Pharmacogenetics - Vicky Pratt

Male Speaker:
Hi, great so we're in the final, final call of the Insurer Staff Education Webinar series. And Doctor Vicky Pratt from Indiana University is going to talk to us about pharmacogenetics.

Vicky Pratt:
All right. Great. Thank you Bob for having me talk for a final, final, final, one on pharmacogenetics today. So, I thought I give you a couple objectives of what we're going to go over today. We're going to talk about the Star Allele Nomenclature, which is specific to pharmacogenetics. And then differentiate between various metabolizer phenotypes. And this is all part of the pharmacogenomic and pharmacogenetic words that are often used when we talk about pharmacogenetics. And then recognize the common drugs that can have adverse drug reactions. So, I'll use pharmacogenomics and pharmacogenetics somewhat interchangeably but really, we're talking about precision medicine and getting the right dose to the right patient.

So, if you look really what is pharmacogenetics you can Google on the Web and look at different sort of definitions, but it's really about genetic changes that can give rise to different responses to different drugs. And looking at those genetic changes and how they affect drug metabolism. So, this is from the Personalized Medical Collation from a report a few years back, and if you look at various different kinds -- or types of drugs people respond to them differently. If you look at hypertension, specifically Ace inhibitors, about a quarter of folks who take this drug, it doesn't work for them. And beta blockers it's about 15 to 25 percent of those drugs don't work well for them. Antidepressants, up to 50 percent of antidepressants are ineffective. Statins, it can be up to 70 percent and asthma or the beta two-agonist, can be also up to a 70 percent. So, there's a lot of trial and error to see if a medication will work for people. And looking at pharmacogenetics is a way to help reduce that trial and error.

So, this a partial list that I put together a few years back, of some various kinds of changes in genes and some of the drugs that are involved with sort of a drug gene pair. There's two important concepts when you're thinking about pharmacogenetics. And I'm a geneticist so my caveat is I try to make this -- if I can understand it as a geneticist then hopefully everybody else can understand it, is that pharmacogenetics is what the body does to a drug. So, if we look at the first image, this is an active drug that the body inactivates over time. Then in the second profile this is an inactive drug that the body activates and then slowly inactivates over time. Pharmacodynamics is what the drug does to the body. Where is the most effective dose of the drug? This is when you take -- so when you take a medication you take it twice a day or three times a day with meals. So, you will see peaks -- or I mean troughs and peaks of drug concentration in the body. And the idea is to eliminate the effects of the peaks and troughs and keep the drug concentration in the body at the most effective concentration.

So, a lot of what we're going to talk about today is not necessarily the pharmacodynamics, but we're going to talk about pharmacokinetics, especially related to some of the drugs and genes that we're talking about. So, if we look at adverse drug reaction, about six to seven percent of all hospitalization have an adverse -- or are a result of an adverse drug reaction. And it accounts for about 100,000 deaths each year. About the fourth leading cause of death. One in five, or 20

percent of drug candidates that are under development are actually terminated due to an adverse drug reaction that is seen in patients. So, I like to think about, and here I'm talking about pharmacogenomics, that there are three major kinds. We have our inherited or constitutional changes in our DNA, in a patient's DNA or our DNA that effects how drugs are metabolized in our body. So -- and that's where we're going to spend a lot of this talk today. The other one is the somatic or tumor specific changes and this is the KRAVS [spelled phonetically], and the BCR Ables [spelled phonetically], and C-kit's, and B-RAP [spelled phonetically], where there is a lot of work really targeting that cancer to a specific drug to kill that cancer, or control that cancer. And then what we're not going to talk about today that I like to think of in pharmacogenetics is also for infections such as HIV and HCV. There's changes in those viral genomes that drugs are specifically targeted against. So, based on the variance seen in HIV or HCV there are certain drugs that are more effective in treating those infections. But we're not going to talk about those.

I want to introduce you to a specific term called a Companion Diagnostic. And that's where most of the oncology type stuff area is right now. And this is where the drug and the pharmacogenetic test are approved by the FDA at about the same time. So, a drug manufacturer they're working on looking at lung cancer and they see that out -- this drug works in out positive breast cancers and so that test and that drug went through the FDA at the same, or similar time and were approved together by the FDA as a Companion Diagnostic. So, let's talk about the inherited or constitutional variance. The primary close up of a gene family called the Cytochrome P450. Most of these proteins are located predominantly in the liver and they're involved in the toxin and drug metabolism of the body. So, I want to introduce you to the nomenclature around the Cytochrome P450. Because it can be a little bit confusing. So, it's called Star Allele Nomenclature and a Star One is considered the normal allele where no variant or mutation is detected. All the Star Allele are numbered in order of description and there are sub alleles that are alphabetized in order of description. And there's a website that was started out of the Karolinska Institute in Sweden that summarizes all these Star Alleles. And I will disclose that this is actually -- the folks that started it in Sweden are actually retiring, so this is moving being a U.S. and multinational consortium and I am on that consortium that we're taking -- where we're taking over the Star Allele Nomenclature.

So, if I show you an example, so if we look inside a CRUMP 2D6 [spelled phonetically], so cytochrome, CYP is for cytochrome. This is the protein family the 2D6, so it's the family to subfamily D isoenzyme six if you're looking at the protein. The CYP2D6 itself is just is also the gene. So, since I'm a geneticist we're mostly going to talk about the gene. Then, we have a nice Star here and after the Star is -- so if we have a Star Four it’s the third -- remember Star One is the no variant detected. So, it's the third variant described and then if we have an F it's the fifth subvariant described in that gene. So, this is an example from the CYP Allele website looking at 2D6 Star Four and this is just a partial list. So, to be a Star Four you have to have an 1846 G2A [spelled phonetically], and this is in HGVS nomenclature. So, you have to have an 1846, and that's what's in bold in this slide. So, that's the defining variant. This is old school haplotype analysis. So, also on that same allele you usually see a 100 C2T-variance [spelled phonetically] and a 4180 G2C variant [spelled phonetically]. And you can see in all these sort of sub alleles there's different combinations of other variants that were observed in that haplotype. I will also point out that specifically down here, remember our 1846 is our defining of variant in Star Four.

But in this instance here in Star Four M, 100 C2T and 418 ADG2C [spelled phonetically] were not observed. So, there can be Star Four alleles that don't have the 100 C2T or the 4180 G2C in it.

So, if we take a look at each allele, one that we inherit from mom and one we inherit from our father. That taking all those variants we are going to assign a function to that allele. So, CPIC which is the Clinical Pharmacogenetic Implementation Consortium, CPIC, there's a website here, put together a project in trying to standardize that nomenclature of allele function designation. So, a normal -- well, there's such -- so a normal allele or even if most of the time it's like our Star One, that is a normal function allele. An allele can be a decreased function allele, you can have a no function or nonfunctional allele, an increased functional allele. And then I'm certain that you can have an uncertain or unknown functional especially in newer alleles at different methodologies such as next generation sequencing. And as a unique combination that's observed and you really don't know whether the function of the allele in that individual. So, when a lab looks at the various combinations of alleles and assigned a function, they use that to assign a metabolizer status. And a metabolizer status is just the phenotype or the predicted phenotype based on the genetic variance observed in a person.

So, if you look at a normal metabolizer, and I have in parentheses that it's called an EM. It used to be called an extensive metabolizer, but most -- but again back to CPIC that group standardized the nomenclature in pharmacogenomics. So, if you have to functional alleles you're called a normal metabolizer, and in old school it was previously known as extensive metabolizer, which you may see in the literature. Somebody who has a decreased functional allele and a nonfunctional allele, or no functional allele that person is called a reduced -- or excuse me I have this one in sort of a different, it's called intermediate metabolizer, and that's my bad. And --but it's sort of a reduced functional metabolizer. So, the correct nomenclature here is intermediate metabolizer which is this IM. But think of this as a reduced metabolizer. There's a poor metabolizer that has two no function alleles, or a PM. And then there's a rapid metabolizer, which has one increased function allele, or an ultra-rapid metabolizer which has more than one increased function allele.

So, I want to sort of give you how I think of this, is that if you look at a normal distribution of people. And in general, when you're talking about drug metabolizers, most of the time you're worried about the people at the far end. The ultra-rapid metabolizers and the poor metabolizers. In the middle is the normal metabolizers, oops I clicked quick, are the normal metabolizers. And then you have this sort of reduced intermediate metabolizer between the normal and the poor metabolizers. If you're looking at different -- even though your gene type doesn't change you can look at various different drugs and in some people that window is really a narrow window between -- for the intermediate reduced metabolizer. And in others that window can be much bigger. And that is drug specific not necessarily genetic specific.

I want to introduce you to also it's not just your genetic changes, but there are other things that effect metabolizer status. There are certain non-drugs that can affect metabolizer status. So, if you've ever taken a medication that says do not take with grapefruit juice, and the reason is – I should say grapefruit and grapefruit juice, is that that it inhibits Cytochrome 3A4. And this is one of the major pathways that many drugs go through. Broccoli, actually if you eat your

broccoli, it actually induces cytochrome 1A2 to work a little bit better. If you take Saint John's Wart, and some people this is an herbal supplement that many people take over the counter when they're feeling a little blue or for depression, this actually induces the 3A4. Now, if you look grapefruit inhibits and Saint John induces, I'm not sure that they cancel each other out. But -- and I wouldn't try this at home, but there are things that can affect how our Cytochrome P450's work.

So, I'm going to go over one of our first examples, it's Cytochrome 2D6. There are more than 100 different unique alleles that have been described. And it's estimated to metabolize about one-fourth of all drugs. Remember I told you that we need to worry about our ultra-rapid and our poor metabolizers. About five to ten percent of Caucasians are actually poor metabolizers, for Cytochrome 2D6. Some of the medications that 2D6 metabolizes, are antidepressants such as fluoxetine and I will apologize in advance that I screw up the pronunciation of many medications. It's involved in pain management such as Codeine, antipsychotics. And then there are drugs such as fluoxetine, if you're taking it actually can inhibit 2D6. So, that's important for the people that are intermediate or reduced metabolizers that -- where fluoxetine may not work very well because while it goes to the 2D6 pathway it also inhibits the 2D6 pathway.

We're going to talk about a specific sample with 2D6 related to Codeine. Codeine can be used in the treatment for pain, it also can be used to treat cough, and diarrhea. You may have seen on T.V. there's commercials that say, what is it, opioid induced constipation. So, Codeine is one of those that is an opioid induced -- causes opioid induced constipation. So, it can be used to treat diarrhea. In the U.S., it is currently accepted for medical use, but it has severe restrictions. So, essentially you need a prescription to get Codeine. In Canada, and other countries you can actually get it from behind the counter in the pharmacy without prescription. There is abuse of Codeine in that it can lead to severe psychological or physical dependence on Codeine. So, Codeine is largely an inactive drug. It does have some pain -- can alleviate some pain, but it's largely an inactive drug that is metabolized through 2D6 to its more active form morphine. And then there's clinical Pharmacogenetic Implementation Consortium guidelines related to your genetics and how to dose for that.

In the U.S., there's actually a black box label or black box warning on Codeine, especially for nursing mothers. Codeine and Morphine -- actually I should say Morphine can get into the breast milk and there's been babies that were nursing that actually died because they got too much Morphine at one time and these babies have died. So, this has led to a black box warning about Codeine that people that are ultra-rapid metabolizers get too much Codeine too fast especially children. And this is why Codeine is also contraindicated in kids getting tonsillectomies. That also rapid-metabolizers get too much Morphine and they can stop breathing. So, about one to ten percent of Caucasians are ultra-rapid metabolizers, three percent of African Americans are ultra-rapid metabolizers, about one percent of Asian, especially Chinese, Japanese, and Hispanics are ultra-rapid. And in the population, that's really high ultra-rapid metabolizers that is North African, Ethiopians and Saudi Arabians, a little over a quarter of people are ultra-rapid metabolizers.

So, this is from PharmGKB website, and if you look at Codeine, and remember all our Cytochrome P450's are mostly in the liver, so Codeine gets into the liver, and then goes through

the 2D6 pathway here to become its more active form Morphine. So, remember if we look at the -- see now I get confused again -- if we look at -- to profile this drug, this is the inactive drug that gets activated and then inactivated through these pathways and eliminated from the liver and the body. So, if we look at dosing for Codeine in intermediate metabolizers it is recommended to increase the dose of Codeine because it may have insufficient pain relief. And either that or consider alternate analgesics. For poor metabolizers Codeine doesn't really work at all for these folks. And that you should avoid giving Codeine to them and another drug that's also used for pain relief which is Tramadol that goes through the same pathway. And ultra-rapid metabolizers, so this one you're using for avoiding because of inefficacy of the drug, the drug just doesn't work very well. In ultra-rapid metabolizers, it also is recommended to avoid Codeine and Tramadol because in these folks the Codeine gets changed into Morphine way too fast and it can cause issues with people to stop breathing, so in -- especially in children and newborns, though in adults most people tolerate it fairly well. But I've known a few ultra-rapid metabolizers and they really like Codeine because it really kicks the pain real fast. So, if you're looking at CPIC guidelines, and this is from CPIC guidelines, that ultra-rapid metabolizers, and this is sort of what I just put in that summary slide, is that avoid Codeine due to potential toxicity, and poor metabolizes avoid Codeine due to lack of efficacy.

I'm not going to go into this slide way too much, but there are DNA tests, or DNA testing platforms that are available for lab. This is more for lab folks who would be interested. Another example we're going to talk about today is Cytochrome 2C19. There's more than 25 alleles described with this gene and about three to five percent Caucasians are poor metabolizers and about 15 to 20 percent of Asians are poor metabolizers for 2C19. Some of the medications that go through 2C19 are the proton pump inhibitors such as Prilosec or Omeprazole. And antidepressants like amitriptyline, citalopram, escitalopram, Clonidine, and then an example we're going to talk about today is clopidogrel, or Plavix. This is looking at the Star Alleles and this is how the lab and people predict the metabolites or phenotypes is looking at the various combinations. So, as you can see where no variant is detected or our Star One, Star One, or our normal metabolizer isn't it and about 35 to 50 percent of people sort of fall in this range. The more common alleles are Star Two in Caucasians and Star Three in Asians. And the rest of these changes in 2C19 are far more rare.

So, if we look at our example of clopidogrel or Plavix, it is used to treat coronary artery disease, peripheral artery disease, and cerebral vascular disease. It is metabolized by Cytochrome P450, again this is an inactive drug that gets activated in the body, and it has this nice big long name that I'm not going to talk about today. A few years back the FDA announced that if you're taking clopidogrel it can't be taken with omeprazole or esomeprazole because they actually inhibit 2C19. It's used to, it's also, Clopidogrel, is also used in end stenting and stenting, and along with aspirin to prevent thrombosis after stent placement. In 2010, the FDA changed the black box warning on the label to say that poor metabolizers do not effectively convert Plavix to its active form. And then there was a big media campaign in magazines and on T.V. to let people know that poor metabolizers should not be treated with Plavix. At the time this black box warning went into effect there were no other medications that were available as alternatives to Plavix or clopidogrel. The FDA recently updated the label and I've put this in red, just this past fall in 2016 that the drug label suggests that there is different platelet P2Y12 inhibitors that can be used in patients identified as poor metabolizers.

So, if we look at clopidogrel here, remember it's an inactive drug that goes through -- and this is a little always sort of different these pathways. They're probably a lot of things that are not here, but it goes through, and in 2C19 here as well as various other genes to become the active metabolite. And then this active metabolite with the big long name then binds to the receptor on the platelet to prevent it from aggregating or developing a clot. So, if this is blocked then clopidogrel is just eliminated through the body and then cannot bind to the platelet. So, the CPIC guidelines recommend that if you're an intermediate metabolizer that you take prasugrel, or ticagrelor, or some alternative therapy if there's no contra indication. As well as the poor metabolizers, also you take prasugrel, or ticagrelor, or some other therapy if there's no contraindication. In the ultra-rapid metabolizers, it's fine to take clopidogrel you get a little bit more in the system a little bit faster. It doesn't cause any issues. Though it has been reported with some association for a risk for bleeding. Again, this is the CPIC guidelines that I just summarized on a previous slide so I'm not going to go through that again. And for the lab folks or the people that are interested there's lab developed tests or lab developed procedures as well as FDA and research only platforms for performance testing. There is one test out here, I'm just going to remark on this one, this is more of a point of care test, it's verified now. It's a platelet function test. A platelet function assay that does not test for the genetic variance, but only looks at the platelet function to see how well the clopidogrel is binding to the receptor. I'm not going to go too much over this slide only to say that there is some variability in the platform in what alleles that they test.

We're going to go into our third example which is Warfarin or Coumadin. And it was named I thought an interesting bit of trivia that Warfarin got its name from the Wisconsin Alumni Research Foundation, or WARF, that originally patented it. So, just to be a little silly, so, if Indiana patented it, it would have been IARF, I think WARF sounds a little bit better. So, good thing it was named in Wisconsin instead of Indiana. So, it was originally marketed as rat poison. So, basically it was mixed with corn the rats would go eat the corn with the Warfarin on it and then they go off and bleed to death and die. So, in the early 1950's there was a military recruit that really didn't want to go into the army and so tried to become rat like and eat Warfarin, eat the rat poison, and then really started research into the anticoagulation properties of Warfarin. Right now, it's prescribed more than 30 million times in the U.S. each year and accounts for a little over 40,000 ER visits each year. As once people are on it gets unstable on it. There's a very narrow therapeutic window for Warfarin. So, get a little too much you're bleeding. Not get enough you clot. So, it's part of that whole clotting cascade that keeping that in control can be difficult at times.

There's two major genes associated with about 40 percent of the variability in the drug response for 2C9, and those are 2C9 and VKORC1. I will tell you – I think I got this slide in here – there's a website called Warfarindosing.org, there are some other websites, but this is probably one of the ones that many people use that can take somebodies genotype and look at their genotype their weight, their height, their age, other medications that the patients taking, and then help predict what's the most optimum starting dose, and how to change the dose of Warfarin for a patient. Currently, patients are monitored with an INR or an international normalized ratio. So, somebody who's had a blood clot and are taking Warfarin really want their INR between two to three. If it goes significantly over four that patient is at risk for a bleed. And my grandmother

who has since passed away, she had a blood clot in her leg and was prescribed Warfarin. And the first time she took her first dose of Warfarin her INR, and she was in the hospital at this time, her INR went to 12. And so, just to say that that one dose that's how fast the INR can go up and change and cause a bleed and somebody can die from that. So, if you do a genetic test or have the genetic information that can help with -- that can help keep that from going up so high.

So, if you look at the package insert on Warfarin, based on the genotype it really says how to get to a therapeutic INR. So, if you have, remember Star One, Star One is no variant detected. So, if you're a Star One, Star One, and you have the GG, or nonvariant for VKORC1 you really start this dose at five to seven milligrams per day. So, in somebody that's a poor metabolizer for 2C9, somewhere down here you want to start them with a much lower dose because -- then avoid their INR from getting too high. So, if we look at 2C9, there's more than 35 alleles described and what I haven't completely mentioned, I touched on a little bit, is that certain alleles are more common in certain ethnic populations. So, for 2C9 the more common alleles that you see in a Caucasian frequency were Star Two and Star Three, and when originally were for dosing. And on a package, insert you really only see the Star Two and Star Three, and it doesn't really account for other ethnicities. People of other ethnic backgrounds as well. So, in African Americans you'll see the Star Four --I mean the Star Five and the Star Six, and some other ones. So, I do know CPIC is updating that and their guidelines around that for different ethnicities. And I do have a slide on that coming up.

So, VKORC1, vitamin K, two three epoxides reductive subunit one, really is a haplotype. Most people test for this minus 1639. There are some people that may also test for this 1173 C2T. But there's other variants in the haplotype. And I believe at Warfarin.org it really only accounts for the 1639 because you only really need to test this one. These are additional variants that aren't necessarily needed to be tested. So, this is the updated algorithm that CPIC just published earlier this year in 2017. That if you look at Warfarin dosing, so is there a genotype available? Yes or no. Then, it really talks about the different ethnicities that if it's non-African ancestry it's really fine to do the VKORC1 and the 2C9, Star Two, Star Three. And then do a Dowds calculation on that. If you look at the African American ancestry you really need to test for different variants. Specifically Star Five, Star Six, Star Eight, and Star Eleven. And then that dosing may change and then there's another recent variant that's been published. And I'm not sure which gene this is in, that looks at this, and you change the dosing because Warfarindosing.org originally didn't have good algorithms around African Americans. But I believe they have updated that, but I'm not sure. So, there are different platforms to test for Warfarin that include 2C9 and VKORC1. But the variants are different among those different platforms.

Our fourth example that we're going to talk about today is UGT1A1. So, mostly we've talked about phase one metabolism. You know taking a drug sort of at the beginning of the pathway. UGT1A1 is about phase two metabolism. And this is about eliminating the drug from the body. So, UGT1A1 is a complex and I'll show you a slide in a second. It's used for metastatic colon cancer, drug irinotecan. And also, irinotecan is in a drug combination such as fluoxetine, sulfanilamide, and then atazanavir for HIV therapy. This also is a gene that's involved in Gilbert Syndrome a genetic disorder of hyperbilirubinemia. That just causes transient hyperbilirubinemia or jaundice. So, if we look at -- this is the UGT1A1 gene complex. So, there's the common exons two, three, four, and five, down here. But there's different alternative

first exons. So, depending on which first exon is spliced onto it is which complex it is. So, we're going to talk about UGT1A1 right here, which is spliced to the common exon. There in the promoter of UGT1A1 is the TA repeater. A TATA box that turns the gene on. And this is most of the variance that we're going to talk about for the drugs that we're going to talk about today.

So, if we look at UGT1A1 and irinotecan the TA repeat in the promoter or the TATA box, can affect how well the metabolism of an irinotecan. So, irinotecan is an inactive drug that gets activated to SN38. And then it's inactivated through UGT1A1 and I'll show you that slide in a second. And this is called phase two metabolism. So, in the TA repeat normally you have seven -- or six TA repeats. But there are some people that have seven TA repeats or eight TA repeats. So, that causes irinotecan – so, there's a promoter problem with the protein and it causes a buildup of that active form and it inactivates irinotecan more slowly, which causes an increased risk for toxicity including high grade neutropenia and or diarrhea. So, irinotecan inactive, goes through this pathway to become SN38, its active form, and then is inactivated through the UGT1A1 pathway here, and eliminated from the body. But if there's a blockage in this pathway, or a backup you know a partial blockage in this pathway this builds up too much causing neutropenia and the severe diarrhea. This is like death by diarrhea here. Bad, bad diarrhea. So, if we look at the UGT1A1 frequency in Caucasians about a third carry this TA repeat, about half of African Americans, and about 10 to 15 percent of Asians. There is you can have five TA repeats and this is called a Star 36, or you can have eight TA repeats, which is a Star 37. And both of these are a little bit more common in African American population.

So, because irinotecan is used for metastatic colon cancer there's not really very many drug alternatives by the time a patient gets put on irinotecan. So, it is recommended to reduce the dose. So, this testing is not used so much anymore because most people give the patients a rolling dose because there's not really any alternative. And then just see how well they respond to it. And then slowly increase the dose for tolerance. So, in the FDA label it does say that there is a UGT1A1 test that's available and can detect the -- and remember six repeats is our Star One, Star One, Star One, Star 128, and our Star 28, Star 28, genotype. So, here's the decision tree. Remember in [unintelligible] this is irinotecan in this sort of drug combination. And it's more about if you're doing high doses you really need UGT1A1 genotyping or actually this is your low dose, sorry. Low dose you don't really need it, sorry I got that backwards for a second, the high dose it's really recommended to do the UGT1A1 genotyping and then looking at that there is toxicity around it. But mostly in the U.S. what they do is they give you the low dose and then titrate it for till you sort of don't get -- till it starts making you sick. So, there was an FDA clear platform that's been discontinued. So, it's not really used so much in the U.S.

I'm going to introduce in sort of the end of our time here, and talk a little bit about – we spent the most time on constitutional and inherited ones, where a lot of pharmacogenetic testing is done, but I wanted to mention briefly about somatic variance. So, this is again a lot of our companion diagnostics where you have BRAF, or ALK, or various other ones, and then there are drugs that go with those changes in the tumor. Our last and sort of final example that I'm going to talk about is chronic myelogenous leukemia. It was in the early 60's described as the Philadelphia Chromosome, which is a translocation -- a 922 translocation. And then in the '80's it was determined that there were two genes that were fused together and there's several -- there's a

major breakpoint, a minor breakpoint, and another breakpoint, or a very minor breakpoint. But in the late '90's Imatinib mesylate or Gleevec was discovered that it can be used to treat CML or chronic myelogenous leukemia. So, Gleevec is a small molecule inhibitor of tyrosine kinase, or TKI's tyrosine kinase inhibitor. One thing that's not really discussed much is that Gleevec is also largely an inactive drug that is metabolized through the 3A4, the 3A5 pathway. Remember this is one of those medications that you can't take with grapefruit or grapefruit juice because it inhibits the 3A4 pathway. And in Caucasians actually, most all Caucasians are poor metabolizers for 3A5. So, if you're Caucasian and you're a poor metabolizer for 3A5, this 3A45 complex, and you take grapefruit juice and you block this you're really blocking Gleevec to prevent it from becoming its inactive form. And won't be able to work on the chronic myelogenous leukemia.

You also take Gleevec for gastrointestinal stroma tumors or GST's that have a kit mutation. So, if we look at Gleevec or Imatinib and it gets in the body, again this is its major pathway through 3A4 to become its active form, which then can be bind to the BCR-ABL fusion gene or fusion protein to prevent and treat CML. There are people that over time become resistant to Gleevec or Imatinib mesylate and that many of them develop a second mutation in the tyrosine kinase binding domain, and the most common one is called T3151I. And if they develop this there are additional drugs available that can be used to treat that, especially when you become resistant to Gleevec.

I will remind you that much of this information is available on PharmGKB as well as on the CPIC websites. Here's an -- I don't remember when I last updated this, but a fairly recent list of many of the drugs and the genes that have drug dosing guidelines. I just wanted to mention largely the CPIC guidelines, CPIC has walked a fine line in the sand. They neither promote nor do they not promote genetic testing for this. They actually look at is there evidence for the gene and the drug that if you have the genetic information you can guide the dosage, or recommend alternative drugs based on that. And they do systematic evidence reviews and they update this probably about every two years they update the guidelines and the literature around each of the genes, the drug gene pairs.

So, our sort of last slide here in conclusion is that this a -- pharmacogenetics is a rapidly growing filed it's just not your genetics that affect drug metabolism, but also the environment affects drug metabolism. And genotype phenotype correlation while it can help guide drugs information and prescription information are still somewhat imprecise, but can serve as guidelines to personalized medicine. And that's the end of my talk today. Thank you.

Male Speaker:
Thank you Vicky very much. I appreciate it, it was a fantastic talk, and I have a couple of questions. One is what do you think are the drug gene pairs, or let's just say the drugs to start with, which are getting the most attention in real practice right now? In other words what are the ones that insurance companies may be most likely to see come across as tests with request to pay for?

Vicky Pratt:
So, a few years back one of the ones that probably would be seen quite a bit definitely the

companion diagnostics. So, those are sort of a given. The other one's people may see is for stents. For stents, you would see with clopidogrel and 2C19. That seems to be well covered by insurance and insurance companies. Some of the other ones which are probably a little more bit more rare, maybe TPMT with the atheroprone, especially in children. It's one of the drugs that I didn't mention that's used in some childhood cancers. That one -- let me go back to my list and see. The other ones are the HLA ones. Such as, I'm like looking at my list really quick and I know I I'm overlooking them, carbendazim, a little bit less so Abacavir is companion diagnostic. And if you have HLA-B 5701 and you take Abacavir you're at increased risk for Steven Johnson Syndrome which is a severe allergic reaction to the drug. Where your skin sort of comes off. But that's one that is being seen. And the other one interestingly enough, is ivacaftor for cystic fibrosis. Before somebody is put on ivacaftor they already should know what their CF mutation status is. So, I'm not sure that one is really combined because it's used to make the diagnosis of CF. And then once you know what the mutations are then you can take ivacaftor. Some of the other ones less so.

Male Speaker:
And so, just to get back to the companion diagnostics, so basically those drugs are approved for use in partnership with the tests. So, in some ways you're not supposed to use the drugs without doing the tests, is that correct?

Vicky Pratt:
Yes, that's correct.

Male Speaker:
Okay, according to the FDA? Yeah.

Vicky Pratt:
Yes.

Male Speaker:
So, if there's a good indication for that medication and poor indications for alternatives, then it sounds justified to go ahead and do those tests.

Vicky Pratt:
[affirmative]. Yeah, that's correct.

Male Speaker:
So, my next question is about what insurers will see when a test is ordered or when it's billed. Do they see CYP label, do they see the lists of Star Alleles that are tested for, what do they end up seeing? Or do they just see like a Tier Two CPT code?

Vicky Pratt:
So, most of the main pharmacogenetics genes, the HLA, the 2C9, 2D6, 2C19, there is actually gene specific, or the Tier One CPT codes. As well as CS has a specific Tier One CPT code. Some of the other genes such as DPYD, TPMT, Sico 1B1, CYP 3A4, 3A5, those one's are currently in Tier Two, currently in Tier Two that's as of 2000.

Male Speaker:
That makes it even harder for the insurance companies to sort of track what they're actually paying for, and seeing, and what the requests are.

Vicky Pratt:
Yes.

Male Speaker:
Yeah. So, they may have to do a little extra work to figure that out?

Vicky Pratt:
Yes.

Male Speaker:
Based on clinic supports and so forth, yeah.

Vicky Pratt:
Right. But normally and I don't know how each insurance company would do it, it is recommended in the AMACPT Coding Book that if it's a Tier Two gene that you're supposed to provide the Hugo Gene name. And I don't know if all systems are set up to transmit the Hugo Gene name or not.

Male Speaker:
Interesting. So, you're supposed to include it, but the systems may not have a field to transmit it so they may not on the other end see it.

Vicky Pratt:
Correct.

Male Speaker:
And then it also doesn't transmit what he Star Alleles that are being tested for are?

Vicky Pratt:
No.

Male Speaker:
Right, okay. I have another just sort of final -- just information question. So, there's a high incidence of G6PD deficiency in like Mediterranean populations.

Vicky Pratt:
Yep.

Male Speaker:
And there are medications that those people shouldn’t' take, or which the doses should be adjusted for is that considered a pharmacogenomic allele?

Vicky Pratt:
Yes. And if you look there's rasburicase --

Male Speaker:
Oh, okay.

Vicky Pratt:
-- that is associated with G6PD or G6PD deficiency. And interestingly – so there is CPIC guidelines around some G6PD deficiencies. Most G6PD, especially because it's X-linked in males it's very easy to diagnosis by a biochemical assay. The problem is that in female carriers who have one G6PD deficiency allele and have a normal one it's hard – that biochemical test doesn't work very well for them. And unless their sick or they're taking a medication and then it makes them sick or sicker the biochemical test isn't very good and then the DNA test would be the preferred method for women who are carriers for G6PD deficiency.

Male Speaker:
Great, interesting, super. Well thank you Vicky very much for coming and giving this talk to round out our Insurer Education Webinar series sponsored by NHGRI and the ISCC, Insurer Education Working Group. And I look forward to hearing more from you in the future.

Vicky Pratt:
Great, thank you.

Male Speaker:
Thank you, so much.

Vicky Pratt:
All right, bye.

Male Speaker:
Bye, bye.

[end of transcript]