todays speaker is dr michael

associate director of genomic and

targeted therapy in the fdas office of

clinical pharmacology

during his tenured at the fda he has

advised on scientific and regulatory

aspects of hundreds of biologic

biomarker and diagnostic products

in 00 michael received his doctorate

in pharmacy degree from the university

of science in philadelphia and a

masters in public health from the

university of florida in 00

he completed research in clinical

pharmacology at bassette healthcare and

a clinical research fellowship in

cardiovascular pharmacogenetics at the

university of florida

please enjoy todays lecture

hello my name is mike pakinowski im the

associate director for genomics and

targeted therapy in the office of

clinical pharmacology at fda

as part of this course youll have three

lectures on the topic of

pharmacogenomics related to general

principles of pharmacogenomic study

designs

dosing

of drugs that have pharmacogenetic

interactions as well as the clinical

implementation of pharmacogenetic

testing

in this initial lecture well walk

through the general principles of

pharmacogenomics research and clinical

study design and walk through some

representative case studies related to

pharmacokinetics drug response and drug

safety

in closing well touch on a couple of

issues that are generally related to the

regulatory environment and drug

development context for application of

pharmacogenomics

as part of this lecture well cover some

basic principles and how pharmacogenomic

studies are conducted well walk through

a couple of case studies related to drug

disposition response safety as well as

multifactorial approaches to

implementing pharmacogenetic testing and

then at the end briefly touch on some

issues related to drug development

regulation and clinical practice

now we all know that drug responses can

be highly variable in fact the numbers

needed to treat for most of the highest

grossing drugs in the united states

ranges anywhere from to based on a

recent publication

that is you need to treat that many

people in order to derive one clinical

benefit and a single positive outcome

at the individual level having to try

multiple drugs or take a medicine that

is being used to prevent a

lifethreatening event without any way

to monitor it

is clearly not the ideal scenario for

practicing medicine

so the obvious solution to this would be

to have some noninvasive means to

identify which patients are going to

respond well

whether the drug might need to be dose

adjusted or whether an adverse event has

a higher chance of occurring and ideally

youd want to take out those individuals

and treat them differently either

excluding them from treatment altogether

or adjusting

doses or alternatively selecting those

patients in whom the drug is expected to

work enriching the population for those

responders and treating with standard

doses where theres a positive benefit

risk relationship

now i think we can all appreciate how

such precise discrimination of

responders versus tox respon toxic

responders is really pure fantasy we

humans are very complex biological

systems but practically speaking

clinical decision making is mostly

binary and this is how it sorts itself

out in the clinic

now precision medicine has become the

term of art to describe the approach to

health care that i just mentioned each

of us conceivably has different

environmental exposures concomitant

medications body habitus and so on and

all of these features could possibly

influence where we fall on the

distribution of responses

now pharmacogenomics is one aspect of

precipitation precision medicine thats

garnered a tremendous amount of tension

because weve seen incredible advances

in the ability to examine the human

genome at a scale that wasnt really

possible just even a decade ago

now put simply pharmacogenomics is

really just the study of dna and

ordinary rna characteristics as related

to drug response this definition is

obviously quite broad and covers

everything from clinical or nonclinical

studies of discrete dna sequence

variations that can impact drug

disposition response or therapeutic

outcomes all the way to the use of gene

expression profiles as pharmacodynamic

response biomarkers

but under the umbrella of precision

medicine we are generally mostly talking

about the use of genetic tests to

predict drug response

so armed with the ability to

interrogate the human genome we now have

the ability to better define the

pathology of a given disease and an

understanding of that mechanism sheds

greater light on how to manage it or

perhaps even alter its course through

pharmacological interventions

apart from diseaserelated factors use

of the drug itself can benefit from an

understanding of what drives variability

and exposure and what types of

monitoring might be needed to ensure

therapy is having its intended benefit

without causing any toxicities

so in actuality what we have the ability

to do is understand where a certain

subset of patients may fall in the

response distribution

there will be individuals that we would

expect to respond who do not and others

that will benefit greatly even if we are

not anticipating that they will respond

now pharmacogenomics has a very long

history that predates completion of the

human genome project in 00 perhaps

dating back all the way to observations

that some individuals dont have the

ability to taste

phenol thyroiria in the 90s and

perhaps even farther back to the

observation that certain people

do not tolerate eating fava beans very

well

however in the past decade weve made a

really remarkable progress in our

ability to study the human genome

following the initial sequencing of the

human genome the hapmap project gave us

a really clear map on the

human genetic variation across

populations

and shed light on

new markers that were discovered through

the use of genomewide association

studies now these were very large

studies that had the ability to look

across the entire genome to identify

novel markers of response

fast forward a couple of years we have

the first personal genome that was

sequenced and then more recently

we have

numbers of genomic association studies

that have been published and with

advances in sequencing technologies have

now generated full whole genome

sequences on tens if not hundreds of

thousands of individuals

so weve

really made quite a bit of progress in

terms of our ability to study the genome

as well as identify novel markers of

disease that would not have been

uncovered previously

so what do we know now well we know that

our haploid genome has about

billion nucleotide base pairs

in that theres about 0 000 protein

coding genes and about 0 000 noncoding

rnas and pseudogenes

and what makes up the the variation

among humans is really a small portion

of variation in the human genome and

weve identified roughly 0 million

single nucleotide polymorphisms and many

more rare variants now that sequencing

studies have become

much more common

so theres a number of different types

of dna variations that distinguish each

of us individually so i wont bore you

with basic biochemistry but the the

central dogma of molecular biology is

you know dna is the basic sequence from

which rna is coded

produces mrna and thats translated into

a protein

now theres a number of different single

nucleotide variations that can disrupt

the amino acid translation

by way of changing the three base codon

that is the basis of encoding the amino

acid there are a number of changes also

that produce what are called synonymous

changes which dont disrupt the amino

acid thats encoded but do disrupt the

sequence

there are also a number of noncoding

variations in untranslated regions

splice sites and intergenic regions of

the genome that we

still have much to learn about

on the more severe side of the equation

there are a number of frame shift

mutations that can alter the the reading

frame as well as insertions and

deletions that could potentially disrupt

the ultimate protein thats encoded by a

gene

there are other variations such as you

can have different copies of a

particular gene which can produce higher

effects of the higher expression of the

protein as well as epigenetic changes

related to methylation patterns

so with all of this what can genomic

biomarkers tell us well being that these

are relatively static biomarkers theyre

very useful at

as a predictive factor or as a

diagnostic factor

so a biomarker thats genetic in nature

can tell us if youre susceptible to a

given disease for example bracket

mutations are a common risk factor for

the development of breast cancer

can also be used in the diagnosis for

example cf

cystic fibrosis is

in part diagnosed by sequencing the gene

to understand whether or not there are

mutations present there can be

prognostic differences which might tell

you

in a patient who has a disease how long

they might live or what type of

morbidity they might expect

as well as predictive biomarkers that

can be used to predict the response to

an individual treatment a common example

of this is the braf mutations and the

setting of skin cancer

now not all drugs necessarily require a

pharmacogenetic test clearly if you have

a drug that is used to treat something

symptomatic in nature has a very wide

therapeutic margin and is used for a

short period of time you might not

expect necessarily

to be concerned about chronic toxicities

for example and you can evaluate an

individual patient response and whether

or not they should continue to use that

medication but there are a number of

cases where pharmacogenomic markers can

be useful

some of those are highlighted here

so there are many drugs that have

exhibited multimodal pk where you see

differences in the distribution of

concentration

there are many drugs that have narrow

therapeutic indices where toxicity and

benefit is a very uh steep curve

there are also drugs that have very high

variability in their pharmacokinetics or

pharmacodynamics

additionally race effects tend to be on

drug response tend to be a marker of

some underlying genomic differences

as has been the case with

many of the polymorphic drug

metabolizing enzymes and there are

certainly drugs that cause

adverse reactions that we really dont

quite understand the mechanism and

pharmacogenomics can be a useful tool to

understand the mechanism of those

toxicities as well as to shift the risk

benefit through patient selection

so to go on

to go about

identifying a

pharmacogenomic biomarker basic study

design follows one of a couple different

types

you can use population cohort studies

where you sample a population who might

be exposed to a particular medication

and evaluate whether there are treatment

differences based on genetic factors

in that overall population you can also

sample patients based on whether or not

they experience an adverse event or an

unfavorable treatment outcome or

favorable treatment outcome in a case

control type of study

much less commonly there are case only

methods and this is really useful only

if youre interested in studying

pharmacogenetic interactions

because you do not necessarily have a

control population so it really only

tells you about

the presence of whether a gene is

modifying the drug

so

these are the basic

patient sampling approaches now once

that is set in place just for practical

reasons in most circumstances

the next question then becomes how to

select markers and what platform to use

now we have now a number of different

hypothesis driven approaches where your

lower throughput platforms are used to

test single variations within a gene or

multiple genes that we expect to have

some biological relevance

but now more commonly we often see

hypothesis free approaches which is

relies on higher throughput platforms

such as next generation sequencing or

genomewide chips

and then once thats

the data have been generated its a

simple matter of analysis and the basic

question is really whether or not the

marker frequency differs in cases versus

controls or whether responses or

outcomes differ based on the genotype

those relatively straightforward

statistics from that point on

now the genotype genotyping approach as

i mentioned can be either hypothesis

driven or a hypothesis free

now we with the left panel here you can

see that you could select genes in a

particular drug disposition and response

pathway that might affect absorption of

the drug its metabolism as well as the

drug target this is really useful for

really well characterized and well

understood functionally relevant

variants that are identified within a

gene

in addition this is useful for drug

metabolism and transport studies

or as well as and as well as drug target

and disease risk alleles

at the other end of the spectrum you

have hypothesis free approaches which

are really useful when

the pharmacology is not well

characterized and can be used to

evaluate un resolved variability and

drug disposition or response one common

and very successful example was the

number of genomewide association

studies that were conducted

to identify factors that

were increased risk for type diabetes

this is a study that was recently

published looking at

exome sequencing and one of the markers

that came out of that was tcfl

which has now been one of the most

robust and reproducible

susceptibility factors for type

diabetes

now

the methods that we have have really

evolved quite a bit over the past couple

of years

there have been a number of

more targeted types of genomic analyses

that are depicted on the top

and some of the more recent next

generation sequencing technologies shown

on the bottom

not really relevant necessarily to go

into the

weeds of each of these different

platforms but suffice to say that we now

have a number of different

nextgeneration sequencing methods that

can generate gigabytes gigabases if not

terabases of data

in periods of

hours and weeks rather than years

so the technology has advanced quite a

bit now with the use of these higher

throughput platforms and perhaps at some

level even more candidate gene

approaches theres a couple of factors

that must be considered in determining

whether or not its a clinically valid

and real

association with the disease

the first and foremost is replication

its it goes without saying that a study

that has not shown uh replication

of

a genetic factor that predisposes to a

health condition

is is not necessarily believable and we

need to see this in multiple studies

that are independently conducted in

different populations and using

different designs

other factors that make a compelling

argument that a genetic factor is indeed

a real predictor of human health is the

magnitude of the effect the statistical

significance of its association in the

in the case of pharmacogenetics whether

or not there is a gene by drug

interaction

and then the rest is really bradford

hill criteria for epidemiological

studies and making causal inferences

from those things like analogy is a drug

interaction also indicative present that

would indicate that theres a genetic

interaction

experimental support that establishes a

mechanism by which a certain genetic

factor

influences disease risk

a biological gradient

and concentration response in the

setting of pharmacokinetic issues

now once we

have a valid biomarker in hand we

understand that it you know has some

basis for influencing

influencing health or disease

the next question then becomes well how

is it managed and what types of studies

can be done to

validate that it does in fact have a

tangible impact

so the top left

basically shows the the typical design

thats used to study

a pharmacogenetic interaction and also

is very useful in understanding whether

the biomarker does predict in fact what

you think it does

so basically patients would be enrolled

and tested for a certain genetic

characteristic and then randomization

would be stratified on the basis of that

genetic factor to treatment a or

treatment b

so this not only gives you information

about the effect of the treatment and

the different subgroups of patients that

are defined by the biomarker but also

about whether the biomarker

is prognostic versus predictive because

you have

the ability to compare treatment based

outcomes by biomarker

what we see more commonly in the setting

of drug development at least in the

setting of oncology

are enrichment types of trial designs

where individuals with a certain

biomarker might be selected and only

those patients will be exposed to

the experimental and control

interventions

there is a more hybrid design where that

type of enrichment strategy can be used

and you might follow individuals who are

marker negative with the standard of

care and this gives some insight as to

whether or not the marker does have

prognostic utility

and then at the far right corner we have

a basic utility trial design where this

actually doesnt necessarily evaluate

the effectiveness of an intervention in

particular subgroups of patients but

rather tests the utility and

effectiveness of a genotyping strategy

to alter treatments based on genetic

status versus a usual standard of care

type of approach

now these are obviously very simplistic

designs theres clearly a lot of

variations on this

in the setting of oncology there may be

um

some

local testing

thats performed as part of an entry

criterion into clinical trials uh there

may be adaptations to the study design

that evaluated an interim time point how

the the therapies are

working and stopping rules may be in

place if in a marker negative population

for example the drug does not seem to be

working

and

much more recently we have a number of

master protocols socalled umbrella

trials that are in place to

establish a framework for testing and

assigning patients to one of many

different types of therapies on the

basis of their genetic test results

so a lot of different options

for carrying forward a valid biomarker

into clinical trials

now when the clinical trials are

complete

its not necessarily always a simple

type of analysis

theres a number of different outcomes

so basically what you have here in red

is a marker positive subgroup and in

black the marker negative subgroup and

you can see in the top here

the the risk benefit of the risks or

benefits of the experimental therapy

might be the same

over a control in both the marker

negative and positive patient

populations this would suggest that the

biomarker is not predictive

in any way shape or form however it may

still

have prognostic value insofar as it

increases event rates but the treatment

might be effective at

equally effective at reducing

risk in both of the biomarkerbased

subgroups

the next series you basically have

subtle variations on differences

in the treatment effect between

biomarker negative and positive patients

here theres more subtle overlapping

outcomes here you have much more

separation

and in some cases here you might see no

effective an experimental therapy

in the biomarker negative population so

theres a number of cases where

each of these outcomes have been

observed

and it does raise the question of you

know whether a biomarker testing is

useful

in terms of informing therapy how well

the control

therapy does

and seldomly

what we might see also is

at the bottom here where you have very

clear separation uh you know poor

outcomes in the marker negative

population with an experimental therapy

much better outcomes in the marker

positive and there was a case like this

with one of the antiegfr

tyrosine kinase inhibitors for lung

cancer

so what ill do for the next several

minutes is go through a number of

different case studies touching on a

variety of different uses of

pharmacogenetics

to look at drug disposition response

safety

and

prediction of outcomes

so drug metabolism and transport is is

probably the most straightforward of the

the pharmacogenetic approaches this is

really the the classical

pharmacogenetics if you will

you have here an example on the right of

a drug

where you might observe

in a population type of study

different peaks in the amount of drug

that ends up getting into the blood so

you have on the far right here a number

of patients who end up with very high

exposures a normal distribution here in

the middle and then some individuals

that may eliminate the drug very quickly

this has been observed with the number

of sip d substrates

and

is related to the fact that theres a

lot of genetic variation underlying the

activity of sipd

so for sip d many of the classical

interactions are for beta blockers a lot

of psychiatric drugs

oligostat tetrabenezine and other

related compounds codeine

dextromethorphan obviously being a probe

and atomoxetine

sypc9 also has some relevant

interactions related to warfarin and

some of the nonsteroidal

antiinflammatory drugs uh cypc9 with

clopidogrel voraconazole proton pump

inhibitors and clobizam and then a

number of other phase one and two

metabolizing enzymes that are listed

below

oatp is a transporter that also has

genetic polymorphisms that can influence

drug disposition

particularly noted with the statins

where its also been observed that its

a risk factor for developing

muscle toxicities

now one thing thats important to

consider

in looking at genetic variation in drug

metabolism and transport is the

variation that can occur across

different racial and ethnic populations

you can see here down at the bottom

that there are a number of different

genotypes that can basically be

translated into an activity score which

then would put an individual into one of

these phenotypic categories theres

ultra rapid metabolizers extensive

metabolizers which for all intents and

purposes are normal metabolizers

intermediate metabolizers which have

reduced function but not completely

abolished as well as poor metabolizers

where the ability of the enzyme to break

down a substrate is virtually absent and

thats present in about five to five to

ten percent of the population

um in the united states

so you can see here up in the the top

portion theres a a number of studies

that were conducted looking at the

genotype distribution this is

one where they genotyped a large number

of different populations and basically

looked at the the frequency of these

different phenotypes across the

populations and you can see here theres

some subtle variations across the

different populations in terms of the

frequency

you can see here there are some

populations that very commonly have

ultrarapid metabolism and some where

poor metabolism is relatively absent

so for d this is this has been

observed its also important for sypc9

where poor metabolism is much more

common in populations in southeast asia

as well as some of the other genetic

variations that are involved in drug

metabolism

now one question that often comes up as

i mentioned before is that

drug interactions um are often analogous

to

pharmacogenetic interactions

uh and and weve looked at whether um

you know the data from a drug

interaction study could be extrapolated

to

inform a pharmacogenomic interaction and

we see that for sip d

where we have some relatively clean

inhibitors of the enzyme and some

relatively clean substrates

that in a lot of cases

when based on pbpkk modeling you can see

that there is convergence between the

drug interaction and the genetic

interaction

uh this is also observed to some extent

for sip c9 but less so for sipc9 and

thats perhaps in part because of the

fact that sypc9 genetic variations tend

to have some substrate specificity in

terms of their impact on drug exposure

and also perhaps because some of the

inhibitors may

affect other pathways

so it then begs the question of whether

or not we can rely on the drug

interaction studies or genetic studies

to inform one or the other and if you

look at tertiary resources theres

obviously a lot of clinically relevant

drug interactions that are noted in

resources that are used at the bedside

and you can see that

frequently

the genetic interaction is also alluded

to

even though patients may not be

routinely tested

in terms of sip d

you can see here there are about

drugs that had clinically relevant drug

interaction in a tertiary resource

the drug drug interaction was described

in labeling in most

but the gene drug interaction

description was not as common so you can

see that there is some gap here but

it stands to reason that in most cases

the information can be portable from one

to the other

now ill walk through a briefcase

for atomoxetine

this is a drug thats a selective

norepinephrine reuptake inhibitor thats

used for the treatment of attention

deficit and hyperactivity disorder

this drug is metabolized quite

extensively by sipd

as you can see down here and it produces

this

hydroxyatomoxetine metabolite this is

the major pathway of elimination

in the clinical studies uh that were

conducted even before the drug came to

market it was obvious that there was a

clear separation in the distribution of

concentrations that were observed in

those studies and you can see that there

is a

a number of patients who had relatively

low exposures

at the left of this figure

reflecting the the population that

genetically is not able to eliminate the

drug

and carrying that forward you know

relative to normal metabolizers poor

metabolism for this drug was shown to

result in much higher exposures to the

parent compound roughly 0fold higher

areas under the curve and fivefold

higher cmax

there were higher rates of adverse

events you see roughly a doubling across

a number of different adverse events

that are related to the drug

and because of that the the

drug has dosing recommendations that are

tailored based on genotype so for those

patients who are less than 0 kilograms

typically youd give a half a milligram

per kilogram per day and then titrate it

up to a target dose of milligrams

per kilogram per day every three days

based on their response and tolerability

and in patients who are over 0

kilograms a similar approach starting at

0 and hopefully landing at 0

in those patients who take spd

inhibitors or known poor metabolizers

based on genetic testing

the recommendation is really to hold

dosing

titration for a period of four weeks

until its been well established that

the patient tolerates the medicine well

or if symptoms are failing to improve

now some would argue that that this

titration approach which tends to be

common across

a lot of the central nervous system

drugs actually might end up under dosing

certain individuals and that certainly

is a possibility and thats been

suggested widely in the literature but

nonetheless the poor metabolizers do

tend to have higher adverse event rates

that that could be treatment limiting

so well shift gears and speak a little

bit about drug target pharmacogenomics

evaluating mostly the efficacy of

therapeutic products

now in the past several years there have

been a number of medicines that have

been approved for only certain subsets

of patients who are defined by molecular

characteristics you can see here theres

a couple of drugs that have been

approved for cystic fibrosis

an

oligonucleotide therapeutic for duchenne

muscular dystrophy and a number of

different drugs for cancer

one of these notably was a recent

approval of pembrolyzumab for patients

who have microsatellite instability high

cancer

or

mismatch repair deficiency

and thats agnostic to the type of

tissue that the tumor was identified in

its really targeting the the molecular

basis of the disease so clearly this has

become a common pathway

to

to drug development and you can see

there are a number of examples that have

been approved

the first example well talk about is

cystic fibrosis so cystic fibrosis is

generally thought to be a disease of the

lungs although it has various

manifestations throughout the body

but basically is a disease where theres

reduction

in the activity of a chloride

transporter that results in loss of

chloride transport

the gene for this was sequenced back in

99 by francis collins and others

and really identified that there are

certain patients with cystic fibrosis

that have dysfunction in this

transporter

and 0 years later

some would argue that thats quite a

long time

we finally now have therapies that

potentially target this underlying

defect and have the potential to to

modify the disease course

so

mutations in

cystic fibrosis uh cftr is the gene uh

there are upwards of 000 that have been

documented and there are a few hundred

that are known to

be responsible for for causing uh the

clinical manifestations of the disease

uh these have been broadly grouped into

different types of defects

some of them

introduce premature stop codons

resulting in no synthesis of the protein

there are others that block the the

processing of the mature protein to the

cell surface and others that impact how

well the channel

moves chloride

so

several years ago there was a drug

called evictor that was developed as a

potentiator of cftr and basically it

works by opening the channel and

increasing its channel open probability

for specifically

for specific mutations that have a

gating defect and among the most common

of those is the gd mutation

luma caftor is another product that was

approved

this acts to stabilize the cftr

confirmation which increases processing

and trafficking of the mature protein to

the cell surface and this is approved in

combination with evac half door for

patients who have the f0 deletion

mutation

now the clinical program for this really

started out with

comprehensive in vitro studies that

demonstrated that if a caftor was active

against certain forms of

that against certain cftr mutations

notably as i mentioned the gd

mutation

uh this is a mutation thats present in

about four percent of cf patients and

the clinical trials that were designed

to

develop and approve this product uh were

basically conducted in in this enriched

population

so there were two clinical trials that

showed a clear benefit of

a caftor

on lung function parameters into

clinical trials

there was also another clinical trial

that was conducted in the more common

f0 deletion mutation which

demonstrated that there was a small to

no benefit which was consistent with the

proposed mechanism of action of this

product

now being that theres a number of rare

mutations

that also are present that behave

somewhat similar to the gd mutation

there were some additional studies that

were conducted in patients who have

uh

some of those rare mutations and this

was done uh in a small prospective trial

uh where again the benefits on lung

function were observed

now

weve weve come a long way with evac

after weve learned quite a lot about

its benefit and risk profile over the

years

and more recently

based on the the accumulated benefit and

risk database

ivik after was approved much more

broadly for

patients who had actually demonstrated

in vitro responses

so this builds on the clinical database

and now given the confidence in

the in vitro assay

to

adequately identify those patients who

are likely to benefit

the drug may be used in those patients

where the mutation is documented to have

a response in the experimental studies

so you can see here the indication now

reads

if a calf door is a cystic fibrosis

transmit transmembrane conductance

regulator thats indicated patients over

the age of two

uh

who have one mutation in the gene that

is responsive to evac after based on

clinical

and or in vitro assay data

so its not possible to really talk

about precision medicine and

pharmacogenomics without touching on

the the

setting of oncology

lung cancer is among the more common

causes of death from cancer in the

united states and weve come a long way

in terms of our understanding of the

molecular pathology of the disease

there have been a number of studies that

have been

performed very deep molecular

profiling of a large number of tumor

tissues

and show that theres quite a number of

mutations and other factors that really

are present that can drive a tumor and

are thus amenable to treatment with

certain certain drug products so you can

see on the left side here this was a

study evaluating a number of different

tumor tissue specimens and basically

demonstrated that theres a number of

mutations and all the genes listed here

in each of the different specimens

and broken down on the right hand side

here you can see that there are a number

of

pathways that are particularly

implicated for example egfr is commonly

mutated and lung cancers as well as k

ras

so these mutations

really

given us great insight into the

molecular pathology of lung cancer and

has

led to the approval of a number of

different therapies its also raised a

lot of complexities

beyond the mutations and and molecular

profile thats shown here there are also

differences in methylation patterns copy

number variations uh p loss and a

number of other molecular aberrations

that can be detected in a tumor so with

all of that its obvious that each tumor

can possibly be its own unique

entity

now gefitinib is a drug that has had a

rather interesting history to fit nib

is an antiagfr

tyrosine kinase inhibitor

and it was initially approved in 00

under the accelerated approval program

for patients that had locally advanced

or metastatic lung disease

lung cancer after failing

conventional chemotherapy regimens

the drug was approved brought to market

and then the phase three confirmatory

trial that was required as part of the

accelerated approval process actually

failed to demonstrate a benefit

in the nonsmallcell lung cancer

patient population

in 00 its use was restricted to

patients receiving and benefiting from

jafitnib and several years later the nda

was voluntarily withdrawn

now its interesting because in this

time period we began to have a much

greater insight into the molecular

pathology as shown on the previous slide

and there was a number of studies

evaluating the impact of egfr mutations

on the response to these these medicines

so egfr mutations are are present in

roughly 0 of tumors

lung tumors

it does vary a bit based on geography

it tends to be more common in patients

in southeast asia and you can see here

theres obviously a number of different

mutations that can be present in the

egfr gene

most of them reside in the tyrosine

kinase domain

the ones that are of particular

importance are an exon 9 where you see

theres a number of different deletions

that affect the

that affect the protein

in addition there are some

mutations that are present in exon 0

the most common of which is t90m which

is known to confer resistance to some of

the drugs that target this particular

this particular target

so the the

basis for um

to fit nib response in the setting of

different mutations of

egfr was really first established with

the ipas trial which was a study of

first lines of fitness versus

carboplatin and paclitaxel

in nonsmall cell lung cancer patients

in east asia who were light or never

smokers a population that really in in

some way is already enriched for the

presence of these types of mutations

because the mutations tend to be more

common in those two populations

and you can see here uh with the

survival plot up on the right hand

corner and the egfr mutation positive

cohort you can see that there is a

benefit of geofitinib over chemotherapy

and in the mutation negative cohort you

see that your fitness patients tend to

fare somewhat worse than conventional

chemotherapy

so this shed light on the fact that

there may be

relevance of the tki relevance of egfr

mutations and determining the response

to fitness

it isnt worth noting that

this population that was the basis for

the genomic substudy of this clinical

trial was relatively small relative to

the overall trial population you can see

here that those without

known agfr mutation status

there were several hundred of those

patients whereas there was a couple

hundred in

the mutation positive and negative

cohorts collectively

so fast forward a couple of years there

was another trial conducted that was

performed in patients who had egfr

mutations detective in their tumor

tissue this was an open label single arm

study

and really demonstrated that there were

very significant responses

in terms of tumor shrinkage uh in this

cohort of of patients you see upwards of

response rates with a couple of

complete responses

and the mutations that were largely

enrolled in this trial were the exon 9

deletions being some of the most

prevalent sensitizing mutations to tki

therapy

but also

a couple of less common mutations

now on the basis of this trial

and the accumulated evidence about the

relevance of mutations on the response

to these types of medicines uh the new

nda was submitted

and uh subsequently it was approved and

indicated for patients who have exon 9

deletions or the exon substitution

lr

and this was as detected by an fda

approved test that was codeveloped

and brought to market and approved

simultaneously with

the approval of this indication

one thing thats worth noting i

mentioned there are a couple of other

rare mutations that were included in the

clinical trial and the responses for

those patients are shown

um basically in the clinical studies

section of the labeling that theyre not

necessarily included in in the

indications

now the uh

the companion diagnostic which is a test

thats essential for the safe and

effective use of a drug product uh was

brought to market with uh with the

approval of the drug for this indication

and you can basically see that its

approved for the detection of the

mutations uh that are expected to

respond uh but bears the caveat that

efficacy has not really been well

established in patients with some of

these rare mutations

so that that shows a typical

drug development scenario where theres

targeting of a specific specific

molecular defect and there are a number

of other

egfr terracing kinase inhibitors that

have been approved that share similar

indications

with

for patients who have mutations

in the egfr gene such as a fatinib and

herlotinib

so well shift gears again and talk a

bit about safety pharmacogenomics

which is a

very important and

interesting issue that has a lot of its

own unique challenges

over the years there have been a number

of different examples of how genetic

factors can predispose one to developing

an adverse event

some of those are listed here

youll see that a couple of them such as

for codeine and pimazide and citalopram

a lot of it might be based on the

disposition of the drug product

pimazide and citalopram for example tend

to have higher concentrations in

patients who are poor metabolizers of

sipd and c9 respectively

both carry the potential for for qt

prolongation and arrhythmic events

codeine on the other hand is a pro drug

thats activated by sip d

in patients who are ultra rapid

metabolizers they can get a lot of the

active metabolite which is morphine

and then that produces toxic effects and

this has been particularly problematic

for

for young children especially those who

have undergone

tonsillectomies

valproic acid is an interesting case

it basically

was an adverse event that surfaced out

of

experience in young children who had a

mitochondrial disorder that

basically is defined by uh

the the presence of fatal hepatic

failure when exposed to valproic acid um

and this is the result of pole g

mutations uh so there were some safety

related labeling changes

to to warn physicians of this particular

risk factor

a couple of years ago

and then

on the more immunologic and

idiosyncratic reaction front cutaneous

reactions such as stevensjohnson

syndrome have occurred with a number of

drugs

phenytoin and carbamazepine are

two such drugs where theres been

interactions identified and well well

talk a little bit more about

carbamazepine

so cutaneous reactions such as steven

johnson syndrome or toxic epidermal

necrolysis uh occur in about one in ten

thousand uh of carbamazepine treated

patients this is something that tends to

be a bit more common again in southeast

asian populations

uh but its also an adverse reaction

that tends to have very high case

fatality uh for those patients who who

develop ten um there is very significant

morbidity and mortality associated with

with that adverse reaction and you can

see here on the right the uh adverse

events are essentially defined by the

the coverage of the body surface area

with um this very severe decimating rash

so there were a number of studies that

had been conducted

in china and thailand and various other

countries

using case control approaches

basically that identified hla b0 as a

very significant risk factor for the

development of stevensjohnson syndrome

in patients who had been exposed to

carbamazepine

so this is the results of a

metaanalysis that was published which

consisted of about 0 cases and 9

controls and you can see here at the

bottom the odds ratio

for

uh

developing the adverse reaction was

upwards of 0 which is very substantial

in terms of being a predictor of

the risk for this

particular adverse reaction

based on you know that accumulation of

evidence there were some changes to

the therapeutic products

labeling

you can see here theres a boxed warning

that that describes some of the the

racial ethnic differences in the

development of this adverse event

but also goes on to recommend that

certain

certain individuals with ancestry that

would

cause this potential reaction to be more

prevalent

be targeted for screening for hla b0

prior to starting carbamazepine

and you know on the basis of a lot of

these compelling findings

some countries had implemented

prospective screening programs where all

patients who were candidates for

carbamazepine

were screened for

this genetic risk allele

and not treated with carbamazepine and

you can see here a paper that was

published a few years ago

that

basically all of the patients who were

hlab 0 negative

went on to to receive carbamazepine

and had a

very low if not any

incidence of

the severe skin reactions

when about two and a thousand would have

been observed uh in the study population

had screening not been performed

now this is

not always so straightforward um clearly

theres a potential for other

antiepileptic drugs to cause

stevensjohnson syndrome and severe

cutaneous reactions

and in fact for oxcarbazepine and

phenytoin there are published data that

suggests that hlab0 is a risk factor

for developing skin reactions in

patients exposed to those two drugs

esther carbazapine being structurally

related to carbamazepine

at present doesnt have any very well

validated reports of stevensjohnson

syndrome

as related to the hla b0 allele

but stands to reason that potentially

could carry the the same risk and there

are studies in experimental models that

have shown that there are common

structural elements that do interact

with hla b0 across a number of these

compounds

carbamazepine oxcarbazepine

estocarbazepine and so on

so it is potential that by using one of

these medicines in an hla b0 positive

individual

may also expose them to the risk for

developing an adverse reaction

and this was the experience of

one region where

screening for hla b0 was implemented

basically

they saw elimination of stevensjohnson

syndrome and tea and induced by

carbamizapine

but

they saw a rise in the number of

reactions that were caused by phenytoin

which resulted in no obvious net

difference in the rate of the adverse

event

so it is important to consider

the risks associated with alternative

therapies uh when prospectively managing

some of these pharmacogenetic

interactions

now a lot of this

has been a lot of these studies have

been performed in

primarily asian populations and a few

years ago there were some studies that

looked at what risk factors were present

in european populations

in this study this case control study

of various types of skin reactions

including

maculopapular

exanthema steven johnson syndrome

as well as other hypertensive

sensitivity syndromes uh we did see a

new risk factor surface which is hlaa

star l and this was an allele that

was

associated with the development of these

adverse reactions in carbon mesotheli

carbamazepine treated patients

however relative to the

size of the effect that was observed in

the southeast asian populations for

hlab0

you can see that the relative risk here

is roughly on the order of tends to

be a little bit less robust of a

predictor

and theres also differences in the

frequency of this adverse event in this

population which raises several

questions about the effectiveness of a

screening strategy to prevent this

adverse reaction in this population

now moving on to a different adverse

reaction that tends to be a bit more

common a baccavier is a very

prototypical example of safety

pharmacogenomics

a bachavir causes a hypersensitivity

reaction and about five to eight percent

of individuals receiving this medication

consist really of a fever rash gi

symptoms respiratory symptoms a very

nonspecific presentation

and now this reaction was identified

prior to the drugs approval in 99 and

there were warnings about it that were

included in the the products labeling

at that point in time

there were a number of studies that had

been conducted looking at genetics and

basically hla b 0 surfaced as a risk

factor for these hypersensitivity

reactions

and there had been some efforts to to

begin screening patients and clearly

demonstrated that

you know taking these patients out of

the pool that were treated with the back

of ear

did in fact

result in a significant reduction in the

incidence of this adverse reaction

um it was really hammered home with this

prospective trial called the predict

trial where

one of these

types of utility trials where patients

were randomly assigned to

no genetic testing versus genetic

testing and withholding of therapy and

those patients who were

uh positive for the allele and basically

showed that uh when genotyping was

implemented there were virtually no

cases of immunologically confirmed

hypersensitivity reactions whereas it

was roughly three percent in those

patients who did not undergo any

genotyping

uh in clinically suspected cases

obviously also reduced as well

so really drove home the point that a

baccavier

could be used safely and effectively as

long as this as long as patients with

this particular risk factor were removed

from the treated population

and there is a boxed warning for this

medication that

basically advises prescribers to screen

for hlab0

prior to initiating therapy with the

baccavir

and this is also something thats become

standard part of of clinical practice

for for

the treatment of hiv

its an essential part of use of this

medication and the basis for the

recommendation obviously has very clear

and compelling evidence from a

randomized controlled trial that it has

utility in preventing the adverse

reaction

the last batch of

case studies slides well go through

really talk more about multifactorial

approaches

to implementing pharmacogenetic testing

warfarin is is a poster child for

pharmacogenetics in many ways its a

very highly variable drug

it requires

monitoring

through blood tests to maintain and

achieve a stable dose of the medicine

and it clearly

has a very narrow therapeutic index

at one end of the spectrum

the potential to cause bleeding and at

the other end of the spectrum its

preventing

strokes and very disabling

lifethreatening

clinical outcomes now there have been a

number of studies that have looked at

the factors that contribute to warfarin

response variability a very large

portion of that is

a base a combination of clinical factors

such as age and concomitant medications

weight racial background

and and very importantly diet as well

but a very large portion of this is

actually driven by genetics as well and

you know the drug being metabolized by

sip c9 and targeting vitamin k epoxide

reductase those surfaces the two main

genetic determinants of warfarin

response accounting for very substantial

proportion of of the response

variability

so you can see here

weve got you know a number of different

factors that can affect the disposition

of the drug its pharmacokinetics

both clinical and genetic factors

as well as the the pharmacodynamics of

the product so the drug targets v core

c and there are a

couple of polymorphisms that increase

the the sensitivity

of um the receptor to warfarin

inhibition

so basically um

the

drug ostensibly could be

improved in terms of its use through the

use of genetic testing basically to help

guide the initial dose selection and to

understand where patients are likely to

end up with with continued dosing

so the

fda approved product labeling

essentially has a table thats broken

down by v core c genotype and sipc9

genotype

and proposes what stable doses

might be needed for patients with

various combinations of those genotypes

and these ranges should be considered in

choosing the initial dose of the drug

product

and patients with

poor metabolism you know taking a longer

time to to get to steady state might

require more time to

understand whether the drug has had its

full effect

before dose adjustments be performed on

the basis of inr testing

now this has evolved over the years

there have been a number of

multivariable models that have been

developed

one commonly referred to is at

warfarindosingorg

you can see here

the computer interface basically allows

you to put in

a variety of demographic variables the

number of doses the patients received

what their inr baseline

and what their target inr is

as well as what other potential

medications they may be taking in

addition to a number of genetic factors

here its v core c uh cf sipc9 and

and others

so once all of these variables are put

in the model then calculates a potential

stable dose that the patient

will likely land up land on

and offer some initial dosing

recommendations

to help achieve that therapeutic inr

thats in the target range

now thats the story that continues to

evolve theres a number of outcomes

trials that were performed and

some showing that there was a benefit of

genetic testing in terms of

you know achieving stable doses of

warfarin

others showing no such effect

so it remains a question as to whether

or not um

pharmacogenetic testing for warfarin is

something that is uh essential to its

use

inr testing obviously being a

pharmacodynamic measure of the drugs

activity

is clearly

a means to understand and personalize

the therapy

so moving on for the last portion here

ill touch briefly on a couple of

different aspects related to the the

translation of pharmacogenetic testing

you know so weve talked i think at a

high level about

uh you know the the conception of the

need for pharmacogenomics

how some of those studies might be

conducted and what types of studies

would be used to validate the presence

of a pharmacogenetic interaction

weve also touched briefly on

the

approaches to establish utility of a

genetic test in terms of

its benefit on therapeutic outcomes

and then that leaves the question of of

whether and how it can be implemented

which is the subject of another lecture

but

theres a number of factors that go into

that there has to be some

clinical decision support infrastructure

the predictive models have to

continually be refined over time as as

new evidence emerges and clearly the the

effectiveness of of implementing such

testing needs to be evaluated

backing up a little bit the you know the

factors that really guide the strength

of of prescribing and testing

recommendations for pharmacogenetic

interactions and their management um

really is driven i i think in part by by

two major things one is the therapeutic

context and the other is you know the

residual uncertainty that that may be

present about

uh its utility for example

um again for situations where you know

were trying to prevent severe

lifethreatening clinical outcomes

in situations where theres available

therapies that may or may not have

the the liability associated with the

genetic factor

you know those types of things have to

weigh into the equation about whether or

not theres going to be a good use for a

pharmacogenetic test

or its result

at the other end of the spectrum on the

uncertainty side of things you know we

we deal a lot with

study designs that may not necessarily

be ideal a lot of this

the data that informs the presence of

pharmacogenetic interactions comes from

observational studies or retrospective

substudies

that werent necessarily designed to

evaluate pharmacogenetic interactions so

there do become a lot of challenges

associated with interpreting some of the

evidence base and it does uh

does result in some uncertainties

um

but that said you know the the amount of

uncertainty one is willing to tolerate

again depends on on the context and

whats trying to be prevented

and its also not to say that

genetic testing has to be performed at

baseline or before treatment of a

particular medicine

you know there are various approaches to

implement testing you know we do have a

couple of drugs where everyone

is to be tested such as for a baccavir

and oligostat for gaucher disease

but there also may be situations where

were targeting a specific atrisk

subset as is the case for carbamazepine

and valproic acid or when a certain dose

threshold is achieved as is the case for

for pimazide and tetrabenzene

so there are a variety of ways to to

deliver

genetic testing in the clinic that could

be pursued

so genomics has

a number of uses in in drug development

beyond

what we are trying to achieve through

precision medicine approaches where we

genetically test patients and then try

to to determine what therapies to use

often genomics can inform what drug

targets are

suitable to pursue for drug development

there have been studies that show that

drug targets that do have some evidence

from genetic studies as being relevant

to a particular disease do tend to have

a higher probability of success

successful translation to market

but also you know in sort of a more

preemptive role genomics can be used to

define the target population as was the

case for for evic half door

dna that can be collected throughout the

course of a drug development program can

also be used in many ways it can be

used to establish variable responses to

the drug or identify the risks for

serious drug interactions

perhaps in conjunction with with more

formal healthy subject pharmacokinetic

studies

and it can also be used prospectively

not only again to to select patients for

predictive purposes and codevelop a

test

but also really to minimize noise in the

clinical trial population to reduce that

heterogeneity so a clinical trial is

more likely to detect an effect of a

drug if one does indeed exist

and i think the

the value of this has been demonstrated

in some surveys of the pipeline

basically you can see here that clinical

trials and drug development programs

that rely on biomarkers as part of

the patient selection process

do tend to have lower attrition rates

here you have phase one to approval

success rates of percent

when patient selection biomarkers are

used versus eight percent which is the

roughly the typical industry average for

for phase one to market um you do see

higher success rates when when patient

selection biomarkers are used now that

could perhaps in part be

related to the fact that youre using

patient selection biomarkers because

theres an understanding of the the

pharmacology of the product so there

could be some bias there but

nevertheless

you know shows the point that that there

is a potential for a positive impact on

drug development

uh now these biomarkers are often used

in the drug development process

for enrichment purposes to conduct

relatively smaller clinical trials

in order to evaluate the safety and

efficacy of the product

codevelopment is what this is commonly

referred to as where theres a

diagnostic test thats also being

developed in conjunction with the

therapeutic product

so really at the outset of a development

program its its determining whether or

not there is a

possible pathway to pursue with

enriching the clinical population

for a certain biomarker

and the population you know if it is

clearly defined you know whether the

factors

uh that are conducive to a successful

outcome of both the biomarker and the

therapeutic product

are looked at such as the mechanism of

the drug its preclinical profile as well

as you know other related compounds that

might be in class

and then its a decision of whether or

not to enroll

the biomarker positive patients or

whether there needs to also be some

assessment of the marker performance

through a more allcomer type of design

but in in

the setting of oncology uh often it is

the case that just marker positive

patients may be enrolled and benefit

risk is evaluated only in that subset of

patients

in a drug development program the marker

negative population can also be

evaluated as part of other clinical

trials

there may be two

confirmatory trials that are conducted

and one of those may be

targeted and the other one enrolling an

allcomer population so there are

different approaches to this but the

basic gist is that theres a diagnostic

test thats used very prospectively as

part of the development program

and i showed a couple of slides where

you know theres been a large number of

drug products this again sort of

reiterates that point theres a

whole number of drugs um

depicted here in the middle and on the

right you see the various biomarkers uh

that have been targeted and have been

the basis for fda approvals some of

which relate to to dosing of the

therapeutic products

but there has been a fair amount of

success in this arena

now thats not the only use of genomics

and drug development as i said often you

know there may be

genetic factors that are used as part of

a trial design but do not necessarily

translate into the clinical use of the

medicine

you can see here a survey of drug

products that have labeling related to

pharmacogenetic factors

shows that theres roughly 0 biomarker

drug pairs that covers about

biomarkers and the large

bulk of these are related to metabolism

and transport but really only about half

of those

actually provide some prescribing

recommendation around the genetic

characteristic

and otherwise it might be descriptive of

a study design feature or that there was

a an assessment of a potential for a

pharmacogenetic interaction but in it

may have not existed

um so weve seen a lot of growth in this

area i think and and parallel with that

theres been a lot of

activity in terms of developing guidance

uh on the regulatory approach to

not only the therapeutic products but

also the the in vitro diagnostics that

are used in conjunction with the the

tests or the the drugs

pharmacogenomic data submissions

guidance was was one of the initial

guidances that was published back in

00

and you can see that thats evolved

quite

quite a bit over time

more recently weve had the clinical

pharmacogenomics guidance which talks

about dna collection and clinical trials

a number of guidances related to

nextgeneration sequencing

that are in drafted at the moment

so to summarize very briefly just a

couple of these guidances the clinical

pharmacogenomics guidance and early

phase studies it really focuses on the

the best practices for collecting dna to

facilitate biomarker development

in certain situations for example if you

have a drug thats metabolized by a

polymorphic enzyme

its really essential to begin

collecting dna and exploring whether or

not theres a potential for an

interaction very early in the course of

development

but in other cases it also highlights

some of the areas where there may be a

need to collect dna for retrospective

studies

the clinical trial enrichment guidance

is a guidance that discusses mostly

the the use of various strategies to

select patients for clinical trials

and this may be done via trial design or

a biomarker based selection approach

and can be

used to serve one of many purposes

whether its to decrease heterogeneity

in the clinical trial population

increase the event rates so that theres

a more statistically robust ability to

differentiate the benefit of a treatment

versus control

or for predictive purposes to enhance

the treatment effects and

to make that

ability to detect that much much better

companion diagnostics was a policy

document that was released

in a couple of years ago

which basically

stipulates that intravitro diagnostics

you know if theyre required for the the

safe and effective use of a therapeutic

product uh that they will undergo

premarket review uh and and have a

riskbased regulatory approach

and the codevelopment guidance

picks up on companion diagnostics and

provides more of a howto guide

in terms of

how to

bring an invitro diagnostic along

in a therapeutic product development

program so that there is successful

approval of both products at the same

time

beyond

the diagnostics and

targeted therapeutics were also seeing

a number of genetically targeted

therapies now

crispr cast 9 therapeutics or something

that

come across the headlines quite

frequently

rnabased therapeutics such as antisense

oligonucleotides or drugs that

affects splice altering such as the

topless and nucinursen

have been approved and this is a very

active development space that is really

targeted to the genetic factors that

drive human disease

next generation sequencing is also a

very significant developing area you

know with traditional testing and

you know what many of the

pharmacogenetic examples have been to

date you know youre testing one marker

and and making one decision on an as

needed basis

you know when youre about to prescribe

a drug uh next generation sequencing

really changes the paradigm quite a bit

because you can perform the testing

um

get a lot of information about the

genome and then sort through that and

you know thinking about you know just

the volume and complexity of these types

of tests its its really um quite

remarkable but there are a lot of

centers that are performing next

generation sequencing particularly in

the setting of of oncology

and there are approaches at fda to to

modernize the regulatory oversight of

these of these tests

so to summarize precision medicine

really does require a couple of

different elements to to realize this

vision first we need safe and accurate

diagnostic tests that can reliably

identify

specific alterations in a given patient

we need health systems that have the

ability to

capture information on patient

experience and understand

how risks and benefits may differ in one

patient population versus another and

particularly important as the subsets of

patients get smaller and smaller through

the use of genetic testing

and different therapeutic approaches

we need targeted therapies that are

efficacious and have less deleterious

side effects and the hope is obviously

that genetic testing can help

shift that benefit risk balance

so that we have

really robust therapeutics

and lastly that we have updated research

and regulatory policies that really

stimulate a continued development of new

treatments that also continue to protect

patient uh wellbeing

so with that ill ill close out my talk

and just acknowledge

all of my colleagues at the office of

clinical pharmacology its a tremendous

place to work and a really exciting team

to to be around

thank you very much for joining the

session and listening to the lecture i

hope you found it valuable

if you have any questions please contact

the program coordinator