Im Elvin Price the director of the GeriatricPharmacotherapy Program and Victor A Yanchick I am here to provide the introduction to ModuleSeven: Pharmacogenomics and Pharmacotherapy

So why would we have a module on pharmacogenomicsand pharmacotherapy?

Well its an accepted fact that the effectivenessof medications could be improved

Heres an example provided extractedfrom the report Paving the Way for Personalized Medicine: The FDAs Role in the New Eraof Medical Product Development

And clearly if we take a look at the slideyou can see that the effectiveness of medications that are commonly used for chronic disordersthe effectiveness is variable and in some ways disappointing or theres great roomfor improvement in optimizing the responsiveness to drugs

So this is a great question

Can we do more to increase the responsivenessto drugs?

Pharmacogenomics and some of the tools thatwe will identify in this topic that will be reviewed in the module actually have the greatpotential to improve outcomes related to the responsiveness to drugs

So heres an overview of how the howpharmacogenomics could potentially be applied to improving the outcomes associated withmedications

So heres an example pulled from a paperpublished by Julie Johnson over years ago that is a great illustration of what thismodule will cover

So basically there are groups well withinthe general population that are predicted to respond well to certain medications

And there are others in the general populationthat are predicted to not have a positive response to certain medications

And then there are those within the generalpopulation that may have an adverse event or a toxic response to medications that arecurrently used

Tools that will allow us to be able to identifythese individual groups or subgroups of people from the general population hold great promisein helping us to improve outcomes or to improve the responsiveness to drugs

So one of the topics that will be coveredin this module that holds great promise is pharmacometabolomics

As we consider the promise of pharmacometabolomicswe can examine how this could add to the potential of pharmacogenomics or it could be how thistopic can be used in combination

So here on this slide we can examine thatthe phenotype of responsiveness or nonresponsiveness to a certain medication can also be furthercharacterized by the biochemical using chemical biomarkers that may exist within an individualsplasma or a serum

So here in this case theyre giving youan example of the metabolome being able to be correlated with the responsiveness to aparticular medication

And heres a further example giving youhow showing you an illustration of after having the phenotype of responsiveness whethersomeone is a good or poor responder to a certain medication you can further characterize themusing their plasma profile and analyzing before and after treatment using highleveltechniques

So different types of different techniques

So showing you over here an example of electrochemistryor NMR and that combined with multiple chromatographybas techniques gas chromatography or a liquidwith tandem aspect to analyze the metabolite profile or the lipidomic profile in this case

And the data being generated from this approachbeing useful in characterizing an individuals profile before and after treatment and thisbeing further analyzed and broken down into pathways to identify potential targets thatmay be useful in predicting responsiveness to certain medications

So novel tools and techniques that can beutilized to predict responsiveness to medications

So heres an example of a publication thatwas from that was published from the Pharmacometabolomics

Research Network a few years back in PlosOne

And in this example a drug that we are familiarwith Atenolol was associated with different profiles based on an individuals selfidentifiedethnicity

So here you see theyre showing you datafrom for select metabolites based on an individuals selfidentified race

And theyre able to show differences inthe Caucasians versus the selfidentified African Americans in this population and identifya signature that was predicted of responsiveness to Atenolol

And on the right side of the screen you thisis figure three from that paper where they then created a model to summarize the effectof Atenolol on these novel lipidomic biomarkers that were identified using this pharmacometabolomicapproach

So this shows great potential of how youcould potentially identify novel biomarkers and pathways that can help us to predict theresponsiveness of drugs in individuals

So how could this be combined with pharmacogenomics?

So going back to the famous bubble peoplefrom the 00 Johnson paper what else can we use to predict responsiveness to drugs?

So weve cover or introduced the conceptof pharmacometabolomics which will be covered in this module but lets take a deeperlook into what direction pharmacogenomics is headed in

So we know that in recent years pharmacogenomicassociations have been made for targets of pharmacotherapy so those receptors that drugsbind to those targets of drugs or pharmacotherapy

We also know that genetic variability in thetransport is associated with the uptake or elimination of drugs have been associatedwith responsiveness or theyve been useful in predicting responsiveness to drugs butalso genetic variation in metabolizing enzymes have been associated with the responsivenessto medications

So considering these the targets thetransporters the metabolizing enzymes associated

with responsiveness we can divide these intotwo major categories those variants that affect pharmacodynamics and those that affectpharmacokinetics

Together this information can be used to predictthe efficacy or toxicity associated with drugs

So here are some examples coming up

This is an example of the betaadrenergicreceptor and showing you that polymorphisms at codon 9 so shown here and at codon 9that have been shown to alter the functionality of the betaadrenergic receptor and thus influenceresponsiveness to drugs like Atenolol that actually bind to this betaadrenergic receptor

So if the pathway is altered this has beenassociated with altered pharmacodynamics response

In this module you also receive informationabout pharmacokinetics

So in these examples were just showingyou that the percentage of commonly used drugs that are metabolized by phase one and phasetwo metabolizing enzymes

And genetic variation within many of thesetargets have been associated with altered drug response and have an influence on responsivenessto drugs

And so finally here there is growing evidenceand exciting evidence and exciting work that is being done that focuses on the effect ofgenetic variability on transporters and the associated adverse events or efficacy or lackthereof of medications that are substrates for these various transporters

So variability genetic variability inthe transporters in drugmetabolizing enzymes and in the targets of pharmacotherapy havebeen shown to influence responsiveness to drugs

And these are will be covered in this module

And this this slide actually shows youthat it that where were headed or maybe weve arrived at this point now of pharmacogenomics

In the literature youll see the termspharmacogenetics and pharmacogenomics used interchangeably but nowadays with more robusttechnologies and that are affordable were

headed towards being able to use pharmacogenomicsapproaches where we can evaluate genetic variation within the genes that may influence the pharmacodynamictargets the pharmacokinetics targets all in one as we determine the efficacy of orlikelihood of responsiveness to certain medications

So were headed towards pharmacogenomics

And I have an example coming up with one ofthe current recommendations that are actually within the package insert of a commonly useddrug

And in that package insert you actually havesome recommendations of starting dose for a particular drug and its highlighted hereon this slide

Warfarin one of the leading causes of hospitalizationsassociated with prescription medications in older adults

So in the package insert of Warfarin is itsnoted that genetic variability in the metabolizing enzyme cytochrome P0 sub CYPC9 is actually variation there is actually associated with the elimination of Warfarin

As you can see here the plasma levels areaffected by genetic variation here in C9 and this starts to give us information thatsomeone is a variant carrier

They have higher levels of Swarfarin overtime compared to the wildtype eliminators of Warfarin and that this could potentiallyinfluence the dose requirements

Thats what this is exactly what yousee here in this study published by Chris Aquilante and Associates back in 00 werebased on genetic variants in C9 you could predict the weekly requirements of Warfarin

And if you see here the homozygous variantcarriers if we flip back to this slide those individuals that would have higher Swarfarinlevels over time or slower elimination of Swarfarin those individuals require a smallerweekly amount of Warfarin compared to those wildtype individuals that would eliminateWarfarin in a faster at a faster rate

A lot in parallel to this growing datafor Warfarin as an example you also have information thats now available on thetarget of Warfarin

So variation in the target of Warfarin VKORCillustrated here in this publication by Sadler and Associates have also been associatedwith Warfarin requirements

On this slide in this table you have haplotypesthat are indicated here and the haplotypes capture genetic variability in this 0basepairsequence

The percentage disproportion if you convertthis to percentages this is the percentage of this particular population of individualsthat carry this particular genetic sequence or this particular haplotype and the requiredWarfarin amounts per day

And so over here in this category we cansee that theres a percentage of the population and in this study this was about percentof the population if we just collapse these two groups that actually require only about milligrams per day of Warfarin

So thats a little bit less than the normalstarting dose

Well thats its less than the normalstarting dose of five milligrams per day

And then theres another group within thisstudy

About percent of this population that actuallyrequired more than the normal starting day dose of Warfarin per day

So the normal starting dose based on guidelinesor treatment regimens is usually five milligrams so you have about percent of the populationthat required more than that normal fivemilligram starting dose

And then you add the remaining percentageof the population about 9 percent of the population if we collapse these two haplotypegroups that require approximately that five milligrams dose of Warfarin per day

And so this information starts to informhow Warfarin dosing may actually be influenced by genotypes

And so this is an example of the Warfarinpackage insert and a dosing table that is added to the package insert that is usefulfor clinicians or a starting point based on pharmacogenomics

So as an example of the types of implementationefforts for pharmacogenomics that are currently encouraged or that are currently underway

So additionally we have organized effortsthat are supported by NIH and by other organizations for the clinical implementation of pharmacogenomicstesting

And one of those groups the Clinical PharmacogeneticsImplementation Consortium is highlighted here

And so heres an example of one of thedrugs that the CPIC or the Clinical Pharmacogenetics Implementation Consortium that they actuallyhave a guideline for and that is for clopidogrel

We know that clopidogrel has a black box warningfrom the FDA

And in this black box warning you have recommendationsthat are made based on pharmacogenomics

So CYPC9 genotype and what recommendations whats recommended if you have a persons genotype

And so heres a screen a snapshot fromthe CPIC guideline that was published in 0

giving simple or easy to follow directionsif you have a genotype what to do based on genotypes

So standard or functional C9 statusyou can start a particular patient on clopidogrel

but if you have either poor CYPC9 functionor diminished CYPC9 function then its recommended that you consider additional options

And so an example of how this has been implementedKristin Weitzel and Associates published a paper demonstrating their experience withthis implementation at the University of Floridas Personalized Medicine Program

And so here you see their alert based ongenotyping and the recommendations that are made

And in this case the physician has an opportunityto make their to make adjustments to their orders or to select the drug of choice withtheir genotype information in hand

So this module will also cover the topicsof clinical drug interactions and adverse

drug reactions

So this is an interesting space and we canimagine that this is interesting as we consider cases like this case that was published inpediatrics in 00

And this gives you this is an example ofdrugdrug interactions combined with pharmacogenomics implications

So here this was a case where a child withcomorbid conditions received an antibiotic clarithromycin

The patient was receiving clarithromycinvalproic acid and hydrocodone for all at once

And in this case it was discovered laterthat this individual was actually a CYPD poor metabolizer

This influenced the ability to eliminate thishydrocodone and the interaction with valproic acid

Valproic acid interfered with the eliminationpathways for the metabolites of hydrocodone and also CYPA

The secondary metabolism pathway of hydrocodonewas also inhibited by the drugdrug interaction with clarithromycin and this led to fatallevels of hydrocodone being circulating in the system

And this was a unfortunate lethal wellunfortunate adverse events associated with the young patient not surviving the drugdruginteractions

So in summary this is an exciting module

Omics informed approaches for optimizing pharmacotherapywill ultimately lead to decreased health care expenditures and hopefully they will limitthe occurrences of suboptimal clinical outcomes

So hopefully the flow of this Omics informationinto clinical practice will steadily increase as we noticed current increase in adoptionof implementation efforts and hopefully we are preparing a workforce of clinicians andresearch scientists that are prepared to help

with the implementation of or the integrationof these Omics approaches into current care

Thank you and this ends my introduction toModule Seven