im very excited to introduce the next

dr dick wenchelbaum is a professor of

cancer genomics research and professor

of pharmacology and medicine at mayo

clinic

he received his medical degree from the

university of kansas and completed

internship and residency at mass general

additionally he completed a pharmacology

training program here at the nih with

the nobel laureate dr julius axelrod

dr winchelbaum has devoted his career to

the study of individualized drug therapy

his research focuses on the utilization

of genomic techniques that include

genomewide association studies next

generation whole gene genome dna

sequencing in patients with cancer and

depression

hes received numerous awards and honors

in the field of pharmacology including

aspets harry gold award for clinical

pharmacology and the oscar b hunter

award from ascpt for career scientific

accomplishments im confident you will

enjoy todays lecture

hello im dick winchelbaum professor of

pharmacology and medicine at the mayo

clinic in mayo medical school its a

real pleasure to take part in this

series because what were seeing is an

evolutionary process for the discipline

of clinical pharmacology

my topic today is

pharmacometabolomics and clinical

pharmacology as someone whos devoted my

entire career to what was

pharmacogenetics and then evolved into

pharmacogenomics

its really interesting to see the

further evolution of ohmic science as

applied to clinical pharmacology and i

think we can take pride in the fact that

clinical pharmacology has taken a

leadership role in terms of bringing

omic science to drug response phenotypes

this first slide the title slide

pharmacometabolomics and clinical

pharmacology really those little logos

at the bottom are there for a reason

at the left hand side

what you can see is that little thing

that looks like a tooth fairy or

something that is the logo for the

center for individualized medicine at

the at the mayo clinic and over on your

right is the logo for the nih

pharmacogenomics research network and

those are there to make the point that

really what were engaged in all of us

is a partnership between the national

institutes of health which is frankly

one of the great social inventions that

this country has produced which

catalyzes change but its a partnership

with all of our academic medical centers

i just use the mayo clinic as one

example

in order to bring the latest science to

the bedside to try and benefit patients

everywhere

in the middle you see that thing that

looks like sort of an explosion thats

the logo for the nih

pharmacometabolomics network which i

have been a part of since it began and

that ims thing is the logo for the rican

center for genomics and and basically

thats to make the point that what were

engaged in here is an international

collaborative and cooperative effort to

move the science forward that said i

teach medical students and graduate

students and postdoctoral fellows all

the time so i have an outline

i promise you there will not be a

posttest unless the nih comes up with

one and im going to make a few

introductory comments

im going to very briefly talk about

metabolomics a brief overview and then

the focus here since after all this is a

clinical pharmacology lecture series is

pharmacology metabolomics informed

pharmacogenomics has applied to drug

response phenotypes and then a few

concluding comments

so pharmacogenomics and pharmaco

metabolomics are critical components of

what is today referred to as

personalized individualized or since

president obamas

0 state of the union address

precision medicine

we all know what the clinical goals of

pharmacogenomics and

pharmacometabolomics are number one

to help us first of all avoid harm to

avoid adverse drug reactions

because the drugs we use today are not

placebos theyre powerful agents many of

them are highly targeted but they also

can do great harm in addition to great

goods so our first responsibility is to

avoid adverse drug reactions number two

they work theyre not placebos so we

want to maximize drug efficacy and

finally at the bottom select responsive

patients right at the very beginning so

we can avoid churning in the system and

going on a purely a hit or miss passion

from one drug to another

theres a science here though too

there are scientific goals to both of

these disciplines first of all

to link genomic and metabolomic

variation to phenotypic variation the

phenotypes being what i outlined on the

immediately preceding slide

second and ive highlighted this this is

a science we are scientists engaged in

trying to understand underlying

mechanisms or to determine the

mechanisms responsible for that link and

ill give you a couple of examples

before were done here and finally were

physicians so we want to translate that

link into enhanced diagnosis treatment

and prevention of disease and that

applies to pharmds it applies to phds

who are engaged in clinical pharmacology

and it applies to those of us who have

md or md phd degrees

so

what is this broad topic that ill be

speaking about for the remainder of this

presentation it is as i said at the

beginning the application of ohmic

science in order to study variation drug

response phenotypes and once we

understand it to bring that

understanding to the bedside

heres my view of the evolution of

pharmacogenetics into pharmacolomics

which would include pharmacometabolomics

we began

with

what my medical students tell me are

those boring cytochrome p0 drug

metabolizing enzymes and why was that

because at the beginning these were

candidate genes and we knew that blood

drug levels were related to the outcomes

of drug therapy and so that was where

our focus was was on drug transporters

genes encoding drug transporters genes

encoding drug metabolizing enzymes

at the beginning of this century we

began to have the ability to move beyond

candidates that we knew on the basis of

biochemical studies to form what ive

called pharmacogenomics here that is

unbiased genomewide studies that

frankly when i began doing this no one

had cloned any gene i know thats hard

for many of you to believe but

thats actually where this field came

from

now we can scan an unbiased passion

across the genome and what we find is

all kinds of genes that we had never

thought of before with names we had

never heard and ill show you examples

of that before were done today that

have an important

effect on drug response phenotypes and

finally what we have now learned is that

genomics is not a dna sequence is not

everything

and we need to bring in metabolomics

transcriptomics proteomics and multiple

omics

so with that background lets focus

briefly on metabolomics just a brief

overview

so here is this little uh

this little ladder that even the male

medical students whom i abused terribly

would know

that is dna now that is the genome

encodes messenger rna the transcriptome

which encodes proteins thats proteomics

and the proteins do things and thats

metabolomics and the metabolites are

right up against the clinical phenotypes

that presents an opportunity but also

significant challenges if were going to

bring all of these omics together and

bring them to bear on drug response

phenotypes

what do we do in metabolomics we use the

assays that generally will go right back

to liquid chromatography or high

performance liquid chromatography or

ultra high performance liquid

chromatography it gives us the ability

to simultaneously assay a large number

of small molecules in biological samples

of all sorts in plasma of course in

cerebral spinal fluid and lysates of

cells etc so first weve got to separate

those small molecules and thats where

gas chromatography liquid chromatography

etc are used

we need to quantify them and well come

back to that in a minute by the use of

standards and then we need to identify

them because at first theyre just a

peak coming off of an lc

and we can do that with nmr and

generally its done with tandem mass

spectrometry so

a whole series of things that all of you

are familiar with already

the ideal platform for metabolomics has

great sensitivity

its quantitative and it has broad

specificity it enables you to look at a

variety of different kinds of compounds

therell be endless debates about

what platform to use and what i would

suggest to most of you is that your

academic medical center like mine will

have a center for metabolomics that is a

core and you need to go and get advice

with regard to the particular problem

that youre looking at i recently

received a grant to begin to study drugs

that are used in alcohol use disorder

and we sat down and had exactly that

discussion with our core metabolomic

center with regard to the platforms that

are available focusing on quantitative

platforms with high sensitivity and it

will be a different detection system

depending on the on the nature of the

small molecules that you want to

identify

im going to show you just a couple of

examples of the application of

metabolomics to make some points that

that may seem obvious but werent so

obvious to begin with

heres a metabolomic study of

metabolites in some fairly large

populations of women and men

and notice one of them was 00 men and

00 women

and

this was a broad metabolomics but it was

quantitative metabolites

and by using principal components

analysis you can sort out

rather striking differences looking at

the principal components analysis on

your left and on your right theres a

two populations one was the original

large population then a replication

population

showing that the blue dots are different

than the green dots and this is making

the point that the metabolomics profiles

in men and women differ now weve all

been to medical school or graduate

school so i think we know that there is

a difference between boys and girls but

i think we need to bear this in mind

hold this thought because im going to

come back at the end and make a point

that this became very important when we

were trying to use metabolomics to study

patients with major depressive disorder

twothirds of whom are women

this is talking about the next slide

well just give you some idea of

metabolic individuality

and here were looking at some of the

same populations and some different

populations now were up to 0

metabolites and over 0 metabolic

pathways and what was done here was to

do g was to identify genes associated

with variation in the metabolite

hold that thought because im going to

come back to that at the end of this

presentation when i use major depressive

disorder as an example of the

application of genomics put together

with metabolomics to give us novel

insights into the underlying

pathophysiology of disease and response

to therapy and what you can see here

ive just picked these examples because

they happen to be among some of the

boring stuff that i lecture on drug

metabolism onto our medical students and

graduate students if you use bilirubin

as a metabolite that

and look for the gene the variance in a

gene the snips that were most highly

associated with variation in plasma

bilirubin guess what it was in the

ugta gene uh and with a pvalue notice

of times 0 to the minus th power

for

androsterone sulfate it was cytochrome

pa

and for caffeine which i probably would

guess that many of you have already had

today as youve watched this lecture

it was a snip

near the ahr gene with a pvalue of 0

to the minus th so this is an example

of taking the metabolite concentration

as a phenotype

and then doing genomewide association

study to ask the question

are there genes that are associated with
the variation in the metabolite and if
the concentration of metabolite is
associated with the uh disease phenotype
or drug response phenotype youre
interested in you can find
what underlying genes and snips are
related to that variation in the
metabolite and i put this here as an
introduction to what im going to show
you later
now with that as background using
variation and concentration of
metabolites as a way to begin to
understand variation in the patients
were looking at and in our case
variations in drug response phenotypes
lets talk about how metabolomics can
inform genomics now i think i said just
a moment ago that my entire career has
been devoted to dna sequence variation
in its relationship to variation in drug
response phenotypes
now what well talk about is how we can
use other omics information to inform
the genomic analysis and give us provide

us insights that we couldnt have

otherwise had

what are the challenges well there are a

lot of challenges but one of them is how

do you actually in real life terms merge

metabolomic information with genomics

and other omics transcriptomics

proteomics

number two

when we look at metabolomics we can

obviously extract

metabolites from cytosol in cells

we can look at plasma but most often it

will be plasma metabolites and thats

the end result of a variety inputs from

a variety of organs how do we relate

that to a specific organ and

the

since i told you that the example ill

use is for major depressive disorder how

do what does that have to do anyway with

whats going on in the brain and i can

tell you that psychiatrists are

concerned

that what is looked at in the periphery

in terms of metabolomics or

transcriptomics might have nothing

whatsoever to do with whats going on in

the brain so hold these thoughts there

actually is

a method to the madness and were going

to come back and put these challenges

together and address them individually

so lets begin

with one study of major depressive

disorder

this is the number one psychiatric

disease worldwide lifetime risk in

virtually every population of about

percent and

clearly its a disease that we dont

talk about as much as we do breast

cancer or coronary artery disease

because of the stigma thats associated

with psychiatric disease heres a study

this is so common that we could do this

study entirely in olmsted county

minnesota where the mayo clinic in

rochester is is based 00 patients with

major depressive disorder

how did the psychiatrist currently how

do they determine

how severe the major depressive disorder

is do they have a blood test that they

can do and you know that the answer is

no

they ask a patient questions about his

or her mood

they ask about sleep patterns they ask

about sex life and sex behavior and then

assign a score and you do not want to

get a high score on this test because

the higher the number the more severely

depressed the patients are this is the

quick inventory of depressive

symptomatology or the hamilton d these

are you ask questions in order to

determine how ill your patient is what

was done in this case was to have four

psychiatrists it was always the same for

see these patients and determine quids

and hamdi at baseline at four weeks and

eight weeks

and then we did genomewide genotyping

and first gc toft that is so gas

chromatography time of flight mass

spectrometry and then lc electrochemical

array which is very sensitive for

neurotransmitters and neurotransmitter

metabolites on 00 of these 00 patients

now remember its three time points

and what that meant was that it was over

a thousand samples and i can tell you it

was an extremely expensive study to get

both the g was genotyping and the

metabolomics on just these 00 out of

the 00 patients and what was the

approach

we

looked for metabolomic signatures

then we analyzed pathways and determined

which metabolite was related to what the

psychiatrists were measuring that is

change in hamilton d or change in quids

in the first studies before we had

genomewide data we did tag snipped

determination and then functional

validation of any snips or genes that we

saw later we could go across the whole

genome using giwas so im going to show

you the way our understanding of these

patients evolved over time

what we found was that glycine was the

metabolite that appeared to be most

highly associated with

with response to ssri therapy

and im just showing you here response

for most of these psychiatric studies

means that your quids or hamdi

decreases by 0 and remember a high

score is bad so you want it to decrease

when you treat

remission means that it goes for the

quids to a value of less than five for

the hamilton d a value of less than

seven our chair of psychiatry at the

time we did this study explained that a

quids of less than five

is

happier than any mayo clinic doctor is

on monday morning now i dont know what

he meant when he said that but i think i

can guess so you can see that

that were looking at what happens with

baseline glycine levels and its

relationship to these phenotypes

response and remission and it appeared

that change in glycine was associated

with response and was nearly

significantly associated with remission

just taking the extremes of response and

remission

we could then go back to the pathway

whereby glycine is synthesized and

metabolized into tag snips across all

these genes that i have listed here and

one of those genes

which we wont bother you with showed

that it had a series of snips that were

related to response to ssri therapy so

this is this is the the neolithic period

of five years ago when this study was

done and we published this study in

clinical pharmacology and therapeutics

as you can see on the bottom of the

slide in 0

and this just shows you that what we

this was a beginning to move toward

taking a genomewide approach

to take a genomewide approach we did

genomewide gwash genotyping snipped

genotyping out of about 00 000 snips

and imputed that to million so now

weve got seven million snips on each of

these patients and we used a different

metabolomics platform

getting

900 samples on 00 of these patients and

only using about metabolites but with

high degree of sensitivity

for monoamine neurotransmitters like

serotonin and the catecholamines this

work was done by dr wayne matson in

bedford massachusetts so now were going

beyond

just a few snips that is tag snips

across a pathway and were going to look

across the whole genome

looking at variation in the metabolites

determining how that variation is

associated with variation in response to

ssris and then saying what are the genes

that are respond that are associated

with this variation in response to

in response to ssri therapy

and lo and behold what we found was and

and i just put this up here so you can

see ive got remission response percent

change in quids this happens to be with

the with the quids at baseline after

four weeks of ssri therapy after eight

weeks of ssri therapy and the plasma

metabolite that was most closely

associated with response to

among depressed patients to selective

serotonin reuptake inhibitors was plasma

serotonin and i said this is too good to

be true but as a matter of fact it

actually was true and these are all

nominal pvalues because were now going

to go back and select serotonin to do a

genomewide association study so what

this slide shows is that variation in

plasma serotonin

appeared to be very closely associated

with who was and who was not going to

have the remission or response or

percent change in remission response to

ssri therapy and that was determined

purely by asking the patients questions

about their mood about their sleep

pattern and about their sex life

this slide shows you what happens to

plasma serotonin after both four weeks

and eight weeks of exposure to ssr ssris

it drops precipitously that makes sense

because plasma serotonin predominantly

comes first from the gut but the

platelets take up the serotonin from

enterochromafin cells in the gut and

store the serotonin and what we

basically are doing is directly

inhibiting that uptake process which is

the target of the ssris so

as you think about it it shouldnt have

been surprising that plasma serotonin

concentration might be highly associated

with what serotonin reuptake inhibitors

might do

now looking in the periphery not in the

brain and well come back to that in

just a minute because clearly thats one

of the worries that the psychiatrists

have

i just want to review with you a sort of

slide that i would show to the mayo

medical students that is this is where

does serotonin come from it is a

metabolite of the amino acid tryptophan

ltryptophan about five percent of the

tryptophan goes down the pathway going

to serotonin 9 to kind urine in both of

these pathways can affect in the central

nervous system respon neurotransmitter

system serotonin obviously can affect

serotonin urging neural transmission and

kiney uranine will interfere with

glutamatergic neurotransmission and if

you were male medical students rather

than the very sophisticated audience

whom im addressing i would say for the

medical students serotonin good kind

yearning bad now thats a gross

oversimplification but it may help a bit

in terms of thinking about where were

going next

so what did we do

on these 00 patients

we then

did a genomewide association study on

baseline plasma serotonin serotonin

at four weeks at eight weeks change in

serotonin and what did our statisticians

tell us

they told us what the statisticians

always tell us

you are underpowered and you are doomed

this cannot possibly work you will not

bind any genomewide significant hits

to their terrible disappointment we

actually found two hits one that was

genomewide significant in this gene

tspan five with a pvalue of about

eight times ten to the minus ninth

e ridge which was close to genomewide

significant and 9 times 0 to the minus

nominal genomewide significance is

times 0 to the minus

i would assume that nobody in this

audience had ever heard of tspan or

erich before you saw this slide i

certainly i never had actually you rich

at the time we did the study didnt

even have a name it was just

annotated as an open reading frame so

what are these genes that none of us had

ever heard of

well first of all

why could we find this signal

in only 00 subjects which of course

horrified the statisticians

its because

it

the pvalue depends on the minor allele

frequency and the effect size how big is

the effect size what im showing you on

this slide

is if you look at the erich three snips

the genotypes for low and high serotonin

and the t span five sniffs for plasma

serotonin and put them together

the difference between being homozygous

for the low serotonin snips in both

genes or the high serotonin snips in

both genes is 0fold

we are not looking at an effect size of

0 were looking at a 0fold effect

size so clearly these genes have a very

major role in terms of determining the

variation in plasma serotonin well come

back to why that might be in just a

moment

what im showing you here are socalled

locus zooms or regional plots and youre

looking at your left at the

plot of the snips that we had after

imputation in the g wes across the rich

three gene and on your right at the

snips that were five prime that is just

upstream of the t span five gene so for

t span these snips were socalled

expression quantitative trait loci

translated into english that means they

are associated with variation in the

expression of the gene that is the

messenger rna thats made from this gene

depending on your genotype

this snips any rich three as ill show

you in a minute were nonsynonymous

snips they were there were two of them

that changed the encoded amino acid

sequence and one of the common things

that happens if you change encoded amino

acid sequences the protein misfolds and

is rapidly degraded and thats what

happens d rich three so these steps

basically for e rich three represent if

you have two copies of the variant they

represent a knockout of the eridge

gene

now lets go to what bothers a

psychiatrist

theyre going to say immediately

whats in the plasma what does that have

to do with the brain anyway

well in todays world we now have

something called gtex which is a

database where you can go and look at

human tissues obtained soon after death

rapid autopsy in patients who generally

died in automobile accidents or

motorcycle accidents in which the tissue

they got informed consent was taken and

rnaseq was done on these tissues and

all you really need to know looking at

this slide is yellow is different areas

of the brain and this is showing you

which tissues tspan is expressed in

and its mainly expressed even though we

found it in peripheral plasma its

mainly expressed in multiple areas of

the brain you can see the yellow little

boxes are very very high expression of

tspan so what we saw in the

periphery told us about a gene thats

mainly expressed in the central nervous

system and erich is even more

dramatic eridge is predominantly

expressed once again in different

regions these are just different

regional areas of the brain in the human

brain

so

what we saw in the periphery is telling

us something about variation that may be

occurring in the brain

i put this up just to to take you back

to with

sheer horror to those lectures on

tryptophan pathway metabolism just to

point out that to get serotonin you have

to go through tryptophan hydroxylase one

and two and dopa decarboxylase and

eventually you get serotonin and then

that can be metabolized by monoamine

oxidase etc taking you back to very

early pharmacology lectures either in

graduate school or in medical school so

what we did was take a neuronally

derived cell line the neuroblastoma and

we knocked down an over express tspan

and if you look over at the left you can

see that tryptophan hydroxylase one and

two and dopey decarboxylase if you knock

down tspan five

these biosynthetic enzymes that make

serotonin go down

if you overexpress tspan they go up

so you dont just find a signal you want

to functionally

validate its not a replication but

functionally validate what this might

have to do with in our case serotonin

levels it looks like what happens here

is tspan is playing a role in the

biosynthesis and degradation of a

serotonin

for erich what youre seeing here are

western blots where we could take the

erich gene

and find an example a construct that had

the variant this l0

v

and just express it in a mammalian cell

and what you see is that the protein is

way down and in the bottom of your

at the lower right you can see that if

you then block

if you then

block the proteasome which degrades

misfolded protein its right in the

middle there

that you can prevent the degradation of

the protein so the erich threesnit is

a nonsynonymous nip changes the encoded

amino acid and that apparently leads to

rapid degradation of erich iii

and if you take those erich threesnips

and look at other

ssri studies and ispc is an

international

ssri consortium with about a thousand

patients that we put together those

snips were related to outcome

to outcome in that study and in

something called star d which was

another study that had about 00

patients who were caucasians and similar

to our patients now remember

that gwasps was done for plasma

serotonin but the snips we found on the

gwasp are associated with outcomes in

these studies and i can tell you theyve

been replicated in something called the

mars study of munich study of depression

too so we have replicated these at least

the rich three snips in three other

studies

lets look at baseline severity

of

symptomatology because we had

metabolites at baseline and we could

look at the hamilton d in the quiz and

say which metabolite is just related to

how severe the symptoms were how high

the ham d or quid score was at baseline

and right at the top of the list was

kind uranine and i showed you that

metabolism that came down from

tryptophan to serotonin on the other

side of the of the pathway was kine

uranine and you can see that

this was the number one metabolite

variation and plasma kind urinary

metabolism

and plasma kinearine concentration

appeared to be most closely related to

the metabolites that we examined in this

in this study

with

severity of depressive symptoms as

determined by asking questions about

mood questions about sleep questions

about your sex life

so we did a g was for baseline plasma

kine uranine and the number one hit was

not genomewide significant his pvalue

was about 0 to the minus seventh but it

was in a gene called death b

now i didnt know what that gene was

there may be somebody in the in the

audience looking at this who knows but

when you look at the plasma tying

urinary concentration there was another

signal in the ahr gene you can see that

this also is related the two genes are

related to plasma kine uranium

concentration but theres not a tenfold

difference if youre homozygous for low

kineyorning versus high kind urine snaps

its only about a twofold difference

fb

what is this thing

its a beta defensin what is it what are

defensins these are small peptides that

are generally encoded by genes that are

found in the intestinal mucosa and

thats where death b is located and

what does it what does death b do

it interacts directly with bacteria and

bores holes in the bacterial cell wall

and it also inactivates lps and

everyone whos been to medical school or

graduate school knows that you dont

want a lot of lps floating around in

your plasma thats associated with

endoplasmic

with shock and

clearly this is a way for the body to

protect itself so wait a minute i can

see the psychiatry

the psychiatrist in the audience saying

what in the world does the gut have to

do with the brain and in todays world

of the microbiome

we know that there is absolutely no

doubt that there is a gut brain access

and is diagrammed

schematically here were showing that

basically what def b does is inactivate

certain bacteria in the gut and also

inactivate lps that probably has

something to do directly with the

tryptophan to kineranine pathway and we

know that it does we have experimental

evidence that it does and so what the

world is now showing us

and what i think of all the omics the

one that that has surprised me the most

is the rapidity with which the

microbiome has been shown to have

profound effects throughout our bodies

and that we need to be thinking along

these lines irrespective of what the

underlying pathophysiology is that were

studying and this is just an experiment

done in the lab to show you that

that you can make the kineranine go down

if you can add

def b to lps and that the tryptophan

goes up its just making the point that

indeed functionally deaf b is playing a

role in tryptophane and kine uranium

metabolism

and

if we took those snips from def b which

were related to the concentration of

kineranine

guess what they were directly related to

the hamilton d and quid scores

statistically significantly when we went

back and looked at the patients theres

no reason why

something that you find in a kineranine

jiwas should be related to the change in

hamdi or the severity of hamdi or quid

scores

in the psychiatric patients

so what have we done here ive shown you

use of metabolomics

to inform genomics

for two metabolites that were highly

related to a clinical phenotype either

severity of depressive symptoms or

response to ssri therapy and we have

erich tspan def b ahr all right

now where are we going to go with this

and im going to carry you now into the

world of artificial intelligence machine

learning and what

people like to call now augmented human

intelligence because artificial

intelligence sounds like the robots are

going to take over the world and

augmented human intelligence

is a little less threatening

but lets go here first

i am not a psychiatrist i did my

research training with a man named

julius axelrod at the national institute

of mental health and i bought his

champagne the morning he won the nobel

prize for discovering the neural

membrane reuptake mechanism that the

ssris block so i can tell you its its

actually quite rewarding to come back

decades later and be able to look at the

basic mechanisms of how these ssri drugs

work but this is from a real

psychiatrist the head psychiatrist for

the united states in one way a man named

tom insult in 0

when the

dsm and the dsm as those of you who

went to medical school know is the bible

of psychiatry i think psychiatrists

sleep with the dsm under their pillow

and heres what heres what the head of

the national institute of mental health

said in 0

said unlike

heart disease or lipid disorders where

you can measure lipoproteins in the

blood or aids where you can directly

measure the virus

psychiatric diagnosis are based on a

cluster of clinical symptoms without any

underlying biological he says objective

laboratory measure

and i think his last sentence deserves

to be highlighted patients with mental

illness deserve better so what youre

seeing here

is an attempt to bring metabolites and

genomics to bear

on in the same way in psychiatric

disease that we do for

cancer and we do for coronary artery

disease

so what did we do

with the information we had in these 00

patients well we collaborated with

computer science department at the

university of illinois urbanachampaign

those of you on the west coast are going

to be blissfully unaware of this but

netscape did not come from silicon

valley it came from the corn fields of

illinois and from the department of

computer science there

and using hierarchical clustering

then said can we begin

to cluster patients with major

depressive disorder into different

groups and can we begin to predict who

will and will not respond to uh ssri

therapy in a way that could be used in

the clinic so what this slide shows is

that first of all

it was abundantly obvious using these

machine learning and artificial

intelligence techniques that you had to

deal with men and women separately that

takes us back to what i showed you right

at the beginning the difference in the

metabolic profiles of men and women if

you separated the men from the women you

could reproducibly both in our study and

in the

other studies that i showed you the ispc

and the star d study separate patients

with major depressive disorder into

three separate groups

referred to here as a a a and even

follow them through therapy

now

do i

understand

how the neural networks did this

not a clue but im sure theres some

computer scientists sitting there

snickering saying well its obvious how

that might work

and if you then apply this you can go if

you use the clinical symptoms alone

your accuracy in in predicting who will

respond to ssris is about

better than flipping a coin but only

marginally better certainly nothing we

could use clinically

if you apply these predictive algorithms

that come out of the machine learning

world

and the artificial intelligence world

and separate men from women

you can determine with an accuracy of

about 0 to to 90 percent in both men

and women whos going to respond

remember that in order to get ketamine

which is used only in patients who fail

on ssri therapy in our ketamine clinic

you have to fail on three different

ssris it takes two months to know

whether the ssris worked that means in a

potentially suicidal patient you might

wait six months before giving the

ketamine

if this algorithm which is replicated

now in a series of studies by the way it

replicates in the mars study in germany

also if it gives you a high degree of

prediction accuracy this patient is not

going to respond to

ssris i think what the day will come

soon when you will move directly to

ketamine which in patients who failed on

ssris about 0 of them will respond to

ketamine infusion therapy that has

immediate clinical implications

and heres a paper that was published

just this month august 0 which is

when im making this tape in the ieee

computational intelligence talking about

the use of these machine learning

techniques and their application to ssri

response now

ieee for those of you like me who had no

idea what that meant thats the

institute for electronic and electrical

engineering and i have to say i probably

embarrasses the electrical engineers

that im one of the coauthors of this

paper i never thought i would be

publishing in an ieee journal so

theres another point here

in todays world we dont just need to

move beyond genomics to include

transcriptomics and proteomics and

metabolomics we need to have the

computational tools that will enable us

to deal with these large data sets in

ways that can give us provide novel

insights so lets conclude

pharmacogenomics and

pharmacometabolomics

are not just stuck with the boring

cytochromes b0 and phase ii drug

metabolizing enzymes and transporters

that i teach about in my drug metabolism

course

we are going to move very rapidly beyond

pharmacokinetics to pharmacodynamics and

mechanistic studies that will take us

through all of biology at the genomic

level we clearly are going to move

beyond the open reading frame and the

vast majority of the snips that are

significant that we find on g was in our

studies in other are not snips that

change the encoded amino acid not these

nonsynonymous snips that we have in

erich three but theyre more like what

we saw in tspan five they generally

will alter transcription of the gene

were going to have large and expensive

multiple ohmic status sets that go

beyond genomics which was horrendously

expensive if you wanted to go

genomewide and will include

metabolomics transcriptomics proteomics

and the microbiome

and we need to reach out for

complementary expertise especially

computational expertise and that

requires crossdisciplinary dialogue

where we think we know what the other

person is saying and where they really

are saying something quite different

so what are we talking about with these

multiple omics the application of ohmic

science to study variation in drug

response phenotypes and this is an

absolutely critical component of

precision medicine and clinical

pharmacology i have no doubt will lead

the way

in terms of bringing this type of

knowledge to bear on drug response in a

variety in every possible clinical

setting finally i want to show this this

is last years slide showing my

laboratory and my

colleague dr leeway wong a stan off the

two of us standing on either side of one

of our t clinical pharmacology

trainees who im happy to say is off in

a pharmacy school teaching

pharmacogenomics as we speak and

if this slide does not look like your

image of minnesota then i think that

that says good were attracting the best

and the brightest minds from all over

the world to come to some place where

the ground is covered with snow six

months out of the year its been a real

pleasure to participate in this series

a pleasure and an honor

and im looking forward to seeing the

other lectures in this series thank you

very much