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DEPARTMENT OF HEALTH AND HUMAN SERVICES

FOOD AND DRUG ADMINISTRATION

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CENTER FOR DEVICES AND RADIOLOGICAL HEALTH

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JOINT PUBLIC WORKSHOP: RISK PREDICTION DEVICES OF OPIOID USE AND OPIOID USE DISORDER (OUD) - OPPORTUNITIES AND CHALLENGES

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Virtual / MS Teams

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INDEX

INDEX

M E E T I N G

(10:00 a.m.)

DR. CUNKELMAN: Good morning. My name is Jacqueline Cunkelman, and I'm a physician in the Office of Product Evaluation and Quality's Clinical and Scientific Policy Staff at FDA. Welcome to our public workshop on Risk Prediction Devices of Opioid Use and Opioid Use Disorder: Opportunities and Challenges.

This effort is co-hosted by FDA and the National Institutes of Health. Thank you to all the participants who have joined the webcast for what we believe will be an engaging and informative workshop. We look forward to an exciting program that promises to bring unique and diverse perspectives on this topic.

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

I'm delighted to introduce our first speaker of the day, Dr. Bill Maisel. Dr. Maisel is the Director of the Office of Product Evaluation and Quality, in FDA's Center for Devices and Radiological Health.

Welcome, Dr. Maisel.

DR. MAISEL: Good morning. On behalf of FDA and our colleagues at the NIH, I'd like to welcome you to today's important workshop on Risk Prediction Devices of Opioid Use and Opioid Use Disorder: Opportunities and Challenges. The opioid epidemic is one of the most serious and complex public health challenges facing our nation, and there have been

devastating and far-reaching consequences, extending into nearly every community. More than 80,000 Americans died from opioid overdoses in 2021, a staggeringly high toll, and a trend that continues in 2022.

As a result of the consequences of the opioid crisis affecting our nation, the Secretary of Health and Human Services determined, under Section 319 of the Public Health Service Act, that an opinion public health emergency exists, nation wide. And most recently that determine was renewed in early October. It's an epidemic that requires innovative solutions.

The Food and Drug Administration, with our other federal partners, remains committed to addressing this national crisis, in part by encouraging and fostering the development of innovative medical devices that provide more effective measures to prevent, diagnose, treat and predict the risk of developing opioid use disorder. In keeping with efforts to promote innovation, FDA's Center for Devices and Radiological Health and NIH's National Institute on Drug Abuse are holding two related public workshops to promote medical device innovation.

These workshops are consistent with the Health and Human Services Overdose Prevention Strategy, and with FDA's Overdose Prevention Framework. Specifically, FDA's Overdose Prevention Framework identifies four priorities: Supporting primary prevention by eliminating unnecessary initial prescription drug exposure and inappropriate prolonged prescribing; encouraging harm reduction, through innovation and education; advancing development of evidence-based treatments for substance use disorders, and protecting the public from unapproved, diverted or counterfeit drugs presenting overdose risks.

Our workshop discussions are inspired by patients and driven by science.

Collectively, the aims of these two workshops are to obtain patients' perspectives on opioid use and opioid use disorder, and the impact on their daily lives, to provide a forum for device manufacturers and researchers to discuss challenges they may encounter along the total product lifecycle of medical devices related to opioid use, to promote medical device innovation by fostering necessary and productive discussions among stakeholders who provide services to people experiencing opioid use disorder, to develop medical devices and research interventions for the prediction, prevention and diagnosis of opioid use disorder, and to foster informative discussions around health equity, perceived stigma, and digital inequalities that affect people using or misusing opioids, or living with opioid use disorder.

Yesterday, we were privileged to hear from patients and family members who shared, with candor and courage, their personal journeys of recovery. Yesterday's workshop also included perspectives from patients, caregivers, healthcare providers and other stakeholders, concerning diagnostic and monitoring devices for opioid use and opioid use disorder.

Today's workshop will complement yesterday's discussion. We'll be spotlighting opportunities and challenges related to the development, commercialization and adoption of devices indicated to predict the risk of developing opioid use disorder. Specifically, we'll be discussing novel approaches in study design considerations for device evaluation, opportunities to incorporate devices that predict opioid use disorder risk into clinical care paradigms, and some of the potential challenges associated with such device use. Our sessions today will again feature multi-stakeholder discussions on these important topics.

Patients are at the heart of what we do, and many lives have been touched by the opioid crisis. We appreciate your attendance, and are looking forward to hearing the

perspectives and discussions during today's workshop. We hope they will lead to device innovation and clinical advancements that make a meaningful difference in our patients' lives. Thank you.

DR. CUNKELMAN: Thank you, Dr. Maisel. Next, I'm please to introduce Dr. Jonathan Pollock. Dr. Pollock is the Chief of the Genetics, Epigenetics and Developmental Neuroscience Branch at the National Institute of Drug Abuse, or NIDA. He will be making some opening remarks for NIH, followed by a presentation on the current landscape of predicting risk of developing opioid use disorder.

Dr. Pollock.

DR. POLLOCK: Hi. I'm Jonathan Pollock, Chief of the Genetics, Epigenetics and Developmental Neuroscience Branch here at the National Institute on Drug Abuse at NIH. I want to welcome you to the FDA and NIDA public workshop, Risk Prediction of Opioid Use and Opioid Use Disorder: Opportunities and Challenges.

The NIDA mission. The National Institute on Drug Abuse supports over 85% of the world's research on all drugs of addiction potential, both legal and illegal, with the exception of a primary focus on alcohol. NIDA's mission of bringing the power of science to bear on drug misuse and addiction is accomplished through its extramural funding of grants and contracts to universities and research institutes and through it's intramural program in Baltimore.

NIDA and its sister NIH agencies fund science to improve public health and to provide information to regulatory agencies such as the FDA. My branch, the Genetics, Epigenetics and Developmental Neuroscience Branch supports on the genetics, epigenetics and developmental mechanisms that underlie addiction and substance use disorders. My

branch funds 304 grant applications, and the NIDA Center for Genetic Studies contract, and with a total budget of $184 million.

Today, I want to talk about the current landscape of predicting risk for developing opioid use disorder. Why do some people become addicted while others do not? Many people have experimented with addictive drugs, but do not become addicted. There are people who drink, but do not develop alcohol use disorder. Substance use disorders run in families. So is it environment, or genes? Adoption studies and twin studies suggest there is a large contribution that is heritable.

As I just said, genes, environment and gene-environment interactions all contribute to the variants or factors to a phenotype, that is, an observable trait or disease. And heritability is the proportion of the variance or factor that can be explained by genes alone. Twin studies compare the difference between identical and fraternal twins, to determine what is heritable, what is due to shared environment, and what is due to unique environments, that are not shared by twins.

Studies on drugs with addiction potential show heritabilities between 40 to 80%, with heritabilities to becoming addicted to an opiate in the range of 50 to 70%. So what are the molecular mechanisms underlying heritability to becoming addicted? Genome-wide Association Studies have been highly successful, reproducible, and provide a unbiased approach to discover multiple diffusely-located genetic variants that are associated with complex traits and diseases.

The human genome is encoded by a chemical molecule called DNA, or deoxyribonucleic acid. There are four different types of DNA molecules: Guanine, represented by G here, cytosine, represented by C here, Adenine, represented by A, and

thymine, represented by T. There are 3 billion of these nucleotides all strung together in different combinations.

In every human being, there is a sequence variation that makes us unique. At many positions within the genome, there are differences in the sequence called a single nucleotide polymorphism, or SNPs. These SNPs are associated with a chunk of DNA where the gene contains a causal mutation. The SNP itself is not causal for the trait, or a disease of interest, but rather acts as a signpost to indicate where the gene might lie.

So what does GWAS do? DNA from an individual is hybridized to a chip, containing 300,000 to 1 million SNPs. GWAS associates the frequency of a SNP that hybridizes to the chip with a trait or disease and compares it to controls. The probability of it being associated with a trait is then plotted across the genome in different positions on a chromosome, called a Manhattan plot, shown on the bottom here.

The threshold for statistical significance is set to 5×10^{-8} because of multiple comparison problems. So shown in the Manhattan plot on the bottom, we see that there is a SNP that is statistically significant on Chromosome 3. Eric Johnson and the Psychiatric Genetics Consortium, led by Hank Kranzler and Joel Gelernter, have identified genetic loci associated with opioid use disorder. This paper by the Psychiatric Genetics Consortium, using 31,480 cases of OUD, and 394,484 controls, largely obtained from the Million Veterans Program, identified 10 genetic loci.

One of the genetic loci is the μ-opioid receptor, *OPRM1*, the target receptor for morphine and heroine and other opiates and opioids. A potassium channel, KCNN1, FURIN, a protein that digests or processes proteins and peptides, an adhesion molecule, NCAM1, RNF114, an enzyme that ubiquitinates proteins, rab31, a protein involved in transport of

mannose 6-phosphate receptor from the endosomes to the trans Golgi network, and CDKL1 and CDK5 regulatory protein.

This shows that opioid use disorder, like other complex genetic disorders such as type II diabetes and coronary heart disease is polygenic, meaning that multiple genes, each with small effects, contribute to the disorder. It is not a monogenic Mendelian disorder like cystic fibrosis or retinitis pigmentosa, or Huntington's disease. Most of the causal variants lie in non-coding regions that control expression of the gene, not in the region that codes F4R protein.

Also, the SNP heritability, or percent is not as large as the heritability found in twin studies of 50 to 70%. This may be because the chips used do not detect other types of genetic variation, or because twin studies over estimate the amount of for OUD. The big challenge of these studies is the difficulty in obtaining cases of OUD, and many studies have ascertained OUD in different ways. Also the studies are done mostly with people of European ancestry, thus not capturing all of the genetic variation in the human population.

GWAS studies have also identified genetic loci for smoking, alcohol use, alcohol use disorder, and cannabis use disorder. These studies, together with GWAS, for opioid use disorder suggest that substance-specific genetic loci exist for these addictions. But the question is, is there a common genetic liability, or multiple problem substance disorder trait? Addition to one substance is frequently comorbid with other substance use disorders.

Alex Hatoum, using structural equation modeling, used it to identify a common genetic addiction factor that underlies opioid use disorder, problem alcohol use disorder, problem tobacco use and cannabis use disorder, so looking at the underlying factors that underly this to produce an addiction factor. And what he found was that of a general

addiction vulnerability factor that accounts for nearly all of the cannabis and opioid genetic liability.

So Alex Hatoum and the PGC, applying GWAS to the common addiction factor phenotype, identified 17 common addiction loci in people of European ancestry. These loci include the dopamine receptor 2 gene, known to play a role in reward, PDE4B, or phosphodiesterase E4B, a molecule that modulates phosphorylation of proteins, and ADH1C, or alcohol dehydrogenase 1C, that may regulate the synthesis of retinoic acid, important in the development and wiring of the nervous system.

The inclusion of non-European ancestries is likely to include the number of genetic loci. So, can we use genetics to predict risk of disease? Polygenic risk scores have been used to predict disease risk. What is a polygenic risk score? A polygenic risk score assesses the risk for developing a disease by totaling the number of genetic variants associated with the disease that an individual carries.

Panel A shows the distribution of polygenic risk scores for coronary artery disease, or CAD, from 290,000 people in the UK Biobank, with values scaled to a mean of 0, and a standard of 1. The shading reflects, in panel A, the proportion of the population with three or four or fivefold increased risk versus as compared to the rest of the population. Those that had a number of risk variants at the 98th percentile or greater, had a fourfold increase in coronary artery disease, equal to what is seen for monogenic mutations such as cystic fibrosis.

And seen in panel B, just compares the difference in the polygenic risk score between controls and cases. And seen in panel C, if you are at the 98th percentile, 10% of the population has that prevalence for coronary artery disease, whereas if you are at the

bottom, you'd have a very low frequency or prevalence of coronary artery disease.

So, can polygenic risk be used to predict clinical outcomes for opioids? Opioid use -- the graph shows that polygenic risk score for OUD as a function of the decile. In the upper 10th decile, there is a twofold increase in being at risk for OUD. A bit problem with polygenic risk score is that they do not predict risk well in non-European populations. The human genetics field is now trying to collect individuals with non-European ancestry for GWAS studies to improve prediction for polygenic risk score and to capture all of the genetic variation in the human population.

So, another approach to looking at risk is to look at metabolites, to see if they predict opioid use disorder. Dr. Susan Sumner at the University of North Carolina, in collaboration with investigators at the Medical University of Tehran, National Cancer Institute and myself examined the metabolite profile of urines from high opium users, from the Golestan Province in Iran, which is a province along the Caspian Sea, to determine whether a metabolomic profile could distinguish between high opium users with OUD, versus those high opium users that were not OUD, as diagnosed by DSM5. And these chronic opium users had used opium for an average of 13 years, and they're part of a larger epidemiologic study, studying gastric and esophageal cancers.

The study identified 16 metabolites unique to the diagnosis of OUD that differentiates high opium users diagnosed as OUD positive, versus high opium users diagnosed as OUD negative. The 16 metabolites gave an AUC of 0.7, compared to an AUC of 0.62 when using only the subject characteristics. And the metabolomic profile together of using both metabolites and the subject characteristics gave an AUC of 0.75.

The results are consistent with a dullness wonder (ph.) hypothesis, that described

opioid addiction as a metabolic disease. Dr. Sumner, in her presentation, will give greater details about this study.

Dr. Donaldson of SOLVD Health developed a gene-based learning approach to predict the risk of developing OUD in opioid-naïve pain patients, such as those that undergo surgery or dental procedures. Dr. Donaldson and his team curated 600 genes from the literature associated with OUD. His machine learning algorithm found that these genes here, these 15 genes here were the best predictors of OUD status. The algorithm uses different combinations of these genes to make a probabilistic prediction from 0 to 1.

In a prospective trial of 484 opioid-naïve acute pain patients, Dr. Donaldson and his team found that his machine learning algorithm performed better than other risk assessment tools. The machine learning classifier had a sensitivity of 83%, and a specificity of 80%. Other risk tools had either similar sensitivity or specificity, but not both. To illustrate the difference in a different way, shown here are the diagnostic odds ratios for a genetic risk assessment tool, versus commonly used risk assessment questionnaires. And as you can see, it has a far better ability to predict.

Now pain is undertreated in African Americans. The Psychiatric Genetics Consortium raised the concern that the machine learning algorithm used by Dr. Donaldson would reinforce this health disparity, because in their hands, with their data, and their own machine learning algorithm, their machine algorithm predicted ancestry for being African American better than the risk for OUD. And thus, African Americans would be classified more as having an OUD risk, and thus reinforce this health disparity in terms of treatment for pain.

And showing here, there is no significant different in sensitivity between white and

non-white and between Hispanic and non-Hispanic. And there's also no difference in the specificity between white and non-white, and Hispanic and non-Hispanic. However, the number of non-whites in this sample is small, and a larger prospective study in the future perhaps will resolve this issue.

Clinical characteristics and patterns of drug use can also be used to predict OUD. Appriss, now Bamboo developed an algorithm called NarxCare based on the prescribing patterns, to predict adverse outcomes to opioid stimulants and sedatives. The data that's used to make this prediction comes from the prescription data management programs that are supported by Emory State (ph.).

Now NarxCare provides a weighted score, called a Narcotics Score from 000 to 999, that is based on the number of prescribers, the number of pharmacies, milligram equivalents that is being given to an individual. Increasing the number of providers, pharmacies, milligram equivalents, and overlapping prescriptions results in a higher Narcan, or Narc score. Overlapping prescriptions by two different prescribers for the same type of medication on the same day is heavily weighted in the score. The risk threshold for the Narcotics Score for high versus moderate risk was a score of 602, and the moderate versus low risk was a score of 291.

When compared to Assist, that is a validated inventory instrument to diagnose OUD, the AUC for moderate versus high discrimination was 0.74, and for low versus moderate risk discrimination, AUC was 0.7.

So some of the issues we need to consider in this workshop are: Does genetics predict risk for problem use in opioids better than what is currently achieved? Will such a test improve clinical outcomes? What specificity and selectivity are needed to predict OUD

in a clinical setting? What are the consequences of misclassification? What is the best experimental design to validate prediction for OUD? And if we validate genetics and other biomarkers for risk for OUD, how do we use it clinically for acute pain, and for chronic pain?

What are the potential misuses by clinicians of genetics tests and other biomarkers for problem misuse of opioids? And does current genetic data or other methods reinforce bias against any ethnic group? Will a device that predicts OUD be accepted by patients? And what impact does genetic liability for OUD have on stigma associated with opioid use disorder? What implications does it have for insurance? And will genetics and other biomarker tests for OUD be cost effective?

Thank you for your attention.

DR. CUNKELMAN: Thank you, Dr. Pollock.

Our next speaker, Dr. Kotarek is the Toxicology Branch Chief for the Division of Chemistry and Toxicology Devices in the Office of Product Evaluation and Quality, in the Center for Devices and Radiological Health, where he oversees premarket and postmarket reviews, including drugs of abuse assays, therapeutic drug monitoring devices, and genetics tests. He'll be speaking on the application of an evidence-based regulatory framework.

Dr. Kotarek.

DR. KOTAREK: Good morning. Thank you for joining us for today's meeting. My name is Dr. Joey Kotarek, and I am the Branch Chief for the Toxicology Branch within the Division of Chemistry and Toxicology, or DCTD. DCTD is in the Office of Health Technology 7, Office of In Vitro Diagnostics, within the Office of Product Evaluation and Quality in the Center for Devices and Radiological Health, or CDRH.

Before we get into our discussion today, I would like to confirm that I have no

conflicts of interest to disclose. During the next few minutes, I would like to provide FDA's perspectives on how opioid use disorder prediction devices might fit within an evidence-based regulatory framework, and describe the means by which FDA can interact with sponsors developing such devices.

To provide some background, the Division of Chemistry and Toxicology Devices, DCTD, is within the Office of Health Technology 7, Office of In Vitro Diagnostics, within the Office of Product Evaluation and Quality. In vitro diagnostic products are those reagents, instruments and systems intended for use in diagnosis of disease and other conditions, including a determination of the state of health, in order to cure, mitigate, treat or prevent disease or its sequalae.

Such products are intended for use in the collection, preparation and examination of specimens taken from the human body. In vitro diagnostics such as these are reviewed in the Division of Chemistry and Toxicology Devices, DCTD, which is comprised of four branches, each of which reviews different types of in vitro diagnostic devices. The four branches within DCTD are the Chemistry Branch, Diabetes Branch, Cardio Renal Branch and the Toxicology Branch.

Among other types of devices, the Toxicology Branch is responsible for the review of devices pertaining to drugs of abuse, and for the review of some genetics devices. Tests of human specimens, such as urine or oral fluid, for the detection of drugs that are commonly abused, such as opioids, falls into the category of drugs of abuse devices that are reviewed by the Toxicology Branch. Some tests of human specimens, such as DNA from blood or saliva, for genotyping to enable users to access information about their genetics that could aid discussions with a healthcare professional are also reviewed by the branch.

These can often be pharmacogenetics tests, but also include some other genetics tests. Genetic tests that are included for OUD risk prediction are one of these other genetic test types that would be within the purview of the Toxicology Branch. Prediction of OUD risk is an area of great importance for the agency and the public, as demonstrated by the recent introduction of the FDA's Overdose Prevention Framework.

Four priorities are outlined in the framework, among which is supporting primary prevention by eliminating unnecessary initial prescription drug exposure and inappropriate prolonged prescribing. Through this priority, the FDA has expressed a continued commitment to facilitating medical device innovation for addressing opioid use.

Although there are currently no marketing authorizations for devices that help to predict risk of OUD, potential opportunities exist for innovation and development of devices of this type, that may help to predict the risk of OUD. This may come in many forms. For example, as a software medical device that may facilitate patient data gathering and analysis to support OUD risk prediction, or an assay designed for the identification of biological markers, such as genetic variants and metabolomic profiles that are associated with the risk of developing OUD.

These types of devices could help to curb the epidemic by providing healthcare providers with a knowledge of the individual's risk, and potentially inform clinicians' decisions about administrating or prescribing opioids to a patient. These devices could also alert patients and caregivers and others to the need for increased monitoring and vigilance. The field is ripe for innovation, and one of our goals in this workshop is to gain multi-stakeholder input on areas for innovation.

However, we are cognizant of the issues developers face in bringing such devices to

market, as there are currently no tests with FDA marketing authorization with this indication. There is little information to reference as a guide when designing studies to validate the device for its intended use. And because opioid use disorder affects such a broad range of people, it can be difficult to design studies that adequately demonstrate device performance in the appropriate population.

Because of the multi-faceted nature of the crisis, and the different patient populations it affects, a single device alone may not be enough to change the course of this crisis. Rather, the input of patients, clinicians, device manufacturers and other stakeholders, supporting a combination of many devices with a range of technologies, indications, and intended patient populations are likely to provide the most significant public health impact.

In a recent public meeting, the FDA sought the opinions of experts in the field to discuss whether our clinical study adequately captured performance of one such new-of-a-kind device in the population it would be marketed for. The input of experts has been highly valuable in ensuring that devices are fit for purpose, and designed to target appropriate patient populations. Further input is needed to provide further clarity and facilitate growth in this field. As such, we hope to gain valuable multi-stakeholder input on study design considerations that move us closer toward innovation.

Next, I'd like to discuss means by which FDA can work with specific device developers to help bring these products to market. Several existing pathways are available to aid developers in overcoming challenges and facilitate innovation. Mechanisms to obtain feedback include presubmission requests and breakthrough device designation requests.

Presubmission requests are a mechanism by which all developers may seek input

from the FDA. The breakthrough device designation program is designed to provide developers of devices that could address a life-threatening disease or condition, such as opioid use disorder, with a pathway for expedited communications with the FDA. Breakthrough designation requests must be submitted prior to submission of marketing applications.

The FDA feedback provided in this program is intended to accelerate innovation by facilitating the preparation of such marketing applications. Once granted breakthrough designation, FDA will work with developers to create a data development plan, optimize their clinical study design, and to otherwise support development efforts as they prepare to submit their device for FDA premarket review. More details can be found in the publicly available breakthrough designation guidance.

Developers that do not choose to utilize the breakthrough device designation program may still receive FDA feedback on device development through the traditional presubmission process, as outlined in the Q-Submission program guidance. There are also several premarket submission pathways, including de novo classification requests. Once a sponsor has completed studies for device validation, they can submit their device to FDA for premarket review.

New-of-a-kind devices are often reviewed in a de novo classification request, through which the FDA assesses whether probable benefits of the device outweigh the probable risks. Other regulatory pathways, such as the 510(k) premarket notification pathway, or premarket approval pathway, also exist. However, it is anticipated that the de novo regulatory pathway would be most appropriate for new-of-a-kind OUD risk prediction devices.

In order for a device to be legally marketed, a reasonable assurance of safety and effectiveness must be demonstrated. The manner in which a reasonable assurance of safety and effectiveness is demonstrated depends on the regulatory pathway. Safety and effectiveness is typically demonstrated by adequate analytical and clinical testing. Analytical validation studies that have supported previously cleared assays using similar device technology, as described in publicly available FDA databases, may help inform analytical studies of genetic OUD risk prediction devices.

Clinical validation studies for this device type may have unique considerations that should be taken into account. For example, comparison of performance to an established reference or method may not be possible for a first-of-a-kind device. In this case, accuracy of the new device can be demonstrated by comparison to a standard of care, or clinical diagnosis.

The design of the device should also be taken into account. For example, disparities in the healthcare system may result in differences of the types of information collected and stored during clinical visits amongst different populations. Software devices that rely on medical records as device input should be designed to account for this. As another example, devices that detect genetic variants should consider the frequency and penetrants of genetic variants in different populations and should be designed to account for this.

There should also be consideration of the specificity of the variants to OUD when designing studies. Clinical study design for any specific device may often be very nuanced, taking into consideration the device design and specific device indications. However, the overarching expectations for clinical trials also apply to devices of this type. This means that the trial should demonstrate the clinical accuracy of the device as it is intended to be

used.

In designing clinical testing, there are several considerations for developers. For example, the better targeted the device is for the specific needs of a particular patient population, the more likely it is to achieve its intended purpose. Thus, understanding different patient populations, different subpopulations within a patient population and their different needs can help steer the development of successful devices. A deep understanding of the intended patient population allows for the selection of an appropriate clinical study population, such that the pertinent study population can be effectively identified and recruited from appropriate clinical study sites. This is an essential step in designing a clinical study that collects information that supports the device's indications for use.

If clinical data is collected from a patient population that is not clearly defined, or not clearly aligned with the device indications, results of the study may not be interpretable, and may not allow for the assessment of the device's performance in the indicated population. Understanding the population also includes an understanding of potential confounders that can impact the way the device performs.

For example, elements within the environment or other medical conditions within the patient population may confound study results. This means that it is possible study results can be driven by the environment or other medical conditions and not actually reflective of OUD risk. These factors should be accounted for.

The OUD population is a complex population that includes many subgroups. We understand that there are difficulties that may come with trying to identify an appropriate subgroup or designing a trial that adequately encompasses the entire intended population.

Therefore, understanding the population and recruiting study subjects that are representative of the intended population are crucial steps. Performance estimates from clinical studies should evaluate the appropriate endpoints as well, for example, device sensitivity, specificity, positive predictive value, negative predictive value, et cetera.

In the context of a de novo submission, study results should demonstrate that the probable benefits of the device outweigh the probably risks of the device. This means that there should be a comprehensive understanding of the risks associated with the device being used in the intended population, as well as the risks of alternative approaches. Risks of the device failure, such as providing false results, should also be carefully considered and weighed against the probable benefits.

The benefits of the device, which are supported by the results of a clinical trial, should outweigh the identified risks. Developers should also consider how device results should be interpreted, as this can significantly impact FDA's assessment of the clinical data and the overall benefit-risk assessment. For example, a device with low specificity but high sensitivity may not be suitable for an overall risk prediction indication, predicting both high and low risk, but may be appropriate for a rule-out indication, predicting low risk, but not to be used to predict high risk.

These are general considerations for clinical study design of any device coming to market. Additional information describing how FDA assesses the probable benefits and probably risks in premarket submissions can be found in the FDA guidance document, "Factors to Consider When Making Benefit-Risk Determinations in Medical Device Premarket Approval and De Novo Classifications."

In addition these general considerations, FDA also intends to publish a draft

guidance describing clinical considerations for medical device premarket submissions targeting opioid use disorder, which would be helpful for device manufacturers to reference once finalized.

As has been discussed, there are not as yet devices with FDA marketing authorization for prediction of OUD risk. And as such, there are no clear examples to guide device developers, or the agency, in development of such devices. However, there are opportunities for innovation, and together we can develop devices to support the many different patients afflicted by the opioid crisis.

Through breakthrough designation and Q-submission programs, the agency can provide guidance to device developers as they prepare de no submissions that fit within an evidence-based regulatory framework. These efforts can support device development and enable patients access to new and validated devices. We are committed to supporting development of devices which have the greatest potential to impact the ongoing opioid crisis, and hope today's workshop will further these efforts.

Thank you very much for your attention.

DR. CUNKELMAN: Thank you, Dr. Kotarek.

We'll now move on to our first session of the day. In this session, we've lined up an impressive group of speakers, who will discuss novel approaches and study design considerations for devices to predict the risk of opioid use disorder.

We'll first hear from Dr. Joel Gelernter. Dr. Gelernter is the Foundation Fund Professor of Psychiatry and Professor of Genetics and Neurobiology, as well as the Director of the Division of Human Genetics and Psychiatry at the Yale University School of Medicine. Dr. Gelernter will speak about genetic predictors and opioid use disorder.

Welcome, Dr. Gelernter.

DR. GELERNTER: Hi. I'm going to talk about genetics of opioid use disorder and risk prediction. The use of very large sample sizes has been hugely important in increasing the impact of genome-wide association studies for complex traits, including psychiatric and substance use traits. But very large samples are not yet attainable for illegal substance use disorders.

We can consider, in particular, opioid use disorder genetics, and it's well known that opioid use and opioid overdose are at epidemic levels in the United States now. Better understanding of the biological mechanisms that can come from understanding the genetics can help to prevent and treat the disorder. GWAS before 2020 identified risk variants, but none reported a clear external replication, and that is attributable to the fact that sample sizes were limited to no more than thousands of affected cases, up to that point.

The Million Veteran Program sample has been hugely valuable as a gene mapping resource for complex traits, has large sample size, and it's still growing, so far over 900,000 recruited. It has very good representation for non-Europeans, which is very important and which is a rarity in large biobanks. It's mostly male, which reflects the veteran population. It has electronic health record or EHR linkage, including some longitudinal repeated measures, and it also has data from self-report surveys. And the sample is relatively old and sick, which makes it quite informative. These are people who have used VA health services.

Some of these features are clear advantages compared to other biobanks. We based a genome-wide association study for opioid use disorder mostly on the Million Veteran Program sample. The study was published about 2 years ago. We were able to include over 10,000 cases in the study, but still identified only a single risk locus, as OPRM1. OPRM1

encodes the μ-opioid receptor gene, which is the main biological target of opioid drugs. These analyses were led by Dr. Hong Zhou.

Our challenge now is to go beyond a single risk locus for opioid use disorder. And in our next study, we did this in two ways. We completed a meta-analysis, and we completed an MTAG analysis, or multi-trait analysis of GWAS for opioid use disorder. The meta-analysis included seven different cohorts. We then did a linkage-disequilibrium score regression, or LDSC analysis, to examine SNP heritability and genetic correlations. We used the genetic correlations to select other traits to use in our MTAG analysis, to be sure to use traits that were as closely related to OUD as possible.

We also did phenome-wide association analysis by means of collaboration with the Vanderbilt BioVU study. And then we did polygenic risk score analysis, to compare the results for opioid use disorder and from the MTAG analysis, as predictors for OUD case status. These analyses were done by Joseph Deak, and were published in *Molecular Psychiatry* several months ago.

This slide shows the overall design of the study, and identifies the sample size from MVP and also the other samples that were included in the meta-analysis. You can see MVP is still by far the largest of those samples. But by this meta-analysis strategy, we were able to go from a sample size of just over 10,000 cases in the Zhou et al study from 2020 to over 20,000 cases in this study. So we doubled the number of cases for this analysis.

So, what did we get from this? And here is the Manhattan plot, showing the results from the meta-analysis, and we confirm the μ-opioid receptor, and we add one additional risk locus at the FURIN gene, which has come up in numerous psychiatric traits and also other substance use traits.

This slide shows the linkage disequilibrium score regression analysis based on the OUD meta-analysis. So, it's a dense slide, but you can see there are significant correlations with many other psychiatric and metal traits. The top two after opioid use disorder were cannabis use disorder and alcohol use disorder. So we took those traits, moving forward, to provide additional data for the MTAG analyses.

This slide compares the results from the meta-analysis, which we already discussed, where the top associations were with OPRM1 and FURIN, and the MTAG analysis. And you can see that the MTAG analysis greatly increased locus discovery, going up to 18 genome-wide significant risk loci. However, in the MTAG analysis, OPRM1 fell below genome-wide significance.

So to summarize the results from this study, the OUD GWAS meta-analysis now identifies two risk loci, FURIN and OPRM1. The OUD MTAG, incorporating data from alcohol use disorder and cannabis use disorder, increased genetic discovery from 2 to 18 risk loci, but at the cost of OPRM1 now falling below genome-wide significance, which suggests potential loss of specificity.

In the linkage disequilibrium score aggression analysis, we showed OUD correlated with chronic pain, functional impairment and a range of mental health traits. We looked at PheWAS and PRS analysis, which I didn't go over in detail, that suggested that OUD and OUD MTAG captured similar opioid-related risk, with OUD MTAG capturing more of the variants than OUD and meta-analysis alone. So, results captured genetic risks specific to OUD, as well as genetic risk shared with other substance use disorders.

I'll discuss one more study, which is a study from the Million Veteran Program sample that just came out last month, increasing sample size of ascertained opioid use

disorder subjects further. And with this study, and a larger sample study, we're able to increase discovery for opioid use disorder cases to 12 genetic risk loci, now with the specificity that includes OPRM1.

A paper from Pat Sullivan a few years ago noted the phenomenon that for GWAS discovery, there's first an area that N cases, where very little happens in terms of more discovery, and then you reach a level where adding N cases, pretty reliably, results in discovery of X more genome-wide significant risk loci in a more or less linear fashion. And it seems like we're now reaching that state for opioid use disorder where Zhou et al had one good genome-wide risk locus, Deak at all raised that to two, Kember raised it to 12. In the context of opioid use disorder only cases, the Deak et all study had raised that to 18, including MTAG analyses. And now we can see that we seem to be on a trajectory of increased discovery for opioid use disorder, but we need to add more cases, in order to make more progress.

So to summarize results so far, for opioid use disorder genome-wide association studies, more studies are needed, especially in non-European. Discovery is moving forward, but it lags compared to legal SUDs and most other psychiatric traits because we don't have enough cases. MTAG analyses leveraging genetic information from other traits that we showed were genetically correlated to OUD increased our analysis power to 18 genome-wide significant risk loci, the best we've been able to do for opioid use disorder only is 12 risk loci. But in the MTAG analysis, we lost the most characteristic OUD locus, OPRM1. So we gain with MTAG, but it doesn't replace purposed-directed recruitment, because we lost specificity.

The MVP study of a larger OUD sample resulted in discovery of 12 risk loci.

Polygenic risk prediction is statistically significant, but not yet to the point where it's clinically useful. So, why has there been progress in opioid use disorder gene mapping lately? Almost all of the gains are attributable to the MVP sample. We really need more purpose-directed recruitment.

And finally, I would like to acknowledge the contributions of my many collaborators, as shown on this slide. And thank you very much for your attention.

DR. CUNKELMAN: Thank you, Dr. Gelernter.

Next, we'll hear from Dr. Susan Sumner. She's a professor of nutrition and pharmacology at the University of North Carolina at Chapel Hill, whose research is focused on personalized medicine and pursuits in nutrition.

Dr. Sumner.

DR. SUMNER: Hi. I'm Susan Sumner, and I'm a professor in the Department of Nutrition, and in the Department of Pharmacology at the University of North Carolina at Chapel Hill. I'll be speaking about objective biomarkers and mechanistic insights regarding opioid use disorder.

I've worked with Dr. Jonathan Pollock at NIDA, and investigators at the University of Tehran, and at the National Cancer Institute to address critical needs in the development of biomarkers of opioid use disorder. The strategy and results of this investigation are relevant to the development of a diagnostic tool for opioid use disorder. As you know, objective biomarkers of OUD are needed, since current diagnostics rely on subjective criteria as evaluated through the DSM-5 questionnaires.

In addition to investigating objective biomarkers, our studies point to nutrients to mitigate against the acquisition or progression of addiction, and point to co-exposures that

may enhance the negative outcomes associated with illicit drug use. We used UHPLC high-resolution mass spectrometry in this study. Using urine samples that were obtained from the Golestan cohort study in Iran, we compared the untargeted (indiscernible) features of urine samples obtain from opium users with those obtained from individuals who reported never using opium. This was to reveal metabolic perturbations of opium use.

We also compared urine samples obtained from opium users who were diagnosed as OUD positive, compared with urine samples from opium users who were diagnosed as OUD negative, to reveal markers of OUD. Note that these were all opium users and high opium users, based on the number of (indiscernible) reported for daily use, and that all of the individuals in our sample were healthy, with the exception that some had been diagnosed as OUD positive.

As expected, we saw very high levels of metabolites derived from opium in opium users, and increased levels of metabolites derived from tobacco among opium users, consistent with subject characteristics for our sample. We saw perturbations in numerous pathways of post-metabolism, including neurotransmitters, Krebs cycle, lipid and sugar metabolism, 1-carbon metabolism, and in vitamin and vitamin-like compounds.

In addition, environmentally relevant phthalates were higher among opium users. And these phthalates could come from plastics used in the smoking of opium, and phthalates have been linked to learning and cognition, factors consistent with some of the DSM-5 criteria to diagnose OUD. In this analysis, we also saw metabolites derived from the combustion of plant matter, that may be -- that are higher in opium users, like metabolites of the know chemical carcinogen called acrylamide. Because we know that cancer rates in Iran are higher among opium users, we speculate that these know chemical carcinogens

may have a role.

Let's look at some details of metabolic disruptions. We saw a general disruption in metabolites in the neurotransmitter pathway, as depicted here. And we saw perturbations in vitamin B2 and in vitamin B6. As you can see depicted here, B6 is involved in the conversion of tyrosine to dopamine. It's also involved in conversion of tryptophan to serotonin, and tryptophan to kynurenine. And B2 is also involved in the further metabolism of kynurenine. It's possible that opium use interferes with the utilization of B2 and B2, and contributes to metabolic disruptions of neurotransmitters.

Note that four metabolites that are circled in purple here were significantly different between opium users diagnosed as OUD positive and opium users diagnosed as OUD negative. And these may hold promise in that diagnosis of OUD. We also saw a general disruption in sugar metabolism, Krebs cycle metabolism and many related amino acids, as shown here.

Looking at the role of vitamins, we see that B1, B2, B3 and B5, three of which were perturbed in our studies, are important in the conversion of pyruvate to acetyl CoA, and in the conversion of alpha ketogluterate to succinyl CoA. And B vitamins that we saw perturbed are also needed to convert alpha ketogluterate to succinyl CoA, in the Krebs cycle. Note that the Krebs cycle provides the NIDH and the FADH2 needed for the electron transport chain. And this electron transport chain requires B2, B3 and B5, which we saw perturbed. It needs those to produce ATP. Thus, perturbations in the B vitamins among opium users may lead to the general disruption in Krebs cycle, and could lead to lower ATP levels among opium users.

One of the most significant vitamin perturbations was B5. B5 is widespread in the

diet, but opium users had much lower levels. And we know from studies with model systems that a diet deficient in B5, or treatments with drugs that prevent B5 metabolism results in symptoms like irritability, fatigue, apathy and sleep disturbances, and these of course are symptoms that are evaluated as part of the DSM-5 criteria for OUD. Last, I want to mention that several metabolites in sugar, and Krebs cycle metabolism, circled in purple here, were also significant to defining the diagnosis of OUD.

A pathway that we'll look at involves choline. Choline is a vitamin-like compound, and it was decreased in opium users. Choline is metabolized to acetylcholine, a precursor of neurotransmitters, which could also help explain the perturbations in neurotransmitter metabolism. Note that low levels of choline are associated with cognition and memory disorders, and mood disorders, consistent with the DSM-5. Many factors influence the amount of dietary choline that individuals need, including several common genetic polymorphisms that have substantial impact on choline metabolism and bioavailability.

In addition, low levels of the B vitamin called folate can make a higher demand on choline, and cause choline to decrease. In the U.S., folic acid is fortified in our foods, but fortification is not provided in the Golestan cohort region of Iran, and may be related to the higher demand on choline. Note again, some metabolites circled in purple are important to define the OUD-positive diagnosis.

We did use logistic regression modeling to produce a curve, shown in green on the left, that has a 95% chance to predict opium users who tested OUD-positive, compared with opium users who tested OUD-negative. This model selected 16 peaks to make this prediction, including pterin and tryptophan. Pterin is part biopterin, and biopterins are cofactors for aromatic amino acid hydrolases, which are involved in the synthesis of

dopamine, norepinephrine, epinephrine and serotonin. So these may be biomarkers for OUD that mechanistically link to the targeted pathway of neurotransmitter.

To conclude, metabolites were found that are unique to an OUD-positive diagnosis, which need validation in a larger sample or other cohorts. Opium users have significant metabolic perturbations that can be related to nutrition, and based on this data, it may be possible to derive a nutrient cocktail composed of vitamins, vitamin-like compounds, sugars, fatty acids, et cetera to mitigate against the acquisition or progression of addiction.

Exposures to environmentally relevant analytes such as phthalates or metabolites derived from plant combustion may exacerbate the impact of opium use, and could be related to the higher incidence of cancer and other diseases in the Golestan cohort study, as well as impact memory and cognition.

There were many contributors to this project, and here I wanted to point particularly to Dr. Reza Ghanbari, who conducted a NIDA Invest Fellowship in my laboratory at UNC Chapel Hill. I'd like to acknowledge NIDA, for funding his time in my laboratory as a NIDA Invest Fellow, as well as thank Dr. Reza Malekzadeh for his support and collaboration as the PI of the Golestan cohort study.

DR. CUNKELMAN: Thank you so much, Dr. Sumner.

Our next speaker is Dr. Laura Bierut. Dr. Bierut is a physician scientist, and internationally recognized expert on the genetics of substance use disorder. She is the Inaugural Alumni Endowed Professor in the Department of Psychiatry at Washington University School of Medicine. Dr. Bierut will speak on the challenges of clinical study design and conduct.

Welcome, Dr. Bierut.

DR. BIERUT: My name is Laura Bierut, and I'm the Alumni Endowed Professor of Psychiatry at Washington University in St. Louis. I'm a researcher who studies genetic risk factors involved in the development of addiction. I'm a member of the National Advisory Council for Human Genome Research, and I'm a former member of the National Advisory Council for Drug Abuse. I will talk about challenges in clinical study design and conduct.

The goal of large-scale genetic research has been to differentiate between those at low and high genetic risk of disease, with the aim of eventually bringing these discoveries into clinical care. Since the publication of the first human genome in 2005, we have witnessed a revolution in genetic research. Over 10,000 genetic variants associated with a variety of diseases have been identified, and these discoveries include genetic variants that increase a person's risk for the development of opioid use disorder. Now that we have these genetic discoveries in hand, we are challenged with how to bring this science into clinical care to improve human health.

Genomic variation identified in genome-wide association studies predict disease. Though each genetic variant associated with disease, such as obesity or opioid use disorder, has a small effect on risk, when hundreds, thousands and tens of thousands of variants are combined into a single risk score, clinically meaningful differences between low and high-risk groups can be identified.

A great example of the potential utility of polygenic risk scores is seen with obesity. Obesity is a common complex disorder, and is associated with stigma. Low and high genetically at-risk individuals can be identified at birth. Those at high risk are more likely to have extreme obesity, undergo bariatric surgery, experience coronary artery disease and have an early death. The increased risk can be identified at birth, and continues through

childhood, adolescence and adulthood. The use of polygenic risk scores allow the potential of targeted behavioral interventions earlier, and hopefully more effectively.

Similarly, adding polygenic risk scores to demographic predictors can improve risk classification for smoking behaviors. In this graph, we have characterized participants based on the decile of risk. In the highest 10% risk group, 80% smoked cigarettes regularly. In the lowest 10% risk group, only 38% smoked cigarettes regularly. An important point here is that improvement in risk by adding polygenic risk scores was seen at the extremes. This smoking behavior example illustrates an important differentiation between the potential for clinical utility and a metric often discussed in genetic research, the percentage of variants explained.

Though the percentage of variants explained by genetic risk factors for smoking behaviors is modest, there can be meaningful clinical differences based on this genetic risk. Why does this happen? Why is there a discrepancy between percentage of the variants explained and clinical utility? This occurs because those near the midpoint of risk are not changing their classification. Thus the percentage of variants explained can be modest, but nonetheless, changes in the classification at the extremes of risk, in the upper and lower 5 to 10% can be clinically meaningful.

So what are the challenges, moving forward? Though there's increasing evidence of clinical validity, we need more evidence and this evidence needs to be developed in a manner that is faster and more cost effective. Additional genetic risk prediction is needed across many disorders, cardiovascular disease, pulmonary illness, cancer, obesity, dementia, and mental illnesses, including addictions. Given the number of studies needed and the burden of time and cost involved, we need to innovate, to accelerate science and build our

evidence base. There currently exist several large genomic datasets with hundreds of thousands of participants linked to electronic health records. We can and should use these databases to increase our evidence of clinical validity.

One innovation that could be implemented is emulated trials. Emulated trials grow from this proposal by researchers from the Harvard School of Public Health. Large databases exist with meaningful information that could be mined. Emulated trials were proposed for databases, such as electronic health record data, and medical claim data that include clinical diagnosis, interventions and pharmacologic treatment information.

We could extend this paradigm of emulated trials to the large-scale human genetic databases that are linked to survey data and electronic health records. Three examples include UK Biobank, the Million Veteran Program, and the All of Us project. These large databases include hundreds of thousands of individuals with extensive health information and genomic risk data.

Rigor must be taken with an emulated trial. Preregistration of the trials, listing inclusionary and exclusionary criteria for participant selection, the designed intervention and the analytic plan and primary outcomes will be needed.

Making the leap from genetic discovery to clinical care is another challenge. A test that determines risk for the development of opioid use disorder will be a behavioral intervention. We can leverage a framework that has been developed called the NIH Stage Model for Behavioral Intervention Development. This framework helps us focus on the multitude of issues ahead in clinical study design and conduct.

Stage zero is the basic science discovery of genetic variants associated with opioid use disorder. Stage 1 is the intervention development. What is the device? How will the

tool be used? How is the information communicated? Will the information be communicated as a dichotomous risk or a continuous risk? When will the tool be used?

The development of opioid use disorder is a many-step process, with genetic and environmental influences contributing to each step. We've implemented many restrictions on the prescription of opioids, such as limiting medications to a 3-day supply. This environmental intervention targets the first step of the initiation of opioid use. When should we intervene with a genetic risk predictor? Before any opioid use? At pre-addiction, when individuals are transitioning from established opioid use to opioid use disorder? Or potentially when someone has opioid use disorder? There are arguments that could be made for intervening with a genetic test at all of these steps.

Let's focus then on the target of the intervention, and I propose that the target include both healthcare providers and patients. We want to see a change in the behavior of healthcare providers. We hope that this tool will simplify and improve their assessments of patients. We hope that they'll be more precise and tailor treatment for each patient. Those at high risk will be counseled and followed closely. And those at normal risk will receive treatment without unnecessary barriers.

We also want to see a change in the behavior of patients. We hope that this tool will inform patients about their individual risk and guide their own risk reduction. The overall goal is to reduce opioid use disorder, and we could study the effect of this intervention on behaviors at both the patient and the provider level, to determine the efficacy and effectiveness of a device to predict opioid use disorder.

In summary, there are many design considerations and potential innovations that we can implement now to speed discovery, and move genomic interventions into healthcare

fast, and in a safe manner. We must review what things we've done in the past and build upon what we have learned. We want to know what is common to all genetic tests, what is common to genetic tests for mental illnesses, and what is common to genetic tests for addiction, so we could then focus on what we specifically need for a genetic test for opioid use disorder.

Thank you very much.

DR. CUNKELMAN: Thank you for your presentation, Dr. Bierut.

It is now my pleasure to introduce Dr. Alexander Hatoum, who will speak on potential bias, uncertainty and faulty prediction challenges in artificial intelligence, machine learning algorithm development and use.

Dr. Hatoum.

DR. HATOUM: Hello. I'm Dr. Alexander Hatoum, and I'm a research assistant professor at Washington University in St. Louis. Today I'm going to talk about what can go wrong with genetic prediction of opioid use disorder. I have no financial interests to disclose.

The main purpose of this talk is to explain how we should judge whether a test of opioid use disorder, a genetic algorithm is right for the market and the clinic. This would technically be the first time that a complex disease has a genetic test. Further, for opioid use disorder in particular, we know that there are going to be stigma associated with positive test results, that patients could be given a free pass without opioid monitoring if they do have low risk, and the minority populations already suffer from poor pain management. So we want to at least ensure that the test is based on sound scientific principles.

I have laid out three scientific principles that we're going to go over today, that anytime you're judging a genetic test for opioid use disorder, you should check. First, does the test use whole genome methods? And further, you should always avoid the candidate gene methods.

Second, specificity. The genetics of opioid use disorder could relate to similar conditions or comorbidities, and we have to check the specificity of opioid use disorder genetic predictors. Finally, we should ensure that the model accounts for ancestry in model development and model training.

First, the test should use genome models. Now, Joel Gelernter spoke earlier on genome-wide association studies, and his lab has been a leader in this field since the beginning, so I'm not going to speak too much more on GWAS. I will tell you that a red flag should be the use of candidate genes.

So candidate genes are anytime a researcher has picked their genes before doing the research. Some common ones are DAT1, 5HTTLPR, DRD1, COMT, DBH for example. You can see more in this Border et al paper. And if you see those genes and the terms, *a priori*, that should serve as a red flag. Candidate genes have largely failed to replicate, and this is because of large false positive discovery rate. They've never been seen in any of the large genome-wide association studies, and generally they're found in small datasets with high false discovery rates, and with large sample confounding.

However, this has not stopped some individuals from engaging in the use of candidate genes. The typical sophistry argument that's used to defend candidate genes is the argument that the phenotype that they're using in their small study with candidate genes is a much better measure of the trait than the large sample used, for example, a

better measure of opioid use disorder than was used in the genome-wide association studies.

This has become such a common argument that Border and Keller actually developed the P criterion. So we can plot directly, how much worse does a course phenotype have to be before it finally loses out in discovery to these deep phenotypes? And so I've plotted that statistic, and I don't have enough time to go into gory math details, but if we take an example of a deep phenotype of 1,000, and a course phenotype of 260,000, we can see that there would have to be an *r* of 0.04, an incredibly small association for the D phenotype to win out in discovery to discover the candidate genes.

That wouldn't happen in opioid use disorder. Most measures of substance use disorders have correlations between 0.8 and 0.1. So the deep phenotype would really not exceed the power we have in GWAS.

The next principle we need to focus on is the specificity of the test. Do the genes' influence in opioid use disorder influence other traits, and to what extent? Now we know that unfortunately, the genetics of OUD often predict other psychiatric disorders. In fact, opioid use disorder might be the trait that suffers from confounding the most, compared to any other substance use disorder.

And so to the right here I have a structural equation model, which is a statistical representation of the degree to which traits overlap. Now what I always like to tell people is, you can just think about this as a fancy Venn diagram, where we have the genetics of each of these traits, and we've derived the genetics using genome methods in one million individuals. And then when we look to the degree to which those overlap with kind of a common risk that could predict other similar comorbidities, we find that opioid use

disorder, its prediction and its genetics is almost entirely subsumed by that common risk factor.

Kember et al, 2022 took this a little bit further and actually generated a genetic predictor for opioid use disorder in particular, and they found that opioid use disorder is likely to predict diagnosis of all other substances, and even measures of the environment, educational attainment and psychiatric treatment.

Psychiatric treatment is the one that scares me the most, because we don't want to further stigmatize individuals that are already going through psychiatric treatment, are at the risk of psychiatric disorder, by giving them a high-risk opioid use disorder test. Instead, we need to be incredibly careful that the tests are specific to OUD. Unfortunately, OUD in particular is a difficult disorder to establish that specificity.

Finally, I'd like to talk about what I think is the most important principle to consider before engaging with any test, and that's to ensure that the test has proper control for ancestry. We know that genetic models are incredibly sensitive measures of where we come from, particularly unsupervised and supervised machine learning models. In fact, I have a quick little display of this right here, where an unsupervised machine learning model was used, and then used to identify individuals, and then it plots quite nicely on a map of Europe.

This is because we, as humans, do not mate randomly, and over time, genetics becomes a measure of geographic environment instead of objective biology. There's a very simple correction for this, which is to control for ancestry, to locate it in your sample, using whole genome methods, and correct for it in the model development. If a researcher or company does not do that, that is a red flag. That model will likely be confounded and not

have a true null, or zero prediction, even when no prediction exists.

Here's a good example of that. Remember those nice genome-wide association plots Joel presented earlier? We had one gene that was associated. If you don't control for ancestry in a GWAS, we have this red line here, which represents significance. Every SNP in the genome is significant. We can't identify the biology. The entire genetic study is meaningless without ancestry controls.

This becomes worse when we start to use machine learning. And so I'm going to actually engage in an example with machine learning right here. So for the methods for this example, I have two samples, 250 African cases, 250 European cases, 250 African controls, 250 European controls, a perfectly balanced dataset. I have training and test samples that look demographically identical.

I'm going to plot the degree to which models trained in the training set are biased by ancestry. My outcome is actually going to be a random coin toss. The coin was flipped separately for African and European samples, and then the samples were combined with one another to mirror the fact that there is some stratification between those samples. I'll use standard machine learning approaches, and for every published paper I have, you can find my machine learning approaches, exactly what I did, using my GitHub. They are all publicly available.

These genetic variants that I will train the test on are also going to be randomly selected from the genome. So we have randomly selected meaningless variants, predicting a meaningless outcome. What I'm going to do is essentially start in a case where we're perfectly confounded by European cases and African controls, so European heads and African tails. Then at each iteration, I'll add ten African cases and ten European controls. I

will retrain the model, and I will take the predictive accuracy from the out-of-sample test set. So these two sets don't overlap.

If we do that, across *kth* iterations, we can essentially plot the degree to which the model is confounded by ancestry. Now this is a nonsensical model. It is random SNPs predicting random noise. And I can still classify the random noise with 80% accuracy when the sample is highly confounded. That should be a red flag. The null model in machine learning is not zero. It's dependent on how stratified your original population is. As we balance by ancestry, our prediction reduces to no better than a coin flip, which it is a coin flip, so that's what we're hoping for. And at each iteration of the model, we are a more sensitive predictor of ancestry than we are the coin flip, which is what we hope for, since the model is driven by ancestry.

Now, if we take an existing opioid use disorder test, which is based on 16 candidate variants that use machine learning, and a prediction accuracy of 90 to 95%, but also had a very ancestrally confounded sample, we find the exact same thing. At every iteration of the model, it is a more sensitive predictor of ancestry than it is opioid use disorder. And in fact, it's completely driven by ancestry.

If we take a consequence of this test, and take a specific iteration, and compare it to the degree to which populations in the U.S. are admixed for multiple geographic populations, we are a five times more sensitive predictor of underlying geographic admixture, which can only be detected from genome-wide methods, than we are opioid dependence.

And therefore you have three principles by which you should judge an opioid use disorder genetic test. First, avoid the candidate genes and ensure that it uses the genome-

wide methods that Joel talked about earlier. Second, ensure that clinical tests are specific to that particular disease, although that is a problem in particular for opioid use disorder, and finally, you need appropriate controls for ancestry in the machine learning and algorithm development stage. So there is a call for expertise. This literature has been developed by people in the academic side, and as we begin to develop the first test for complex diseases, we need to ensure that those scientific consensuses are used for the test.

And with that, I'd like to thank the FDA and my funders for their allowing me to participate. Thank you.

DR. CUNKELMAN: Thank you, Dr. Hatoum.

Next is Dr. Travis Rieder, a bioethicist, philosopher and widely-published author, currently serving as Director of the Master of Bioethics Program, and associate research professor at the Johns Hopkins Berman Institute of Bioethics. He also has secondary appointments in the departments of philosophy and health policy and management, as well as in the Center for Public Health Advocacy. Dr. Rieder will discuss ethical considerations for opioid use disorder prediction.

Welcome, Dr. Rieder.

DR. RIEDER: Hello. My name is Travis Rieder, and I am an associate research professor at the Johns Hopkins Berman Institute of Bioethics. Today I'm going to be giving a very short, high-level overview of the ethical considerations for OUD prediction.

This first slide portrays a suspicion I have, which is that OUD prediction is what I call ethically fraught, which is to say the development and use of the technology concerns lots of ethical considerations. So why do I think that? The goal of OUD prediction is preventing harm. And harm here is a salient ethical consideration. When we are thinking about ethics

and morals, harm is one of the main things that we think about trying to prevent, or not to commit ourselves. But there is a risk of harm from the technology itself.

So why does harm show up in these two places? Well, I said the goal of OUD prediction is preventing harm because I think often what we want to do is we want clinicians to know if there's a high risk of opioid use disorder development, so that they can prevent sorts of interventions that might cause or help lead to iatrogenic use disorder. But there is a risk of harm from the technology itself if there are, for instance, risks of false positives, or false negatives, and those can come with harm. So I'll talk about those in a bit.

The technology, I'm going to suggest, might also limit the autonomy of patients, especially if we're not careful about implementation. And these harms and autonomy limitations may be inequitable, which raises another big concern. All that to say, the moral stakes here are very high.

So let's dive in. That's basically a preview of the considerations we're going to talk about. Let's take a little bit more detailed look. These two handsome fellows are Tom Beauchamp on the left and Jim Childress on the right. Any of you going to medical school or have ever studied bioethics all are quite familiar with Beauchamp and Childress. They cowrote this book. "The Principles of Biomedical Ethics" is now on its eighth edition, and fourth decade. It has been incredibly influential.

And what people tend to know about the book is the four principles. So beneficence, nonmaleficence, respect for autonomy and justice, these are the four, kind of paradigmatic principles of biomedical ethics, so think research and clinical practice. I am not -- as a working bioethicist, I am not a sort of card-carrying principlist. I don't think we need to go around and deductively apply these to all sorts of situations. But the reason

these principles have lasted so long is because they are a really nice attempt to bring together categories of high-level considerations that we ought to be on the lookout for.

So here is the background assumption that I have when I'm trying to do some issue spotting for OUD prevention technologies. OUD prevention will affect pain care. That's because pain care utilizes opioids, and so opioids have an OUD risk liability. So let's think through this. False positives, so predicting OUD when none is likely, or predicting a high probability or an unacceptably high probability of OUD when it is not the case will always be part of prediction, because prediction's not going to be perfect. And that could reduce otherwise responsible opioid use.

So insofar as there are cases where opioids would be a perfectly responsible form of pain medication, this sort of thing could -- this false positive could reduce that responsible use. But false negatives, failing to predict OUD when it is in fact likely, will also be part of prediction. And that could license irresponsible pain care. So if we got to the point where we became so comfortable with the technology that we saw a negative result from a prediction technology as really saying that this person is not at risk of use disorder at all, that might make us a little too free to prescribe medications in a careless way. So both sides carry risks here.

This fellow here is Hippocrates, of the Hippocratic oath, and so I'm going to go through the four principles and try to articulate basically some issue spotting for each one. So, Hippocrates famously said, "First, do no harm." So part of the Hippocratic oath is *primum, non nocere,* and this is encapsulated in the principle of nonmaleficence, which basically says that each individual clinician should not themselves do harm.

The indication of first here, or *primum*, okay, can make physicians feel like this

principle takes priority. It's most important that you do not do harm, whatever else you do. But this can lead to a sense that it's especially morally important that harms don't flow from the clinician's hands. It can give us a sort of like clean hand sense, that oh, it's okay if harms result, as long as I didn't create them. And that's really problematic, because what it leads to is this idea that OUD, as an iatrogenic harm.

So if a physician prescribes opioids, and that patient then develops an opioid use disorder down the line, that's taken to be a particularly serious violation, whereas we might see other sorts of harm coming from not prescribing opioids as not as important. So let's flip to take those into account in a second. So the priority goal of preventing iatrogenic opioid use disorder motivates predictive technology, this idea that clinicians want to know if there's an unacceptably high risk that a patient will develop use disorder so they can be especially careful with opioids.

So, why is this idea that first, we should do no harm gives us a sense of priority, why is that problematic? Well because nonmaleficence is not the only principle here. So take the principle of beneficence, which basically tells us to do good. So philosophers like to say things like, promote the good, promote happiness, pleasure, relieve suffering. So for medicine, particularly in this context, treat pain, that relief of suffering is really morally important.

And this principle is not secondary to nonmaleficence. There is lots of literature in medical ethics that makes it clear that there is no hierarchy here. It's not that it goes nonmaleficence takes priority, and then beneficence can come into play later. And we can see that, if we think about, you know, what would it really mean to take nonmaleficence as, you know, the top of the hierarchy? Well then the model would be something like, no risk

for OUD is unacceptable.

And I have had physicians tell me that that's sort of how they feel. But that's just not how we do medicine. So you think about it, surgery risks infection. All meds have risks and side effects. Medicine is not a risk-free endeavor, and OUD isn't special. It's a risk, and it's a risk that has to be weighed, but it's not a trump card. It isn't a risk that ends the clinical conversation.

All right, so we have beneficence and nonmaleficence, but then there are these other sorts of principles that work really differently. They're not about harms and benefits at all. So there's a principle that says that we should respect patient autonomy. So respect for autonomy or sometimes respect for persons is typically seen as especially important for protecting patients from having their negative rights violated. So, we talk a lot about informed consent to do procedures.

So, if I'm a patient, you're a physician, I have to give my informed consent, otherwise you cutting into me is assault, right. So, this respect for autonomy is really about protecting my negative right to bodily autonomy. But we could understand autonomy to be something that medicine should scaffold, or should promote. That is to say that part of the job of medicine is to help patients live a more free life. And so the worry is that prediction technology could undermine autonomy, if it were to replace clinician judgment, right.

So if there came a time that this sort of technology supplanted physician judgment, and it led to too many calls of ah, you scored too high on the OUD risk predictor, so you don't get, you know, opioids for your pain, and in that case opioids would help me live a freer life, that's a sort of autonomy violation by, you know, failing to promote autonomy. So it's different than this negative rights violation.

And lastly, we have the principle of justice. So that concern that I highlighted at the beginning about inequitable treatment, that's what raises our concern for justice. So, much predictive technology raises a version of the worry, garbage in, garbage out, so I especially think about this with reference to algorithms, but I'm sure it comes up in a lot of different sorts of predictive technologies.

The worry here is, we already know that pain care is inequitable, so whose pain testimony is heard, whose pain is treated. Well we know that women and people of color are less likely to have their pain testimonies taken seriously, and therefore they're less likely to have their pain treated aggressively, including with things like opioids. So, if we allow technologies to take, sort of, the way we practice medicine now into account, we might worry that they're going to actually encode our biases, and make them more, rather than less likely. And that's a thing that we must not let happen.

Okay. So that was a really quick, really high-level overview of how I as a bioethicist, knowing something about opioids and opioid use disorder, and then worrying and thinking about these prediction technologies, how I might start the process of issue spotting, what things should we be on alert for.

Here are just some concluding thoughts. OUD prediction isn't new. Screening tools are a part of clinical practice, and these can be perfectly responsible. Screening tools should be a part of practice, because an increase in risk can change the risk-benefit ratio of an intervention. And so, if I'm a physician and I'm trying to decide whether prescribing opioids is responsible in this context, I should be doing a risk-benefit calculus. And if what I learn is that your family has a long history of use disorder, this might be the sort of thing that, in conversation with you as a patient, we decide tips the scale from responsible use of

opioids into irresponsible, because that calculus is always weighing, and this can change the weights, right.

So all that is to say that prediction isn't new, and can be perfectly responsible. What I think the challenge of predictive technologies is, is the way in which they can become ensconced and then authoritative. So, if a high OUD risk score comes to determine treatment, or worse, if it comes to justify policy, such that, you know, if you get a certain risk score, a little message pops up in Epic and says, you may not prescribe opioids to this patient, that would heighten all the ethical considerations discussed. Because pain medicine is hard, and it's fraught, and it's nuanced, and it should done in a patient-centered way.

And so, if these sorts of algorithms or other prediction technologies take decisions out of clinicians' hands and turn them into something automated, that would give them the sort of authority that we might be especially worried about. What that means is, many of the moral worries here are about implementation as much as they are about development. And so implementation worries should be part of the development process, thinking about how these technologies could be developed that minimize the worries about bad implementation.

That is all I have time for. Thank you very much. I'm looking forward to further discussion on the panels.

DR. CUNKELMAN: Thank you, Dr. Rieder.

Our final speaker for Session 1 is Dr. Kelly Clark. Dr. Clark is a psychiatrist and addiction medicine specialist, who has worked broadly within the behavioral health arena. She is President of Addiction Crisis Solutions, assisting stakeholder groups, transforming

addiction care into evidence-based, cost-effective systems. Dr. Clark will speak on digital health technologies and predicting risk of opioid use disorder.

Dr. Clark.

DR. CLARK: Thank you.

So, my first slide, would -- talks about what really our -- there we go, what we are going to be talking about today, digital health technologies, and predicting the risk of OUD. And we're talking about innovation, because innovation is what we're trying to drive here today. So, if I just start with the general construct that -- next slide -- data is not knowledge. And the collection of data, they're just, they're little points. They can become knowledge. If they're analyzed, they can become knowledge, and knowledge can lead to innovation.

I'm going to define innovation as when a product, service or program, a new one is driving the improvement in prevention, diagnosis, treatment and management of health conditions. So, if something gets FDA approved, if something uses science and becomes a new widget, and comes to market and no one uses it, it is not innovation. There is no innovation there. Okay. It's simply something that has got the approval but nobody wants, or is using.

So what we're looking for here is innovation. So in this general field, so we're talking about preventing OUD, opioid use disorder, which is, by definition, a psychiatric condition in DSM-5.

Next slide, please.

Where are we in psychiatry? It is noted that in psychiatry we lack reliable tests that predict illness risk, predict treatment response, remission, or predict recurrence likelihood.

That's where we're starting, okay, across the board.

Next slide, please.

So, in talking about -- oh, sorry. We've got the hidden slides. Let me take the slides out, and just go to mute then.

So, if we're talking about the spectrum of -- sorry, I'm a little -- I've got my slides that are there for you to use later but not for me to talk about. I'll just blow through them and then you'll be able to have them for reference later. Okay.

I'm not talking about here, opiate use or dependence. I'm talking about opioid addiction, opioid use disorder, which is the chronic relapsing, remitting brain disease. Okay. It is not the same thing as a person misusing opioids.

Next slide.

Opioid misuse is when a person takes an opioid in a way that is not exactly as prescribed. That's opiate misuse. I am not talking about -- next slide, please -- problematic opioid use, which I see in the literature, which I think is just a researcher making up an outcome, a definition, because this is not a clinical condition. Okay. I'm talking about opioid use disorder itself.

So let's go -- next slide -- to, what is OUD? OUD is really a checklist, which is how we diagnose most brain disorders, like Parkinson's disease, is by a checklist. When people are doing research on claims data, they're using ICD diagnostic billing codes. It's for opioid dependence. It's not actually the same thing as the diagnosis of OUD, the criteria. It's not, OUD's not the same as DSM-4's diagnostic criteria of opioid dependence. Okay. Again, this a chronic relapsing, remitting brain disease. Okay.

Opioid misuse, physical dependence, these are risk factors to develop OUD, but

they're not the same thing. Okay. And even in clinical practice, we don't really use DSM-5, the full criteria to make diagnoses. If people come in and say, I want help because I've been snorting my oxycodone and I can't stop, they're getting a diagnosis. No checklist is going to be necessary at that point. Okay.

Next slide, please.

So, digital health, really easy to define. There are no generally accepted definitions of terms. You can go to yesterday's talk with the FDA and NIDA for more information on that.

Next slide.

We talk about predicting risk, generally. What we're talking about here, because again we're talking about innovation, is we want to predict who is of clinical relevant high or low risk of developing a disease or developing an adverse event, or of developing response to a treatment. And the key here, that I want everyone to keep in mind is, we're talking about clinically relevant risk, okay. 100% is not prediction, it's diagnosis. Okay. But clinically relevant risk depends on the clinician, and the patient, and the disease state.

A genetic factor that might define a 20% risk of something happening, or a 2% decreased risk of something happening, those numbers are incredibly relevant in cancer care. Those are not going to have that kind of relevance in addiction, or psychiatric care. So, when talking about what is relevant risk, you need to talk to the clinicians, to the patients. You need to understand the disease state you're talking about and how it's being treated.

Next slide.

So, what do we do now when we're predicting risk? We look at the risk factors that

we know about. So, we know that risk factors for developing any adverse events from opioid use, including developing OUD are opioid misuse, or the amount of opioid exposure that the person has, so amount of dose, frequency, intensity of the dose, how young they were when they started doses, genetics, family histories, epigenetics, other medications and other substances being used, comorbidities. All of these are risk factors for developing adverse events, including addiction.

Next slide.

And so now we get our clinical risk factors by asking patients during the clinical encounter. This is really how we do it now. And we would like to do it better than this, is true, but that the processes in place are for this history to come up during the clinical encounter. There might be some prior diagnoses that are easily accessible, but there is a silo in medical records between addiction treatment and psychiatric treatment and other medical conditions that get in the way. So, we take a history during a clinical encounter to figure out sort of, de novo, from the beginning of prescribing what a risk -- how much risk the person might have.

Next slide.

And then we manage and predict ongoing risks in time. So, what we're looking for, there is, is a person showing that they are maybe developing OUD? They're developing some of the increased risk factors, early refills. We check their electronic medical records, et cetera.

Next slide.

And we do this in order to monitor for people who might be developing OUD or other risk factors by watching for these risk factors, signal changes.

Next slide.

So, where it can be clinically relevant, in some world, is if I happen to know that you are, have a genetic variant which means you're a really slow metabolizer of a certain opioid. Well, I would be less likely to prescribe that certain opioid, or more likely to describe a low does of it, because what I'm doing is decreasing a risk factor. I'm decreasing the total amount of opioid exposure that you're getting in your brain by decreasing my prescription of something that's going to be building up in your body. Okay, so what we're really doing is to look to decrease this risk by prediction.

Next slide, and then next slide. Oh yes, thanks.

So, when we're looking at claims data, from history, there are issues with claims data. But the biggest issue that I have -- I'm supposed to bring the clinical, the business, the policy and the payment viewpoint here, okay. So, the one thing I want you all to maybe leave here with from me is that it is incredibly important for researchers to talk to the clinicians in the field. Talk to the patients, and talk to the clinicians, because what you're looking for is clinically relevant information, okay.

So as the clinician -- next slide -- this study, published study on machine learning approach to predicting OUD from claims data, this is an outcome that was published. We found that if a patient was diagnosed once for poisoning involving heroin, he/she was approximately 12 times more likely to develop OUD as compared to a patient who has not been diagnosed with heroin poisoning, and their algorithm to predict who will also develop OUD included a history of opioid dependence, opioid abuse, and poisoning by opium. Okay.

They're not predicting who will develop OUD. They're simply predicting who in the end is sometime going to end up getting diagnosed with what they already have, which is

opioid use disorder. The person coming in with heroin poisoning is almost entirely likely to have opioid use disorder. So this is just a lot of time and energy that's going down a rabbit hole, in terms of what's clinically useful.

Next slide.

So, there's also digital risks that can come from history, okay. So, going through the electronic medical record, there's some pluses and minuses of that.

Next slide.

But here's what I see published about an EMR predictive approach. So to predict OUD development in ICU patients, they used four different models, and the common risk factors were, age at admission, hyperlipidemia, alcohol use disorder, and current or past nicotine dependence. So again, this is not something that we can utilize, clinically, at all.

Next slide.

And now, talking about genetic data, I'm going to talk about PRSs, my term for polygenic risk scores.

Next slide.

Really, this is something that is not there. I just got my *American Journal of Psychiatry* 2 days ago, all about genetics. And the summary, the summary is that polygenic risk scores are now well established as a research tool, but they are not yet ready for clinical implementation.

Next slide.

When you go to the NIMH website, they say, can genetic testing help predict my risk of developing a mental disorder? The short answer is no.

So, next slide. And next slide.

Going back to, where are we, data can become knowledge. Knowledge can drive innovation, but -- next slide -- in order for there to be some kind of uptake, we need to consider the patient. Consider the clinician. What is a clinically relevant risk score? How does that drive actual clinical changes? And consider the regulators, and consider the payers. And whose need are you fulfilling with this tech? Okay. Whose need are you fulfilling? Because what we've seen repeatedly, and this is something we'll talk about in our panel discussion, is that new tech, coming into this space, for psychiatry and addiction, is just, gets very little market uptake, because you don't start with that end in mind.

And last slide.

So, my example of what is needed is science plus wisdom. So if you go to Dr. Bierut's actual faculty website, you'll see a really high-level view of all the amazing science that she does and that we need having done. But the thing that struck me is this wisdom of saying that we're currently exploring how to translate genetic information to guide more effective clinical care. And that is what we're really needing to focus on here.

And sorry to be running over late. Thanks.

DR. CUNKELMAN: Thank you, Dr. Clark.

Now we're going to shift gears to a question and answer session featuring our speakers from Session 1, Drs. Gelernter, Sumner, Bierut, Hatoum, Rieder and Clark. Joining Dr. Pollock as co-moderator for this session is Ken Scodacek. Ken currently serves as the CDRH Deputy Ombudsman, where he provides an independent, impartial and confidential resource that informally investigates complaints and resolves disputes.

DR. POLLOCK: So, okay. I think the first question is directed to Dr. Gelernter. And the question is, "The statistical genetic approach that you have described, Joel, as in GWAS,

is known for almost every disease to be limited in that it misses polygenic targets. Furthermore, the approach may create confounding, not more power. Do you have any thoughts on this question?"

DR. GELERNTER: I don't really fully understand the premise of what targets the questioner is saying we missed. But, you know, there's really a very impressive record in GWAS of complex traits, and not just in psychiatry but in the range of medical traits that are genetically complex also, which is almost all of them. And that's what -- as you increase sample size, you increase discovery. And when you increase sample size a lot, you increase discovery a lot, and your discoveries become more replicable.

And there is really enough experience with it for us to have very high confidence that that's true. And you can go to the NHGRI website at your leisure and look at the number of risk genes mapped for complex traits via GWAS, and they just dot with colorful dots on every part of every chromosome at this point. So, we're very, very confident in the technique. And we see replicability specifically for opioid use disorder, but also for other substance use traits, like alcohol use disorder, and cannabis use disorder, and just all across psychiatry where large enough samples have been used.

MR. SCODACEK: Maybe Jonathan, if I could cover some of the housekeeping questions that we got as well.

DR. POLLOCK: All right.

MR. SCODACEK: So, one thing. I think we're getting a lot of comments through the Q&A. I just want to remind people that there's a link to the docket, to submit all of your comments. And that link to the docket is on the website for this workshop. So definitely, if you have comments, and you want them to be part of the record, and you want to share

them with FDA and other participating in the workshop, please submit them through the dockets link for the workshop.

Also, we have some questions about the recording for the workshop, and it's my understanding that the recording will be available by the end of this week. So if anyone missed or has to miss some part of this discussion, they can check out the recording. And the link will be on the website.

Maybe Jonathan, do you want to handle the second question, or do you want me to handle that?

DR. POLLOCK: Why don't you take a crack. I'm probably going to have another question --

MR. SCODACEK: No problem.

DR. POLLOCK: -- on the genetic panelists on the -- on it, but why don't you go ahead?

MR. SCODACEK: No problem. Yeah, I'm just not sure. So, what about under -- so this is for Dr. Laura or maybe Joel. "What about under-represented populations? What are approaches to ensure that all populations impacted by opioid use disorder are represented in the clinical studies for predictive devices for opioid use disorder?" Was that clear, Laura and Joel?

DR. GELERNTER: Yeah, and I'll have a go at it, and then maybe Laura wants to comment also.

I agree. I would venture to guess that all of us agree that this is a critically important question. But the starting point is having enough subjects to study for our genome-wide association studies. At this point, the best source of non-European studies is the MVP, but

even in the MVP, we can't build up sample sizes that are sufficient to map opioid use risk genes. So, we really need directed recruitment efforts, and they're expensive. But if we don't recruit enough African and Hispanic ancestry, and Asian ancestry subjects, then we just won't be able to answer the question, because there are population differences that we always have to be aware of in these kinds of studies.

DR. BIERUT: I agree completely with what Joel said, but I would also say that there are analytic techniques that we can use to move forward for populations that are not represented. And -- because I'm concerned about the lag time that we will have recruiting people into the study. So I think we should both take an analytic approach and recruiting more individuals.

MR. SCODACEK: Great, thank you.

DR. POLLOCK: So my question is this. In GWAS, you're really looking at a frequentist approach. You assume that every variant is independent of one another, but genes are not independent. Whereas if you look at a Bayesian approach, you're looking at the frequency of co-occurrence of a set of alleles together. So with that, you know, might that be a better way of predicting risks?

DR. RIEDER: Yeah, so Jonathan, that's -- I think you're right in that approach. So that the frequentist approach is what has been historically used in polygenic risk scores. But actually those polygenic risk scores that you showed at the beginning that I developed, those are actually a Bayesian approach, which considered joint distributions of SNPs. And that improves our ability to predict substance use disorders by about a percent or two, which is, you know, doubling what we already have, but it's not enough to overcome the lack of sample size. No analytical technique is enough to overcome the lack of generalizable

sampling, large samples that we have.

And in fact, I actually use Bayesian approaches quite frequently in relation to the last question, with minority populations. So you can, analytically, as Laura pointed out, extend to minority populations. But there is a lower bound of the number of minority populations you need in order to extend effectively, and we haven't quite hit there yet. So yeah, and Bayesian approaches are typically what's used to correct for that.

DR. POLLOCK: Thank you.

MR. SCODACEK: All right, I can go to the next question here. This is maybe for Laura and maybe Alex. "What about methamphetamine overdose? Is anyone looking for genetic markers for stimulant use disorder? How do we ensure that people with ADHD or others who safely take prescribed stimulants don't mistakenly get identified? How do we know that people with chronic pain on long-term opioid therapy are not mistakenly identified by these genetic OUD markers?"

Alex, do you want to go first, or Laura?

DR. BIERUT: I'll go first. So, I think that this question is really identifying really the crux of where we are, which is how do we balance risk and benefit with these tests? And that's why we're here today. It's like, I can see potential benefits with these tests. If an individual is identified at high risk and appropriately identified, and the individual has this information, and their healthcare providers have it, you know, I could see a more precise treatment, going forward.

We all have the concern that there may be misclassification of individuals, and then the withholding of appropriate care. So, you know, and I think that these are two issues. Travis kind of brought this up as, there is going to be the implementation issues. The tests

can be perfect. So let's just assume the test is perfect. But then how it is used in real world settings, you know, it may not be appropriate.

DR. HATOUM: Yeah. And so I can answer the first part, which is, are we doing research on amphetamine use disorder, and the answer is, we're trying to. Amphetamine use disorder has even smaller sample sizes than existing GWAS. And so we don't have any signals for amphetamine use disorder.

In terms of developing polygenic predictors, and in terms of ADHD, relationship with ADHD, we have to recognize that the etiology of ADHD and amphetamine use are shared. And therefore creating a test that is specific to amphetamine use that does not just pick up ADHD patients is going to be a challenge. That's the same with pain and opioids. The etiology of pain and opioids is going to be shared, and so therefore that is an additional challenge in terms of not just the implementation, but it's a practical issue that is going to affect how we use the test in the clinic, the fact that those tests will predict patients that are similar. And so those need to be built in to the applications of the tests, and the tests in clinical trials.

MR. SCODACEK: Okay, thanks.

Jonathan, do you want to take the next question, or you want me to march on?

DR. POLLOCK: I'm not seeing the questions, so.

MR. SCODACEK: No problem.

"Does directed recruitment contribute to bias?" Maybe Kelly and Laura, if you could handle these questions. Kelly, you want to go first?

DR. CLARK: Actually, I'd rather go back to the earlier question, about --

MR. SCODACEK: Hey sure, of course.

DR. CLARK: Let me go back to the earlier question, because you know, even when, you know, we know there's an increased risk of people having any psychiatric disorder if their identical twin has that psychiatric disorder. We've known this for decades, right. And yet, you know, the question is, how do we use this in actual psychiatric practice? Not a whole lot. You know, I go back to the, how do we use this, these things clinically, predicting how much increased risk, and is it increased risk of developing, compared to a person, or an absolute risk, with use?

Because clinicians don't use a lot of risk tools in actual practice. Things are going really quickly in actual practice. Cancer doctors use a lot of risk tools. Specialists use a lot of risk tools. But when you're talking about something like the enormous number of clinicians, advanced practice clinicians and physicians that are prescribing opioids, it's really difficult to even think about what kind of a risk management tool would change their actual specific management of a patient.

I don't think you've got that information yet. And without that information, it's really hard to start. I think which is where we start in a lot of discussions, like we have these data, we have this knowledge, we have this tech, how are we going to get people to use it, instead of what does the user actually need? And then giving -- looking to build your knowledge and your tech to what the user actually needs.

MR. SCODACEK: Thanks, Kelly.

Laura, did you want to say anything about the original question? I can read it again if you've forgotten.

DR. BIERUT: So I think the original question was directed recruitment, and does that lead to bias. I'd also -- Joel can comment also.

So, you know, I think that when there is directed recruitment, there is bias in all of our studies. We are not looking really at general population studies. But what we try to do is minimize this bias, and get as generalizable a knowledge as possible, and I think we have the tools to do that.

DR. GELERNTER: Yeah, and I agree with that. There is risk of bias, but we're able to look at genetic correlation between samples recruited in different ways, and we find that oftentimes the correlation is high, even with completely different modes of recruitment.

MR. SCODACEK: And then Travis and Susan, do you, either of you have any comments to any of these questions or any of the discussion?

DR. SUMNER: I do. So, thank you for asking. So, I did just want to remind everybody that, you know, we can't have polymorphisms in the metabolism of our vitamins and essential nutrients. This can be very important to being able to, you know, provide. What we need in many of these measurements that we make with the DSM-5 are consistent with low levels of certain vitamins.

So for example, a low level of B-5 is associated with things like apathy and restlessness, you know, so there are certain kinds of measurements that you can see also with this DSM-5. So I wanted to mention that, and to mention the importance in health disparities also, because -- with opioid use or drug addiction, because lack of the right foods, access to the right foods, and even differences in the genetics between people of different backgrounds can be related to how individuals uptake, absorb, metabolize and transport their nutrients, particularly when they have an exposure.

And in this case, the exposure would be the opium exposure. And the opium exposure or opioid exposure may be compounded with tobacco use, or other

environmentally relevant compounds that get introduced. Even in our diet, like to process foods, we get chemicals introduced that can interfere with the transport of these vitamins also.

So I think really, this whole concept of multiple types of exposures, and multiple targets that are being hit is very important for us to come up with something clinically relevant to treat people, because we're going to need to be treating these multiple targets and not just the primary target of the drug of abuse.

MR. SCODACEK: Okay. Thanks, Susan.

Travis?

DR. RIEDER: Yeah, thanks for giving me the opportunity. Everybody was so thoughtful in their talks, maybe you didn't need an ethicist here at all. But I'll accept Laura's call out earlier for balancing costs and benefits. And one thing I'll just note is, I think it can sometimes be helpful to reframe the goal of these sorts of research endeavors.

So at the very beginning, you know, there was talk about sort of response to the opioid epidemic. And I think that what happens is, we then start out with the goal of saying, you know, the opioid epidemic is deeply connected to pharmaceutical opioids, and so our goal here is to create technology that's going to reduce the use of opioids or something.

But this is probably not the best way to actually frame the goal here. The goal is to help clinicians to really spectacular patient-centered care. And so what we're really aiming for is not fewer opioids. We're aiming for the responsible use of opioids, the right tool for the right patient, at the right time, for the right reason.

And what that means is that these tools, like any others, can be really helpful aids to

a clinician, but they don't come in already preframed as helping to reduce opioid use. They come in as helping to get the sort of information that will help the clinician be responsible. So, perhaps that framing is helpful.

MR. SCODACEK: Great. Thanks Travis.

And Kelly, I see you raised your hand. I have just a few minutes before we go on the break, but go ahead.

DR. CLARK: Oh sorry. Yeah, I just wanted to piggyback on that and, you know, remind people that we have as many people who died last year from prescribed opioids as we had in 2008. You know, we have -- the epidemic we have is an overdose epidemic, not an opioid epidemic. We have an opioid crisis, and public health emergency. But we have an overdose epidemic, and a lot of those overdoses are coming from the elicit supply of cocaine and other things being really just contaminated with fentanyl and other things.

So, I think it's really important for us to think about -- you know, I talked today about preventing opiate use disorder, and then monitoring as signs and symptoms of it, and additional risk factors may come out. But I think it's super important to keep in mind, you know, what is it we're really trying to predict along each one of those kinds of constructs, and what impact we might have if we were able to do it, as well as thinking about, you know, what do the clinicians, what do the patients really need at that level, and aiming for that.

MR. SCODACEK: Great. Thanks, Kelly. I appreciate that context. I'm sure the participants do as well.

So, thank you all for your presentations, and for answering the questions during the Q&A. I am looking at the schedule and I think we have a break of about 10 minutes. So,

everyone get up, stretch, take a short break and we'll be back at 12:15 promptly. All right? We'll see everyone soon.

(Off the record from 12:06 p.m. to 12:15 p.m.)

DR. CUNKELMAN: Welcome back, everyone. We will now begin our multistakeholder panel discussion, moderated by Dr. Pollock and Ken Scodacek. I'd like to welcome the panelists, and thank each of them for participating in today's session. Our panel includes a variety of perspectives and backgrounds, and will include Drs. Gelernter, Sumner, Bierut, Hatoum, Rieder and Clark, from our morning session.

I'd also like to introduce and welcome two additional members of the panel, Bilal Muhsin, the Chief Operating Officer for Masimo Corporation, where he leads the global launch of innovative medical devices. I'm also pleased to introduce Keegan Wicks, from Faces and Voices of Recovery. Keegan works in the recovery field through roles in advocacy, counseling, management, and is himself a person in long-term recovery. I will now turn it over to our moderators.

MR. SCODACEK: Thanks, Jacquie.

Let's see, I'll get started with the first question. Is it not better to have an objective genetic screening test, used in conjunction with traditional subjective screening questionnaire, to be used in toto for physician-patient shared decision making for prescribing opiates? Does genetic risk information provide patient empowerment when having a discussion, and allow for better shared decision making when possible using opiates as a treatment for pain?

Maybe if we could start with Keegan, since you're new to the panel discussion.

MR. WICKS: Sure. Thank you so much.

So, I think a couple of things come to mind. I think, you know, having a conversation with a patient certainly provides opportunity, I think, for one of the best case scenarios of really a collaborative process in determining the proper form of treatment. So, I think that there's always risk involved in that, and I think that that's kind of something to be mindful of, with prescriber discretion. But overall, I think the kind of understanding is that it would be better to know than to not know, and have that be part of the conversation.

MR. SCODACEK: Maybe Travis, can you provide your perspective, from an ethics point of view?

DR. RIEDER: Yeah, sure. So I was definitely thinking, as you read the question, there is something about the insertion of objective in there, right. So isn't it better to have this sort of objective information? And so on the one hand, that sounds great, right. Objective sounds better than subjective. But there are a couple of things that I immediately just get put on alert for, and so I ended, you know, my little 10-minute talk with sort of being on the lookout for lending more authority to these devices than may be justifiable. And so this sense of objectivity, I think, gives us the tendency to lend that sort of authoritativeness.

And then also, it could just not be as objective as we want it to be, right. And so, when we encode our own biases into these technologies in various ways, through mistakes, through sampling size errors, et cetera, then now if we call it objective and it's not objective, now we're really in trouble if we lend that authority, and it's wrong, right. So, none of that is to say these aren't really helpful technologies used in the right way. It's just to say, objectivity isn't always quite what it's cracked up to be. It should put us a little bit on alert.

MR. SCODACEK: And Kelly, I see you nodding. Did you have some comments too?

DR. CLARK: No, I'm just, I'm agreeing with everything that Travis just said. You know, objective tends to make us value it in a way that subjective doesn't. But in the practice of medicine, subjective is really what we're treating often, the patient's experience, and then the patient's quality of life, in addition to the things that are more objective.

MR. SCODACEK: Joel, I see you have your hand up.

DR. GELERNTER: Yeah. Could we clarify though, that this question has to be a hypothetical? There's not enough genome-wide data in the universe, opioid use disorder data, to get anywhere near something that would be clinically useful to add to the discussion. I hope someday there will be, but we're not at that point now, and we're not close to that point yet. And considering that the whole genome's worth of data is not sufficient to be a useful part of this discussion, we can also say that no subset of that data will work better than all of the data.

So, it will be an extensive and useful discussion once the science catches up to the point where there's enough genetic information for it to be usefully predictive, but we're not there, so the question is a hypothetical.

MR. SCODACEK: Okay. And Laura, I see you had your hand up.

DR. BIERUT: So, I appreciate what Joel is saying, but I would disagree with it somewhat, because I think that we should not wait until these genetic tests are perfect, and have enough information with them, because they are clearly coming. And we should start this research of what happens with implementation. How are the physicians potentially using them? How are the patients potentially interpretating them? And I think we need to be prepared with that implementation and start researching that absolutely now. And I tend to be more optimistic, and think that we will get this genetic information sooner than

later.

DR. POLLOCK: Let me draw a follow-up question, then. So, let us say your test predicts 75% risk of developing OUD. What are the next questions that a physician or healthcare provider should ask, in evaluating whether to give, you know, opioid therapy for treatment of pain versus some other type of pain management?

Dr. Clark.

DR. CLARK: So, when you're saying a 70 percent risk, what do you mean by that? You mean an absolute, that this person, if ever given an opioid has a 75% chance of getting it? You mean a person's got a 75% chance of getting it, higher risk than somebody, than the average person? Are you talking about a person who's on it for 6 months has a 75% risk?

DR. POLLOCK: I'm saying acute -- if we're talking about acute pain. And you could also ask that question about chronic pain as well. But I mean, and you framed the question, you've parsed the question even more deeply than I have.

DR. CLARK: Because that's what's clinically relevant. So, if a person's got a 75% higher chance than an average person, it's meaningless, speaking as a clinician. That's not helpful. If you're saying they've got a 75% chance of developing an opiate use disorder if they are, have been prescribed X milligram, you know, Murphy milligram units, over the course of their lifetime, that's a different utility to me. That's what I want to get down to on some of this.

And I agree with Laura entirely. We need to think about these things from the get-go, because it's not just a question of what will clinicians do with it, it's -- these things are marketed to the direct public. What does the direct public do with some of this?

MR. SCODACEK: Okay. Jonathan, do you see the next question in the queue?

DR. POLLOCK: Yeah, I have -- the next question is, and I think Joel Gelernter can answer this, because I think he has some data that speaks to this. It says, "I appreciate the attention to opioid use disorder, and note Dr. Clark's caution to find precisely, but isn't opioid overdose risk distinct and important? Are there any genetic markers for this?

DR. GELERNTER: I think it's a good guess that it's probably distinct. We really don't have the data to look at that yet.

DR. POLLOCK: And haven't you found a identified genetic loci for that?

DR. GELERNTER: Well, we only have small samples.

DR. POLLOCK: But also, it's also been validated -- well I won't say validated, but there is some evidence to suggest that, in genetic studies in mice, that there's a similar loci. That's what I'll say.

DR. GELERNTER: So, I think small samples are useful in bringing up ideas, and it's encouraging that something that can be seen, but until we have a large sample and have, you know, hits that are better than just sneaking above 5×10^{-8}, I wouldn't say with any confidence what it's similar from or different to, because you just need more information. And when you're working just at the limit of power, the locus that you happen to discover may not be the most important locus.

DR. POLLOCK: Thank you.

Does anybody else have a comment to that? I think now Ken has a question.

MR. SCODACEK: Yeah. So maybe -- let's see here, "Much attention, discussion here is focused on clinical use. But isn't it possible or likely that insurers or payers, or even law enforcement might use these predictive models to decide what they will pay for, and who to flag for investigation? Couldn't that, or fear of that change clinical practice?

Maybe Bilal, you want to start us off, if you have some thoughts?

MR. MUHSIN: Sure. You know, I think all this data is going to be impactful, be it to clinicians, be it to law enforcement, and in reality, I think we should take advantage of it. You know, coming from industry, I think, the more we have people looking at this data to see what kind of impact it'll have in terms of studies, or encouragement in terms of what we can do in terms of outcomes, I think it'll be powerful.

Now I know it can be abused, and it can be, you know, can take people into different directions, but I think at this point, really the problem is so vast, and the goal is something that we all want to achieve, which is saving these patients' lives. My opinion is, we should expose a lot of this data, be it studied fully or not, and see what kind of impact it can make in terms of saving lives. That's how we look at it from industry, and that's my view on it.

MR. SCODACEK: Thanks.

Keegan, I see you have your hand up.

MR. WICKS: Yeah, thank you. So, I think the short answer is, yes of course. I mean, I think, you know, agencies and outside enterprises and law enforcement and the like will absolutely utilize these tools, whether directly or indirectly. And, you know, I think that that needs to be a consideration of this. And specifically, when we start looking at, you know, what are -- what's the regulations around privacy relating to these tools? I mean, is this something that is going to be protected under HIPAA or is this something that's going to be protected under 42 C.F.R. Part 2? If it's HIPAA, then an individual is very -- you know, it's very possible that their information can be utilized and held against them for using substances.

I also think it's worth kind of noting that when we look at an individual, you know,

kind of what it looks like to have OUD, versus what it looks like to be kind of like chemically dependent on a substance so, you know, anyone can have a physical dependence to opioids, you know, provided time and dose. And so, that is not, kind of, a discussion. I mean, it's just, it's fact. And so I think it's important to consider that just because an individual may not qualify as kind of having OUD, they very well may have factors that are worth really noting and being mindful of, and that should be handled very delicately, really, by experts.

MR. SCODACEK: Travis?

DR. RIEDER: Yeah. I mean, I'll just second the beginning of Keegan's comment especially, like yes, absolutely, of course, this is the way things work, which means that it has to be a part of the development process to think about unintended consequences. You know, it didn't require anything so sophisticated as an algorithm or GWAS studies for guidelines to be adopted by policy makers and medical licensing boards, right.

So, when you have something that has -- sorry, broken record, that has this air of authority about it, like you absolutely better believe that policy makers were being pressured to address the opioid crisis, right, are going to respond in these sorts of ways. So, that's really important to keep in mind.

I think there's a separate point that's clearly related that we should just kind of flag, which is that law enforcement is yet another, and kind of separable component here, that when we talk about law enforcement as sharing information, we talk about policing patients, which is like yes, there are a lot of the same sorts of concerns, but yet more so. So this is a stigmatized and, as of now, criminalized activity or behavior.

And so, the idea of, you know, same datasets being used by healthcare and law

enforcement is even more problematic than all the sorts of considerations we might have just about patients receiving substandard of care if payers refuse to pay or something like that. There's this additional criminalization and stigmatization element. So, really important question. I'll stop there for now.

MR. SCODACEK: Okay, thanks.

Kelly, I see you have your hand up.

DR. CLARK: Yes, thanks. So, just a couple of things. Insurers already use this information. They already run algorithms finding people who are on high morphine milligram equivalents who have multiple prescribers, who are doing early fills, and utilize that information to outreach clinicians and outreach their members. That's already done. And sometimes it's done only when the purchaser of the health plan pays for that service, but this is done pretty routinely right now. So, that predictive analytics with claims data being utilized currently to flag people, that's done.

The issue of, about this criminal justice peace, and then insurance coverage for underwriting purposes, I think gets back to this construct of, prediction is not diagnosis. And there's some, you know, possibility that saying, oh look, you're at high risk for this, therefore you have this, therefore we are going to act in this way, is a real thing that we need to be concerned about, and think about, because of the, you know, the old, what is now the old, you know, saw that like when people fill a naloxone prescription for, so they have it around, for their family members, that they can't get health insurance, because they're flagged as now backwards, having opiate use disorder. And that whole thing goes up backwards.

So, there's a real -- our healthcare system is byzantine. We need to untangle some

threads before we go forward with some things.

MR. SCODACEK: Okay. Laura, I see you have your hand up.

DR. BIERUT: Yes. I also want to bring up this issue, you know, we're worrying a lot about stigma and, you know, the adverse consequences that can happen in psychiatry. But I do not want to pull opiate use disorder out of medicine. It is a medical condition, and I could think of a plethora of medical conditions that are sensitive, HIV, pregnancy, cancer, a variety of things. And I don't want us to treat, for us to be stigmatizing OUD and say oh, it needs to be treated separately.

And we have seen the adverse consequences of that, when our healthcare record was split with opiate -- with substance use disorder being separate from the rest of the medical record. And that was done for, to protect the substance use disorder treatment, but it had that adverse consequence of actually harming our patients. So I want us to be very careful.

MR. SCODACEK: Bilal, did you have a comment as well?

MR. MUHSIN: Yeah. You know, when I was thinking about my first answer, we -- you know, I was looking at first responders, really, in terms of when they ride to a scene, and what does it mean if they knew that the person in front of them has an opioid use disorder. How could that impact the care they're giving them versus from a law enforcement perspective, how would they treat them differently?

I still think it's important. I think, look, when we're looking at these people, and we can get first responders there early, if they have that additional information, it may make an impact in terms of their care, whether it's CPR, the type of CPR they provide to them, whether it's naloxone or any of the other things they can provide at that time. So I still

think it's important, and it needs to be separated from, you know, misusing that information.

MR. SCODACEK: Thanks everyone, for your comments.

Jonathan, do you want to take the next question?

DR. POLLOCK: The next question is about bias. So, empirical studies in machine learning have shown that noise, both class and attribute, in real-world datasets can dramatically lead to decreased classification accuracy and poor prediction results. Plus, the use of non-validated databases for developing clinical classifiers has been shown to be even more challenging. How were you able to overcome the use of non-validated data for both the class and attributes used in your study? And this is directed towards Alex and Joel.

DR. HATOUM: Yeah. So, let's talk about that point really quickly and take a step back for people who are not familiar with the machine learning literature. And this is known as the problem of algorithmic bias, which is really what that paper that I published on the third part of my talk is about, right. And so, algorithmic bias exists, it's when there's patterns in your data that you have, that you did not objectively measure, and therefore they drive the prediction of your model.

And the only way you can know that they're there is if you model the sample appropriately. For example, in genetic data, the largest source of algorithmic bias is ancestry. Okay. Now, in -- so, what I did was I essentially took a coin flip, and random DNA variants, and showed that that there is this non-null deliberation, that you'll get non-zero prediction even when the prediction should be zero, right. And that's an example of algorithmic bias.

It doesn't need to be so complex as oh, your sample isn't validated. In our opiate

use disorder sample study, we actually took people that were all measured on the same exact measure of opioid dependence, and so that helps to reduce some of the bias. But then also we look at things within the context of controlling for ancestry. And so you can actually plot, using those ancestral informative learning curves, that are completely publicly available, the degree to bias that you see in your data.

With things like candidate genes, for example, huge biases. That's why there is not a single person who represents or understands the scientific consensus in GWAS that would agree with using candidate genes to develop one of these tests, right. So, right there -- the other thing is, Obermeyer Zaid has a book called, "The Algorithm Bias Playbook," and he talks about how you have to know what the bias is. So ignoring scientific consensus on things like candidate genes, ignoring GWAS data, that's going to lead you directly towards algorithmic bias.

So, what I'm trying to point out is that in all instances, trusting expert critique, using additional methods, that's how we particularly control for those problems in our data. And that's how we should expect, and how we should hold up companies who are applying these tests to clinical populations.

DR. POLLOCK: All right.

MR. SCODACEK: Does anyone else want to comment on that? I think you mentioned Travis, maybe, Jonathan.

Travis, did you have any comments?

DR. RIEDER: No. No, nothing for me.

MR. SCODACEK: Great.

DR. RIEDER: I mean, bias is bad. That's all you need.

DR. SUMNER: I did want to add a comment to that. And I definitely agree, but I did want to just mention that our other types of mixed data, you know, can certainly be leveraged to boost the power of this genome-wide association studies or, you know, looking at particular steps, and metabolomics, you know, has been used in this way before. And I don't think that we've really talked about combining that mixed data between the GWA and the MWA and even the microbiome data, to try to get this multi mix approach to understand more about narrowing down the important loci. I should -- I guess I'll put it that way.

DR. HATOUM: Right.

And having these, like objective biomarkers, based on biospecimens from individuals who use the drug, don't use the drug, you know, individuals who've never used the drug, and then individuals who are diagnosed as ODU positive, that are diagnosed as OUD negative is a really good way to sort of narrow down these gene candidates with what's happening at that time, metabolically, and not just risk but what's occurring.

MR. SCODACEK: Thanks, Susan. I think we have a follow-up question for you and the rest of the group that'll sort of shift us from concerns about these tests to sort of how to be a little bit more proactive with incorporating patient feedback. So a patient buy-in, how can developers incorporate patient feedback to ensure they develop devices that patients and providers will use?

Laura, go ahead.

DR. BIERUT: So, I'll start with this. I think that was we're developing the tests, I think that the users, which includes potential patients, need to be at the table with us, discussing how they thing it should be used, how the data's presented. Need to do testing

of how individuals interpret the data, because, you know, am I, as a physician, interpreting it one way, but patients are interpreting it another way. So I think that we need this participatory design, with patients at the table, with those of us who are working to develop these tests.

MR. SCODACEK: Thanks, Laura.

Bilal, I see you nodding. Do you have some comments?

MR. MUHSIN: Yeah. I think it's extremely important. Look, I think a solution, whatever it may be, a device or, you know, drug or anything like that, the feedback loop that you get from the people using it is the biggest benefit you actually see, right, as how they're feeling, how they perceived it. That's a way of feeding that loop back, and then improving on what you're doing, right. Because you're trying to have the biggest impact. And the biggest advocate for that is going to be the person that receives that treatment.

And no matter what, you know, anybody says, that's really what's going to deliver the message over and over, so it becomes a very essential part of your design, the development process, in terms of how we create products and solutions out there.

MR. SCODACEK: Travis?

DR. RIEDER: Yeah. I'll just add, so everybody is zeroing in on, you know, nothing about us without us, right. People have to be at the table during these early conversations. So let me just say concretely that one of the best reasons for that is not just representation. It's not just respecting the population, which is super important. It's that they have information that experts don't. They know what it's like to live with use disorder, to be in recovery, to live with chronic pain, to be a chronic opioid therapy patient.

And for those of us who sit at expert roundtables all the time, and we have access to

all this great information, which is really cool, if you've never tried to fill opioid prescriptions at multiple pharmacies because they keep denying you, right, like if you've never had to, you know, find a new doctor to refill your high MME dose because your old one died or retired, and now no one wants to touch you with a 10-foot pole, like that's information that we do not get just from data. It's what it's like to live with these various conditions. So yeah, there's real information, there's real expertise that we miss without these voices at the table.

MR. SCODACEK: Great. Thanks, Travis.

Keegan, did you have some comments too?

MR. WICKS: Just briefly. I think, you know, when we're looking at that kind of, the pool of individuals that we can utilize for this discussion, I really echo what Travis had mentioned here. I think, looking at family members, you know, adults that are at higher risk of OUD, naturally, and so, you know, I think they would be great individuals for discussion around this, or looking at individuals who have lost family members to substance use. You know, there's so much value in even looking at the community-based staff in this field, like peer support specialists, I think, could provide indispensable contributions to this conversation, when individuals are looking at this.

And I also think, you know, one of the often kind of forgotten pieces of any type of development of treatment or tool to provide care is what patients are actually seeking out of, you know, the tools. What are they trying to seek out of treatment? And I think that that's often not asked first. So, Faces and Voices of Recovery, the organization I'm employed by, ASAM and Community Catalyst had put out a report last year that took a look at kind of what patients want most out of SUD care. And the results were kind of, you

know, not very astonishing, in that they wanted to stay alive, to reduce harmful substance use, connection to local services, help meeting their basic needs, assistance with mental health.

And so I think, you know, that this provides an opportunity to look at, okay now, the tools that we're developing, these instruments that we're developing, will they actually help address what patients are actually desiring out of the care they're trying to seek?

MR. SCODACEK: Thanks, Keegan.

Susan, I see you have your hand up.

DR. SUMNER: Yeah. So, I wanted to say that I think, since we do know that the use of illicit drugs results in a metabolic disruption, and we do know that those metabolic disruptions that we see are associated with nutrients. And I think it's really important that individuals that are at risk for OUD development, or their family is at risk for OUD development, that we really have a firm understanding of their nutrition.

And through this may be dietary assessments and understanding of how their nutrition links with those individuals who are at risk, that develop opium use disorder, and those individuals at risk that don't develop opium use disorder could really help us improve treatments to individuals by understanding what their nutrient requirement needs are, that can prevent the acquisition of the addiction or its progression.

MR. SCODACEK: Thanks, Susan.

And Kelly, you want to wrap up our comments on this topic?

DR. CLARK: Yeah. I wanted to go back again to some of those underlying constructs. And what I said earlier was a really different slant on what Keegan just said, which was around thinking of the patients and what are they seeking. Now, I know Keegan's thinking

about, talking about people who are seeking treatment for substance use disorders, for opiate use disorders. And I think much of the panel is talking about people who are seeking treatment for pain, or even other kinds of disorders for which we use opioids, chronic cough, air hunger. You know, there are a variety of things we use opiates for, not just pain.

But, you know, I go back to the, what is the need of that patient that you're serving? What is the need that you're trying to fulfill? What is the need of the clinician that you're trying to meet? Right. So, sort of starting at that, and I think we've talked about, a lot about that de novo needs, or before a clinician starts an opioid, you know, we should always keep in mind that there is an overriding risk factor, for anybody we're prescribing an opioid for, to develop OUD, and that person is a human. They're at risk for OUD if they're a human, and they are taking an opiate.

Okay, so that we want to always keep that in mind, no matter how we think about risk stratification. But beyond the de novo construct, we're also talking about that, predicting the development as people go along and as we're monitoring them for developing what we're really talking about are a large number of risk factors here. So, I would go back to, what is it that you're trying -- that the person wants to know -- the patient. Do they want to know?

And what's a meaningful thing for them to know about their risks for a variety of disorders, and then what's meaningful to a clinician to make clinical decisions. Because again, a lot of what we're talking about with overdose, we're not talking about opiate use disorder. We're not talking about opiate dependence. You know, we're talking about one-time uses, or people with cocaine use disorder that are taking fentanyl-laced cocaine and et cetera. We need to be, again, clear about, what are we aiming for in our discussion.

MR. SCODACEK: Great. Thanks, Kelly.

Jonathan, you want to take the next question?

DR. POLLOCK: Yes. I'll take the next question. How can developers incorporate patient feedback to ensure --

MR. SCODACEK: We got that one already. I think it's the next one.

DR. POLLOCK: Oh, I'm sorry. I'm sorry.

MR. SCODACEK: It's okay. It's a long list.

DR. POLLOCK: It's a long list.

Travis, can you share your thoughts on how to ensure our policy makers have the access to bioethics perspective when considering implementation of risk prediction tools?

DR. RIEDER: They can ask. But, you know, we do this work quite a lot, so my colleagues and I at Johns Hopkins and other bioethics institutes around the country, we sit on consensus panels, we advise policy makers. So we can do that work, kind of at the level of translation to policy, and we do, and it's important and we enjoy it. But the only other thing I would say is that it's much easier to build it in from the beginning, right.

So the conversation that we're having now about predicting problems so that the conversations can happen in industry as technologies are being developed, that can make the translation to policy much easier.

DR. POLLOCK: And the next question was, which do you see providing the bigger impact to solving the crisis, OUD detection or opioid-induced risk, you know, death of overdose, death prevention?

Kelly, Laura?

DR. CLARK: Death prevention. So, what is -- again, I'm going to go to, what is the

crisis you're talking about? Our epidemic is an overdose epidemic. And the way to get to overdose epidemic is not going to be by predicting who's going to be at risk for developing an addictive disease. You know, anybody has a risk of developing an addictive disease, even if somebody is, that have hugely heightened risk of developing an addictive disease. Right. There's more than just who's at risk that is at play in who's going to develop and how do they develop.

So if we're talking about what our overdose, our overdose epidemic, how to get to that, we would need to get to, you know, the overdose prevention. And by which -- I'm not sure what the questioner, if they were looking for, like technologies that are going to be detecting people who are about to undergo overdoses or just in a larger way. But I think, in terms of where we're going in the short and long term, we're in a toddler situation with predictives, analytics and predictive genetics here. And hopefully we're going to be able to do something a lot faster than we would get any of these technologies in an innovative place in the market.

DR. POLLOCK: Next, Bilal.

MR. SCODACEK: What? Sorry.

DR. POLLOCK: Bilal has his hand up.

MR. SCODACEK: Okay. My apologies.

MR. MUHSIN: No problem. I was just going to comment, saying, you know, if we can get industry to focus on it, I think we'll have a lot more solutions, right. And I think what the FDA did with COVID and having the emergency use authorization really kind of ignited industry to do a lot more. And I think we need something like that when we look at the products that are currently out there, what we need in terms of saving lives, that people

that have overdosed and need to kind of be revived, right.

Narcan was one solution that came in, that really helped, you know, post. But what can we do in terms of supporting that and getting ahead of it, right? And I think that's what we should focus on. And if we can, I think it will have a huge impact, from that perspective. And I look to, you know, what the FDA has done with the Opioid Challenge, and this kind of forum with NIH, that really, you know, creates that motivation and vision for industry. And I think it needs to go even further, you know, with CMS, with all of that, to really push industry to innovate here.

And I think, Kelly, we would make an impact. And I think -- I agree. I think there's all the studies and everything that's going on, on that front, but I think if we push industry in this right direction, we will see progress being made.

MR. SCODACEK: Laura.

DR. BIERUT: So, the way that I heard the question was, what do we think about prevention versus, kind of, treatment is kind of how I heard the question. And I think back at what I believe is one of the greatest public health successes of the 20th century, is what happened with smoking. We decreased smoking initiation, and we got people to quit smoking. It was both of those things. And so I think that we need to be working on both of those fronts with opiate use disorder and this opioid crisis that we're having.

MR. SCODACEK: Okay. Kelly, you have some comments to close out this question?

DR. CLARK: Yeah. Just to go back to, you know, both of what things were said, I think smoking is a great example, but there we're going from something that was socially okay, and acceptable, into something that was socially not acceptable and utilizing restrictions around that. So you can't smoke inside here, or near a building or et cetera.

And to do that for opioids would require what we've essentially done for the past 10 years, which is penalize doctors who are prescribing, and patients who are on opioids, et cetera. So I don't think it's going to be a perfect parallel.

But back to Bilal, I am all in favor of industry, but the question here is not around, you know, getting the private sector involved, because I'm very involved in the private sector. The question is around this kind of predictive analytics and predictive genetic type tests, versus looking at things that could be even, that could be industry focused around -- naloxone is rescue medication. It's not treatment, it's just rescue. And the person -- it just, it doesn't save lives. It postpones a death, if that person doesn't get into appropriate treatment. Right. So a way to have an impact on our death rates is going to come way downstream from prevention.

MR. SCODACEK: Thanks, Kelly.

Jonathan, you want to take the next question, or you want me to (indiscernible)?

DR. POLLOCK: I think the next question, we actually talked a little bit about, which is what protections will be implemented to protect chronic pain patients from predictive devices, algorithms and genetics? Shouldn't safeguards be put into place first? Is this a consideration?

MR. SCODACEK: Alex, do you have some comments?

DR. HATOUM: Yeah, I can start. I mean, I think the first consideration should just be, you should recognize that there's scientific consensus on what makes a, like good and poor genetic predictor. And so that should always be like the first standard, right. I think -- and, you know, trust the experts on that because you don't want to be misdiagnosing pain patients because you have a poor test on the market.

I think the other thing that needs to be taken into consideration is the knowledge that minority populations in particular are undertreated with pain and more likely to face discrimination in terms of opioid prescribing. And so, any type of algorithm needs to have particular tests within those populations, and those populations need to be well empowered to ensure that they're not going to be discriminated against.

And a third point on that is that they may face discrimination from a genetic test just do to the fact that their population structure is different. They're more likely to face geographic admixture, and be more misclassified by genetic tests. So specific protections for minority populations need to be put in place and tested for genetic tests in addiction. You can't just say that this works within Europeans and it's not that different within another population. You have to actually measure the population differences in those populations, care about those differences and test them before you can say this test is safe.

Of course there's going to be other things that the panel can talk about, but those are the main points I'd like to focus on from my expert perspective in genetics of addiction.

MR. SCODACEK: And Keegan, did you have some comments? You might have raised your hand during the previous question as well.

MR. WICKS: So, nothing quite pertaining to this, but I would just add, you know, another consideration, kind of briefly, of what happens after the device has been used to predict OUD. And so -- or to predict risk of OUD, I should say. And I think that consideration is one of great value that could be easily lost, as to what types of services, what conversations are had, what is the kind of follow up. And, you know, are we providing treatment prematurely to something that has not yet occurred, or may not occur?

DR. GELERNTER: We also have to consider that chronic pain patients can also be at

risk for opioid use disorder, and it's a medical and ethical question to decide what to do with that information, and if you want to dial back on opioids, even if they might be helpful, or switch more aggressively to another class of medication. But we shouldn't get in the trap of thinking that just because someone has chronic pain, they're not at risk.

MR. SCODACEK: Thanks, Joel.

Let's see, maybe another question. This is for Susan. Someone says, "I would like to know more about metabolomics. Is there information on opioid use disorder in the U.S.?"

DR. SUMNER: Okay. So, we did recently write a review article on metabolomics and drug addiction that I think you'll find, and then have published a couple of papers on using metabolomics to identify metabolic perturbations, pathways perturbations associated with opium use, and opium use disorder. And so, those are accessible. So, it's a really open field of study, though.

And to really be looking at what I'm going to call the internal exposome -- and when I say internal exposome, this would be, we have technology platforms that we can look at metabolites, so post metabolism simultaneous with microbial metabolism, a wide range of environmentally relevant exposures, that we can look at simultaneously with these technologies that I will file under the category of internal exposome, to the extent possible.

We can capture all that. I think it's very important that we're capturing these together, because when we look at an individual, we can see how that genetic profile links with the profiles that we're seeing that are associated with tobacco use simultaneous with alcohol use, simultaneous with drug use. So it gives us more of a, you know, holistic view of what's going on with this person.

And this is also really important because these same simultaneous measures that we

can make are telling us about the patterns of essential nutrients and vitamins, and how some of these may be lower in opium users who actually have reported dietary intakes for total calories that are very similar to non-users. And so why are these lower? So it could be that the drug is interfering with the uptake and transport and metabolism, the absorption of these.

And these actually drive our biochemical profiles. So, and that's what's needed for us to have a healthy metabolism. And an unhealthy metabolism is linked with many of these DSM-5 diagnoses. So yeah. So there's some literature, but there's lots of room for doing these studies, and particularly for linking with the genetics profiles. It's so important.

MR. SCODACEK: Thanks, Susan.

DR. POLLOCK: So, let me comment. So, I can say it's an area of interest to NIDA, and we're very interested in biomarkers that can actually serve as a clinical endpoint for, you know, treatment studies and for interventions. So, I mean, we'd love to see stuff done that might replicate the study that Susan and I were involved in, in a U.S. population.

MR. SCODACEK: Thanks, Jonathan.

I think, if I'm looking the schedule correctly, we have a lunch break now. But I'd like to thank Jonathan, my co-moderator and all of the panelists for joining us today. We do have more questions, but only a finite amount of time, but I appreciate everyone's participation and sharing your expertise with the workshop participants today. Thank you very much.

And I'm not sure if Dr. Cunkelman is coming back to say something before we go to lunch break, or we're just concluding here and they're going to put up a slide. I'm not really sure.

DR. CUNKELMAN: Thank you, Ken.

I just wanted to thank all of our speakers for their wonderful presentations and interactive discussion. We are going to take a 45-minute break for lunch, and we'll convene with Session 2 at 1:45. So we'll see you then.

(Whereupon, at 1:00 p.m., a lunch recess was taken.)

AFTERNOON SESSION

(1:45 p.m.)

DR. CUNKELMAN: Welcome back, everyone. Our second session will focus on devices to predict risk of opioid use disorder, with a focus on the opportunities and challenges of implementation. It's my pleasure to introduce our first speaker, Dr. Keri Donaldson.

Dr. Donaldson is an assistant professor of biochemistry and molecular biology, and an assistant professor of public health sciences. He's also a director of the CLIA laboratory in the Institute of Personalized Medicine and Clinical Processing Specimen Laboratory at the Penn State Hershey College of Medicine. He is the founder and CEO of SOLVD Health. Dr. Donaldson will speak on potential opportunities for integrating predictive devices for opioid use disorder into clinical care paradigms.

Welcome, Dr. Donaldson.

DR. DONALDSON: Good afternoon, and thank you for your attention today. My name is Keri Donaldson. I'm the CEO of SOLVD Health, and a board certified clinical pathologist, specializing in pharmacoepidemiology and genetics.

Today, we will review the limitations of current risk assessment tools, as well as the opportunity to better inform the shared decision of oral opioid prescribing for acute pain by providing genetics-based risk assessment. I'll also briefly describe limitations of these assessments, provide recommendations on best practices on design and development of additional risk assessment tools, and give a real-world example of a genetic risk assessment towards the end of the presentation.

We now know addiction is a chronic disease, best addressed through prevention and

treatment rather than judgment and punishment. However, despite efforts to reduce prescription opioid use, people are still becoming addicted, indicating that additional measures are needed to develop safer prescribing practices. These measures include the use of risk assessments that allow patients and prescribers to understand the risks of developing OUD prior to prescribing. But currently, the available approaches and tools for risk assessment of OUD are limited, as they fail to bring the patient's genetics into the discussion.

Let's start by first describing the current landscape of opioid prescribing. Opioids can be safe and effective for the treatment of pain of some patients. However, it is well known that there is a risk of addiction for all patients, and for some patients, that risk can be higher. The goal therefore, is to identify which patients may be at higher risk of addiction, thereby informing the decision by prescribers on how to safely and effectively prescribe opioids.

Opioids are prescribed to millions of people every year for a variety of indications, with varying dose and duration. Two of the major indications for opioid prescriptions are to treat either acute or chronic pain. The distinction between these two indications is how long the pain is expected to last. For acute pain, it is shorter than 1 month, and for chronic pain, it is greater or equal to 3 months.

The risk of opioid addiction is different from these indications, and therefore the use of risk assessments for each indication must be considered independently. For the purposes of discussions today, we will consider the use of genetic risk assessment in patients who are taking oral opioid for the first time to treat acute pain. The specific patient population in the study of the genetics is where I have focused my work.

For these patients, the opportunity for effective risk assessment is significant, as it is important to understand the risk, including an individual's genetic risk, prior to being exposed to opioids for the first time. Additionally, the CDC recommends minimizing or eliminating opioids for this indication, recognizing that opioid alternatives are effective for frontline pain management. Combined, these factors create a significant opportunity.

To better understand where this opportunity lies, we performed a study interviewing 165 prescribers. This work showed that more than 90% of primary care physicians and surgeons are currently using forms of risk assessment prior to prescribing opioids. These risk assessments include patient interviews, review of medical record, evaluation of PDMPs, as well as risk questionnaires.

Prior to elective surgeries, roughly 80% of surgeons are assessing addiction risk so that they can develop an individualized post-surgical pain management plan, that is both safe and effective for their patients. What we also know is that prescribers are looking for better tools. In fact, almost half of surgeons in this study stated that current risk assessment tools that they have in use, such as risk assessment questionnaires, are not working effectively, and are quite simply not enough.

Here you can see the performance of various risk questionnaires currently in use by prescribers today. Our research shows that approximately 40% of surgeons and primary care physicians are using these tools. As you can see that some of these tools are specific, but not sensitive, and some of the tools are sensitive, but not specific, limiting the diagnostic utility.

Also on this slide, I am showing the performance of a genetic risk assessment, highlighting the opportunity of incorporating genetic information into the clinical care

workflow. To illustrate this in a different way, shown here are the diagnostic odds ratios for a genetic risk assessment tool, versus commonly used risk assessment questionnaires. As you can see, this genetic risk assessment tool compares very favorably.

So why are the current tools not working? Patient interviews and medical history reviews are subjective, and non-standardized. They are best at identifying patients with a history of abuse, not preventing addiction from occurring. The critical limitation of all the existing tools is that they are only considering approximately half of the problem. We know that genes may account for up to 50% of a person's risk for addiction. Gender, ethnicity and the presence of other mental health disorders may also influence risk for drug abuse and addiction.

A person's environment includes many different influences, from family, from friends, to socioeconomic status and general quality of life. In addition, genetics and environmental factors interact with each other, at critical development stages in a person's life, which may affect their addiction risk. Being able to provide information on an individual's genetic risk would be a significant addition to the tools clinicians have to understand an individual patient's overall risk of addiction, and ensure that pain treatment is effective and as safe as possible.

Here's an example of a clinical workflow, including the addition of a genetic risk assessment in the current clinical care paradigm. The additional information can then be included with the provider's overall assessment, including clinical evaluation, and discussed with the patient during their shared decision-making process of defining a personalized pain management treatment plan.

The workflow is not new, and is not different from the workflow for making

decisions about prescribing things like warfarin and clopidogrel after pharmacogenomic or PGx testing. Genetic information is brought into the decision-making process at the time where a prescriber is considering a medication. Based on all clinical and genetic information, the prescriber and patient can decide what treatment is most safe and effective for the individual.

If a risk assessment comes with a low-risk result, the provider will still follow the current standard of care guidelines for acute pain. If a risk assessment comes back with a high-risk result, the provider and patient discuss a personalized pain management plan to either minimize or avoid the use of opioids by choosing alternative pain relief treatments.

To be certain, the addition of genetic information in making prescribing decisions is not about withholding care to a portion of the patient population. It is about a patient and provider using all available information to make a shared and informed decision about what medication is most appropriate.

Next, let's discuss developing genetic risk assessment classifiers for clinical use. It is critical to follow best practices in order to avoid missing signals, or identifying signals that do not appropriately classify the disease. Commonly, the first step in risk assessment development is to throw the proverbial kitchen sink at it, both from a dataset perspective -- bigger is not always better -- and from an analytical approach. All methods have limitations.

As highlighted above, here are some common errors to consider prior to developing a risk assessment. First, is there selection bias in your population? Subjects in aggregate datasets may have significant biases, subject recruitment or demographics, making generalizability to the intended use population challenging.

Second, how is the outcome of interest, OUD in this case, validated against an independently derived clinical truth in your datasets? Diagnostic reliability of outcomes in many datasets are not externally validated. Commonly, these datasets contain results from interview instruments with varying interrater reliability for qualitative items, like diseases, commonly referred to as Cohen's kappa statistics. It is important to note that interrater kappa statistics describe a quantitative measure of reliability for two raters within the same study, using a survey instrument. It does not establish the external validity of the measure or disease.

Thirdly, how are the data being used as covariates in the modeling generated? Datasets may also contain unrealized assumptions on covariates. For example, from a genetic perspective, aggregate research databases often use imputed SNPs for data modeling, which is not accurate enough to develop or validate a clinical risk assessment tool.

Lastly, you should ask, what type of modeling is appropriate, given the dataset? Limitations in datasets commonly affect the choice of appropriate modeling approaches. Each approach has numerous considerations. Not surprising, especially in the setting of complex diseases like OUD, these pitfalls often lead to the introduction of bias and confounding. They may also create significant noise in the data, preventing the researcher from identifying a signal that isn't present. It is important to remember that in this setting, the absence of evidence is not the evidence of absence, when in fact, what may be occurring is a failure to understand the limitations of aggregate datasets and modeling.

In summary, not recognizing these pitfalls of classifier development and correcting for them can lead to inaccurate conclusions. It is critical, therefore, to validate a classifier

once it's been developed. The best practice is to conduct a blinded prospective study, with a prespecified statistical analysis plan, to evaluate for differences in performance by multiple subgroups. Let me show you an example.

Research tells us that racial and ethnic disparities in pain treatment are not intentional misdeeds. Healthcare providers do not decide that some groups deserve pain relief while others should suffer. Instead, inequities are the product of complex influences, including implicit bias that care providers don't even know they have. Inadequate treatment of pain because of a patient's race, ethnicity, gender or any other characteristic is simply not acceptable.

A genetic classifier has the potential to impact clinical care and decisions. Such classifiers must be developed with eyes wide open, to ensure that we adequately address any potential bias or confounding, especially from race, ethnicity and ancestry. To evaluate if our classifier is biased, or confounded by race, ethnicity and ancestry, we did the following.

First, we ensured that we had a racially and ethnically diverse population in our development datasets. It should be noted that enrichment may be needed in appropriate certain stages in classifier development.

Second, we assessed the possible confounding by ancestry, European, African and Asian, by performing an in silico analysis of global aggregated datasets. Although these datasets have significant limitations, the results show no meaningful ability to distinguish a population based upon ancestry.

And finally, to determine generalizability, we ran a prospective blinded clinical trial. We enrolled a study population that mirrors the intended use population of patients being

prescribed oral opioids in the U.S. We had a defined disease outcome, DSM-5 OUD, and a defined exposure of prescription oral opioids for between 4 and 30 days. Let's take a look at the race and ethnicity results more closely.

Here you can see that there is no statistical significant difference in sensitivity and specificity across race and ethnicity in our clinical study data. Seeing no statistically significant differences across race and ethnicity was also important, given the diverse nature of the U.S. population and our mindfulness around the potential for performance differences in race and ethnicity, which may lead to inadvertently increasing healthcare disparity.

With that background on development in mind, now let's look at the challenges and opportunities of implementing a risk assessment tool for OUD and the clinical care paradigm. All too often, there is a stigma associated with OUD, and more broadly, with many mental health disorders. The negative perception that comes with an OUD diagnosis, that it is a moral failing instead of a chronic disease, contributes to, at least in part, disparity in treating pain.

Implementing a standardized risk assessment may help reduce the stigma, by defining OUD as a chronic disease, not a moral failing. The challenge posed by this negative stigma is also a major opportunity for implementing a genetic risk assessment in the shared decision-making pathway of prescribing oral opioids for treating nonemergent acute pain. As I stated earlier, in this setting, guidelines already specify that risk assessment should occur prior to prescription, and that alternatives exist that have been shown to be as effective as opioids.

Providing additional information on genetic risk in this setting can facilitate a more

comprehensive discussion between the provider and the patient, to choose the best pain management treatment strategy. The standardization of education and training is also an important part of implementation into a clinical care setting. Prescribers need to be provided with materials that explicitly state the appropriate use of the risk assessment device, and how to clearly interpret the results.

In regard to access, the implementation of an objective risk assessment device would allow the opportunity for the manufacturer to collaborate with government insurers, which would increase access for everyone who could benefit from the test across the U.S. Another opportunity is when it comes to cost savings. When implementing a standardized risk assessment device for OUD with sensitivity and specificity of approximately 80%, one study has shown that when deployed into clinical care, genetic risk assessment for OUD is a dominant healthcare strategy.

In other words, when the test is run prior to prescribing oral opioids and the information from the test is used to determine the appropriate prescribing, in this case, specifically whether or not opioids should be minimized or eliminated for high-risk patients, costs are reduced and the quality of life of patients is increased. Conceptually, when the test is used to identify patients at higher genetic risk, opioids are prescribed more carefully, thereby reducing or eliminating opioid addiction.

The healthcare costs associated with that patient's addiction are then eliminated, and the patient has an improved quality of life. It is also important to remember that critical to cost effectiveness, is that prescribers are using the results of the genetic information to alter their pain management. If a test is run, which has associated cost, and the high-risk test results are disregarded, the test may not be cost effective. For this

reason, it is important not only to educate prescribers about the value of the test, but also to implement the test in a standardized way.

To summarize what I've presented today, we know that current workflows already include prescribers using risk assessment tools to evaluate a patient's risk of developing OUD, but those tools are missing the genetic component. Having this information provides a significant addition to the tools clinicians have, to understand an individual patient's risk, and to ensure their pain treatment is as effective and safe as possible.

It also facilitates the shared decision making about acute pain management between the patient and the prescriber, by giving them an objective piece of information to discuss. It can also help reduce bias and stigma by viewing OUD as a chronic disease instead of a moral failing, and ensure that all patients are assessed using the same tools. Genetic risk assessments prior to prescribing opioids for pain allow for a standardized and scalable approach to help providers make the most knowledgeable decisions when it comes to pain management by providing an additional tool.

Thank you for the opportunity to discuss, and I look forward to the panel discussion.

DR. CUNKELMAN: Thank you, Dr. Donaldson.

I'd now like to welcome back Dr. Laura Bierut, who will speak on challenges and other considerations associated with use of devices that predict risk of opioid use disorder development.

Dr. Bierut.

DR. BIERUT: My name is Laura Bierut, and I'm the Alumni Endowed Professor of Psychiatry at Washington University in St. Louis. I will talk about challenges and other considerations associated with devices that predict risk of opioid use disorder development.

I want to touch on five issues. First, what are factors that push and pull innovation, development and the implementation of tests and devices into are? Secondly, how can we speed translation of findings by working on discovery in pre-implementation issues at the same time? Next, how could we anticipate unintended consequences with the use of tests, and mitigate these risks? Next, how do we reduce the disparities that will occur with the introduction of any new test or device? And finally, I want to challenge us to remove the exceptionalism associated with mental illnesses and opioid use disorder in particular.

There is a push and pull for innovation and implementation. Innovation can be thought of as our efforts to develop a new test or novel intervention. In our current context, innovation is the development of this new test that predicts the risk of opioid use disorder development. Implementation is the phase once an intervention exists. It is how fast is the translation into clinical care.

The push and pull of innovation and implementation can be modeled as a function of four characteristics. The first characteristic is evidence, the evidence of clinical validity and the potential utility of the intervention. A high degree of evidence supporting an intervention will speed innovation and implementation.

The second characteristic is the demand for the intervention. How many people will potentially use this intervention? How much do people want this intervention? And will individuals use this intervention? A low demand slows innovation and implementation, whereas a high demand speeds the process.

Then there is the risk of the intervention. A low-risk intervention is more likely to be incorporated quickly into clinical care. However, as the risk of an intervention increases, there is a slowing of development, innovation and implementation. Finally, cost is a factor.

Low cost of an intervention will speed the translation into care, whereas a high cost will slow this process.

So what do I think about a genetic test for the risk of opioid use disorder development? Well, evidence exists for genetic variants increasing the risk for the development of opioid use disorder, and this evidence is only growing. The demand is relatively high. People are interested in genetics, and there's a strong, direct-to-consumer genetic testing environment now, with companies such as 23 and Me.

People are interested in their ancestry, and individuals want to know their genetic risk for diseases. We're all aware also of the public health emergency surrounding opioid use disorder, with over 100,000 deaths per year from drug overdoses. Finally, the risk and the costs are more difficult to determine. Nonetheless, I see genetic testing for the risk of opioid use disorder development coming into clinical care sooner, rather than later.

The next issue to review is the speed of the translation of knowledge into action. Currently, there is a wide gap between what we know and what we do, in medicine. This lag in translating knowledge into clinical care is an implementation gap, and this gap is estimated to be 17 years long. It is critically important for us to shorten this gap, and accelerate the translation of findings from the point of discovery into clinical care.

So how could we reduce this gap? We need to realign our science to speed translation. Historically, we've worked in series, where we link discovery, then to implementation. We wait until our discoveries are finalized, and only then do we begin work on implementation. One effort to speed the translation of findings into clinical care is to work in parallel. As we increase discoveries and clinical validity, we can begin pre-implementation work. We need to start with our basic science, and keep our eye on

dissemination and implementation at the same time.

The next issue to consider are the unintended consequences associated with a new test. The final steps of bringing a test into care examine clinical utility and ethical and social issues. We hope that a test will have clinical utility and allow healthcare providers to better assess, treat and monitor patients. In addition, we hope that the patients will improve their own care, their own health, and modify their own risk factors. Yet, there are likely to be unintended consequences of introducing a new test.

Let's focus again on the specific test under consideration, a genetic test that predicts the risk of developing opioid use disorder. What are the potential unintended consequences? Healthcare providers may be reluctant to prescribe opioids to someone at high risk and withhold acute treatment of pain. Conversely, healthcare providers may not monitor those at normal risk as closely as needed, and there may then be the risk for increased risk for developing opioid use disorder.

Similarly, patients identified as high risk may avoid opioids and experience unnecessary pain. More worrisome is that patients identified at normal risk may see this test as a health certificate, and inappropriately believe that they are immune from the development of opioid use disorder. We can hypothesize a plethora of other issues with the implementation of genetic testing for opioid use disorder. And our efforts need to be addressed at how to mitigate these potential risks.

Next, let's consider disparities. Every time a new technology is introduced, there is an increase in disparities. For example, we saw this with the development of the COVID vaccine. Those with more resources get the intervention earlier, and those with fewer resources obtain the intervention later or not at all. We should not be surprised that

genetic testing will increase disparities. The ethical and social issue that must be addressed head on is the potential for increasing healthcare disparities by ancestry. The vast majority of genetic testing findings have been identified in populations of European ancestry.

Even if the genetic testing reaches all groups, and all ancestries, the intervention may not work as well in these different ancestries. We need to increase diversity in genetic studies, but this effort will take a long time. In the meantime, we must focus analytic methods to address this issue of differences in genetic architecture between ancestral groups, to improve the validity of this test across all populations.

Finally, we must take care not to marginalize a test that predicts the risk of developing opioid use disorder. All the challenges that I have raised are general, for any test. I am not a believer in the exceptionalism of mental illnesses and opioid use disorders. Mental illnesses and opioid use disorders are part of medicine. When I have seen concerns raised at systems levels, regarding the exceptionalism of addiction, and then features are put into place to give, quote, "added protection," unquote, these protections have often led to increased marginalization, and reduced treatment for substance use disorder.

So I want us to consider carefully our concerns about a test for opioid use disorder development. I want us to think that, are we concerned because this is a test for opioid use disorder, or are we concerned about the general features associated with any genetic test? Importantly, we can argue that it is unethical to bring a test into clinical care before it is ready. But we can also argue that it is unethical to delay the incorporation of a test into clinical care.

So in summary, I am convinced that genetic risk testing for the development of opioid use disorder is coming, and it is coming sooner than later. Our efforts need to be

focused on how can we safely speed this innovation, how can we mitigate potential risks? Can we put efforts into place to reduce the potential widening of disparities? And finally, let us not continue the stigma associated with opioid use disorder, and move forward with this genetic testing in a safe and effective manner. Thank you.

DR. CUNKELMAN: Thank you, Dr. Bierut.

For our next question and answer session, I'd like to welcome Dr. Courtney Lias, who currently serves as the Director of FDA's Office of Gastro-Renal, OB/GYN, General Hospital and Urology Devices in the Center for Devices and Radiological Health. She joins Dr. Pollack as co-moderator. Our discussants will be Drs. Donaldson and Beirut.

DR. LIAS: Thank you, Jacquie.

Hi, everyone. I've been really enjoying the talks today. These topics of innovation and health disparity are really near and dear to our hearts here at FDA, and I know that's true at NIH as well.

I'm going to start off with the first question for our two speakers. So, there are risk predictors, diagnostic tests, genetic tests used to predict risks in other areas of medicine, including oncology for example. Given the many unique characteristics of opioid use disorder, which is a chronic condition, can you share your perspectives on whether we would consider this condition differently than other conditions?

I know, Laura, you touched on this a little bit. Should we use risk assessment information about OUD differently when a test is developed, or when tests like this are developed in the future, than we would for our other types of risk prediction tests for other types of conditions? Maybe start with you, Laura, since you touched on this a little.

DR. BIERUT: So, I am a believer that we should be thinking about these genetic tests

the same way that we think about them across medicine. One aspect that is different with opioid use disorder is you have to use an opioid to develop opioid use disorder. But other than that, I think we should be thinking about the same types of standards, the same types of stigma associated, the same type of concerns about family members, policy issue. And, you know, I think that really, OUD is a health problem, a medical problem and, you know, it is sensitive, like all healthcare is sensitive.

DR. LIAS: Thank you very much.

Keri, I'd like to hear your perspective.

DR. DONALDSON: I would agree with Dr. Bierut. I mean, overall I view opioid use disorder as a chronic disease. And I think, as we start to understand and change the perspective of opioid use disorder from what, maybe historically, was thought of as a moral choice or a failing, to a chronic disease, one step in the right direction is to start to put it on the same playing field, in particular from a genetic risk prediction, as some of the other areas that historically have seen risk predictors developed for it. So I would agree with Dr. Bierut in that regard.

I also agree with her comment. And I think it's an opioid, probably more so than a challenge, in this particular space, and that you know, at least in part, what can drive a patient to develop OUD, where in certain other settings, that's not the case. But here, we do know that, for some, if they don't get exposed, they don't develop the disease. And I think that's something else that really leans in towards the benefit of thinking of this as a chronic disease where we know clearly what a portion of the exposure is, versus some of those other diseases.

DR. LIAS: Thank you very much. We'll throw this over to Jonathan.

DR. BIERUT: You're muted.

DR. POLLOCK: Consistently, throughout the morning panel discussion, it was discussed that large datasets are always better than small datasets, and genome-wide data should be used when trying to build a device that has clinical value. Is that true?

DR. DONALDSON: Can I start this one, Dr. Bierut? Because I did mention in my talk, and it's something that we found. You know, we've been developing this device for over a decade. Okay. And we've looked at large datasets. And, you know, I think there is value in them, but one of the things that I mentioned is that you have to be really cognizant of both validating the dataset for the exposures, in this case, as Laura just mentioned, we're talking about people that took oral opioids for a defined amount of time, really honing in on what disease you're trying to study.

And we heard this numerous times this morning as well, from Dr. Clark and others. And you also have to make sure that the data that you're looking for is appropriately ascribed in your datasets. All too often in these large datasets there is significant heterogeneity between the groups, in particular in meta grouping. So when you take different studies and put them together, there is significant heterogeneity in the group.

The other thing is that there can be unrealized bias, or challenges. And I know we talked about one of the largest studies that's available for opioid use disorder groups, the GWAS and Million Veterans Program this morning. And I'll just use that as one example, right. So, folks this morning were talking about this program, and they're much more experts in it than I am. But they said that it could be described as, you know, consisting of old sick men, right. That's not good enough, just on a superficial level.

When you're talking about genomic effects and diseases like this, you can't bias the

study population to old sick men, first level. Peel back the next level, when you're using aggregate datasets. It's important to know that the disease is what you're actually trying to model. Here, specifically, the genetic use test that we're talking about is conditioned on acute pain, short duration oral opioids for 4 to 30 days, and an opioid-naïve population. That's really specific, right.

So if you're trying to look for genomic signatures, it's important that you understand that, as opposed to large GWAS datasets that may not capture exposures consistently. They may include very different populations like acute and chronic pain. Lump them together and that decreases the ability to distinguish or create, even within restrictions of old, sick men, of predictive classifiers.

Third set, still in the same dataset, OUD is not the same thing as opioid dependence. That dataset, to my knowledge, is talking about opioid dependence. Dr. Clark, rightfully so, said this morning, opioid use disorder, or DSM-5 opioid use disorder, how we diagnose opioid use disorder now is not the same thing as opioid dependence. So that's a challenge.

Next level, same dataset, opioid dependence within that dataset, and this will be maybe my last one, within that particular dataset, is only right somewhere in the neighborhood of 60 to 90% of the time. So that's a kappa Cohen statistics on how they measured opioid dependency within that dataset. So if you're trying to figure out how genetics correlate to disease, you should really look at validated datasets that discretely capture the exposure, that discretely define the disease, and that are validated to some external measure.

Because if you don't do that, there is significant limitations in the ability to define modeling, in particular machine learning. So I appreciate the question.

DR. POLLOCK: Laura, you want to follow up?

DR. BIERUT: I'll follow up with, I love data. I love as much data as possible. And I like to see convergence of findings across datasets. So what I do know is that it's been the large genetic datasets that have really led us to discovery.

DR. LIAS: Thank you very much.

DR. POLLOCK: And I have a follow-up question, please.

DR. LIAS: Oh sure, go ahead.

DR. POLLOCK: Dr. Donaldson, I understand that your machine learning approach uses a Bayesian approach whereas the approach used that Joel Gelernter presented, and a lot of the GWAS is basically a frequency approach. And, you know, it's what Fisher uses. Can you comment on why you might get different results from, with GWAS. And there also seems to be some convergence of your results, I think, at least for the μ-opioid receptor, with the GWAS. Could you just comment on that?

DR. DONALDSON: I can, at least to the best of my ability. So, I am not a classical, statistical geneticist. But as you state, there are differences in the approach between, in particular, in large amounts of data, you know, 300,000, a million different targets and how you assess whether there's relevance of those particular targets of association with disease. That's done, at least to the best of my knowledge, in some of these GWAS datasets, by modeling the set's p-values, that looks for individual affect sizes, that have to be fairly large, before you pull out a gene or a target in a GWAS approach.

And I agree with Dr. Bierut, in particular in certain diseases where there's a large association between that particular gene or SNP and a disease, these things have been incredibly informative or important. When you start to decrease the effect size, this

classical, statistical or linear approach tends to fall out. And the real question is, how do you go from large SNPs or genomic data down to small, more meaningful groups of data, and what is the differences of those approaches?

And in machine learning, there's any number of different ways to do this. You know, we did not follow a candidate gene approach. That's, it's a misinterpretation of dimensionality reduction in machine learning. But you start with a large amount of data, and Bayesian preconditional probability is one of those approaches that are incorporated in decreasing the dimensionality of the data in our approach to eventually identify the 15 genes.

So, the question that you're asking is, are there differences in between a classical, statistical approach that are normally followed in GWAS data, that then people say confirmed targets in GWAS data, versus, you know, combinatorial approaches that allow you to dimensionally reduce the total dataset in machine learning? Yes. Number one. Number two is, you know, is one better or worse?

I would say that over time, there's consensus that for effects modeling where you don't have a very strong association between single SNPs or genes, and outcomes, GWAS data, in particular has shown to be limited. And I think -- and that statistical approach is limited. The Bayesian preconditional probabilistic approach has shown increased utility, in particular when it's combined holistically with machine learning.

DR. POLLOCK: Thanks.

Courtney?

DR. LIAS: This next question is for you, Laura. We have just heard some discussion about some of the datasets behind these things. And I'd like to really hear your perspective

on the differences between maybe, as people are developing these types of tests, a test intended for the acute pain population versus tests intended for the chronic pain population. It'll be interesting to hear your perspectives on certain considerations for developing or finding those types of datasets, and any differences in the clinical need, or clinical risk across those two intended uses.

DR. BIERUT: So I'll -- there's a lot to that question, and let me talk first about this, kind of, potential for clinical need with this. So, the acute pain, I think is actually a very difficult issue to deal with, with these tests. I think it's difficult to deal with, you know, if we think that, you know, if someone comes in with a broken bone, someone comes in with a gunshot wound, someone comes in with something, you know, very acute, we really are not going to have time to do this genetic testing. And we're going to need to rely on just clinical judgment, moving forward.

And really, it's the most ethical thing for us to do, is to treat pain, in an acute setting. You could think of some settings where the acute pain may be more predicted. For instance, if a young person is going to have their wisdom teeth removed, you know, that is generally a scheduled event. You know when it is. So, at that point you would have a better idea of, you know, how to go forward with this acute pain.

So, there's going to be benefits and drawbacks with it. I think that this risk is going to be there, whether it's acute pain or chronic pain. Chronic pain really is another, you know, fascinating issue also. So you -- with chronic pain, you are going to have time to do this testing. But, you know, the treatment of opioids for chronic pain is also somewhat controversial, thinking about, you know, are opioids necessarily the best way forward for chronic pain, and what is the evidence, you know, scientific evidence that chronic pain

works on a population in general?

So, I think if this test comes in, I think that just knowing medicine, as a physician, I think the test is going to leak all over the place, and be applied at multiple steps, going from initiation to established use, and to people with opioid use disorder, just because that's generally what happens, as people see some use in one place and move it into the other.

DR. LIAS: Thank you.

DR. POLLOCK: So the next question is, in a prior -- Session 1, ethical considerations of OUD prediction presentation by Dr. Rieder, you mentioned significant ethical considerations to be evaluated before a device should be marketed. Can you share your thoughts on what key ethical considerations for a device, you know, in terms of developing a device, should be considered?

DR. DONALDSON: Who do you want to start with?

DR. LIAS: Keri, you get to go first.

DR. DONALDSON: Sure. I'll take this one. So, you know, it's interesting, and I appreciate Dr. Rieder's comments, and I think that one of his comments was, start early, in terms of your ethical considerations, and I would add to that comment, often. So it's voting day today, right. So, we start early with our ethical considerations. In fact, we -- as part of the design of this test, we had an independent group, based out of Stanford, review almost, I would argue, every aspect, or at least from their perspective, every aspect of how this test could inform caregiver decisions, how it could change perceptions, how it could go through and impact the patient.

Dr. Bierut just mentioned family members. Again, that's something that people may not consider when they're thinking about a genetic test, but I would argue, you have to

think how these tests are interpreted. So we started that process extremely early. I believe it was 3 to 5 months of going back and forth and trying to figure out how to define this test in a way in which it sort of enhances or maximizes the risk-benefit of how these types of tests go to market. It's incredibly important to do that, as a first-in-class device, and really spend time doing it.

So that's how we started, right. I said it's often, right. So we've continually gone through that process with some of the folks at the FDA. There was a panel member, or a panel on this a few weeks ago, where we've learned even more about how this test can be interpreted. And I don't think we're ever done, right. So, the next portion of it, that you heard multiple times this morning, is once a test gets into practice, you have to be very purposeful, and thoughtful about how it's used.

And one of the things that we've proposed with this particular test is focusing on a controlled rollout, where we can engage a defined set of providers in making sure that the information is understood, and understanding how that information is used in terms of clinical decision making. And that can better inform and minimize some of the misinterpretations Dr. Bierut was talking about, minimizing the risk associated with the test.

This is a very purposeful, continual process to not only take in the ethical considerations from the very beginning, but hone them over time, and then monitor them, to make sure it's done the right way. And I think it's incredibly critical to do that with this test. And it's in line with a few of the things that Travis was talking about this morning.

DR. LIAS: Thank you very much. That ends the time for this part of our Q&A session. We really want to thank Keri Donaldson and Laura Bierut for very intriguing thoughts and an engaging Q&A session.

DR. CUNKELMAN: Thank you, Drs. Donaldson and Bierut, and thank you to our co-moderators.

We're going to take a 15-minute break, and we'll see you shortly.

(Off the record from 2:31 p.m. to 2:45 p.m.)

DR. CUNKELMAN: Welcome back, everyone. For this afternoon's panel discussion, I'd like to welcome back Drs. Donaldson, Bierut, Rieder, and Mr. Wicks. I'd also like to welcome and introduce four additional members to the panel, Kathy Sapp, the CEO of the American Chronic Pain Association and cofounder of Patient Mind Inc., Kirsten Tulia, Vice President in the Payment and Healthcare Delivery Policy Department at AdvaMed, Jessica Hulsey, founder and Executive Director of the Addiction Policy Forum, and Dan Jacobson, a computational systems biologist with Oak Ridge National Laboratory.

Drs. Lias and Pollock will rejoin us as co-moderators. Please begin.

DR. LIAS: Thank you very much, Jacquie. We're excited to have this new session.

As you all know, the focus of today's conversation is really about innovation. How do we promote the availability of new types of tools for clinicians and patients and their families to use to understand the risks of opioid use disorder and related conditions. And, you know, we've been talking a lot today about datasets, and the datasets people have, and the pros and cons of different datasets. But I think probably everyone would all agree that we would love to have access to additional ways of getting information.

It's forums like this where we can really try to work together and figure out ways, as a community, we can improve our ability to have access to creating or accessing new datasets that people can use to create and validate tools like this.

So, I'd like to hear some perspectives on how, as a community, with different

perspectives, different access, different information at hand and different expertise, we can work together to encourage the development and/or availability of datasets that can be used in the development and validation of new risk predictors for OUD. Perhaps let's hear from a couple of our new members here.

Daniel, would you like to weigh in?

DR. JACOBSON: Sure. I think --

DR. LIAS: You may want to turn on your video.

DR. JACOBSON: First, one of the challenges and --

(GPS instructions.)

DR. JACOBSON: Sorry about that. Flights were cancelled, so I'm driving right now. So, one of the challenges people have mentioned are that the heterogeneous nature of these architectures. And so that's, as a key concern, is measuring enough of the right populations to capture the architectures to sort of prevent false senses of security, and also the realization that these disease states are not all genetic and not all necessarily just environmental response, and all the other omics matter.

And certainly when we look at the combination of genetics and omics together, we find key in some (indiscernible) --

DR. LIAS: So Daniel, we're not having a good connection with your phone right now. So maybe we can come back to you. Thank you for -- well we did hear some of your answer. We really appreciate it.

DR. JACOBSON: That'd be fine.

DR. LIAS: Jessica, we'd like to hear your perspective on this.

MS. HULSEY: Sure. So, Jessica Hulsey with the Addiction Policy Forum, so we

represent patients and families struggling with all SUD. I'm an impacted family member, so I bring that perspective to the table.

I think, in terms of risk predictors, we think of this a little bit more globally, and not just OUD, because it's hard to look at any particular substance use disorder in a vacuum. We know that many of the patients -- and the other key thing to focus on is, there's such a tremendous difference between having an opioid use disorder and opioid dependence, after an opioid prescription.

And I think, for a lot of our patients that we work with, who do struggle with OUD, a lot of times there's a slow burning substance use disorder. It could be an alcohol use disorder, or a cannabis use disorder. And the opioid that is prescribed is the accelerant that's added to the fire. So I think understanding how other SUDs, whether they're a full-blown addiction, so severe, or if a patient has a mild or moderate substance use disorder, I think is one of the most important risk factors to consider.

We've mapped the patient journey, and not just the journey through treatment and recovery, but also understanding onset and progression. And some of the findings from our work is that the age of initiation, so when someone had started using any substance, and most adolescents begin substance use with alcohol, nicotine or marijuana, but that age of initiation is so critically important to long-term risk.

It also can signal if there's -- and a way of looking at this as a developmental disorder, if there have been patterns of substance use that enter that -- not physical dependence, but the psychological and social components, that really make up that biopsychosocial framework of looking at a chronic disease.

So, in terms of risk predictors, I think our input would be yes, genetic predisposition

is so important to know. We don't do a good job of the health literacy component, so patients understand that having a history of addiction in your family, like I do, is a risk factor. And it's not just a risk factor for opioid prescribing, it's a risk factor for all substance use. So we might have to be more careful, or have different behaviors that we exhibit, and choices that we make.

I think age of initiation, other co-occurring mental health disorders, adverse childhood events and trauma that we've experienced. And then, like I mentioned, understanding. I know that Dr. Clark talked about this earlier, but one of the best tools to really understand in that OUD framework, if you're really focusing on opioid prescribing, is to rely, and use those 11 criteria in the DSM-5.

The education that takes place and the opportunity for early intervention, not just preventing an opioid use disorder, but preventing the escalation for any SUD. When you really walk through the criteria for developing a substance use disorder, when we go through patients and explain that if you've developed a tolerance, you're having a hard time quitting this alcohol use or marijuana use, even though you've tried, and that they're -- you're using, despite consequences in your life, whether that's a relationship or something happening at school and work, those are 3 of the 11 criteria.

So if I check yes on those, then I would have a mild substance use disorder, whatever that substance is. That's going to make me even more at risk for that opioid prescription. And I also think, just to put a -- I'm going to put this maybe -- I don't know if we'll call it a plea, but a recommendation, that as we're looking at all these devices, or assessments or new innovations to detect or predict opioid use disorder, that I don't think it's a win if we predict OUD, and yet that patient still struggles with other SUDs, because we don't look at a

whole patient framework.

So I'm hoping that as more of these innovative solutions come together, that a whole patient, a patient-centered approach means that the avoidance of an OUD, when I develop still an alcohol use disorder, or a stimulant use disorder, particularly with adulterants that are so (indiscernible), and maybe I still have an overdose, and will come in contact with opioids. I think that patient-centered focus, and that assessments being for a big-picture reduction of risk and overall health and wellness, is a really important way or framework to look at this.

DR. LIAS: Yeah. No, I think that that's really important. The patient perspective on this is super critical. I think you've really highlighted some of the complexity, and the heterogeneity in some of these patients and disorders.

I wonder, Laura, if you could weigh in on how that impacts our ability to collect datasets that might be used to develop new tools in this area.

DR. BIERUT: Right. You know, when I think of the new datasets, you know, the best data in this area, what we really are thinking about is not only datasets that have a person's characteristics, you know, how old they are, how old they are when they started first using a substance. Did they start smoking, using alcohol, marijuana, other substances? And then marijuana use, but we also have to have the genetic data embedded in these datasets.

And the wonderful thing now is these datasets are now coming to maturity. In the U.K., they have UK Biobank, which is a large dataset with over 500,000 people. It is the U.K., but they're connected with the electronic health record. We have the Million Veteran Program, that Joe Gelernter talked about, which does skew very heavily for men, but nonetheless is a very valuable dataset that has led to a lot of discovery. And, you know, in

the United States we're developing the All of Us program, which is another large-scale, you know, genetic database that will have a million Americans in it.

So, you know, these databases exist with genetic data. We also have electronic medical record data in the hundreds of thousands and millions of participants. So, we can -- I think we need to start developing tools to mine these datasets, and to learn from all the healthcare interventions we've done already, to help us do better in the future.

DR. LIAS: Thank you very much.

Jonathan? Jonathan, I think you're still on mute.

DR. POLLOCK: I was just saying that the University of Michigan also has a large genetic database. It's associated with, you know, electronic medical records. One of the problems is how good the electronic medical records are, in terms of trying to deduce, you know, and going forward with a prospective genetic trial, whether it's, you know, polygenic risk score or a machine learning based approach, to validate.

Anyway, I'm going on to the next question. Can you share your perspective on the current medical device solution pathways conducive to the innovations needed to solve this debilitating crisis? A rather open-ended question, so anybody want to take that one?

MS. TULLIA: If it's okay, I think I just beat others off mute. I'm Kirsten Tullia. I work for the Advanced Medical Device Association here in the United States. And one of the real issues that we see is a lack of a pathway for these types of technologies, particularly in the Centers for Medicare and Medicaid space. You know, they do have a very high charge in that environment, that they are literally providing care for everyone over the age of 65 or with specific medical conditions in the United States.

However, they are generally a slower adopter of these type of technologies and

other innovations. And this is a particular issue in this space at AI. They've come to this issue of software as a service or software as a medical device multiple times over the last few years, but have never really comes to grips with something beyond, really in this case, use of imaging.

And so, what we would be looking to do is establish not just the evidence base for these technologies, but a coverage pathway as well. I think what many folks who are familiar with insurance would say is, you know, Medicare is not the be-all and end-all, but it is a very strong start, especially when you're trying to convert over to commercial coverage.

And so what we would look to again is to establish a clear pathway with Medicare, and have them be working alongside folks like these innovators, to better understand where they can fit these technologies into the existing systems, and where, you know, we might need to break some longstanding rules in order to invite this type of innovation for their patients, which would then be passed on to the larger commercial space.

DR. POLLOCK: So I have a follow-up question to you. So, I mean, Medicare wants us to show that something is cost effective, you know, and (indiscernible) it's effective. So, how would you do these studies? I mean --

MS. TULLIA: Yeah, so cost effectiveness is a very difficult hurdle to meet in many of these cases, particularly when we're looking at prevention. This is part of the reason there's not a screening category in Medicare when we look at the benefit system, because it's very difficult to sit, look at an individual patient and say, how much money have I saved by preventing progression?

And so that's really a question maybe more for Daniel, as a mathematician. I am just an ersatz lawyer. But what we would look to see is being able to indicate that, you know,

by preventing progression to OUD, we have saved, in general, X amount of money to the system, and then to be able to frame that as savings for the Medicare trust. As folks who look in the governmental side of things, we often see the trust is constantly in the news, that it is rapidly decreasing, and we're looking for ways to save money.

And so I think what we can do is present CMS with compelling cases to say, prevention is a curative form for the Medicare trust, by preventing that money from leaving the system later, and spending a little bit more on the front end.

DR. POLLOCK: So I think the -- I forget what the reimbursement for a treatment for OUD is. I think per session is like $540, but I don't remember how many times you're allowed to go in a year. So the cost can really add up.

MS. TULLIA: They absolutely do.

DR. DONALDSON: It's about $16,000 a year.

DR. POLLOCK: Anyone else like to take a swipe on that?

DR. DONALDSON: Can I just answer very briefly, because I would agree with what Kirsten said, and it's very similar to the answer that I gave in terms of understanding stigma associated with the disease. As a medical developer, not only do you have to engage thought processes around FDA approval early and often, you have to do the exact same thing with CMS.

So these discussions, in terms of how the test will be utilized, how it works into an existing structure, how there may be a need for alternative structures have to start years before you get a test to where it shows clinical validity. Right. So this is one of those things where you have to think about medical care delivery from both a patient's perspective, a provider perspective, and then ultimately, although I hesitate to use these words, an overall

cost effectiveness perspective.

And that structure, Jonathan, really has to happen early, and I would also say often, because it's something that as you go through it, you have to show and be able to demonstrate benefit to all of those different groups, a patient group, a provider group, an insurer group. And it's something that's a continual process. And I think it can be very beneficial, so I don't mean to seem negative on it. But it's something that you should do sooner versus later.

DR. POLLOCK: Courtney, you want to take the next question?

DR. LIAS: Sure. So, in a medical device, you know, we have a lot of information coming at us from various sources. But what we learn the most from is really patients and providers, from the community, from the researchers who study these tests. And we're hearing today from people who are within this community, who work with patients, who are patients themselves, potentially.

And you already sort of know a lot of the nuances here, of how you would use, you know, tests like these to treat your patients. Let's say in the future we're in a happy place where we have, you know, multiple types of these tests developed and validated, and they become available to providers. What types of things are really important to help providers understand complex information, like the portion of a person's risk related to the genetics, and how to integrate that with other risk tools that they use?

In device development we often call this human factors. How does somebody take the information that they, you know, see from a device, or use when interacting with a product, and integrate that into the actions that they take? So, can you comment on, you know, when tests like these become available, how can we as a community help providers

best learn how to interpret them, what they can do and what they can't do?

DR. POLLOCK: And can I add one other question to that is, should one look at, you know, risk along a continuous variable, or is there, you know, some test might just have a cutoff. So how would you deal with -- what's the best approach?

DR. LIAS: Now that's a great question. Perhaps we can do them in sequence, first with, you know, whatever the output would be. Now how do you help providers who aren't geneticists learn how to integrate information like this? And secondly, you know, as experts in this area, what type of output of tests, you know, whether it be continuous or, you know, binary or some other way of expressing risk, what types of things do people find helpful?

Kathy, I don't know if you have any thoughts on this.

MS. SAPP: Actually, no. I think that, as you all know, this is going to cause these, risk assessment tools in the community -- you know, I hear from patients all the time that their, you know, drugs are being taken away from them. They're treated like a drug seeker. And so these assessment tools are going to cause anxiety. They're going to cause fear, even paranoia.

But I think, I do believe that they're coming. I'm realistic. And I think that we need to start educating people now about them, and understand what OUD is. I don't think we do enough of that, and that's our job at the American Chronic Pain Association to do that. But the one thing that I think that's missing in the healthcare team is the compassion. And I think we need to start teaching and training on compassionate, thoughtful delivery of these devices, so that we really encourage the patient to be part of that healthcare team. But if they're not -- and we want them to be part of the decision making.

But if these tools come in, and this tool says you have this chance of being addicted,

they're going to have so much fear of coming in that you're going to lose a lot of people. They're going to have that fear. So we need to train those people in a thoughtful, compassionate way, as do the physicians, the whole healthcare team.

So, I just want to say that I think that they are important, but the stigma is huge. And it is such a problem. And standardization is a great idea, but it comes with flaws. If you've got somebody that has severe chronic pain, and they come in, and they're going to take this risk assessment tool, and it comes out that they're at high risk, you know, what do we do with this person?

So, I mean, it has its flaws, but I think it's about education, and soon. I agree that we need to start, because they are coming. And they're important, and we need to shift in the way we treat people, so.

DR. LIAS: Thank you very much.

Keegan, do you have anything you'd like to add?

MR. WICKS: Yeah. Thank you so much. So I have a few things here, and I'll try to be succinct. A couple of thoughts around implementation. I think about how urine drug screens have been implemented, and how they've been utilized to criminalize patients, or at a minimum make them feel criminalized. Thinking about people who are required to provide a negative urine drug screen for a particular job or a particular background, you know, and how, you know, it's -- I think somebody had talked about it on an earlier panel, the idea of policing care.

And so I think that that's something that's really important to be mindful of, in that this tool, this potential tool has the idea or the opportunity to be utilized in the same kind of weaponized fashion, to further criminalize people who are already marginalized and

oppressed. So I think that that's something important to kind of remember.

I completely agree, I think training is of paramount importance, and is something probably outside of the, kind of, scope of the development of this particular instrument. But I really, I cannot recommend this enough. You know, I think about -- or who's providing this test? Is it, you know, a home test? Is it a nurse that's going to provide this? Is this, you know, a physician that's trained and understands how to interpret the results? I can't tell you how many prescribers I've met who are just unaware of how to interpret some other results kind of pertaining to substance use disorder.

And kind of finally, I would offer that this has implementation widely, much beyond substance use disorder, you know, really pertaining to anyone that may be subject to a risk of having an opioid use disorder, which could include chronic pain patients, which could include patients who have never been prescribed an opioid before. And so I think that there's a lot of kind of wide, a wide ability to utilize such a tool.

DR. LIAS: Sounds great. And, you know, one more thing, I think, try to get at the question of how to communicate risks through sort of the output of these types of tests. What types of risk communication techniques should test developers think about, when they're thinking of, you know, how clinicians might best understand risk?

You know, and this doesn't touch of feasibility or things like that, but -- I don't know, Laura, do you have any thoughts on the types of information that clinicians find easiest to understand when it comes to partial risk or the pieces of genetic risk?

DR. BIERUT: Right. So, you know, I think that we should -- the way that I view this is that, you know, physicians get a lot of information all the time, and they don't need to understand, necessarily, all the biology behind it to use the test. For instance, you know,

we use MRI scans and CT scans all the time, but if you asked a physician, you know, tell me really how that MRI works, they'd go well, I don't know, I just kind of read the report and, you know, see what it comes out.

So, I think we have to focus on the communication, not necessarily the education underlying the genetics. What is this communicating, how does it go forward? Now thinking of physician education, there is one, not much education about addiction, just to begin with, within physician training, and two, this is a nuance of addiction training. So again, you know, we are challenged with, it's going to need to be simple and straightforward to use.

I do want to touch on Jonathan's point about, you know, a continuum, because really, these tests are going to give us a continuum of risk. But, you know, again, physicians know how to interpret continuum of risk because we see that all the time with blood pressure. And we know, once you're over a certain number, that's when you start being worried about it.

So, you know, I think that it's going to be, this is going to be a tough road, just because physicians have so much information that they're already doing, and to think we're going to really give a whole lot of education is probably not too feasible.

DR. LIAS: So clear and simple to interpret, easy to understand, sounds great.

All right, Jonathan.

DR. POLLOCK: Okay. I was still listening. The addiction drives opioid overdose and death. What should be the target? Should the target be addiction, or rather overdose and death, or something else? Anybody want to take that? I think Laura has spoken to that before.

DR. BIERUT: Right. And what I would say is, you know, we don't want death, but if we could intervene earlier in this trajectory, that is, you know, prevention, I think of it as kind of preventing death at the end.

DR. POLLOCK: And what is more of a treatment side or there are things that one can do also in terms of prevention of overdose, perhaps, or --

DR. BIERUT: Right. So --

DR. POLLOCK: -- for people who are using opioids, either acutely or chronically.

DR. BIERUT: So, kind of let me riff -- I'll riff on my physicianhood here for a little bit. So, you know, Jessica mentioned age of onset is really critical. And so, individuals who have a high risk, let's see if we could delay the age of onset of any substance use as long as possible. Individuals who at high risk, well can we minimize exposure? Can we, you know, can we minimize the prescriptions for individuals who are at high risk?

You know, them knowing, and individual knowing their risk, what activity can they take? So, this is really all on the prevention side. I think individuals who are already receiving opioids and who are doing fine, in some ways, we don't need this test, because we've already -- they've been challenged with an opioid, and they're doing fine. So, you know, that's how I'm thinking of this test.

DR. POLLOCK: Would anybody else like to take the opportunity --

MS. HULSEY: Just to chime in, in agreement, I think when we can focus on preventing addiction or addressing addiction, we obviously need to simultaneously prevent overdose. We want to keep people alive, but we want more than that for folks, right. We want to see them whole and healthy and well.

And sort of piggybacking on the previous comments, I think there's a lot -- one, we

need a lot of provider education. We need much more understanding about SUD. And I think that there's a capacity or a possibility for these tools to be used in many settings, really going upstream to engage people, whether that's in pediatrics or family practices, or in other OB/GYN offices. This is where we get trusted, have trusted advisors for our health.

We also have the challenge of, we're still integrating the care of addiction or the treatment of addiction into our healthcare system, that's been external for so long, and still is, for so many families. So there are challenges here, but it's worth focusing on fully integrating, and then using tools and innovations like this, not just to prevent overdose, but to address addiction, and to look at the whole continuum of someone's life.

DR. POLLOCK: Keri.

DR. DONALDSON: Well I think, Travis, you want to go first? Go ahead. I'm sorry. I think you're on mute. All right.

DR. RIEDER: At least once during every webinar, have to stay on mute. Okay. So, I just want to -- so whenever these questions come up, in the background is often a resource allocation question or concern, right. And so the one thing that we just say really explicitly is, there's a role and a need for these technologies, but also, it cannot be the answer, right. So we're looking at a drug overdose crisis that killed 108,000 people in our last 12 months of record.

We need harm reduction, scale up evidence-based addiction treatment, look at the social determinants of health, right. So if you get a perfect technology that rolls out next year, which isn't going to happen, right, but per impossible, a perfect technology that rolls out next year, there will still be a hundred plus thousand people who die that year. And so, if this is a question about resource allocation, it's just kind of like, call the troops. This is an

absolute tragedy of epic proportions, and we need to do all of it at the same time.

DR. DONALDSON: I get the next one.

DR. POLLOCK: And also, some of the, not only the genetics, but some of the other biomarkers that are associated with the genetics, the metabolomics or some of the microRNAs and other biomarkers may be very useful in terms of treatment endpoints that are conceived to actually reverse, you know, OUD. Instead of just using, you know, opioid agonist therapy to basically level and, you know, make people functional, actually find, you know, treatments that actually, you know, work at the underlying disease. So anyway, that's just my --

Keri.

DR. DONALDSON: Sorry. I want to just echo what everybody's been saying here, and I've lived this from a device manufacturer's perspective. I've lived this from a test developer's perspective. I've lived it from sort of a regulation perspective as well as a reimbursement perspective. And I'm trying to give advice here from a overall 30,000-foot view.

I think that I view this particular discussion as a huge opportunity, more than it is a detriment. And I think that what we're hearing here is, you know, there's a responsibility to do something, right, to move forward and do better than we're currently doing. You don't want to put all your apples or eggs in one basket, that is not to say that. And I'm only really paraphrasing what Travis said in a Central Pennsylvania way.

But in reality, one of the things that we're talking about, or quite a few of the things that we're talking about, really is device mitigation or risk mitigation, right, from a developer, a test developer's perspective, right. How is this information going to be used?

How can we make sure that it's not misinterpreted? How can we make sure the right patient gets information that doesn't stigmatize their thought process, but empowers them to understand, you know, decisions that they have and better inform them? And I think that is a very large win for everybody on this call to be having that discussion, right. We can talk about, you know, what's the right size of the education. How do you implement it? How do you think about the stigma from different patients' basis?

I will tell you, from my perspective, I have to start small and go slow, right. So the diagnostic test that I have most experience with is really looking at opioid-naïve individuals, prior to short-duration exposure, so somewhere in between 4 and 30 days, right. And it's informing that decision on what their risk is. I agree with many people on this call, that there's a need for additional information in other settings, right. I think chronic pain is a key portion of where we need to inform and help people understand and empower them, because there are people being denied care, right.

And I'm not responsible for that, I'm just aware of it, right. And I think that our purposeful next steps of action, very similar to the discussions in terms of engagement of regulatory authorities early, engagement of reimbursement structure early, understanding the ethics of how these things are used, not only does it have to be done early, it should be continual.

So as we think about how to implement these tests, we should do it in a way in which we understand that the right patient population is getting the test at the right time. We should understand that the provider who's ordering this test, and the test that I'm talking about, have most experience with, is a provider-only test. I think that was a question or comment Jessica brought up. But we have to make sure we not only try to do

our best as it rolls out, but continue that process, because what will happen with this epidemic, as it has changed over the last 10 years, it's going to change over the next 10. Right.

And even though this is an improvement right now, you want to build in to the system some thought process on how we can do better over time. So that would be my other comment on this is, you know, as we're thinking about this, not only should we think about the needs for yesterday, or today, but we should think about a structure that allows those technologies to integrate and modify over time, because I think it's incredibly important for a disease like this.

DR. JACOBSON: I think there's a big point to make there, that's a major concern of -- you know, we all know the datasets that the majority of the genetics is coming from. And they're very European biased. The sum whole numbers we have of other ancestries is much, much lower. And a major concern is the misapplication -- and you've raised it several times about making sure the test is used in the right population.

But as soon as you put a test out there for clinical use -- and now we're back to educating the provider to apply it to the right ancestry group, that's a really tough ask. So I would actually urge the test itself has built-in markers for determining, is this coming, is this test being used on the right ancestry group for which we do or don't know these architectures?

That's a technology innovation that can be fed into the results itself. And we can go beyond that to say the sample numbers we have now are low compared to other diseases. And we know, when we look at nicotine, we find much more complete to complex genetic architecture, so we have orders of magnitude higher sample sizes. We're just not there

with opioids yet. So we're already, even in our largest populations, looking at very fragmented architecture.

So we're missing a lot, and that is amplified in other ancestry groups, which are -- and so I really worry about, you know, the inadvertent misuse of these tests in different populations and, you know, a false sense of security being developed, if we don't address that within the test itself, to give warning flags to physicians, that hey, this test may not apply to the patient you're applying it to.

DR. LIAS: Yeah. I think that really highlights what we talked about earlier about the need to work together to understand, you know, the tests being developed and the datasets we have.

So, I want to -- we have about 8 minutes left in the session. We'd love to get through as many of our audience questions as we can. Next, I'd like to mention -- we could do two minutes on this topic. Laura mentioned earlier that one of the challenges to implementing predictive devices is patient stigma of a high-risk result. So how do we result this?

I wonder, Kathy, if you might want to weigh in on this.

MS. SAPP: I'm not sure what you mean. What's your question?

DR. LIAS: So, I mean, the topic was brought up, and maybe you have a different opinion, that a high-risk result in the test -- if someone who is determined, through a test, to be at high risk of OUD might introduce stigma, patient stigma. How might we reduce the types of stigma based on a test result that is intended, for example, to be one piece of the puzzle?

MS. SAPP: You know, that's -- I mean, that's a challenge. I don't know that I have

the answer to that, because I think what we have to make a decision on is, is it more important that they -- you know, we have this test, and if they're at high risk, do we take them off of the drug? The risk, to me is higher, taking them off of a product, a drug that's working for them, because you have the risk of suicide.

We don't -- we want people, we want to be compassionate and give them the care that they need for their pain. So, I mean, it is a challenge. And I don't know that I have the answer to that. It goes back to what I was talking about, the standardization. You know, that's a challenge, because you have the false positives, the false negatives, and I just have a lot of concerns with these, you know, these tests, and how they're implemented.

So, I think it goes back to, it's going to take a while. It could take years. So, I really don't know that I have the answer to that.

DR. LIAS: Understandable.

Travis, do you have a 1-minute answer you'd like to contribute, to reduce the stigma?

DR. RIEDER: Yeah. It's a very short answer. Unfortunately, it's depressing. You know, there is literature on de-stigmatization efforts. It's pretty disheartening. The interventions that have been identified and designed so far don't have a real high rate of success. So, I think the answer right now is something like ah, we're trying. You know, one of the most sustained efforts so far has been to medicalize, like take away from the realm of moral failing to the realm of medicine.

The problem is, we're perfectly capable of stigmatizing medical conditions. Just ask people who are suffering from mental health disorders, right. So, it sometimes re-entrenches stigma if it feels as centralizing in any way. All that is just to underscore, the

person asked a really good question that's really hard, and we're working. And, you know, all of us can just keep trying to normalize it, and care about and love people who use drugs and suffer from use disorder, and try to move forward.

DR. LIAS: All right. Well, thank you very much for trying to answer that hard question.

Jonathan?

DR. POLLOCK: Travis, just one follow-up. So I think at one time, you know, cancer was stigmatized, and it was like, you wouldn't talk about it. So how did that cultural change take place?

DR. RIEDER: Well, so there's probably a history of medicine person who like, knows the answer, historically, how it evolved, but here's a hypothesis. We live so long now that cancer is at such a high rate that it's just really, really normalized. So the number of people who live with cancer and who know somebody, who love somebody who has cancer is really normalized.

So the sort of dark analogy is, the United States is in such a tragic place with drug use, addiction and overdose that we might actually be getting a little bit normalized with reference to this topic as well. And so the very dark silver lining could be that this can help push us forward as we all like, care about people who use drugs and suffer from use disorder.

DR. POLLOCK: Thank you.

DR. LIAS: I can take the next one.

DR. POLLOCK: Oh, thank you. I'm just losing track on the list.

DR. LIAS: No problem.

DR. POLLOCK: Thank you.

DR. LIAS: So, you know, we talked a little bit about, sort of, you know, the challenges that we're going to face integrating these types of tests into clinical practice in the most reasonable way. So, do you worry about burned out clinicians, with little or no time, and how they'll be able to do this?

Keri, why don't you take the first?

DR. DONALDSON: Sure, happy to. You know, this is part of sort of the lifecycle of test development, and it gets into the question on education and everything else. This has to be thought about, and Dr. Clark mentioned this morning, somewhat holistically. And you have to be cognizant of -- and Travis was walking about, from a resource perspective, you know, a zero sum game.

So you have to be cognizant of how this type of technology or any type of new technology will interact in the patient care paradigm. Right. So that's both from a physician burnout perspective. That's from a payer perspective. It's most importantly from a patient perspective, but there's a whole universe of the way you have to view this, or think about it.

And from a provider perspective, one of our -- or at least my key thought processes is, you know, physicians are trying to do the right thing, right, in general, or prescribers. They're not in these positions, in general, you know, to do harm, right. So, you know, if a physician recognizes information as being provided that allows them to treat the patient better, that's a good start, but it's not enough. So you have to be cognizant of working or integrating into a workflow.

And as we do that, we think about it as almost as simplistic as keystrokes, like you literally count the keystrokes of a physician or a prescriber, of how they have to interface

with your test, right. And that's something that will get less invasive over time.

But at the very beginning when you're trying to figure out how people will use information, how they interact with the patient, how is that counseling done, it tends to be more cost intensive, in terms of time from that prescriber, and it's, I would say, almost paramount that as you bring a new technology to market, you do a purposeful rollout, where you're enabling -- and Kathy was answering this a little bit, you're enabling, in a very purposeful way, where you can invest, or people will invest the amount of time that's needed, to pressure test, you know, the educational materials that's needed, that will pressure test how that interaction occurs.

And then you get meaningful feedback, so eventually you can make it as efficient as possible, so that that prescriber and that patient have a shared decision that should be empowering. So, I appreciate the question.

DR. LIAS: Thank you. We have our 1 minute left. Any of the clinicians on the panel? Maybe you, Laura? Want to weigh in on clinician burnout?

DR. BIERUT: Clinicians are burned out. I mean, we know that physician are burned out. Nursing is a disaster now. There are not enough nurses in the healthcare system. So, I'm actually going to flip it, and I think we've been focusing so much on the physician and the healthcare providers. I think we are not empowering people enough about their own genetic risk.

And, you know, we're kind of being gatekeepers, holding these tests in our hands, but I think people deserve to know what their risks are. And everyone loves hearing what -- I think that most people love hearing what their risks are. And it's not that the risk is destiny. But I think we should be empowering individuals with their own healthcare much

more.

DR. LIAS: Well what an optimistic note to end this panel on. Thank you very much to all of the panelists here. What a great discussion. I certainly learned a lot. I'm going to end this.

Back over to you, Jacquie.

DR. CUNKELMAN: Thank you, Courtney. And thank you to all of our speakers and panelists, and thank you to Courtney and Jonathan for their moderation of this panel. We appreciate all the informative presentations and interactive discussions during today's workshop on Risk Prediction Devices of Opioid Use and Opioid Use Disorder: Opportunities and Challenges.

We'll conclude with closing remarks from NIH and FDA. I will first turn it over to Dr. Pollock for closing Remarks from NIH.

Dr. Pollock.

DR. POLLOCK: I want to thank all of you for a wonderful discussion. We've covered a lot of ground on a number of issues. And these issues of concern whether, you know, genetics can -- for problem use of opioids is -- at our -- you know, are we there yet, in terms of, you know, risk prediction? And what is the best -- we've talked about the best experimental designs to validate risk prediction for OUD, and in what populations it should be used.

We've also discussed how one might implement it on acute pain versus chronic pain, and what might be the potential misuses of it, and the possibility of certain biases that might be introduced against certain ethnic groups. And let's see, what else? And we've also discussed the issues about the cost benefits as one of the discussions that we had. And

I will now just turn it over to my colleague at the FDA. Thank you all.

DR. CUNKELMAN: Thank you, Dr. Pollock.

And now Dr. Maisel will end the workshop with his closing remarks for FDA.

Dr. Maisel?

DR. MAISEL: Good afternoon. Let me start by thanking all of those who made these workshops possible. Our work is inspired by patients, and we're grateful to the patients who participated and shared their perspectives during these past 2 days. I'd also like to thank our speakers, panelists and moderators for informative, engaging and thought-provoking discussions today.

I'd like to acknowledge our workshop co-hosts and federal partners at the National Institute on Drug Abuse as the lead federal agency supporting scientific research on drug use and addiction. Their work is vital and we look forward to our ongoing collaboration.

I'd like to acknowledge the fantastic work of our MC today, Dr. Jacquie Cunkelman, and our lead workshop organizer, Dr. Jisun Yi, not only for ensuring today's workshop went off without a hitch, but also for their weeks of preparation and organizing today's event.

I'd like to acknowledge the fantastic women and men working at the FDA Studio who helped bring you today's workshop, and finally, thanks to all of you watching today for joining us. We appreciate your attendance.

Today's workshop was intended to spotlight the opportunities and challenges related to the development, commercialization and adoption of devices indicated to predict the risk of developing opioid use disorder. It's clear from the discussion today that devices that predict the risk of opioid use disorder are an emerging and important area of interest.

Some themes discussed today include the importance of ensuring that device

development and performance should not be biased for or against one particular race, ethnicity, demographic or genetic ancestry. Devices should perform well for everyone, and not just a segment of our population. We heard suggestions to consider not just device development, but also clinical implementation. We should be thinking about how these products will impact clinical care delivery, and incorporate both clinician and patient input.

And I really want to emphasize this latter point, which came up repeatedly. It's critically important to consider patient perspectives. It's essential to engage with patients, and the communities that support patients throughout device development and implementation. They have unique and valuable expertise to bring to the table, and partnerships with patients and patient groups can help ensure that new devices succeed in addressing the challenges we've heard discussed today.

It's clear from our discussions today that the field of opioid-related predictive medical devices is evolving, and efforts to date show promise. We at FDA remain committed to working with patients, caregivers, consumer advocates, healthcare providers, researchers, medical device companies, our federal partners, and all other stakeholders to facilitate timely and continued access to safe, effective and high-quality medical devices for the diverse populations impacted by the opioid crisis.

We are hopeful, and optimistic, that the multi-stakeholder perspectives and valuable information from discussions with patients and others during these workshops provided valuable insights that will help drive innovation forward in this important space. The opioid crisis is a complex problem, and there are no shortcuts to identifying, developing and deploying solutions.

We recognize that no one action, no one person, and no one organization will solve

this crisis. However, we do believe that our collective efforts, in partnership with you and many others, can make a difference and move us in the right direction. We thank you again for your attendance today and we look forward to continuing our work together. Thank you.

(Whereupon, at 3:36 p.m., the meeting was adjourned.)

C E R T I F I C A T E

This is to certify that the attached proceedings in the matter of:

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were held as herein appears, and that this is the original transcription thereof for the files of the Food and Drug Administration, Center for Devices and Radiological Health.

TOM BOWMAN

Official Reporter