today were honored to have mary relling

dr rayleigh earned her undergraduate

degree

in pharmacy from the university of

arizona and her doctorate in pharmacy

from the university of utah

she completed postdoctoral fellowship

training with bill evans at st jude

and erst meyer at the university of

basel

she joined st jude as a faculty member

in 9 and in 00 was named chair of

the department of pharmaceutical science

she is also professor at the university

of tennessee both the college of

medicine and pharmacy

her primary research interests are in

the treatment and pharmacogenetics of

childhood leukemia and clinical

implementation of pharmacogenetic

testing

dr rolling is chair of the nihs

pharmacogenetic research network and

cofounder of cpic

the clinical pharmacogenetic

implementation consortium

she was elected to the institute of

medicine in 009

please enjoy the

presentation okay welcome

my name is mary relling and i am the

chair of the pharmaceutical department

at saint jude childrens research

hospital in memphis

i also colead cpic the clinical

pharmacogenetics implementation

consortium with terry klein of stanford

and ill be talking about this resource

throughout my talk today which is on

clinical pharmacogenomics testing

actionable pharmacogenetic gene drug

pairs have been known for a very long

time um since about 90 its been known

that by altering the dose of primaquin

in patients who are gpd deficient one

could avoid serious adverse reactions

and several other gene drug pairs have

really been worked out um as long ago as

as three decades ago

uh and and many more continue to be

discovered in the present day

so what do i mean by actionable

for example the data that relate to tpmt

and thiopurines are particularly strong

back in the late 90s

before

bioperine doses were adjusted based on

thiopurine methyltransferase genotype

a hundred percent of patients who are

homozygous deficient for this

uh gene product had lifethreatening

myosuppression

about

of those heterozygous for low function

alleles had lifethreatening mild

suppression compared to only about seven

percent of the majority of patients who

are

homozygous for normal function alleles

for tpmt

and

um

subsequently

in

in followup studies

we started adjusting the dose of

thiopurines based on tpmt genotype

and by doing that

we had the same amount of myosuppression

a much lower amount of higher

myelosuppression

in those individuals who were

heterozygous for low function alleles

versus the majority of patients who were

homozygous for

normal function alleles

and the other very important piece of

evidence that leads us to be confident

using tpmt status

for adjusting thiopurium doses is that

the risk of relapse was not higher

in the

patients that were heterozygote for low

function alleles shown in red compared

to the majority of the population that

was homozygous for normal functional

alleles shown in black

even though those patients that were

heterozygous for

tpmt status received lower doses of

thiopurines

so if we can reduce toxicity without

compromising efficacy then thats

exactly the kind of actionability on

pharmacogenetic testing that will be

comfortable

moving forward in the clinic

another example of something that is

frequently used in the clinic is

screening for hlab

variants

prior to prescribing a baccavier and in

this new england journal paper from

about 0 years ago

but it was shown that by prospectively

screening hiv positive patients before

making the decision about prescribing a

bacca fear they could

avoid clinically diagnosed

hypersensitivity reactions or

immunologically confirmed

hypersensitivity reactions

um substantially by using

a patients hlab genotype to withhold a

baccavir in that minority of the

population that has a high risk hlab

allele

so these are the kinds of gene drug

pairs

that have lived risen to the level of

clinical action ability but

for the most part the use of these

pharmacogenetic tests in the clinic is

still rare

in fact a recent survey

of pharmacies in the hospital setting in

the us

found that the vast majority of

hospitals did not offer pharmacogenetic

testing only seven percent offered

pharmacogenetic testing and that was up

slightly from percent in 009

so you can see

that genomically informed prescribing

even in the hospital setting

which probably is more advanced than the

outpatient setting remains underutilized

another piece of evidence showing the

low uptake of the clinical use of

pharmacogenomic tests

is provided in this summary from a large

academic medical center these were

medical centers associated with the

university of washington in seattle

and it was

however it was a setting in which there

werent any directed efforts at

preemptive genotyping for

pharmacogenetic tests it involved over

0 000 patients and over million

hospital or clinic visits and they

looked at medication orders

for 9 drugs that had germline

pharmacogenetic testing mentioned in

their fda approved drug labels

about half of which were considered

actionable by cpic

and they found that less than one

percent of the prescriptions for those

9 drugs were accompanied by any

pharmacogenetic testing

and when they limited their analysis not

to just mention a pharmacogenetic

testing in the fda label but fda

actually recommending or requiring

pharmacogenetic tests it only rose to

percent

so this gives some idea in this paper

just published a couple months ago again

that pharmacogenetic tests are really

underutilized

this has been

reviewed recently by the

dutch

pharmacogenomics consortium and they

reviewed

programs

primarily in the united states but a

couple in europe as well that are doing

some kind of preemptive strategy for

implementing pharmacogenomics

and

this is a an increase from a few years

ago but again the vast majority of major

pharmacogenomic

testing implementation programs are

centered in a few academic sites

back in 009

before we started cpic we did a survey

of pharmacogenetic experts these were

members of the pharmacogenomics research

network and of the american society for

clinical pharmacology and therapeutics

and we found we asked them what their

challenges were to implementing

pharmacogenetics because these were

people who had a stake in trying to

implement pharmacogenetics in the clinic

and 9 percent of respondents said that

the process required to translate

genetic information into clinical

actions was a major barrier and the next

two most frequent responses were a

genotype test interpretation so how to

move from the genotype to the phenotype

and also

which gene drug pairs should be selected

to implement first

in fact this

last

barrier is one that i think has become

even more challenging in the last few

years this is just a sampling of the

many many direct to consumer

directtoclinician

forprofit pharmacogenetic testing

companies that are putting a lot of

pressure on patients and on clinicians

to order pharmacogenetic tests and

sometimes theyre pressuring to order

these pharmacogenetic tests for gene

drug pairs for which the evidence is

really not adequate to have clinical

action ability so not only is it

important for clinicians to know which

gene drug pairs to implement but also to

know which gene drug pairs not to

implement

ill talk about what were our work at st

jude because were approaching clinical

implementation on two fronts as i

mentioned we have a coformed

cpic with our colleagues at stanford and

this is an international consortium of

experts to facilitate clinical

implementation and really we did this

somewhat selfishly because at about the

same time we started a protocol here at

saint jude called pgen for kids the goal

of which is to implement preemptive

pharmacogenetic testing for patients and

so we needed to have these kinds of

clinical guidelines international

guidelines to do our own clinical

implementation

cpix website is indicated uh here

and as i mentioned its an international

consortium

primarily composed of volunteers and a

small group of dedicated staff

who are trying to facilitate use of

pharmacogenetic tests for patient care

and we have members

from all over the world i think probably

over 00 members at this point

and what we do is create very specific

gene drug guidelines clinical guidelines

and these guidelines are designed to

help clinicians understand how to use

available genetic test results to

optimize drug therapy its a pretty

important assumption of cpic that its

not whether pharmacogenetic tests must

be ordered because we believe that we

will be moving from the current status

of ordering primarily genespecific

tests to someday it will be true that

many people will have their entire

genomes or exomes

sequenced and then the challenge for

clinicians is not whether the test

should be ordered but how to use the

genetic test the results that have been

generated

to um

utilize them to improve prescribing

and

so so this has been a key assumption

that helps cpic avoid questions of

things like cost effectiveness

again its if the question is not

whether to order the test but how to use

genomic information to inform

prescribing its a completely different

set of considerations

our cpic guidelines are posted on our

website and they work capitalize on

pharmgkb resources theyre freely

available no limits on use

peerreviewed with cpt having the first

right of refusal and they have

standardized formats

and a minimum set of elements

we have standardized grading of evidence

and of recommendations

we can update them as needed on the cpic

website without waiting for an updated

publication we have a conflict of

interest policy and we closely follow

ion best practices for clinical

guideline development and this is just a

screenshot of a few of the

um front pages of the about 0 cpic

guidelines that have been published so

far

so indicated here are the genes that are

the subject of cpic guidelines and the

applicable drugs

that are covered by those cpic

guidelines

in progress right now is the tamoxifen

sip d guideline which we hope will be

submitted this month as well as a sip

b ephaverins and inhaled anesthetics um

guideline

so again the guidelines are available on

the website and every guideline has its

own home page

and

at the top of each one of the guidelines

home pages are any

updates since the publication

and this has been a useful way of

showing our users how to keep up with

new information

so one of the most utilized web pages on

cpic is this gene drug page and i think

thats because it provides the community
with a grading of gene drug pairs to get
a quick assessment of whether those are
deemed to be
likely to be actionable and whether they
will be the subject of cpic guidelines
so we do have an algorithm by which we
evaluate gene drug pairs
if the gene is already subject to a cpic
guideline then again one can imagine
clinicians are really faced with a very
strong imperative to decide are there
other drugs besides the one
already subject to a cpic guideline that
are actionable
and we consider each drug gene pair to
be in four levels cpic level a or b is
that a prescribing action is recommended
at some level of strength
based on the gene drug pair as well as
very importantly
the evidence that supports the
alternative therapy to be used for
individuals that have a high risk
genetic status and are prescribed a high
risk drug and examples of these would be

tpmt and thiopurines or

warfarin and its associated genes

sepic level c

is one in which no prescribing changes

are are recommended based on genetics

and that could be because the

alternatives are unclear

or the evidence is weak and this is

especially true for genes for which

testing is common for other sepic level

a or b genes a good example of this is

cd and propranolol theres no question

that sipd metabolizes propranolol but

because of the involvement of other

enzymes and because of the way that the

drug is titrated theres really no

actionability that is recommended based

on septum b d status and propranolol

and then of course there are many many

publications that link a gene to a drug

pharmgkb does a good job of annotating

these publications and these are ones

for which theres

publications but which the evidence is

definitely weak alternatives are unclear

and testing may be rare so an example of

this might be gstm and cisplatin

so the way that gene drug pairs get to

be evaluated is by

them being actionable in other

professional society guidelines

nominated by a cpic member

a high level of annotation on pharmgkb

and

were always continually evaluating gene

drug pairs and giving them a provisional

status as cpic level a b c or d

we have a grading system for the

prescribing recommendations

which

is a simple system where theres strong

moderate or optional

um prescribing recommendations

and

all of these are considered to be

potentially actionable especially in the

situation where the genotyping has been

done preemptively we also have a fourth

category that we added in the last year

or two where there is no recommendation

we really try to avoid writing

guidelines where theres no

recommendation for any genotype for any

drug

however there are examples where theres

just insufficient evidence or confidence

to provide a recommendation to pro to

guide clinical practice and ill give

you an example of that in a moment

so here is an example where um

this is on dansatron and trapezotron two

antimedics that are definitely

metabolized by sipd

and sipd can be classified into four

main phenotypes ultra rapid normal

intermediate and poor metabolizer and

there is evidence that for those rare

two percent of the population that are

ultra rapid metabolizers

that they metabolize those drugs so

quickly that an alternative antimedic

agent should be

considered and that that is a moderate

recommendation and for normal

metabolizers theres no evidence that

prescribing need be informed by sip d

status thats a strong recommendation

for intermediate and poor metabolizers

even though it seemed to make intuitive

sense that poor metabolizers might be at

increased risk of some of the toxicities

associated with these antimedics such

as qrs prolongation theres actually

data to suggest

data addressing this topic and not

finding any evidence to support any

dosage change for poor metabolizers

although the rationale certainly seems

plausible that such individuals might be

at increased risk for toxicity so the

guideline authors voted to have no

recommendation for intermediate or poor

metabolizers so this is an example of a

guideline where there may be multiple

type strengths of recommendation

depending on the phenotype and the drugs

overall this gene drug

pair page

gets

many

views weve had 0 000 page views in the

last year it covers gene drug pairs

of which are level a

99 level

b level c and the

biggest chunk are level d gene drug

pairs

so although this is always in flux and

it would require a full literature

review to definitively decide decide on

a level this provides clinicians with

one of the things that they said

identified as a barrier and that is to

help prioritize which gene drug pairs to

implement

we think that the number of gene drug

pairs that are going to be actionable in

the foreseeable future is relatively

small

so weve estimated the workload

for the foreseeable future and estimate

that there will be

genes covered by cpic guidelines and

that would be

involving

about 0

cpic guidelines overall that need to be

written so far i think we have 0 that

are published or in press and of course

many of the genes that are actionable

for some drugs are not actionable for

for other drugs

so is this going to revolutionize

prescribing does pharmacogenomics affect

all drugs

if we think that theres something like

00 chemical entities that are approved

as drugs in the us and theyre

something like 000 genes we have to

acknowledge that the number of gene drug

pairs where theres going to be

actionability accounts for only a

minority about seven percent of fda

approved medications are covered by the

about 90 drugs that we think will be

covered by the cpic guidelines and this

does make up a slightly larger

percentage of all prescriptions in the

us because some of these drugs are

extremely widely used maybe as many as

percent of outpatient prescriptions

in the us

but still the likelihood that a

gene defect is going to have essentially

monogenic effects on a drug making it

actionable in the clinic is uh small and

we neither want to oversell or undersell

the importance of pharmacogenomic

testing for prescribing in general

the way in which guidelines or gene drug

pairs are prioritized includes a number

of different

elements

is there prescribing actionability

whats the severity of the clinical

consequences if genetics arent used to

inform prescribing

is there an available genetic test for

that gene how commonly used are the

drugs or how common is the genetic

testing

how common are the high risk genetic

variants

is there mention of genetic testing in

the drug labeling

and are there

pharmacogenetically based prescribing

recommendations from other organizations

so all of these go into how we are

constantly reprioritizing

which gene drug pairs to tackle and

prioritize first

we have a gantt chart that indicates all

of the gene drug pairs that have been

identified as level a and b

genes and even a few level c genes that

we think are very important for having

guidelines available if possible so

these would include things like factor

five light and estrogen use which is

again very heavily marketed to

clinicians into patients but which most

experts agree the evidence is not clear

enough to allow prescribing

recommendations so having negative

guidelines for some of these gene drug

pairs might be useful

weve surveyed our members and have them

reprioritize

gene drug pairs that arent currently

the subject of cpic guidelines and when

we did that we found that c9 and

proton pump inhibitors came to the top

of the list and another gene drug pair

that is

of a lot of interest especially to the

public is sip d and adhd drugs which

again theres heavily heavy marketing to

pediatricians and directly to consumers

claiming a benefit for that when in

actuality theres probably very little

actionability there

so

as i mentioned we try to update the

guidelines when important new

information comes out at least to make

users aware of that so heres an example

for iva caftor and cftr where the fda

approved additional cftr variants that

should benefit from the use of iva

caftor from the original

approval of the drugs several years

earlier and so just adding variants is

something that can be easily done online

one of the challenges in clinical

implementation and i guess in in many

different areas of trying to change

medicine is maintaining links with all

of the players in the community

so there are many different um

nih supported groups that are working on

uh implementation of genetic testing in

the clinic theres professional

societies such as acmg and ashg that are

involved as well as pharmacologic groups

at the fda

theres groups involved in

the medical

record business that provides the

infrastructure by which most of these

pharmacogenetic tests are going to be

rolled out so theres quite a bit of

effort involved in in maintaining links

and trying to avoid duplication of

effort

resources page on cpic

provides a list of individuals who are

using cpic guidelines to do

clinical implementation of

pharmacogenomic testing and this

provides a way for investigators and

clinicians to find each other

and

now ill kind of move into how cpic

relates to a real implementation project

using our implementation project at st

jude pgen for kids as the example

where our longterm goal is to have

preemptive pharmacogenetic testing

adopted as the standard of care for all

saint jude patients and our goal is to

implement all cpic guidelines

this is a protocol that we started in

0

we basically try to enroll every patient

at st jude who might receive any drugs

and the only exclusion criteria are

patients whove received a prior

allergenic or liver transplant

allergenic because the blood from which

we would extract their dna and even the

buccal cells

will be primarily

from donor

and liver transplant because so many

actionable pharmacogenes

are genes that are expressed primarily

in liver

our process is that we do obtain

informed consent we get a blood sample

we send the sample for genotyping which

covers around 0 genes and the vast

majority of those genes stay in a

research database

and the whole idea of the protocol is to

selectively put results into the ehr

as we develop clinical decision support

that

informs our clinicians about how to use

that information for prescribing for at

least one drug and then we follow up

with patient education

these are the gene drug pairs that weve

implemented since we opened in 0 we

started with a tpmt and sipd then

slcob sipc9 dpyd

ugta a uh nut t and our most

recent is sipc9

and this just looks at the same data in

a different way showing that drugs

have been implemented as linked to these

nine genes

and um sometimes were just

adding new drugs for a gene thats

already been implemented at st jude

if we look at these nine genes and

drugs by the first four thousand or so

patients that weve studied the

percentage of individuals will have a

high risk genotype for each one of those

genes is indicated here so for some of

them its extremely low like 0 for

dpyd and for other genes like c9 its

extremely common

to have an actionable diplotype

in fact if we look at all of the

patients that we have its a very small

percentage of patients who have no

highrisk genotypes

and there are a fair percentage of

patients who have as many as five

highrisk genotypes

overall 90 of patients have at least one

highrisk genotype in those first 00

patients and we can extrapolate based on

the known frequencies of the actionable

pharmacogenes that this will increase to

99 percent once we implement all

the first or actionable cpic genes

weve enrolled more than four thousand

patients or uh

weve approached more than four thousand

patients for enrollment 9 percent were

enrolled on the protocol

a special consideration is in pediatrics

is that when children reach years of

age they have to be reconsented at the

age of majority and 99 percent of kids

who turn want to stay on the study

and out of all these patients weve had

two incidental findings where a

pharmacogene predisposed to a disease

risk and both of those cases were klein

felters because were studying gpd

which is an xlinked gene we

occasionally have boys that have

have a

an extra x chromosome and thats obvious

from looking at their gpd genotype

so how do we get from genotype to

interruptive clinical decision support

for prescribing how do we go from these

raw genotype data

with the position of the genome and the

and the variant thats present

to a very

um textbased

understandable

point of care alert alerting prescribers

how to change their prescribing and ill

talk you through how we do that and how

cpa guidelines help us to do that so if

we look at the cpic guideline for vory

conazol and c9

as an example

here were going from

genotypes to alleles

and so we have tables that translate the

raw genotypes into sypc9 alleles and

we assign function to those alleles and

these are done by these genespecific

tables that are linked to each of the

cpec genes maintained on pharmgkb

every

row is an allele here for sipc9

every column is a nucleotide position

which is uh

mapped to the human genome using five

different systems of mapping so theres

unequivocal identification of which

alleles are which and then we use

standardized terms to assign function to

each of the alleles for that gene and

these are updated online as needed

so then we need to go from alleles to

diplotypes because everybody has

generally two copies of each gene and

this is particularly important in

pharmacogenes as compared to other areas

of genetics in other areas of disease

related genetics the question is often

just

who has the variant or not

whereas for

its usually very important to

distinguish between individuals

homozygous for variant alleles versus

heterozygous for variant alleles and

listed here with the yeses are those

actionable genes for which its

important

for which the prescribing

recommendations are completely different

based on diplotype compared to just the

presence or absence of the genes

so we have to go from the genotype or

sequencing data

to haplotypes and diplotypes now at st

jude weve been using the dmed array for

several years and actually the software

associated with these arrays is very

helpful every row is an individual

variant position but it does come up

with a called diplotype based on the

likely frequencies and phasing of the

variants that are present in the genome

and weve checked and that phasing works

very well in the afi software

to specifically address this challenge

thats going to be coming more and more

common that sequencing of whole genomes

is going to be done

pharmgkb has

partnered

with marilyn richey and others to

develop software called

farmcat which will go from vcf files the

variant files that are generated from

sequencing to generate the haplotypes or

diplotypes that are important for the

cpic guidelines and generate a report

that corresponds to the cpic guideline

prescribing recommendations and there

are

many other tools that are being

developed to try to help users go from

genotype to phenotype

so we have to go from diplotypes to

phenotypes and we have to be able to

interpret those phenotypes in light of

drug therapy so again those

genespecific information tables posted

along with every cpa guideline heres

the uh diplo types for sip c9 you can

imagine that for genes like c9 or

especially d these tables are

thousands and thousands and thousands of

rows long

with the possible

phenotype associated with each of those

diplotypes indicated intermediate normal

rapid poor metabolizer as well as some

kind of indicator whether thats

considered an abnormal

actionable result versus a normal or

routine result

how we translate that at st jude in

rpgen for kids study is that we have

created a pharmacogenetics tab in our

ehr

thats important because its not

encounter specific most genetic tests

are lifelong tests and so you dont want

to have to dig through

dates of different dna samples you want

to be able to look for all the dna

samples for a patient what are the

pharmacogenetic test results that have

been generated

and

theres a consult thats associated with

every

gene test result

and that provides a passive level of cds

for clinicians who want to look at

pharmacogenetic test results and see

what the passive static interpretation

is for that so heres an example of

for a sip c9 rapid metabolizer

diplotype and how that is interpreted

also

now we have some consults that are based

on the results of more than one gene so

for example for thioperians we need that

consult to include the genetic test

results from both ned t and tpmt so we

bring both gene tests

together under one consult

that is reachable by linking to either

one of those gene test results by

themselves

weve created a system for building

templates for these consults

based on the sections that we think

should be included in every

pharmacogenetic test result that is the

phenotype assignment the diplotype

interpretation

the phenotype interpretation and a quick

review of medications that might be

affected

some basic prescribing recommendations

and an educational

link for people who want to learn more

and we put together those consults based

on software that weve built called

consult builder so here we are

pulling down the gene of interest of

c9 we can pull down the diplo type of

interest from a pull down menu and then

for every one of those set of diplotypes

we have some

text sentences that apply to the

interpretation of the diplotype that

will go into each applicable consult and

this is just showing that consult

deconstructed into those colorcoded

forms

this has also been useful because we

want the exact same information to

populate the saint jude formulary which

is our goto resource for our clinicians

for medications and so if a

clinician at st jude goes to the

formulary they will see

that there is information

on pharmacogenetics for all the

applicable drugs theres also a place

where they can just see all of the

therapeutic guidelines including

pharmacogenetic guidelines

and by clicking on that hyperlink they

can see

all of the pharmacogenetic

guidelines that apply to medications

that we use at saint jude and all of the

associated information that might be

available for them again the same

language thats used to populate the

interruptive alerts

the consults is also used to populate

the formulary

again someone can look up here theyre

looking up sipc9 and celacoxib and they

can see what the dosing recommendations

would be for a poor metabolizer for uh

c9 if the clinician wants to consider

prescribing celacoxid

so this actionability is the bottom line

that we get to of how to act on

pharmacogenetic test results and again

every cpic guideline now has

example language that can be used

uh to interpret the different phenotypes

for each of the actionable genes and

downloaded into an ehr system we also

provide algorithms for how to go through

each result for each gene thats the

subject for

a pharmacogenetic

cpic guideline

and

uh were well ill talk for a second

about our interruptive alerts which is a

form of active clinical decision support

we divide them into two main categories

the first is the pretest alert

so

if a patient is prescribed a highrisk

pharmacogenetic drug

how does one decide whether a genetic

test has already been ordered on that

patient and if there is no

pharmacogenetic test result on that

patient how does one alert the

prescriber

and the second is the post test

situation where the test result has been

generated so there we just need to be

sure that if the test result is high

risk and a high risk drug is prescribed

for that patient that an interruptive

alert

fires at the clinician

so these pretest alerts

this is an example of one for sip d

encoding which is again very important

in a pediatric hospital where we really

should not use codeine unless we know

the septum d status of the patient

and it not only alerts the prescriber

that there is no d genotype test yet

on this patient but it allows them to

click a box and order the test right

then if they want to

now

the other is this posttest result

uh alert which fires if there is a

highrisk uh test result already present

for the patient and here we say based on

this genotype the result the patient is

predicted to be a poor metabolizer we

give them alternatives that they can use

to codeine and how they can consult with

a clinical pharmacist to get more

information if desired

the way that we handle

firing alerts based on highrisk

pharmacogenetic test results at st jude

is to create a problem list entry based

on the highrisk genotype that

problemless entry resides with things

like the underlying disease so here the

presence of hepatocellular carcinoma and

this patient has two highrisk

pharmacogenetic test results

its an automated process to go from the

test result to the

problem list entry and then we create

cds that drives off of

the problem list entry of course it

could be done directly from the high

risk test result one disadvantage of

doing that is if the test result is

generated by an external lab

more and more patients are coming in

with their own genetic testing results

from

from direct to consumer testing

companies we still need to have a way of

driving cds off of high risk uh test

results no matter where they come from

so thats why weve elected to do it

from the problem list instead of

directly from the genetic test result

so

another principle is that were trying

to incorporate nongenetic information

into some of these interruptive alerts

for example for vory conazol not only is

c9 important but so is the route of

administration oral versus parenteral

and so is age kids less than need a

different dose than kids greater than

regardless of their sepc9 status

so here where were firing the alert not

only are we taking into account

age and route

and genotype but were also telling the

prescriber were taking it into account

and we found that this is also a big

challenge in implementing genetic tests

prescribers need to know what was

considered when we fire these alerts at

them they dont like seeing alerts that

they dont understand what the basis for

the alert is

and this is another example of how these

alerts are having to get a little more

complicated for thiopurines

were having to incorporate both the

tpmt and the nut t genotype result

into the alert to tell the prescriber

that thats how weve come up with the

recommended doses for that patient

another challenge that weve run into

and we knew that this would be likely

is that we have implemented genes that

saint jude

even when we know there are other drugs

affected we may not have built the cvs

for every single affected drug at the

time the gene goes into the ehr and that

can result in us missing important

interactions

so an example of this happened within

the last few months here we had an

year old boy with leukemia who was laid

in therapy he was having intermittent

thrombocytopenia episodes of hematemesis

and was started on omeprazole

after he had more hematemesis endoscopy

showed that he had developed esophageal

varices

and uh the outside physician who was

treating this patient asked us for a

consultation because the liver enzymes

were increased but we looked in the

saint jude ehr found that the patient

was an ultra rapid metabolizer sypc9

that diplotype was in the ehr but we

hadnt built yet any cds for proton pump

inhibitors and so the clinician had no

easy way of understanding that they

might need to use a much greater dose

than normal of omeprazole because we

hadnt alerted them to this problem now

luckily cpic hasnt gotten around um to

writing a guideline for ppis and sipc9

st jude hasnt either but the dutch

working group in pharmacogenetics has

and this information is uh easily

available both in the publication and on

pharmgkb

and indicates that a one to two hundred

percent increase in dose is recommended

for ultra rapid metabolizers and so in

this case that patient had a big

increase in their ppi dose and

eventually was doing um fine

so uh the cds thats needed for clinical

actionability of genetic test results i

hope ive given you a flavor that there

has to be

a way to

unambiguously

and uniformly refer to genetic test

results in order to build clinical

decision support that can be useful for

prescribing information

and for the most part genetic test names

and results and phenotypes are not

standardized across health care systems

and therefore ehr vendors are stating

that it will be very difficult for them

to build clinical decision support tools

based on genetic tests if the community

of clinicians and researchers doing

pharmacogenetics cant do simple things

like come to terms on standardized terms

so cpic collaborated with many other

groups in coming up with some

standardized terms for pharmacogenetics

and these include

allele function

for all of the pharmacogenes where we

use increased normal decrease no

function unknown function or uncertain

function as standardized ways of

referring to

allele function

and then standardized terms for

phenotypes that differ if its a drug

metabolizing enzyme a transporter or a

different type of high risk gene like

like hla

b

the other thing that having standardized

terms will help with in addition to

driving cds is to try to detect

accidental duplicate genetic testing so

its been shown by the mayo clinic and

others that

unintentional duplicative genetic

testing is becoming more and more common

and of course not only is that a waste

of resources but it also results in the

possibility that there will be

disagreement between two different or

three different

tests for the same gene so again one

would never be able to fire an alert to

to ask do you really mean to order that

second test of ugta or tpmt

or do you want to use the preexisting

result no one would be able to make that

determination unless we have

standardized terms for referring to

genetic test results

we also are highly engaged in patient

education about pharmacogenetics and we

offer to send a letter to the patients

house

for every gene test result as it

migrates into their ehr

9 percent of patients participating in

pgn for kids ask for having that

information again we have standardized

on templates for putting together these

letters and here is for example at

sipd gene result has been put in your

ehr

the majority of the population is here

in green youre here in red youre a

poor metabolizer we give them a little

bit of information about what that might

mean and give them or their clinician a

link and a phone number for more

information if they would like it so of

course this is an optimal

but given that we have a fragmented

healthcare system and we dont have an

underlying ehr that will allow these

lifetime genetic tests to be used as a

patient moves from system to system to

system

this is one way that um patients can

inform their all of their prescribers

about their um status and this letter is

posted in the ehr and at st jude we do

have a patient portal as most

healthcare systems do now so patients

can directly assess

access their genetic test results via

this mechanism as well

now many others throughout the world are

trying to come up with uh more

electronically based

more more systems that will require more

action on the part of patients

so again in the european ubiquitous

pharmacogenomics group theyre coming up

with a qr code card

that can be scanned

and then well directly access all of

the updated pharmacogenetic information

for that patient via any

computer that can access their websites

so this may be uh something that can be

done in the in the future and were

looking into such systems at st jude as

well

we have these patient

information sheets that are publicly

available to anyone

some of them are drug specific so like

heres a patient medication

sheet on codeine and it talks about the

fact that genetics can be important and

refers them to another do you know sheet

on sip d which they are also given

every time they have a high risk result

or are prescribed a high risk drug by

one of our clinic staff

were using pharmacogenetic testing as a

metric for patient safety and quality

so tpmt guided thiopurine dosing is one

of those metrics this is incorporated

into our quality and patient safety

teams institutional safety metrics

where our threshold goal is to have a

hundred percent

of leukemia patients

have their tpmt genotype known prior to

initiating therapy at st jude you can

see this is varied a little bit over the

years but for the last few quarters we

have been hitting our goal of 00 of

patients having their tpmt status known

before they get their first dose of

thiopurine drug

sipd is another gene for which we

would like to see the percentage of

patients who have sipd results in

their ehr go up over time and this green

line indicates that it has

and therefore the number of alerts that

have had to fire

the pretest alerts that have had to

fire has gone down over time as a higher

and higher percentage of our population

are already genotyped before they get

their first dose of codeine and in fact

we showed that in our sickle cell

population there were no coding

prescriptions given to patients who had

a high risk ultra rapid or poor

metabolizer phenotype after a couple of

years of implementing preemptive

pharmacogenetic testing into for all of

our patients including sickle cell

this process of rolling out each gene

drug pair so every column here is a gene

drug pair at st jude and every row is

something that has to be done

before we say hit the button and make it

go live

and you can see these include things

like evaluating the evidence and

developing the cds and getting all of

our software and look up tables and

consults

and patient letters and do you knows

updated and working with the patient

education committee working with our pnt

committee we have an oversight committee

for the institution that reports to pnt

and they have to approve every gene drug

pair before we roll it out and make it

go live so theres many many steps that

have to take place before we roll out a

new gene drug pair and this is why this

process has

taken some time

we share all of the information that we

have on our website at pgen for kids

so this includes a lot of information

about the protocol

we

update the website every time we roll

out a new gene and every time we add a

new drug to one of those genes

so theres a little bit of information

thats available to both patients and

clinicians

we have an educational video that shows

patients and families talking about

using pharmacogenetic tests and thats

available for anyone

all of our publications related to the

study

we have competencies that our

pharmacists complete as we roll out

every gene drug pair so depending on the

level of practice of the pharmacist they

have some basic training

in how to answer questions about

pharmacogenetics and to make them aware

of what pharmacogenetic testing is

available

and we have a ashp accredited pgy

residency in pharmacogenetics and these

people are getting great training and

going out into the world and helping to

do implementation at other sites

and finally links to some other

resources

so i will

stop there i would like to acknowledge

uh fursy pick especially my copi terry

klein and our collaborators at stanford

who are involved with cpic

uh our director of cpic is kelly caudle

and she is works here at saint jude and

we have some other individuals here at

saint jude who also work extensively on

developing cpic guidelines and policies

as well as

external members of cpic who are

volunteers and provide a tremendous

amount of input

our guideline authors play a critical

role because without their

expertise our guidelines wouldnt have

the peerreviewed status and acceptance

that theyve gained in the clinical

community

id also like to acknowledge all of my

collaborators on the pgenkids protocol

here locally at st jude that involve

many members of our department but also

information sciences and representatives

from all of the clinical departments and

divisions at st jude and my colleagues

at medical college of wisconsin who have

done our genotyping for us on this

protocol

so i thank you for your attention if you

have any questions please contact the

program coordinator

and thank you