home user have to be a lot more
11 simple than a trained clinical laboratorian.
12 Their other things include warnings, limitations,
13 how is the user going to interpret the results,
14 and IVDs required a summary of the performance
15 characteristics, both your analytical and your
16 clinical data that you've derived in the pre-
17 market submission.
18 So clinical performance, so as -- same
19 as those -- the imaging markers, we're also
20 looking for clinical validity. So your device for
21 an in vitro diagnostic must have a clinical
22 indication and have clinical validity to support

1 it. And we do see a variety of different kinds of
2 evaluations but your samples should represent the
3 intended use population. We see prospectively
4 collected samples. We see retrospective studies
5 and we also see people support their IVDs with
6 literature.
7 The only caution is if you're doing a
8 retrospective analysis, for example, stored bank
9 samples from a previously-performed prospective
10 study, make sure that the study reflects your
11 intended use population, you know, looking at the
12 inclusion-exclusion criteria, that it matches, you
13 know, what you want your device to be used for.
14 And if you're talking about bank samples, sample
15 storage is very important. You know, if you are
16 taking samples that have been stored for five
17 years at minus 20, is your analyte still going to
18 be stable after 5 years at minus-20?
19 And obviously, we're looking for the
20 number of positives to be statistically
21 appropriate.
22 I have an example just to -- you know,

1 we do see, unfortunately, sometimes where the
2 clinical studies that are available don't match
3 exactly what your test wanted to be and so just to
4 sort of come up with an example here of -- with a
5 cautionary tale. So let's say that someone is
6 interested in a novel biomarker test to rule out
7 TBI in at risk- patients so you want to offer this
8 test so that you can actually send people home
9 without any further evaluation. You've used a
10 previously performed study so you're doing a
11 retrospective analysis and you're looking at the
12 predictive value of your biomarker test to some
13 outcome; and in this case, CT scan. Negative
14 predictive value is excellent. Everyone is
15 excited. But sometimes you have to look at some
16 of the finer details. So the study used bank
17 samples from a study intended to assess a
18 different use; only included patients that had had
19 a CT scan and excluded all others; different
20 performance seen when used in your whole intended
21 use population, people that aren't going to get a
22 CT scan; selection bias here is not controlled

1 for; this design favors patients more likely to
2 have a CT scan ordered in this timeframe, so
3 you're missing that information on all those other
4 people that have been excluded. So the baseline
5 risk of included versus excluded patients may not
6 be the same. The inclusion-exclusion criteria for
7 the study may not be appropriate for the test and
8 what you want it to be used for. PPV and NPV or
9 even relative risk may not be accurately
10 calculated for what you want.
11 So, you know, you consider a study
12 design where you can follow patients that don't
13 get a CT scan and I think what we're, you know,
14 saying is that we can be fairly -- I think we've
15 all said is we can use a lot of information, not
16 just CT and we'll, you know, consider any proposal
17 that you have and discuss it with you.
18 So here I have a number of FDA guidance
19 documents that I like to refer people to. I think
20 the fourth bullet is especially important. This
21 is the guidance document on our pre-submission
22 program. This is a free program where FDA can

1 provide you feedback before you do your analytical
2 and clinical validation studies; if you have
3 questions about the regulatory pathway; before you
4 go on the market, are you class 2, are you class
5 3; I don't have the regulation; you know, what's
6 the best path for me. You know, we love this
7 program and it allows us to have that early
8 interaction with companies before they do their
9 studies.
10 And for IVDs, we recommend the Clinical
11 Laboratory and Standards Institute Evaluation and
12 Protocol Guidelines, and these are guidelines that
13 are written by groups from industry, academia,
14 regulators to sort of come up with protocols for
15 how you evaluate linearity and precision and limit
16 of detection and all those things and so I refer
17 you to those.
18 Lastly, OIR, the in vitro diagnostics
19 side, for a number of years, since 2003, have been
20 putting up summaries of the information that we
21 review in 510k's online. So although we may not
22 necessarily have a TBI biomarker test there yet, I

1 encourage you to go and look up other tests,
2 whether you want to look at what data people have
3 done for other kinds of tests, you can look at
4 that here and it's similar to what we do for PMAs.
5 And this is just an example of a newborn screening
6 assay, and if you click on "decision summary," at
7 this link when you find, for example, an assay
8 you're interested in, you'll see a summary of the
9 data, the precision, the linearity, and the other
10 studies that people have done and it gives an
11 example of what people have performed.
12 So, that's it for me and I look forward
13 to hearing more from you. Thank you.
14 (Applause.)
15 DR. KUMAR: Thank you, Kellie. I'd now
16 like to introduce Dr. Peter Como with the Office
17 of Device Evaluation, CDRH.
18 DR. COMO: Thank you and thanks to all
19 of you for coming. Since I've been at FDA for
20 about 6-1/2 years, I've learned that the purpose
21 of these workshops is we need to learn from you.
22 So we appreciate you coming and we look forward to

1 your input.
2 As Allison said, I'm a medical reviewer
3 in the Division of Neurological and Physical
4 Medicine Devices. I tend to be the main clinical
5 reviewer for most of the TBI diagnostics and
6 therapeutics, and what I'd like to do is spend the
7 next couple of minutes, being mindful of time, on
8 some of the clinical trial design considerations
9 that myself, as a medical reviewer, needs to sort
10 of take into account when I'm reviewing an
11 application from a sponsor or an investigator.
12 Some of this information you've already heard this
13 morning and, hopefully, I'll have a couple of
14 other points to make.
15 So I think first and foremost, the
16 clinical trial design challenges in TBI are
17 noteworthy. As I've heard Colonel Hack and others
18 say many, many times, we really, unfortunately, do
19 not have gold standard diagnostic criteria for
20 TBI. Therefore, studies are really free to use a
21 variety of diagnostic criteria to determine
22 eligibility for our clinical trial. As you heard

1 Dr. Manley say, there's the ACRM criteria. The
2 CDC has criteria. There's various other criteria
3 that have been published. I believe at last
4 count, there were 42 different diagnostic criteria
5 schemes that were available.
6 And as you heard Drs. Levin and Manley
7 also say, there's actually a lack of gold standard
8 in terms of TBI clinical outcome assessment
9 measures. So a particular biomarker may be very
10 specific for detecting changes for a specific
11 aspect of TBI like cognitive function, but if
12 you're cohort enrolls TBI plus PTSD or some other
13 behavioral conditions, the biomarker sensitivity
14 may actually go away or be insignificant.
15 And as we've also heard, the level of
16 TBI severity is important and I agree with Dr.
17 Manley that we do need to move away from this
18 mild, moderate, severe. But we do have to have a
19 continuum of severity mainly because the biomarker
20 validation study, in my opinion, would need to
21 include the full spectrum of TBI severity in order
22 to come up with valid cutoff ranges or thresholds

1 or sensitivity calculations, because it may be
2 that a particular promising biomarker, as we've
3 seen with imaging, may be very, very, very useful
4 for detecting structural lesions but may be less
5 useful until we -- you know, as we hear new
6 research coming out about its sensitivity for
7 individuals that, quote, unquote, "look normal" on
8 imaging.
9 And as you've also heard, the biomarker
10 obviously has to demonstrate a robust relationship
11 with the clinical condition so, therefore, the
12 assessment of -- you know, the selection of
13 clinical assessment tools is very critical. And I
14 think one thing that is, I think, obvious to most
15 people but a validated TBI marker, if we're
16 fortunate to have one of those come on board soon,
17 is probably going to be insufficient to provide a
18 stand-alone diagnosis of TBI, which I think the
19 general scientific opinion is continues to be a
20 clinical determination
21 You've seen this slide already so I'll just skip
22 over it in terms of classifying TBI severity in

1 the interest of time. Some other clinical trial
2 design challenges that I come up against w hen I'm
3 reviewing a part application is that the use of
4 change in biomarker to assess recover, so we're
5 switching more from a diagnostic biomarker to a
6 prognostic biomarker-type of study design. So
7 obviously, that requires some degree of clinical
8 correlation as well.
9 And if we're using some type of a
10 determination of "return to normal," quote,
11 unquote, for a biomarker, you obviously have to
12 have some type of a reference or normative
13 database, because if you don't know it's normal,
14 how can you determine if an individual has
15 returned to normal in order to clear them to
16 return to the athletic field or the military
17 theater or return to work?
18 The return to normal range needs to be
19 associated with robust clinical evidence of
20 recovery from TBI. So just because the TBI
21 biomarker value went from an abnormal result to a
22 normal result, if indeed the patient is still

1 experiencing symptoms, behavioral, cognitive,
2 other functional symptoms, then we have a problem
3 because we have a patient who clinically doesn't
4 look ready to return yet their biomarker value
5 says they're fine.
6 And there are numerous examples in the
7 scientific literature over the years in which
8 we've seen therapeutic interventions in which you
9 could see a clear change in MR spectroscopy that
10 doesn't seem to correlate with the change in
11 clinical condition, so that's going to be
12 obviously very important.
13 The use of return to a baseline value,
14 which is another way of looking at a biomarker
15 obviously requires pre-injury data. If you don't
16 have a baseline, then it's hard to determine
17 whether or not that individual has returned back
18 to their baseline and that's not always readily
19 available in the clinical setting, although we're
20 starting to see now more and more, especially in
21 the athletic arenas and professional and
22 collegiate and high school sports that, you know,

1 many times the athletes are assessed with some
2 type of either a clinical assessment and as
3 biomarkers become available, hopefully, with
4 biomarker tools, at the beginning of the athletic
5 season and then if they sustain some type of a
6 concussive head injury, you have a baseline by
7 which you can compare.
8 One of the things that my colleague, Dr.
9 Biswas, is going to talk about in just a minute
10 after me is one of the cardinal fatal flaws that
11 we have seen here at FDA with regard to studies
12 that want to validate a diagnostic. And that is
13 the fact that you cannot use the same data set to
14 both determine your biomarker values, i.e., your
15 cutoff ranges and then use that same dataset to
16 validate it. That's sort of a major statistical
17 and clinical trial validation flaw. And in many
18 cases, we've actually had to tell sponsors that
19 they need to go back and conduct a second study
20 which, obviously, is more time and money on their
21 part but we cannot really accept that kind of data
22 because of the inherent flaws.

1 And of course, as is obvious, the
2 algorithm needs to be fixed prior to any clinical
3 validation study. You can't have a study that is
4 continuing, a biomarker or any other diagnostic
5 that's continuing to evolve before you're, you
6 know, going off to do your validation study.
7 So in terms of some other study design
8 considerations, as far as we're concerned right
9 now, tell us the diagnostic criteria you used in
10 your study. Many times we get applications that
11 say we plan to enroll people with a suspected head
12 injury and that's it, that's the main inclusion
13 criteria. That's not enough. The issue of
14 comorbidity needs to be addressed. The intended
15 use population needs to be described. Are you
16 validating biomarker in a TBI population or a TBI-
17 plus population? The specificity of the biomarker
18 may be used to enrich a study population as I
19 think you've heard already today. You need a
20 clear definition of the study population including
21 any features that you know from the scientific
22 literature or its use that may affect the

1 performance of the biomarker test performance, you
2 know, things that we often think about; age,
3 education, physical disability, ethnicity, other
4 kinds of medical or physiologic states that could
5 alter the biomarker results like other health
6 issues, medications that a person may be taking
7 that may alter the result, etcetera.
8 And then given the lack of a gold
9 standard diagnostic criteria, what we have
10 suggested to sponsors is the use of a best
11 estimate diagnosis which then becomes the
12 reference standard by which you're validating your
13 diagnostic against. And typically, that involves
14 a panel of experts that are blinded to the
15 biomarker result, that reviews all of the clinical
16 data and then determines whether or not the person
17 met the criteria for TBI. And we often will
18 require at least a majority consensus, such as a
19 two-thirds majority. You've heard from Dr. Kelm
20 that data is needed for the stability of the
21 biomarker and I think this is an important area in
22 TBI because we all know that TBI symptoms can

1 begin to resolve fairly soon after the initial
2 injury. So the position of the biomarker is a
3 critical component.
4 And then, you know, finally, last but
5 not least is one of the critical components of our
6 review is the level of risk that's involved with
7 false positive and false negative results because
8 obviously, a false negative result could delay the
9 need for immediate surgical intervention. As
10 you've heard, that can be life-threatening.
11 The study should also specify things
12 like phase of injury, the clinical setting, if the
13 biomarker results are being compared against a
14 normative database. These demographic factors
15 need to be taken into account.
16 So take home points then; the
17 development of TBI biomarkers is going to be
18 highly dependent upon the establishment of gold
19 standard diagnostic criteria; take into account
20 the heterogeneous clinical presentation; as we've
21 heard, the development of sensitive clinical
22 outcome assessment tools; we're hoping the TED

1 project is going to give us some of those answers;
2 and as you've heard, from our perspective, engage
3 FDA early and often via the pre-submission
4 process, and there's the link to the guidance that
5 Kellie just had up.
6 So thank you very much and we appreciate
7 your comments.
8 (Applause.)
9 DR. KUMAR: Thank you, Peter. I'd now
10 like to introduce Dr. Bipasa Biswas who is from
11 our Office of Biometrics and Surveillance and
12 there we go.
13 DR. BISWAS: Good morning and thank you
14 for coming here. So I'm going to present the
15 statistical issues and considerations for
16 evaluation of traumatic brain injury, the TBI
17 test.
18 So this is a basic outline, the
19 introduction as to what kind of biomarker tests
20 are available, test versus validation which was
21 alluded to in Dr. Como's presentation, then
22 intended use and indications for use and how it

1 impacts the study evaluation measurement or
2 analytical validation and then clinical evaluation
3 of the diagnostic test and finally, the summary.
4 So TBI biomarkers, as we have seen in
5 the morning, can be very diverse in nature. It
6 could be EEG-based, imaging, or a protein
7 biomarker, protein assays. And so there are
8 diverse challenges for evaluating these tests and
9 this depends on the intended use. As we have seen
10 before, that indications for use and intended use
11 has to be specified and that kind of determines
12 what would be the study that would follow. And
13 then the types of measurement and analytical
14 studies also depend on the test and the intended
15 use and indications for use.
16 So development and validation of a
17 biomarker test, the key point is that measurement
18 validation and clinical evaluation has to happen
19 after finalization of the TBI biomarker test. So
20 what does that mean? That once the test is
21 finalized and locked down with regard to its
22 design parameters, like an algorithm, and the

1 cutoff selection is finalized, the measurement
2 validation and the clinical evaluation happens in
3 a study which is in a population independent and
4 separate from that used in the development of the
5 test.
6 And why is there an independent
7 validation design? Because it objectively assesses
8 the device performance external to the conditions
9 and the data set used in the development of the
10 test, and thus it (inaudible) something -- issues
11 related to training bias. So to perform an
12 unbiased study, it's always recommended to have a
13 separate and independent data set on which you
14 evaluate the clinical performance of the test.
15 So what is the intended use and
16 indication for use and how does it impact? It
17 basically determines the device classification;
18 the clinical purpose of the study, what is it that
19 you want to claim; is it for screening, for
20 diagnosis, for monitoring; the study design, the
21 study population; the statistical hypothesis or
22 the estimation goals and the analysis that

1 follows. And some of the confidence of
2 indications for use, among many others, are what
3 does the device measure, detect, or what does it
4 identify; where does the device measure, the
5 anatomical region where it measures and on what it
6 measures so the analyte or the sample on what it
7 measures. Where is the device used has a big
8 impact on the performance of the device, so if the
9 device is going to be used in an emergency setting
10 versus as a home use, it will have a difference
11 performance. What does the device report; is it a
12 quantitative output; is it a continuous score, or
13 is it a categorical output? So those are the
14 important features that need to be laid out in the
15 indications for use and for what condition. So is
16 it for -- what is the target condition that is
17 being evaluated and on whom, so the target
18 population is important and by whom, so the user
19 could be a well-trained user of the device or it
20 could be a lay person, and that device performance
21 will also depend on who the users of the device
22 are.

1 So test validation and evaluation -- so
2 test validation, you would have a measurement or
3 analytical validation. So measurement validation
4 involves the characterization of base aspects of
5 the biomarker test's ability to measure the
6 biomarker; in this case, the biomarker for TBI.
7 And the measurement validation involves
8 measurement position, measurement bias, and
9 analytical studies like determination of limit of
10 blank, limit of detection, linearity, bias,
11 position, etcetera.
12 And clinical validation, there are two
13 approaches for clinical validation of a diagnostic
14 test. One is a clinical performance study which
15 you have seen in some of these examples before,
16 reporting sensitivity and specificity, and
17 sometimes we see what is called "clinical outcome
18 study." So I'll go over these.
19 So -- but measurement validation and
20 intended use and indication for use, how does it
21 impact? Basically, you could have a measurement
22 validation study but it also depends on what the

1 device output is. So if your device output is
2 categorical versus quantitative, you would have a
3 different measurement validation or different
4 positional bias assessment, different analyses for
5 that. The measurement validation also depends on
6 the setup, whether it's being used in an at home
7 versus in a clinical lab. And for a test with one
8 or more clinical decision points, it's important
9 to assess the test-measuring ability near the
10 medical decision point so that the user is aware
11 of the variability around the cut point.
12 What does the clinical evaluation
13 involve? The important considerations for a
14 clinical evaluation study often would rely on what
15 is the intended use or indication for use which
16 has been belabored in the previous presentations;
17 the study design as to what should be the study
18 population; how should the study be conducted; how
19 do we minimize and completely avoid the bias
20 associated with these types of studies;
21 statistical analyses of the collected data which
22 has to be pre-specified; and then finally,

reporting of the results taking into consideration what was the study population and the variability associated with these performances.

So diagnostic clinical outcome study -- so there are two types of diagnostic studies. One is the diagnostic clinical outcome study and the other is diagnostic performance study. So diagnostic clinical outcome study actually involves use of the device, result during a treatment or management intervention. And the performance is assessed, in part, by the intervention's affect on the subject outcome. So as an example, it could have a two-arm randomized trial; in one arm, you get the diagnostic device and the result kind of manage -- you use that -- the result from the diagnostic device to manage the patient and the other arm gets the standard of care. And we may sometimes look at clinical performance or the diagnostic performance of the device as well.

In the diagnostic clinical performance study, basically you look at the performance

1 characteristics of a test to inform how well the
2 test measures classifies or predicts what it
3 intends to measure compared to a comparative
4 benchmark, which is gold standard or the clinical
5 reference standard. So what are the typical
6 common clinical performance measures for
7 qualitative or a dichotomist test which gives you
8 an answer of "yes" or "no" or presence or absence
9 of a particular disease? We look at sensitivity
10 specificity pairs which kind of -- which evaluates
11 whether the test is able to detect the condition
12 per se; likelihood ratio positive and likelihood
13 negative pairs. You can also look at positive
14 predictive value and negative value but with the
15 caveat that it also depends on the prevalence of
16 the condition or the target condition in this
17 study population.
18 And then if you don't have a clinical
19 reference standard, the best measures to report
20 performance would be positive and negative percent
21 agreement which is estimated in the same manner as
22 sensitivity and specificity except that you don't

1 have a clinical reference standard here.
2 So clinical reference performance for a
3 quantitative test almost always involves
4 assessment of measurements, so similar to
5 measurement validation, you will be looking at
6 position, so closeness, like repeatability and
7 reproducibility. You will be assessing bias from
8 these moments and one thing to note is that
9 position and bias can be evaluated at the bench or
10 analytically or part of a measurement validation
11 of the biomarker test and also clinically
12 sometimes.
13 So the common clinical performances for
14 a quantitative test are clinical position, which
15 is repeatability; reproducibility; slope and
16 intercept from a linear regression, so there are
17 many different kinds of linear regressions; and
18 then the scatter plots from the test device versus
19 the comparator; and bias which is a mean
20 difference between the new test and the reference
21 method; 95 percent limits of agreement for and
22 (inaudible) difference plots to assess how well

1 the new test compares to a reference method.
2 So in summary, the take home message is
3 that intended use and indication for use is very
4 important. It needs to be -- it needs to specify
5 what is the type of test result, whether it is
6 continuous, categorical, or qualitative. And it
7 drives the design of the study, the target
8 population, the setting of the test, and planning
9 of the measurement validation and clinical
10 studies. And the development of the test and any
11 parameters associated with the test, all the
12 cutoffs need to be finalized before the validation
13 study happens and the validation study is in a
14 data set which is completely separate in
15 independent from the development study or
16 development of the test. Statistical analysis and
17 reporting of results depend on the intended use
18 and indications for use, and thus it is important
19 to plan the study carefully at the beginning to
20 align the performance with intended use and the
21 indications for use.
22 And these are some acknowledgements and

I have some references in terms of what the guidance is for statistical analyses and CLSI as well as ISO guidances. Thank you.

(Applause.)

DR. KUMAR: Okay. And to round out our last talk in the regulatory considerations section before we move on to questions is Dr. Diane Stephenson who is the Executive Director at the Critical Path Institute and to talk about her really important initiatives that she has going on with FDA.

DR. STEPHENSON: Thank you so much. It's a joy to be here. I'm speaking on behalf of my role at Critical Path Institute, a non-profit organization that, thanks to the support of FDA, is now just celebrating its 10 years.

And I start this talk off with thinking outside of the TBI world. I spent my whole career in industry trying to get therapies for these many devastating brain disorders, and those of us in industry may think that TBI is far behind. But

1 what I hope to share with you in this brief time
2 today is to tell you why I think TBI, and thanks
3 to the TED initiative, is really ahead of the game
4 and realizing that, as we've discussed today, this
5 is not a single magic bullet therapy or a single
6 magic bullet biomarker.
7 I also highlight these diseases because
8 just 10 years ago, the disease of multiple
9 sclerosis was in the same ballpark. My colleague,
10 Lynn Hudson, who leads our MS consortia, asked me,
11 in fact, to take this name, MS, out because we do
12 have therapies now. But it's because of the
13 recognition, just like oncology in precision
14 medicine, we can't take all comers into trials.
15 And as you know, therapies are targeting patients
16 with primary progressive versus relapse and
17 readmitted, and all these diseases, especially
18 TBI, tremendously benefit from the importance of
19 biomarkers, particularly in Alzheimer's disease.
20 So Critical Path Institute was
21 highlighted in 2014 with some great review
22 articles and Janet Woodcock is responsible for the

genesis of C-Path with our founder, our former CEO, Ray Woosley. And what we do that's unique is to bring all these stakeholders to collaborate, and the TBI community is already there and has been for quite some time.

This is a slide that was presented by Dr. ShaAvhree Buckman in OTS and CDER that shows there are so many public-private partnerships that exist today. The ones that are circled in "red" are all Critical Path Institute consortia and we received funding from FDA and our goals are to advance regulatory science through pre-competitive data- sharing and consensus data standards genesis.

I have the joy now of leading a newly launched consortium on Parkinson's disease that hopes and aims, with its mission, to integrate data from global sources with the goal of developing disease progression models for Parkinson's disease; there's a press release that just came out last week. We have a lot of stakeholders involved and again, core to our

1 mission is data-sharing and data integration,
2 something that TBI really does keenly own in their
3 successes to date.
4 There are 12 consortia at Critical Path
5 Institute and although we target distinct diseases
6 that may seem disparate in terms of their origin,
7 things like polycystic kidney disease which you
8 head Shashi talk about and other -- many disorders
9 of the brain, other disorders, even in pediatrics
10 recently, we share in common this concept of
11 precompetitive data-sharing to enable regulatory
12 decisions that one stakeholder cannot do on their
13 own. This includes qualification of biomarkers,
14 development of improved outcome measures, and
15 disease progression models to aid anyone working
16 in this disease. This is not target-specific.
17 It's not sponsor-specific. It's not drug-
18 specific.
19 We have a number of regulatory successes
20 that we've achieved over the years across the
21 disease we work in. I'm going to highlight just
22 briefly the successes in Alzheimer's disease

1 considering some of the challenges that are shared
2 in that disease with TBI and then other diseases
3 we won't have time to talk about today, but the
4 successes include biomarker successes, disease
5 modeling successes, this recent letter of support
6 that Shashi talked about, all aimed to try and
7 incentivize the use of biomarkers and improved
8 outcome measures in trials.
9 Our core mission is in data integration.
10 We are located in Tucson, Arizona and about a
11 third of our staff are really talented folks who
12 came from IBM; one of the largest facilities is
13 there in Arizona. We also get funding from the
14 State of Arizona. And core to our strengths is
15 integration of data, so this is not a repository
16 that just houses individual data sets. Our data
17 scientists work on pooling data through the
18 utilization of consensus data standards that we
19 developed and these integrated databases that then
20 can be brought to regulators to help achieve these
21 regulatory goals.
22 We have in our mission the development

1 of consensus data standards and I'm proud to say
2 through the support of One Mind, NINDS, and the
3 TED initiatives, there are the newest developed
4 therapeutic-specific standards. These are the
5 CDISC standards, were developed for traumatic
6 brain injury.
7 Soon FDA will be requiring all new drug
8 applications to be submitted in CDISC standards.
9 This really is known to accelerate the rate of
10 review of any new drug applicants. In addition to
11 helping accelerate drug treatments, these CDISC
12 standards are the core in which we integrate data
13 for our programs. We have several databases that
14 are available to qualified researchers beyond the
15 consortia that use these for regulatory goals. We
16 can find other experts and academics to answer
17 specific research questions in diseases such as
18 Alzheimer's, polycystic kidney disease, and
19 tuberculosis.
20 And the success we've had in
21 Alzheimer's, I probably won't have time to go
22 through this in detail, but I do want to highlight

1 to you an example because it's consistent with
2 some of the themes today. We heard about one
3 single source of data not being successful for
4 what we need to have confidence, but this is a
5 project that started many years ago and companies
6 were able to share through this mechanism, through
7 C-Path, placebo arm data from over 24 clinical
8 trials. All that data was pooled together along
9 with ADNI, the public-private partnership that is
10 responsible for biomarkers for Alzheimer's
11 disease. And that integrated data was used to
12 develop a disease progression model and a clinical
13 trial simulation tool.
14 This tool allows you to have a computer-
15 based model that takes all the parameters of the
16 subjects, age, baseline cognitive status, genetic
17 information and project the outcomes. This is the
18 first ever model-based drug development tool that
19 was achieved for regulatory endorsement by both
20 FDA and EMA. This was done for Alzheimer's
21 disease and we think that based on the success of
22 what's happening in the TBI field, this is a great

1 goal because by integrating data now as the data
2 is coming together and being collected, this type
3 of model can help feel confident in how to think
4 about designing trials for the future.
5 We're seeing broad use of this tool so
6 it's been really great, and we've also at C-Path
7 had two successes in qualification of biomarkers.
8 One you heard about this morning from Dr. Amur and
9 another one that we've achieved with the EMA is
10 the qualification of low baseline hippocampal
11 volume for use in trials targeting subjects at the
12 pre-dementia stage for Alzheimer's disease; again,
13 because the challenge here is if you take all
14 comers, these trials are so heterogeneous.
15 So similarly, in TBI, there is a lot of
16 interest and you've heard some -- seen some
17 beautiful data today around the use of
18 neuroimaging to select subjects for trials.
19 There are a lot of needs to make this
20 work better in the future. All of us have seen
21 these tremendous publications that talk to us
22 about there's a new diagnostic that we all hope,

1 even -- but years later, were still not seeing
2 that see the light of day so that everybody can
3 know and use these biomarkers for the future. We
4 need to do the things that TBI is doing today. We
5 need to think about sharing of data, data
6 standardization, and the FDA -- in fact, this is
7 another slide from Dr. Buckman's talk at the
8 Faster Cures webinar -- has come up with this idea
9 of incentivizing groups to come up and share the
10 biomarker data as it's being collected, put it
11 into some kind of a database warehouse for
12 biomarkers, and have all that data collectively
13 come to the regulators to enable these biomarker
14 qualification decisions.
15 We're clearly not there yet but I do
16 feel confident that the TED TBI project, which has
17 made some amazing progress in a very short time,
18 is really on the right track. The TED initiative
19 is very unique to me and all the projects I've
20 worked on because they really do own and
21 understand and take seriously the concept of
22 consensus data standards. They've had seed grants

being funded to help with the type of validation that you just heard about today in the sessions. They've submitted comments to some federal register notifications for promising biomarkers that you heard about today. Thanks to Lakshmi -- she's the federal commissioners fellows research project and we will soon be going to the FDA CDER group for a critical path innovation meeting to talk about data and where we are and how we can get along this exciting path to achieving regulatory acceptance and then qualification for TBI.

So I want to thank everyone, particularly the TED group that is here and especially for funding from FDA and our collaborators to helping us be at this time -- at this really exciting time for TBI research. Thank you.

(Applause.)

DR. KUMAR: I'm going to invite all of the speakers to come up to the table, and we're going to open up to the audience for questions

now. We'll probably cut the question period short by maybe five minutes but I encourage anyone to come up and ask questions based off the talks that were just given.

MR. MOBERG: I'm Dick Moberg and I've been in the medical device business for 35 years and I've seen a lot of changes in the FDA. And I actually wanted to commend the FDA for what I've seen in the past five or six years of becoming a real partner to industry and clinicians in some of these issues. You know, as a device manufacturer, you know, it's hard for us to even keep wit our own field it's going so fast and for you guys to both regulate and keep up with it, it's quite a challenge, so that wasn't my question but thanks.

So my question goes back to the relationship between a claim and a device. So a claim for a device is specific to a device and specific to a manufacturer, but one of the beautiful things about TRACK is we're getting all this comprehensive data together and I think a biomarker, which I'm sure everybody shares this,

is probably going to be a combination of some of these things. There's probably not going to be just imaging or physiology or something, and we're seeing that in our little slice of the pie which is the high resolution physiology, the relationship of this data. So let's take three of the devices that were mentioned this morning. Let's say you're on a battlefield or an injury or something and you have in InfraScanner; you collect some data on that. You have the brain scope, and then you have, you know, one of Ron's biomarkers, the little Philips thing, and those three devices are giving you information that, you know, in concert, you know, I need to treat this patient that way. So now how does that relate back to the individual manufacturers? Can they say I have a claim for this and -- but it's dependent on two other manufacturers' devices? And actually, does it even matter? I mean is that something that the clinicians just use it for or what?

DR. COMO: I'll take a very poor stab at

1 answering that question. I mean this is going to
2 probably sound like FDA-speak but I think each
3 individual product that gets cleared or approved
4 by the Agency stands on its own, you know, with
5 its own indications for use and all of -- and its
6 -- the intended use population is all described in
7 the labeling that accompanies that product. I
8 think if a sponsor came into the Agency and which
9 they said, you know, we want to build upon the
10 results of device a and b and c, that's probably a
11 fairly complicated submission. And the regulatory
12 requirements, in order to seek that type of claim,
13 I think, would be something we would have to spend
14 a lot of time thinking about and discussing. But
15 right now the short answer is each product sort of
16 stands on its own intended use and the data that
17 supported its clearance or approval.
18 DR. HOFFMAN: I'll just add a quick, I
19 guess -- when I joined FDA and still today,
20 generally FDA doesn't' regulate the clinical
21 practice so if a clinician wants to use multiple
22 devices in the context of making a diagnosis,

that's perfectly all right. That would be clinical practice. And then I would also just mention several things were mentioned today about using CT or MR to diagnose TBI. I'm pretty sure none of the manufacturers for those types of devices have specific claims related to TBI so, hopefully, that gives a little perspective on the landscape.

DR. WANG: So Kevin Wang from the University of Florida. For the panel -- so there are the two tracks, the mutual diagnostic track as well as the biomarker qualification. Let's just take the bio-fluid biomarker. I think it's reasonable to assume in the next five years, maybe shorter, there will be -- within the community, there will be initiative to push for both. And from my understanding, there's two parts of a non-mutually exclusive -- but are there any caveat or any things that we should watch for that, you know, in terms of the two kind of not tripping over each other? Can you just comment on that?

DR. KELM: Well, we work together,

1 Shashi and I are talking all the time. So I think
2 -- and I think pretty often, things that we clear
3 or approve can be used then in drug development or
4 drug studies. So they are mutually exclusive and
5 you can obviously do both or you can decide that
6 one makes more sense for you. Obviously, if you
7 want it to be used clinically, then you should
8 consider clearance or approval because if you're
9 going through the drug development pathway, then
10 it's only for drug development. It's not for
11 clinical use but obviously, if -- you know, we've
12 talked about some cases where it maybe makes the
13 most sense to go more for your clearance or
14 approval and then it could be used obviously also
15 in drug development. And there may be other
16 intricacies for how you're going to use it but
17 then Shashi can tell you (inaudible).
18 DR. AMUR: I just want to add that for
19 every biomarker qualification submission, we have
20 a biomarker qualification review team. And one of
21 the members is always somebody from CDRH so we
22 have a lot of crosstalk going on, and so we keep

1 each other apprised of that.
2 DR. WANG: Thank you very much.
3 FEMALE SPEAKER: Can I just make one
4 quick comment? I think this has been a very --
5 issue of confusion where many people, particularly
6 in the Alzheimer's field, have felt that they want
7 to do either or but you can't do both.
8 Particularly, on data-sharing, this is a big issue
9 and I think the more we can have these kind of
10 conversations to make everybody realize there is
11 value to both, it is definitely not an either or,
12 it's going to help advance the field for
13 treatments and for clinical use.
14 DR. KUMAR: Okay. Well, I might take
15 just one more question for you all sitting there.
16 And when we're thinking about integrating
17 biomarkers into medical product development, what
18 should be considered when deciding whether the
19 biomarker qualification is the appropriate pathway
20 and what categories of biomarkers can be qualified
21 through that pathway? And I think that's kind of
22 a lead-on to that last question.

1 DR. AMUR: I had mentioned how you would
2 decide between going for acceptance into drug
3 development. You know, in the context of a single
4 drug, you go through the IND and the (inaudible)
5 submissions, but if you need to establish a
6 biomarker for use in multiple drug development
7 programs, you would go to biomarker qualification.
8 You can come to us with any type of biomarker for
9 qualification as long as there is a drug
10 development use that's tied to it. If it's meant
11 for clinical practice, then it's not fit for our
12 program, biomarker qualification program.
13 One of the things I can think of is if
14 it's a prognostic biomarker and you want to use if
15 for patient stratification, which is dividing the
16 biomarker positive and negative people equally
17 between the placebo arm and treatment arm. I
18 don't think you need to qualify that in a
19 particular context of use. I think you can use it
20 directly in drug development. But other ones, we
21 have had lots of discussions, Diane and I, about
22 enrichment biomarkers, for example. One can use

enrichment biomarkers directly in drug development in the context of a specific drug but in some scenarios, it will be -- it is useful. One-third of our submissions that we have are on enrichment biomarkers so the field sees the advantage of getting an endorsement, if you will, from FDA showing the vote of confidence that this biomarker is really useful as an enrichment biomarker. And we also say, you know, these are the performance characteristics of the assay and this is the kind of benefit you will get by using the biomarker for enrichment, which may or may not be required in every scenario. So that's why I think it's a little context-dependent, depends on the what the person who is intending to use the biomarker in drug development for.

DR. KUMAR: Okay. Well, if there are no other questions, I'm going to mention again that we are posting the speaker slides on the website so you'll have their contact information if there is anything that you would follow-up with them specifically, and thank you so much for all of

1 your talks.
2 (Applause.)
3 DR. KUMAR: So at this time, we're going
4 to be moving into our first moderated panel
5 discussion and for those of you that would like to
6 follow along, I'd first like to invite our
7 panelists up to the front to come and start off
8 our discussion. But within your program booklets,
9 you should find our discussion paper and in the
10 discussion paper, we have questions outlined of
11 what we will be discussing today. So we're going
12 to go through those and we just have one change in
13 the lineup. Dr. Mike Hoffman will be sitting in
14 for Tim Marjenin.
15 So what I'm going to do first is ask the
16 panelists, starting at the beginning, to go ahead
17 and introduce yourselves for the audience.
18 DR. DIAZ-ARRASTIA: I'm Ramon Diaz-
19 Arrastia. I'm a Professor of Neurology at the
20 Uniformed services University.
21 DR. MacDONALD: I'm Christin MacDonald.
22 I'm an Assistant Professor of Neurological Surgery

at University of Washington in Seattle.

DR. GHAJAR: Jan Ghajar, Clinical Professor of Neurosurgery at Stanford and President of the Brain Trauma Foundation.

DR. H. WANG: Hao Wang, NINDS in the Office of Translational Research.

DR. S. HOFFMAN: Stuart Hoffman, Department of Veterans Affairs, Office of Research and Development Program Manger for Brain Injury.

DR. AMUR: Shashi Amur. I'm the Scientific Lead for the Biomarker Qualification Program, Office of Translational Sciences at CDER, FDA.

DR. KELM: Kellie Kelm, Branch Chief, Cardio-Renal Diagnostic Devices in the Office of In Vitro Diagnostic Devices and Radiological Heath.

DR. M. HOFFMAN: Mike Hoffman, Acting Deputy Director for the Division of Neurological and Physical Medicine Devices in the Office of Device Evaluation in CDRH.

DR. KUMAR: Okay. Well, I'm going to go

1 ahead and start off with a question for the entire
2 panel, so if anyone would like to take a stab at
3 this first question, please feel free.
4 But we've heard a lot of presentations
5 in the beginning of the morning on the different
6 screening and diagnostics and monitoring methods
7 for TBI. I would like you all to talk about the
8 strengths of the scientific and clinical evidence
9 that support those measures. And I think this is
10 going to be important for us to lay the groundwork
11 as we move forward in the conversation, as we talk
12 about comparing biomarkers to these current -- the
13 current strength of this evidence that we have
14 that we're currently dealing with.
15 DR. MacDONALD: Well, someone has to
16 start off, jump in here. So building -- and
17 Allison knows this but as a preface, for many of
18 us up here, we all have different areas of
19 expertise. Mine is mostly focused in
20 neuroimaging, I will confess. So in speaking to
21 evidence, building off the fantastic talk of Dr.
22 Yuh earlier today, within imaging, I can tell you

that -- and this is something that we hope to highlight through some of the previous or additional discussions that will be had with the FDA over the next couple of months -- the big take home messages on what is the evidence is number one, in the imaging side, and it depends on modality, but there's a lot of both pre-clinical and clinical evidence. So there are truly some translational aspects there to be aware of.

Number two, there's been a lot of development, as you've heard, to design and devise standards, template standards for the evaluation of these imaging changes. The exciting part is not only do we have neuroimaging CDEs in the human realm, we have a series of developing pre-clinical CDEs that we can also use in parallel, so, again, thinking about the translation there.

In the domain of time, the exploration of these imaging findings at various time points has been fleshed out in different capacities in both humans as well as pre-clinical models.

And then in the dimension of age, as a

1 last example so I don't take too much of the time
2 from this very esteemed panel, we have quite a bit
3 of evidence now going as low as infants -- I
4 myself do abusive head trauma work in infants --
5 all the way up to -- we were just talking about
6 this earlier -- new centers, things like the
7 Senescence (ph) Brain Injury Center that are
8 studying brain injury in later-aged adults. So
9 different domains of evidence and different arms,
10 I think, are definitely there through published
11 work and some really exciting continuing work, too
12 -- at least I can speak on the imaging side -- to
13 support the use of that going forward.
14 DR. DIAZ-ARRASTIA: Let me try and take
15 a stab at that from a little different angle from
16 Christine. I think from the point of view of a
17 clinician who is either working in the emergency
18 room or the ICU or the clinic in the kind of
19 subacute or chronic patients, I would say that the
20 current measures are actually quite poor, right.
21 They're mainly relying on history and physical
22 examination. You know, history, sometimes if

1 you're lucky, there was a witness. That's often
2 the case but not always, right, in terms of
3 details, what's going on. You know, the CT scan
4 is almost universally used in emergency room
5 settings and it's given more weight than it
6 should. It's actually very, very common for
7 patients who have had even pretty significant TBIs
8 with a negative CT who are told "you didn't have a
9 TBI, you're fine, go home, get back to work on
10 Monday." Get there, they're still amnestic and
11 they may flunk an exam if they had one on Monday
12 or whatever.
13 So I would say that, you know, in a
14 sense, that's good because we are starting off
15 from a very low level, right, so we can improve
16 things with --
17 FEMALE SPEAKER: Consider (inaudible).
18 DR. DIAZ-ARRASTIA: -- improved imaging
19 or improved physiology or without necessarily
20 getting to perfection because we're starting off
21 at a pretty low level.
22 DR. S. HOFFMAN: I'll take it from

1 another angle. I work at the -- with the VA and
2 our problem is that when the service members
3 separate and they come to the VA, a lot of times,
4 when they come in and they identify as an OAF/OEF
5 veteran, a lot of times it's months to years after
6 they've had any exposure to their brain injury or
7 brain injuries. So we're faced with a situation
8 where we have to identify the injury long after it
9 occurred. We currently have a screen and a
10 comprehensive evaluation in place that has
11 identified at least 80,000 veterans who had not
12 been identified with TBI before.
13 So from our perspective, you know,
14 having a screening and diagnosis, it's a unique
15 situation then to the civilian population. So we
16 almost need, I guess, evaluation or methods to
17 detect the brain injuries long after they have
18 occurred to make sure that they do have brain
19 injuries and be able to monitor them and perhaps -
20 - one of the things I'm involved with, Ramon, is
21 the Chronic Effects of Neurotrauma Consortium --is
22 does this confer to something that's

1 neurodegenerative? So can we detect something
2 like that before it occurs so we might be able to
3 develop treatment down the road? That's from my
4 point.
5 DR. KUMAR: Okay. And I do just want to
6 also invite any members of the audience that may
7 also have thoughts to any of these questions to
8 get up and share your thoughts as well.
9 So based on what we just discussed,
10 there are different assessment methods; how does
11 the lack of a gold standard of these, from a
12 clinical diagnostic, perspective, of these
13 assessments for the spectrum of TBI limit our
14 ability to identify biomarkers and develop tests?
15 And there are multiple add-ons to this question
16 but maybe let's try to tackle that first one.
17 What do you see the barriers are to developing
18 biomarkers in the face of this?
19 DR. GHAJAR: I'll take on something. So
20 I'm a neurosurgeon. I take care of -- my DNA --
21 our DNA is usually severe TBI, people in coma and
22 it's usually operative. And I don't think very

1 many of us take care of mild TBI, concussion; I
2 think a few of us. I have a clinic at Stanford
3 taking care of concussion patients so I see both,
4 severe, people in coma, and people that are awake
5 after a hit to the head. I do think that there is
6 some efficiencies in dividing people up a little
7 bit in terms of their level or arousal which is
8 the Glasgow Coma Scale does measure that and sort
9 of awake people who have a head injury versus
10 people in coma who have a head injury. I think
11 it's very different.
12 We're trying to put everything together
13 and I'd like to see a continuum, and I think that
14 the path of biology, there is a continuum. I
15 think you could look at axonal shearing or, you
16 know, those kinds of things, the continuum. You
17 can do that but clinically, what we do is, and
18 unfortunately right now, is just subjective
19 measures in people that are awake. Because a
20 neurological exam, the imaging is usually normal
21 and usually we're getting from the complaints of
22 the people and so there is no gold standard.

1 I think the big problem right now is
2 concussion. I think severe TBI has its own issues
3 but it is a big problem and I think that for -- to
4 get at probably "b" here, which is "How should you
5 evaluate it," a biomarker, at the end of the day,
6 the clinician is making the diagnosis, I mean,
7 okay, they're not -- there's not going to be sort
8 of a tri-quarter Star Trek thing that waves over
9 somebody and says "bingo, you have a concussion or
10 a severe TBI." I just don't see that for a very
11 long time. So in the meantime, the clinician needs
12 tools and they usually make a diagnosis by
13 multiple -- the history, the exam, a biomarker,
14 whatever you want. They all come in and they say,
15 ah-ha, that's a concussion or that's whatever the
16 disease process is.
17 So I think that what they should be
18 doing in terms of the biomarkers is they should be
19 accurate, precise, reliable, and they should be
20 measuring whatever they have the intended
21 population intended milieu that they're measuring
22 it in and give an accurate result to the physician

who's got to make a diagnosis. So instead of us jumping to the gold standard, I think that there's a lot of work we can do in defining what the measures are in the normative population that you are looking at; so athletes a little bit different from the ER population, from the military population, a lot of work to be done for whatever biomarker you got to look at norms in those different areas and then establish what the difference is in people that have, after a head injury hit. And I think they're going to have to have some marker of injury and then some marker of a brain change. Those are the two things that are going to add up to a physician making a diagnosis, because right now the biomarkers are not specific for traumatic brain injury. So until they do, you need two things: the injury plus the biomarker.

DR. DIAZ-ARRASTIA: You know, I mean I think, essentially, I agree with Jam. I think it's pretty unrealistic that we're ever going to have a gold standard to cover the whole spectrum of TBI.

On the other hand, another way of looking at it, you know, we do have a gold standard for diagnosis of acute epidural hematoma, right, and that's the CT, and that has clearly saved many lives. So obviously, that's a very, very small chunk of the whole problem.

But I think perhaps a better way of thinking about it is that, you know, we're going to have diagnostic biomarkers of axonal injury or diagnostic biomarkers of vascular injury and the reason that's likely to be helpful is that my gut feeling is that when we eventually do have therapies, we're not going to have a therapy for TBI in general, right. We're going to have a therapy for axonal injury, or a therapy for neuroinflammation, or a therapy for vascular injury. And I think sort of cutting down the problem into smaller chunks like that is probably going to be helpful down the line.

DR. KUMAR: Could you identify yourself for the transcriptionist?

DR. VESPA: Sure. Paul Vespa from Los

1 Angeles. I'd like to go back to what Ramon just
2 said. My sense is that there's a lot of
3 uncertainty in mile traumatic brain injury or
4 concussion and the focus has been let's try to
5 look at biomarkers for this because that's really
6 where the uncertainty is and yet we don't have a
7 gold standard for that. And I think "a," if you
8 get down to, you know, how do you do this on "b,"
9 I think we should really focus on more severe
10 brain injuries and definitely validate whatever
11 biomarkers there are, imaging, blood, etcetera in
12 this where we know the pathology and validate
13 those first and then back up and look at that in
14 mild traumatic brain injury. They may not be the
15 same but at least they would be the validated
16 markers. And I think that part of the problem is
17 that we're searching two unknowns at the same time
18 and I don't think we can do that.
19 So my push would be -- now on conflict
20 of interest, that's what I do so that's what -- I
21 mean I do more severe injuries -- but I think that
22 the idea is start with the known and definitely

1 move forward from there rather than trying to
2 start with an unknown. That's a very difficult
3 sort of scientific premise to work with.
4 DR. MacDONALD: So I just wanted to
5 respond to your comments. I agree with you. Even
6 from an imaging perspective, one of the biggest
7 things that we can use to our advantage is
8 pathology and radiological pathological
9 correlations will allow us to understand what
10 those signal changes in any modality may be driven
11 by when you're able to do that. That absolutely
12 does fall more on the severe side of the fence
13 because we often don't get concussion brains right
14 after the concussion. It's good for, you know,
15 the patients. They live a long time. But on the
16 severe side that there are potential opportunities
17 for that and that -- you know, to the "c",
18 efforts, absolutely there are current efforts of
19 people exploring much of this to expand upon this.
20 And then in thinking in minds with our
21 industry partners, to Ramon's comment about the
22 TBI drug, that's, I think, the big part for us

1 when we think about diagnostics is of course -- or
2 a new, you know, imaging biomarker, for example,
3 of course the drug isn't for brain injury; the drug is
4 specific for mitochondrial dysfunction or maybe
5 it's inflammatory and so it would --you know, to
6 me it seems like it would behoove us to think
7 about our biomarkers as being pathology specific
8 or at least allowing that to be defined so that we
9 can have something to work with when it comes to
10 drug targets, because those are really pathology-
11 specific targets so can we get pathology-specific
12 biomarkers.
13 DR. KUMAR: So in relation to those
14 consensus efforts, what do you see being the
15 biggest hurdles they're currently dealing with?
16 Well, I'll say the provocative comment
17 which is the lack of standardization but we've
18 done a lot to attempt to standardize; the lack of
19 good data-sharing but lots of active efforts to
20 harmonize data; the TED metadata set is an
21 excellent of this within traumatic brain injury
22 and that field is growing. Those would be two

1 examples that come to mind.
2 DR. GHAJAR: So you were also funded on
3 BTEC, which is Brain Trauma Evidence Based
4 Consortium, sort of the sister to TED looking at
5 evidence based definition and classification of
6 TBI and we published in Neurosurgery about a year-
7 and-a-half ago on concussion guideline step one
8 and unfortunately, looking through 5,000 studies,
9 only about 12 qualified for it. So we really have
10 a lack of evidence so the more evidence we get,
11 the better we can get to evidence based rather
12 than consensus. There's a lot of -- we can sit
13 here and come up with a consensus definition, then
14 next week somebody else will come up with another
15 one. So it has to be evidence based but we have
16 to do better studies for that. I do think that
17 there -- you can draw a pretty clear line between
18 somebody in coma and a normal population. That's
19 pretty easy to do. I think it's very difficult in
20 concussion because at some point, you've got to
21 draw a line saying this is abnormal and that's
22 normal, and I think that's going to be very

1 difficult.
2 DR. KUMAR: Dr. Wang, did you have a
3 comment?
4 DR. K. WANG: Yes. I want to kind of
5 continue this concept. You know, I think
6 standardization of terminology is also important,
7 right, as I have already heard. A severe TBI is
8 easy; mild TBI and concussion. So where is the
9 line? I think each of us has maybe a different
10 definition of concussion versus mild TBI. But
11 sometimes it's actually not helpful to have the
12 two distinct entities out there because I often
13 get asked, you know, is a test good enough for
14 looking at concussion. You know, now we have to
15 go into this long conversation; "yeah, we can
16 detect mild TBI." So I think I'm not pushing for
17 one direction or another but I think this is
18 something that's kind of emerging, you know,
19 particularly now with so much concussion in sport-
20 related activity as well as in military. So we
21 need to kind of define that (inaudible) and being
22 defined by each of us individually, (inaudible) my

1 -- so
2 DR. MacDONALD: Yeah. I guess, you know,
3 the irony is really the consensus of the consensus
4 and as we heard, the 42-47 that are out there, I
5 know there are 17 consensus guidelines. So I
6 think that it's not for lack of effort and that I
7 think at this point, you know, it's trying to come
8 to an agreement about what the systematic
9 standardized approach will be.
10 DR. KUMAR: So let's move on to the next
11 question and Ramon, I'd like to give this to you.
12 What current or perceived barriers to conducting
13 successful, clinical trials in TBI, which we know
14 have had many, would be addressed by regulatory
15 qualification of biomarkers and associated tests?
16 DR. DIAZ-ARRASTIA: So I think the
17 biggest barrier is actually an intellectual
18 barrier. We've been assuming that the animal
19 models tell us more about the disease than they
20 actually do, right. And in fact -- and I'm going
21 to use a baseball analogy; I'm a baseball fan --
22 many times when someone gets something to work in

1 an animal, they think that they've hit a triple
2 and all they have to do is round the bases and
3 head for home when in reality, if you get
4 something to work in an animal model, that means
5 that you've barely beat out an infield grounder
6 and you've barely gotten to first base. So, you
7 know, there's a long way and obviously protect
8 investigators are so confident because they had
9 hundreds and hundreds of animal studies. And, you
10 know, my guess is that they were really over-
11 interpreting what the animal models tells you.
12 So I think that's the first thing. We
13 need to have the intellectual humility to realize
14 that, you know, it's great that something works in
15 an animal model but there is still a long, long
16 way to go. And what I think we're going to need
17 is, in parallel, we're going to need to develop --
18 obviously, we're talking about a biomarker. So
19 far the discussion today is mainly in biomarkers in
20 humans with a disease , but if this is ever going to
21 be taken to developing drugs in successful
22 clinical trial, we're going to have to take those

1 same biomarkers back to the animals, right; the sort
2 of bedside to bench backward translation in a way,
3 and in the animal, learn in the particular models,
4 you know, how good is the model, how well does it
5 replicate the biomarker and the evolution of the
6 biomarkers; have we seen it in the humans; do we
7 then have drugs that can impact that biomarker in
8 the animal; and then once you do that and you can
9 prove in the animal that the biomarker is, in
10 fact, related to a clinically meaningful
11 behavioral improvement and a pathologic finding,
12 and then you can take that to humans in early
13 phase clinical trials and your very early studies
14 are going to be, you know, driven by
15 pharmacodynamic biomarkers.
16 I mean are you engaging the molecular
17 target that you think you're engaging: do you
18 have the right dose; do you have the timing; do
19 you have the right duration of therapy? Right now
20 we've been extrapolating from -- you know, we say
21 that well, an hour in a rat is the same as 24
22 hours in a human. That is totally, you know,

1 pulled that out of thin air, right, and I think we
2 can't assume those things. And the only way that
3 we're ever going to really tie those down is by
4 having biomarkers that are useful, really, in both
5 animal models and humans.
6 DR. H. WANG: So I agree with that. I
7 just want to add that clinical trials, in essence,
8 are test of a hypothesis. And unfortunately,
9 there are many failed clinical trials that didn't
10 give a definitive answer whether it's positive,
11 negative, but it's more inconclusive. And so the
12 barrier -- I mean for neurological disorders, this
13 is -- you know, we're falling in this trap and
14 TBI, unfortunately, is in this category.
15 I can think of three things that are
16 really contributing across different trials that
17 are in this category; for example, like using the
18 wrong patient population that doesn't match the
19 mechanism of action of therapeutics; or not
20 stratifying patients according its match to the
21 action of the therapeutics; and not stratifying
22 patients according to prognosis so you end up with

a lot of noise and also with a noisy endpoint measurement that are either not reliable or not discriminative or not sensitive. So I think that, you know, removing these barriers by qualifying biomarkers or developing biomarkers that can help to stratify patients according to the mechanism of action, that match the therapeutics that you're going to be testing; you know, stratifying patients according to the prognosis and increase the sensitivity and reliability of the measurement of the endpoints are going to be key to success of future clinical trials.

DR. AMUR: I agree with both of the panelists and I want to start with a disclaimer that I'm not a TBI expert by any stretch of imagination. But what I have heard so far today suggests that there is a lot of heterogeneity in the patient population and any kind of, you know, efforts, including using biomarkers to identify more uniform populations might be helpful in drug development.

DR. KUMAR: You have a question?

1 DR. POULSEN: Yeah. Dave Poulsen,
2 University of -- at Buffalo, Neurosurgery. And,
3 Ramon, I totally agree with what you're saying. I
4 totally get it. There are clearly issues with
5 regard to translating pre-clinical to clinical.
6 Humans are not rats. But I think it's important
7 that we need to consider that on the pre-clinical
8 side, if we were depending entirely upon the
9 Glasgow Coma Scale as an outcome measure, you
10 would never have anything to test in a clinic.
11 DR. MacDONALD: So Dave -- hi, Dave.
12 DR. PAULSEN: Hi.
13 DR. MacDONALD: How's it going? So to
14 that point and I think expanding, and I don't mean
15 to take liberties for Ramon, but I think the point
16 is that in thinking about new biomarkers, again,
17 total bias here as an imager, I can scan in a
18 mouse and I can scan in a human and it just turns
19 out that holy moly, when I scan that (inaudible)
20 mouse -- this is a true story; the papers are out
21 there; they're published -- I see the same time
22 course of DTI metric change during the same time

1 period as I see in a human. There are a million
2 reasons why those should not add up. Those are
3 completely different mechanics. I'm not saying
4 (inaudible) but I have a surrogate marker, so I
5 don't think it's we should be doing GOSE or GCS in
6 the animals but could we be considering -- correct
7 me if I'm wrong -- in my own humble opinion, if
8 we're going to design biomarkers that the GFAP
9 biomarker, the imaging biomarker, that we are
10 focused on a human is utilized in those animal
11 studies as well that gives us dynamic information
12 and more specificity to even understanding who to
13 select when we go back to the human and vice
14 versa.
15 MALE SPEAKER: Absolutely.
16 DR. DIAZ-ARRASTIA: I mean I think
17 you're, of course, right. You know, I think we
18 need to get away from the idea that we're going to
19 be developing drugs for TBI, right. I think we
20 need to be developing drugs -- I like to use the
21 word -- endophenotype of TBI.
22 And we also need to get rid of the idea

1 that we're going to be developing for mild TBI
2 that are somehow going to be different from severe
3 TBI because in reality, it's the same mechanisms.
4 Obviously, there are less of them in mild TBI but
5 the imaging studies that Esther and Larry Latour
6 and others have done, you know, it's the same
7 pathophysiology. I mean in mild TBI, even the
8 mildest form of concussion, you frequently see
9 axonal injury, vascular injury, small contusions.
10 Obviously, they're small but it's the same thing
11 that we see in the ICU, that Paul sees and the
12 others of us sees, it's just less of it.
13 And I think at the end of the day, when
14 we have therapies, you know, we're going to use
15 them across the spectrum, targeted at the
16 particular mechanism. And I think what we should
17 do in the animals is the same thing. We should
18 focus on the mechanism that the drug is actually
19 going to be targeting, develop biomarkers that
20 measure the mechanism in the animal, develop
21 biomarkers that measure the affect of the drug in
22 the animal, and then you can go into early-stage

1 human trials.
2 DR. KUMAR: Next comment?
3 DR. BELLGOWAN: Yeah. Pat Bellgowan.
4 I'm at NINDS. And so I mean I'm glad that Dave
5 stood up because I mean the issue that is we see
6 every time I go to meetings is, you know, we're a
7 lot of clinical researchers here who are
8 complaining about pre- clinical data. And then if
9 -- you know, I get the luxury of going to talk to
10 a lot of pre-clinical people, too who then
11 complain about the clinical researchers. And when
12 -- and, you know, as we see here, we often don't
13 come together. Well, and we both understand the
14 problem.
15 So I was wondering -- I mean this is
16 like the mind trust of clinical research of TBI.
17 You know, do you have ideas about how we can
18 accelerate this process of brining better, more
19 appropriate animal models for the clinical and
20 outcome measures for the clinical -- in pre-
21 clinical area that match clinical and vice versa?
22 I mean do the reverse translation, how do you do

that in a more rapid way rather than, you know, Ramon found this particular protein and now we got to wait for someone to submit a grant in a pre-clinical model? I mean do you have any ideas about this?

DR. H. WANG: So I think this concept of bi-directional research, you know, translation and reverse translation -- you know, translation from benchside to the bedside and back has been touched upon by many of the panelists and it's critically important. And, it's -- you know, here we're talking about developing biomarkers for clinical use and we also know that there are a lot of questions about the pre-clinical models and whether that would be predictive or not for the translational value of a particular therapy, the agent.

But I think in the context of our discussion here, it is also very important to consider the biomarkers that are translatable from animals to humans and aback. So for example, you could ask questions about in animal models, what

are the biomarkers that link the particular animal models according to its pathophysiology to simulate a particular population or that's classified in the future according to certain types of biomarkers, so that's more like matching the mechanisms of the therapeutics with that particular population but you can also do that experiment in the animal models and you can establish that qualitative relationship.

And the other type of question you could ask are what are the efficacy biomarkers that can translate from animal models to humans. I think that this close collaboration between the pre-clinical researchers and the clinical researchers is critical. And I think developing these biomarkers for -- starting from the clinical is fundamental to therapeutic development.

DR. BELLGOWAN: So is that like a pre-clinical TED? I mean is that -- that's -- is that what you're saying?

DR. DIAZ-ARRASTIA: You know, I think -- if I can tackle Patrick's question, which I think

is an operationally very important one, so, you know, the investigator-initiated RO1 system is great for funding very innovative science and making really good discoveries. But I mean I think we all realize it's not great for everything and one of the things it's not particularly great for is fostering these interactions between across different disciplines.

You know, NIH used to have quite a few program projects and centers. A few of them are still around. I think something that has happened in the last decade or more is that many of them fall out of the way. That certainly has happened in the TBI world. And I think perhaps it's time to reconsider that view and I think now the buzz word is "centers without walls" maybe are cheaper than centers with walls. But something like that I think is what it's ultimately going to take and obviously, what the right balance is between RO1s and centers, I think that's something that needs to be decided. But my gut feeling is that we've gone too far away from centers.

DR. S. HOFFMAN: Yeah. Almost like a consortium, right? The other aspect is I think there's a lack of a translational bend a lot of times where the biomarker studies begin in the animals. How often in the clinic do you see especially the moderate-severe brain injury by itself? If they're in a motor vehicle accident, they're going to have contusions and orthopedic injuries. How many biomarkers have been developed in the lab take into account those secondary injuries.

And for instance, with the gut injuries, there are astrocytes in the enteric system. If you have a bruise to your thoracic region, you could end up releasing GFAP. How is that going to affect your assay? So that -- we also need to improve how we look at the biomarker development in the lab before we try to start translating it to the clinic.

DR. GHAJAR: Yeah. I think also we need more bedside to bench. There are a lot of things that we do at the bedside that don't get

1 translated into research. I mean one of the big
2 things is just profusion. You know, I think for,
3 you know, having a rat looking at CPP manage --
4 you know, cerebral profusion pressure management
5 is -- I don't see too many models of that but you
6 got a small, you know, animal. So there are a lot
7 of things happening in the ICU that are really
8 interesting. I think sort of moving a lot of the
9 research into the clinical domain and finding out
10 what we're doing at the bedside that makes a
11 difference could really help out a lot.
12 DR. MacDONALD: I could say that in the
13 mild and also just the appreciation and just
14 realization of comorbidities. And the good news
15 is that there are labs and there are grants that
16 are out there of people that are now doing, for
17 example, repetitive concussive injury as well as
18 stress responses for things that would look at,
19 for example, PTSD, anxiety, post traumatic
20 depression.
21 The challenge there is also the
22 secondary component which is slightly technical

1 but an important one which gets to Pat's comment
2 about GOSE, and I think Dave's as well, which
3 is just the behavioral evaluations that are used
4 pre-clinically -- I mean I've done Morris water
5 maze myself I admit -- you know, have a certain
6 limitation to them. And so trying to not just
7 develop biomarkers but developing the crucial
8 behavioral evaluations that would give us the more
9 translatable piece that we're talking about.
10 That's the point. Brain injury doesn't
11 happen in isolation both during the exposure as
12 well as the recovery. The comorbidities
13 considerations, especially in the mild side, I
14 think, really needs to be further thought out.
15 And the good news is there are people, great
16 scientists out there that are starting to do this
17 more and more.
18 DR. KUMAR: So, Jam, I'm going to give
19 you this next question. We obviously know that
20 there's a need for screening outside of a clinical
21 environment or, you know, we all have the example
22 of the football player on the sideline to

1 determine whether or not they've had a concussion
2 or to further assess their injury. So what
3 benefits and risks do you see associated with
4 these device-based assessment methods and how
5 could they be further validated?
6 DR. GHAJAR: I have direct experience
7 with that so, you know, bias is eye tracking but
8 we're using this on the sideline football games.
9 And frankly, in the athletes, the athletic
10 directors want to know right away whether somebody
11 had a concussion and they have limited time to be
12 able to do that assessment. And I think that
13 there's really a need on the sidelines to do some
14 kind of screening test, whether it be eye tracking
15 or EEG or biomarkers or portable scans, whatever,
16 there is really a need. Now they're picking up on
17 symptoms, people who have a headache and they pick
18 them out. I think you need, in combination with a
19 detector of injury, so accelerometers, I think,
20 combined with some kind of sideline assessment,
21 those two together are really needed. That's sort
22 of where technology comes together. And also, I

1 think some really good research because these are
2 young people without -- generally, without
3 comorbidities and we can study them and see what
4 happens.
5 So the challenge is, I'll just say, you
6 know, what I've seen as a PI on the eye tracking
7 from the sidelines, is creating an environment
8 where you can get the test done reliably,
9 accurately, and very quickly. You can't have a
10 one-hour test on the sidelines. You've got to do
11 it under a few minutes so I think that sort of
12 limits White House at you can and cannot use. And
13 one day, I guess you can bring an MRI scanner to
14 the sidelines but for right now, we can't do that.
15 And the cognitive tests, I think, are --
16 some of them are good, some of them take a long
17 time, require -- and there's effort in learning it
18 issues, and so -- but definitely, we do need
19 something on the sidelines so that's my
20 experience.
21 DR. KUMAR: So Mike, one thing I haven't
22 heard discussed too much in our regulatory talks

1 today was how we make our regulatory decisions
2 based off our benefit-risk paradigms that we see.
3 Could you talk a little bit about that in the
4 context of some of these assessments?
5 DR. M. HOFFMAN: Sure. So obviously,
6 when we approve a device or clear it; in most
7 cases, approve a device, we're looking at the
8 benefit and risks of the device and that includes
9 all the risks that, you know, we would observe in
10 a trial or observe in how it's actually going to
11 be used, and that incorporates who's going to be
12 using it, who's going to be interpreting that
13 information and making a decision based on that.
14 And for this question specifically, that's one
15 area where would be -- we'd have concern who would
16 be interpreting that information because,
17 obviously, if you take away a medical
18 professional, which right now is usually taking a
19 lot of different information to make a diagnosis
20 and you're consolidating that into maybe one
21 outcome, maybe two measures that a non-medical
22 professional has to evaluate, that's something we

1 have to consider in terms of the risk. And then
2 the benefit though is, obviously, maybe you're
3 getting that information faster. So those are two
4 things that we have to weigh considerably when
5 we're trying to make those decisions and then
6 based on that, what can we do to actually mitigate
7 some of those risks, are there ways that we can
8 better inform who the end user will actually be.
9 So there are different ways we can approach that
10 and there's a wide spectrum of benefit-risk ratios
11 and scenarios that we have to consider and often
12 see.
13 DR. KUMAR: Thank you. So I think that
14 we have one more minute before lunch and I know
15 that everybody's hungry and it's definitely
16 getting passed lunchtime. So instead of
17 necessarily asking this question, I think maybe
18 very briefly if any of the panelists have
19 knowledge of other NIH or government funding
20 opportunities that are available to continue
21 further studies in this specifically related to
22 biomarkers, we'd be very interested in hearing,

1 the audience would and so would FDA. But I'd also
2 like to hear from the panel is what can FDA do to
3 continue to help you as you move forward with your
4 work that you're doing?
5 DR. H. WANG: So just a comment on the
6 NIH funding. We really have a broad spectrum of
7 funding that span from basic research,
8 translational research, to clinical research and
9 many people are familiar with our mechanism. So
10 in addition to the traditional RO1s that fund
11 basic research and probably exploratory biomarkers
12 and disease mechanisms, we also have dedicated
13 translational programs that span from proof of
14 concept in animal models to the first in human
15 clinical trials.
16 So we have, for example, the IGNITE
17 program that kind of enables -- studies animal
18 efficacy, (inaudible) of animal models that are
19 for the purpose of translation as well as assay
20 development and at the latter stage, we have
21 programs that start from (inaudible) to first in
22 human clinical trials for large molecules and

1 biologics that are Create Bio program this BPM
2 program. That's for small molecules and device
3 program.
4 And then clinical trials, we have the
5 exploratory clinical trial mechanism, the UO1
6 mechanism for a little bit later phase clinical
7 trials as well as clinical trial network, that
8 NETT, and that's for neurological emergency
9 treatment trials that will be applicable for TBI.
10 That's for late-stage clinical trials.
11 DR. KUMAR: Go ahead.
12 DR. S. HOFFMAN: i. Yeah. I'm with the
13 Office of Research and Development. We're an
14 intramural program with the VA so in order to be
15 able to apply for our TBI announcements, you would
16 need to have a 5/8 appointment at the VA or
17 collaborate with an investigator that has a 5/8
18 appointment who would be the PI.
19 The VA's priorities are probably much
20 different than NIH's and DoD at this point because
21 by the time the person has come to the VA, they're
22 separated from the military and they probably have

1 received their brain injuries already, if they
2 have a brain injury. So we are looking at later
3 stage detection of the TBI and also ways to link
4 that surrogate biomarker or other types of
5 measurements to outcome, to their cognitive
6 performance, behavioral health issues. And that's
7 the type of angle that we're coming from. So if
8 anyone's interested and they would like to have
9 what we call a merit application for a merit
10 award, please come and talk to me. Thank you.
11 DR. GHAJAR: I just also encourage -- we
12 just got FDA approval for the eye tracking and I
13 think that the approach has been to do a stepwise
14 approach with the FDA. Don't suddenly jump to
15 your biomarker device is going to get diagnose
16 concussion. You're not going to -- it's sudden
17 death. So I think a stepwise of showing that your
18 technology is accurate and precise in the intended
19 population is number one and just about everybody
20 can do that so you do that. And then define your
21 norms and then gradually get more and more into
22 where the device or biomarker is being used to be

1 clinically useful. And I don't think you have to
2 jump all the way to -- if you start jumping all
3 the way to this diagnosis Of concussion or TBI,
4 you're dead in the water. I mean that's the end
5 of it. I think a lot of you who are shaking
6 heads, you've been through that experience. So I
7 can just say with the EyeTracker, with a company
8 called SyncThink went through very quickly and it
9 was a pleasure working with the FDA. And I think
10 if you just do it step- by-step, it's to your
11 advantage.
12 DR. KUMAR: Okay. Well, if there are no
13 other comments, please enjoy your lunch. We're
14 going to start as promptly as we can around 1:30,
15 so it's a shortened lunch but thank you so much
16 for sticking with us this morning.
17 (Whereupon, off the record at 12:50
18 p.m., and back on the record at 1:34
19 p.m.)
20 DR. KANNAN: Hello, everyone. I request
21 everyone to take their seats, to get started. All
22 right, folks, we're going to start the afternoon

1 session with patients' perspective focusing on
2 incorporating patient input into research and the
3 mechanisms available for doing so. We would like
4 to hear the thoughts and insights from patients
5 and patient-centered groups on ways that high-
6 quality and reproducible data can be collected and
7 used to support the development of biomarkers as
8 they correlate to outcome assessments and if the
9 data currently exists, where it can be found.
10 So our first speaker is Johnny Cebak.
11 He is currently a medical student at Lincoln
12 Memorial University and he is also an Iraq War
13 veteran. Welcome, Johnny.
14 MR. CEBAK: Good afternoon, everyone.
15 My name is Johnny Cebak. I want to send a special
16 thank you to Ms. Kumar for the invitation. It's -
17 - I'm very honored to be here, a part of this
18 noble endeavor.
19 So, as you just heard, I'm a first-year
20 medical student -- here's me in the white coat
21 ceremony -- and right before that, I finished my
22 PhD under the direction of Dr. Ed Hall at the

1 University of Kentucky looking at pharmacological
2 interventions for traumatic brain injury. And the
3 reason I put this two pictures up here is to show
4 the unfortunate circumstance of being a forever
5 student. I'm still wearing the same tacky shirt
6 and tie five years apart.
7 (Laughter.)
8 MR. CEBAK: So I still have room to
9 improve. I'm also in the military. I'm a First
10 Lieutenant. I was enlisted for approximately 9-
11 1/2 years and I converted over to the dark side or
12 became an officer and then I redirect commissioned
13 again for the Medical Corp. And I also enjoy
14 motorcycles and I have a cat named Ipsy (ph),
15 which is short for ipsilateral.
16 (Laughter.)
17 MR. CEBAK: But on a more serious note,
18 these are the things that describe me today and
19 the truth of the matter is I wasn't always like
20 this. I actually couldn't even stand in front of
21 people or make jokes because several years ago, my
22 life was completely falling apart and it was very

1 difficult for me and I was, full disclosure, on a
2 path of self-destruction.
3 See, in 2005 to 2006, I was an Army
4 combat medic and I served in Iraq between Ramadi
5 and Fallujah in a place called Habbaniya. And the
6 unit I was with served between these two cities to
7 keep the main supply route open or the MSR. And
8 here's an abandoned radio-controlled tower that I
9 lived out of. So as I'm sure all of you are
10 aware, the signature injury for these wars is
11 traumatic brain injury but for a frontline combat
12 medic, that meant blasts. It meant explosions a
13 lot of the time, and this is an image from a scene
14 that I was personally present at and I was the
15 senior medic and you can see this is where a
16 Marine foot patrol was happening. An IED had just
17 went off and some marines were wounded. And then
18 the people in this truck, this started recording.
19 Please excuse the language.
20 (Whereupon, plays recording.)
21 MR. CEBAK: You can imagine the shear
22 devastation that this does to the human body even

1 if you survive the blast and the shrapnel and the
2 small arms fire that usually accompanies it. And
3 having been through multiple explosions like this
4 myself, treating people wounded from these types
5 of blasts that aren't so fortunate is very
6 grounding. And this isn't' even the full story
7 that I want to share with you today which is
8 something that I've come to call "the rollover."
9 //
10 In one particular mission, I was acting as support
11 inside of a tracked vehicle. The good guys went
12 in, did a raid and they were coming back out and
13 it was time for the convoy to leave. I told my
14 driver to pivot steer our tracked vehicle and
15 which means you engage one track in one direction,
16 the other track in the opposite and it pivots in
17 place. And what happened is that this vehicle
18 destroyed the road and we flipped end-over-end
19 into a ravine that we found out later was built to
20 house local sewage.
21 And during the inversion, I was
22 partially flung from the vehicle and I lost my

helmet and I hit my head multiple times. And this is where I was in the cupola. When the vehicle stopped flipping, I was trapped inside this chamber and it was very hard for me to understand, obviously, what was going on. I don't remember quite a lot of it but when I started to get my senses back, I was upside down. I was trapped. I was in pain. I was very confused and I was drowning.

I stayed in there for what I was told was several minutes and I held my breath as long as I possibly could. And it obviously became more and more difficult. I was tired and at some point, I had to give up. I obviously survived and the water was receded just enough and I was inverted so I was able to cough up water and breath air occasionally. And my buddy pulled me out into the hull of the vehicle and myself and the two other medics stayed inside the small vehicles for an hour in human excrement up to our chest for an hour until another tank could pull us out.

1 Traumatic brain injury wasn't on the
2 radar so there was no treatment. There wasn't
3 really even a diagnosis. Someone literally said
4 that I got my bell wrung, and I know that's like
5 something colloquially we all say but it actually
6 was said to me. I started developing symptoms
7 immediately but there, it was completely different
8 because I was in the moment and there was a lot of
9 adrenalin and it made me very functional. But
10 when I got home -- and Dr. Levin touched on this
11 before; and actually, he hit it out of the park --
12 you can see some of the symptoms that were taking
13 place but one of the hardest things to deal with
14 was -- hardest things to reconcile were my new
15 limits, because I wouldn't just struggle; I would
16 just fail. I didn't know what I was capable of
17 and what I wasn't capable of so when I would
18 engage something, I would just fail. I'm talking
19 about my relationships, my academics, intimacy,
20 everything would just fall apart and all the
21 typical things were there like reduced psychomotor
22 visual and reduction in working declared memory,

1 all those typical things.
2 But what was most provocative was having
3 a new set of faculties, a new set of limitations
4 for which I had to deal with and that's what
5 started the downward spiral and that's how the
6 behavioral consequences started to get out of
7 control and I went into a very difficult time in
8 my life. But there are a couple of factors that
9 led me back out of this dark hold and one is my
10 brother, three years younger than me, Tony Cebak.
11 He kept me alive and unconditional love. He was
12 with me every bit of the way.
13 And then this man, Ed Hall, gave me
14 purpose, so relationships and vocation are huge.
15 And over time, with their encouragement, I sought
16 treatment at the VA, which Dr. Hoffman said
17 earlier, yes, most veterans don't seek it. It
18 comes way after. And with time, I pursued more
19 and more intensive VA therapy and was able to
20 adapt. And I use this analogy but whenever
21 somebody tests -- a physician tests your reflexes
22 in your knee, you know, that's physiological. But

1 you can also anticipate that and you can tighten
2 your leg up to anticipate that physiological
3 response. It's just an analogy but what I'm
4 saying is that I did that with my behavior. So I
5 tried to anticipate where my limits were and I was
6 able to modulate my behavior and influence my
7 actions. And it was extremely difficult but I was
8 able to not just compensate for a new set of
9 limitations but I was able to become competitive
10 again.
11 And I realize that I'm very lucky and
12 I'm very fortunate and I know that there are so
13 many that are not at all. There are some that
14 don't have the capacity, some of my own friends
15 that don't have the capacity to do the things that
16 I have or be able to fight as much. And it is for
17 that reason, it is for them that I personally can
18 never stop, that I can never give up now. And if
19 you are someone suffering or you know someone
20 suffering or you study or treat these horrible
21 pathologies, then I encourage you not to give up
22 as well. Thank you.

(Applause.)

DR. KANNAN: Thank you, Johnny, for sharing your personal story, the emotional and the difficult journey you went through and how you overcame it.

So our next speaker here is Rebecca Lorraine, retired Colonel, and she's the Ex-Chief of the U.S. Special Operations Command Clinic at the MacDill Air Force Base.

COL. LORRAINE: Good afternoon. Johnny, that's a hard story to follow but I really appreciate your service. I am retired. I'm a family nurse practitioner and I had the experience of, not in battle but in clinic, having epilepsy begin, going from a clinical practice taking care of patients and inputting information in computer systems to having seizures, not being allowed to drive, being put on tons of medications. And I turned and went to the dark side also from provider to patient and I got to tell you, it's a rough road so that's what I want to talk to you about today.

1 Okay. So through my efforts, even as a
2 family nurse practitioner, to figure out what a
3 partial complex seizure disorder is with secondary
4 generalization, I could not get the information
5 that I really wanted and needed so that I could
6 adapt and adjust. The Air Force, once you have
7 epilepsy, that's kind of a no-go and they
8 immediately started processing my medical
9 retirement, so I no longer had a job. I did find,
10 through an online media program for patients
11 called "PatientsLikeMe" that many of you may have
12 heard of, but for me it opened a door that I
13 needed to read about other patients' experiences,
14 because even though I was a provider and I should
15 know this stuff, and I probably knew enough to
16 make myself dangerous, I didn't really understand
17 what it was like to be a patient. And so for the
18 last six years, I've become a professional
19 patient.
20 Okay. PatientsLikeMe -- I just put this
21 slide up so that if you aren't familiar with it,
22 and I know that Ben is going to be talking about

1 it after I finish -- but it does provide a forum
2 like Facebook for patients with any diagnosis,
3 especially chronic issues, fibromyalgia, PTSD.
4 You can meet other patients. You can read their
5 profiles. You can talk but the really great side
6 is that I can track my seizures, my medications,
7 my side effects. All the data that I enter in
8 there about me, it tracks it for me. It keeps it
9 in my head because I don't always remember.
10 But PatientsLikeMe also mines that data
11 for good and that's the model that they use. That
12 information will be turned around and given back
13 to pharmaceutical companies; the FDA uses it; many
14 other organizations will use that information to
15 really get the after research information on how
16 patients in the real world, not in the clinical
17 laboratory, are doing on medications or treatment
18 or kinds of things that they're looking for and so
19 that's kind of the outside the test tube
20 application of medications. And when you talk
21 about the biomarkers that you're looking to use,
22 this is another way that you can consider

1 applying, evaluating what's happening the real
2 world with a patient.
3 All right. For me, after I got
4 connected with some other patients with epilepsy
5 and about two years after I got epilepsy, I also
6 got breast cancer so it just added to my issues.
7 But my oncologist decided that I really needed to
8 go to NIH and perhaps have a more comprehensive
9 workup for my epilepsy. At that point, I was on
10 three medications and I had never seen an
11 epileptologist. I had really never had a PET
12 scan. I had not had the workup I should have had
13 when the epilepsy started in the beginning because
14 on top of the epilepsy, I did also have a head
15 injury but that -- was when you talk about
16 multiple injuries, it's never one thing just
17 isolated. There are multiple factors.
18 So I did -- I was referred for possible
19 surgery up to NIH. I spent 19 days hooked up to
20 electrodes and I really like the selfie; it's
21 pretty bad when you take selfies of yourself but
22 when you send 19 days in a bed with those things

on watching yourself in a video, it's no fun. You have to figure out something to do.

All right. So there were two major points from my patient perspective that I wanted to bring out as you all are trying to consider how to make biomarkers to test TBI. There's the trend to go to personalized medicine where we're looking at individuals, not as a lump sum, everyone's a human being, but everyone's a very unique human being with a unique body and genomic profiles. And my experience was having an alpha genomics, actually because I was having reactions to so many medications, do the genomic testing to see what my profile was and what medications I could tolerate. And this is kind of after the fact. I'd already been on just about every medication there was and if they had done this to begin with, it would have saved all of us a lot of problems because I wouldn't have had to go through the process of titrating medications we knew would never work or now we know would never work.

So I have a very complex -- well, it's

1 not complex -- but I understand it -- but it's
2 information about what medications I can process,
3 which one's I'll over-metabolize or
4 hypermetabolize and which ones I won't metabolize
5 well at all, some that I should never take at all.
6 And I was told to take that to all my physicians'
7 appointments and discuss it with my providers.
8 Only two of them actually looked at it. The rest
9 of them had comments like, "Well, who ordered
10 that?" And "Who paid for that?" Medicare paid
11 for it. It was ordered. It's a legitimate test
12 that's been validated as being an effective way of
13 going to personalized medicine.
14 But my point is at the clinical
15 end, where the rubber meets the road, where you
16 have a provider that has to see 30 or 40 patients,
17 they don't have the time to really spend looking
18 at complex information. They don't process it.
19 They don't have the time. So when you come up
20 with biomarkers and information that needs to be
21 applied at the bedside or in the clinical setting,
22 it has to be something that's realistic and that's

1 going to be able to be used by the clinician and
2 well-received by the patient because, ultimately,
3 that's what we're trying do, is help the patient/
4 The second thing was I -- the biggest confounding
5 thing -- and as new generations come out, they're
6 more tech savvy but everything has become
7 computerized and every hospital, every clinic you
8 go to now has your medical records online that you
9 can access and you have to have passwords and
10 entry information so that you can collect your
11 medical records and you can see your labs. Well,
12 there was a beta test for a program called
13 "Glimpse" for patients like me, and I usually sign
14 up for most of their research and test subjects.
15 I feel that's a good way to use my time. But in
16 this case, I tried to integrate my VA records, my
17 health records from all these other databases so
18 that I wouldn't have to go into individual
19 databases to see what was done with each provider,
20 because I do have multiple providers. And I
21 couldn't get into any of them and none of them
22 would talk, even using this beta test, it locked

me out. The VA doesn't want to integrate with anyone beyond itself. And so those are some limitations on the patient side that, you know, these are systems that are being built, IT that are hopefully going to pull this all together but if they can't be used by the patients and they aren't effective for the patient, then we're kind of missing the mark on that and that's just another lesson learned that I want to transmit as a patient.

Okay. I think that's really it. Thank you. I really appreciate being asked to come. Thanks.

(Applause.)

DR. KANNAN: Thank you, Rebecca, for sharing your experience and providing that high-level overview on patients' perspective, covering the two major points.

So our next speaker here is Ben Haywood. He's the Co-Founder and President of PatientsLikeMe organization.

MR. HEYWOOD: Thank you, guys. Thanks,

1 everyone, and Johnny and Rebecca, thank you guys
2 for sharing your story. I think, you know, it's
3 incredibly powerful and thank you for your
4 service.
5 So, you know, Rebecca talked about this
6 a little bit but I'm going to tell you a little
7 bit more about PatientsLikeMe and some of the work
8 we've done. I got into this, unfortunately,
9 because my family was affected by a pretty nasty
10 disease, Lou Gehrig's disease, or ALS, and we
11 started PatientsLikeMe. At the time, we were
12 running a non- profit biotech doing in vivo drug
13 discovery. We actually knew many of the most
14 networked and activated patients and well-
15 resourced. We knew all of the researchers in ALS
16 and so we thought we could actually start this
17 network where patients could share data about
18 themselves and also have a social experience to
19 enable others to sort of have what we had access
20 to from an information standpoint. What was
21 interesting is when we launched the ALS community
22 in 2005, literally, within days, we realized how

1 little we knew as a family even with the resources
2 we had. So I think, you know, one of the take-
3 aways is there's a lot to learn from patients.
4 But I think ultimately what we need to
5 do is we need to take those stories, those
6 incredibly powerful stories, we need to take those
7 patient experiences, and we need to take the
8 presentation of the phenotype and the experience
9 of the patients and actually capture that in a way
10 that they can engage in and the system engage in
11 and that's what we've been trying to do over the
12 last few years.
13 I know PCORI is going next. I think we
14 were the PPRN before that term was dubbed. So we
15 are about 400,000 patients, as she mentioned;
16 2,500 conditions; we've done about 70
17 publications, a majority of which were peer
18 reviewed over the last few years. It's a patient-
19 generated technology which I'm going to talk
20 about. We have a safety monitoring platform which
21 actually feeds into some of the work we're doing
22 with the FDA. And then we also have a patient-

1 reported outcome measurement development platform
2 called the "Open Research Exchange."
3 But just to talk a little bit about what
4 patients do, and I think Rebecca talked about,
5 well, but, you know, obviously patients are
6 tracking their treatment, symptoms, outcomes, and
7 it's structured data. Unfortunately, today it's
8 primarily patient- entered so even labs and other
9 data is although, again, as she mentioned, we're
10 trying to get that data out of the system to
11 enable patients into it more easily.
12 Obviously, connecting and I think, you
13 know, Johnny spoke about having meaning. I think,
14 you know, one of the things patients really want
15 to do, and this is so true in the ALS community,
16 they want their disease to have meaning, and so
17 connecting into others and helping others to share
18 those experiences is really powerful. And then,
19 obviously, learning from others as she spoke
20 about.
21 So again, you know, I think this is
22 emerging science, patient-generated data and I

1 think it's -- the methods are getting better and
2 better and we're working to share what we've
3 learned. But we take all of the data that
4 patients share and map it to sort of standard
5 ontologies, ICD-9 -- ICD-10, SnoMed, Meddra,
6 RxNorm so that that can be computable and utilized
7 in the back end for research.
8 And again, broadly, we're in a lot of
9 diseases. Our largest community is multiple
10 sclerosis. We have a fairly strong
11 neurodegenerative as well as, you know, mental
12 health numbers. And then the last few years,
13 we've luckily been working with One Mind for
14 research, a great not-for-profit looking --
15 working to further traumatic brain injury and PTS
16 research. And so that started us on this journey
17 to work a little bit in PTS. So, you know, I'm
18 just going to share a little bit of top-level data
19 about our PTS -- I mean, I'm sorry -- our TBI
20 community and some numbers on it and then I'm
21 going to talk a little bit about some of the other
22 work we've done in other diseases that actually

1 can demonstrate what you can do when you sort of
2 go -- the opportunities with direct to patient
3 engagement.
4 So when we started with One Mind, we had
5 about 900 patients with TBI in the system. As of
6 today, we have about 4,700. I think I actually
7 just checked; it was almost 5,000 today. Patients
8 come to PatientsLikeMe with a primary reason so we
9 sort of ask them what's the primary reason. So
10 that's the number with the primary condition
11 (inaudible) about 2,900. Here's just the age
12 distribution. You can see sort of 42 is the mean
13 age distribution. We tend to skew -- well,
14 certainly older than social networks because it's
15 a chronic disease but a site for chronic disease
16 in general but this is -- you know, this is about
17 the average of our site. And we have some other
18 biases around broadband and sort of similar to
19 broadband access and tend to be a little bit more
20 female just because of information seekers in the
21 household, what you'd expect for an online
22 engagement like this. Just the age first symptom,

so a lot of younger people who were -- initially had the injury in their -- under 20.

We also collect activities of daily living data so patients can get pinged every day with a five point Likert scale that they can look at and respond in email. And then a lot of our patients, even particularly in our depression, major depression and bipolar communities use that to actually understand when and where during the week or during the day that they actually have a better or worse mood.

Again, you know, I'm blessed to follow a couple of military -- people from the military, you know, I think we are doing this partially -- One Mind is really focused on the military and I think there's an opportunity to help Vets here, so about a third of our TBI patients previously served or are in the military and we do track data on them and even more detailed down to the -- from the -- more than just the service area but much more detailed into what they did within the military.

1 So symptom severity -- so, you know, one
2 of the things we track in the system and enable
3 patients to track in the system are symptoms.
4 This disease, there are symptoms we track across
5 everyone, so fatigue, pain, insomnia, and mood and
6 depression. What's useful about that is you can
7 actually begin to look against that against --
8 across all the different clinicians in the system
9 to get some relative data. We did a large study
10 in insomnia across about 150,000 of our patients
11 looking at insomnia. And then additionally, some
12 disease-specific ones that we've coded in and
13 enable patients to track.
14 And then also, patients can track
15 anything they want so if you look at an individual
16 profile, you'll see individual things, symptoms
17 that patients really care about tracking and
18 understanding.
19 This is -- just to give you just the
20 sense of the scale, though, that's about 715
21 severe fatigue rating. So that recent
22 symptomology in the system is about 715 patients

1 who have told us they have severe fatigue. And
2 actually, in the upper right, you see it's the
3 highest severity ever. We also have sort of
4 longitudinal data on symptomology as well as sort
5 of relative to where it was, where the injury
6 occurred.
7 So, we've started -- it's pretty early
8 in TBI and PTS. TBI is actually a pretty
9 challenging disease for our platform on some
10 level; you know, particularly sort of not --
11 severe TBI due to sort of patient-reported data,
12 although we do -- we are working on sort of
13 figuring out how to do better caregiver entry and
14 engagement. But we've done some initial -- just
15 some initial surveys around symptom experience and
16 impact. As you can see, I mean as we heard, you
17 know, it really does begin to affect the quality
18 of life significantly. You know, majority of the
19 responses are not sort of receiving treatments for
20 the things that they really most wanted treatment
21 for. There's also this challenge of patients with
22 underlying physical issues sort of feeds some of

1 the emotional symptoms and then the emotional
2 symptoms tend to have a domino effect on other
3 areas of their life.
4 We also just looked at treatment
5 experience and again, I think patients are not
6 really -- you know, particularly in the military
7 patients, although the end there was relatively
8 small in TBI, you know, not seeking treatment for
9 some of the issues that civilians were. But
10 cognitive function and managing emotions were some
11 of the most important factors for seeking
12 treatment in TBI, partially, I think, because of
13 the availability for treatment.
14 So I'm just going to quick wrap up a
15 little about what's possible. Again, as I
16 mentioned, we're just staring in TBI. Those are a
17 couple of research studies over the last few
18 months but we've done a lot of work over the last
19 10 years in a lot of diseases, and they really
20 demonstrate what's possible when you go direct to
21 patients. So this is a study we did when patients
22 online initiated a study of taking lithium for ALS

after a clinical study. It was published in Nature Biotech but it begins to show that you can do predictive modeling using patient-reported phenotypic data to actually predict the progression of the disease and then actually model interventions against that. It's a great paper and data is available for anyone who wants to look at it.

We're actually taking that to the next level. We're actually doing sort of an integrated virtual study of a nutraceutical intervention in ALS with Duke. This is just some of the collateral for patients but it's in -- at Duke as well as remotely tracking data on the system. Trial of lunasin. And then just really quickly, some sensor data work we've done. We've done a number of sensor studies. This one's one that Biogen funded in MS but again, in 24 hours, we were able to get almost 300 patients enrolled immediately. Over 85 percent of them attached that data to the platform and then we were able to follow up with them. And actually, a year later,

1 we still have, I think, about 20 percent of those
2 patients still tracking with their FITBIR data.
3 And that system, that methodology can apply to
4 digital sensors. We're doing it more and more
5 with clinical devices being put into the homes and
6 then also looking at emerging diagnostic and
7 biomarker work.
8 And just a couple -- I think last one
9 here. This is work we did in Parkinson's where we
10 had really significant between visit data, and we
11 showed that the week-over-week variability of the
12 disease was higher than previously understood for
13 trial design. And I think that really affects how
14 you look at that, so
15 And then lastly, just to end on, we are working
16 with the FDA. They have access to our data and so
17 there is opportunity to actually utilize some of
18 this in some of the work here as well. So I'll
19 leave it at that. Thank you, everyone.
20 (Applause.)
21 DR. KANNAN: Thank you, Ben. That's
22 awesome. It's very interesting to see how we can

capture all this patient information and build this database. And I'm sure a lot of research communities would benefit from this.

And our next speaker here is Suzanne Schrandt from PCORI. She's the Deputy Director.

MS. SCHRANDT: Hi. Good afternoon and I just want to say thank you for the invitation to be here and thank you as well to Ben and Rebecca and Johnny for their amazing information.

So if you're not familiar with PCORI, I'm just going to provide a little bit of background on what we are. It's the Patient-Centered Outcomes Research Institute and we are funder, so we were created by Congress back in 2010 but we are a non- governmental entity. We're actually an independent non-profit and our task is to fund comparative effectiveness research, or CER. And so to date, we've funded just over $1.2 billion across about 600 studies in CER.

But the real sort of -- the real import of this research and the reason I'm here to talk to you about it is that one of our hallmarks is

1 the requirement of patient engagement, meaning
2 patient partners involved in study design, study
3 conduct, study dissemination from start to finish
4 in everything that we fund as well as in
5 everything that we do at an enterprise-wide level,
6 so from identifying high-priority topics to
7 selecting what we're going to fund to overseeing
8 what we fund and then helping disseminate those
9 results. We want patients involved throughout all
10 of that.
11 Typically, when I go out and speak to
12 groups about patient-engagement, I have to start
13 with the value proposition: why, why would you
14 have patients involved like this. And today I
15 don't' have to do that because you just heard from
16 three people who beautifully articulated why you
17 want that patient perspective in the room. That's
18 what should drive this process.
19 So instead I'm just going to go right
20 into -- I'm just going to tick through a couple of
21 the sort of really tactical ways that this happens
22 in the research that we're funding at PCORI. And

1 even though we fund clinical CERs, so these are
2 existing interventions that are already out being
3 used, it doesn't mean that these aren't applicable
4 across a wide variety of other efforts. So
5 discovery and development of drugs and devices,
6 that's not something we fund but all of these
7 practices, all of these concepts are universally
8 acceptable and really can and should be used in
9 other domains.
10 So first, when we talk about functions
11 patient partners can play on a research team, this
12 can really be anything. We have co-investigators
13 who are patients. We have consultants, any type
14 of engagement body, committee, advisory panel,
15 etcetera, task forces, any kind of partner you can
16 imagine. I think the critical distinction is that
17 when we're talking about patient-engagement at
18 PCORI, we're not talking about subjects. Yes,
19 you've got to have subjects and we know study
20 recruitment is so critical if we want trials to go
21 anywhere. But we're talking about partners who
22 are not enrolled as study subjects. They're parts

of the research team and they help design and conduct the study.

When we think about meaningful outcomes and the functions that patients can play in helping articulate those meaningful outcomes, you know, PROs, patient-reported outcomes are very exciting. We've heard those mentioned a lot this morning. One of the things we're uncovering through the studies at PCORI is PORs are incredibly important. It's great to get data right from patients. But what if patients weren't only the people delivering the answers, they were also the people helping define the questions? So I'm a patient myself. That's why I have this job and when I fill out one of those questionnaires and I provide 20 answers to 20 questions that may not matter to me at all, what information have you really gained about my quality of life and my function when I leave that office? So we're seeing a lot of work with patient partners trying to articulate those outcomes that really matter and capture what's important, and sometimes they're

1 clinical outcomes; they're not necessarily PROs so
2 there's a nice blend there of how to land on a
3 PCO.
4 Ensuring relevant questions, that sort
5 of goes with the outcomes. We want to make sure
6 we're asking the right research questions and
7 conducting this research the right way, creating
8 accessible patient-facing materials, and I'll kind
9 of wait for that and circle back to it when I talk
10 about recruitment and retention.
11 I want to speak on these next two
12 bullets quickly about data, although Ben just did
13 a great walk-through of how patients can be
14 involved in data collection, data storage. In
15 addition to the CER we fund, we also have a very
16 large data repository and infrastructure project
17 that we call PCORnet. And even though that's not
18 necessarily right now conducting a lot of
19 research, we didn't let loose on our requirements
20 that patients had to be engaged. So we said, yes,
21 we know you're creating a huge data repository and
22 you're building this infrastructure, you still

1 have to have patients engaged as partners. And so
2 what have they done? They've done just that. So
3 we have patients helping write the data use
4 agreements, thinking about privacy implications,
5 thinking about how do we access this data and keep
6 patients engaged and active in this process;
7 they're part of the governance structure; you
8 know, really high up in the governance structure
9 making sure that that patient input is genuine and
10 really meaningful and authentic. So data is
11 another place where we're seeing patients have
12 such power.
13 This recruitment and retention bullet,
14 it's got an asterisk so that I wouldn't forget
15 this incredible point and I would never forget it.
16 Recruitment tends to be the thing that is a nice
17 orienting point. If I'm talking to folks who are
18 not very familiar with the concept of patient-
19 engagement, of patient partners playing these
20 functions, recruitment seems to be the area that
21 we can all sort of visualize "oh, I see how if you
22 had patient partners on a research and maybe they

1 were very connected to the arthritis community,
2 then they'd be able to go out and get fellow
3 arthritis patients and pull them into the study
4 and that helps you with recruitment and there, I
5 get it; I see why you would want to do this." And
6 that's certainly true. We can see patient
7 partners as sort of extenders, as champions into
8 their community but it's really one small slice of
9 the benefit.
10 What we see instead is that recruitment,
11 especially in the studies that we're funding,
12 recruitment goes up because patient partners have
13 had touches on that study from day one. So I'll
14 give you a quick example. We have a comparative
15 effectiveness trial. It's a choice between
16 surgery and watchful waiting. So when you go into
17 this emergency situation, you're faced with this
18 decision. I have this thing going on; I either
19 need to have surgery or I need to do watchful
20 waiting and someone approaches you and says, "Hey,
21 if you'd like to be in this study, we're going to
22 randomize you so you won't have a choice but it's

safe, either way you're going to be fine" and it turned out that people were not jumping at the bit to sign up for this study. So they went to their patient partners who were affected by this particular health condition and they said, "What can we do? We are not -- there's no yield for this study. We're getting very worried."

And the patient partner said, "Well, let's deconstruct this a little bit. Who's presenting with this information? Who's the point of contact? Where is this happening? Is it in a busy fast-paced ER and what's this look like?" And they were able to peel it back a little bit and they determined if it's a surgeon that approaches me, there's only one person that's going to make me feel comfortable about being randomized to surgery and that's a surgeon, and there's also only one person that's going to make me feel comfortable about not being randomized to surgery and it's a surgeon, so I think it needs to be a surgeon and I think it needs to be in these certain scenarios, in a calm, quiet place removed

1 from the hustle and bustle. They changed the
2 entire protocol and guess what. Recruitment went
3 up.
4 So it's not just about being extenders
5 to the patient community. It's that there's
6 demonstrated value, the study itself has become
7 more accessible and more meaningful to me as a
8 patient and that makes me more likely to be
9 involved.
10 Encouraging active data-sharing and then
11 back up to the accessible patient-facing materials
12 - - just getting that sort of excitement and
13 building up the trust of these patients who are
14 going to enroll as subjects can identify with
15 these people serving as partners. It doesn't seem
16 foreign; it doesn't seem removed. It seems like
17 this is something my peers are involved in so,
18 therefore, I'm going to trust it and be more
19 likely to be involved.
20 And then lastly, one of my kind of
21 personal areas of interest is personalized
22 dissemination. We're just getting into this in

1 PCORI because we're just now getting to the
2 endpoint for some of our studies. We're so new
3 that we only have a handful that have reached
4 conclusion. But when it comes time to share
5 results, what better way to make results really
6 stick than to take patients with you or have
7 patients out there sharing results from this work.
8 So data is incredibly important. We want to show
9 evidence. You want to show why intervention "a"
10 works better than intervention "b." But if you can
11 attach a personal patient story to it, this
12 patient that's either delivering at a CME or a CE
13 or at a conference or even at a patient advocacy
14 organization event and saying this is why this
15 intervention was so important to me and my quality
16 of life is so much better because of if we're
17 seeing that really take shape and it's been really
18 incredible.
19 So I know I'm short on time. I'll be
20 very quick with this last slide. I just wanted to
21 provide a couple really tangible sort of
22 facilitators. These are some of the things we've

1 had to uncover in our short time in existence so
2 far. One is compensation and again, I'm talking
3 here about partners, not about subjects. Paying
4 for people enrolled in studies as subjects is a
5 whole different topic, but compensating and really
6 valuing the involvement of your patient partners
7 is something that we see really yield not only
8 more involvement but it sort of equalizes that
9 relationship. If everyone at the research table
10 is receiving some sort of compensation except for
11 the patients, what does it say about the parody,
12 about the equity, the value we place on those
13 patient contributions? It also is a great
14 facilitator for people who might not be able to
15 afford to be involved otherwise. So if you only
16 can invite people who sort of have time and
17 resource to be able to get there and be there,
18 you're going to leave out a really important
19 subset of patients that we want to make sure are
20 included.
21 Formalized roles and agreements -- this
22 is just being real; you know, really writing out

1 what is your function on our team; what's your
2 decision- making authority; when are you looped
3 into decisions; when might you not be. We don't
4 want token patient involvement. You don't just
5 call grandma and say, hey, grandma, I know you
6 have a bad hip; can you come be the patient on
7 this study that has nothing to do with you. We
8 want patients that represent the population being
9 studied who can really communicate from that very
10 personal experience.
11 I would say ask first, exclude second.
12 I know this is all incredibly complicated science
13 but patients might want to be involved in even the
14 very complicated stuff so just ask and if they
15 don't want to be involved, they can self-select
16 out.
17 Engagement has to be relational and not
18 transactional. So these are long-term efforts and
19 we've seen today already trials sometimes fail.
20 You want to build relationships so that you, as a
21 unit, can keep trying again for newer and new
22 opportunities.

1 And then lastly, engagement does take
2 time. We've seen some studies dedicate an entire
3 FTE to manufacturing the engagement, making sure
4 you've got patient partners and that they're being
5 meaningfully incorporated. It takes energy. It
6 takes resource but we definitely believe and we're
7 building an evidence base to prove that it is
8 worth it. So thank you.
9 (Applause.)
10 DR. KANNAN: Thank you, Suzanne, for
11 sharing PCORI's perspective and beautifully
12 illustrating the importance of engaging patients
13 in studies to demonstrate more meaningful clinical
14 outcomes.
15 So with this, we are going to move on to
16 the next set of talks that are going to revolve
17 around big data sets and what are t he strategies
18 for improving data standardization, sharing, and
19 applying big data analytics. And our first
20 speaker here is Dr. Daniel Sullivan. He's a
21 Professor Emeritus in the Department of Radiology,
22 Duke University, and he's also the Founder and

Chair of
QIBA.
DR. SULLIVAN: Thank you. I'd like to add my thanks to the organizers and to many of the speakers that have been very moving this afternoon. We're going to switch gears now and talk about to a topic that came up this morning which is related to how do biomarkers get validated.
And my particular interest is on the quantitative imaging biomarkers. It's a concept that was introduced by Dan Krainak this morning from the FDA and this is the formal definition that we have in QIBA which is almost the same as the definition you've seen earlier from the FDA about a biomarker but this includes the word "measured." This is a measurement that comes from scans and the phrase about a ratio or interval scale simply means that these numbers can have an arithmetic basis. They can -- arithmetic operations can be performed on these numbers and the purpose of this phrase is to distinguish it

1 from scales which are arbitrary numbers. For
2 example, the Glasgow Scale that we've been hearing
3 is a set of arbitrary numbers. In imaging, we
4 have a lot of scales, from 1 to 5, for example, in
5 bi-res (ph) and although those appear to be
6 quantitative because they have numbers, they're
7 not. You can't do arithmetic operations on them.
8 They don't have arithmetic meaning.
9 These numbers do and these numbers are
10 derived from the number that are behind every
11 pixel or voxel in every image. Every image now is
12 digital and those numbers have real meaning. They
13 have a real biological or physical meaning
14 associated with the interaction of energy with the
15 biological substrate that's being imaged.
16 So this organization of QIBA started in
17 2007 sponsored by the Radiologic Society of North
18 America and although it's an organization, it's
19 really also a set of concepts and methodology that
20 we hope many others will adopt as well. Our
21 mission is to improve the value and practicality
22 of quantitative imaging biomarkers by reducing the

variability across patients, devices, and time. What this means, in other words, is that just as if you were taking a temperature of a patient, you would not care who the manufacturer of the thermometer was. You would expect to get the same reading no matter who manufactured the thermometer.

That's not currently the case with imaging. If you go to a hospital down the street today and get scanned on a scanner from manufacturer "a" and get some number, and then tomorrow go to a hospital across town and get scanned on a scanner from manufacturer "b" for the same thing, you would likely get a very different number and that's the situation that we are setting out to change.

So we're not in the discovery business. We are working with biomarkers that have been through the discovery development feasibility stage and are at the point where it makes sense to what we call industrialize them for widespread use in clinical trials.

1 This is the schematic from the IOM
2 workshop on biomarkers a few years ago about
3 assays. And the other concept to keep in mind here
4 is that we are approaching these imaging
5 biomarkers as if they are assays. These are
6 numbers just like numbers from a laboratory test
7 and should adhere to all of the concepts that have
8 been developed for laboratory assays over the last
9 several decades, and that's not been the case up
10 until now. The IOM suggested that assays be
11 thought about as having this bright line between
12 technical performance, or analytical performance
13 is a term that others have used here this morning,
14 and a clinical performance. That is you need to
15 understand the performance of the assay in the
16 laboratory setting under fixed settings before you
17 can reliably understand its clinical performance.
18 And in QIBA, we focus on the technical
19 performance of these imaging assays. We don't get
20 involved in clinical performance. That's for
21 other groups and clinical trials and so forth. But
22 our belief is that you cannot effectively do that

until you really understand the technical performance of the imaging assay.

We have participants from a wide group of stakeholders. We have committees that cover all four of the major modalities. We have committees focused on about 12 or 13 biomarkers at present. There are literally hundreds of volunteers from all of these various organizations. And importantly, we have a lot of involvement from the FDA in our committees and our workshops and so much of our terminology and concepts and methodology are very much infused by the thinking of the FDA and benefit from their input.

A couple of the speakers this morning talked about -- the speakers from the FDA In Vitro

Center talked about the parameters that are important to understand for an in vitro assay. And in concept, most of those should also apply to imaging assays and we have adopted and adapted most of those. But because this is a relatively immature field relative to in vitro diagnostics,

which has been ongoing for decades, we formed this metrology working group a couple of years ago to give us advice about a variety of things. And their advice was the three most important technical parameters for us to understand, to characterize an imaging biomarker are bias, precision, and linearity. Just a note: we don't use the word "accuracy" and I noticed when Dr. Biswas this morning was giving her talk, she talked about bias and precision frequently, I think, in her whole talk and she didn't use the word "accuracy" at all. This is preference for metrologists, measurement scientists and statisticians.

The variability that occurs in any number extracted from imaging could be related in a broad sense to one of these three categories: image acquisition; variability -- that's the scanner and the software involved in that; the measurement method variability -- that's usually an algorithm that's used to extract the number; and radiologist or reader variability. Ideally,

1 the first two steps would be automatic and there
2 wouldn't be a radiologist involved but that is not
3 the current situation and probably won't be for a
4 long time. So there is a need for some observer
5 to accept the output of the algorithm or edit it
6 in some way and that does introduce some element
7 of variability, but it's a much smaller component
8 than the variability associated with the
9 qualitative or the subject interpretation of other
10 types of imaging results.
11 So that variability could occur at any
12 of these steps and we take all of this into
13 consideration in the QIBA process. We essentially
14 are developing a systems engineering document that
15 deals with all of this. And to find the sources
16 of variants, we use a variety of sources of data,
17 the scientific literature. There are some
18 published data, not as much as we'd like. We do,
19 in QIBA, a lot of studies of our own using
20 phantoms. This is the term that's used in the
21 field. These are physical reference objects. We
22 also, in QIBA, in the last few years, have

1 increasingly relied on synthetic scans because
2 this allows us to know truth unambiguously in
3 these synthetic scans and it has been enormously
4 helpful and this concept of hybrid scans where
5 lesions or noise can be superimposed onto clinical
6 scans. And many of these studies are funded by a
7 research contract we have from the NIBIB at NIH.
8 We're very appreciative of that funding. And so we
9 do a variety of studies looking at sources of
10 variability. And we also get some data from the
11 manufacturers themselves.
12 So the general approach is to identify
13 these sources of variation, write a profile which
14 is a document of solutions and test those.
15 Profile is essentially a document. It's a long
16 document. It's a systems engineering document
17 that says how everything has to perform in order
18 to get the result. And the profile is structured
19 around a claim. There are two types of claim
20 statements. One we call a cross-sectional claim.
21 That's a measurement at a single time point. And
22 the longitudinal is a change in measurement. An

1 example of the cross-sectional one that we heard
2 about this morning is Shashi Amur talked about the
3 qualification of total kidney volume. That's a
4 single time point measurement for eligibility into
5 a clinical trial. That would be a cross-sectional
6 measurement.
7 One of the potential strengths of
8 imaging is to look at change, to look at
9 pharmacodynamic change or change in any -- in
10 response to any therapy, for example, over the
11 natural course of the history and so there, we are
12 interested in serial measurements and longitudinal
13 change.
14 The steps we use in coming to the claim
15 for a profile are listed here. I won't go through
16 them but we have documents on our website and Wiki
17 that describes all of these steps and once we go
18 through this process of analyzing the data that's
19 available what's needed clinically and so forth,
20 we develop a claim statement which has something
21 of this form. This is a general template which
22 says "For this biomarker measurement of "y" units,

1 the 95 percent confidence interval for the true
2 value is "y" plus or minus the precision value."
3 Precision is a general term that
4 includes either repeatability or reproducibility.
5 Repeatability is when the conditions of
6 measurement are the same. Reproducibility is when
7 something changes which is likely the situation
8 over time serial measurements. But for a single
9 measurement, an example of this from our CT
10 volumetry profile is for a measured long-term
11 volume of "y" cubic millimeters to a 95 percent
12 confidence interval for the true volume is "y"
13 plus or minus 1.96 times "y" times 0.14. The 0.14
14 here means that the variability being used in this
15 situation is plus or minus 14 percent.
16 Longitudinal claim is a little bit more
17 complicated because the issues associated with
18 precision are likely to be more complicated across
19 the two time points. And I will just skip through
20 to the end to say that we have methodology to
21 account for that complexity. Just wanted to
22 mention that we have all of this information up on

1 our imaging archive which is available to anybody
2 to look at.
3 And in terms of the topics being
4 discussed today, there are draft QIBA profiles
5 existing for CT volumetry, DMRI- diffusion-
6 weighted MRI, fMRI. And a profile for DTI, QIBA is
7 just in the early development. The committee has
8 been formed. Committees are open to anybody who's
9 interested.
10 Processes for people to demonstrate
11 conformance are in development and all the data
12 are available. And there are also affiliates
13 internationally, so these standards will become
14 international standards as well. Thank you.
15 (Applause.)
16 DR. KANNAN: Thank you, Dr. Sullivan,
17 for providing QIBA's perspective on neuroimaging
18 biomarkers. And our next speaker here is Dr.
19 Patrick Bellgowan, Program Director of the Repair
20 and Plasticity from the National Institute of
21 Neurological Disease and Stroke, NIH.
22 DR. BELLGOWAN: Thank you for inviting

1 me to speak. This is a really exciting title
2 slide for a fairly dull topic. But CDEs, what
3 I've learned about CDEs is that, you know, no one
4 wants to talk about them but they're very, very
5 passionate about them. And they're a very
6 important at NINDS and across TBI. I think TBI --
7 you know, being at NINDS, which is one of the
8 institutes that's spent the most effort on CDEs,
9 TBI, we're a clear leader in CDE development and
10 TRACK-TBI is a big part of that. And many of you
11 here actually know much more about the CDEs than I
12 do because you developed them.
13 But, you know, I'm not going to talk
14 about the next phase but the next phase is where
15 we've actually developed -- Dr. Mona Hicks and a
16 lot of pre-clinical investigators have developed
17 pre- clinical CDEs which are also right now being
18 tested. They're not available but they're being
19 tested.
20 This is our website that hosts all of
21 our CDEs and a CDE is just a common data element.
22 What I really want to show you on the website here

1 is that, you know, while we're going to be talking
2 mostly about -- exclusively about TBI that, you
3 know, we have them for a lot of diseases. And
4 what I find is that people who are looking at
5 extending even within the field of TBI, so if
6 you're looking at headache, there are headache
7 TBIs, so there's a whole field of headache TBIs.
8 We don't have to recreate all the TBIs for all the
9 fields, okay. Epilepsy -- if you're looking at
10 seizures and post traumatic epilepsy, there's an
11 epilepsy CDE. So please look in here. Look for
12 your diseases and use your CDEs.
13 So what are the motivations for using
14 them? Well, it's partly financial, partly effort,
15 and partly the power of big data. The first is
16 the time and effort of choosing your CRFs. So,
17 you know, when we talk to investigators as they're
18 designing the clinical studies they hem and haw a
19 lot about what they're going to do, what measures
20 do they gain, what outcome measures do they look
21 at. And CRFs give them a more limited universe to
22 search, which is one good thing. So it kind of

1 reduces the amount of time that they have to think
2 about it. It also reduces the amount of time that
3 they have to try to find them.
4 Second is that the trials are -- they're taking --
5 well, this is not -- these are not my slides so I
6 don't necessarily agree with this next one -- but
7 they're taking a lot of time and they have a lot
8 of costs. And so this has reduced the startup
9 cost and accelerates the amount of time for the
10 trials to get up and going.
11 The data quality varied so this is
12 really where the meat of the subject is, is in
13 data quality so if we can get people using CDEs,
14 we know we're at least going to have the same
15 value range. The next step is to get them to, you
16 know, when you're looking at a particular CDE, you
17 actually apply that CDE in the same way. So
18 TRACK-TBI is a leader in that in that they've
19 standardized across all their sites and have high
20 data quality.
21 Data collection is not consistent and
22 that has a lot to do with data quality. We're

1 hoping to actually, at some point, get this so
2 that it's an automated process that, at least for
3 TBI -- and you're going to hear about FITBIR from
4 Dr. Crowder next -- but that can automatically
5 update it into FITBIR. And then most of all, it's
6 important for comparing between studies so that
7 we're -- you know, when I -- when Geoff says he's
8 looking at the global -- the GOSE and Harvey Levin
9 says he's looking at a GOSE, they're actually
10 looking at the same thing so we get the same
11 values between studies.
12 You know, so what is a CDE? Well, a CDE
13 is range. So CDE is not a great term right now
14 because CDE means really two things and I like to
15 refer to CDEs as the actual individual question
16 items versus the CRF which is the clinical report
17 form which is made up of multiple questions so
18 it's made up of multiple CDEs. And they just --
19 you know, they provide -- there are specific
20 ranges for age. There are specific definitions
21 for gender or race that need to be followed under
22 federal regulations.

1 This is -- it's not an effort that NINDS
2 is just going to make itself. There's a lot of
3 collaboration here so there are 17 federal
4 agencies that contribute. Many of them are here
5 today and have spoken already. And then there are
6 a lot of non-profits who also contribute to this.
7 And then of course, you know, the experts, the
8 investigators themselves drive this process, and
9 particularly in TBI have done a really good job in
10 keeping -- staying together, staying the course,
11 and making sure the CDEs are being tested in the
12 way they should be.
13 So what is it that you know, where do
14 we use these CDEs; where can we store them; how do
15 they interface with other parts of our research
16 enterprise and infrastructure? Well, the National
17 Library of Medicine, of course, is very interested
18 in common data elements and is developing large
19 libraries across multiple diseases and NINDS CDEs
20 are involved in those.
21 More importantly, from my perspective
22 and from the perspective here, we're talking about

1 data- sharing, is that these CDEs are coordinated
2 with the FITBIR which is the Federal Interagency
3 TBI Repository for data. Their data dictionary is
4 consistent with the NINDS CDEs so you can put the
5 data in there. Then the PDBP is, I think, a good
6 model. I think it's something we should start to
7 think about. It's Parkinson's Disease Biomarker
8 Program and that's looking at what we heard about
9 earlier which was actually sharing biomarkers more
10 rapidly than we currently do.
11 And then of course, you know, where
12 we've seen success, if you look at ADNI(ph), you
13 start to see success in data standards,
14 particularly if it's international and there's a
15 big international effort, TRACK-TBI, and most of
16 the TED investigators are cooperating in this
17 international effort called InTBIR(ph) which is
18 really important and we're trying to align across
19 with European partners and Canadians, these data
20 standards.
21 And then we already heard today that the
22 same CDE group of investigators worked really hard

1 to develop -- to change -- do the slight changes
2 that were necessary to the NINDS CDEs so they
3 could fit the CDISC standards and be usable for
4 FDA -- for the FDA requirements and, you know,
5 that's really important.
6 And in the next line, I should have put
7 it in "red" too. Currently, I think where we're
8 really starting to push this is at both NIH, at
9 least NINDS and NICHD, and the DoD-funded studies
10 now require the use of CDEs for TBI clinical
11 research studies.
12 These are just some of the diseases again
13 just to give you an idea. Traumatic brain injury,
14 I really think we're a leader in the CDEs,
15 particularly because, you know, the TRACK pilot
16 was a good test. We've tested ours pretty
17 thoroughly relative to the other diseases. We
18 have pre- clinical CDEs at a much advanced state
19 than any other disease, and we're hoping that, you
20 know, this is really going to come together and
21 accelerate TBI and we can, you know, again be the
22 model.

1 So this is what CDE looks like, the
2 nitty gritty. It really just looks a lot like an
3 Excel row and in each row, it has descriptors like
4 the variable name, the question, the data type,
5 references. It tells you if it's required or if
6 it's a core CDE and most importantly, what it
7 really does is it limits the values, so what are
8 the permissible values. This -- you know, one of
9 the great things about this that goes unsaid often
10 is that this actually works as a data quality
11 assessment so when people submit their data, what
12 we'll find -- they'll find errors. So this checks
13 for errors. If your data are out of range, you
14 have to go back and try to figure out why that is
15 and correct for that. So it gives you that extra
16 level of security.
17 These are how they're developed. It's a
18 long process. You can see it takes a year, a
19 year- and-a-half to develop them. It starts with
20 working groups of experts who are going to tell
21 you which particular instruments -- generally
22 instruments they think should be used and required

1 and which ones maybe are repetitive and don't need
2 to be done. And then as you work through the
3 process, you end up with a public review of these
4 which is six weeks, and then they're published,
5 and then we put them to the test. Right now it
6 says version one but we're actually on version two
7 of the TBI CDEs which we will try not to get into.
8 People get fired up.
9 So disease-specific -- so within our
10 disease, I mean we have CDEs for biomarkers. So
11 Ramon did a really good job putting -- you know,
12 working with some of the Parkinson's disease
13 people, I believe, to put together a standard SOP
14 that contained CDEs for biomarker collections. We
15 have imaging CDEs that Dr. Yuh was talking about
16 today, and then we have a lot -- you know, we have
17 like 160 outcome measures in TBI alone that we're
18 creating CDEs for and we're trying to get those
19 done ASAP.
20 This is the TBI website. You can just
21 see, you know, it's going to be laid out -- so
22 it's laid out for CDEs. It's laid out by what

type of test you're looking at. This is the disability rating scale so it gives you a short description. It tells you the scoring and it tells you the psychometric properties and how it's been supported.

And then I just wanted to make sure that you saw this. So this is the bio-fluid protocol, so it shows you how to do it and it shows you the CDEs to be used and the imaging CDE protocol that we have available on the website and in FITBIR.

What are the lessons learned? Well, you know, CDEs always need to be tuned, right. We're always testing them. If there are problems, you need to bring them up and we're going to tune them. Of particular importance are the investigators because they are the ones who are using them and decide whether they're appropriate and fit their purpose or not. There are CDEs that we can get rid of more CDEs we need to add.

I only have three seconds, uh-oh. So let me skip ahead -- sorry -- to just show you the website. So if you go to -- if you search CDE

1 NINDS -- I don't know why they're called the NINDS
2 CDEs. I think -- I don't know, it's ridiculous but
3 you can find them on our website. We maintain
4 them. The main contact person for that is Joanne
5 Odenkirchen. She'd be happy to talk to you about
6 CDE usage and how it fits into your study anytime,
7 so, thank you.
8 (Applause.)
9 DR. KANNAN: Thank you, Dr. Bellgowan,
10 for walking us through the objectives of the CDE
11 project and its importance in applying these for
12 data standardization and harmonization.
13 Our next speaker here is Dr. Manley and
14 he's going to talk about the TED metadata set.
15 DR. MANLEY: Thanks. That's actually a
16 very tough talk to give about the CDEs. I know
17 that people sometimes, you know, go half mast or
18 their eyes glaze over but without data
19 standardization, we're really not going to be
20 anywhere so I think it's a very important topic.
21 What I thought I would do in the short
22 time period that I have, I know today you've been

1 hearing a lot about, you know, TED and TRACK and
2 I'm just going to, as part of talking about the
3 TED metadata set, give you a just a brief overview
4 of where all these things coming from.
5 But first of all, just to let you know
6 that somebody's referred to me as the PI of these
7 grants. I'm actually the contact PI. These are
8 multi-PI grants. That's a very important thing
9 because we have to work together as teams.
10 There's no way that I could do this. There's no
11 way that UCSF could do this. Really, this is
12 truly a team effort and a lot of our partners are
13 here. I know Nancy Timkin's (ph) here who is on
14 virtually every phone call that's part of all
15 this, and we have lots and lots of conference
16 calls.
17 We are really a center without walls.
18 We're a large team science effort and while it may
19 seem like you've heard a lot of talk about TRACK
20 and TED this morning, it's because basically we've
21 embraced a large percentage of the TBI community
22 in this team effort. And so we've really tried to

1 build a really big tent with a lot of people that
2 are getting a very small percentage of effort,
3 that are really coming together because we know
4 that not one of us is going to be able to solve
5 this problem independently and this has got to be
6 done together.
7 So just to give you a timeline, you
8 know, we talked a little bit about it this
9 morning. Ron mentioned this, that there was a
10 consensus conference in 2007 where we really
11 questioned the utility of mild, moderate, or
12 severe. And so from this actually came the idea
13 of the common data elements that you just heard
14 about. We then had these common data element
15 working groups which was more than just the NINDS.
16 The DoD played a big role in that. So did the
17 Department of Education with the TBI Model
18 Systems. There was actually -- this is an example
19 of where government works -- we had many, many
20 people coming together to work on this.
21 We had the pilot study which Pat just
22 referred to where we started to validate these and

1 we were able to start to look at some of the MRI
2 data that you showed this morning. One Mind came
3 on the scene which has been a very important
4 philanthropic partner, so it's not just academics
5 but it's philanthropy and I'll show you how our
6 corporate partners have come on as well. We got
7 funding from the DoD to help us analyze some of
8 the data that the funding didn't cover with the
9 NIH-funded TRACK-TBI pilot.
10 And then Pat just alluded to this idea
11 of InTBIR, which is the international TBI research
12 initiative where we have now a companion study
13 that's going on in Europe; also, partners in
14 Australia and in Canada. So this is not just a
15 U.S. North American effort but we've broadened out
16 around the world and with these efforts, we're not
17 getting large-scale imaging markers, proteomic
18 markers, genetic markers, etcetera.
19 And then the current study that's
20 running now is the TRACK-TBI study which is 3,000
21 subjects. Again, I really appreciated the talk
22 earlier about standardization of data,

1 particularly around the imaging, and we've been
2 using phantoms to get ground truth and really
3 paying a lot of attention to the pipeline so we
4 can do quantitative imaging.
5 Then we also received additional funding
6 here from the DoD to add on some more imaging
7 analyses that we're doing and that really then
8 brought us into TED which is really closing the
9 regulatory part. So I think that's -- as Ron and
10 others mentioned this morning, if we don't have
11 regulatory approval and we don't embrace the
12 regulatory science, it's never going to get to the
13 patients. And so what I hope you see is that
14 there's sort of been a method to all of our
15 madness and working together to try to put this
16 into a comprehensive plan to try to move the field
17 forward.
18 And as Pat also mentioned, we took the
19 common data elements, which was an academic work
20 product, worked with OneMind, worked with the
21 people at CDISC and C-Path and really now have
22 conformed this to FDA data standards for TBI. So

1 a lot of work has been done in the last few years.
2 We now have 36 universities and institutions under
3 this big tent along with 75 investigators and now
4 16 corporate partners.
5 So we're really trying to accelerate
6 research, building infrastructure, increase
7 efficiency and quality, and hopefully, one day,
8 you know, to do better clinical trials and to do
9 them in a more efficient way because we understand
10 for our corporate partners, there has to be a
11 business model and we've got to figure out a
12 cheaper way of doing some of this. So this is
13 just an example of some of our corporate partners.
14 I know the logos are small there but a lot of the
15 people that are in the room, your stuff is up
16 there and we appreciate the support and
17 partnership. And it's not just about financial
18 contributions but it's about in-kind
19 contributions, and it's really about all of us
20 working together as a team.
21 So with the TBI endpoints development
22 grant, and we're going to talk about the metadata

1 set, we're currently in stage one. So we're 16
2 months into this grant and I think we've been
3 pretty successful at establishing a collaborative
4 multidisciplinary team. We're starting to look at
5 these clinical outcome assessment tools. We're
6 looking at the biomarkers, again, with this theme
7 that you've heard today, which is moving beyond
8 the GCS and GOSE. We've already, as we've
9 discussed, initiated the CDEs data standards and
10 that was completed and was published, I think, in
11 December of 2015, so just a few months ago. The
12 thing that we really have a unique opportunity
13 here, and you brought up a question in the last
14 session about validation -- excuse me -- about how
15 do we move all of this forward; how do we get the
16 regulatory science going. And the fact is that
17 there's really not funding for regulatory science.
18 We can't go to the NIH and write an RO1 and say we
19 want to do regulatory science. They don't fund
20 that kind of work. And so, you know, the vision
21 of Colonel Hack and others at the DoD to realize
22 that this was a huge gap, that we really needed

1 the regulatory science -- we can do all kinds of
2 science but, you know, they're really science fair
3 projects unless they come into something that's
4 approvable that can go to a patient.
5 So I think, you know, there was a lot of
6 vision and wisdom in putting this together. And
7 what we have a really unique opportunity and why
8 this meeting is so important --and I will lay out
9 a challenge for our FDA colleagues -- we're not
10 just here to talk about this today. We're here to
11 get input because we have funding that's coming up
12 in stage two that's going to allow us to do the
13 prospective validation that we heard all of our
14 FDA panel talking about today. So when we talk to
15 you about what do we need to do for an imaging
16 marker; what do we need to do for a proteomic
17 marker; what do we need to do for a clinical
18 outcome assessment, it's not that we're just going
19 to -- we're here to talk about it, we're here to
20 actually do something about it. So we're very
21 encouraged and looking forward to our CPI meeting
22 to get the kind of guidance that we need to

1 actually make a difference and to move forward
2 because we're a very results- oriented team of
3 folks here.
4 So I want to just touch on a little bit
5 about integrated -- you know, the existing data
6 and, really, this idea of creating a TBI
7 "collaboratory." We've heard a lot of talk about
8 silos and how people are doing different things.
9 We've all recognized that we're better off working
10 together than working apart. And I know that you
11 can't read this but these are all the current
12 studies that we have that we're trying to pull
13 together as part of TED. And we have -- and it's
14 more than just the data -- everybody's like, well,
15 let's look at the data. These -- remember there
16 weren't common data elements when these things
17 were put together. You actually need to have the
18 data providers as part of your team to basically
19 shepherd you along because, you know, if you look
20 at the GOSE for example, we found out in the early
21 stages of putting the TED grant that not
22 everybody's doing the GOSE the same way; horrifying

1 thought, right? But if you just look at the GOSE,
2 there's an eight point scale; it said an eight
3 point scale but until you talk to them, you
4 realize well, boy, this was administered a little
5 bit differently from site to site. So we think
6 it's not only important to have the data but to
7 actually have the people that generated the data
8 to help inform us as to what we're actually seeing
9 in these data sets.
10 Now with that -- and you would say,
11 well, gosh, we've got the people that actually
12 generated all the data and we've got them all
13 together under this big tent, let's just start
14 sharing the data. Well, I can tell you over the
15 last year, we hit all kinds of brick walls from
16 our own institutions that wouldn't even let us
17 share the data that we had generated with
18 ourselves all working together. And so, you know,
19 we spent the last 12 months recoding some of these
20 data sets and I won't even -- you know, if you
21 want to catch me at break, I'll tell you about all
22 the craziness with trying to do this because as we

1 learned from a One Mind summit that was put on by
2 the One Mind team in May of 2014, data-sharing is
3 a lot harder than you think. It's a lot -- sure,
4 I mean nobody's going to stand up here and say,
5 oh, data-sharing is bad, right? We're all going
6 to say, oh, data-sharing is good but the fact is
7 it's really, really hard. Why? Because most
8 current incentives encourage hoarding of data.
9 You're not really rewarded for sharing your data.
10 Why? Because we have to write papers and we have
11 to get funded and we have to have recognition
12 within our own institutions. The promotions
13 happen because of your funding and these other
14 things and, you know, there are publication
15 policies and people are worried about who's the
16 first author and the last author on these things.
17 And when we start thinking about working
18 with our corporate partners, there has to be a
19 business model. I mean you guys, you know, you
20 can't pay your own salaries, you can't develop a
21 product, you can't go out and get stuff to
22 patients for free. I mean you're not running a

1 non-profit organization so the IP is important for
2 the companies and it's important for us to
3 recognize the importance of the IP because we need
4 to get products to our patients.
5 So what we've done over the last year-
6 and- a-half, and I really have Amy Markowitz to
7 thank for a lot of this work, is we've put
8 together a series of publication and authorship
9 guidelines that basically reward everybody for
10 participation. This isn't that one person's going
11 to get all the credit because you're writing the
12 paper with the data. Everybody goes on an author
13 block with our thing. It's a bit like particle
14 physics. We have data use agreements not only for
15 the data in but the data coming out. We have
16 collaboration agreements that are both for
17 academic and also for private partners. And we
18 have a policy by which we're taking these analysis
19 plans and they have to be published within the
20 data that you're looking, so if you come to us as
21 an outside investigator with a collaboration
22 agreement, we'll say "yes, but we need to know

1 your pipeline about how you analyzed your data and
2 you need to put those results back into the
3 metadata," because what happens is that even
4 though people are sharing data, they then go off
5 and analyze it and build new little silos that are
6 analytic silos. So we're trying to repurpose that
7 data and get that back into the fold again.
8 So how do we prepare this data for the
9 TED metadata set? These are the studies that we
10 currently have. TBI Care is actually a European
11 study and a very important study that has mild
12 traumatic brain injury patients. And these are
13 the various studies that we're looking at today.
14 We identify the data that we want to share and we
15 also -- today people talked about the inclusion
16 criteria, the exclusion criteria, the baseline
17 data, and the outcomes. You may not be able to
18 read t his but all this is available on the TED
19 WEBSITE. These are just some of the basic
20 demographics. Those little "x's" are showing you
21 the commonality across these studies, so you can
22 see some of these measures are very common across

all the studies that we're looking at, some of them are used infrequently. Same thing -- this is looking at, you know, drug screens and CBCs and things of that nature. This is looking at things like all the outcome measures which, again, there are many and everybody sort of had a different take on how they were going so there's less commonality than we would like to see.

And so basically, what we do is we create a harmonization workbook. We put these worksheets together. We divide all of this and basically, what we're doing, because none of this was collected with common data elements, all this has to be extracted and then conformed back to the common data elements, so COBRIT/TRACK-TBI, the pilot are more similar to the common data elements so we're having an easier time with that but the rest of this remains a lot of work.

So I'll just go through this. We can talk about this later if you'd like. There are many steps to being able to harmonize this data and to bring it together. Our colleagues at

1 University of Pittsburgh have done a wonderful job
2 helping us with this. They built harmonization
3 workbooks and tools to help us conform to the
4 common data elements. And again, this is the sort
5 of stuff that can be repurposed by anybody in this
6 room. We're very open with the protocols and the
7 things that we develop. We want to see these
8 things replicated, repurposed in other studies.
9 So basically, after we do the
10 harmonization process, at the end of this, we take
11 this data and we send it to Palantir for loading
12 and currently, we have about 4,000 subjects in
13 this and you'll hear a little bit more from Chloe
14 form Palantir as to what they're doing to help us
15 out with some of the in-kind contribution to our
16 effort here.
17 I'll close by showing you why is this
18 important. This is a paper that was published
19 last year and this is looking at a hypothesis-
20 driven study looking at a genetic polymorphism.
21 And this is using both COBRIT and TRACK-TBI pilot
22 data. And the bottom line is that we could have

both tried to do this study separately and we would have not had the results we had here. And it was only through sharing these samples, sharing the genetic analysis, and bringing these studies together that not only this paper got published but there are several other papers that are in the pipeline. So I just show you this as, you know, as they say, to put some meat on the bone that this isn't just a philosophical thing. This is absolutely a requirement for us to make progress but we need to understand that everybody needs to be able to sustain their operation. Whether it's a company or whether it's a philanthropic organization, or whether it's a group of investigators, we all sort of need our own business model and that's what we've really tried to address with these data-sharing agreements, publication policies and so on.

And what I can say is, you know, for now, it seems to be working very well and we'll see how we proceed in the future. So thank you again very much.

(Applause.)

DR. KANNAN: Thank you, Dr. Manley, for walking us through the different collaborative efforts within the TED/TRACK-TBI and for sharing with us the ins and outs of the data-sharing and also on how the TED metadata set is built and being harmonized.

So now let's invite Dr. Tammy Crowder, who's going to talk about the TBI registries. She is the Neurotrauma Research Portfolio Manager at the Department of Defense-Combat Casualty Care Research Program.

DR. CROWDER: So as Lakshmi said, I'm going to give you an overview of key registries for TBI research. And during our time today, we've discussed a lot of research, specifically research on biomarkers or indicators of traumatic brain injury.

We've discussed how to collectively manage that research, the research knowledge we're generating, and we know that due to technology advances, data pools are growing much, much more

1 rapidly than we can analyze them. And frankly,
2 they're growing logs more rapidly than we can
3 thoughtfully or strategically analyze them. And
4 we all want to take advantage of these massive
5 amounts of data to provide the right diagnosis,
6 the right intervention to the right person, the
7 right patient at the right time. Challenges
8 include capturing, storing, searching, and
9 analyzing that data.
10 Pat gave us a great overview of the
11 utility of common data elements in all research,
12 specifically human subject research, to improve
13 data quality and how it give us opportunities to
14 compare and combine data from multiple data sets,
15 multiple studies, and compare them with electronic
16 health records. But common data elements can't
17 overcome the challenges of these disparate data
18 sets.
19 So the National Research Action Plan, or
20 NRAP, called out specifically the need for us to
21 consolidate TBI study information. And as a
22 result, the DoD, the VA, and the NIH include all

1 their data in NIH's Federal Reporter. We include
2 the researcher, the organization, the study
3 details, the cost. It's public accountability.
4 All of our research is now uploaded into the
5 Federal Reporter. In the past, it wasn't that we
6 didn't have our data, the DoD didn't have their
7 data in a consolidated data set. Many of you are
8 familiar with the electronic grant system, or EGS,
9 or the electronic data management system, or EDMS,
10 and those were the two data repositories that
11 CDMRP used and TATRC used. So Federal Reporter is
12 a consolidated place where you can find all
13 federally-funded research to include TBI research.
14 TBI research information is another
15 place where we had challenges that we needed to
16 overcome and even before the NRAP, the TBI
17 community recognized the need for consolidation of
18 research data to accelerate discovery. And as a
19 result, the Federal Interagency TBI Research Data
20 Repository was born, if you will. In 2011, NINDS
21 and the DoD collaborated to develop the FITBIR
22 research data program. It was developed to

1 provide a common data platform to accelerate
2 comparative effectiveness research and allow for
3 post-talk analysis of TBI data. So at this time,
4 data from DoD and NIH-funded TBI research is
5 required to go into FITBIR.
6 In addition, both Combat Casualty Care
7 and NINDS have provided funding for legacy data
8 projects to be uploaded into FITBIR and we will
9 continue that funding.
10 It's important to note that disparate
11 data sets aren't unique to TBI research. In the
12 absence of coordinated efforts, in the absence of
13 infrastructure support, investigators created
14 their own disparate data sets to get the science
15 done. But what that did was silo our research
16 efforts.
17 So FITBIR is a collection -- Pat went
18 into this a little bit -- FITBIR is a collection
19 of modular components which include account
20 management, a global unique identifier, or GUID
21 tool, and that's actually critical for matching
22 subjects with their data and matching subjects

1 across studies, has a data dictionary tool. It
2 has the ProFoRMS tool to allow for automated data
3 uploading, medical imaging, and query tools. It
4 supports the storage of forms, of imaging, of
5 neuropathological and genomic data.
6 So using both Federal Reporter and
7 FITBIR, we, the TBI community, have built a system
8 to cross- walk research information with research
9 data. And to earlier points today that -- about
10 animal studies, I just want to let you know that
11 though FITBIR does not currently incorporate
12 common data elements from animal studies, we're
13 working to build that out and in fact, the common
14 data elements working group has -- are finalizing
15 their common data elements now.
16 So research data is difficult to
17 interpret in the absence of injury event data.
18 The Department of Defense Trauma Registry,
19 formerly known as the Joint Trauma Theater
20 Registry, was established in 2004 as a performance
21 improvement tool for clinical care in OIF/OEF.
22 The DoD TR has records from point of injury

1 through rehab across the DoD and is a critical
2 part of our DoD Combat Casualty Care research
3 program providing a link between clinical care,
4 needs, and outcomes.
5 It's the largest combat injury database
6 in existence. As of April 2015, we had data on
7 nearly 80,000 patients, 130,000 patient records.
8 Patients with TBI can be identified with their AIS
9 scores and ICD codes but there are very, very few
10 concussions or mild TBIs. Largely, it consists of
11 injury data from theater and CONUS medical records
12 primarily for patients admitted to a Role 3 or a
13 combat support hospital. It includes, as I
14 mentioned, ICD diagnosis and procedures, the AIS
15 scores, the injury severity scores, outcomes to
16 include mortality. The DoD TR is expanding data
17 abstraction from Role 1 or point of injury at the
18 battalion aid station forward to encompass the
19 full continuum of care. And currently, the data
20 is most complete for data from Role 3 or the
21 combat support hospital through Role 4 launch tool
22 and Role 5, BAMC, and Navy.

1 So the DoD TR, as I mentioned, didn't
2 have many mild or concussion data sets in it.
3 Working with the Defense and Veterans Brain
4 Center, we've developed a new module, a new TBI
5 module, which hasn't quite launched yet but it is
6 designed to facilitate abstraction of data, more
7 detailed mild TBI data, Glasgow Coma Score, MACE
8 score, details on loss of consciousness or
9 alteration of consciousness, post traumatic or
10 retrograde amnesia symptoms, any imaging results,
11 ICD-9 codes, ICD-10 codes, TBI-related injury
12 details, the event itself, details of poly trauma.
13 So someone could have a mild TBI and have a poly
14 trauma, liver laceration or amputation and that
15 mild TBI with blood loss will progress quite
16 rapidly to a moderate TBI. Things that are also
17 important was the helmet worn; what is the
18 patient's disposition.
19 And I vacillated about including another
20 data repository. It's a little -- it's less
21 relevant to our charge for today but I'm going to
22 go ahead and mention it now. Some of you may be

1 familiar with the Joint Trauma Analysis of Injury
2 in Combat, or JTAPIC organization. JTAPIC has a
3 database that contains a lot of injury event
4 information. Largely, that database was meant to
5 support and assess the performance of blast
6 protection systems. But again, I mention it
7 contains a lot of injury event information. And
8 part of JTAPIC's charter is that they must
9 coordinate with other DoD organizations to include
10 the Joint Trauma Registry. So while most of you
11 outside the DoD cannot access JTAPIC directly, you
12 can make a query for data to the Joint Trauma
13 Registry. They can then query JTAPIC and you can
14 get your data.
15 So the absence of validated TBI
16 biomarkers has limited our ability to understand
17 the history of TBI, to diagnose it, to monitor
18 response to treatment, track recovery, and to
19 develop drug therapies. The good news is even
20 though we have several large studies collecting
21 bio-samples and multiple bio-repositories, there
22 are standardization processes --again, Pat

1 Bellgowan alluded to or actually described -- in
2 place and they're paving the way for enhanced
3 integration. Standardized practices support
4 reproducibility of studies, reproducibility of
5 knowledge and that's key for FDA approval. We
6 have a standard operating procedure to standardize
7 sample collection procedures, collection and
8 storage of brain tissue, of blood, of cerebral
9 spinal fluid, of DNA as well as a standardized TBI
10 history interview form. Bio-repositories and
11 standard protocols exist within various projects
12 such as the NINDS bio-repository, the NIDRR TBI
13 Model Systems. Uniformed Services University
14 CNRM, Center for Neuroscience and Regenerative
15 Medicine houses many, many bio-samples to include
16 the DVBIC 15-year longitudinal TBI study and most
17 recently, the Service Academy Cadets and
18 Midshipmen Arm of the NCAA Athlete Study.
19 Two other key studies, the DoD and VA
20 co- funded Chronic Effects of Neurotrauma
21 Consortium, or CENC, and Transforming Research and
22 Clinical Knowledge in TBI or the TRACK-TBI study

1 that we've heard a lot about today. They're data
2 samples, I believe, are in NIH's NeuroBioBank; is
3 that right? Yeah.
4 So keys to success; in addition to
5 money, in addition to time, in addition to
6 targeted focus is collaboration. As a community,
7 I think we've made tremendous strides, PI to PI
8 collaboration, the FDA to the TBI community
9 collaboration. I think we've heard the urgency.
10 We realize that no one person, no one group is
11 going to solve this problem working alone.
12 Another key to success is infrastructure
13 support and, really, that's what I talked to you
14 about. These registries are infrastructure
15 support. They need to be smart. They need to be
16 well-resourced and they have to have sustainment
17 costs built into them, an up-front investment with
18 sustainment costs or it's just simply not going to
19 work.
20 Data sharing is key; common platform for
21 research data and data-sharing; FITBIR, the NIH,
22 and the DoD are tying the inputting of TBI funding

to putting your data into the FITBIR system.

And finally, incorporating these legacy data sets, a lot of great work has been done and there's a lot of nuggets in there and we need to find a way to link that data to the community. I'm not saying we have to take someone's disparate data set and plunk it inside FITBIR but we have to find a way to link that data. And I know that's something that NINDS and the DoD are working on this very hard. In fact, we have a three-hour meeting tomorrow to discuss it.

So I think that's all I have. I think I bought us a minute and 15 seconds. Great. Thanks.

(Applause.)

DR. KANNAN: Thank you, Dr. Crowder, for the nice overview on the TBI registries and other trauma registries.

So it's time for a short break now and I would request everyone to assemble back by 3:25.

(Whereupon, off the record briefly.)

DR. KANNAN: All right, everybody, it's

1 time to take your seats and get started with the
2 next session. Okay. We are going to begin with
3 the next set of talks and our first speaker is
4 Chloe from the Business Development Team from
5 Palantir Technologies and she's going to talk
6 about the big data analytics using the Palantir
7 platforms.
8 MS. COUGHLIN-SCHULTE: Hi, everyone.
9 Thank you, Lakshmi. It's a pleasure to be here.
10 My name is Chloe and I am the Program Manager for
11 the Palantir-One Mind partnership. For those of
12 you that don't know about Palantir, we are a
13 Silicon Valley-based data integration company.
14 And what that means is we work with organizations
15 in all different sectors, so government,
16 commercial, non- profit, medical to solve sort of
17 their biggest data challenges. We were founded by
18 the original creators of PayPal who premised this
19 company on the idea that in order to solve these
20 data challenges, you -- did I do that?
21 UNIDENTIFIED SPEAKER: No. I think
22 (inaudible).

(Laughter.)

MS. COUGHLIN-SCHULTE: Let's try this again. I don't know what's going on. It's okay.

DR. KANNAN: All right.

(Laughter.)

(Whereupon, technical difficulty with slides.)

DR. KANNAN: Okay, let's just close and start it again.

MS. COUGHLIN-SCHULTE: All right. Let's try that again. I forget where I was now. Basically -- so the PayPal founders created Palantir with the concept that in order to really solve data challenges, you need to combine sort of the power of computing with the power of human intelligence and intuition. So these companies that we work with, though, they have overwhelming amounts of data. It's rapidly diversifying in type; it's growing sort of exponentially in size; and as many other people have talked about today, it remains siloed and disconnected.

But the people who need answers and who

1 need to work with this data, they don't view it in
2 terms of spreadsheets or rows or columns or sequel
3 databases or anything. They view it in terms of
4 their mission and sort of the day-to-day problems
5 that they try and tackle. And so what they need
6 is to be able to ask questions of their data and
7 receive responses that make sense in terms of
8 their mission. And that's sort of the capability
9 that Palantir provides.
10 We're based on sort of four foundational
11 capabilities that enable us to deliver these
12 transformative results to the organizations that
13 we work with. The first is data integration, so
14 the ability to pull in disparate data sets from
15 different places and different formats and make it
16 discoverable in one platform -- that an analyst
17 has never had access to in any type of holistic
18 sense before is a pretty powerful capability.
19 The knowledge management tools that we
20 provide enable analysts and users to interact with
21 and enrich their data but provide everybody else
22 with a clear data pedigree of any changes that

1 have been made to data over time.
2 We provide search and discover tools
3 which enable analysts or investigators to test
4 hypotheses or run queries over data in a manner
5 and at a speed, you know, not previously possible
6 with disparate or siloed databases.
7 And finally, our intuitive and really
8 user-friendly collaboration tools make
9 communication and data-sharing much more
10 efficient.
11 To sort of understand these sort of
12 pillars in context, I'll give you a sort of brief
13 example of some of the work that we do outside of
14 the TBI community. So for several years now,
15 we've been working with the U.S. Special Forces
16 community helping them with their intelligence
17 operations, so the Palantir platform sat on all
18 these different database -- or all these different
19 intelligence databases making this information
20 discoverable and queriable by analysts and
21 operators around the world.
22 But a couple of years ago, the SEALS

1 came to us with sort of a more important problem.
2 They wanted us to help them find a holistic view
3 of the state and the readiness of the Force and
4 the family, so all of their operators and those
5 people that support them. To do this, we did sort
6 of a pretty massive data integration for them, so
7 we pulled everything from enterprise-wide
8 databases to really small disconnected Excel
9 spreadsheets that just lived on someone's desktop,
10 pulled them all together and for the first time,
11 gave a truly holistic view of the Force. So that
12 included databases from personnel records, health
13 records, training data, safety information, drug
14 and alcohol reports, potentially medical reports
15 from the field, things like that and enabled the
16 force to take a proactive approach to preserving
17 the Force readiness. So that's being able to see
18 who is at risk of quitting, who needs to be in a
19 different unit, and not only that but then
20 identifying the people best in place to reach out
21 to these individuals; is it their family; is it
22 someone from their unit; is it their commander.

1 And so this was sort of a really transformative
2 ability and opportunity for the SEALS to much
3 better preserve the state and readiness and
4 wellbeing of their Force.
5 These were capabilities that we
6 presented to General Chiarelli, the CEO of One
7 Mind, as well as Dr. Manley, last fall and I think
8 that they both really saw sort of the
9 transformative impact that Palantir could have in
10 the TBI and the TBI research community. So given
11 that, we kicked off a partnership with them last
12 fall and have deployed a software platform called
13 Contour which is built to - - or which we hope
14 will help develop a prediction model for mild to
15 moderate TBIs. Contour was build to handle
16 incredibly high-scale data and also comes with
17 very user-friendly statistical and analytical
18 investigative tools baked into the platform. It's
19 also incredibly lightweight and can be accessed by
20 a web browser which we hope will increase user
21 adoption as we move forward.
22 So far, since the start of our

1 partnership, we've integrated six studies with a
2 bunch of harmonized metrics and Geoff sort of
3 walked through that process. And what we hope to
4 enable is for investigators to stratify all of the
5 patients in Contour currently along any of the
6 different biomarker or demographic information
7 that we've included.
8 As per One Mind's mission as well as a
9 couple of other people earlier today, we've tried
10 to really facilitate collaboration with the
11 Contour platform so you can share the data or the
12 investigations that you've been doing just by copy
13 and pasting the web browser link that you have and
14 we also have a central data repository where
15 anyone and everyone can upload data and share it
16 with their colleagues both within their team and
17 within different universities.
18 As we go forward, we're working with the
19 UCSF and the University of Pittsburgh teams to
20 harmonize more metrics across additional studies,
21 so we're both hoping to increase the number of
22 studies hosted in the Contour platform as well as

1 expand some of the biomarkers that are in there
2 available for analysis. And we're also looking to
3 integrate imaging data into the platform and then
4 sort of finalize the development of the prediction
5 model. We're also hoping to expand the user base
6 by embedding Contour directly into the One Mind
7 portal for those of you that use that and also
8 expanding access to TED initiative seed project
9 awards as a platform to undertake research.
10 We're incredibly proud to have supported
11 this effort so far and we look forward to working
12 with all of you in the future. Thank you.
13 (Applause.)
14 DR. KANNAN: Thank you, Chloe, for the
15 nice overview on Palantir platform. And our next
16 speaker here is Dr. Paul Vespa. He's the Director
17 of Neurocritical Care and Professor of
18 Neurosurgery and Neurology at UCLA School of
19 Medicine, and he's going to talk to about TBI big
20 data and the IBM platform use.
21 DR. VESPA: Well, thank you, Lakshmi.
22 I'd like to thank the FDA and for all the members

1 of the military here today, I'd like to thank you
2 for your service.
3 Well, this is a very interesting topic
4 to sort of consider and that is trying to analyze
5 a lot of the data that we have. And what I want
6 to show to you today a little bit is some of the
7 methods that we've been working on. We've been
8 focused on severe TBI but some of the methods
9 we've been working on, both internally and across
10 collaborative, like with the TRACK-TBI study, this
11 is kind of a landscape of the different kinds of
12 clinical data that we see in severe TBI but you
13 can imagine that there are similar sorts of
14 landscape for mild TBI, concussion and so forth
15 where there's a variety of data sources, different
16 timing of the data, different duration of the
17 data, different data types occurring at various
18 points in time. And some of these occur
19 repetitively, like some of these arrows are
20 occurring repetitively or along certain periods of
21 time and then others are critical periodic events.
22 And it's very difficult then to integrate these

1 various data types. How do you put this all
2 together; how do you analyze it for an outcome?
3 These are some of the monitors that we
4 use in severe TBI; again, showing different
5 resolution, anatomical imaging, EEG electrical
6 activities, chemistry, looking at various kinds of
7 brain fluids, blood fluids, etcetera, TCD,
8 transcranial Doppler, and other blood flow
9 studies. This is an example of a patient just to
10 kind of show you a single patient may have
11 thousands upon thousands of data points and these
12 vary over time and there are -- sometimes you can
13 see relationships with various biomarkers going up
14 and down but there's a lot of variability. And
15 how do you assess this; how do you judge this; how
16 do you put this into a format that you can
17 separate signal from noise and come up with some
18 degree of monitors, of biomarkers of what's
19 happening with the patient?
20 And so the scientific and clinical
21 agenda, really, is -- has been, for scientific
22 studies, to sort of get a large amount of data and

1 do traditional statistics with this, sort of
2 aggregate the data and look for one outcome or
3 look for one sort of determinant factor. And in
4 some cases, like we've heard about the clinical
5 trials, many of the clinical trials are collecting
6 some of this data at a different and a smaller
7 resolution and they're not even analyzing it
8 really. I mean the primary outcome for a drug
9 trial is the Glasgow Outcome Score, and if it
10 misses, it misses and that's it. The study is
11 positive or negative and then we never really go
12 into, you know, was there a difference in the
13 patients and is that explanatory because that's
14 too hard to do. Maybe those are secondary
15 analyses but they're not the primary analysis.
16 And so there's too much data. There are
17 hidden relationships that stay hidden because
18 we're not smart enough to see them. Clinical
19 trials are not informed by these vast data and
20 they're not really -- most clinical trials have
21 not been geared to use what we call multi-modality
22 monitoring or at least these data points, so

1 there's a lot of unmet need. And how do we try to
2 address that?
3 Our roadmap at UCLA Brain Injury
4 Research Center has been to try to capture a lot
5 of this data in real time using our clinical
6 legacy systems that output to a program called
7 BedMaster which basically collects second-by-
8 second data. And I know that this is used
9 elsewhere, at UCSF and other centers. BedMaster
10 then can input that data to a variety of central
11 analysis systems; one of them happens to be IBM
12 Streams and I'll show you some examples of that
13 but there can be others.
14 And then there are some intermediary
15 analyses that can occur based on this. I'll show
16 you some proprietary algorithms which we've
17 devised to give us information, but a lot of this
18 data can then be actually exported and put into
19 more complicated analyses and we actually share
20 this with USC Laboratory of Neurological Imaging,
21 which is a center repository for TRACK-TBI as
22 well, and they actually go ahead and perform more

complicated cluster analyses and principle component analyses, and I'll show you an example of that.

And then you can have a variety of outputs. You can have simple trends but you can have more complicated algorithm-derived data that comes out.

I'm going to show you three sort of examples of how we're trying to take some of this big data and move it towards an analysis. And this is the first. This is supported from the Laboratory of Neurological Imaging; Arthur Toga, who's one of the PI's of TRACK-TBI. And the hope is that some of the TRACK data will be similarly analyzed in this way. But this is data that we've collected just at our single center which has been through this complicated pipeline of imaging analysis and biomarker analysis. This was actually built originally for ADNI and has now been used for a variety of projects, modified accordingly and as necessary. And what you can do is put data in, have this go through this pipeline

1 analyses, look for any number of different
2 combinations that you can believe or think about,
3 and then you can have outputs that give you some
4 kind of information, either a clinical decision or
5 a result.
6 Here is one example of one of these
7 little pipelines blown up. This is stuff we're
8 looking at for traumatic brain injury and long-
9 term -- and the prediction of epilepsy. This was
10 actually funded by a planning grant to try to look
11 at epileptogenesis and these are pipelines of --
12 each of these are programs that analyze data,
13 analyze both metadata and imaging data. This
14 actually is an output that analyzes and
15 incorporates data from EEG and then you can put
16 this into a variety of steps and at the end, you
17 can get some prediction of various things
18 including prediction of perhaps long-term
19 epilepsy, so all the common data elements,
20 etcetera get factored into this.
21 This is one example of an output from
22 about a year ago where we put together imaging

data and EEG data and other meta data, the common data elements, that you can come up with a predictive model, if you will, or a series of models for predicting epilepsy, long-term epilepsy. And this is actually backed up by actually long-term determination of epilepsy in this cohort of patients. So you can do an acute study. You can do a longitudinal study but this is only made possible by analyzing big data sets in ways that we can't simply do one project at a time.

This is an example of ICU high-resolution data, intracranial pressure data which comes from a variety of ICU beds, gets filtered through BedMaster, gets then put into the IBM Streams environment, and IBM Streams can handle different data types and different durations and resolution and time frequency and so forth. On top of that then, you can insert a specific algorithm and our colleague, Xiao Hu, who was at UCLA for many years, is now at UCSF, has developed proprietary algorithms to look at the intracranial

1 pressure wave form and you can generate then this
2 kind of summary statistic that can actually tell
3 you about the biology of the brain.
4 So it's taking -- this data is taking
5 data streams and allowing you to put it into an
6 environment that then you can put in analytics and
7 then have outputs, and that's very powerful and
8 systems like Streams and others are able to do
9 this for you.
10 The third example is what we call a
11 clinical alert map in which you take that kind of
12 data and you put it through an algorithm -- this
13 is an algorithm in Streams -- where you have all
14 kinds of data about the patient, laboratories,
15 common data elements; again, ICP, blood pressure,
16 and you can come up with a map that looks like
17 this. This is actually a schematic of one half of
18 our ICU. You have a variety of data points here
19 and then you have relationships between blood
20 pressure and intracranial pressure called "PRX"
21 which is an autoregulation index. And this is
22 then described or displayed as these dots and the

1 smaller the dot means that you have less auto
2 regulation -- or actually, more
3 auto regulation, and the bigger dot means you have
4 less auto regulation.
5 And so in a snapshot, what you can see
6 is -- you can see your ICU and you can see who's
7 in trouble and who isn't, and then you can try to
8 determine what you're -- hopefully, what you're
9 going to do about it later on. You can imagine
10 doing this for a variety of different kinds of
11 techniques but these kinds of big data analyses
12 actually let you take the data and then put them
13 out in a way that's easy to understand, and that's
14 a cool sort of thing to sort of think about.
15 So in summary, there are multiple data
16 streams that need to be integrated. There are
17 analytics that are needed to be derived to
18 interpret the research. Some of our simple
19 statistics are not enough and as you've heard
20 about already, there are large consortia that are
21 moving towards sharing these algorithms. There
22 are a number of people that are really looking

1 forward to working together on open platforms so
2 that we can apply these tools. We want to get
3 towards a treatment. We're not so interested in
4 creating, you know, proprietary information. We
5 want to get to a treatment, so we want to share
6 these algorithms across investigators.
7 So with that, I, again, would like to
8 thank Lakshmi and thank you for your attention.
9 (Applause.)
10 DR. KANNAN: Thank you, Dr. Vespa. and
11 our next speaker is Lisa. She is a Health
12 Scientist in the Division of Epidemiology in the
13 Office of Surveillance and Biometrics, CDRH, and
14 she's going to talk about the big data analytics
15 and the in-silico approach.
16 DR. TOROSYAN: Thank you, Lakshmi, and
17 good afternoon, everyone. I would like to start
18 with a disclosure that this presentation
19 represents my personal views and it discusses the
20 research approaches and not the regulatory aspects
21 pertaining to TBI biomarkers.
22 Our Division of Epidemiology at CDRH is

1 involved in translational regulatory research and
2 my research in particular is focused on developing
3 in-silico framework for integrating epidemiologic
4 and genetic evidence. So this new evidentiary
5 approach is based on the re-utilization, the
6 repurposing of preexisting data and, therefore, it
7 has the potential for delivering more efficient
8 and less burdensome solutions that can be
9 applicable to various medical projects.
10 So today I would like to give you a
11 brief overview of the in-silico approach and the
12 bioinformatics-based solutions that can be applied
13 to development of TBI biomarkers in particular.
14 So as we all know and as it is highlighted in this
15 slide, the validation qualification steps and the
16 following implementation efforts consume most of
17 the time and resources that are needed for
18 biomarker development. However, consistent with
19 the saying that "well begun is half done, the
20 first step of biomarker discovery can actually
21 pre-determine the overall success. Once pre-
22 selected, the biomarker candidates become the

1 endpoint in some second steps. And if the
2 selection process results in numerous false
3 positive and false negative results, it can drain
4 the steady resources and can lead back to square
5 one requiring complete redesign of the study.
6 So how can we enhance this crucial step
7 of pre-selecting biomarker candidates for
8 subsequent validation, and can we use
9 bioinformatics for preventing the biomarker
10 selection pitfalls and thereby reducing the
11 burdensome time and cost requirements for
12 qualification and implementation steps? So in the
13 following slides, I would like to talk about the
14 explorative bioinformatics-based approaches that
15 have the potential to deliver that just that,
16 efficient solutions for the arduous process of
17 biomarker development.
18 As a starting point, this slide compares
19 the conventional and the emerging paradigms for
20 biomedical data integration and evidence
21 synthesis. So the conventional paradigm is based
22 most of the time on one study, one type of data,

1 and one set of results. It's usually one
2 directional or starting with the clinical data,
3 going through analytical phase and ending up as
4 clinical data set. And the biomarker pre-
5 selection is largely based on statistics. Most of
6 the time, p-value-based cutoffs but not on
7 bioinformatics approaches.
8 So the main limitation of this
9 conventional paradigm is that single-source
10 studies, which are usually based on one hypothesis
11 and one set of objectives and which are usually
12 carried out by one group of investigators. They
13 may not ask all possible research questions or may
14 not use all possible analytical approaches and,
15 therefore, may not exhaust all possibilities for
16 delivering the expected results, especially in the
17 data-rich environment such as omic spaced
18 biomarker studies. So, therefore, with the ever-
19 escalating amount of big biomedical data, there is
20 a growing trend advocating for the need for
21 linking and reanalyzing the existing data using
22 new data-mining approaches that can improve the

1 scope, repeatability and action ability of the
2 results.
3 So the new emerging paradigm can be
4 described as use of unconventional data sources,
5 repurposing of preexisting data, multidirectional
6 integration of different data types from disparate
7 source and knowledge bases, and in-silico evidence
8 integration and interpretation using big data
9 analytics and (inaudible) tools. So this slide,
10 first, it illustrates the difference between the
11 one-directional conventional from pre-clinical to
12 clinical evidence stream which is illustrated on
13 the right and the proposed simultaneous in-silico
14 analysis and integration of multidisciplinary
15 evidence which utilizes multidimensional de novo
16 and preexisting data from different sources like
17 bench and animal studies, RCTs, real-world
18 performance data from registries and which
19 obviously uses the big data analytics for
20 delivering both; in this case, bio-fluid and
21 imaging-based TBI biomarkers.
22 As a further example of this new

1 evidentiary approach, I would like to use this
2 figure from our manuscript on ventilation-related
3 iatrogenic pneumothorax event IP which recently
4 accepted to JAMA. As shown in this figure, our
5 pilot on in-silico discovery of candidate
6 biomarkers for the ventilation-associated lung
7 injuries was based on the integrated epidemiologic
8 and genetic evidence that was derived using mostly
9 two sources of preexisting data: AGRQ registry
10 and NCBI Gene Expression Omnibus. So the study
11 was mainly based on the hypothesis that the genes
12 associated with spontaneous pneumothorax and
13 fibrosis may serve as potential biomarkers for
14 ventilation-associated pneumothorax. The
15 epidemiologic evidence which is shown on the left
16 was derived using (inaudible) and AGRQ registry
17 data, and it stakeholder owed that along with some
18 demographic factors, the comorbidities such as
19 cystic fibrosis, Marfan syndrome and other
20 diseases associated with spontaneous pneumothorax
21 and fibrosis do increase the risk for iatrogenic
22 pneumothorax in patients on ventilator support.

1 So the genetic evidence which is shown
2 here on the right was based on the gene expression
3 data and it was further corroborated using sources
4 such as PubMed publications and genetic testing
5 registry queries. And consistent with the study
6 hypothesis and the epidemiological evidence, the
7 reanalysis of the raw data from animal models
8 showed that the profiles of spontaneous
9 pneumothorax- related genes are indeed indicative
10 or (inaudible) ventilation-induced lung injury and
11 can be pre-selected for developing the
12 ventilation safety biomarkers.
13 And at the end, I would like to
14 emphasize that this entire study was based on
15 preexisting data and, therefore, zero dollars were
16 spent on the discovery of this biomarker candidate
17 that were described in the manuscript.
18 So the next question would be can we
19 apply this in-silico framework for facilitating
20 more effective and less burdensome development of
21 TBI biomarkers. More specifically, can we use the
22 same nationwide, in-hospital sample needs database

from AGRQ registry or, which would be, of course, a better choice, TBI-specific registries for delivering the TBI-related epidemiological evidence and can we integrate that evidence with genetic evidence which would be derived from a singular source, like Gene Expression Omnibus from NCBI. And as you can see from the next slides, the answer is yes, it's quite possible to find a TBI-related evidence using the same approach and the same data sources that we used in our event IP pilot.

So this slide shows the results of H-CopNet (ph) and the AGRQ queries and the clip below shows the annual numbers of discharges from the needs database which are identified using one of the TBI-related ICD-9 codes. And obviously, this can be used for deriving the epidemiological evidence on TBI. And more importantly, this is a confirmation that NCBI databases contain a number of TBI-related or mixed data sets that can be used for conducting in-silico research on TBI biomarkers.

1 So this slide is based on the reanalysis
2 of two of these NCBI data sets that I've just
3 shown to you on the previous slide, and it shows
4 GFAP which is a recognized TBI biomarker
5 candidate, and it was mentioned in today's
6 discussion. So as expected, GFAP expression was
7 clearly upregulated at 24-72 hours in both mouse
8 and rat TBI models as shown on the right compared
9 to the sham controls which are on the left. So
10 these TBI-responsive expression profiles for a
11 recognized TBI biomarker demonstrate the
12 reliability of preexisting or mixed data, and they
13 render these two particular TBI models as a valid
14 source for further search for potential novel TBI
15 candidates.
16 And I'd like to note that each study
17 point was represented by triplicate and the
18 multifold application was replicated in both
19 studies and to a rendering GFAP as a close species
20 TBI biomarker. So by comparing the preexisting
21 results from two independent studies which are
22 using two different animal models, this approach

1 tackles the notorious problem of reproducibility
2 and applicability from the very start of biomarker
3 discovery.
4 As a next step of in-silico discovery,
5 this slide shows a snapshot from ingenuity pathway
6 analysis, IPA, that was used for further analysis
7 of the list of genes upregulated in mouse and rat
8 TBI models. And as you can see from this ven
9 diagram, GFAP was obviously not the only gene
10 up-regulation in both studies and many of the
11 common genes from both TBI models showed
12 functional relationships such as this single
13 example of concordant up-regulation of a
14 transcriptional regulator which is on the top and
15 two of its downstream targets.
16 So further illustrating the same
17 example, the left panel on this slide shows the
18 IP-based prediction that the up-regulation) of this
19 transcriptional regulator is expected to result in
20 the up-regulation of its target number one. So
21 consistent with this prediction, please note that
22 this prediction was based on an independent in

1 vitro study from the IP knowledge base. So the
2 same two genes were concordantly upregulated in
3 the mouse and in the rat TBI models from NCBI as
4 shown in the background images on the right.
5 So similarly, this slide shows the
6 second pair of the genes, the same transcriptional
7 regulator and the downstream target number two and
8 please note that the up-regulation of this
9 downstream gene was shown in multiple rat models.
10 So in addition to simply predicting the
11 concordant expression patterns, IP can provide in-
12 depth insights into functional relationship and
13 allows the testing for biological plausibility,
14 clinical utility and potential detectability in
15 bio- fluids. And as you can see here, you can
16 explore connections to the known TBI markers like
17 GFAP or Tau and for their connections to neuro
18 functions and diseases.
19 So some of the broader possibilities of
20 TBI research are outlined in these three scenarios
21 and the scenario number one shows the discovery of
22 sex-ethnicity-specific TBI biomarkers such as

1 snips (ph) which can be guided by demographic
2 trends from registry data.
3 In scenario number two, the imaging and
4 bio-fluid biomarkers can be co-discovered in the
5 same study population using big analytics and
6 preexisting data.
7 And scenario number three presents a
8 multi-omic study which can be used for the meta
9 analysis and analytical approaches such as
10 selection of protein coding, non-coding
11 transcripts and corresponding probes.
12 So in the end, I would like to emphasize
13 the role of big data analytics which is the engine
14 of in-silico approach and multidimensional
15 integration. And here is the (inaudible)
16 presentation image that was supposed to be the
17 next as an illustration of these approaches and
18 that's presented in this brief overview. In
19 silico approach can enhance the entire process of
20 biomarker development and improve replicability
21 and development of biologically plausible and
22 clinically relevant candidates. So this is truly

the last slide.

Thank you. The only thing that I can add at the end, I really would like to conclude that the growing biomedical presents great opportunities but I want to emphasize that it's more than just an opportunity. It's actually dire necessity because it's dictated by the rising cost of drug and device development. So that's why we need data-linking, repurposing, and using in silico approaches and preexisting data. Thank you.

(Applause.)

DR. KANNAN: Thank you, Lisa. Our next speaker is Vahan Simonyan. Could you please come to the podium, Vahan? All right. So it looks like our last speaker is not here so in one way I think which is good, we got time to start our panel.

So I'd request -- so we are going to skip the Q and A session and go to the panel directly. And as you see, most of the speakers are also on the panel so the audience can feel free to

1 pose questions to the panelists. So all the
2 panelists, could you please come front to the
3 table? And I would like to invite our moderator,
4 Danica, the Director of the Division of
5 Epidemiology from the Office of Surveillance and
6 Biometrics, CDRH.
7 DR. MARINAC-DABIC: Well, I just would
8 like to greet everyone form here and then I'm
9 going to join the colleagues at the table. It's
10 easier to actually moderate the discussion. But
11 it's really unfortunate that we didn't hear Dr.
12 Simonyan who would have actually walked you
13 through the capabilities of these high-performance
14 integrated virtual environments that he, in fact,
15 developed. He's a quantum physicist and brought
16 the code and donated it to the FDA, in fact, and
17 that was the basis for the whole build of this
18 platform that it's now being used for regulatory
19 purposes and it can, in fact, host I'm not sure
20 how many thousands of times more data than the
21 Library of Congress has. And it's really more than
22 just his conceptual development but rather

1 something that, in practice, is -- but
2 nevertheless, who knows why this is good. We have
3 a little bit more time to, in fact, engage in the
4 discussion.
5 I direct the Division of Epidemiology
6 here at Center for Devices and before I go with
7 reminding everyone what are the objectives of
8 today's session, I really wanted just very briefly
9 to tell you that in addition to the tools and data
10 sources and the entire partnership that we heard
11 so wonderfully presented during the entire day, I
12 wanted you also to know that there is another
13 public-private partnership that we from the FDA
14 stood up and it's called "MDEpiNet" and stands for
15 Medical Device Epidemiology Network. And if those
16 of you that not necessarily deal with
17 epidemiologic data or are part of the
18 epidemiologic discipline, the reason why we, in
19 fact, insisted that this is called epidemiology is
20 because epidemiology is the basic science of
21 public health and in its core is really looking
22 into determinants of human disease in human

population.

So basically, we felt that the field of epidemiology is capable of integrating this pre and post and basic and clinical and pre-competitive and competitive, kind of from that perspective. So it's not to mean that we are going to insist only on methodologists but rather have a discipline that will pull all this data together.

So we launched this as an initiative back in 2010 and then stood up as a public-private partnership that is operational right now. It has over 100 organizations. The methodology center is run from Harvard University; science and infrastructure center from Cornell; and partnership management or coordination is at Duke University, and it has over 60 ongoing studies in various work streams. Some of the bio-research work that Lisa was talking about is part of the MDEpiNet, and we also have (inaudible) development working with various data sources combining the data and having a lot of projects in the

1 international space.
2 So I just wanted you to know about this.
3 There is also the MDEpiNet.org website that you
4 can look up, and I didn't want to use any more
5 time to actually talk about this but just wanted
6 you to have yet another asset and another
7 machinery of collaborators that potentially can be
8 at the disposal if this group should desire, comes
9 to expand the collaboration.
10 So basically, I just would like to
11 remind the audience that we have four specific
12 objectives that are listed in this brochure and
13 I'd like just to quickly through that and we'll go
14 to the questions. So first, we need to explore
15 existing and potential big or clinical and non-
16 clinical data sets including patient registries
17 that are pertaining to TBI. We heard a lot of
18 great presentations today and the goal and the
19 objective in front of this panel is going to be,
20 again, to look into these and provide specific
21 recommendations to the FDA.
22 Number two, to identify the key areas

where big data can be used in discovery or validation of TBI biomarkers as well as in improving patient outcomes and designing more successful clinical trials.

And number three, to explore hardware platforms, software and analytical tools that can be sued for big data applications and identify the barriers to data aggregation, dissemination and application and discuss the strategies to address these barriers.

So these are very ambitious objectives but I also know that we have a distinguished panel members here and I know we can do it. So let's start with question number one. So existence of multiple data collection and storage sources present challenges in data integration and application of big data analytics for TBI. So let us think about and really talk from various perspectives what are those specific challenges. How can consortia, registries, funding agencies, and other collaborative groups reinforce a culture of data- sharing to maximize the overall utility

of big data sets? And how can this data be harmonized and aggregated? So that's, in essence, the question number one and I'm going to join you at the panel so we can actually talk and I can see you.

So who would like to start with looking at specific challenges? You are all the leaders in this field and all bring such a unique perspective from the agencies or groups that you're coming from. So let's talk about potentially three leading specific challenges that you actually face in your work and especially knowing where you're going with this collaborative work and the ecosystem environment. What would be those areas that we need to overcome?

DR. BELLGOWAN: Well, I think -- so I deal with -- you know, so I, unfortunately, am the person who has to tell PIs often that they need to spend their time, effort, and money to try to upload data into FITBIR, which is a good thing, but it is their time and effort. And I think Geoff really nailed some of the problems earlier

1 when he was discussing it's a cultural issue of
2 particularly -- not so much everyone wants to
3 share their data, they're happy to share the data,
4 but when can they share the data. They don't want
5 to get scooped because, you know, if you get
6 scooped, you lose your publication and you may not
7 get that promotion. And I think, really, the
8 funding agencies have started to change their
9 culture for improving data-sharing but I think at
10 the academic level, we need to start to see
11 universities and find different ways to reinforce
12 data-sharing amongst their groups. I mean I've
13 seen one idea where sort of like people have an
14 "H" index for their publications, you could have a
15 sharing index which would contribute to your
16 tenure committee.
17 DR. MARINAC-DABIC: Any thoughts?
18 DR. HACK: This is Dallas Hack. Again,
19 just first, introduction -- just retired from the
20 Army as was the previous Director of the Combat
21 Casualty Care research program, Dr. Colonel
22 Rasmussen's predecessor and was the one that

1 actually was able to work with the teams to get
2 some of these efforts going.
3 The -- a number -- first, the specific
4 challenges, I think, in this, to start with, is
5 that it's a change in opportunity -- I'll put this
6 out -- is that there are 20-some years of clinical
7 studies that have been done which exist in
8 machine-readable form where the data already
9 exists. And I would say it was about 1990 where
10 we actually can go back to in terms of having --
11 the decade of the brain was in the 1990's and
12 that's where there's a tremendous number of these
13 databases. NIH actually has an institute that
14 manages a lot of these databases.
15 So that's the challenge because these
16 were all collected early on with all kinds of
17 different parameters, all kinds of different
18 understandings of what TBI is and so on. And so
19 now we have such a rich amount of data but
20 completely in different planes and completely
21 uncoordinated. And going back and understanding
22 that data and being able to -- how it was

1 collected and under what conditions and getting
2 the meaning behind all that, so having the PIs
3 available as part of that process.
4 I think one of Geoff's main points this
5 morning was that you have to involve the people
6 that collect the data in bringing this data
7 together. Trying to do it after the fact doesn't -
8 - we get a bunch of numbers but we don't know
9 their meaning unless we actually get that from the
10 investigators. So that's one I see as one of the
11 biggest challenges in opportunities we have right
12 now.
13 Moving forward, you know, it's this
14 issue yes, you know, the funding agencies can have
15 sticks that say you don't get funded unless you do
16 it, but it's like anything else. Unless the
17 investigators actually believe in it that it's
18 going to help them, if we find ways for them to
19 win as part of that process, they might meet the
20 letter of the quote, "law," but to actually get
21 value out of it is a lot more difficult unless
22 they're actually fully vested and vetted in the

1 process. I'll leave -- I have more but leave with
2 that --
3 DR. BELLGOWAN: So one way to do that
4 that I think we're starting to bring up is to
5 reward, in review of grants, data-sharing plan and
6 data-sharing the utility of someone's data. So if
7 someone's collecting great data, they're sharing
8 it and other people are using it, I think they
9 should be rewarded for that in the review of their
10 next either renewal or their new grant.
11 DR. MARINAC-DABIC: So I'd like to pose
12 one question as maybe just driven by working
13 within the context of this public-private
14 partnership that I was describing. We, very early
15 in the process, had to decide that before we enter
16 into discussion about a particular topic or even
17 strategically how we're going to approach certain
18 issues, we've decided that we're going to take off
19 our hats in front of the room where we are going
20 to be meeting. For example, if I come as a
21 regulator, I have to not only be thinking about
22 the regulatory value-added, and the same as with

1 academia, especially in the context of active
2 surveillance, for example, which is very relevant
3 to the epidemiology work. You'll appreciate that
4 we would have situations where certain signals are
5 percolating in many data sources so they can go in
6 different directions. It can go waiting to be
7 published and in the process of clearance and that
8 could be the main goal, but at the same time, I
9 would say if we're really building the national
10 evaluation system, the right way would be to
11 actually work with regulators, with academia, with
12 actual manufacturers understanding, you know, what
13 needs to be done with that signal, because the
14 true impact should not be just publication. True
15 impact what comes out of the publications and
16 there are many players that need to be involved.
17 So to that extent and saying -- I heard
18 you saying very clearly that there is a lack of
19 strategic -- maybe strategically coordinated work
20 nationally, and I also see this from this pre-
21 competitive space, there are so many of these
22 questions that involve more than one manufacturer,

more than one entity. So how much can we from the FDA side or even sister government agencies can do to lay out this strategic pathway so that, in fact, some of these investigator-driven very, very relevant and very important research can begin to be part of the strategic pathway? Is there anything more that we can do? I mean having this conference, I think it's a great step forward. You talked about funding agencies. What about other sister government agencies; is there anything more that we can collectively do?

DR. CRUTCHFIELD: In medicine, you behave the way you were trained so if you had a mentor that you really liked, you want to behave the way they did. So I think we need to get back down to the academic level of the researchers in training and start to incorporate a culture of collaboration at that level as well if we're going to have long-term survival of this initiative, because if they see their mentor very competitive and holding onto data and grumbling every day about I can't show these data because I'm not

1 going to get tenure, they're going to want to
2 model that behavior. So just a suggestion we need
3 to have some type of outreach at the grassroots
4 level of people in training that this is now the
5 new norm.
6 DR. MARINAC-DABIC: That's a great
7 point. There is also the issue of policy. Often
8 the science goes ahead of the policy and we do
9 this -- we see that every day. So there is more
10 to the sharing than just the feeling of the data
11 owners that they don't want to share because of
12 some of this value that the data brings
13 specifically to them. There are really a lot of
14 policy issues. Even if we go back and see how FDA
15 can use the data, if the data is collected, for
16 example, you know, without informed consent or
17 even repurposing of certain data, even the data
18 are there, we can't necessarily use them under the
19 current legal environment. So I think there is a
20 lot of work that needs to be done for legal folks
21 to help us and for the patients to get their voice
22 of how much they can benefit. Wouldn't you agree?

1 DR. HACK: I agree. It does -- we need
2 to do some better work on the -- some standardized
3 informed consents right off of the start. As we
4 do these studies, we need to do a better job,
5 every investigator needs to do a better job of
6 selling that patient on the value of sharing that
7 data and putting that into the public.
8 A couple of more things is to carry on
9 the issue about the reward to the investigators
10 themselves, I think we need to find how -- and I
11 hope the federal government can take some role in
12 this and maybe other groups, like the National
13 Academy of Medicine and some of this in terms of
14 changing the valuation systems and so on and
15 having a way for people to actually publish their
16 data in machine-readable form in some kind of a
17 standard -- just like they publish an article in a
18 journal now, be able to actually get the same
19 academic credit for publishing the data that goes
20 along with that --
21 DR. MARINAC-DABIC: Um-hmm, um-hmm.
22 DR. HACK: -- making that something

1 that, you know, they get credit for that equal to
2 the actual publication itself.
3 DR. MARINAC-DABIC: Yes, Dr. Sullivan.
4 DR. SULLIVAN: I wanted to come back to
5 your comment about the consent forms and so forth,
6 giving permission. That is a huge hurdle. A lot
7 of IRBs interpret it differently as to whether
8 there is approval from the patient to do secondary
9 analyses with the data or transfer them somewhere
10 else. And in the past several months, so maybe a
11 year, the common rule has been undergoing
12 discussion about some changes.
13 DR. MARINAC-DABIC: Yes.
14 DR. SULLIVAN: And I'm not an expert on
15 that and what's being included. Maybe there are
16 some people here but what I've heard from people
17 who are familiar with that is that it isn't clear
18 whether the proposed changes that were published
19 are actually favorable or not in this direction,
20 because there's a lot of concern, particularly
21 about genomic information and privacy associated
22 with that. And I think that -- I've heard that

they're going to revisit a lot of the proposed changes and again, it's not clear which direction that's going to go because of the comments coming in. So back to your question, could the FDA and other sister agencies do anything. I don't know if there is anything you can do to influence that activity but that is a huge problem. And so if changes can be brought about in the common rule, that would be a huge help.

MALE SPEAKER: So just a couple of comments. First of all, I think that words matter and I think when people say "share," what they mean often is "give." And give is unidirectional and share is a bidirectional, and that's one of the reasons why we've really tried to talk about collaboration which is really a higher order of sharing. And so, you know, the way that we see this is I could give you some data and you may or may not generate some information based upon the quality of data that I give you and what you can infer about this. And we have a lot of experience over the years working with some very good

1 informaticists where we've gotten some just, you
2 know, absolutely impossible results because they
3 didn't understand the data and we didn't spend
4 enough time talking with them about it. And we
5 had more collaboration and more back and forth
6 that we would have been more productive.
7 And it's also incumbent upon the people
8 that are sharing the data, I think, and
9 collaborating that there has to be knowledge on
10 both sides, so you can't just have somebody, just
11 a simple informaticist, and they're going to have
12 some, you know, groundbreaking idea, in my
13 opinion, about how TBI is going to work. I think
14 they need to understand a little bit about TBI. I
15 also think that the people that are doing the TBI
16 that are working with the informaticists need to
17 understand a little bit of the math that goes into
18 this: what is a principle component analysis, what
19 are dynamic Bayesian networks; you know, how do
20 you do support vector machines? And so I mean we
21 have to have a conversation.
22 And the one thing that I think we've

1 missed talking about from question one is
2 curation. Data curation is something that nobody
3 wants to do. It is the least fun of everything,
4 you know, and we're in the middle of this right
5 now and looking at relational inconsistencies.
6 And, you know, fortunately, we've just got a
7 phenomenal team of people that have been doing
8 this forever and that can look at this data and go
9 "this doesn't make any sense" and get on the phone
10 because we're still in the process, go back for
11 source data verification. And, you know, I mean
12 it's the old adage, "crap in, crap out." And
13 unless the data is really clean -- so I think
14 there's a couple of things we can do but I
15 actually think that, you know, we went from a very
16 sort of philosophical view on this to now a very
17 pragmatic view and then trying to really fashion
18 this to where we can work on this and, you know,
19 many people in our group, like Ramon has brought
20 in people from outside our group, young
21 investigators that have written papers. We're
22 trying to help them K awards. We had another

1 person that came from outside of the group.
2 So I think part of this is bringing in
3 young people, too, to be role models and show them
4 how this works in a collaborative fashion and open
5 this data up to these folks to where they can
6 actually get some funding, because we've got to --
7 you know, I'm seeing a lot of grey hair in the
8 room and we've got to repopulate the field and
9 these big data sets are a great way to bring on
10 young investigators.
11 DR. CROWDER: So I just wanted to add to
12 what everyone's saying. I think what we're saying
13 is we're managing risk. We want to manage risk in
14 sharing data, being collaborative with data, but
15 we also want to manage risk with human resource
16 protections. I agree that investigators may need
17 to inform the potential subjects better so that
18 their data can be used more widely.
19 But I heard you use the word "policy"
20 and I was thinking what can we do policy-wise, and
21 this is something the DoD, the NIH and VA might be
22 able to do, is get policy changed so that these

1 human research protections -- interpretations
2 reach consensus. I mean dare I say the word
3 "consensus" in a room with, you know, multiple
4 people but I think that's huge and, you know, Pat
5 and Stu, I think it's something we need to take to
6 our leadership to try to get human research
7 protections regulations, our MRMC (Inaudible)
8 office, for example, to modify their position.
9 Sometimes they'll let us use it, sometimes they'll
10 let us upload the data FITBIR, and sometimes they
11 won't. It's just because of one or two words on
12 the consent form.
13 Then we need disseminate that
14 information to all the investigators at time of
15 award or with program announcement or however
16 we're doing our funding so that they are filling
17 out the proper forms and low-hanging fruit. I'm
18 not saying it's going to be easy to get it
19 changed, but it is low- hanging fruit and it's
20 very practical. We don't have to change --
21 DR. SULLIVAN: Can I just --
22 DR. CROWDER: -- yes -- yeah.

1 DR. SULLIVAN: Yeah. I just wanted to
2 add to that saying the same thing you have said,
3 but I think it's not that we're opposed to patient
4 protection or want to lower it but it is confusing
5 and --
6 DR. CROWDER: Right, yes.
7 DR. SULLIVAN: -- people interpret it
8 differently and there is not consistent
9 interpretation from one institution to another --
10 DR. CROWDER: I agree with you 100
11 percent.
12 DR. SULLIVAN: -- from one form to
13 another. And when I read through the proposed
14 changes a couple of months ago, I couldn't tell
15 what they were proposing and obviously, people are
16 going to interpret it differently, so.
17 DR. CROWDER: And it's not my first
18 rodeo.
19 MALE SPEAKER: It needs to be clear.
20 DR. MARINAC-DABIC: So obviously, you
21 know, second question has to do a lot with the
22 capabilities of the big data analytics and how

1 those can actually solve challenges with TBI
2 research. And the reason why this is so relevant
3 from the FDA perspective is that you probably
4 heard -- I wasn't here in the morning but I'm sure
5 that it was mentioned in the context of opening
6 remarks that CDRH's strategic priorities for the
7 next two years are, in fact, very much can be
8 illustrated by increasing the access to real-world
9 data and increasing the number of regulatory
10 decisions we make based on the real-world data.
11 And real-world data come in these big -- with big
12 quantities and various data sources and from the
13 FDA side, we have been very much detached from all
14 the great information that comes from these data
15 sources. So now with these new analytical
16 approaches and the projects that you described and
17 where you see the nation is going with a learning
18 healthcare system, how do you see these helping us
19 with the TBI research agenda?
20 I know this is probably redundant in
21 many ways because we already talked about this but
22 maybe let's just crystallize what we've heard

today and figure out specifically -- we gave here some examples, arithmetic detection and quantification of TBI lesions in neuroimaging for diagnosis, discovery of biomarkers for TBI, fusion of multiple patient data sources, outcome prediction; we've heard nice talks about this, and then impact on selection of patients in clinical trials.

So from everything that we've heard today, what would be, you know, some concrete steps to making this happen and being -- kind of formalizing the way of how we are going to plan the next steps with this, because what we don't want to happen is each of you go back to your respective organizations and continue doing great work but not adding this additional value that comes only if we collectively think about what that would be. So if you would be -- if something that would be on your wish list of how some of these analytics could help your work and how you can help others, what would be those areas in which we can really move forward in a concrete way

1 so that Allison, when she puts together the
2 summary of this, would actually have a great
3 source of information to actually move forward
4 with next steps on our side?
5 DR. CROWDER: I'm just going to jump in
6 and I'm not picking on the MDs here but I mean, I
7 hear you all say it's an art and it is. And so
8 we're back to a little bit of culture change.
9 Geoff, you talked earlier about automating
10 quantification and reducing inter-rater
11 variability, and any time you do that, you improve
12 or you standardize the read, if you will, or the
13 interpretation and you support -- enhance
14 reproducibility of that data set. That alone, I
15 think, will show improved selection and
16 stratification of patients and higher -- better
17 reproducible results, of course, results FDA
18 approval. So I don't want to say we want to get
19 rid of the art in medicine, but we do want to
20 manage the art, if you will.
21 DR. HACK: This comes down to this
22 balance between very -- data that's controlled

very carefully in the way it's collected and collected in a very consistently across multiple studies and someone being able to actually put more weight on the individual data elements. The area that I looked at in the past and unfortunately ran out of time to get this done, but I think that the one area that we have not taken advantage of in TBI research is really access in conjunction with the large insurance companies and Medicare data and all of that. There's a lot more data that's actually collected as part of this process, I mean multiple petabytes of data. I mean there are some groups are at the center of all of that. And using these high- level data analytics tools, we could start to pick patterns out of that. Now you're talking about millions of patients' data that would be available. We have not -- none of the funding organizations have been able to fit that into their funding mechanisms to get those kinds of studies done but I think that's a rich place where we can actually get real-world data that will influence what we're doing.

1 DR. MARINAC-DABIC: That's -- I --
2 obviously, being an epidemiologist, I can't agree
3 with you more. I think one area that we are
4 exploring and actually funding, FDA is funding the
5 effort in orthopedics and vascular space, for
6 example. As you know, there are multiple
7 orthopedic registries, their clinical registries
8 and multiple vascular registries. What we're
9 trying to do now is to create the linkages between
10 those registries and PCORnet sites and also
11 Sentinel and Medicare data. In order to ensure the
12 not just longitudinal profiles of patients but
13 also kind of to leverage that, I potentially see,
14 as you do, a great potential in this type of
15 actually relying on the large patients -- and I
16 saw one light over there --
17 DR. BELLGOWAN: So there is a program at
18 the NIH to do exactly this sort of thing in the
19 BD2K program, which is Big Date to Knowledge.
20 DR. MARINAC-DABIC: Yes.
21 DR. BELLGOWAN: And there is a center
22 that is developed to search medical -- large

existing record sets and develop algorithms for that and so people -- TBI could, you know, join in. I've been trying to push TBI to join some of these Big Data to Knowledge programs because they -- you know, they don't -- we don't have probably really big data, honestly, but we do -- they do have algorithms and they do have methods for pulling out sorts of things. I think if Paul is still here, my guess is he's probably participating in some of those at UCLA, some of the data he showed us.

DR. DIAZ-ARRASTIA: I just want to point out that it's not entirely true that these large administrative databases aren't being exploited. So the VA is probably one of the larger and relatively comprehensive of these databases. And Christine Jaffe and her colleagues, she has a -- she's funded through our CENC consortia, you know, to look at issues related to TBI, so veterans.

There's also a study going on in Seattle, the ACT study which takes advantage of an HMO in Seattle and it's been around for a long

1 time. I mean I agree these are at the infancy and
2 we need to expand on them but there are efforts
3 going on along those lines.
4 DR. CROWDER: So that's a great point,
5 Ramon. It's true. It's not like we're not doing
6 anything. It's not like we haven't been anything.
7 We've done a lot. We have done so much since
8 2007. You had great vision. We've done so much
9 but, Ramon, to your point and to merge that with
10 Colonel Hack's point, maybe we do need an
11 interagency strategic plan for how we're going to
12 put this effort on steroids, if you will. Maybe
13 that's, again, low-hanging fruit, a good next
14 step.
15 DR. MANLEY: Yeah. I think that we
16 would be foolish not to take advantage of the
17 administrative databases that are around us. So
18 one of the things that we're doing this year,
19 because we're concerned about how generalizable
20 the data in TRACK-TBI is, and so what we're doing
21 is we're looking at a very nice administrative
22 database. It was constructed by one of our

1 colleagues at UCSF that has a lot of hospital-
2 based data and also Emergency department- based
3 data because a lot of the registry data that's
4 out there is really for only hospitalized patients,
5 and we know that a lot of these patients are just seen
6 in the emergency department and discharged. So
7 we're --you know, while at the same time we're
8 trying to see do our patients in TRACK-TBI look
9 like these folks in California, which some might
10 argue that California is not so representative of
11 the United States but we can talk about that
12 later, that's a start.
13 And then our colleagues at USC, as part
14 of TRACK-TBI, we have an arm that's a group of
15 health economists and they've already been mining
16 some of these administrative databases, and we're
17 actually finding some very, very important things
18 here. So I think the idea is that, you know,
19 you're only going to be able to do what we're
20 doing at TRACK-TBI in a prospective longitudinal
21 study. I mean this is a precision medicine
22 natural history but you're only going to be able

1 to do that in so many people. And so to figure
2 out how that references out to these larger
3 populations will be important because, obviously,
4 we're not going to have access to the 200,00
5 patients that we have in one of the databases that
6 we're looking at right now, so it's a combination.
7 DR. MARINAC-DABIC: So I would like also
8 to pose one question even though it's not -- it
9 could be interpreted as being built into question
10 number two. I really enjoyed very much the
11 presentations by our patients and patient
12 organizations today, and before we go to question
13 three, if you could just reflect on what can be
14 done to formalize that input throughout various
15 programs. Patients are also invited, in my
16 experience, to come and give presentations or
17 they're part of advisory stakeholder committees,
18 but when you slide the phases of the research into
19 smaller sectors, they don't necessarily, in non-
20 clinical areas, take part throughout the whole
21 process. So I wanted to see from your -- to hear
22 from your experience, in the context of these

1 large databases that you were talking about, how
2 would you engage the patients to be part of
3 looking and guiding our methodologies from their
4 experience, because obviously they may not have
5 the scientific knowledge but they can actually
6 help very much sharpen and focus our research.
7 DR. CRUTCHFIELD: I'll pitch in as a
8 clinician here. Dealing with brain injury
9 patients is a challenge and getting patient input,
10 especially in the early phases, is very difficult.
11 The vast majority of our information comes from
12 caregivers, so it's not just the patients we have
13 to engage --
14 DR. MARINAC-DABIC: Yes, families.
15 DR. CRUTCHFIELD: -- but also the
16 caregivers. And with modern internet
17 capabilities, I think we really ought to be
18 looking forward into how can these people with a
19 tablet at home be inputting their personal data to
20 us on a real-time basis to help us figure out if
21 we're actually intervening and making a
22 difference. And I think moving forward with

1 internet capabilities is probably the best route
2 to go because the caregiver may live in a separate
3 house and inputting data there and may not be the
4 one who brings that patient in particular to that
5 appointment. They may hire a sitter or a nurse to
6 bring them to the appointment. So these are some
7 of the challenges in getting that patient feedback
8 that I see.
9 DR. SULLIVAN: I just want to add one
10 technical note about that. We heard about several
11 of these patient databases, PatientsLikeMe and so
12 forth where people are willing to put up data. It
13 is now possible to also put up the images and
14 there is one model of that that the lung cancer
15 advocacy group has, the Lung Cancer Alliance.
16 They have an image archive called "Give A Scan"
17 and this has just opened for lung cancer patients
18 to upload their CT scans. And for an individual
19 patient to upload one or a few CT scans is not
20 difficult and it's not difficult now for them to
21 get it from the radiology department.
22 But on the other end, the issue that

1 Geoff mentioned earlier, curation, is potentially
2 a big problem because there'll be a -- they won't
3 be collected in a standardized way like clinical
4 trials, and so that is an issue that somebody
5 would have to deal with.
6 FEMALE SPEAKER: Be like a basket of
7 rocks.
8 MALE SPEAKER: One thing we sort of
9 skipped over, before I go over -- before I go out
10 today, I just want to be up front that I support
11 data-sharing. I've been on FITBIR since the
12 beginning and all that. But you're talking about
13 integrating or federating, integrating disparate
14 databases from different areas, CMS, big databases
15 that contain a lot of information where when you
16 combine them all, you add in, let's say, the
17 person's genetic information, you can not only be
18 identified but revealed a lot of personal
19 information. Now the new generation, you know,
20 their issues of privacy are a lot less than, I
21 guess, in the grey-haired people here. But let's
22 say, you know, in your past, while you were

1 married, you had a case of STD or you had some
2 embarrassing, what you find embarrassing mental
3 health condition, it could be out there and it can
4 be mined. And as I was talking to one of the
5 participants here, there's a lot of money to be
6 made on data. And as we combine, put everything
7 together, there are dangers. But the risks, I
8 believe, are worth it but we have to put in not
9 only a process on how to share data but how to
10 protect identities and -- because we're just going
11 after the TBI and some related health issues. We
12 could be opening a lot more information than that
13 in the process. And here it comes.
14 DR. MARINAC-DABIC: Thank you.
15 DR. HACK: I agree that it is a
16 potential issue but the other part about it is I
17 think if we, you know, the collective wisdom, we
18 can figure out ways to prevent that.
19 DR. MARINAC-DABIC: To safeguard.
20 DR. HACK: To safeguard it. Just we
21 need to put in the intellectual effort to do it.
22 DR. MANLEY: So our approach is to, I

1 think, be concerned but not overly paranoid but
2 also be practical, and so what we ask is that we
3 have qualified access to the data. And when you
4 have qualified access to the data, we ask if you
5 have CITI training or some other, you know,
6 similar type thing. And we put some of the
7 responsibility back on you so if someone wants to come
8 in and look at our data, he's going to sign an
9 agreement where he takes some responsibility that
10 if you come across some protected health information ,
11 it needs to be reported back to us. And I think that
12 we do have to be mindful of this.
13 It's one thing, you know, having a bunch
14 of breast cancer samples and genetics and it's
15 another thing when you have very, very granular
16 features about an accident that you can go back
17 and Google this accident and you can Google these
18 people, and you'd be surprised of how often you
19 can pull up some of this stuff. So it doesn't
20 mean that you can't share and shouldn't share. We
21 should but I think that we just need to be
22 cautious and we need to make sure that everybody's

1 taking the appropriate responsibilities themselves
2 when they look at this to do the right thing.
3 DR. MARINAC-DABIC: So let's go --
4 DR. HACK: One point. I just wanted to
5 second a bit of that. You know, in trying to work
6 in and standing up FITBIR, trying to work out the
7 rules and communication, we had a lot of these
8 discussions in standing us up. And as democratic
9 as it would see that this data should be available
10 to anybody who wants it, I think that there --
11 that this danger is really one of the reasons why
12 we need to be very careful on how we do that.
13 DR. MARINAC-DABIC: So let's go now to
14 question number three, and it has to do with these
15 large data sets; again, continuing in the spirit
16 of availability and potential that bringing those
17 large data sets could -- and how much helpful that
18 will be. so since a large number of variables are
19 expected to be involved for TBI, it will require a
20 large quantity of the patient date, so let's talk
21 a little bit more about the gaps and possibilities
22 for addressing this issue. And one question that

1 comes to mind is -- and I don't think we've done
2 collectively methodologically actually exploration
3 of how large registries and how large particular
4 studies need to be. In the clinical trial
5 setting, obviously, there is design considerations
6 and certainly, you know, we know what's driving
7 the size of the study, but here we have the data
8 that are collected already in many instances, they
9 are out there and they are -- they need to be
10 looked at, so how to, in fact, find the right
11 balance between, you know, where and how large
12 data sets you should look at and, you know, how,
13 in fact, resist the temptation to look at all
14 data, because not necessarily you always have to
15 look at everything. And I say that collectively,
16 in other clinical areas, we haven't' done enough
17 to, in fact, create potentially nationally
18 representative sites or sample size of various
19 hospital to actually look into this issue. So
20 what's your feeling about where the future is
21 going to be and how this wealth of data that
22 resides in various settings could be effectively

1 employed to address particular specific questions?
2 DR. CRUTCHFIELD: I'm going to state
3 outright I'm not a mathematician. I'm a
4 physician, but, we fly airplanes now without
5 pilots and they utilized artificial intelligence
6 systems that learn. And I think we need to look
7 forward into some of those systems that as data is
8 put into a larger data set, it is learning as it
9 goes along and then you don't need as much data
10 because you're refining the points of the linkage
11 analysis that leads to a correlation between those
12 two points. Those systems are out there. I'm not
13 expert in them by any stretch of the imagination
14 but that's what I envision with a large data set
15 like this.
16 DR. MARINAC-DABIC: Um-hmm, um-hmm. Any
17 other thoughts?
18 DR. MANLEY: Yeah. Unfortunately, I
19 think these data sets need to be larger than the
20 current funding supports to do this. I think one
21 of the things that I've learned in working with
22 the FDA, and if you look at the documents that are

1 put out about drug development tools and so on,
2 one of the first things that you need to know is
3 what is the natural history of the disease. And I
4 think because we've treated this like an event and
5 not a process, and we've only looked at outcome at
6 six months that we really don't have the spectrum
7 of time and the natural history that we have for
8 many of the diseases that we look at.
9 So I still think we've got a ways to go
10 to continue to follow patients longer than we
11 think that we need to follow them. Those of us
12 who take care of these patients clinically can
13 tell you that these patients really do look
14 different at 5 years and 10 years. And then this
15 whole question about chronic traumatic
16 encephalopathy and things like this and
17 association with Alzheimer's and Parkinson's and
18 ALS, these truths are only going to be seen when
19 you prospectively follow people and in an
20 environment where you live from 5-year grant to 5-
21 year grant, trying to figure out how you're going
22 to fund a longitudinal study over 25 or 30 years

that other people can jump onto is a bit of a challenge. So I think that's a really big issue that we've got is not fully understanding the natural history of the disease.

DR. CROWDER: And not having adequate funding to fully understand the natural history of the disease.

DR. HACK: I would -- I take that -- I think the funding gap is not as much the number of patients as it is the length of time we follow them. I mean this is the thing that we really need to find out a way to solve that. I mean how much have we learned? And I keep using this term every day, the Framingham study, what it taught us about heart disease and that didn't happen in a single 5-year time plot and that's where we need to go with brain injury.

DR. CROWDER: So does anybody know -- I mean they're the third generation now. How did they sustain funding?

DR. MANLEY: Well, it's my understanding that actually, they're going to finally terminate

1 the Framingham study which I think is rather sad
2 given how everybody in this room has benefitted
3 from this. But I mean you might say well, given
4 the decades that's it's gone on, maybe they've
5 learned everything that they need to learn from
6 it. I don't know that that's true but yeah, I
7 mean there was sustained funding by the federal
8 government for this effort and I think this is a
9 political issue and that there needs to be -- if
10 we're worried about chronic traumatic
11 encephalopathy, if we're worried about the
12 association of TBI with psychological health and
13 degenerative disease, then there needs to be more
14 than the budget that Pat has to work with and you
15 guys have to work with in order to be able to do
16 this. I mean this is a problem that affects a lot
17 of people. I don't think that anybody in this
18 room doesn't know somebody that's been affected by
19 a traumatic brain injury. So it's a big problem
20 and this is a political issue.
21 DR. MARINAC-DABIC: So I'm look at
22 Lakshmi. Do we have one minute for the --

DR. KANNAN: So I apologize to interject but yes, we're running out of time so we will take one last question from the audience and the end --

MALE SPEAKER: Thank you. So I had a quick question, follow-up regarding the amount of data and we heard earlier from the regulatory, from the FDA essentially that you have to lock down an algorithm. And we know from data science techniques that algorithms evolve over time, so I guess the question to the panel is how is that going to evolve from the regulatory standpoint as modern data science techniques show that algorithms improve over time with more data?

DR. MARINAC-DABIC: So I can maybe just quickly address from the regulatory perspective. I see, quite frankly, no difference than the way how we handle devices that actually change very frequently and iterations of the models of devices, in fact, are driving the device evaluation. So I think the paradigm change in the FDA that you probably saw is that we recognize we can't do it alone. The whole spirit of building

the national evaluation system of ethical devices is such that we all rely heavily on the stakeholders that work with this both in the research side and also, you know, manufacturers and payers and patients and everyone, so I think this has to be built into our practices that constant evaluation and recalibration of the tools we are using. We can have all the infrastructure in the world, if we do not invest in methodology development, we are going to be, again, behind the developments and not being on the frontline. So I would Agency that that would be our goal, to actually work together and thinking about this is as "our" system and not just the regulatory system.

MALE SPEAKER: Thank you.

DR. KUMAR: I can add on to that a little bit. This isn't a new question that FDA has received recently and there is a lot of medical device technology that is incorporating these quote, unquote, "smart algorithms," algorithms that as additional data is collected,

1 the algorithm becomes more adaptive to the -- as
2 the technology is being used. So as Danica said,
3 we're building these processes and reviewing the
4 software with which these algorithms are
5 contained. We have a guidance out but it's a very
6 living policy I would say and not every software
7 change requires a new regulatory submission to the
8 Agency to be reviewed, and it depends on the
9 change that the algorithm is making. But if it's -
10 - if the intended use is the same and everything
11 continues to be the same, the algorithm just
12 becomes more refined and precise, if you will,
13 based on the information it's gathered, then I
14 don't think there would be such tremendous
15 regulatory hurdles as people envision that there
16 would.
17 MALE SPEAKER: All right. Thank you.
18 DR. MARINAC-DABIC: All right. So we
19 didn't get to the fourth question but in the
20 interest of time and folks not missing the
21 flights, you know, we'll probably do that in other
22 venues at some point.

1 DR. KANNAN: Thank you, panel. So let's
2 give a big round of applause for all the
3 panelists.
4 (Applause.)
5 DR. KANNAN: All right. So we've come
6 to the end of this workshop and I wanted to take -
7 - I'm going to keep this really brief and wanted
8 to take a few minutes, first, to thank everyone
9 who's still sticking around, both the -- both -- I
10 mean those of you in the audience as well as on
11 the webcast. And I also want to extend my special
12 thanks to the workgroup team for their
13 contribution, efforts, and time. And I want to
14 thank my supervisor, Allison Kumar, for giving me
15 this opportunity to coordinate the TBI research
16 efforts across the Center and with our multiple
17 stakeholders. And lastly, I also want to thank
18 our collaborators in the Department of Defense,
19 the TED/TRACK-TBI team.
20 And just to briefly summarize, today we
21 heard the history of the different studies that
22 have been performed in the decades of clinical

trials and TBI that's failed to demonstrate clinically meaningful outcomes in patients despite many ongoing findings and reports on promising therapies and treatment in experiment animal models and how the brain injuries are different and heterogeneous in nature and particularly given that there is no gold standard diagnostic criteria and use of multiple diagnostic criteria and tools has led to some of these failures. And there is definitely a critical need to identify and develop biomarkers to make important and informed decisions.

So some of the key take away points or questions that evolved during the panel session were the use of reverse translational approach and pair it with the translational approach, and I think this has to go hand-in-hand and we need to find a way to do this in a more rapid manner.

And given there is a lot of heterogeneity in the TBI patient population, it is so difficult to just classify TBI by just mild, moderate, and severe, but we also need to better

1 understand some of the definitions and terms of
2 the pathological processes like, let's say, the
3 neuroinflammation associated with it and so on in
4 order to develop better therapeutic approaches.
5 And we keep talking about, you know, the
6 lack of gold standard criteria but again, we need
7 to keep in mind as we keep coming with, you know,
8 consensus criteria, this is a condition that keeps
9 changing and evolving so that's something to keep
10 in mind as we move forward.
11 And in terms of big data, involving
12 people and collecting the data is very valuable to
13 understand the value of that data. And how the
14 government agencies can support this -- building
15 the big infrastructure and there is this lack of
16 strategic -- you know, strategies that need to be
17 worked nationally and how FDA and sister agencies
18 can be involved in the strategic partnership.
19 And one of the steps for key success is
20 collaboration, which we've been talking about
21 since morning, having often conversation and
22 bringing more people and young investigators to

1 the group and also focus on data curation and so
2 on. I guess I can go on and on but I -- running
3 out of time so I'm going to thank everyone again
4 and remind you all that for those who were not
5 able to discuss your thoughts or questions, please
6 go ahead and submit your input, feedback in the
7 pubic docket which will be open until May 3rd, and
8 that will help us keep the conversation going.
9 And lastly, I want to say that FDA is
10 very open and interested in early and often
11 communication, so please come see us whichever
12 biomarker pathway you choose and thank you.
13 DR. KUMAR: So Lakshmi hit on the
14 majority of the closing remarks that I'm going to
15 make but I'm just going to echo her thank you to
16 our speakers who came here on their own time and
17 their own dime to support FDA's interest in
18 partnering with you on this really, really, really
19 important initiative and so that we can bring
20 about products that are going to help the patients
21 that we heard from today that is vitally
22 important. Also, thank you to the TBI working

group from FDA and if any of you are here, if you wouldn't mind standing so we could give you a round of applause, because a lot of this wouldn't have happened without your help. I see some of you.

(Applause.)

DR. KUMAR: And the person that should be standing the most is Lakshmi Kannan right here so you must stand and you must come to the front--

(Applause.)

DR. KUMAR: -- because many of you may not know but Lakshmi has only been with the FDA for about five months and she has hit the ground running, grabbed the bull by the horns, been a tremendous absorption mode from the people, the data, the multiple literature reports that are out there, to put together a really fantastic discussion paper, a fantastic agenda, reached out to all the speakers individually and just her, you know, emotional intelligence in dealing with this subject is above and beyond many, many of the people that I get to interface on a daily basis.

So I think, you know, the round of applause should be twice as big for Lakshmi and everything that she's done.

(Applause.)

DR. KANNAN: Thank you, Allison, and I must say she's the best boss.

DR. KUMAR: Okay. Well, thank you and is it five o'clock? Did we end on time almost? So thank you so much for coming.

(Whereupon, at 4:59 p.m., the aforementioned workshop was adjourned.)

CERTIFICATE OF NOTARY PUBLIC

I, MICHAEL FARKAS, the officer before whom the foregoing hearing was taken, do hereby certify that the testimony appearing in the foregoing hearing was taken by me in audio recording and thereafter reduced to typewriting under my supervision; that said transcription is a true record of the proceedings; that I am neither counsel for, related to, nor employed by any of the parties to the action in which this deposition was taken; and, further, that I am not a relative or employee of any counsel or attorney employed by the parties hereto, nor financially or otherwise interested in the outcome of this action.

MICHAEL FARKAS

Notary Public in and for the

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I, LUCY T. TURNBULL, hereby certify that I am not the Court Reporter who reported the following proceeding and that I have typed the transcript of this proceeding using the Court Reporter's notes and recordings.

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