im excited to introduce dr howard

dr mcleod is the founding medical

director of the departolo family

personalized medicine institute at

moffitt cancer center

dr mcleod has over 0 years of

experience in pharmacogenetics

applied therapeutics and clinical

pharmacology

his research interest focuses on

pharmacogenetics and the role of genetic

differences in individual responses to

cancer drugs

after earning a doctorate of pharmacy

degree from philadelphia college of

pharmacy and science dr mcleod went on

to complete clinical research fellowship

at st jude

and a research fellowship at the

university of glasgow

please enjoy dr mcleods lecture today

hi im dr howard mcleod im going to

talk to you today about dose

modifications based on pharmacogenetics

research

this is work taking the human genome and

trying to make it so that more rational

therapeutic decisions are are being made

over the course of this time well talk

about examples

that are influenced influencing dosage

selection of therapy and other ways that

the genome can be useful in this manner

now lets just start off with a quote

that a surgeon who uses the wrong side

of the scalpel will cut his own fingers

and not the patient

if the same applied to drugs they would

have been investigated very carefully a

long time ago this quote is supposedly

from 9 but its very relevant today

of the medicines that we have available

we know something about them enough to

help many people but theres much work

still to be done to understand why

theres variation

across populations why does one person

have a benefit from a medicine someone

else have a side effect from that exact

same medicine someone needs a big dose

someone might need a small dosage of

that same medicine and so well be

exploring that a little bit more

in the in the following section

now the clinical problem is a really

wonderful problem and that is that for

most therapeutic areas there are

multiple different active therapies that

are available to treat that disease

if there is only one medicine there

wouldnt be a lot of choice we would

just hope for the best

but there there are choices and so how

does one select

from amongst the available medicines

in order to treat a patient we need to

be taking into account the likelihood of

benefit to response to therapy

the the chance that theres a bad effect

an unpredictable toxicity that could

occur

and then theres also an issue that many

of us like to ignore

and that is that medicines cost a lot of

money many of the new anticancer drugs

can cost as much as twenty thousand

dollars a month a wellinsured patient

still has a major financial burden uh

even though they thought they were

covered by insurance and so we need to

be able to make rational choices in

terms of benefit

of toxicity and also making sure the

patient can afford to get the kind of

treatment

that is

needed for their disease whether its

through a societys financial burden or

the individual patients financial

burden and so we need better tools to

make those choices as we go forward

now there are many different factors

that can influence a medicine shown on

the outside of this wheel are a number

of the different factors

outward factors that can be important

there can be things like stress

liver function kidney function

sunlight many different aspects of of

our daily life can be important in terms

of influencing the way drugs are

metabolized the way theyre absorbed

other features of a medicine

at the hub of the wheel though is our

genetic constitution and so the way that

our dna is coded

influences how we look

how we taste things how we smell things

often even the way we walk can be

influenced in part by our dna

that also could influence things like

the metabolism of a medicine or or how

long it will stay in the body and so we

look at genetics as one part of

understanding how to pick the right

medicine and the right dose of the

medicine for an individual patient

now when we look at the human body there

are two different factors that we like

to talk about

involved in pharmacology of a medicine

in a person

the first is the pharmacokinetics and

you can think of that as what the body

does to the drug so a drug is absorbed

it is metabolized by the liver its

eliminated by the kidneys those are

pharmacokinetic factors and so dna

changes in those factors can be

important and well show some examples

of that

also theres the pharmacodynamics you

can think about that as what the drug

does to the body so if a drug binds to a

certain receptor in this case on a on

the

surface of the lung uh an an inhaled

albuterol or cell butymal and as its

known in many countries will bind to

this receptor cause the airway to open

and relieve some asthma uh symptoms so

this idea that a drug hits a receptor

and causes an effect is also an

important feature and so there are

examples where genetic variation in both

pharmacokinetics and pharmacodynamics

can be important for

influencing how a particular patient

will respond to a given medicine

now when we look at the genetic factors

that influence drugs or pharmacogenomics

pharmacogenetics many different terms

that can be used there are many

different examples that are approved by

the us fda

now there are over 0 medicines that have genetic information somewhere in the prescribing recommendations that are put out by the fda but this list thats shown here is a subset of those where in the dosing and administration section genetics as a is a feature now some of these are are genetic abnormalities that are seen in a disease like cancer so gene amplification gene deletion some other gene abnormalities will be in the in the tumor not necessarily in the normal tissues but then many of these uh of these examples uh that are shown here are shown in the normal dna and they can influence the dose of a medicine the toxicity risk for a medicine many different features that one can take and use in terms of guiding the therapies that one receives so pharmacogenomics is not something that might happen someday but rather there are many different examples of commonly used medicines that that for where this is important

and this includes some of the medicines

that we use across many different

diseases

controlling pain uh preventing vomiting

using antidepressants uh adhd drugs anti

blood thinner or blood thinning drugs or

anticoagulants

um its not just for cancer and and the

markers that might be in a tumor but

rather features that are there so

someone getting a surgical procedure no

matter what its its for will have pain

issues if theyre getting general

anesthesia will need to have an

antivomiting medicine

someone that is getting hot flashes from

an antiestrogen or going to just the

the

menopause might need an antidepressant

for the hot flashes

or might need an antidepressant for the

treatment of depression or they can be

used for chronic pain many different

ways that these medicines can be

important and so its not just the

highly specialized diseases

where genetic variability has become

important but really very commonly used

medicines

are being influenced by by genetics

now there are guidelines that have been

put out to to help us use these

medicines so theres a consortium called

the clinical pharmacogenomics

implementation consortium cpic as its

known that has been put together

its based in the united states but has

representatives from uh over 0

different countries there are about 00

different institutions involved and so

we we get input from many different

bodies on how to use these medicines in

a in a safe and effective way if a

patient comes in with a genetic result

how can we use that to guide which

therapy which dose of therapy in some

cases even what route of therapy

intravenous versus oral that one might

use and so these guidelines are very

useful and they go across many different

drugs and many different disease areas

and im not going to list them all for

you you can go to the pharmacogenetics

knowledge base and and see the list for

yourself

but

showing that this kind of information is

available and can be useful for guiding

your health system guiding your

individual practice

guiding your university whatever the

setting is that youre thinking about

this these guidelines can be quite

useful

also theres an opportunity to be

involved in this if youre in a country

that does not have these guidelines and

you want to be involved with cpic

guidelines

um reach out

for for that because its a great

opportunity to get involved and help the

usage of of these medicines

now there are many ways that precision

medicine or

pharmacogenomics pharmacogenetics is a

part of that can be used for for

thinking about medicines one is to avoid

a medicine that might have a very bad side effect and the presentation from dr pakinowski a few sessions ago highlighted some of the allergic reactions that could occur where you would want to avoid that medicine at all costs because of the severe nature of that abnormality including a medicine some tests allow you to know that a medicine is more likely to work and therefore should be included in the options explaining a bad side effect so if a cancer patient has a drop in their white blood count after a chemotherapy drug you want to know is it that medicine or is it one of the other medicines the patients taking thats causing that drop because you may need to use that medicine but if theres a severe reaction you may need to avoid it because so doing genetic testing to explain is it a genetic abnormality for this medicine or for another one it is certainly a part that can be can be can

be done but im going to focus in on

some examples

for choosing the dose of a medicine

or choosing from amongst a number of

available medicines where you need to

pick the medicine and then the dose

in in the uh over the next little period

of time

now one of the examples that was shown

by dr pakinowski during his presentation

was a medicine for

attention deficit hyperactivity disorder

called atomoxetine this is an example of

a drug where in the patient prescribing

information their socalled package

insert

a gene called sipd is listed and

therefore

and anything in the metabolic pathway

thats influenced by sip d

can be influenced by those who have

genetic abnormalities so a small

percentage of the population have extra

copies of this gene

about 0 percent of the general

population in the united states have uh

are are missing this gene and then

theres others that are in the middle

and so you have some people where they

would need different doses based on

their genetics and so within the fda

prescribing recommendations it mentions

the

sip d poor metabolizer status

how that would increase the result in

higher blood levels higher rates of

adverse reactions

and recommends different dosing based on

both body weight

and genetic information so heres an

example where environment in this case

the patients body size

and genetics in this case their d

status both will influence the dose

thats needed and the

the frequency in which one

uses the medicine now look at the

changes here

a half a milligram per kilogram per day

increase every three days

if they have small body weight

if they have a larger body weight 0

milligrams per day not including

kilograms so so a very different way of

dosing and then if theres a genetic

deficiency instead of every three days

its every four weeks that one would

make these changes very dramatic

difference in terms of how one would

manage this medicine

for a child with this disorder and as

you can imagine children with this

disorders have a terrible time in terms

of their education in terms of their

social interactions

giving this in the wrong manner causing

them additional side effects

or not giving them the efficacy they

need could really have a terrible effect

on this child and the in the way that

they can uh

be part of society so its an important

factor and an example where the fda has

made those those important changes

now one of the older examples thats

quite important is with the socalled

thiopurine medicines these are medicines

as a thioprin mercaptopurine guanine or

the ones that are available in most

countries that are used in the context

of a solid organ transplantation so

heart kidney liver transplantation

also in the treatment of leukemia in

particular childhood leukemia and these

medicines azathiprine is a prodrug

which is metabolized

to mercaptopurine

which then can either go and form uh an

active metabolite thioguani nucleotides

as theyre known

or can be inactivated by thiopuri and

methyltransferase or tpmt is as easier

to say

and so theres a competition between

whether this medicine is activated

or inactivated based on the the genes

that are involved

and so as you can imagine genetic

abnormalities that influence the

function of this gene will have an

importance on how much medicine can be

tolerated for a given patient and so if

you look at this slide heres a general

population within a population there are

some people who have the the normal two copies of the gene have normal functioning activity there are some people who have one normal copy and one abnormal copy copy and so i have an intermediate ability to break down the medicine and then there are the the less common individuals that that have uh are either a low activity or are completely missing the gene and therefore have very little ability to break down this medicine now if you give all of them the exact same dose

what youll find is that some people have standard levels of in the of the medicine in their blood

those that are missing one of the copies of the gene will have a little bit higher levels

those that are missing both copies and have no ability to break it down or an effective ability to break it down have much higher levels

and then what that translates into is a normal risk of myelosuppression a drop in white blood cell count

an intermediate risk or a very acute and

high risk 00 percent risk of getting

severe toxicity many of these children

need hospitalizations um there if its

an organ transplant it may result in in

other bad effects terms of losing the

kidney or the liver

and so very different scenarios between

acute toxicity or very manageable late

occurring toxicities that can occur in

these patients and so if one goes and

instead

uses the genetic information to give

either a standard dose

a reduced dose

or a very reduced dose based on normal

intermediate or absent enzyme activity

one will see that the blood levels that

are obtained are fairly even across the

population because just a little bit of

the medicine in a low or absent

metabolizer will result in quite a

substantial blood level

that also means that everyone is at a

very similar risk of a drop in their

white blood cell count and at least in

the context of leukemia

the survival studies have shown that

using this method individualizing the

dose based on genetics resulting in even

an even amount of blood level

even amount of toxicity also results in

a high level of cure of these children

with leukemia so whereas the patients

who are getting are absent for the

enzyme and giving a standard dose have

severe toxicity cannot get their full

therapy and have a higher risk of

relapse

in this case high chance of cure

moderate chance of toxicity a much

better scenario for these very severe

significant diseases that are being

managed

now you can look at cpic guidelines and

see that there are specific

recommendations for each of these

medicines depending on whether you have

normal activity

intermediate activity or low or absent

activity where you would make a a

substantial reduction down to 90 percent

of the normal dose or

only less than 0 percent i should say

reduction by 90

just given three times a week

compared to a full dose given every day

in those with normal activity so a

substantial difference in the use of

these medicines in order to achieve the

same high level of success

that is that is influenced by the the

genetics now these children cannot be

ascertained by their outward appearance

the way they walk their favorite foods

theres nothing about them that would

tell you that they are missing this gene

or have normal copies of this gene its

only at least in the old times when you

gave the medicine and something bad

happened that one could figure this out

now genetic testing can occur prior to

administering the medicine the dose of

the medicine determined based on those

results and those good outcomes are more

likely to happen because of this sort of

approach so an example of how this

this genebased approach

pharmacogeneticsbased approach can be

used in the context of therapy

now a similar finding

for

another cancer drug called tamoxifen

this is a drug thats been used for many

years in the treatment of estrogen

receptor positive breast cancer its an

important drug for curing breast cancer

its been responsible for

saving many lives over the decades

but it has complex metabolism where

this drug is metabolized to this active

more active metabolite called indoxapin

and this enzyme sipd that we already

talked about earlier is an important

factor there and so as i mentioned

before 0 of the population are missing

this gene cannot functionally activate

tamoxifen at the same rate that the rest

of the population could and so one could

go and and decide what to do based on

that now there are studies showing a

relationship between sip d genetics

and recurrence of breast cancer there

are also some studies where that

association was not observed so its not

a clean story where every time the

genetics will be important but in most

of the studies using using standard dose

tamoxifen a difference has been seen

where a patient that has two normal

copies a socalled extensive metabolizer

will have a much better outcome than a

patient with only one normal copy or the

patients with no normal copies of the

gene so you can think of this as a lot

of activation of the metabolite active

metabolite a moderate

intermediate activation of the

metabolite or relatively low activation

and theres an impact on survival

in the treatment of breast cancer based

on these results

so

what can one do for that so a clinical

trial was performed its been was

published initially back in 0 as ill

show you in the next slide theres some

data that has been published in late

0

but this looked at a large number of

patients initially 9 patients

subsequently published over 00 patients

where they took the patients if they

were extensive metabolizers so two

normal copies of the gene they gave them

the standard 0 milligrams per day of

tamoxifen

if they were genotyped and had an

intermediate metabolizer status so one

normal copy one abnormal copy they were

given a doubling of the dose 0

milligrams

every day now the fda approved dosing is

between 0 and 0 milligrams so this is

all within the fda approved dosing

but a doubling of the dose and what you

see is that starting off after four

months of the 0 milligram dose you see

a substantial difference in the amount

of active drug available in the

patients body

when you then keep the standard dose for

the these patients here and give a

doubling of dose for the intermediate

patients you now cannot tell the

difference statistically between these

two groups youve had a normalization of
the blood levels based on a
doubling of the dose for some patients
and a standard dose for the rest of the
patients so this idea that we can use
genetic information
from the start of therapy
choose the right dose of a medicine
and then administer it is really
important now in the example i just gave
you with thiopuri methyltransferase and
the thiopurine drugs
you had an intermediate biomarker you
had toxicity as a factor that could be
measured
in the case of tamoxifen there is no
intermediate biomarker you cant tell
the drug is working or not working
unless a patient has recurrence of their
disease
and so this is a high stakes endeavor
you want to give the right dose from the
very start in this context and not give
a dose that you hope is the right one
and then find out later the patience has
has recurrence of their disease and so

its a serious matter

and not one where theres another way of

managing this and so we need to have

this sort of information

now i showed you a complex metabolism

of tamoxifen in a previous slide

and so one could then go and look at

other factors that are important in

terms of metabolism in terms of other

outward appearances and a study just

came out in october of 0

where a group went and looked at 00

women that got tamoxifen for the

treatment of breast cancer

looked at sip d but also looked at

other genetic factors such as acepc9

sorry sepc9

and then about 0 other genes were also

evaluated looked at body weight they

even looked at what season a patient was

treated and what they found is that the

other genetic factors and the other

clinical factors

were not significant in terms of

statistical values for the

the dose of of tamoxifen needed to get

the adequate blood levels

but sip to c9 metabolism

had some effect

body weight had some effect for reasons

that are not

yet clear

season also had some effect so were

trying to understand why that is and see

whether that can be used in terms of of

uh treatment also can be used in terms

of explaining the mechanism but the

biggest factor was sip d

and so using sip d

supplementing it with body weight with

some other genetic factors certainly can

be a way of trying to normalize this

treatment and theres just an example of

trying to not let one factor be the

explanation our bodies are very complex

the metabolism metabolism of medicines

are complex its no surprise that its

going to be multiple factors that come

together and influence the the uh

way a drug is handled

to get the achieved goal and so we cant

think of life as being too simple we

need to be

embracing complexity and trying to

understand it um and that will allow us

to get to the point where we can really

dial in the right drug the right dose

for a given patient

now

one last dosage example i want to give

is for an antifungal therapy in this

case in the context of leukemia where

where fungal infections can be fatal

and a gene we havent talked about so

much yet called cypc9

now as many of you know these genes

are cytochrome p0 genes therefore the

sip

and then they were numbered based on

when they were discovered and whether

they were part of a family member so the

second family to be discovered

the the uh third branch of it or

socalled c branch and then the 9th

member of that family um is why its sip

c9 now its not very easy to remember

necessarily but there are only a small

number of genes that are are critical

for the use of pharmacogenetics in

patients and so it is one of those that

is worth remembering

now as i mentioned invasive fungal

infections

are a major contributor of morbidity

prolonged hospitalization and mortality

in cancer patients who have dropped

their white blood cell count and

leukemia is a prime area where their

white blood cells are wiped out based on

the therapy so that normal cells can be

reconstituting there

and so we we give

antifungal therapies as prophylaxis you

give the therapy to prevent the

occurrence of a fungal infection not you

dont wait until someone has a fungal

infection when youre then trying to

chase the infection and hope that the

patient doesnt die first and so

voraconozo is one of the the many

medicines or the one of several

medicines i should say

that are effective

for

preventing fungal infection or at least

minimizing the chance of fungal

infection in the context of of acute

leukemia

and this gene cypc9

is one of the genetic variants that can

influence the blood levels of of this

medicine and so if you look at this

medicine its metabolized by several

different genes but sip c9 is the the

predominant one that can cause a

inactive uh version of that and there

are are variations in these genes such

as the star variation

that can influence that now other

presentations have gone into some of the

the nomenclature for these genes but

with each variation that has occurred a

new number has been assigned to it its

basically a way of trying to keep track

of these variations uh its its uh easy

for those of us who work in the field to

remember sip c9 star

but certainly if youre entering this

field

it is complex figuring out what does

that mean

but

these genetic variants as you can get

used to them

will have meaning in terms of their

application now when you look at these

genetic variations and look at blood

levels as i mentioned those who have

a are

extensive metabolizers are shown here in

the middle those are the ones with

normal amounts of the enzyme activity

those that are are poor metabolizers

theyre missing both copies of the gene

have very high blood levels and so you

worry about toxicity in these patients

being caused by the medicine and then

those who are ultra rapid metabolizer

have extra copies of the gene they have

lower blood levels and in many cases can

never get to a therapeutic blood level

of these medicines

and so one can look at a number of

variations i mentioned the poor

metabolizers that would be in this

category here the people who have the

socalled star either together or in

combination with star now star star

can occur but is extremely rare in

most world populations but theyre at

risk for for extra high blood levels and

the toxicities that could occur there

but the ones that were concerned about

in terms of preventing a fungus

infection in in patients with leukemia

are either one copy of this variation

or two copies of this variation because

the star variation causes extra

amounts of the protein to be produced

and so the body gets rid of the medicine

in a much more rapid fashion and so

these folks

have a very low chance of getting the

right blood levels their risk for

low blood levels or extremely low blood

levels and thats a major concern in

terms of preventing a fungal infection

and so

these are the patients where its now

routine many centers to genetically

analyze these patients prior to starting

their therapy their their antileukemia

therapy so that one can get them on the

right antifungus prophylaxis from the

very first dose

rather than trying it out and hoping for

the best

also

an important feature that i wanted to

include here is that when you do genetic

analysis this is from a paper uh from

0 that looked at the cost of

screening all patients for this genetic

factor looked at the blood adding blood

levels to to help manage these patients

looked at how many uh fungal infections

would be avoided and with uh

the lowest amount of savings

still were saving

about

dollars per patient by doing

preemptive testing so in a group of 00

patients a health system would be saving

over 0 000

in this case and

avoiding a severe lifethreatening or

fatal toxicity in the patient and so not

only is there a strong clinical case for

doing this sort of testing but also a

positive financial case for doing this

and so two fantastic reasons to be doing

a genetic test to try to optimize the

therapy

in this very lifethreatening situation

theres also an as an example

dosing algorithms or workflow diagrams

that can be conducted so in this case

you want to use voracons or prophylaxis

if theyve had

a bone marrow or liver transplant then

using white blood cells to do the

genetics might be measuring someone

elses genotype either the bone marrow

donor or in this case the white blood

cells would be from the patient the

liver and the liver transplant would be

from someone else and so you need to

take a different route there but if its

a leukemia patient can be genotyped

based on the results either the standard

dose of voraconazole

a uh higher dose of oroconazole or a

switch to a completely different therapy

um can be can be the result

based on that and so a difference in

dosing a difference in therapy based on

the type of results one gets and we can

know this prior to ever treating the

patient because of rapid turnaround

genetic testing and so is an example

again where pharmacogenetics influences

the dosage or the choice of therapy and

by doing it preemptively you can prevent

that sort of uh effect from occurring

and not have to play catchup when a

patient has a terrible infection and is

uh is at risk for dying from that

infection

now i focused in on examples where

pharmacogenetics could influence the

dose that one might pick for a patient

the last example hinted at a little bit

of selection of therapy and so want to

spend a little bit of time on selecting

from a menu of available therapies

for

by using pharmacogenetic information and

one really important area for society

for this sort of work is in the

treatment of depression and theres two

major classes of antidepressants both of
which have some pharmacogenetic data on
which to influence it now the first
class is the tricyclic antidepressants
these are the older classes of medicines
but but again very very effective
um they are our names are shown here um
and they can have pronounced uh
serotonin or neuro or norepinephrine or
adrenergic effects and so dry mouth some
of the other side effects like that can
occur with these medicines that wouldnt
occur with some of the newer medicines
but these medicines are used for
depression also can be used for chronic
pain and such as trigeminal neuralgia
and other syndromes are like that and so
its important that we understand
can genetics influence the the dose of
these medicines or the selection of
these medicines and so one can look at
metabolism and amitriptyline is
metabolized by this enzyme to
nortriptyline its inactivated by this
other enzyme to this metabolite here
so two different genes you can see

are already important in terms of what

sort of side effects and what sort of

efficacy one might get for from these

classes of medicines and and certainly

one can expand out by going to this

example this is the 00 0 paper

theres a new a new version that will be

coming out in the future of the cpic

guideline looking at these two in gene

these two genes and the doses of

tricyclic antidepressants that one could

use for the treatment of depression or

other disorders and so for each of them

there is metabolism by sip d and the

dose reductions that would that could

occur metabolism by

sip c9 the dose reductions or

avoidance that one could occur

and and so thats important now i want

to also mention that genetics is not the

only way of trying to individualize

medicines

there have been

examples over the years where these

medicines can be have their blood levels

measured so a blood level taken a blood

sample taken plasma or serum
removed put onto a machine that can look
at how much medicine is in the blood per
unit and and one can look and see a
toxic range or a therapeutic range for
these these medicines and certainly if
you have the access to these these types
of blood level measurements in a timely
manner its a very viable and useful way
forward in terms of choosing the dose of
medicine
however many of these assays are not
widely available or are not available in
a timely manner and so waiting a month
for a result is usually not the ideal
for a given patient you dont want to
just try one of these and see what
happens you want to be able to
understand
whats going on also with the genetic
information especially with a rapid
turnaround assay one can understand
which of these medicines are a very low
yield a very have a very low chance of
benefiting the patient and therefore can
be avoided altogether and which ones at

least have a chance of benefiting the

patient and can be tried out

and so having the information prior to

ever giving the medicine gives the best

chance of of having that sort of thing

now if you start the patient on the

medicine you can then get blood levels

and see if theres some finetuning that

can be done but i wanted to mention this

because blood levels therapeutic drug

monitoring is a viable way of trying to

individualize therapy it just cannot be

done prior to administering the dose but

rather the patient has to be on the drug

for a given amount of time

now a second class of these medicines

are the selective serotonin reuptake

inhibitors a little bit newer class of

medicines

they have a similar side effect profile

but a little bit less frequent

occurrence as the tricyclic

antidepressants

and uh therefore

and response rate has been associated

with genetic polymorphisms in these same

genes that i mentioned before and well

get into some of the response data

in a in a few slides uh but uh its the

same genes that are important and again

cp guidelines have been produced

have been important in terms of putting

to pulling together data on how should

these medicines be used and in what way

these medicines are metabolized by

multiple genes in this case with

peroxidant

its subd hip is also featured in

the others

sypc9 is important here

whereas c9 is not important for these

other medicines and so you get into some

some ways of of trying to look at these

these drugs also when you look at the

cpic guidelines and the the online

supplements that are available for them

you also see a lot of the background

data in this case is for peroxison and

septuc sipd you can see

many of the clinical trials and theres

also a rating on the quality of the data

so

this trial here

or these set of trials had a very high

level of evidence uh this study here was

a relatively weak uh study might have

been because it was a case report or

small number of study a small number of

patients in the study or some other

factor

like that but this sort of consensus

around the studies their level of

evidence how they can be used is an

important resource thats freely

available for anyone that has access

to the internet

and so these guidelines again sticking

with proxetine as an example the

guidelines will make

recommendations on if you have a ultra

rapid metabolizer so you have an extra

copy of the sip d gene what the

implications are

whether

a different dose should be given or in

this case ill really select a different

drug

that is not using this enzyme and the

data for that is quite strong

and so

this type of information is quite

helpful in terms of developing local

guidelines for practical application of

this work

knowing someones at high risk is not

enough you want to know the dose or

whether a drug should be avoided and

thats really a key component of these

these guidelines and so in the case of

paroxetine it has a specific percentage

dosage reduction for the poor

metabolizers or avoidance of the drug

for for this other drug fluvox of

fuvoxamine

a reduction in dosage

or avoidance no dosing recommendation

for fluoxetine those studies have not

been performed therefore we couldnt

make a clear recommendation and so this

sort of information is there

publicly available

consensus of multiple different

investigators from multiple continents

to try to pull together recommendations

that you could use

as youre trying to use pharmacogenetics

to dose dose patients

same with these other medicines in these

same categories

so

that sort of information is important

but when you look at the utility

theres also other studies that have

been performed

some of these studies like this first

study looked at whether

testing and acting on the testing would

reduce cost and in this case

it reduced cost

quite substantially

probably mainly because of the longer

the the differences in hospitals stay

but its important in terms of the

different costs that can be there

in some cases testing reduced the cost

by a blanket amount in this case testing

was done but not no intervention

happened and those who would have been

intervened on had a much higher health

care costs based on so you can pull

together individual examples of

literature that really start telling you

theres differences in outcome

differences in cost and its important

so for example this study that thats

shown here um looked at patients who had

been genotype

genotyped versus patients who had not

been genotyped this was not a randomized

study but rather looking at at patients

at a individual center they looked at

sip d and sypc9 and what they found

is a reduction in overall drug costs

during the first year of this evaluation

and it was almost a thousand dollars a

difference

in in terms of the the the costs that

were there um enough to more than pay

for the testing uh for for these these

patients

additional

more more

carefully guided studies have been done

in this case looking at standard use of

of

antidepressant therapy versus genome

guided use in the red

of these therapies and they looked at a

number of the different ways of

measuring success in terms of depression

these are different uh different tools

uh surveys other questionnaires other

clinical tests

that can be used to gut to see is there

a benefit happening and then one can

look at those those effects what you see

as no matter which way you measure the

the

antidepressant benefit it was higher in

the genetically guided treatment than it

was in those who got the standard

clinical management alone

with using other genes not just

metabolism in this case a target one of

the receptors im looking at gene

polymorphisms you you see a a much

better plateau of the of the uh

depression results in uh and much more

quickly uh in the patients um who had a

particular genotype compared to the rest

of the patient just i identifying or

highlighting that response

can be quite different

in these patients

occurring much more quickly and in a

larger number of patients based on the

genetic factors

now this is important because you dont

want to have to go out weeks

to then be able to tell a patient that

the medicine didnt work for them you

want to know early and so by optimizing

the the chance of benefit using whatever

genetic tools are are

most relevant and most most effective

is an important factor in terms of how

one uh really starts treating these

these patients

now there was a recent study that was a

randomized doubleblind clinical trial

um some of the features are shown here

in terms of of what was done in terms of

interventions um you can see some of the

features of the patients theres about

00 plus patients that were randomized

fairly evenly to the the genetics group

or the clinical management group show

you some of the factors theres a whole

table of other factors where there was

no significant difference between the

two treatment groups and what you see

here

is the response rate

it was measured by a number of different

factors i chose one of them from figure

of that paper shown here

was was much higher statistically

significantly higher and clinically

significantly higher in those patients

who got the gene guided therapy versus

those who got standard clinical

management

now an important factor is that the the

severe toxicity

interventions the burden of toxicity as

its called

was was

much

better controlled in the genetic guided

therapy compared to those who didnt get

genetic therapy and so its one of those

situations where better efficacy

lower chance of toxicity was occurring

with genetic guided therapy compared to

what you see with standard clinical

management

now most depression is managed in a busy

primary care environment its its not

that common that a psychiatrist or

psychologist is involved in that

management and so you can manage how you

can imagine how in a busy clinical

environment

understanding the genetic risk of

therapy

choosing the therapy based on the best

chance of benefit lowest chance of

toxicity is going to be

a much more efficient way of managing

patients both in terms of clinician time

and in terms of the patients time a

need for return visits etc and so were

seeing a lot of use of these types of

testing in the context of of

of depression

trying to improve that and theres been

data now for other types of psychiatric

care

that that can be managed and this slide

here is just trying to remind that

theres going to be a genetic

information pharmacodynamics

pharmacokinetics but then other factors

age the severity of disease the

environment both the natural environment

the home environment the work

environment

other factors depression schizophrenia

other mental health disorders are very

complex disease its not just a simple

gene defect and so genetics will help

guide the therapy

but will never be the only tool

for use in in guiding therapy and so

this is just a slide to remind myself

and you

that genetics is a a factor that can be

added to good clinical management

not a replacement for good clinical

management a robot is not going to be

able to take genetic results and manage

depression it still takes good clinical

management but hopefully better results

for the patients better efficiencies for

the practice as we go forward

now

weve talked about dosing about

selection ive talked a little bit about

some of these other issues but

there are important drugs where theres

still additional information needed so

for example the the opiate

pain control medicines all have genetics

that are involved in their metabolism

theres clinical uh studies uh not

randomized trials but uh clinical uh

studies that have looked at these

genetic variants and seen some effect

but there havent been those prospective

randomized trials to really look in and

say

can we use this genetic information

to guide therapy better select therapy

in some way and with the opiate epidemic

thats occurring in many countries

around the world

its certainly an important factor that

if we can more rationally use these

medicines to control pain

and to hopefully manage their their

misuse uh then were going to be in a

much better shape as a society and

individual patients will have better

effects

same with the antimedics the these

antimedics are used of course to

prevent nausea and vomiting from cancer

drugs but a more common use is every

patient getting general anesthesia for

surgical procedures for any other type

of procedure

well well receive one of these

antimedics to prevent

nausea and vomiting

again genetic variation is occurring and

can be important for the effect of these

drugs

heres a chance to try to better

understand this

try to use this as ways of guiding

therapy

there are

multiple millions of patients getting

surgical procedures every year just with

hip replacements its almost 00 000

patients a year in the united states

alone

all of those getting general anesthesia

all those could benefit from genetic

guided antinausea nausea antivomiting

medicines and so a real opportunity that

has not yet been realized to affect the

dosing or dose selection of very

commonly used medicines across many

different therapeutic areas

now

towards the closing here i want to just

mention one thing about how this

information can also be used at a public

health level

when were looking at

major com major influences on health

care modern medical therapy has really

been a key component of improving health

now clean water

other other factors have also been very

important but

access to medicines is an important part

of this

and and choosing these medicines is a

major part of most developing countries

the decision making

and so

basing a decision based on access and

costs is important

but if

a if a

tipping factor in terms of drug a versus

drug b is something like familiarity or

clinical consensus thats fine but its

not necessarily the best way of trying

to select medicines and so can we do

more and so for example warfarin is a

medicine that youve heard about in some

of the other presentations in this

series

its a medicine that is very commonly

used across the world

including over million prescriptions

for this medicine in the united states

alone

its a medicine that is metabolized by a

number of different factors number

different p0 enzymes sip enzymes as

shown here also genetic variation in the

target the vitamin k

oxidoreductase

is also a factor and so one can look at

these genetic features and then one can

put it into a guideline so theres

something called warfarindosingorg

as one example

of a of a tool thats out there where

one can put in features such as age race

weight etc put in genetic information

press the button

and then end up with recommendations on

the dose that should be used per week

to to guide an individual patient

and thats great that information could

be quite useful

but if there is no genetic information

available for your country and youre

trying to look at differences what can

you do

well one can go in and

one has done the pharmacogenetics for

every nation initiative or pgenie as

its also known

went and looked at large cohorts from

across many different world populations

looked at the genetic information as

well as average body size et cetera was

able to were able to look at what is

the average uh predicted dose based on

these algorithms in a given country and

so what whats shown in green is is uh
european countries uh whats shown in in
um in blue is asian countries uh and
whats shown in in red are african
countries and hopefully you can see from
here that most african countries um have
a average dose of warfarin needed to
give anticlotting activity that is much
higher than seen in the european
populations
most asian countries need a much lower
dose compared to the european countries
now theres exceptions such as india
where there are more caucasoid mixed
population so its more close to the
europeans also south africa where the
population that was studied
included a number of the different uh
african tribes as well as the um
socalled uh mixed or or as its known
in south africa colored populations as
as well as the afrikaans white
populations and so you see this this
lower dose but a lot of variation
happening across the world um in in
even within subcontinents um for which

dose of warfarin one might pick

for an average dose within a country

and then whats shown here

is the algorithms from there were

published in the new england journal

applied to

a chinese and japanese population a us

and mexican population and a ghanaian

and

nigerian population showing that uh not

what i showed before that the average

dose needed for uh in this case two west

african populations are much higher than

that seen in the us white population

whereas the asian in this case japanese

and chinese need a much lower dose but

you can see within every one of the

populations theres a big spread

there are people within ghana that need

a lower than us average dose

and there are people that need extremely

high doses there are people within the

us need a

a dose thats lower than needed in asia

and there are people that need a dose

and these are in the us white

population need a dose thats higher

than seen in africa and so its not as

simple as a given continent a given

color a given selfdeclared

race or ethnicity but really needing

individual patient level data will help

us

guide the therapy in a much more useful

way but in the meantime one can start

with a lower dose in asia and a higher

dose in africa and then individualize as

needed because of these these average

features

so i want to finish off with this this

slide

thats thats really reminding us that

there is still a lot of work to be done

we dont know enough about blood level

guided dosing

if blood level guided dosing can be

applied in much

much beyond just antidepressants

that is a feature that is underutilized

and can be can be

a part of the solution

we also have very few examples where

genetic variation in

transporter proteins

or even in pharmacodynamic examples

are are present and are to the point

where we can use them routinely in

clinical care and so i think thats an

important uh research area where we need

to be doing more work in the context of

transporters and in the the receptors

the targets the pharmacodynamic factors

to really be able to better understand

these areas and better individualize

therapy

options are almost are often limited

based on available dosage forms

so you may be able to determine based on

a body weight an age a genetic test

exactly how many milligrams a patient

needs

but the medicines might be only

available in 00 milligram tablets and

maybe in capsules that cant be broken

in half uh to reduce the dosing and so

we need to be thinking about their

practical dosage forms in terms of how

we individualize therapy were not going

to be able to dial in the exact

milligram of a medicine for an

individual patient every single time

sometimes it might be people need one

tablet or two tablets or one tablet or a

half a tablet

that level of precision still is better

than our current approach

but is certainly not to the point where

wed like to be but the practicalities

of available dosage forms have to be

taken into account

also most of the examples are with oral

medicines

and thats great a lot of medicines

nowadays are oral pills tablets

capsules

but there are many intravenous medicines

and other ways of administering

medications that really need to be

studied as well because were not just

choosing the dose but also whether we

pick a different medicine these genetic

factors can be very important in terms

of that and need to be factored in

and then lastly we need more data on the

effect of pharmacogenetically guided

dosing

on the adherence consequences

on economic consequences and on outcome

consequences i i showed you some data

for the antidepressants where there was

superior outcome

i showed you

i hinted at some data for the

thyroipurin drugs where there is equal

outcome and reduction in toxicity but

theres very little data on whether

genetic information can cause someone to

take a medicine at the regular

prescribed rate

rather than

forgetting about it or deciding they

just werent going to take it for a

while so can we increase adherence to a

a medication plan based on genetics

can we show for other medicines as we

did for voroconazole that genetic guided

therapy is going to allow you to have

better effectiveness

and

reduce the cost both the cost to the

health system

and the cost out of pocket to an

individual patient so we have a lot to

be done still to optimize these these

examples but hopefully ive been able to

show you

that there are

many examples already

where pharmacogenetic information can

help us choose the dosage

the the selection of medicines

prior to ever treating a patient

so that we can try to get the right uh

the right medicine at the right dose for

this patient from the very start we have

a long way to go before its perfect but

it is uh it is approach we can now take

so hopefully youve enjoyed this uh this

presentation uh if you have any uh

questions on this presentation feel free

to contact the moderators uh of this uh

of this series and we hope that you tune

in for the other uh presentations in

this series and please feel free to give

comments on how we can improve it and

meet your needs as we go forward thank

you very much

you