“Pharmacogenomics and Dosing” (Kristine Ashcraft) [#25]

Brian McCloskey and Brad Power
September 14, 2022

“Pharmacogenomics is germline genetic testing that helps us understand when our genes would dictate that for a growing list of medications, whether we need a higher dose, a lower dose, or a different medication altogether.” – Kristine Ashcraft

Meeting Summary

We’re being overdosed, underdosed, and misdrugged. People are being given drugs that are ineffective, or in tragic cases fatal, which testing could have predicted. We should get tested at birth to identify our personal drug risks and to inform personalized dosing levels. Our system of drug delivery should be tuned to dose at the right level for individuals, and eventually by measuring the effective level of the drug in the body, and then modulate the dose empirically, as opposed to prescriptively. Instead we have one-size-fits-all (not personalized) rules for prescriptions and a bias to prescribe the maximum tolerable dose, which makes sense for some drugs, but not others.

Kristine Aschcraft has been an innovator in precision medicine and pharmacogenomics since 2000, co-authoring and assisting in study design for some of the most cited publications on the clinical and economic benefits of pharmacogenomics in high risk polypharmacy patients. She led the team that created the first pharmacogenomic-guided clinical decision support tool to be integrated in the clinical workflow in AllScripts, Epic, and Cerner; winning a HIMSS Health 2.0 Open APP challenge award in 2013. She has helped coordinate multiple population-based programs aiming to reduce medication risk and associated adverse outcomes and costs with targeted pharmacogenomic testing and improved clinical decision support. She is committed to catalyzing the adoption of precision medicine to improve care and reduce healthcare costs.

“Pharmacogenomics” is testing that looks at our hereditary (“germline”) genes to help us understand when, for a growing list of medications, we need a higher dose, a lower dose, or a different medication altogether. In cancer care, greater than 99% of patients will have a pharmacogenetic variation that impacts their response to on average more than 10 commonly prescribed medications.

There are guidelines for administering every drug based on drug-gene interactions developed by the Clinical Pharmacogenetics Implementation Consortium (CPIC). You can key in any medication that is being offered and see whether there is a CPIC guideline for drug or dose change guidance or FDA guidance on how that medication would be modified and which gene is impacted. This is a great reference to determine if a gene test should be considered before administering that drug. - https://cpicpgx.org/genes-drugs/. Just key in the generic name of a medication, and if the CPIC level is A or B or the FDA label says a pharmacogenomics test is required or recommended, testing is advisable. If two genes are implicated for prescribed medications or medications under consideration, Medicare will cover the panel in full.

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Unfortunately, guidelines and reimbursement policies do not align with current evidence. They're outdated. Awareness of these specific drug-gene interactions should be widespread and tested for. This is something that can be done once in a lifetime. Although there aren’t many cancer medications that have drug-gene guidance, a lot of the other medications that cancer patients need are impacted by pharmacogenomics and should be considered.

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Meeting Notes

Prostate Cancer Lab Meeting - Pharmacogenomics and Dosing (Kristine Ashcraft)

Wed, 9/14 • 45:20

SUMMARY KEYWORDS

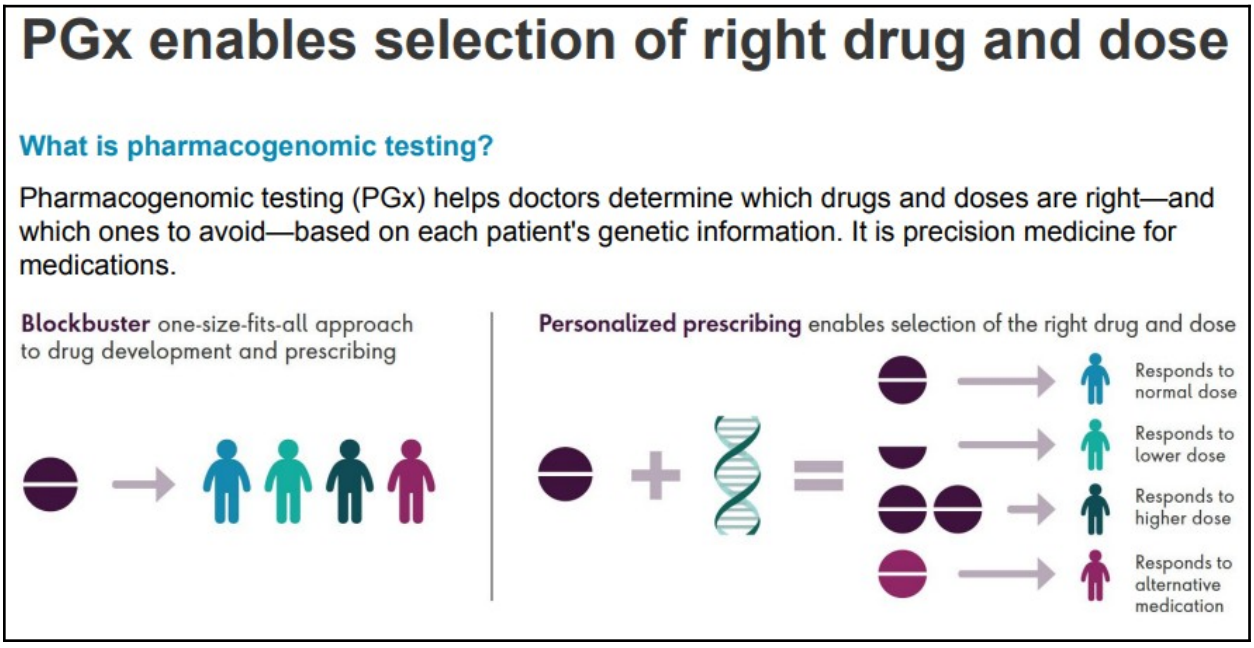
patient, medications, drug, gene, dose, pharmacogenomics, testing, question, impact, interactions, metabolizer, poor metabolizer, ultra rapid, evidence, drug metabolizing, guidelines, cytochrome, pharmacogenetics, cancer, prostate cancer

SPEAKERS

Kristine Aschcraft, Marty Tenenbaum, Ally Perlina, Brian McCloskey, Rick Stanton, Brad Power

Brian McCloskey 00:06

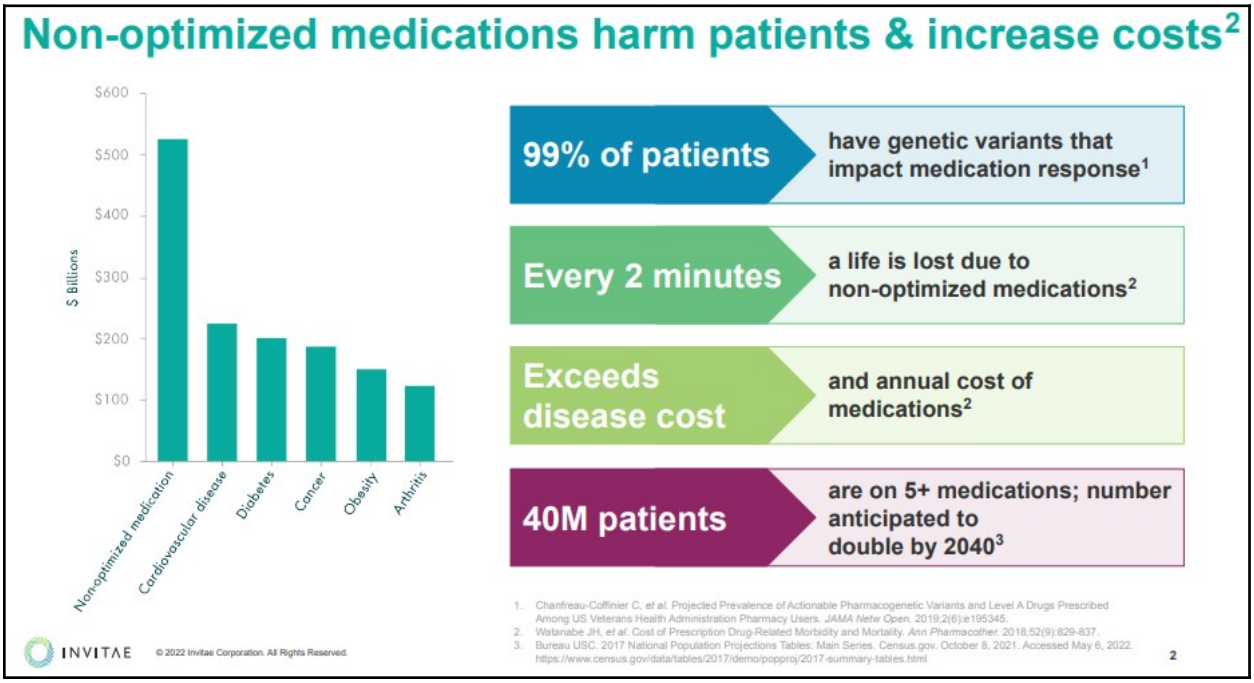
Kristine Ashcraft is with us today from Invitae, and she is going to be talking about pharmacogenomics.



Kristine Aschcraft 00:51

The focus of my presentation is on pharmacogenomics. Invitae offers diagnostic testing as well, like hereditary cancer screening, that clearly would also be applicable. Pharmacogenomics is germline genetic testing that helps us understand when our genes would dictate that for a

growing list of medications, whether we need a higher dose, a lower dose, or a different medication altogether.



In terms of the problem this helps us address, non-optimized medications are a major public health problem. We lose a life every two minutes in the United States due to non-optimized medications. In 2016, the last time it was measured, we spent $528 billion nationally on non-optimized medications, which is more than we spent on the drugs themselves or on any major chronic disease, including cancer. Regarding cancer care, greater than 99% of patients will have a pharmacogenetic variation that impacts their response to on average more than 10 commonly prescribed medications. And the more medications you're taking, the more likely you are to have a problem. Although this may not impact a prostate cancer medication per se, it can impact the overall medication regimen and have an impact on the overall health of a patient.

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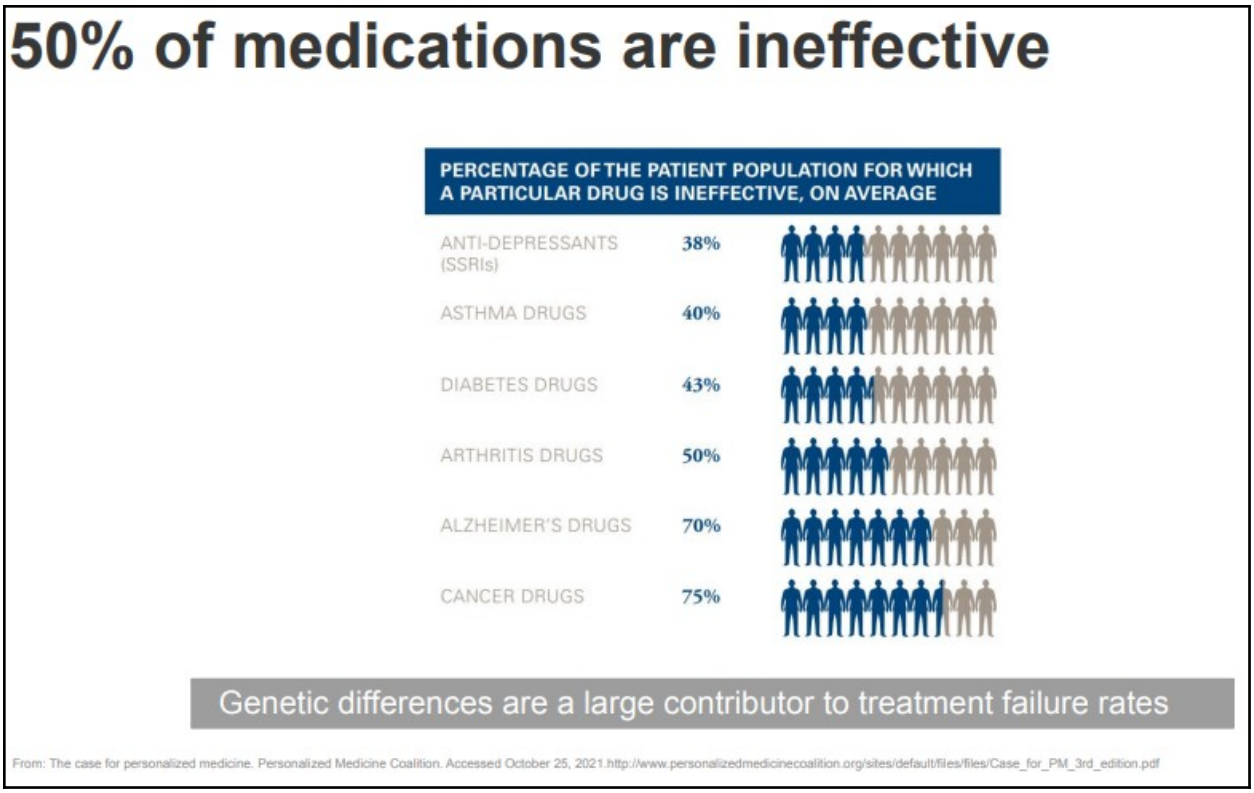
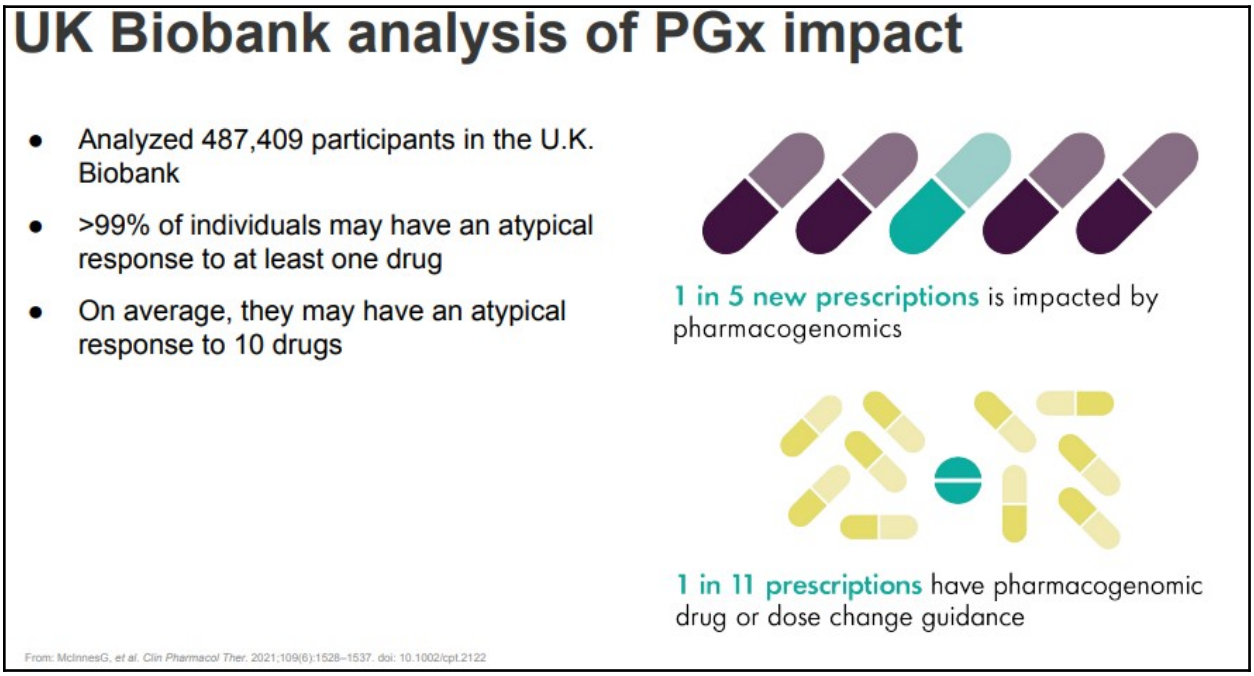
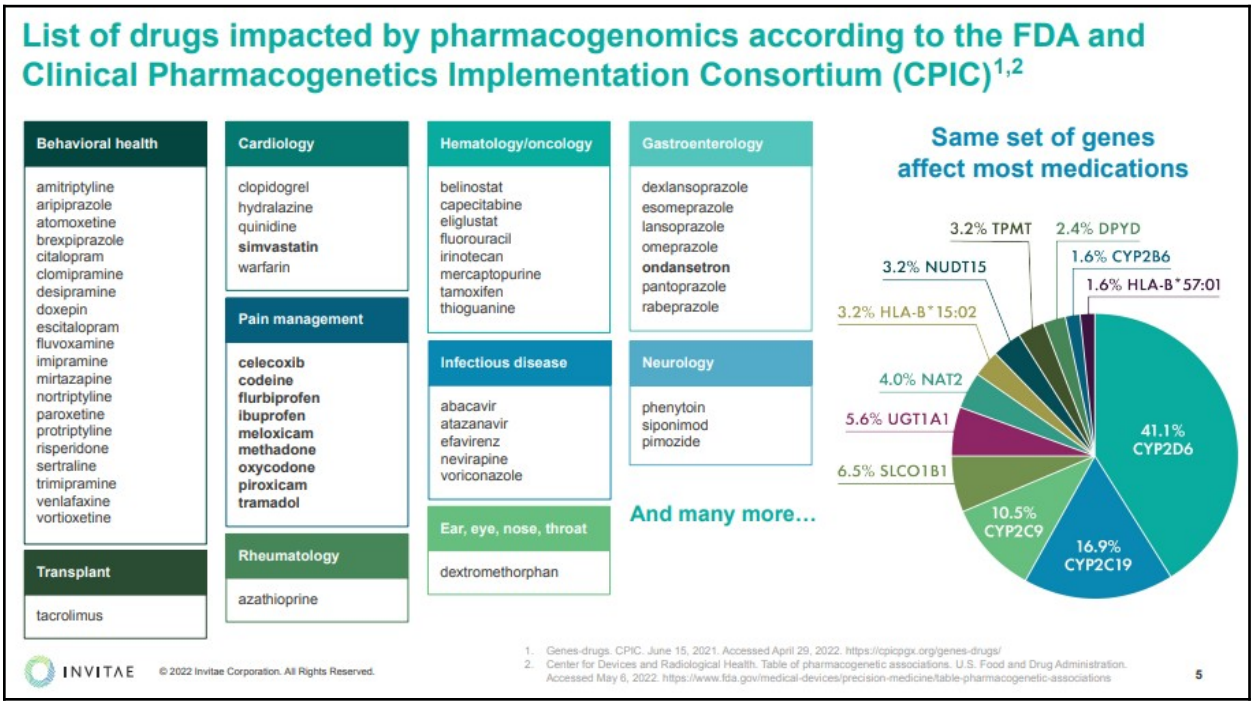


About half of the medications that are prescribed to patients do not work as intended, ranging from about 38% of antidepressants, up to three-quarters of cancer medications. Genetic variability is not the only thing at a play here, but it is a major contributor to treatment failure.



There's a very interesting analysis that came out of the UK last year. They looked at just shy of 500,000 patients in the UK Biobank and again confirmed that greater than 99% of individuals

have an atypical response to at least one medication, but on average 10 drugs. The other thing that was interesting, they have longitudinal data in primary care of the medications that were prescribed for these patients over time, and they found that one in five new prescriptions in primary care was impacted by pharmacogenomics, and one in 11 would have specific drug or dose change guidance associated with them.



This is a snapshot of some, and not all, of the medications that are impacted by high evidence drug/gene interactions, meaning that if testing is done, there is specific guidance if a variation is found on how you would consider modifying the drug or dose selection based on that information. I bolded the medications that I think you may come across in prostate cancer care. I know statins sometimes are utilized. They're certainly pain management, some antiemetics. But the thing to keep in mind over here on the right in the pie chart, is that the same genes impact drug response across all sorts of different clinical areas for life. I think of pharmacogenetic profiling as something like a seatbelt for medication management that really needs to be used every time a medication decision is made the rest of the patient's life to understand if they need different archetypes.

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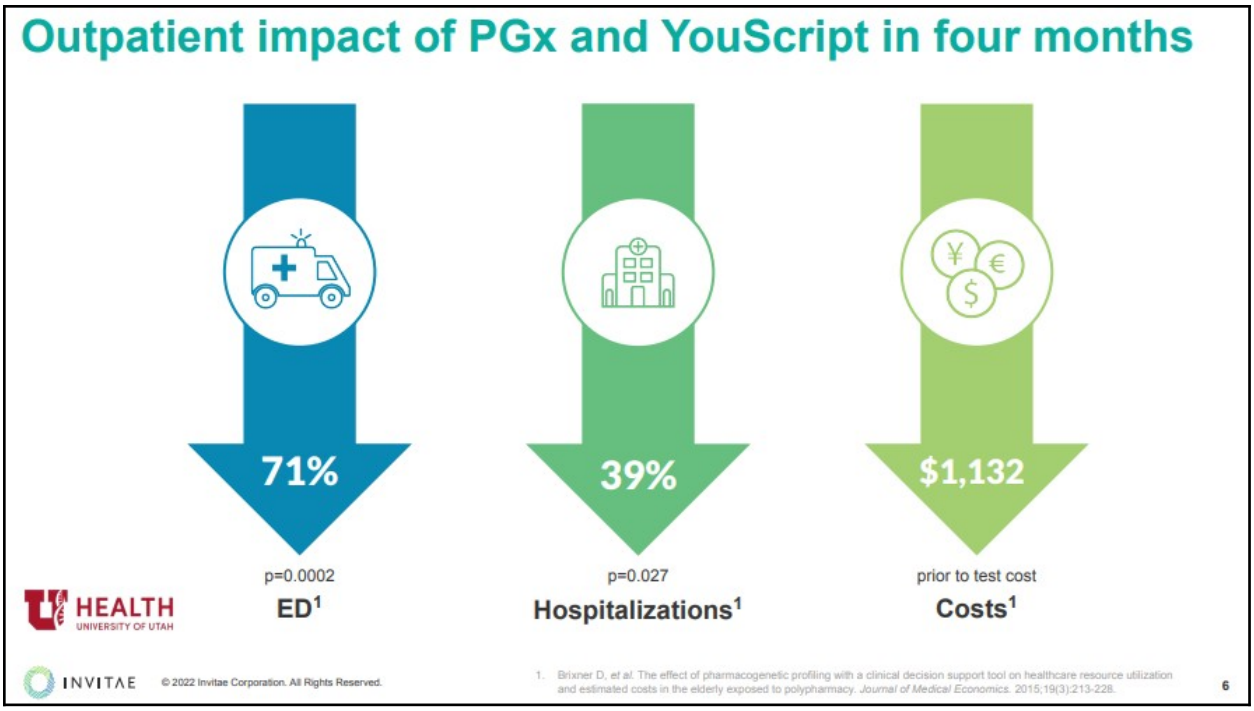
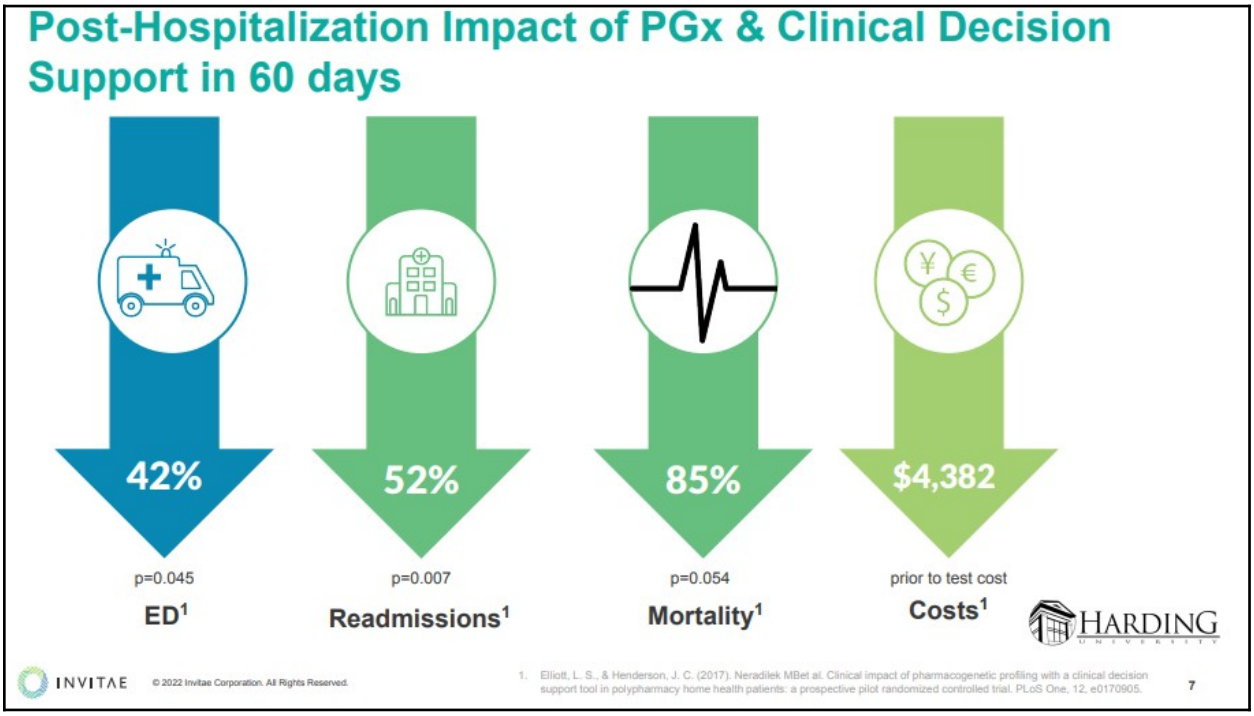


We're working on a study about the impact in cancer care right now, but these are broader. I'm just showing that this can be very helpful for patient care. This was a study that was done in patients 65 and older, taking at least three medications, one of which was known to have high evidence drug/gene interactions at minimum and what was seen in just four months. 71% fewer emergency department visits. 39% fewer hospitalizations. Saving $1132 per patient prior to the cost of testing.



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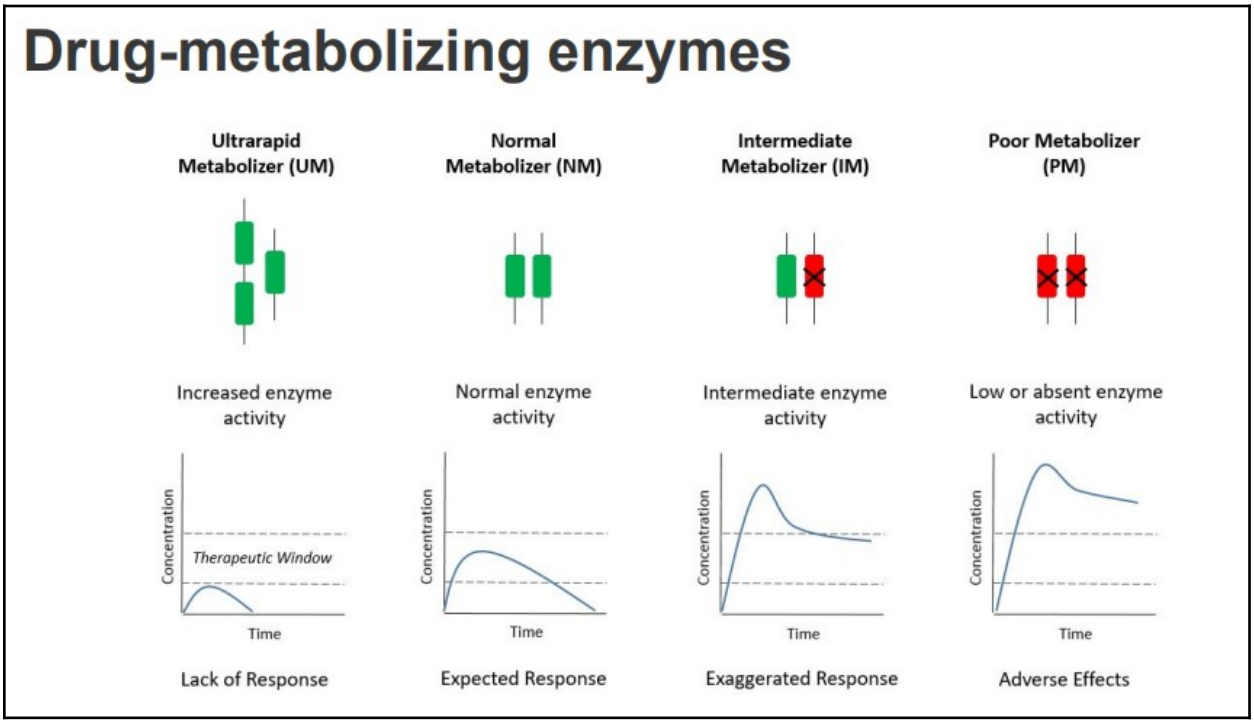
Here's a follow up study. This was done in patients that were flagged as being at high risk of readmission. This was a program that was already doing an exceptionally good job. They were in the top 10th percentile for lowest readmission rates in the country. That's because they had a very proactive program, where a pharmacist would visit the patients in the home and review their medications because medication-related issues are one of the main reasons patients end up back in the hospital. These pharmacists were either randomized to give the patient's treatment as usual or high touch pharmacy care where they were given access to pharmacogenetic testing and improved clinical decision support that didn't just look at drug/drug, but also drug/gene interactions and cumulative interaction risks. What was seen in just 60 days was 42% fewer emergency department visits and 52% fewer readmissions. It was not an endpoint of the study, but 85% fewer deaths, saving $4380 to a patient in just two months.

Kristine Aschcraft 06:05



Here's a quick lesson in pharmacogenetics. Generally, when we do testing, we're looking at these drug metabolizing enzymes, mainly cytochromes, that mainly express in the liver. We place people into different categories or phenotypes, based on the genetic information. Generally, when we prescribe medications, we assume all patients are normal metabolizers, also called “extensive metabolizers” in the literature. I think of this like a two-lane highway. You take medications, and they must go through these enzymes to be converted to something the body can then flush out and get rid of. Your normal metabolizer has two lanes of this highway that processes medications. You have intermediate metabolizers with one active and one inactive gene, or down to one lane of this highway. Poor metabolizers have no, or very, very reduced activity, or no lanes. The ultra-rapid metabolizers have duplications or upregulation, or additional lanes of these drug metabolizing highways.

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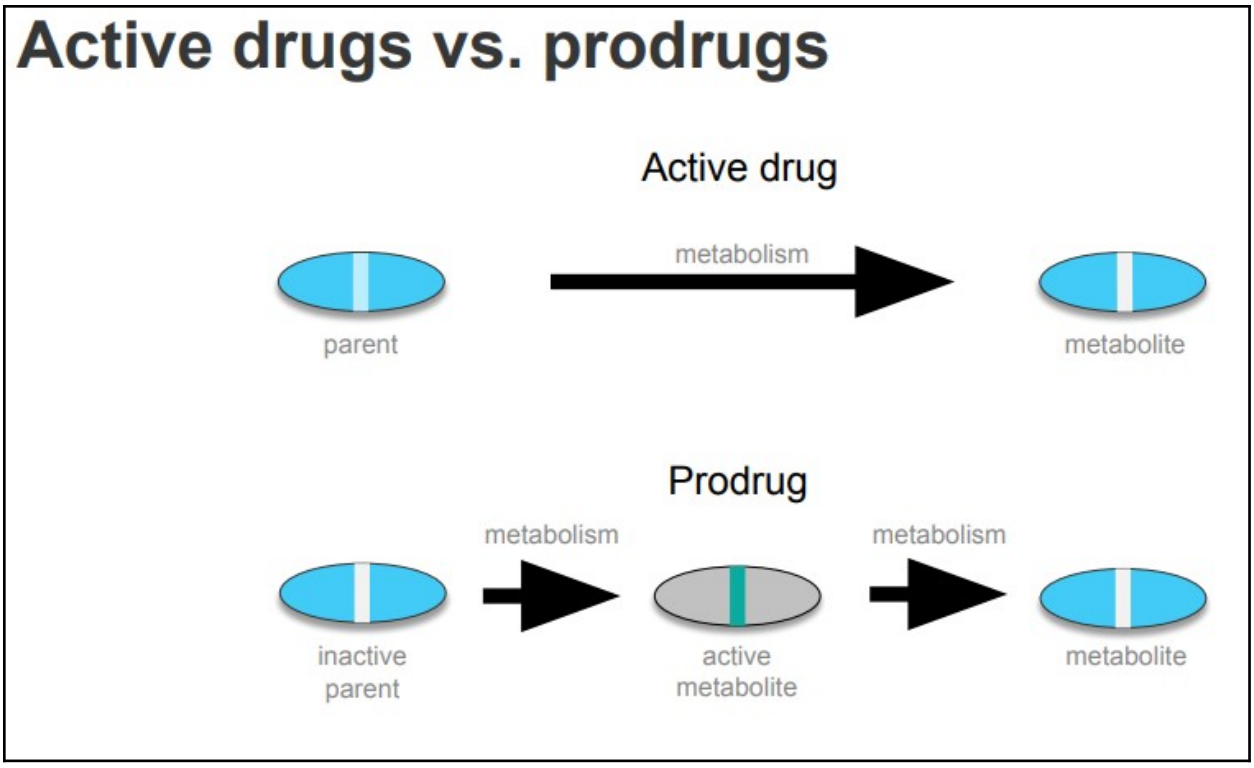
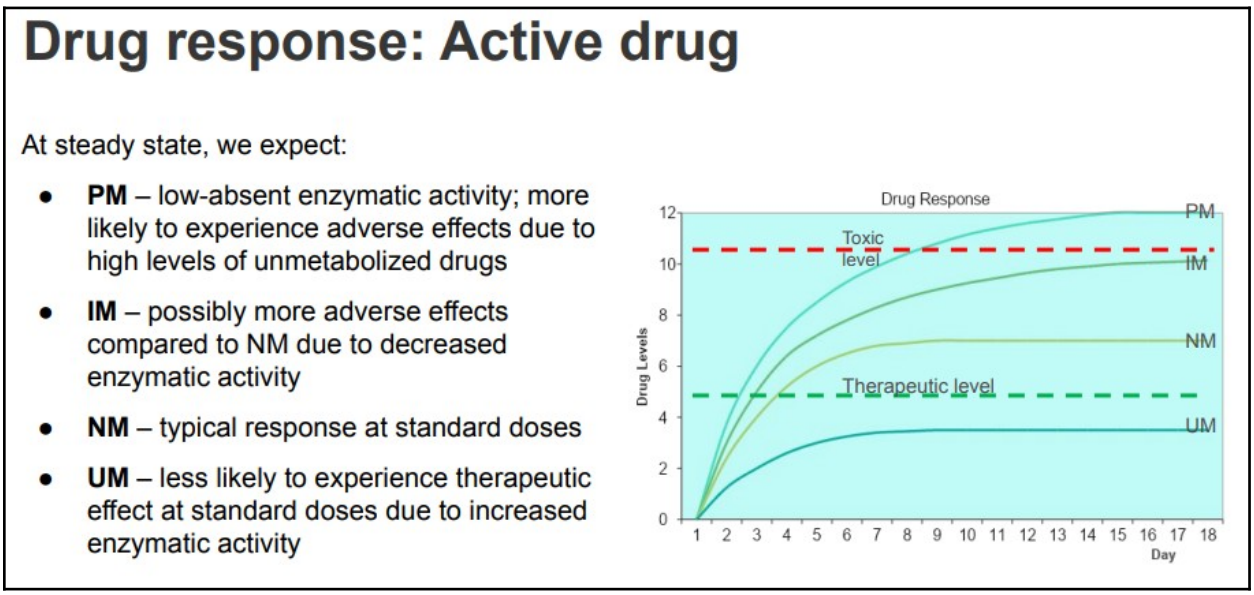
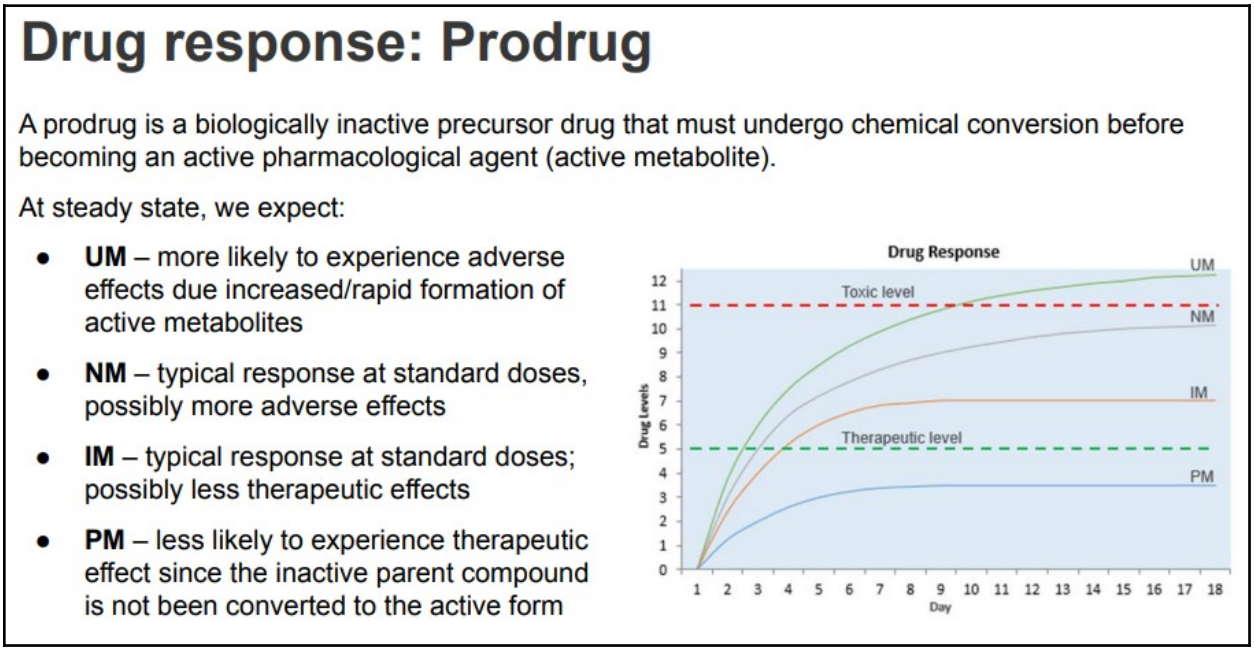


Here's the difference between active drugs and prodrugs. We take most medications in an active form. They often hit the cytochromes or sips in the liver, these drug metabolizing highways, to be converted to something we then flush out and get rid of. Prodrugs are different. Tamoxifen, for example, is commonly given to prevent breast cancer recurrence. It is a prodrug. It is taken in an inactive form. It hits these drug metabolizing enzymes in the liver, specifically Cytochrome P450 2D6 (CYP2D6) to be converted to Endoxifen in this instance, and then that must go through again to be converted to something the body can then flush out and get rid of.



I bring that up because you're going to have a different response if it's an active drug versus a prodrug if you have a pharmacogenetic variation. Poor metabolizers, those with no lanes of this drug metabolizing highway, are at risk of toxicity over time. They're not able to process the medication. They keep taking the dose every day over time, and it's going to build up in their body, and they can have adverse effects. Intermediate and normal metabolizers tend to be in range, and then your ultra-rapid metabolizers process the medication out so quickly that they are at risk of treatment failure. You can see these little dotted lines here: we've got a toxic and therapeutic levels sign. This is your therapeutic range. Some drugs have a very narrow therapeutic range, and some have a very wide therapeutic range. These variants can be impactful even for intermediate metabolizers. For example, it's a narrow range drug.



It's the exact flip for prodrugs. An example here you may be quite familiar with, Tramadol and codeine, are very commonly prescribed pain medications. They are prodrugs taken in an inactive form. They do not give any pain relief until they're converted. If you're an ultra-rapid metabolizer, codeine, for example, is converted to morphine by CYP286. If you're an ultra-rapid metabolizer you convert so much to morphine, you're at risk of toxicity. They've put a black box warning encoding on Tramadol recommending that it not be given to children or nursing mothers because of cases of severe toxicity including death. On the opposite end, poor metabolizers are not going to make that conversion, so they will get zero pain relief from these medications.

Kristine Aschcraft 06:34

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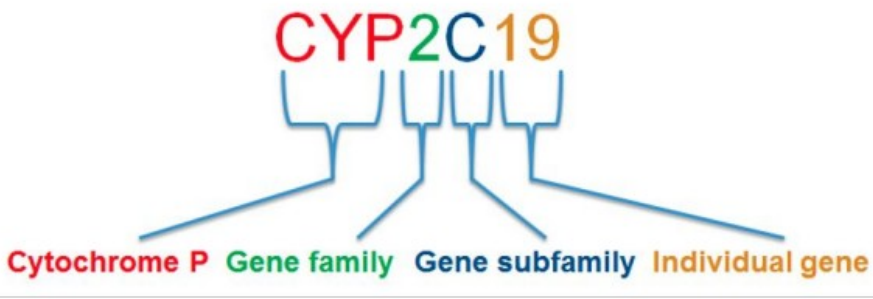
Nomenclature

Genes encoding CYP450 enzymes

- Gene designated with the abbreviation CYP
- Number indicating the gene family
- Capital letter indicating the subfamily
- Numeral for the individual gene

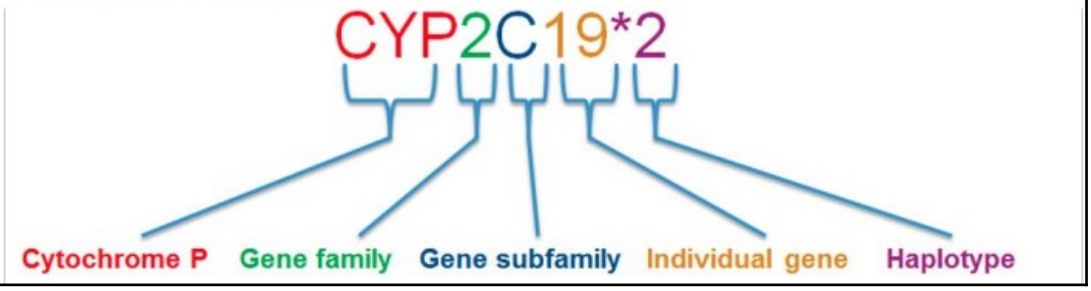


Nomenclature - I've been tossing about the term “CYP”, or cytochrome family, which are the most important pharmaco genes. You'll see that cytochrome is reduced to CYP and then 2C19 2D6, 2C9 etc.

Nomenclature

* (star) alleles – pharmacogenomic haplotype

- Normal function/enzyme activity (wild type) denoted by *1
- Altered function variant: *2, *3, *4, etc.
  - *2x2 copy number variant
- Single genes (CYP2C19) have many star alleles (e.g., CYP2C19*2, CYP2C19*3)
- Results reported as diplotypes: CYP2C19*1/*17



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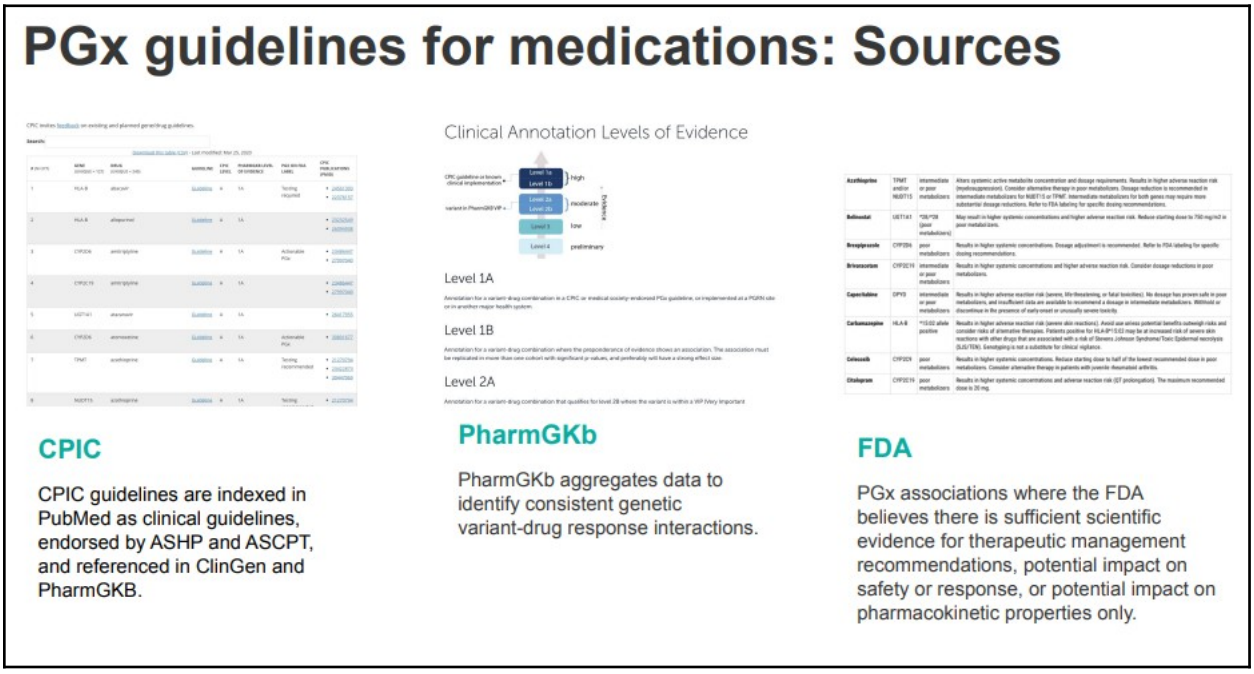
Unlike some other things you may be familiar with, we categorize different variants into alleles. You will see this come out as *1/*2.



There are three main sources for PGx information, led by CPIC (the Clinical Pharmacogenetics Implementation Consortium). If you remember nothing else, I tell you, this is a great, great reference. If you go to Google and type in CPIC, CPIC and drug and genes, it pulls up a great table. You can key in any medication that is being offered to you and see whether there is a CPIC guideline for drug or dose change guidance or FDA guidance on how that medication would be modified and which gene is impacted. A great resource they update all the time, PharmGKb aggregates data on genetic variant drug response. It feeds into CPIC. Then, of course, the FDA s is an important resource because more and more newly approved drugs have pharmacogenetic guidance in the drug approval on the label.

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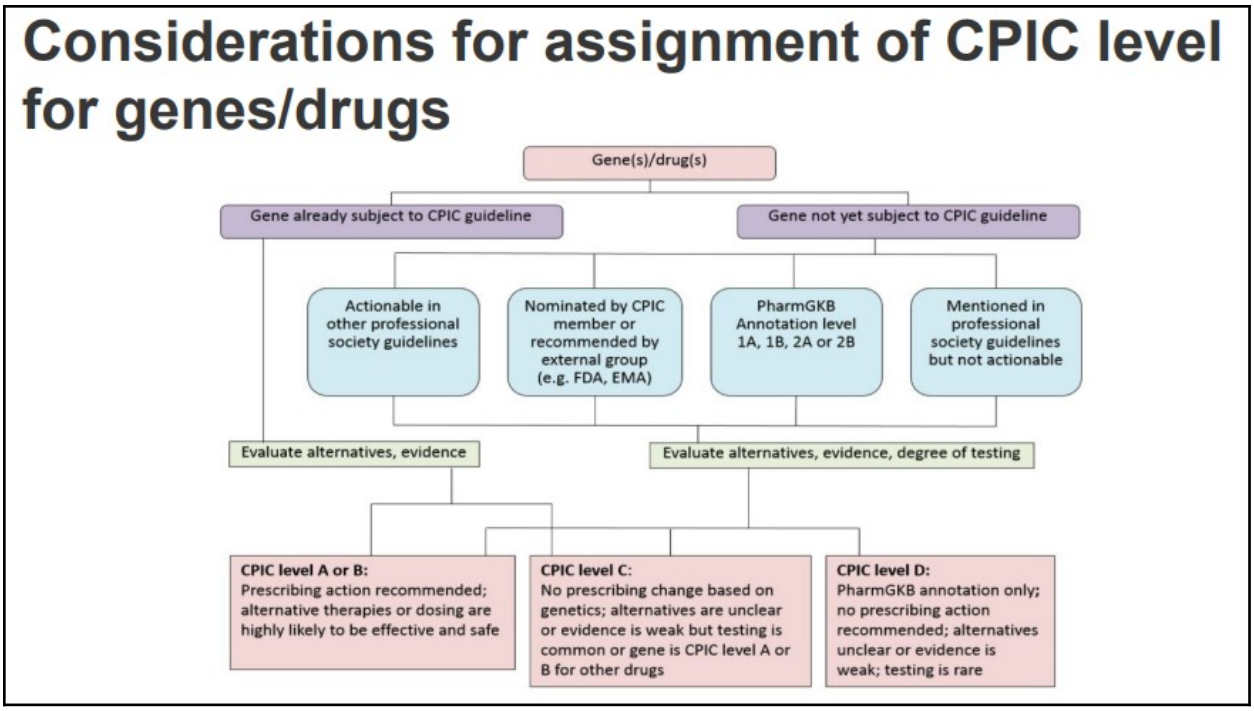

For CPIC, the key thing to keep in mind is the assigned levels. Level A or B is really the one that a lot of laboratories focus on including Invitae. Level A or B means that when we have that information, we can provide guidance on how to act on it. There's going to be drug or dose change information associated with that guideline. CRD usually means developing evidence or the evidence is weak.

Level definitions for CPIC genes/drugs

CPIC level	Clinical context	Level of evidence	Strength of recommendation
A	Genetic information should be used to change prescribing of affected drug.	Preponderance of evidence is high or moderate in favor of changing prescribing.	At least one moderate or strong action (change in prescribing) recommended.
A/B	Preliminary review indicates it is likely that the definitive CPIC level will be either A or B.	Full evidence review needed to assess level of evidence, but prescribing actionability is likely.	Full review by expert guideline group to assign strength of recommendation.
B	Genetic information could be used to change prescribing of the affected drug because alternative therapies/dosing are extremely likely to be as effective and as safe as non-genetically based dosing.	Preponderance of evidence is weak with little conflicting data.	At least one optional action (change in prescribing) is recommended.
B/C	Preliminary review indicates it is likely that the definitive CPIC level will be either B or C.	Prescribing actionability based on genetics is not clear without further evidence review.	Full review by expert guideline group to assess strength of recommendation.
C	There are published studies at varying levels of evidence, some with mechanistic rationale, but no prescribing actions are recommended because (a) dosing based on genetics makes no convincing difference or (b) alternatives are unclear, possibly less effective, more toxic, or otherwise impractical, or (c) few published studies or mostly weak evidence and clinical actions are unclear. Most important for genes that are subject of other CPIC guidelines or genes that are commonly included in clinical or DTC tests.	Evidence levels can vary.	No prescribing actions are recommended.
C/D	Preliminary review indicates it is likely that the definitive CPIC level will be either C or D.	Evidence levels can vary.	No prescribing actions are recommended.
D	There are few published studies, clinical actions are unclear, little mechanistic basis, mostly weak evidence, or substantial conflicting data. If the genes are not widely tested for clinically, evaluations are not needed.	Evidence levels can vary.	No prescribing actions are recommended.

Again, focus on the AB CPIC levels.

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Current applications of PGx: Oncology

Generic name (brand name)	Use	Drug metabolism	Gene(s)	CPIC level
Thiopurines: azathioprine (Imuran®), mercaptopurine (Purinethol®), and thioguanine (6-TG, Tabloid® or Lanvis®)	Acute lymphoblastic leukemia	Varies	TPMT/ NUDT15	A
Fluorouracil (Adrucil®) Capecitabine (Xeloda®)	Colon, rectal, breast, stomach, pancreatic and other cancers	Active	DPYD	A
Tamoxifen (Nolvadex®)	Hormone receptor positive breast cancer, breast cancer risk reduction	Prodrug	CYP2D6	A
Irinotecan (Camptosar®)	Colon, pancreatic and small cell lung cancer	Prodrug	UGT1A1	A (Provisional) FDA Actionable

These are the medications that currently have high evidence drug gene applications in oncology. Again, I don't see prostate cancer. I know sometimes drugs are used depending on the type of cancer that isn't necessarily in that area. I'm not sure if any of these are ever used in prostate care, but these are the drug gene pairs that currently have high evidence.

Oncology genes and actionable phenotypes

Drug	Gene	Phenotypes	Clinical impact
Thiopurines: azathioprine (Imuran®), mercaptopurine (Purinethol®), and thioguanine (6-TG, Tabloid® or Lanvis®)	TPMT	Intermediate metabolizers Poor metabolizers	Dose reduction to avoid leukopenia, neutropenia, myelosuppression
	NUDT15	Intermediate metabolizer Possible intermediate metabolizer Poor metabolizer	
Fluorouracil (Adrucil®) Capecitabine (Xeloda®)	DPYD	Intermediate metabolizer Poor metabolizer	Dose reduction or alternate drug selection to avoid severe/fatal neutropenia, GI toxicity
Tamoxifen (Nolvadex®)	CYP2D6	Intermediate metabolizer Poor metabolizer	Consider alternate hormone therapy (aromatase inhibitor) to reduce risk of breast cancer recurrence
Irinotecan (Camptosar®)	UGT1A1	Poor metabolizer	Dose reduction

https://cpicpgx.org/guidelines/

You can see very specific guidance, and often if it says dose reduction, there's very specific guidance on what that dose reduction should be. This is just a summary when patients are tested and found to have this genetic type thing.

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Oncology case example

- Lynn Stevens was a former machinist who, as a young woman, took part in the landmark 1968 strike for equal pay at Ford’s Essex factory.
- In late 2018, Lynn was diagnosed with an early stage bowel cancer following routine screening.
- In January 2019, Lynn had a successful bowel resection surgery.
- Her doctors recommended chemo to knock out any residual cells
- Lynn and her husband of 47 years, Chris, decided to proceed to increase her chances for long-term survival.

https://www.know-the-risk-of-5fu-chemotherapy.com/personal-stories/lynn-s-story/

One of the biggest examples we hear about quite often is DPYD for Fluorouracil or Capecitabine metabolism. This is a sad story about Lynn Stevens. She was a former machinist who was in a landmark strike for equal pay for women. In late 2018, she was diagnosed with early-stage bowel cancer following routine screening, had a successful bowel resection surgery, and her doctors recommended chemo to knock out any residual cells. She and her husband agreed that this was the best approach.

Oncology case example

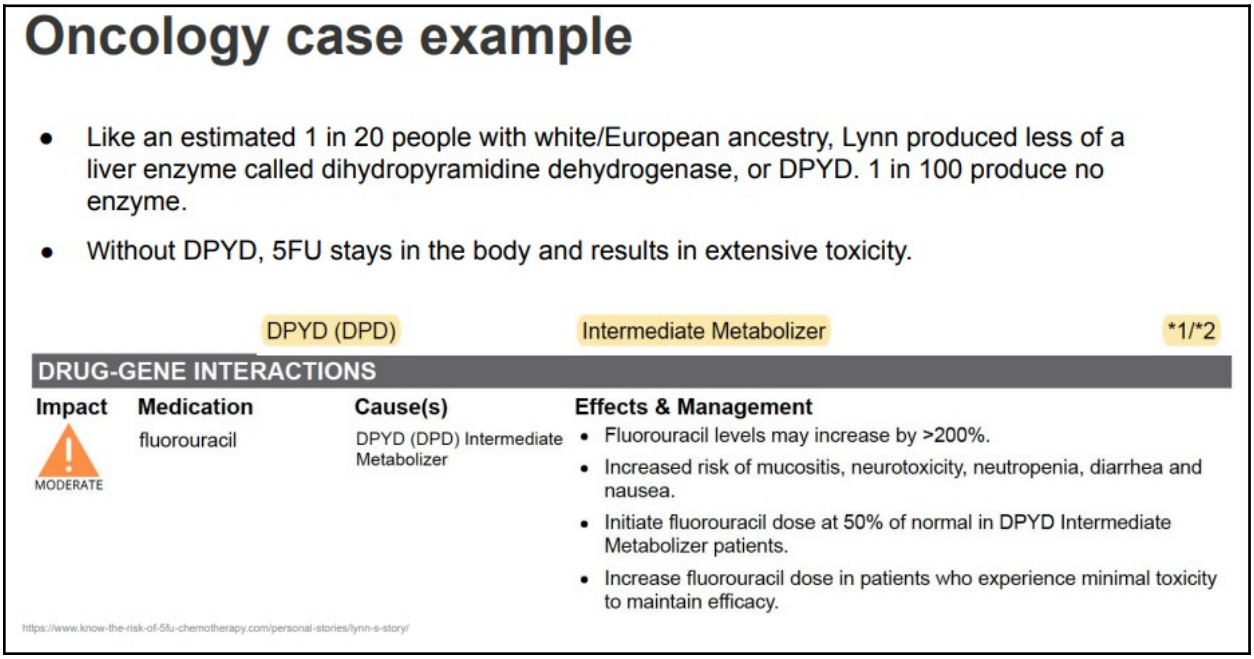
- In March 2019, Lynn had her first ...and last dose of intravenous flourouracil (5-FU).
- Lynn died less than 4 weeks later, but NOT from her cancer.
- What happened?

"Her last weeks were agony," Chris says. "Her entire digestive tract was burnt, as if by acid. She had constant nausea and diarrhea and couldn't process food. No one warned us this might happen. Yet as I know now, Lynn's death was avoidable."

https://www.know-the-risk-of-5fu-chemotherapy.com/personal-stories/lynn-s-story/

In March 2019, she had her first and last dose of 5-Fu. She died less than four weeks later, but not from cancer. Her husband said her last weeks were agony. Her entire digestive tract was

burnt, as if by acid. She had constant nausea and diarrhea and couldn't process food. “No one warned us this might happen.” Yet, as I know now, Lynn's death was avoidable.



Lynn, like an estimated one in 20 people with white European ancestry, produced less of a liver enzyme called DPYD. One in 100 produce no enzyme. Without this, 5-FU stays in the body and results in extensive toxicity. This is just a snapshot of a personalized prescribing report, that you can see has dosing guidance. It doesn't say you have to avoid this medication; you simply have the dose when you have this on the front end to avoid these toxicities in patients with this genetic type.

Kristine Aschcraft 14:10

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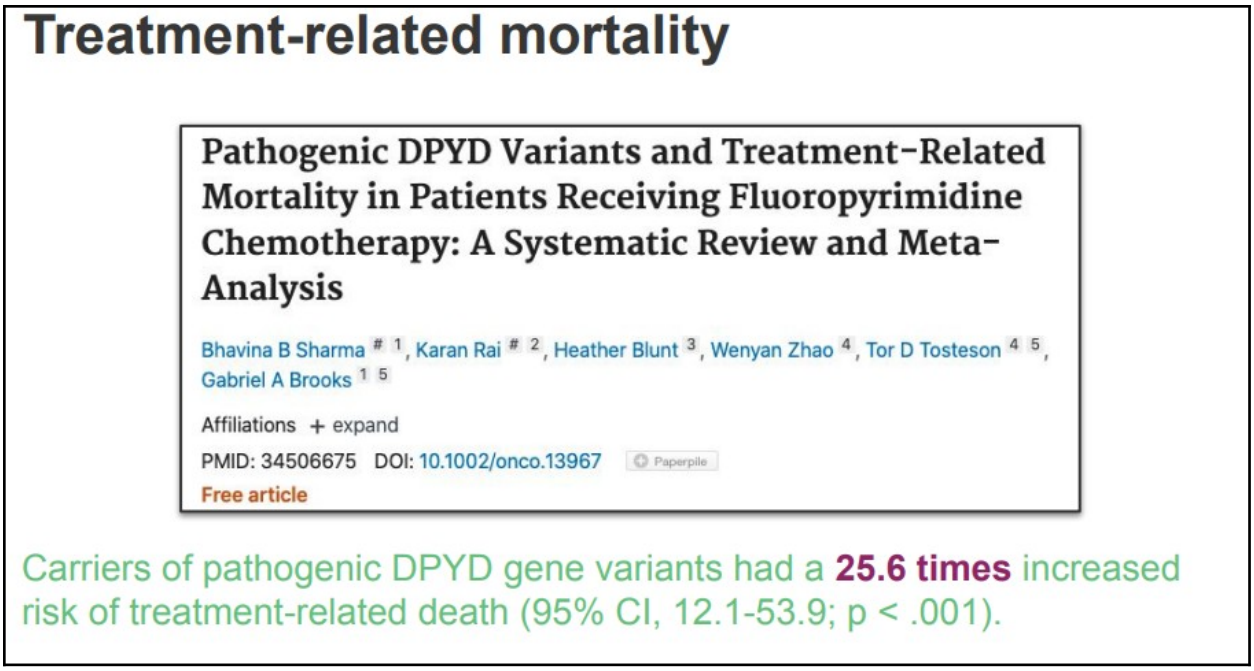


This came out recently, I think last year.

Marty Tenenbaum 14:14

Are you looking for some gene that's missing? Or can you measure whether the enzyme is present in serum?

Kristine Aschcraft 14:28

You can do both. This is looking at the gene, but there are a number of studies that have correlated the levels with the gene.

Marty Tenenbaum 14:37

What do people do in practice for this drug? It's obviously a risk that someone needs to be mitigated.

Kristine Aschcraft 14:44

There are some cancer centers that are starting to utilize this. OHSU, and I think that's in here, got sued earlier this year because a wife lost her husband because they didn't even explain the risks or that this testing was available. They now must talk to every cancer patient about it and make them aware that this is a risk, and the testing is available.

Marty Tenenbaum 15:07

I'm amazed this isn't widespread, known, and tested for.

Kristine Aschcraft 15:11

It should be. I wrote a letter to NCCN to update the guidelines just last month. There's been a bit of resistance, and I think a lot of times people don't order things unless it makes it into guidelines. It currently says there's a correlation, but they don't recommend or say you should test the patient.

Brian McCloskey 15:36

Why would there be resistance?

Kristine Aschcraft 15:39

I will send you an article that Turna Ray just wrote up in Genome Web about this. She interviewed a ton of people. It's a great question. I don't know why there is resistance. But there has been resistance to pharmacogenomics in general during my entire career of over 20 years in this space.

Brian McCloskey 16:05

In my six-year journey, no one has brought up this topic that there might be certain genes that may be indicators that I'm not going to respond to a particular drug. It's “one size fits all” when you get treated. How do we use this capability to optimize dosing for patients? Is that something that you even get involved in? I didn't even know that Invitae was in this space. I look at our patients in the Prostate Cancer Lab, and five of us have germline sequencing, which is negative for all, but one person who has BRCA II. But nobody ever talks about pharmacogenomics like you do. Why is this not more prevalent, and how do we get access to it?

Kristine Aschcraft 17:27

Great question. Just like any other Invitae test, we have a $250 patient pay rate if insurance doesn't cover it. One of the barriers, just like any other biomarker testing historically, has been reimbursement. Medicare did implement local coverage determinations in 2020. That dramatically expanded coverage. It aligns with the FDA or CPIC (Clinical Pharmacogenetics Implementation Consortium) AD. If a patient is either taking, or a medication is under consideration, that impacts two genes, they will cover a full panel 100%. But a lot of the issue, and the pharmacogenomics community is certainly working on this, is that guidelines and reimbursement policies do not align with evidence. They're outdated. I know. I'm on the pharmacogenomics subcommittee or something for the American Cancer Society. They've been pushing biomarker legislation across the country that mandates coverage for biomarker testing, including pharmacogenomics. There's an effort right now in California, and if anybody on the call is in California, please email the governor and ask him to sign SB 1191. This would mandate pharmacogenomics coverage for medical patients that aligns with the Medicare Coverage Determination CPIC AB. But I'd say the other big thing to your point is there's a lack of education. There is a federal act called the Right Drug Dose Now Act that Tom Emmer and Eric Swalwell introduced in February, that would mandate money allocated for both provider and patient education about the importance of pharmacogenomics, the evidence behind it, and how it can help reduce adverse drug events, among other things. They're all very good questions. But pharmacogenomics, if you're familiar with NBTA, can be ordered just like any other test, and follows the same kind of assessment whether it'll be covered giving the patient the option to switch to patient pay, etc., or a Patient Assistance Program for those who have financial need.

Kristine Aschcraft 19:37

“Pharmacogenomics and Dosing” (Kristine Ashcraft) [#25]

In this meta-analysis, patients with variants are over 25 times more likely to have treatment-related death.

DPD testing for 5-FU

Europe has recommended DPD testing for 5-FU since 2020.

EMA has recommended that patients should be tested for the lack of the enzyme dihydropyrimidine dehydrogenase (DPD) before starting cancer treatment with fluorouracil given by injection or infusion (drip) or with the related medicines, capecitabine and tegafur.

Europe has mandated testing since 2020.

Significant pharmacogenomic impact in cancer care

There are over 400 FDA drug labels on pharmacogenomics. **Over 40% are for cancer medications.**[1]

Cancer patients are being treated for more than cancer, and those medications are also impacted by pharmacogenomics.[2]

Cancer patients undergoing treatment with chemotherapy took an average of:

- 5.5 (range 0-13) prescription drugs
- 2.2 (0-20) OTCs
- 1.9 (0-11) supplements

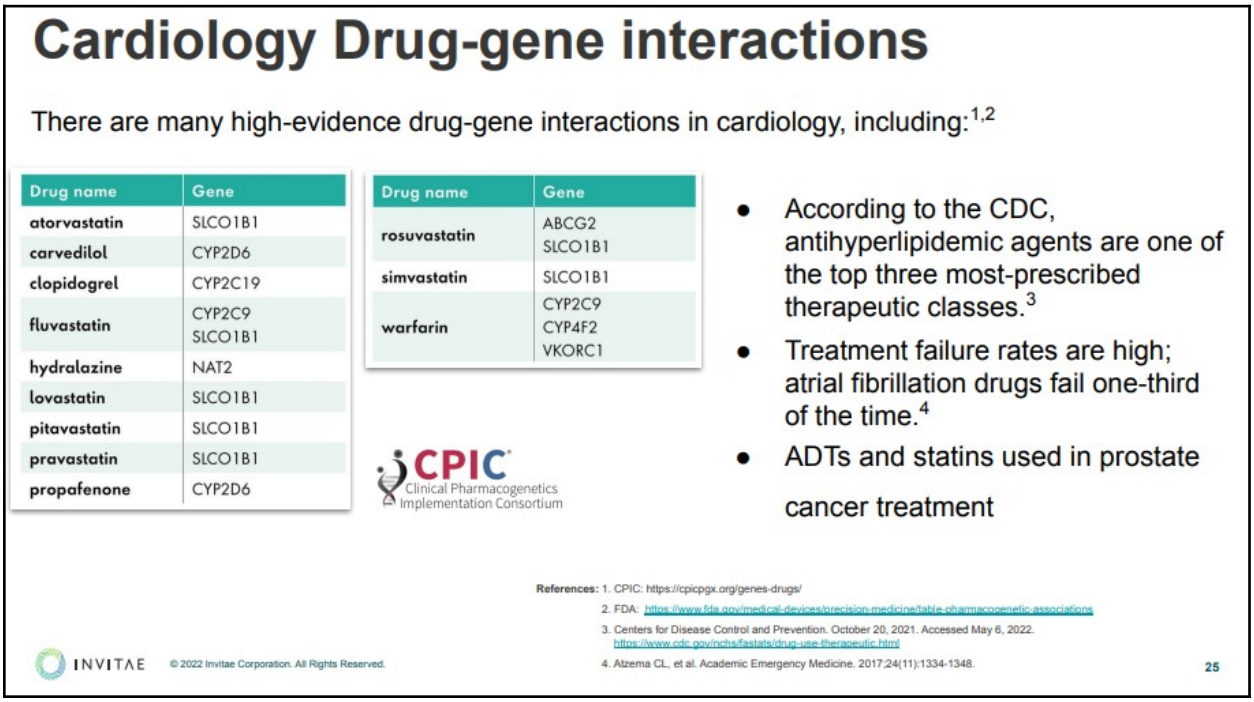
Medication	% taking medication	Pharmacogenomic impact
Acetaminophen	59.6	
Multivitamins	40.4	
Hydrocodone	28.8	YES
Calcium supplements	26.9	
Tamsulosin	23.1 (males)	YES
Amlodipine	21.2	
Aspirin	21.2	YES
Diphenhydramine	21.2	
Potassium	19.2	
Ibuprofen	17.3	YES
Magnesium	15.4	
Metoprolol	15.4	YES
Omeprazole	15.4	YES
Promethazine	15.4	YES
Esomeprazole	13.5	YES
Levothyroxine	13.5	
Pseudoephedrine	13.5	
Dextromethorphan	11.5	YES
Glipizide ER	11.5	YES
Pantoprazole	11.5	YES
Ranitidine	11.5	YES

[1]Table of pharmacogenomic biomarkers in drug labeling. U. S. Food and Drug Administration. Accessed October 25, 2021. https://www.fda.gov/drugs/science-and-research-drugs/table-pharmacogenomic-biomarkers-drug-labeling

[2]Hanigan MH, *et al. J Oncol Pharm Pract.* 2008;14(3):123–30. doi: 10.1177/1078155208090624

I think the main point I want to drive home is although there may not be specific prostate cancer medications that have drug-gene guidance, a lot of the medications that cancer patients need are impacted by pharmacogenomics. It's important to optimize the overall health of the patient

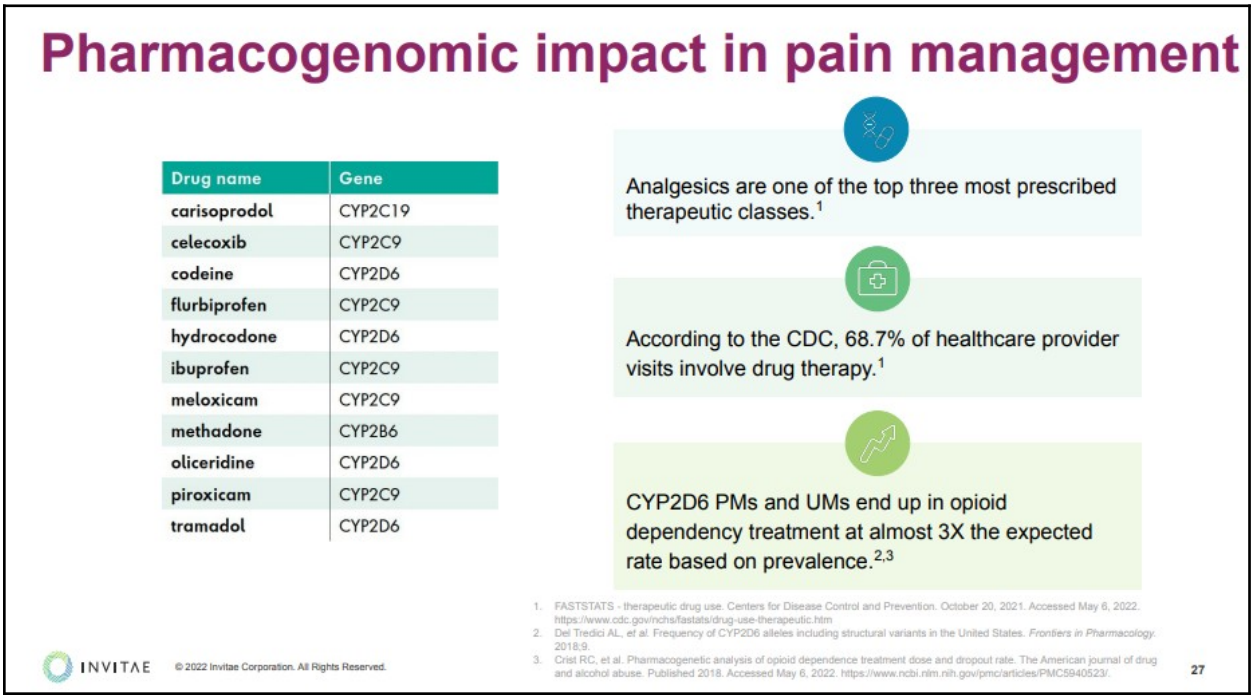
as much as we can. We don't want them getting too much of a beta blocker, for example, that makes them fall and break their hip if we can avoid it, even though it has nothing to do with their specific cancer medications. But a lot of medications with PGx impact are commonly given to patients. I will get to the dosing question in just a moment when I demo the software Invitae includes for providers with testing.



I did see that ADTs and statins are sometimes used in cancer treatment. You can see there are several statins that are impacted by pharmacogenetic variability, specifically SLCO1B1 is associated with increased risk of muscle issues, statin myopathy. If you have this testing proactively, it can guide you to a statin that's going to be lower risk for the patient.

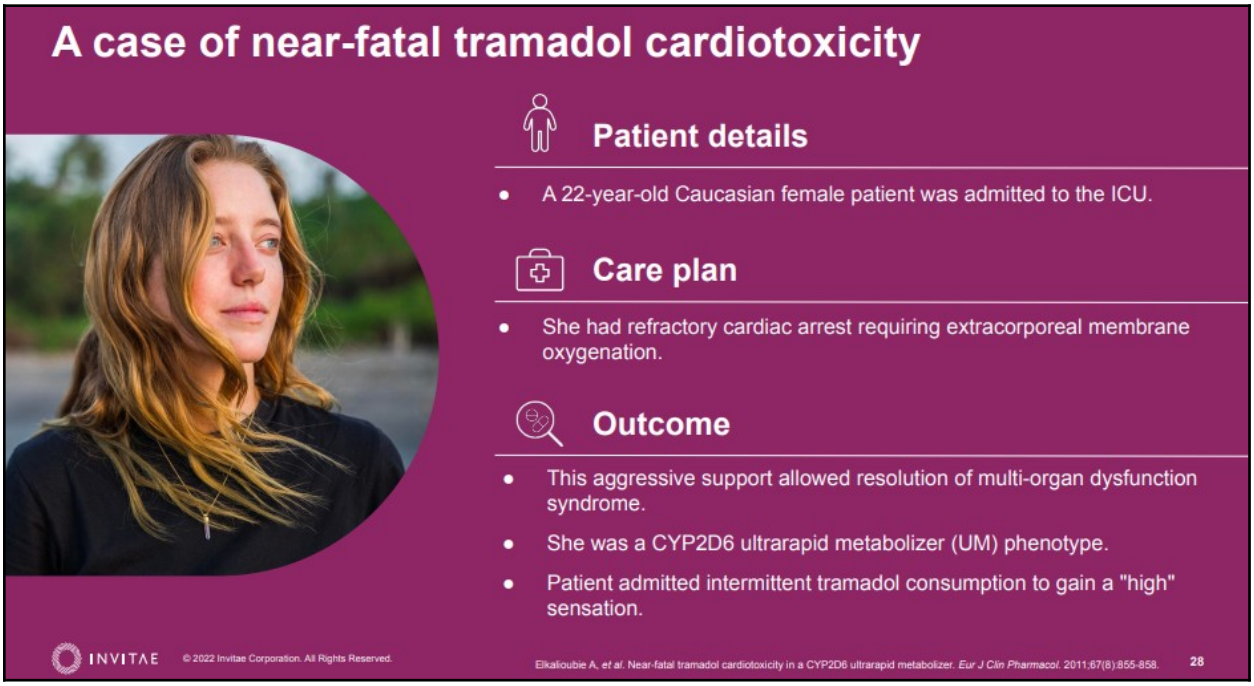
“Pharmacogenomics and Dosing” (Kristine Ashcraft) [#25]

Another big thing that I find very interesting is they haven't done a lot of testing in opioid dependency treatment. But when they do, the rate of CYP2D6, ultra-rapid and poor metabolizers is three times higher than it is in the general US population, leading me to believe that we're either under-dosing or overdosing these people. It leads to downhill or downstream effects that are potentially avoidable.

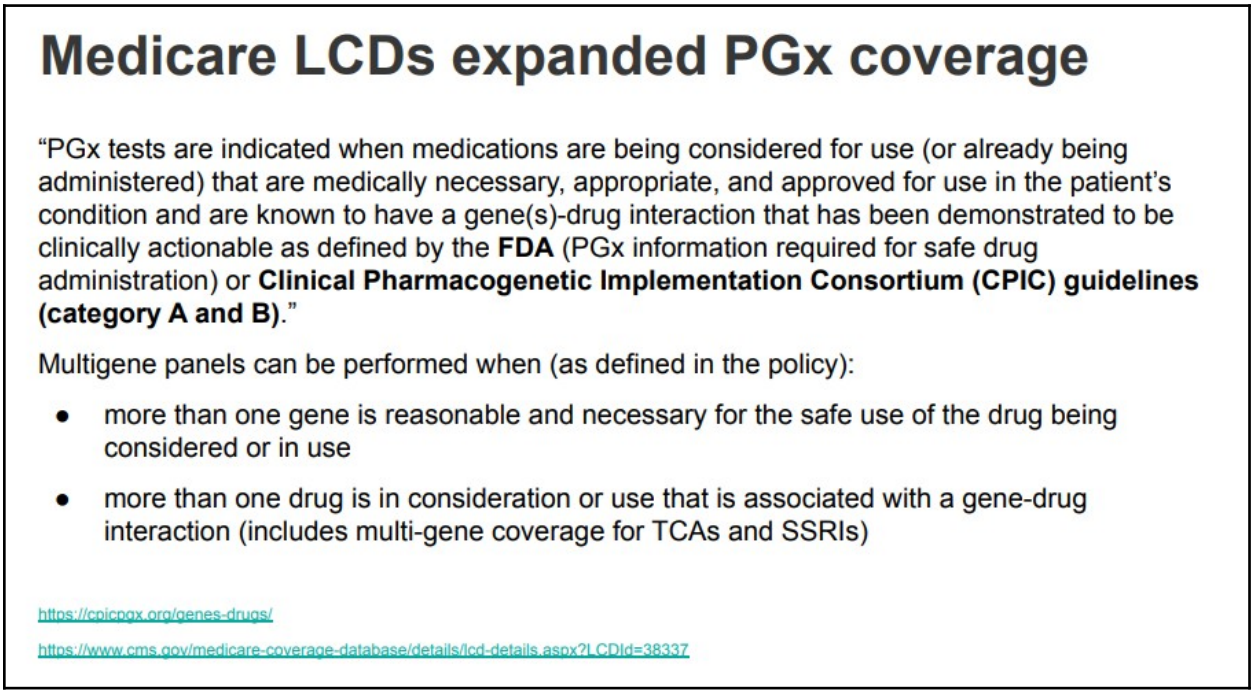


“Pharmacogenomics and Dosing” (Kristine Ashcraft) [#25]

These are the medications currently with high evidence of drug-gene interactions for pain management. I did see that NSAIDs for reducing inflammation are sometimes used to help, but I'm sure also pain management is important in general in cancer care.



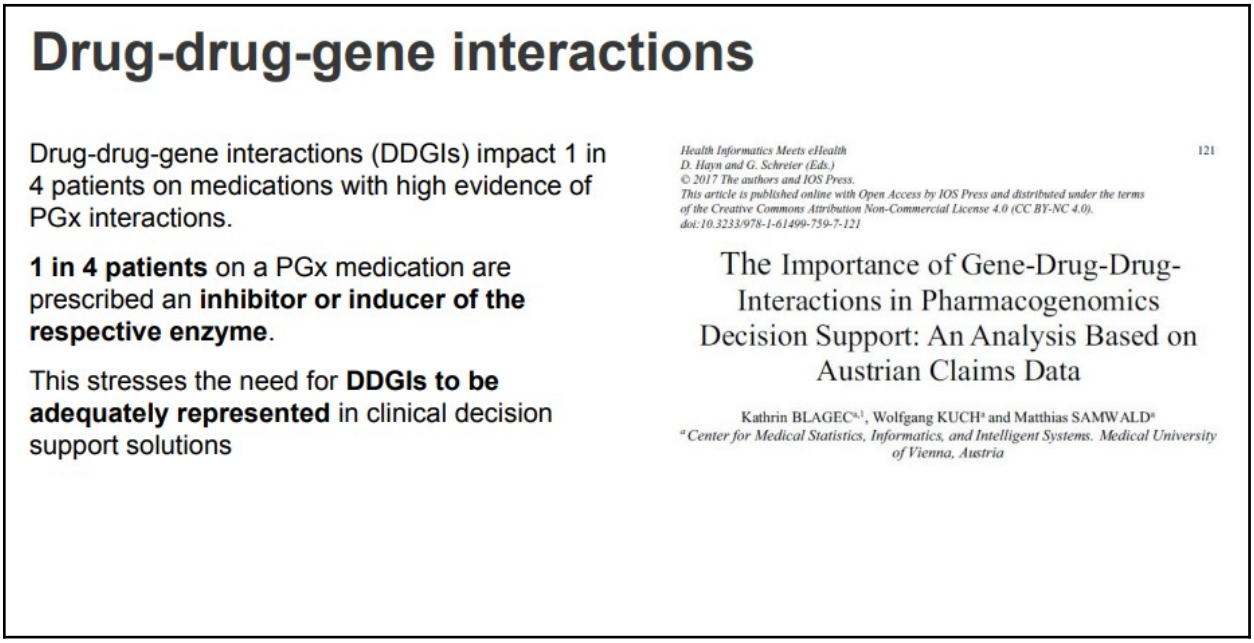
I'm going to pop through this and go to the dosing guidance.



This is the Medicare expanded coverage. In terms of any patients that have Medicare, they have very good coverage for pharmacogenetic panels. So I would encourage ordering,

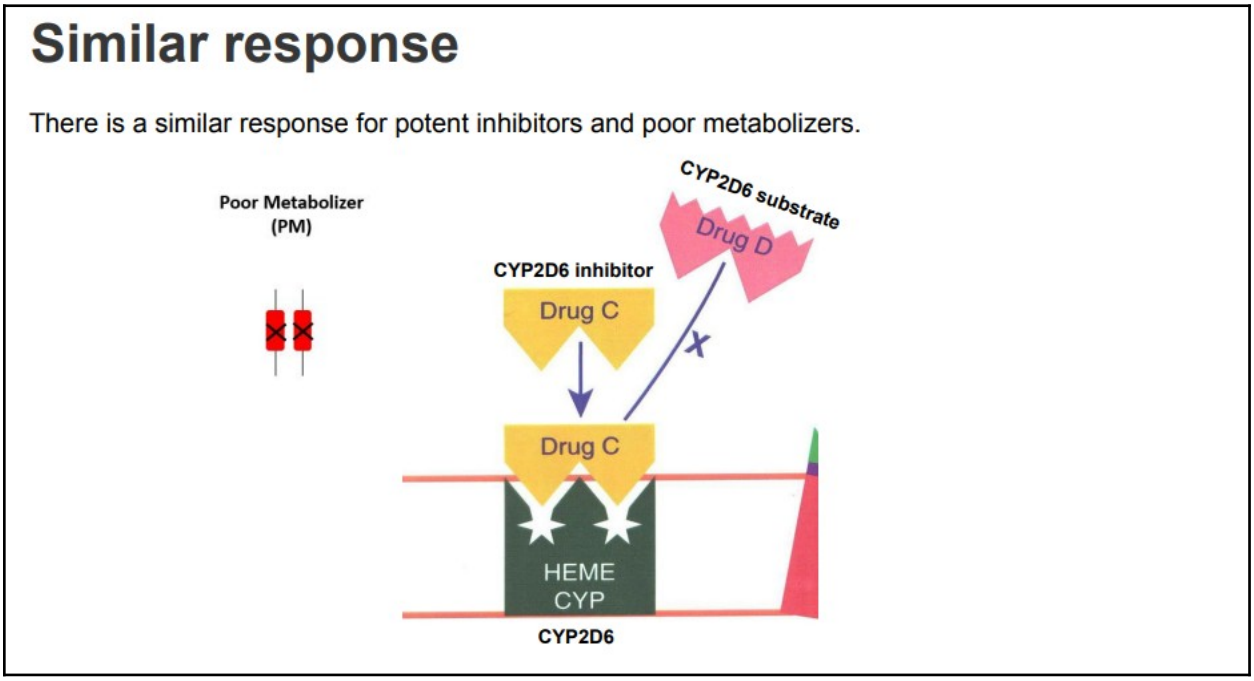
especially for a Medicare patient, at the same time you do hereditary cancer testing, it's a great time to order the pharmacogenomic testing as well.

Kristine Aschcraft 22:15



Just one more thing before I pop into the clinical decision support tool that shows you the dosing because it's a premise for the clinical decision support tool. There are drug-gene interactions, but the drugs that patients take at the same time do something called phenoconversion. You remember from my lane analogy, intermediate metabolizers, one active one inactive gene down

to one lane. If they're taking an inhibitor of the same enzyme, it essentially sends a signal to their body. It's a drug that says, "Hey, shut that other lane down." And we have essentially phenoconverted them to a poor metabolizer if they're taking that other medication. An analysis that came out of Austria shows that one in four patients were taking a PGx med at the same time as an inducer inhibitor of that same enzyme. Inducer does the opposite. It sends a signal to make more of the enzyme in the body.



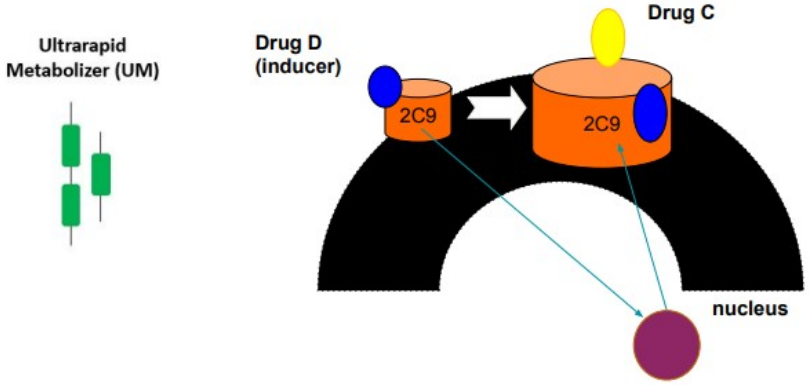
It's a very similar response if you're familiar with drug-drug interactions of the cytochromes. With a poor metabolizer, again no lanes on this highway. Inhibitors are different strings. Some may say, “shut down both lanes”, some “only one lane” or “half a lane”.

“Pharmacogenomics and Dosing” (Kristine Ashcraft) [#25]

Similar response

There is a similar response for strong inducers and ultrarapid metabolizers.

Drug D sends message to nucleus to make more CYP protein---Induction of 2C9 -> lower concentration of Drug C

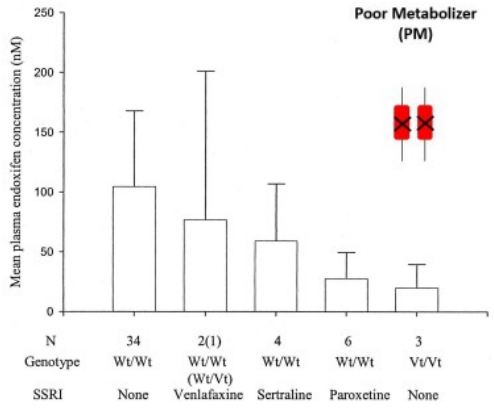


And then the ultra-rapid metabolizer is very much like an inducer sending a signal to the body to process something more quickly. Again, the difference being the genes will never go away.

CYP2D6 phenoconversion

Many antidepressants cause CYP2D6 phenoconversion:

- There are associations between commonly used antidepressants and plasma endoxifen concentration.[1]
- Mood disorders exist in 38.2% of cancer patients.[2]



[1] Jin Y, *et al. J Natl Cancer Inst.* 2005;97(1):30–39. doi: 10.1093/jnci/dji005
[2] Mitchell AJ, *et al. Lancet Oncol.* 2011;12(2):160–74. doi: 10.1016/S1470-2045(11)70002-X

This is an example again using tamoxifen. What happens when we don't take these drugs into account, at the same time we take genetics into account? On the far right we have a variant type. This is a poor metabolizer for CYP286, and there are levels of Endoxifen in the system. Right next to that we have wild type and normal metabolizer taking paroxetine. You can see their levels are pretty low, even though they are a normal metabolizer for CYP286. And then as we shift to the left, these other medications also have an impact on reducing levels, but they're

not as strong of an inhibitor of CYP2D6 as the paroxetine is. But if you have an intermediate metabolizer, for example, and you're giving them sertraline, they're going to shift further over to the right. Just something to keep in mind that this is very important.

Kristine Aschcraft 24:32

We'll pop over to the software. When a patient is tested in Invitae, we ask the ordering provider to submit the cheek swab sample. We can take a blood sample if one's being drawn anyway and a list of all the medications the patient is currently taking as well as any that are under consideration for their care. We will provide three different reports. One is just a standard lab report, your patient's 2D6 intermediate metabolizers *1/*4. The second is a personalized prescribing report, which is essentially grabbing the information from the demo I'm about to show you. And then the third is a high evidence drug-gene table. This is a summary that goes to the patient and provider that will include any of the current high evidence medications that could be problematic by category.

Brian McCloskey 25:23

There are a number of patients that take supplements. Do you also account for supplements beyond just meds?

Kristine Aschcraft 25:31

We do if there's information in the literature about interactions. Unfortunately, not all of that has been well studied. But if there are publications on known interactions, we will have that in there as well.

Kristine Aschcraft 25:52

I'm just going to walk through an example, but if there are medications you want me to add here, I'm happy to do so. This is a patient prior to testing. We've entered in some medications for the patient and already have one moderate interaction that is flagging based on the medications alone, driving you to the information at the top here. These are the different medications. These are the genes. Anytime it says “recommended” next to the gene, that means that there is a high evidence of drug-gene interaction. I will email you all the high evidence, drug-gene table after this. This includes all the medications that currently have high evidence. This aligns with Medicare coverage, but also with guidelines. CPIC AD or FDA. You can see for example, the Fluorouracil DPYD. Irinotecam for UGT1A1 both have testing recommended. For a Medicare patient, if you said, "Hey, irinotecam and 5-FU are under consideration,” boom, they cover a panel. But some are optional. These are developing evidence genes, so we can't yet tell you how to act on the information. But some people want it anyway, so it is in the notes. Let me show you what that looks like tested. If you are familiar with the Invitae portal, when the patient is tested, we will automatically port their results over as well as the medications provided at the time of testing. And this gives you a summary of all the information and enables you to audition any new medications, find safer alternatives, etc. If we pop into the fluoroscopy, you can see that there's a summary. This is what comes out on the personalized prescribing report: just the succinct bullets from the software, there's increased risk. For these adverse effects, you want to initiate a dose at half of what you would normally do. If there's minimal toxicity, you can increase the dose. You do want to dive into the underlying reason behind that. There are detailed effects in management. We have curated over 17,000 publications and product inserts. All our pharmacists are CPIC members. So they add new FDA

approved medications, new CPIC guidelines. We also bring in content from Elsevier gold standard on drug-drug, drug-herbal interactions, etc. But this will go out to the underlying reference if you really want to dive into the detailed effects and management.

Kristine Aschcraft 28:26

If we go to the metabolism tab here, what we do with YouScript, and this is my baby. I used to be CEO of Youscript. It is making it easier to understand when drugs in genes, or just multiple drugs are combining to cause more significant increases or decreases in drug exposure than the binary components. This is an example with Metoprolol. But I will do the same thing for you if there's a drug-drug-drug-drug-herbal-gene interaction. In this instance, we're expecting a 76 to 200% increase in drug exposure because the patient's a 2D6 intermediate metabolizer. Metoprolol is metabolized by 2D6. We're also expecting a 26 to 75% increase in drug exposure because the patient is taking fluoxetine, which is an inhibitor of 2D6, a slight inhibitor. The combined impact is a greater than 200% increase in drug exposure. You could use this to help titrate the dose. If you want specific information on the exact ranges that we're seeing, you can pop onto those notes, and a lot of times they will have the exposure ranges in there as well. We can't get to the point of saying this means giving them three times the dose or a third of the dose because if we did, we would be considered a medical device by the FDA, and we would not like to do that. This is a provider-facing clinical decision support tool. We try to make it as easy as possible to do the other thing that is helpful is this alternates. Maybe you're thinking, “Hey, I'm not really sure how to dose this, so I want to give them a different medication instead.” Either by class or indication, you can find medications that are going to reduce the interaction potential, taking everything you've entered into account. You could also add other things, you just type it in. St. John's wort, for example, interacts with everything, I think. You can go in and find a one click alternative. And it will take everything again, on the left into account. You could do a one click substitution. It'll deselect what you had in there, add the new medication, and you can see just as we saw on the right that comes through is “just monitor”.

Brian McCloskey 31:00

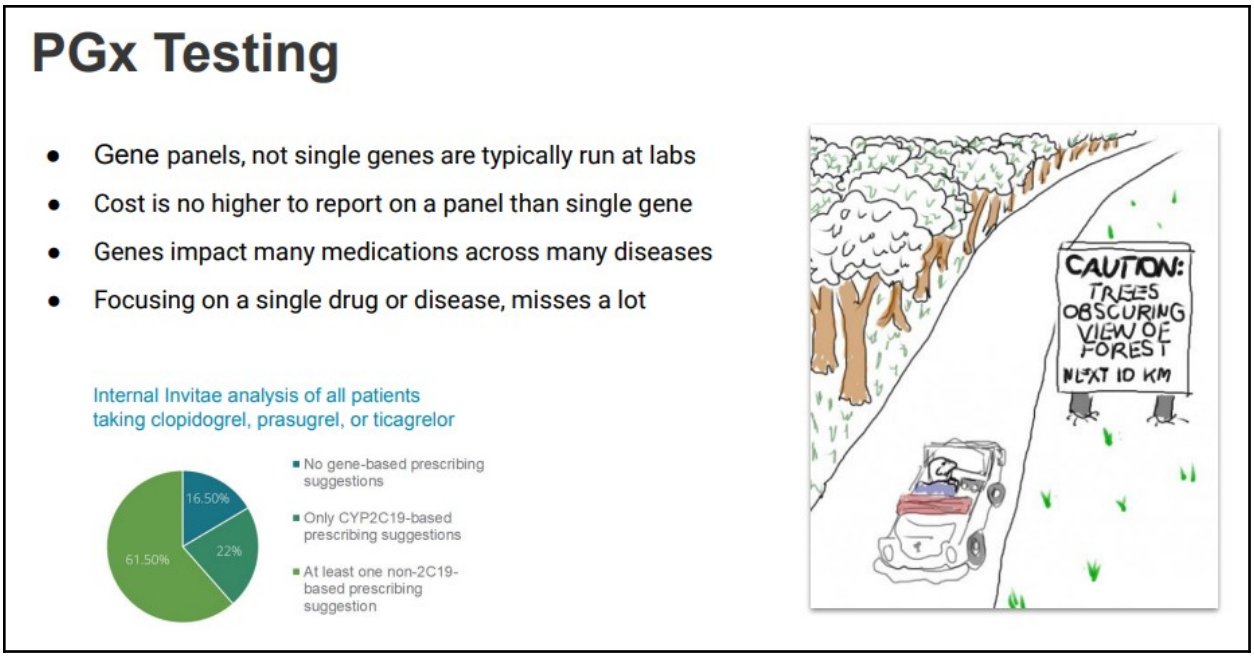
Just for grins and giggles, I know a lot of patients on the call are taking Lupron. What does that look like?

Kristine Aschcraft 31:22

Lupron doesn't have this DNA double helix next to it, which means at this point, there's no high evidence of drug-gene interaction. There are a few just monitor interactions, for different things you can investigate. Different types of metabolism. It will have the most common adverse effects.

Kristine Aschcraft 32:06

“Pharmacogenomics and Dosing” (Kristine Ashcraft) [#25]



The next part of the talk is a summary of takeaways. A lot of times, historically, we have done pharmacogenetics, one gene at a time. "Oh, we're going to put the patient on Irineu T cam, let's order ugt21. At this point, laboratories, whether it's Invitae or another laboratory, are running multi-gene panels. And if only a single gene is ordered, we only report on that gene. And the cost is no higher for us to report on all these teams. We currently, at Invitae, have a 38 gene panel. It includes high evidence drug-gene pairs for 98% of high evidence drug-gene pairs, aside from those that are specifically for disease diagnosis - germline. They impact genes across many, many diseases. If there's a trigger point to order this, ideally do it once. Continue using that information to optimize drug and dose selection. It's vitally important for patients to share it with all their prescribers for ordering providers to make it clear to patients that this can impact drug response across multiple areas for life. And just an example of why this can be so important across different areas. One of the early use cases for pharmacogenetics was clopidogrel or Plavix. This is a drug that's commonly given to keep a patient from having another heart attack or stroke. It's a pro drug and it doesn't work if you're a poor metabolizer - reduced efficacy if you're an intermediate. Patients with variants are three and a half times more likely to have another heart attack or stroke on the drug. We looked at patients that were referred to us for testing on Plavix, and we found that 16% didn't have any gene-based prescribing suggestions. 22% had only 2C19. Maybe more than Plavix even, and over 60% had another high evidence drug-gene interaction for another gene in the panel. This is just a reminder that this is something that can be done once in a lifetime. They can really help optimize drug and dosing across a lot of different areas.

Marty Tenenbaum 34:28

It sounds like the germline doesn't change, right? Why doesn't everyone get it at birth? You use it your whole life.

Kristine Aschcraft 34:43

I am a big proponent of that. I think we should be doing that.

Marty Tenenbaum 34:51

Can't Invitae do some natal testing as well?

Kristine Aschcraft 34:58

We do a lot of testing from prior to birth, at birth, and across the entire continuum.

Marty Tenenbaum 35:06

Isn't this a marketing decision? Or you guys can position products that way and differentiate yourself in the market? Another question. If I got whole genome sequencing, I should be able to pull this information out of that?

Kristine Aschcraft 35:27

Yes, it depends. There are some complications sometimes. CYP2D6 requires the data to be done in a certain way to properly call CYP2D6. It's very complicated. It has a pseudo gene issue, the duplications for CYP2D6 that make a patient in an ultra-rapid metabolizer need to be interpreted in a certain way, and that's a very, very important, oncogene. CYP2D6 metabolizes

about a quarter of commonly prescribed medications, so it's possible, but you must have it set up the right way to read it.

Marty Tenenbaum 36:06

On the other extreme, does it come out of the $99 23andMe panels?

Kristine Aschcraft 36:13

The 23andMe panel has very low snip coverage. If you are found to be an intermediate or poor metabolizer, I would trust it. If you are found to be a normal metabolizer, it quite likely could be missing a variant, especially if you're not of European white ancestry.

Marty Tenenbaum 36:33

My favorite dream is to figure out how to dose people by actually measuring how much active drug is reaching the tumor, and then modulate those empirically as opposed to prescriptively. Does that make any sense?

Kristine Aschcraft 37:03

I think they go hand in hand. In my perfect world, I would test patients at birth as well and have this as part of a permanent and portable medical record that doesn't get trapped into charts or doctor systems. But using that as a guide, so instead of starting this patient on a standard dose in a one size fits all manner, I'm going to start them at half of the dose. Then I'll do therapeutic drug monitoring to see if that was the right choice.

Marty Tenenbaum 37:34

Invitae bought Ciitizen, right? You should talk to the Ciitizen folks about trying to couple this kind of testing to the medical record.

Kristine Aschcraft 37:44

There are a lot of things we were planning to do at Invitae. Unfortunately, there's good and bad. It's a large, multi-pronged company. We plan to make it easier to add pharmacogenetic testing to any other order, for example. But it takes time to add things and update websites. Right now, the pharmacogenetic testing is run in Seattle, in our lab there. And most of our other testing is run in the San Francisco lab. We do have different labs as well that do some of the more specialized testing.

Marty Tenenbaum 38:20

I may have someone named Rebecca Driscoll get in touch with you, who's the CEO of Cancer Commons. We recommend 1000s of patients a year into one thing or another. Maybe there's a way to integrate what you guys offer into our recommendations in some kind of way.

Brian McCloskey 39:02

I just looked at one of our patient's Invitae germline sequencing reports. Obviously, you don't have this information integrated into that report. It seems to me the easiest thing to do is to

integrate it into their germline sequencing report. What would be the cost of that? Or how could we get access to this information if it's not integrated into those reports?

Kristine Aschcraft 39:44

Currently, it needs to be ordered as a separate test. It's a separate sample that's sent to a different lab. The hereditary cancer testing is done in San Francisco. The pharmacogenetic testing is a genome mass array. It's done in Seattle, and we are working right now on some very cool stuff that will enable us to put a lot more on a single platform. But that's early in development. I think that will make things a lot easier in the long run. But I'd say at least for another year or so, we're still going to be in these silos, so you have to order it as a separate test. If you're using the Invitae portal, in the same way, you would have asked to have the PGx added to the compendium.

Kristine Aschcraft 41:09

You asked, "Why haven't we heard of this"? It sounds like Marty had a suggestion for Cancer Commons. If you have any suggestions on how we can do a better job, I'd love to hear them. I'm on way too many PGS committees to count, but we are trying to get the word out to providers, so we're all ears if you have any recommendations on how we can do a better job of sharing this information. I'm clearly, after 20 years, a big believer. I think this can both improve patient care and reduce costs. I think it's the right thing to do, especially for patients that must take a lot of medications.

Brian McCloskey 41:50

Our community is very focused on prostate cancer. Within that segment, we have access to a number of resources that publish. I was just interviewed yesterday for a story, and a couple of weeks ago for another story as well. There are opportunities for us to help you to get the word out. Now that I know about this, I certainly will be an advocate. I'm sure that there will be others on this call that feel the same way that have access to some of these megaphones that can help to spread the word.

Brad Power 42:43

One of the original reasons that I reached out to you is because I know you're an expert on pharmacogenomics, but we ran into something which was a question on dosing. We're proponents, just as CureMatch is, for drug combinations. One of the concerns that prescribing doctors would have is drug-drug interactions, toxicity, and so on. How could dosing perhaps solve that? Are there principles and ideas around dosing that would make it safer for patients and more comfortable and confident for doctors to prescribe drug combinations and understand the interactions? Maybe the rule of thumb is if it's three drugs, maybe give a third of the dose if they're not on similar treatment pathways, and not to think of them all like chemo. Do you have any pointers? I think you didn't have any direct answers, but maybe could point to where we should be looking.

Kristine Aschcraft 43:39

It depends on how they're metabolized. A lot of the stuff that I was looking at in prostate cancer was small molecules. It was not metabolized through the cytochrome system, which is really the big impact for pharmacogenetics. There are some transporters and receptors we're trying to

understand better. But I would say, are you able to do therapeutic drug monitoring to determine what the impact is of these combination therapies? Is that measurable? I think, once that information is out there, and it's published, tools like the YouScript clinical decision support tool will be helpful. We love data. We feed it, and then we say, "hey, when you give these together, this is what you expect to see." But to feed that into clinical decision support tools, and we're not the only ones, we actually need to see published data that when this combination is given this is what happens, or we see that it's feasible. But you need to have the published data to feed into it. I don't know if that's helpful.

Brad Power 44:49

That's a bit of a conundrum because many of these personalized cocktail combinations don't have evidence because they're so personalized.