Using Pharmacogenetic Markers in Clinical Treatment: The Pros and Cons of Preemptive Genetic Testing
Webinar
6 November 2013

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Sean Sanders: Hello and a very warm welcome to this Science/AAAS audio webinar. My name is Sean Sanders, and I'm the editor for custom publishing at Science.

Our genes and variations within those genes impact the therapeutic response in different individuals to drugs by altering their absorption, distribution, metabolism or elimination.

Testing multiple pharmacogenetic factors holds a potential to improve treatment by understanding the effect of important genetic variants in advance rather than waiting to test the patient for genetic markers for each individual drug at the time of prescription.

Now, with higher throughput and more comprehensive clinical genetic testing, clinical testing can be expanded from a single gene to a comprehensive panel of relevant genes, a more attractive and cost-effective approach that has advantages for both patient and physician.

However, it is necessary to carefully consider how medical data is managed and how communication with patients and healthcare providers is handled.

In today's webinar, we'll be taking an in-depth look at this topic, in particular, the recent progress and the current status of pharmacogenetic testing in the clinic and how it might be implemented in the future in clinical practice.

In a slight shift from our usual format, we have just one speaker with us today, Dr. Ulrich Broeckel from the Medical College of Wisconsin in Milwaukee, Wisconsin. A warm welcome and many thanks for being on the line, Dr. Broeckel.
Dr. Ulrich Broeckel: Well, thank you very much for the introduction, Sean.

Slide 1

Sean Sanders: Before we get started with today's webinar, as always, I have some information that our audience might find helpful. You can change the size or hide any of the windows in the viewing console. The widgets at the bottom of the console control what you see. Click on these to see the speaker bios or additional information about technologies related to today's discussion or to download the PDF of the slides.

Dr. Broeckel will be presenting his work, after which we will have a Q&A session during which he would address some of the questions submitted by our live online viewers. So if you're joining us live, start thinking about some questions now and submit them at any time by typing them into the box on the bottom left of the viewing console and clicking the Submit button. If you can’t see this box, click the red Q&A widget at the bottom of the screen. Please remember to keep your questions short and as clear as possible as this will give them the best chance of being put to our panel.

You can also log in to your Facebook, Twitter or LinkedIn accounts during the webinar to post updates or send tweets about the event. Just click the relevant widget at the bottom of the screen. For tweets, you can add the hashtag #sciencewebinar.

Finally, thank you to Affymetrix for their sponsorship of today's webinar.

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Now, I'd like to more formally welcome Dr. Broeckel to this webinar. Dr. Broeckel graduated from medical school at the University of Heidelberg in Germany and followed this by residency training in internal medicine and cardiology and then postdoctoral research at the Medical College of Wisconsin. He joined the faculty there in 2000 and is currently a professor in the Department of Pediatrics and the chief of the Section of Genomic Pediatrics.

His research focuses on the identification of genes for complex diseases, the understanding of gene function, and the application of genetics and genomics in clinical practice. His work combines clinical applications with functional genome analyses using induced pluripotent stem cells for disease modeling and risk prediction.
Dr. Broeckel is also the scientific director of a CLIA/CAP-certified clinical laboratory which conducts clinical testing for structural chromosomal abnormalities as well as pharmacogenetic testing.

A very warm welcome to you, Dr. Broeckel, and many thanks for being here today.

Dr. Ulrich Broeckel: Well, Sean, thank you so much for the nice introduction, and I really appreciate the opportunity that we can present and I can present today some of our research and our implementation of pharmacogenetics and genomics here. Again, I would like to encourage all of you listening in, please type in some questions. I'm really looking forward to discussing any questions at the end of this presentation.

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So at the very beginning, let me disclose my conflict of interest. My research is supported by a number of grants from the National Institutes of Health and local foundation and initiatives as well as my institution. Particularly in relationship to this presentation, I have no financial interest or relationships with any entities which products or services are discussed during this presentation here.

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So at the very beginning, as we talk about what we developed over the last few years in the concept of preemptive pharmacogenetics, I need to give credit to my collaborators at St. Jude’s Children Hospital in Memphis, and I really would like to -- you see from this list a large number of people have been working together with us here on this concept and really implementing this, and I think all through the presentation you will see and hopefully you will appreciate all the work which went into this and the development.

[0:05:00]

This has been really one of my most successful and fruitful collaborations. So as I present here, I'm really presenting in the name and for all of these people who have been working on this project for a really long time.

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So let me start with genetics and genomics. I think there is not a single day anymore where you open a newspaper or you read the news where
genetics and genomics and individualized medicine is presented as that this will really change the way we practice medicine.

I think as exciting as this area is, and I think I truly agree that it will open a new way how we treat patients, how we recognize disease, this is also at this moment still very much technology-driven, and I think we need to be aware of all the things which come along as we really develop individualized and genetics and genomics medicine.

So right now, and this is my statement, this is very much still very technology-driven. Technology drives research. But then the research findings really drive clinical applications, and then it's really the big challenge to combine research and clinical applications and really drive this and bring this towards implementing this in healthcare.

I think as technology advances, as research provides us with the results and really the interpretation of these findings, the challenge really is going to be how do we implement genetic information into clinical practice, and I think this is going to be the challenge over the next few years.

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So one of the areas as we recognize this earlier on that this is a really big challenge and the work ahead of this, so we really thought about so what's an area where we can really implement that? And so we thought, and I think it's really well-established that pharmacogenetics I think is one of these areas where you can do this.

So let me just briefly review with you where I think how the genetic genotyping and the technologies, how it has evolved here.

In the beginning, obviously we analyzed just very single variants. Over time now, it has moved to analyzing candidate genes. I think at some point in time, we might have even the whole genome available. So this really builds the backbone of DNA information.

But what we really thought is what do we really need? And as I mentioned before, the implementation and really trying to make sense of the genetic information, I think that's the challenge. So in 2007, 2008, when we conceptualized this project here and we realized that obviously we are moving from just analyzing one variant to really expanding the genomic information we have to deal with, at that time already, can we start implementing a comprehensive analysis and trying to do this on a
well-established example? So you could always say like we wanted to learn how to walk before we're really going to run.

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So pharmacogenetics I think is a very logical and the very first step, and I think this is also an area where we have tremendously have an impact improving healthcare.

So just to review with you briefly, a definition of pharmacogenetics is really the study of genetic factors and how they influence the response and effectiveness related to drug treatment.

Historically, I think pharmacogenetics always focused on a number of different areas and then phenotypes how genes actually affect it. So either we're looking at drugs and genes which affect how drugs become active component or how drugs get inactivated or excreted, or we're looking at the variation in drug targets. In addition to that, obviously, also, there are genes now which look at side effects, toxicity or off-target effects. In some cases, all those things actually are related to each other in one gene.

**Slide 9**

So where we look this are indeed I don't want to say past but a lot of areas. The current approach to getting pharmacogenetic data and pharmacogenetics analysis is that it's very much currently driven either by a particular drug or a new genotype where you look at a particular candidate gene and you then combine this single drug with this single gene.

In many cases, this is actually quite reactive. So you have a patient who would need a certain drug and then you actually start thinking about genotyping. So that's why we're looking at this today.

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The advantage, again, looking at pharmacogenetics, is not only that we have a well-described body of evidence of the role of genes they're playing in relation to drugs. The number of genes is actually reasonably small. We're not looking really at a large set. A large number of drugs are actually related to a reasonably small size of pharmacogenetic irrelevant genes.
So if you test one particular gene, that actually has an impact on many drugs at the same time. So commonly tested genes are relevant to a broad spectrum of drugs, and the most important thing, I think, which then also directs again to preemptive genotyping, is that the pharmacogenetic testing result will actually retain relevance. So if you test a particular gene for a drug, if the patient gets prescribed a different drug, these genes are still relevant and the results of these are still relevant.

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So that really leads to the concept that would it be advantageous to actually have these results at hand? So that's really what drove our overall approach to this.

In the very first step, we needed to really look at what technologies are out there, what technologies are available to analyze pharmacogenetically relevant genes, and we didn't want to do this as just for a particular gene. We really wanted to comprehensively assess all pharmacogenetically relevant genes at one time and have this data available when physicians really need this.

So we're looking at pharmacogenetics. We looked around in one of the technology platforms at the time which we wanted to implement because it was quite comprehensive. It was an array-based technology called DMET Plus strip. The target population -- and again, as I mentioned in the beginning, our collaboration started with St. Jude's Children's Research Hospital in Memphis and we looked at children with childhood cancer. These children who come to the hospital are taken care of for a long time, and so I think we're having this relationship and going back and forth to the medical record and children needing a number of different drugs which all have pharmacogenetic evidence that appeared as a key target or key population, and we really then started to implement the preemptive pharmacogenetic genotyping.

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So I wanted to introduce to you the study, which again is that we are doing in collaboration with St. Jude's and Dr. Relling who is the leader of this, has been a leader in pharmacogenetics and really supporting the concept as a key spokesperson for this project. The study is called PG4KDS, and really the goal here is to migrate pharmacogenetic testing
from the laboratory array-based into routine patient care to be available preemptively.

And again, our question is not if pharmacogenetics needs to be done. I think we all agree that pharmacogenetics is important and plays an important role in clinical care. Really the question is how to do it, not just that we need to do this or the discussion around it. I think the body of evidence is very strong to really show that it improved patient care, but the implementation was really our key goal here. There is a link to the website if you want to follow up on this.

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So as I said, we look at a number of different genotyping platforms and choose the Affymetrix DMET array. Some of the advantages for this platform are that it really contains or genotypes a large set of pharmacogenetically relevant genes. And as I walk you through you will recognize that not only the genotypes are important, but for some of the most established pharmacogenetic genes, their nomenclature is well-established, which then takes the genotype, translates this to a certain haplotype and then translates this to the function.

And so the software which really combines all of this and really presents this and analyzes this in a way is also critical. So this technology and this platform also provided that.

So we have a tabular comprehensive genotyping report which summarizes the variants, which also translates this to the phenotype of high visibility and important genes and also analyzes for example and reports certain missing genotypes as it relates and describes and certainly relates to that.

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So we published a few years a manuscript really describing this, and for the people who are working in the diagnostic field, you’re intricately aware of that that the quality control and assessment and validation are a key component. And here this just describes then our workflow at the beginning of this project when we started doing this. We really evaluated the overall performance of this, and we started out with a number of SNPs. This just shows you the workflow from the original number of SNPs we excluded a few tests for Hardy-Weinberg equilibrium.
And then the key thing here is that we compared it with -- we took a number of samples and we compared the results from the array with the genotypes and sequencing results for the same samples basically using different technology platforms. At that time, we only had a subset of samples available with genotypes using different technologies. At the end I'll show you actually some examples for a project where we advanced this now and saw it as the research.

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So I just want to review with you here the results. The overall concordance between the different methodologies was quite high. So on the table you see here all the different technologies. We did Sanger sequencing as well as a couple of other genotyping platforms, the number of SNPs we compare it.

[0:14:55]

Between this current array-based platform and these other platforms on the very right, you see here the concordance rate between the genotypes and you can see here that the concordance rate for this platform is quite high, 97%, 98%, up to like 100%.

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There are very different ways how to look at and evaluate the performance of this, and I just want to review a few with you here so we're looking at the concordance between all the different genotyping platforms here on the right. And again, you see that the concordance is extremely high and falls very well into the quality criteria which are necessary or required for clinical genotyping.

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On the next slide we particularly looked at the differences of SNPs which gave us different results here. So you see here the number of genes and the actually array-based results. Most of the time we actually saw discrepancies where one technology was different, and the other three technologies actually agreed to this. That is I think probably as expected because there is not going to be 100% accuracy. With clinical testing, we certainly know that, we recognize that. But overall, the behavior and looking at that, I think it's highly accurate.
We also looked at -- and as shown in this slide, we looked actually at the concordance of the SNPs and the genotypes, and we looked at the most high-priority genes. So these are really genes which we wanted to implement and are implementing in clinical practice in the very beginning. And so you see on the very left the list of genes, TPMTs, CYP2D6, CYP2C19 and other ones. Again, we see extremely high concordance rate between the different genotyping platforms.

That I think is one of the criteria, and we're very impressed by the high accuracy of the genotyping results and also the consistency in the genotyping results between the different technology platforms.

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So since we evaluated the platform, here I just wanted to show you briefly our overview of how we looked at this project. So we have the genotyping platform here. Once we have the results, the key thing is to translate this, translating meaning developing guidelines, consensus guidelines, how we interpret the results and then bringing this together into the medical record and also communicating this to the patients and the families getting the consent.

Really the idea is to migrate genetic genotyping into the medical record so that the results are available for physicians at the time when they prescribe a drug and when they do need this information to make an informed decision.

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So the next slide really shows our overall workflow here, the workflow at St. Jude's Children's Hospital, where the patient gets enrolled in the study. We get DNA or genotype them in my lab and then we'll transfer the results back and the results are then maintained in a database based on the ongoing evaluations of the experts here in the field and I've showed you the large group of people who are really involved in this effort, experts in all areas, from the pharmacy, from the physicians, pharmacogenetics experts. This input really then together brings, develops guidelines and evaluates the drug and the genotype, and the phenotype relationship.

And then for the most important genotypes, genes, and also for the most important drugs, then these results will be translated into the medical record for the patient. And in addition to this, the decision support has
been developed to really help physicians with this information to make the most informed decision around this.

So in the next few slides, I really want to show you what I think a wonderful job St. Jude's did in developing the overall infrastructure and interpretation. I think this is one of the examples how this can be also implemented in other institutions, in other places.

We, in fact, have some collaborations now with other institutions who are taking this as an example and then migrating it in their group.

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So I want to focus on one particular pharmacogenetics gene just to show you some of the complexity and walk you though some of the complexities we see with pharmacogenetic testing.

And so one of the most prominent pharmacogenetics genes is CYP2D6. It's a gene which obviously on the genetic side and on the clinical side offers quite a significant challenge. Sometimes we would wish, I guess, that this gene would be easier to understand, but it's not. And a lot of drugs are using this or are influenced by this gene, and also a lot of research and a lot of focus and effort went towards understanding this.

[0:20:00]

So this is just in the very beginning, from the very beginning, our first patient shows a similarity in the complexity of the genotypes of what we see. We can see quite an array of very different genotypes and genotyping results. So it's not like we see just one group.

And just looking at that, I think you will appreciate that it will be quite challenging to really provide correct interpretation and really link this to the way they had them described it.

**Slide 22**

So let me walk you through what we did in terms of coming from the genetic results and to really then finally translating this and presenting this in a way that physicians really can act on this.

So first, we need to determine based on the genotypes the phenotypes. So what is the phenotype? How does the patient metabolize a certain drug? And then classify this based on whether it's just a routine or we
need to focus on this because we might expect certain severe adverse event and then it would become a priority case. We obviously would like to link this and we need to link this to an appropriate consult and really then provide also clinical decision support and alerts for certain high-risk phenotypes.

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So I want to walk you through some of the software infrastructure which was developed at St. Jude's to really do this. It's all implemented in their medical records, and, as I said before, I think obviously also would be available to translate to other EMR platforms.

So looking at 2D6, the first here, what we have in the middle, so 2D6, to go into this, we obviously have to look at genotypes. Different genotypes, different haplotypes have different enzymatic activities. In addition to that, which makes the gene more challenging, we also have copy number variation. You can either have a deletion or just one copy or two or even a duplication of this gene, and that also affects the activity and the way how we interpret the results. And there are also very complex rearrangements in this gene, and so this makes this a little bit challenging.

But nevertheless, so we start out with a genotype which is in the middle, and then that needs to be translated into the actual diplotypes. So if you look at the very first row up here, total deletion. If you had total deletion of this gene, that translates to a haplotype of *5/*5.

Obviously, if you're totally lacking this gene, your activity score, which shows on the right side, is zero. So you don't have any enzymatic activity at all. Again, if you look at the very right activity score, they appreciate the range of activity of this enzyme, how this then relates to the various genotypes and haplotypes, as what we observe here.

**Slide 24**

The activity of certain diplotypes and how it relates to activity score and how this relates to the phenotype of a patient has been very well-described in studies in the last few years, and I just review with you here real briefly 2D6. So, on the very right you can see the examples of certain diplotypes or genotypes, and we can categorize patients or individuals based on a genotype in a few different metabolizer groups. So there's a group of ultra-rapid metabolizers, extended metabolizers, intermediate and poor metabolizers. And that correlates again to a certain activity
score. And then the metabolizer status, this is what we need and this is the information that we need to adjust the dose for certain drugs.

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So the question really is what is really important and when would we like to and when do we need to inform a clinician ordering a particular drug, and that's again the discussion based on St. Jude's and their prescribing habits and also the number of drugs and what they use and the preferential drugs and what they use. So one of the drugs we started to work on was codeine as well as thiopurines. And so CYP2D6 for codeine and TPMT for thiopurine became key genes which we implemented in the very beginning.

And so for CYP2D6, ultra-rapid metabolizers, obviously, that's important to know if you have a patient who is an ultra-rapid metabolizer or if you have a patient who is a poor metabolizer. And so those two categories became priority for TPMT. Whether you're heterozygous, homozygous or indeterminate obviously all plays a role and so all this became priority results and will reflect in the medical record.

So let me show you and walk you through the decision support. I showed you some screenshots of what was developed there to help physicians guide their decisions on how they describe drug and build the infrastructure.

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And so the first thing was obviously we build the decision support where we looked at the genotyping results, put the interpretation and haplotype and assignment of the metabolizer status together and put this in the context of a specific drug.

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Because as I said before in the beginning, particularly for CYP2D6, there are a number of different drugs, and obviously it will be a challenge and needs a specialist to really know exactly drug, exactly what dosage and what recommendations are available and necessary and link to this and adjustments necessary for a specific drug related to specific genotypes. So I think this is a prime example where intelligent, well-curated decision support and EMR, electronic medical record, will be tremendously beneficial. And incorporating the decision support in the EMR is really a critical tool.
And so there are two areas which you need to focus on this. Obviously you need a pre-alert or a post-alert. Pre-alert is if a physician would like to prescribe a drug and there is no genetic information available right now. So for TPMT and for a lot of other drugs it’s required or it's almost mandatory to obtain genotyping, and in that case we would like to have a warning directing the physicians to the fact that there are no genotyping results available.

Post-alerts obviously are in the context of preemptive genotyping, very important. If the genotypes are already available, and I think it will be important for a physician to know that these results are there and you might want to consider the results of the preemptive genotyping in his decision of what type of drug to use or how he wants to dose the drug so he can adjust the drug or potentially switch to a different drug as an alternative.

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So here is just an example of a screenshot, and we actually published it also. There's a recent publication out from the group here. An example of the pre-alert is if a physician would like to order thiopurines and the TPMT genotypes are not available, and I think for physicians, it's always very easy if everything is easy and very convenient. And you can see it implemented right at the bottom here. You could easily just then order a test. You don't need to switch back and forth ordering the test. It's directed right away to order a genetic test.

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So for post-alert, then for genotypes which are relevant and which are considered priority, those will actually get entered in the patient's problem list, and that really then triggers the decision support if a particular drug which is linked or related to this particular gene is ordered.

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So for example, for CYP2D6, if you're a poor metabolizer and you're prescribed a certain drug, then a window pops up here like in this example where, for example, if you're ordering codeine like in this case here, you will have the warning that this particular patient is a poor metabolizer and the conversion for morphine, obviously which is mediated by 2D6, is affected by that and you might want to consider a
different medication or a consult. It gives the physician then the opportunity to adjust his decision or try to reconsider.

**Slide 30**

Overall, it is very important then also, and this is just the automatic warnings, it's also important to really put together an interpretation of a clinical result. Again, St. Jude's has been a leader in this field, and I'll show you some of the very elegant examples how they developed and implemented this and developed a method to provide physicians an insight to the electronic medical record with a very detailed interpretation of the genetic results.

And if you remember, I showed you a little bit earlier the complexity of doing these things, all the different genotypes. In haplotypes, what we see, obviously it's very important to very comprehensively present this to the physician in their clinical report. So here you see one example of a clinical consult report. And obviously with a lot of patients coming through this, lots of genotypes, this needed to be automated as well, but if you do a really in-person consult for every genotyping result, that would very quickly become unmanageable.

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And so St. Jude's developed this wonderful approach to really combining the clinical results, and I'll show you brief the examples here. The consults and the report really are put together with a few different subparagraphs. Obviously it starts out with, as you can see in color-coded, first of all, the phenotype assignment and a number of different versions here, then the interpretation of the diplotype, whether it is a wild-type, prepare like two copies.

Then next follows a paragraph on the dosing recommendations and also a comment on the activity score. And at the very end, obviously, that's specific to a particular institution, a link which a physician, if you would like to have more additional information, you can follow up or ask for additional consult.

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So particularly for 2D6, I showed you we have the complexity of very different genotypes, a lot of different genotypes, and so the approach
here that we've developed, we almost have different comments, different text questions almost like Lego pieces. And depending on the genotype, on the haplotype, then we have the phenotype assignment follows. So for every different phenotype which is available, there is a text paragraph available which describes different phenotypes.

So for example, if you're Code IA you're a normal person, or if you have reduced activity, then that will be. If you're poor metabolizer, you'll probably fall into that category of IC.

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So this here is the Lego pieces or the pieces here if you look at the phenotype assignments. I'll just walk you here briefly. We'll go through all these different sections that we have here. This here would be the text for the diplotype interpretation for 2D6.

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So we can look also at the consult section which describes that which describes dosing recommendations.

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And finally, we have here the section on the activity score.

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And so if you take this all together, you do get the idea that if we start out with a certain gene and we have a certain diplotype. Having these different pieces here, then the genotype and diplotype then translates into this in an automated fashion and puts together and assembles then this clinical report.

And so this is a way I think to automate the interpretation of a highly complex gene and translate this and present this to physicians in an easily digestible method in a way.

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So when we're looking at 2D6, I told you before there are a lot of different drugs which are affected by that. And obviously, all this interpretation and this report needs to be developed for every different drug because the evidence is different for every drug and the
recommendations are different for every drug. And here is just a list of all the different genes which are affected by that. Obviously there is codeine or what we looked at, but there also drugs such as tamoxifen, a drug we picked. So the decision support really needs to be developed for that.

So in the next few slides, I would like to show to you if I so far hopefully have convinced you that preemptive genotyping or genotyping for pharmacogenetics is important and will improve healthcare. I'll show you some of the examples which are out there if you try to, if you want to implement this, and you move forward in this area.

**Slide 38**

So one of the first examples here, again, kind of following with what we did, developing genotyping platforms, one of the first examples which we've developed just over the last few years is the initiative coordinated by the Center for Disease Control, the CDC, and their laboratory program for standards and serviced directed by Dr. Lisa Kalman.

And basically, this initiative combines and develops a standard set of DNA samples and reference materials and genotyping data so that that can get this DNA sample and validate their genotyping platform in house. So we really need to go and improve and coordinate the information exchange, monitor also the reference material, facilitate the distribution of reference materials, and develop really a community process so that these reference materials are available.

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In this initiative, this list is not only focused on pharmacogenetics, but I just want to briefly mention pharmacogenetics. The study itself is selected based on so that we capture a large variety of genotype. Based on previously known genotypes, we picked 137 Coriell cell lines. So if you're interested in that, you can order these cell lines from Coriell and currently we are in 10 labs which genotyped all these samples on various different platforms. We see a list of platforms. Some of the platforms are only type 2 genes. Other ones, again, the genes have a larger set. But all these samples will all be genotyped or have been genotyped using these different genotyping platforms.

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And the genotypes are currently compiled. We're in the process in compiling this and we'll determine consensus genotypes for all the cell
lines. And in the second phase, we'll also determine haplotypes and curating the sequence data after the samples have been sequenced, and then we can get variation sequencing platforms. So all this data will be combined.

The data then will be published. The website will be a searchable and downloadable database. And so this will be I think a tremendous source as new genetic tests will be developed having well-characterized samples which reflect most of the allele haplotypes which are out there.

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Also, I think it will be a tremendous resource for people who would like to do or implement genetic testing and want to have a well-validated dataset.

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I also want to briefly mention CPIC guideline. Again, this is led by Dr. Relling at St. Jude's. It's really an initiative, the Clinical Pharmacogenetic Implementation Consortium. A lot of the information and the interpretation from going from one particular pharmacogenetics gene to a particular drug and how to interpret that is developed.

And the goal of CPIC is to really bring this together in public reports. Again, our idea is not that pharmacogenetics, if we want to do this or not. Really we all believe in this group that pharmacogenetics needs to be done and the question is how do we implement that, and CPIC developed the guidelines and developed and published the guidelines for a particular drug and linked this it to a particular gene. So the reports of this are published and continuously updated. It is peer-reviewed. And so the data there, I think, is also a good resource if you want to or somebody wants to start and linking pharmacogenetics to a particular drug and wants to implement it in patient care.

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And the next step, also, obviously, if you're interested in pharmacogenetics more on a broader scale, the PharmGKB, the database is a huge resource to look up drugs, to look up genes, to look up the genetic information, the variation SNPs, functional effects and impact and interpretation. It's really kind of the community platform, I would say, for pharmacogenetics. So if somebody would like to dive deeper into this, it's certainly a website which is very useful and helpful.
Finally, I want to mention a few other groups in our collaborators who have joined our efforts for preemptive genotyping and I would like to mention a few projects. So this over the years developed from one site now to multiple sites who really understand and appreciate this concept and really want to implement it and in each of their different disease area will collect their own experience.

So we have on collaboration at Boston Children’s Hospital which just joined us recently, and this group, directed by Dr. Manzi, focused on renal transplantations, epilepsy and children with inflammatory bowel disease. Overall, this program has agreed to this and their goal is to recruit about a thousand patients over the next two years, and it will also preemptive genotyping and they will collect the phenotypic data and the genetic data and provide the interpretation for their selected drug-gene pairs and obviously then also will return these results to physicians.

Most recently, we also had a group from Duke, the Center of Personalized and Precision Medicine joining us, and the PI for this study is Dr. Haga. And they really are looking into how pharmacogenetic results can be implemented in medication therapy management process and how pharmacists can get involved in pharmacogenetic interpretation in a collaborative effort in the studies. I hear it's an observational study. We'll also perform preemptive genotyping. And then as the pharmacists conduct medication therapy management, they will implement the pharmacogenetic guidelines in their consult and will be reviewed continuously as a follow-up and really evaluate the feasibility or benefit of this approach here as well.

So as we're coming here to an end, the title was The Pros and Cons of Preemptive Genotyping. The way I had to think about it, I hope I could make a really strong argument for the pros. Obviously, having an important lab test available and the results from the lab test available when important decisions like what type of drug we're going to prescribe a patient, when that needs to be made should, and I hope I could make the argument that this will deliver better care because we can immediately at the time when a decision needs to be made we can make the right decision, adjust the dose, or switch to a different dose for a
particular drug to avoid side effects and improve the overall treatment of the patient.

What we learned is that preemptive genotyping is feasible and it's often cost-effective. Right now, I think if you would order a clinical test for one particular drug and then you see your patient again maybe in half a year and the patient ordered another drug and you need a different test for a different drug or maybe for a third one, if you ordered it as a single test, the cost for it is much more and it's higher compared to if you do more comprehensive genotyping. This is one test.

So I think in that aspect, the technological changes we observed over the last few years in DNA analysis technologies really drove this and really now drives this towards more panels.

I think there are extensive research results that are really available right now to support the decision process. So it's not so much a question anymore of should we really do and what's the evidence that pharmacogenetics is relevant and is important to implement. I think we're reached the point that absolutely for a lot of drugs, for a lot of genes, it's absolutely clear that pharmacogenetics improves outcome and is important in making decisions what drug to use.

And so in that context, having genotyping results, genetic pharmacogenetic results available we think also increase the overall acceptance of pharmacogenetics. If a result is there, when physicians order it, the hurdle of ordering a test and implementing this knowledge is much lower. Because as I showed to you, if we have this decision support available in the medial record, I think the hurdle to really look at this data and make this part of the decision process I think is much lower. And so I think preemptive genotyping also should increase the acceptance and utilization of these types of results.

The cons, obviously we are biased because we do think that preemptive typing improves healthcare and the healthcare delivery. But really the only cons are that genotyping is always an easy part. The implementation is really the challenge. And that's actually not really a con. It's just really more a challenge.

And as we see there from our collaborators and as we talk to many different groups in the field, the needs, what type of drugs, what type of diseases different healthcare providers are focusing on obviously is very
dependent. So we started out with pediatric disease. We also are in contact with a number of different groups. We look at adult patients. The drugs are slightly different. The drugs are different. Surprising enough, obviously, the genes are almost kind of the same.

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Sean Sanders: So when we look at that, the lessons that we learned as a group and what we continue to learn, this is really a continued learning process because although we've been doing this for quite a few years now, I think we're still at the very beginning, and this is really a continuous learning process.

The implementation, as I said before, is very site-specific. It really depends on your institution where you work, on your hospital, on your clinical needs, and it also depends very much on your patient population. So if you see adult patients, patients with cardiovascular disease, obviously the needs are slightly different, and if you're looking at patients with childhood cancer, as we did before.

But I think one of the key areas which are always necessary if you're thinking of contemplating about implementing this or as we go forward with that, you really need to capture the opinion of your opinion leaders because the physicians and the healthcare provider, I mean these are really the people who make the decisions.

You obviously have to look at what are the needs and where you can benefit and what drugs are mostly prescribed and widely utilized. One key component, I didn't really mention this, is really education and collaboration and continued evaluation in this multidisciplinary team. This is really truly a multidisciplinary approach and it really needs all these different groups. It needs a clinical lab which understands pharmacogenetic testing. You need to have buy-in from pharmacies, from pharmacogenetics experts, physicians, and also medical records.

And I think the lesson which we can summarize this is really the combined effort from all these different groups was really a major strength and it measures strength of our project.

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So finally, if we think about the challenges ahead of us, obviously, a continued evaluation of the scientific evidence I think is absolutely key. You heard about this that pharmaceutical companies are developing companion diagnostics. I think we are also seeing this. We are just at the
very beginning of this. Now, these might be genetic tests. These might also be other genetic tests, other protein tests. It doesn't have to be only genetics.

The concept to this type of data is the same that you have to be able to present this in a comprehensive way to provide decisions for decision support around this. So integrating the avalanche of data, not just genetic but also anything related to the particular drug into medical records continues to be a challenge, and I think progress in terms of automating and developing the infrastructure of this I think will be key.

Obviously, the question is what actionable? I mean medical records over time will collect a lot of this type of information and then bringing this together and determining what is actionable in relation to the particular decision that physician needs to make I think are very key points and need to be discussed most likely at a case-by-case basis for a particular drug or a particular intervention.

[0:45:18]

I still think it will be a challenge for the foreseeable future to present and maintain clinical data so it's available just in time and it's available at the very different sites where a patient gets healthcare services. So obviously, patients go to very different physicians, healthcare providers. And if we have genetic information, that should be accessible to everybody who does that. And as genetic information and pharmacogenetics information retains the value, as I said in the beginning, how do we share this information over different platforms and over time I think is a challenge.

And then really, if we're looking more on the research side, we really need to understand how exactly these genes work, what's the function, what's the biology behind that. And as we get more and more information and we learn more about this that are certainly big challenges on the scientific side because just association from a particular genotype to a particular effect is obviously useful. But I think in terms of improving healthcare, developing new drugs, understanding mechanisms, understanding function I think will be absolutely key.

So with this presentation, this is really the collaborative work of many, many groups, and I've been very fortunate to work with that many groups here. As I mentioned, St. Jude's. I also want to again mention the CDC with their initiative, then Duke, as well as Children's Hospital of Boston.
And finally, I also would like to mention all the people here in my lab and our diagnostic lab who over the last few years contributed to this on the genotyping site as well as in our data processing site.

So with that, I really want to thank you for your attention and I'm very much looking forward to hopefully a very lively discussion.

Sean Sanders: Thank you so much, Dr. Broeckel. Wonderful presentation.

Now, we're going to move right on to the Q&A session. We’ve received quite a few questions to get through. We have about just over 10 minutes to do so. So I'm going to jump right in. But there is still time to submit a question if you want. Just type it into the box and click Submit. If you don't see the box, click the red Q&A widget and it should appear.

So the first question that a number of viewers have asked in different ways is outside of a clinical research protocol, who would pay for this type of preemptive testing?

Dr. Ulrich Broeckel: That is a very good question. And so when we started the project, it was our goal really to implement this first. And clearly, as we now have more data and we have the experience from a few years now, we're really looking at getting reimbursement for this.

And I think the conversations, what needs to happen with various insurance companies that I know are collaborators at Boston Children's are having this discussion, it's that insurance companies do pay in the context of certain drugs. They do pay for pharmacogenetic testing.

And so I think the discussion and I think what we are pushing forward with this discussion is to really make the argument is that it is much more cost-effective and beneficial and it improves outcome to have a broad array of genotypes for a number of genes available compared to just ordering test by test.

And not going into detail to how much it's exactly going to cost, I think technology will advance as well and reduce cost. I mean we've certainly have seen this in the genomics field over the last 5 to 10 years that the cost really decreased substantially and the data increased exponentially. I
think insurance companies should be open to the argument that if we order one gene test and we order another gene test, that's already more expensive than if you have a well-established genotyping panel. And I think in that context, that's the discussion that we need to have.

But I absolutely agree that particularly in the context where we are right now of reimbursement that this is a discussion that we need to have. But I personally am very optimistic that with the data that we collected, we can show the advantage of this, where we can show that this actually does save money in the long return that insurance companies will understand and will pay.

Sean Sanders: So how do you see this kind of preemptive pharmacogenetics being applied in clinical trials especially in the early stages of trials?

Dr. Ulrich Broeckel: Yes. So I'm a strong believer in pharmacogenetics. And over the years we've obviously had discussions with various pharmaceutical companies. And I certainly think that pharmacogenetics needs to be, and the information around this needs to be implemented at a very early stage.

I think pharmaceutical companies do recognize that. I mean they look at obviously metabolizer status for drugs if they are known for example to be metabolized or insulin-spiked 2D6.

So I think it needs to be implemented. I think and I'm not sure if that concept translates in as much as one would say we do pick certain individuals with a certain genotype to do pharmacogenetic studies. I think that's one way how to do it.

But I think over the last two years, the concept of genetics and genomics really matured, and it's demonstrated by the fact that a lot of companies, pharmaceutical companies are now thinking about it and are pursuing development of companion diagnostics. So I think we all realize that we're not all the same and there is variation in direct response that is in part affected by genes and it will be implemented.

So I actually see this coming, and all have been demonstrated by the FDA. They are really recognizing and they are looking for genetic information. I think we're at the beginning of this. I think it's clearly people clearly realize that this is coming.
Sean Sanders: Excellent. Now, what is the approach of pharmacogenetics for treatments that require multiple drugs that have similar or maybe different administration profiles?

Dr. Ulrich Broeckel: That is a very good question, and I think at that point, so it's not only that a gene affects a drug. You can prescribe a number of different drugs which interact with each other which interact with genes. And so at that time, I think this really becomes a truly multidisciplinary question and really needs to involve both the physician, the pharmacist and pharmacogenetics experts. And I think pharmacists are quite well-trained around this. I think we're still short in terms of like developing the expertise around pharmacogenetic and really interpreting this. But there are examples where for example if two or three different drugs are prescribed, pharmacists do consult on how to address that and there are discussions around this.

And so in this context and in this framework, then adding also the genetic information and having the discussion with somebody trained in pharmacogenetics I think will be important. And so we do have discussions, but I think one of the areas where we could improve substantially is really have pharmacists trained in pharmacogenetics and really expand their knowledge by pharmacogenetics as well to really add that expertise to this team.

Sean Sanders: And I've come to a few more specific questions about the study that you did that maybe we can got to quickly. What database did you use to store your genotype data and how did you match it up with the phenotypic data?

Dr. Ulrich Broeckel: So the database currently is developed at St. Jude's, and then the medical record they use is Cerner. But a lot of the logistics of the support behind this is obviously transferable. And if I can make a quick advertising for this, together with St. Jude's and Boston Children's Hospital, we did submit a grant to NIH just very recently to make this more available and to develop this more as an infrastructure.

So I'm not sure if there are any reviewers on this panel, but our goal is obviously to disseminate this. It's also part of CPIC who would like to disseminate this information. And obviously, if people are interested in this and would like to have discussion and collaborations, I think we certainly will be open to that.

Sean Sanders: Can you tell me about how the patient samples were collected and prepared in your studies?
Dr. Ulrich Broeckel: Well, I mean it's a routine blood draw currently because it's a research study. We did the concept as part of research study. The participants also sign a consent form, but that would not be necessary. We have conversations with a number of other groups who basically just ordered this as a clinical test.

It is a clinical test. We're offering this as a certified clinical test by the CLIA. And so if one would like to just order this as a lab test, we have a test request form that can be submitted. And so patients are -- the test is drawn as a normal blood draw, and then depending on how the data will be then added to the medical record it shows up as a normal genetic test.

Sean Sanders: And you mentioned obtaining consent from the patients. Maybe we can talk a little bit about both consent and privacy. What are some of the considerations that physicians should be looking at?

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Dr. Ulrich Broeckel: If you want to do research and want to present the results, and I think that with the approach in the very beginning when we looked at that that it's a research study we'd like to get to experience and we'd like to publish as we did, and so I think in that context, consent makes sense.

Privacy, there's a lot around privacy and genetic data. And I think that we probably would cover that in a whole webinar about how to deal with genetic information.

And so I want to give just a few thoughts. So I think genetic information obviously is critical and it may be different than just a routine blood test. It impacts also new family members potentially and so it needs to be, I think, handled and recognized in this context. I think we feel very strongly that how we handle data is secure and does not get disclosed to insurance companies, and I think the framework there is a place for this particular study.

But there is a difference between clinical data or just lab results over blood tests, hemoglobin or something, and genetic information. And it needs to be protected in a special way to recognize these differences.

Sean Sanders: Getting on to the regulatory side of things, do you have any concerns about FDA regulation of clinical decision support tools as medical devices?
Dr. Ulrich Broeckel: I think there is discussion around this. I think we certainly and I certainly appreciate that the FDA is really getting more involved in this area because I think that really provides the necessary guidance. I think the FDA really recognized that pharmacogenetics is important. They are now looking at this type of information if pharmaceutical companies submit drugs for approval.

So I think this whole area really develops and needs to develop. And so getting guidance from the FDA and having a form with the FDA to discuss this, I think we certainly all appreciate this. I mean ultimately, it's really about insuring good healthcare and healthcare delivery. And so I think really developing this area by the FDA and reviewing this I certainly see is positive.

Sean Sanders: So the next question I think is an interesting wrinkle that somebody poses. What happens when some of the data you're paying supports the use of a certain medication but other data from the same or different test supports evidence against the dues?

Dr. Ulrich Broeckel: So yeah. So maybe the question would be well, pharmacogenetic test results would recommend that we don't use a drug but maybe the clinical evidence or maybe lab results or a histology or pathology results would really direct towards this particular drug.

That is a very good question. I think that's true for many things. So if you go back to the example where we say, "Well, we have an alert coming up," we still have the opportunity or the physician has the opportunity to overwrite it and say, "You know what, I mean I recognize this, but maybe this is the only drug I would like to prescribe to a patient and I'm fully aware of that, and I just need to look maybe for the occurrence of side effects more carefully."

So I think ultimately, any decision or any lab result, any test that we're going to get is one piece of information which will be put together to decide how a patient is treated and decide on the treatment plan. So I hope I didn't make the argument that this is really set in stone, and if we have this genotyping result that's the only way how to do it.

So all of our clinical reports also reflect that the genotyping results, the genetic results really need to be seen in the context of the whole patient. We never only treat a genotyping result. We also never really treat only a histology slide. We always treat the whole patient. I think for that, you really need to bring this all together to come to a comprehensive evaluation. So I think that is true for every decision as a way how a
patient gets treated. So it really comes together and you need to take this together in the context of the whole patient.

Sean Sanders: I'm just going to squeeze in one last question, and a couple of people have asked, "Why not use something like next-generation sequencing for this type of application?"

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Dr. Ulrich Broeckel: That's an interesting question. Again, we can talk a little bit longer about this. I think in any case, if you decide independent of next-generation there is a next next-generation or a couple of other new technologies coming out, who knows, I think there are a few criteria independent of the platform. I think that one is obviously the price. The other one is the ease of performing the test, the liability, the accuracy, and the completeness of the data.

And I think in this whole context, every methodology really would need to be evaluated throughout this. I think currently, if you look at the discussion about whole genome sequencing, I think for some of these drugs, you really need information and all different variants to come up with an accurate assessment of the genotyping results.

And so I think some of the technologies might not be as advanced to really give this complete picture. If it's happening maybe in five years or ten years, it's really hard to predict. But I think if somebody decides on what type of platform you would like to use, you really have to look at how complete is the data, do I really get the results of every variant, what do I need to see to assess fully the structure or what's the accuracy.

And I think there are a couple of other methodologies really out there, and then you look at the cost. And I think some of the not so novel and very new methodologies might just actually also be able to provide this type of test as well.

So I think technology will change. The key thing here, and I hope I made this argument, is how we deal with this type of information and how we build the infrastructure around this.

Sean Sanders: Excellent. Well, we are unfortunately out of time for this webinar. So I wanted to sincerely thank Dr. Broeckel from the Medical College of Wisconsin for his very interesting talk and for answering so many of the viewers' questions.
Many thanks to the online viewers for the questions you submitted. I'm sorry we didn't have time to get all of them. Please go to the URL now at the bottom of your slide viewer to learn about the resources related to today's discussion and look out for more webinars from Science available at webinar.sciencemag.org.

This webinar will be made available to you again as an on-demand presentation within about 48 hours from now. We'd love to hear what you thought of the webinar. Send us an email at the address now up in your slide viewer, webinar@aaas.org.

Again, thank you to Dr. Broeckel and to Affymetrix for their kind sponsorship of today's educational seminar. Goodbye.