“Getting a Better Diagnostic (DPYD) into the Standard of Care” (Karen Merritt) [#137]

Brad Power and Nanthana Ravichandran
April 2, 2025

“When the NCCN just updated those guidelines, they said that there's no concrete evidence on how to reduce the dose, which, as an advocate, I disagree with. I think the CPIC guidelines would be great for dose adjustment, and that's exactly what the institutions that have implemented testing are using.“ - Karen Merritt

Meeting Summary

As a cancer patient, you may not be aware that you are at risk of being overdosed, under-dosed, and being given drugs that are ineffective, or in tragic cases fatal, which testing could have predicted. You should get tested to identify your personal risks and to inform your personalized dosing levels before taking certain drugs or getting radiation treatment. In the future, you will be able to measure the effective level of a drug in your body, and then modulate the dose empirically, as opposed to the one-size-fits-all (not personalized) rules for prescriptions.

Consider the story of Karen Merritt, patient advocate and Co-Founder of Advocates for Universal DPD/DPYD Testing, who suffered the heartbreaking loss of her mother—not to colorectal cancer, but to toxicity from an overdose of a chemotherapy meant to treat it. Her mother could have been tested, but wasn't, for a gene variation (DPYD) which is essential for breaking down and eliminating specific chemotherapies. In most of Europe, testing for this gene variation before administering specific chemotherapies is standard practice. Unfortunately, this is not yet the case in the United States. In 2022, Karen co-founded the nonprofit organization Advocates for Universal DPD/DPYD Testing to push for change. Their mission is to improve patient safety by making pretreatment DPYD testing a standard of care in the U.S. before being administered certain chemotherapies. They have sent in a proposal to get this testing into the standard care guidelines. While organizations like the FDA, NCCN, and ASCO have yet to mandate this testing, several leading U.S. cancer centers—such as Dana Farber Cancer Institute, Levine Cancer Institute, and Ochsner —are implementing DPYD testing for better patient safety and outcomes. Karen's goal is to see this become the norm across the country, ensuring that no more lives are lost due to preventable drug-gene interactions.

Why do you need to know about pharmacogenomic testing?

Pharmacogenomic testing helps personalize cancer treatment by identifying how your genetic makeup affects your ability to metabolize certain drugs. In the case of DPYD testing, it can prevent potentially life-threatening toxic reactions to chemotherapy drugs like fluorouracil (also known as 5-Fluorouracil or 5-FU), a chemotherapy medication used to treat various cancers and some skin conditions, and capecitabine, an oral drug that converts into fluorouracil. By understanding your genetic variants, doctors can adjust drug dosages to minimize severe side effects while maintaining treatment effectiveness, ultimately improving patient safety and quality of life during cancer treatment. You should be tested for DPYD genetic variants if you are

scheduled to receive chemotherapy treatments using fluorouracil (5-FU) or capecitabine. Testing is a simple blood test or cheek swab. If you have a variant, your oncologist can adjust your dosage to reduce risks.

How can you advocate to improve your access to new tests and personalized dosing in standard protocols?

- Get professional organizations (like NCCN and ASCO) to incorporate the pharmacogenomic tests and procedures in their guidelines (insurance companies typically follow these guidelines)
- Submit citizen petitions to the FDA to revise drug labels and guidelines; support efforts by patient advocacy groups like the American Cancer Society Cancer Action Network to pass biomarker legislation in each state to expand insurance coverage, raise awareness and apply pressure on regulatory bodies
- Highlight patient assistance programs offered by labs (e.g., OneOme provides a $199 test with financial support options for patients who cannot afford the full cost)
- Compile and present patient case studies demonstrating the importance of pharmacogenomic tests; advocate for clinicians, hospitals, and oncology practices to include pharmacogenomic tests as a standard part of initial patient workup, making it easier and more routine; showcase institutions that do incorporate new tests, like the Veterans Administration
- Highlight economic benefits to drug companies, such as reduced adverse events and potential liability
- Collaborate with pharmacogenomics experts to provide scientific evidence supporting routine testing
- Educate yourself about tests for side effects and personalized dosing, share what you learn on support groups and social media, and actively participate in your treatment decisions
- Ask your medical team specific questions about testing and dosing
- Take the time to review and understand consent forms

How can you learn more?

- Visit the website of Advocates for Universal DPD/DPYD Testing; advocate for universal DPD testing for cancer patients before starting fluoropyrimidine chemotherapy
- Contact Karen Merritt at karenemerritt@msn.com
- Check the FDA table of pharmacogenomic associations
- Review the Clinical Pharmacogenomics Implementation Consortium guidelines
- See Cancer Patient Lab discussions on pharmacogenomics and personalized dosing:
    - "Pharmacogenomics and Dosing" (Kristine Ashcraft) [#25]
    - “How I Help Patients Access New Diagnostics” (Joanne Weidhaas, MD, PhD, MSM) [#138]
    - Personalized Drug Dosing (Paul Van Camp and Jeff Krolick) [#68]
    - Personalized Medicine and Dosing (Mina Nikanjam) [#38]
    - An Evolutionary Treatment Strategy (Bob Gatenby) [#9]

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For the video recording of this conversation, please see here.

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Meeting Notes

KEYWORDS

Cancer patient lab, patient advocate, DPYD gene, DPD deficiency, chemotherapy toxicity, pharmacogenomics, FDA guidelines, NCCN guidelines, CPIC guidelines, patient safety, insurance coverage, clinical trials, personalized dosing, patient empowerment, legal action.

SPEAKERS

Karen Merritt (67%), Brad Power (10%), Chris Apfel (9%), Roger Royse (5%), Rick Davis (5%), Cindy Ness (3%), Mike Camara (1%), David Plunkett (1%)

CHAT CONTRIBUTORS

Rick Davis, Bill Paseman, Mike Camara, Dennis Watson, David Plunkett, Chris Apfel

SUMMARY

Karen Merritt shared her mother's tragic experience with 5-FU chemotherapy, highlighting the lack of DPYD testing that could have prevented severe toxicity and death. She explained that DPYD deficiency affects 3-6% of the population, with 3% at risk of death, equating to over 1,000 deaths annually in the U.S. Merritt discussed the FDA's recent labeling changes and the NCCN's updated guidelines, emphasizing the need for pre-screening and dose adjustments. She also mentioned ongoing advocacy efforts, including citizen petitions and legal actions, to improve standard care and patient safety.

OUTLINE

Introductions and DPYD Gene Explanation

- Karen Merritt, a patient advocate, shared her story and the challenges of getting a new diagnostic into standard care.
- The DPYD gene has a role in breaking down fluorouracil and capecitabine (chemotherapy agents).
- Karen Merritt’s mother was diagnosed with stage three anal cancer in 2014.
- There was a lack of a pharmacogenomics test for DPYD.
- Her mother had severe toxicity reactions and died.
- There is a lack of informed consent about DPD deficiency.

Challenges and Advocacy Efforts

- Karen Merritt discussed the high risk of severe toxicity and death due to DPD deficiency.
- The supposed antidote, VistoGuard, has a high cost, short time window and prior authorization requirements.
- Pre-screening for DPD deficiency and dose adjustment are based on CPIC guidelines.
- The mission of her nonprofit is to improve the standard of care for cancer patients undergoing 5-FU and capecitabine chemotherapy.

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Legislative and Clinical Efforts

- Karen Merritt discussed the citizen petitions to the FDA to revise drug labels and the changes in labeling for capecitabine and 5-FU.
- The FDA-AACR's DPD workshop led to the issuance of an FDA safety announcement in January 2025.
- Changing NCCN and ASCO guidelines is challenging. There has been progress in Europe.
- A recent update in NCCN guidelines says to consider DPYD genetic variants prior to therapy.

Insurance and Patient Empowerment

- Karen Merritt emphasized the importance of insurance coverage for DPYD testing and the role of NCCN guidelines.
- Fight CRC's care sequences call out DPYD testing.
- Institutions need to make DPYD testing easy for providers.
- Patient empowerment is needed and informed consent.

Personalized Dosing

- Chris Apfel and other participants discuss the scientific evidence for dose adjustments and the need for personalized dosing.
- Roger Royse and other participants discuss the broader issues of patient empowerment, standard of care, and the role of FDA guidance.

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TRANSCRIPT

Brad Power
This is the Cancer Patient Lab. Welcome to our weekly webinar series.

Today, we're honored to have with us Karen Merritt, a patient advocate who will be sharing her story. She was a caregiver for a loved one who experienced an unfortunate toxicity that could have been caught with diagnostic testing. She will tell us about that story as well as the challenges of getting a new diagnostic test into the standard of care.

Before we get started, I will make a disclaimer. This webinar is only informational, and is not medical advice. Our aim is to provide patients and caregivers with information they can take to their medical team to help improve their care.

We are a 501(c)(3) nonprofit and welcome donations from anyone inspired by the services we provide to patients and caregivers.

Karen Merritt 1:26
Thank you so much for having me. It's so nice to see cancer survivors, and all those fighting to get a better diagnostic into the standard of care. My advocacy has specifically been around DPYD.

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ADVOCATES FOR UNIVERSAL DPD/DPYD TESTING

What is DPYD?

The DPYD gene tells your body to make the dihydropyrimidine dehydrogenase (DPD) enzyme.

The DPD enzyme breaks down fluorouracil and your body excretes the excess. Genetic variants in the DPYD gene can lead to DPD enzymes with reduced or absent activity.

Those with reduced or absent activity DPD enzymes are at risk of potentially life-threatening fluorouracil overdose resulting in severe toxicity and potentially death.

The DPYD (dihydropyrimidine dehydrogenase) gene tells your body to make the DPD enzyme which is needed to break down fluorouracil (5-FU) and capecitabine in your body. Genetic variants in the DPYD gene can lead to insufficient or no enzyme function, depending on the specific variant. Those with reduced or absent DPD enzymes, a condition called DPD deficiency, can experience toxicity and fluorouracil overdose that can be life threatening.

ADVOCATES FOR UNIVERSAL DPD/DPYD TESTING

Linda

- Diagnosis: stage III anal cancer - age 73 otherwise healthy & enjoying retirement
- Treatment plan: 5-FU chemotherapy -- “fairly well tolerated”
- What happened:
  - Single treatment without PGx (DPYD) pre-screening or informed of DPD deficiency
  - Early warning signs missed in ER; hospitalization within 11 days – diarrhea/dehydration, neutropenia, mucositis,
  - 46 hour drip started 6/9/2014
  - Death after two weeks in ICU*
  - Died 7/2/2014
  - Death certificate – cardiac arrest=> should read: ADE toxicity to 5FU

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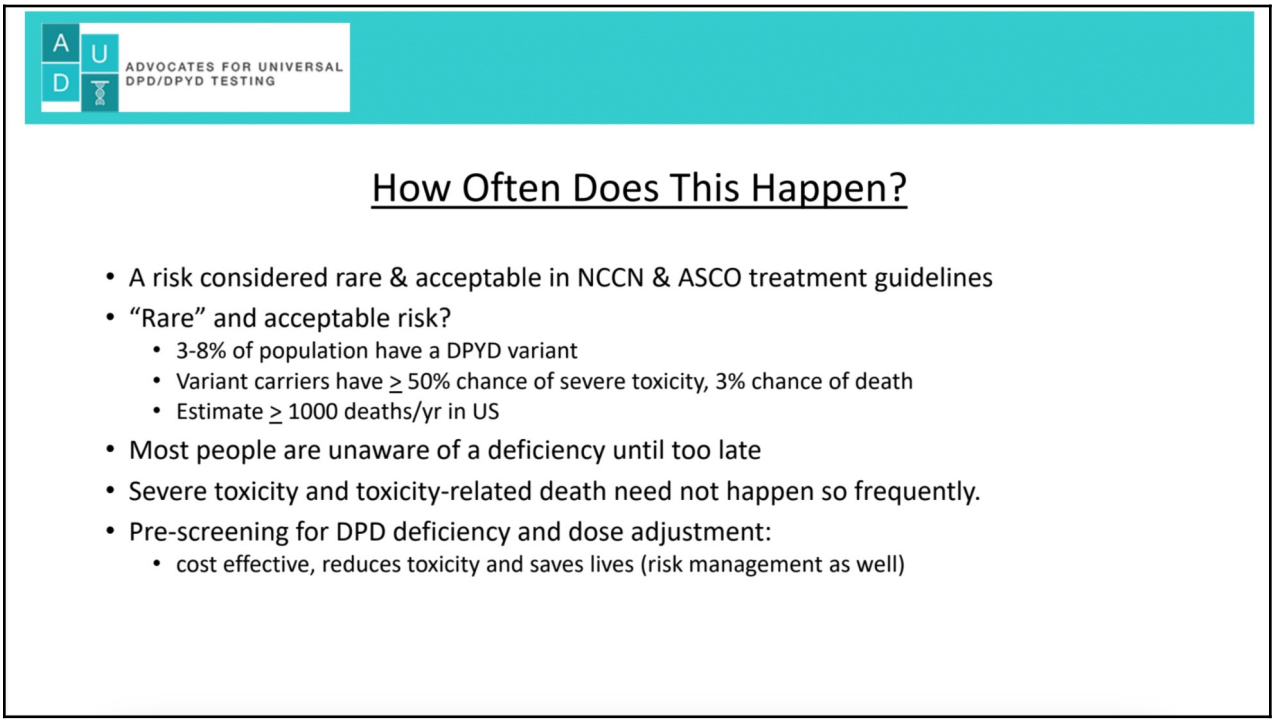
My mom, Linda, was diagnosed in 2014 with stage three anal cancer. At 73, she was otherwise healthy and enjoying retirement. Her treatment plan after a routine colonoscopy was 5-FU chemotherapy with chemo radiation or radiation. Her oncologist told her chemo radiation was fairly well tolerated. She was not prescreened with the pharmacogenetics test for DPYP and not informed about the risks of DPD deficiency. She started her first infusion on June 9, a 46 hour drip. She had been a registered nurse, so on that Friday, she called her oncologist because she knew she had become dehydrated from the continual diarrhea, neutropenia and mucositis. Mucositis sores beginning in her mouth ran all the way down her digestive tract to her anus. There was no conversation about her mouth sores or that it could be signs of a toxic reaction. A couple days later, she falls, while getting up in the middle of the night to go to the bathroom. At this time, she's not eating or drinking because the sores hurt so badly. Swallowing anything is like swallowing razor blades. She goes to the hospital. She's in the ICU. She has round the clock care. We are told by the oncologist on call that there's no way to have known this could have been her reaction before treatment. With what we now know, that is incorrect. She could have had a DPYD test done before treatment started to figure out if she had enough of the DPD enzyme. They told us she was very sick. She'd be in the hospital for a few weeks. She died on July 2, 2014 and unfortunately, her death certificate lists cardiac arrest as cause of death because as part of the toxicity to 5-FU and capecitabine, you end up with multi organ failure. We should have fought to change that death certificate to make it an adverse drug event. Toxicity to 5-FU is the number one cause of death, and as an adverse drug event, it would have been reported to the FDA and MedWatch.



How often does this happen? It used to be considered a rare and acceptable risk in the NCCN treatment guidelines. But 3-8% of the population have a DPYD variant. That is about one in 20 people who are DPYD variant carriers and have a chance of severe toxicity and a 3% chance of

death. This is estimated at over 1000 deaths per year in the United States, as in the US National Libraries of Medicine from a study written by a Dr. Innocenti. That is three jumbo jets every year. If this was regulated by the FAA, they would ground the planes until they resolved the issue. Most people are unaware of this deficiency until it's too late. In 2015 there was a supposed antidote, and I say supposed antidote because Vistoguard has to be administered within 96 hours of the last dose or the end of the infusion. Oftentimes, the toxicity is not diagnosed until after this time. Importantly, VISTOGUARD is about $80,000 and also needs prior authorization, which can be tricky and unreliable when you're working with the time constraint. Pre screening for DPD deficiency and dose adjustment based on CPIC dosing recommendations are imperative. CPIC is the Clinical Pharmacogenomics Implementation Consortium. In Kristine Ashcraft’s presentation with Cancer Patient Lab, she talked a lot about the highways drugs go through, and how CPIC gives guidance for DPYD, as well as other medications.

This is my mom in the middle. We like to say she was so easy to live with and so hard to live without.

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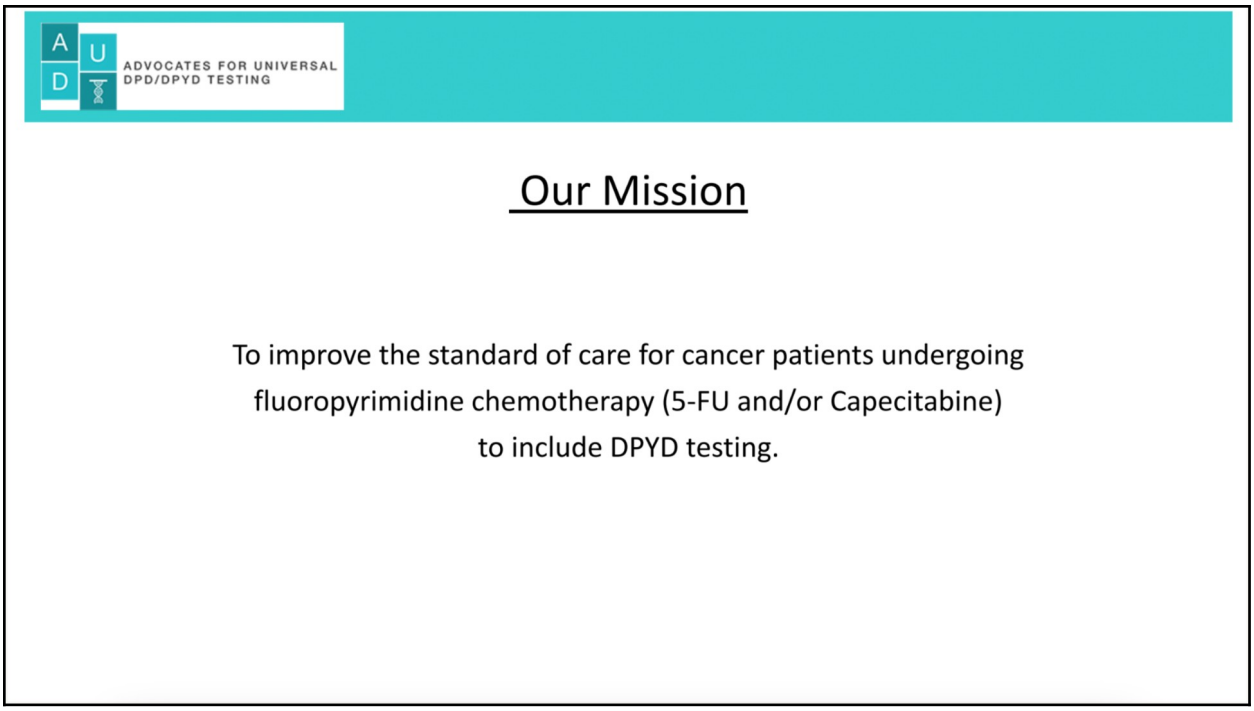
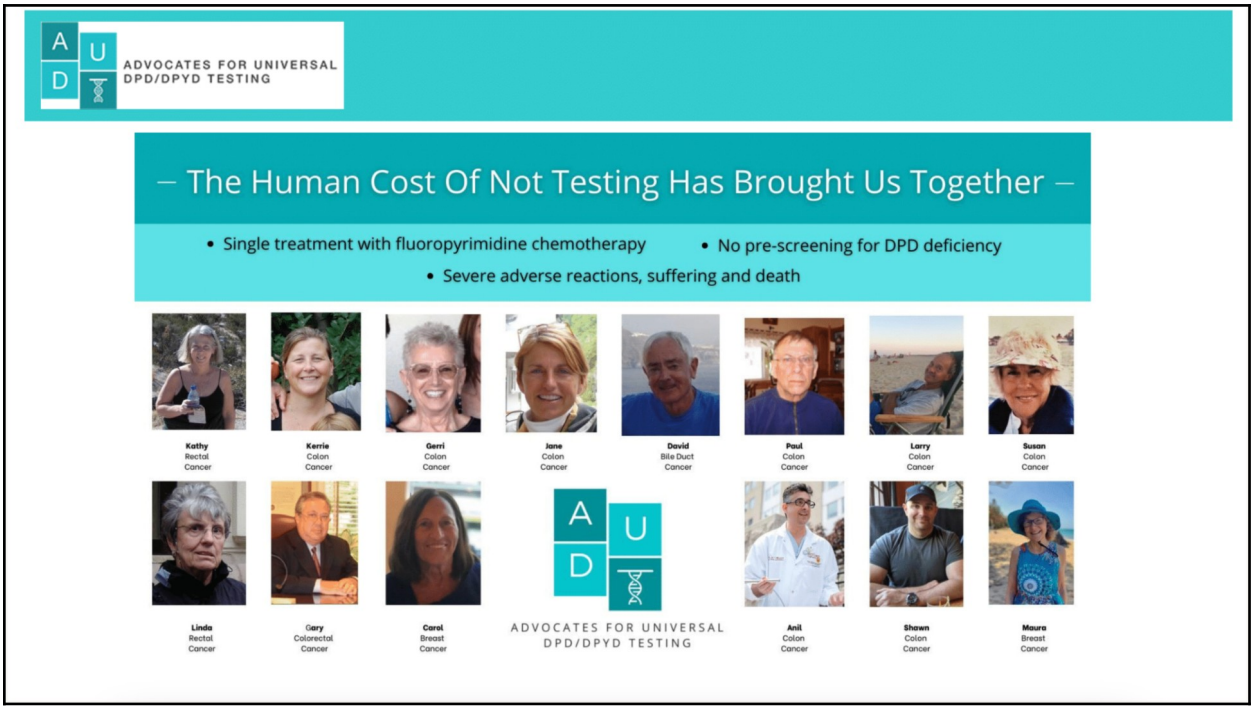
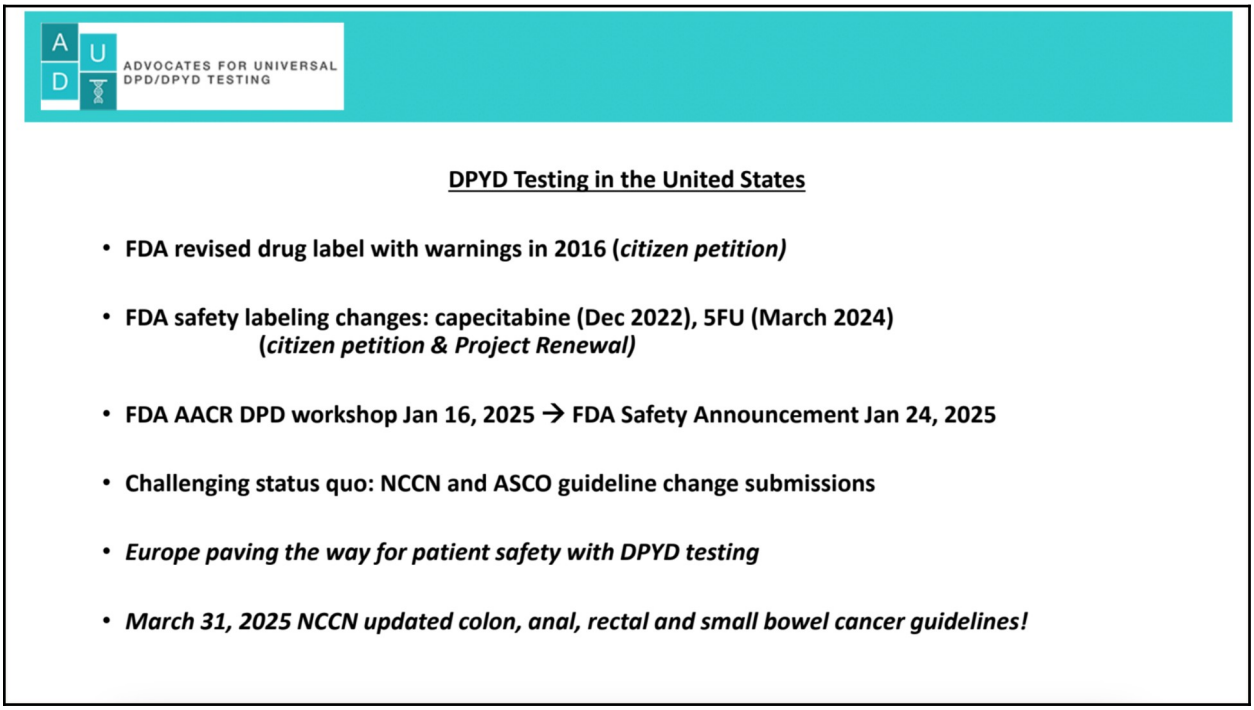


Our mission as a nonprofit is to improve the standard of care for cancer patients undergoing 5-FU and capecitabine chemotherapy to include DPYD testing.



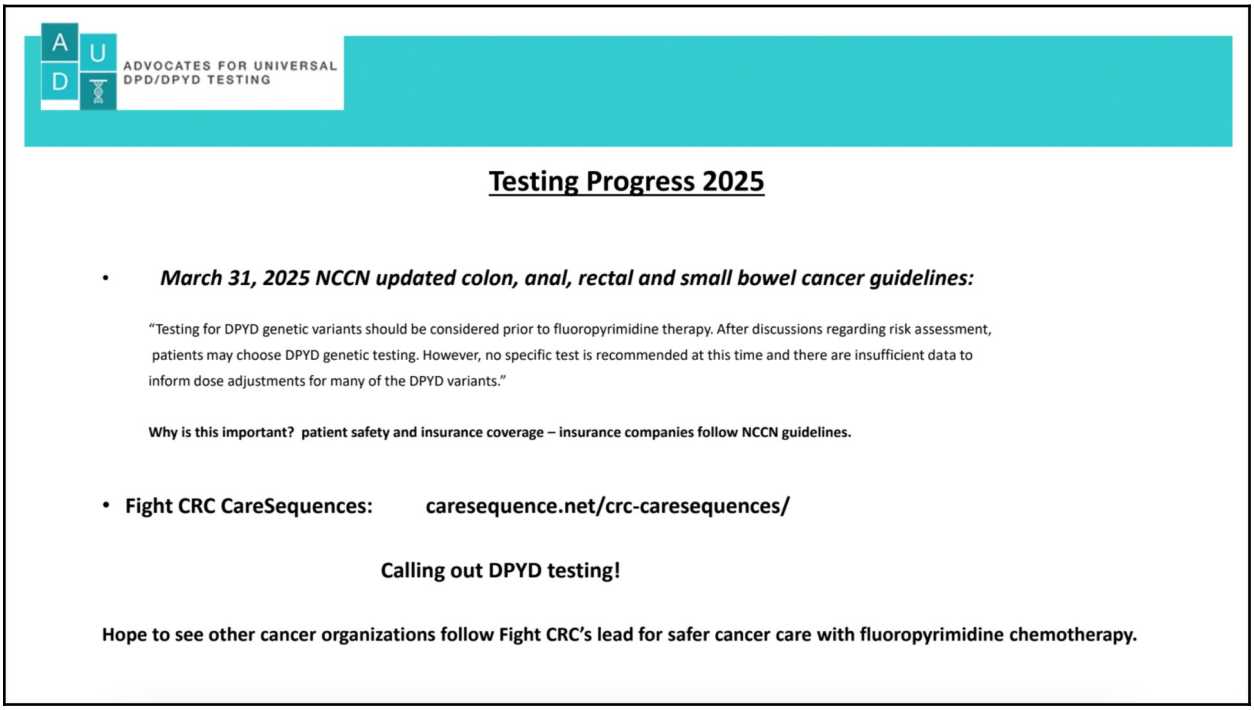
We became a nonprofit in 2022 after many families came together. The human cost of not testing is actually what brought us together. Single treatment, fluoropyrimidine chemotherapy with no pre screening, no information about the risks of DPD deficiency or severe adverse

reaction. The suffering is horrific with the sores from her mouth to her anus. Capecitabine patients end up with scabs on the outside of their body. They look like a burn victim. There are other nonprofits who have written letters of support for pre-treatment DPYD testing. Where does this stand in the United States?



The President of our nonprofit, Ken Surprenant learned that you can write a citizen petition to the FDA to revise drug labels. So in 2016 he did just that, and they dropped the word “rare” from

the drug label. He then wrote another citizen petition in 2020 with the help of our medical advisors, and they answered the citizen petition for capecitabine in 2022 and changed the labeling–the information was that now clinicians need to share the risks of DPD deficiency and discuss testing. They did not recommend testing, which is what we want to happen. 5-FU was changed in March of 2024. The FDA realized there was a problem. They co-hosted a DPD workshop in January of this year with AACR, where I was able to share and other advocates from our group came and were able to ask questions. And what we learned from that meeting is that clinicians were not aware of the drug label changes for capecitabine and 5-FU, so they issued an FDA safety announcement on January 24 of 2025. We've been trying to challenge the status quo of the NCCN and ASCO guidelines by changing the standard of care. You can submit guidelines change requests to each NCCN panel. You need to submit them on their website a month before their meeting, and you can go on the NCCN website and find out when each Cancer Panel is held. ASCO has one submission you can send in, and we did that as well. Europe is paving the way in DPD deficiency testing. It's recommended and in some countries, mandated. It has been recommended since 2020.



I'm also excited to share that just Monday, on the last day of colorectal cancer awareness month, the NCCN updated the colon, anal, rectal and small bowel cancer guidelines. They had in NCCN guidelines a comment of, “we do not recommend testing for DPD”. They took that out and replaced it with this sentence: “testing for DPYD genetic variants should be considered prior to initiating therapy after discussions regarding risk assessment. Patients may choose DPYD genetic testing.” They go on to say that there's no specific test recommended and that there's insufficient data for dosing. Well, we as advocates, disagree with the insufficient data to inform dose adjustments, because, as I mentioned before, we have the Clinical Pharmacogenomics Implementation Consortium dosing recommendations.

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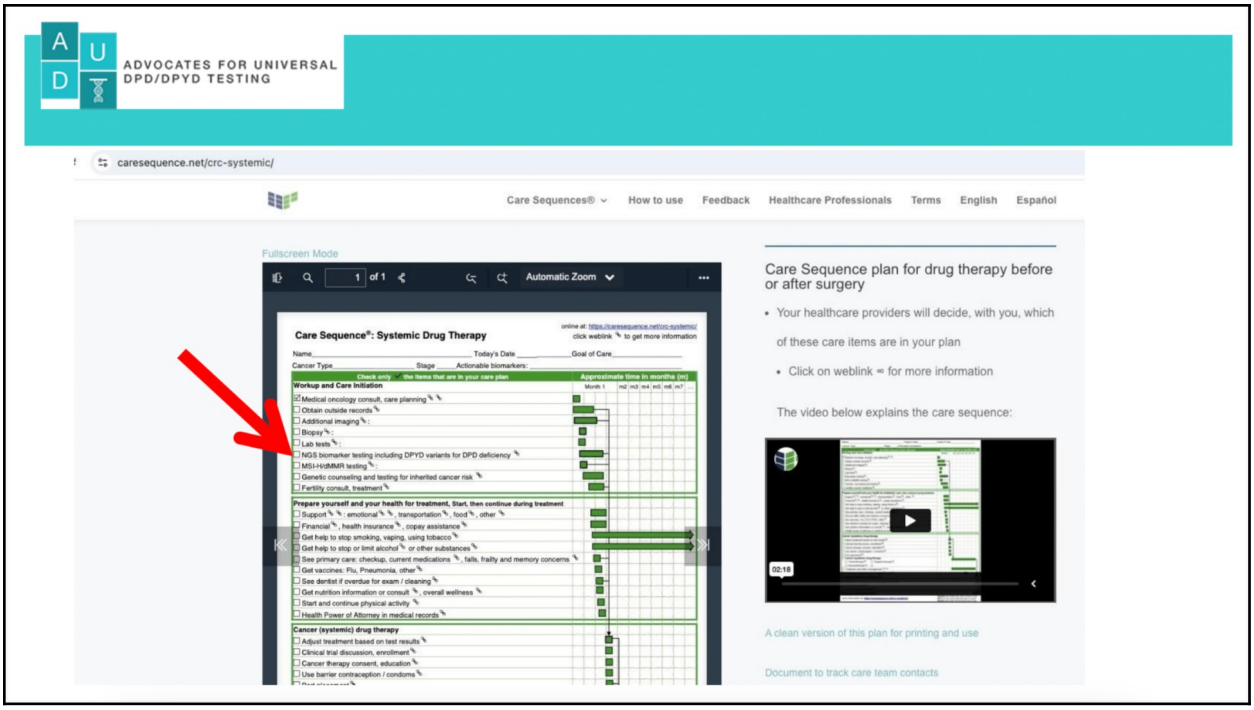
Why is this guideline change important? Well, first of all, patient safety. Secondly, insurance coverage. Insurance companies will follow NCCN guidelines, and often what we've heard is clinicians don't want to talk about another test with a patient, even if the test is only between $100 and $500 because they don't want to add more financial burden on patients.
Another wonderful thing I found out just recently is Fight CRC (Fight colorectal cancer) in their care sequences, is calling out DPYD testing. We hope to see other cancer organizations follow Fight CRC’s lead for safer cancer care.



So far I’ve talked a lot about colorectal cancer, but we're at the cancer patient lab to talk about all cancers. So this is an example of the sequence of care. I'm not sure if you've heard of them, but there is a company called 4R Oncology. They have done studies at cancer centers. Part of what they do is provide care sequences. If you go on their website for CRC systemic, they have sections for chemotherapy before surgery and chemotherapy after surgery, and both call for testing for DPD deficiency.

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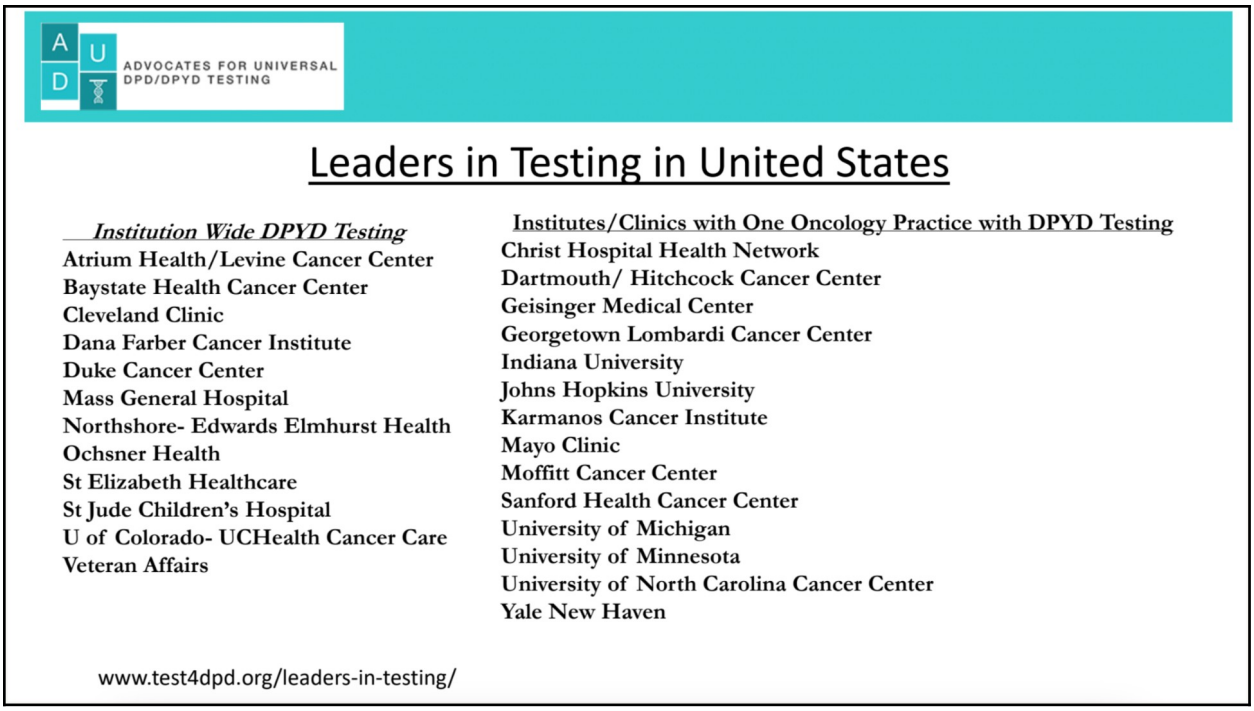

On our website, we are compiling a list of leaders in testing. This has been super effective for patients when they go in and talk to their provider and say, I want a DPYD test. The institutions on the left, they test all their patients unless patients choose to opt out, because their disease is advanced, or super advanced, and chemo has to start immediately. The other list are institutions or clinics where one oncology practices testing. For instance, at the University of Michigan, all breast cancer patients are tested for DPD deficiency. As a patient advocate, and knowing what can happen with this deficiency and chemo, I don't understand why they wouldn't just test all patients, but part of it is systems flow. Hospitals need to make it easy for the providers. One way is to just include it in their initial patient workup, so they don't have to do something more or check another box when they're talking to their patient.

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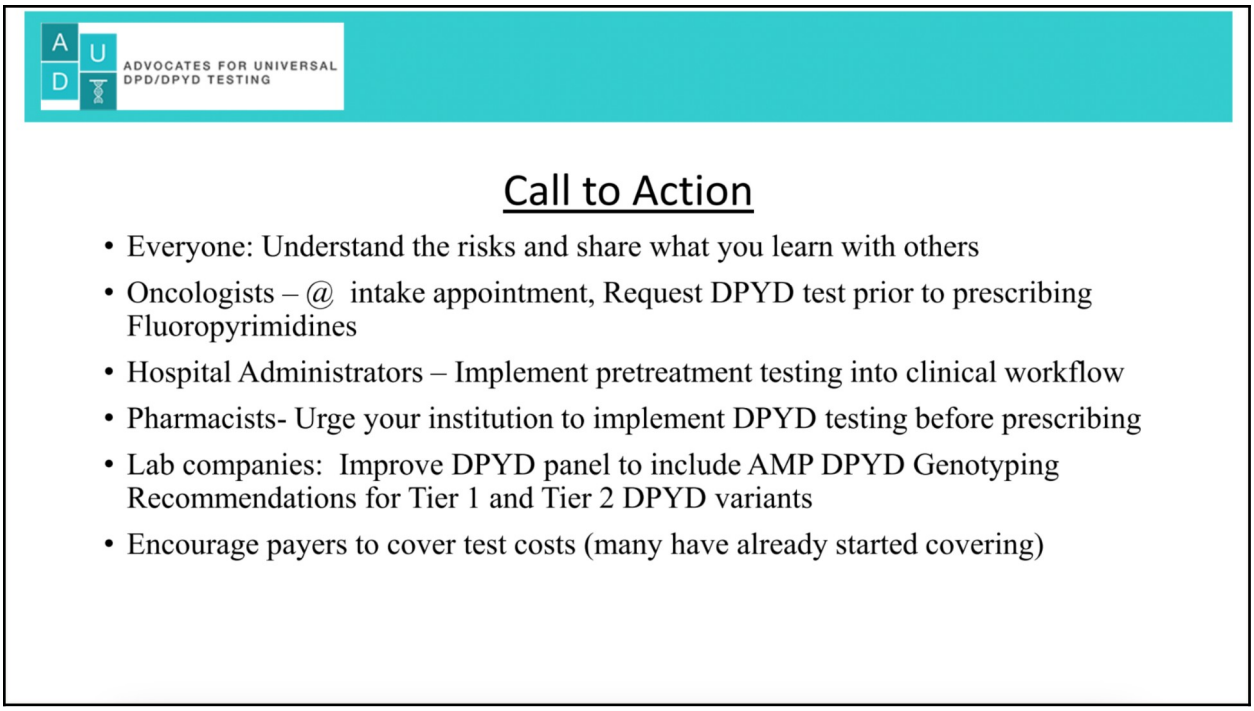

This is my call to action. Lab Companies can have a DPYD panel to include all of the Association for Molecular Pathology DPYD genotype recommendations. The Association for Molecular Pathology (AMP) in trying to standardize labs came out with a DPYD recommendation in August of 2024 and they have two tiers for DPYD variants. Tier one: must have DPYD variants. Labs should have these variants, and tier two: would be nice to have. At the FDA-AACR workshop, there was a clinical oncologist from Mayo Clinic in Arizona. She usually used the eight variant DPYD panel from Mayo Clinic, but after this AMP guideline came out, she now uses the Mayo Clinic full DPYD gene test, because the eight variant panel at Mayo Clinic does not include all AMP tier one recommended DPYD variants.

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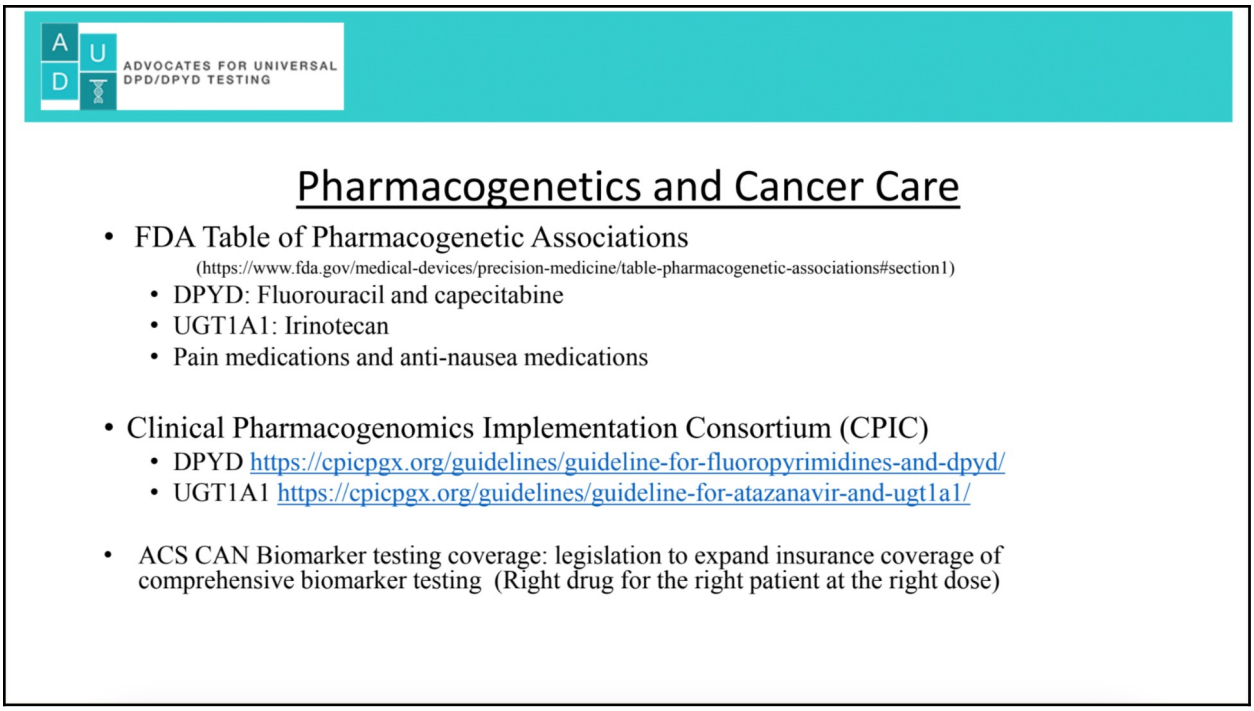

Pharmacogenomics and cancer care is exactly what DPYD is. It's a pharmacogenomic test. The FDA has a table of pharmacogenomic associations. You can go on there and look at the drug name and find out if there's any drug gene interactions. If you don't see the drug there, it doesn't have an association. They list all the associations, tell you what the drug is, what the gene is, a disclaimer, or why it would be important. So for DPYD, fluorouracil, and capecitabine, you can see the DPYD gene and that it's for poor and intermediate metabolizers. If a patient doesn’t know or isn't tested for DPD deficiency, there can be dire consequences. Irinotecan is a drug connected with the gene UGT1A1. And then, in cancer care, there are pain medications and anti nausea medications. And it's very important, because while we are 99.9% genetically the same, the 0.1% difference affects how each one of us metabolizes different medications. I mentioned the Clinical Pharmacogenomics Implementation Consortium, CPIC. They have guidelines for DPYD and UGT1A1. The American Cancer Society Cancer Action Network is trying to pass biomarker legislation in each state, which would expand insurance coverage for biomarker testing. And this is what pharmacogenomics is: the right drug for the right patient at the right dose. This is my nonprofit that advocates for Universal DPD/DPYD Testing. Thank you.

Brad Power 18:20
Is the DPYD test a blood test, or is it something they're doing off of your tissue biopsy?

Karen Merritt 18:49
It's a blood test, but they can also do a cheek swab.

Brad Power 18:57
Okay, so pretty low invasive in that domain of expense.

“Getting a Better Diagnostic (DPYD) into the Standard of Care” (Karen Merritt) [#137]

Karen Merritt 19:02
Yeah, I know. The Veterans Administration handles testing by adding DPYD testing to the initial patient workup. That way if you have a patient coming in and you know you'll likely treat them with this medication, the test is requested at the same time as other tests. You could even get that test back before some other results or biopsies.Timing used to be a reason why oncologists didn't want to order DPYD tests. But now, the test turnaround time is three to seven days, or three to 10 days, depending on which lab you're using.

Brad Power 19:53
While you were presenting, I looked up 5-FU(fluorouracil) and found it is part of FOLFIRINOX, a common standard treatment for pancreatic cancer. You listed colorectal cancer and a number of other cancers, but I didn't see pancreatic cancer on your list. Is there a reason for that?

Karen Merritt 20:24
We want any patient that's going to be treated with this medicine to be tested. I only included the panels that changed their guidelines. So "hepatobiliary", which I think is bile duct cancer, breast cancer, yeah, any cancer that uses FolFox, Folfiriniox, capeox, I don't know some of the other names. All in all, DPYD testing should be done prior to any cancer treatment plan that's going to use fluorouracil or capecitabine, .

Mike Camara 21:15
Yes, irinotecan is also a part of folfirinox. I think we should all be aware that there's another gene that you put on your slide. Yes, yes. So that's important for patients with cancer to talk with their oncologist as well.

Karen Merritt 21:31
UGT1A1, is that another gene?

Mike Camara 21:38
Okay, I have a question, another question, how do oncologists or pharmacists know? Where did they go to find out how to adjust the dose of the drugs that are affected by the genes the

Karen Merritt 21:51
Clinical Pharmacogenomics Implementation Consortium, CPIC, they can go there. Yes, they have dosing guidelines. So the Association for Molecular Pathology that I think I shared with you, they give guidance to labs on which variants have the most evidence or the best evidence that this could be toxic, and then CPIC actually gives the dosing recommendations.

Mike Camara 22:19
That's great, because I would think that one of the reasons why they don't order it is because they may not know what to do with the results. So that would be very important

Karen Merritt 22:29

Yes like for me, I had my DPYD gene test because this is hereditary, right? I inherited this deficiency from my mom. I had my DPYD test done through two places, Mayo Clinic, and when they sent my results back, the report told me, this patient should they receive fluoropyrimidine chemotherapy should have a reduced dose, and they give you a metabolizer status of zero to two, two being full function DPYD gene, and then 1.5, 1 or or zero. I'm a 1.0 so 50% dose is what my report shows. I also, I don't know if you have been hearing about Color Health lately in the news. I agree, David, I also got a Color Health test to test for some hereditary cancers and and their pharmacogenomics panel is really amazing. I mean, that opened my eyes up to some other medications that I've taken, like, I can't take Prilosec, but Nexium would work for me if I had heartburn, and it's just based on the different drug makeup and the way I process it. So I then I had all my children tested through Color, because it was easy. They sign up for it, they mail the tube, they spit in it, zip it back up and send it back to Color, in two to three weeks, they sent the results back. And I'm happy to say none of my kids inherited the DPD deficiency from me, the President of our nonprofit whose wife died two years prior to my mom. Identical story, Katherine. Their four children all inherited DPD deficiency from her. It used to be on the patient to tell the clinician that I have this, but with the labeling changes from the FDA, it's the clinicians now need to make sure they're discussing DPD deficiency with patients and talking about testing and the same should be for UGT1A1.

Brad Power 25:00
From the chat from Rick Davis: is DPYD a risk for gemcitabine use?

Karen Merritt 25:09
I am not an oncologist. I don't think so. We have a DPD deficient patient who was on capecitabine and gemcitabine.

Rick Davis 25:28
yes, it is gemcitabine is gems are okay.

Karen Merritt 25:31
So she got a DPYD test, and one of our medical advisors Dr Gabriel Brooks, out of Dartmouth Hitchcock, and he would have brought that up or let us know. So I don't believe so, but I would be a good question for an oncologist or a pharmacist.

Cindy Ness 26:01
Two questions. Is there any kind of clearinghouse or list of genetic, you know, tendencies toward bad reactions for chemotherapy drugs? It seems like there should be some clearing house that's available in terms of just advocating for patients, where we could say, okay, so and so you have pancreatic cancer. These are the ones you want to look for. So and so you have marginal cell lymphoma. These are the ones you want to look for and not just depend upon standard of care, care, oncology department, so forth, you know, offering this up, that's, that's one thing, maybe you could speak to. And then the other thing is, have any institutions to your knowledge been sued as a result of not, you know, informing patient and then there being

deleterious effects. And I asked this because, very unfortunately, that is often what moves the needle to change. You know, you know, stead best practices, so called Best Practices. Yes,

Karen Merritt 27:17
great question. Cindy, a clearinghouse would be a great resource for cancer patients. I think the only way that right now people can find that out, would be going to that FDA table of pharmacogenetics Association and looking at the medicine. And it's very unfortunate that science is, well, it's great that science is moving so fast, but I don't think that some of these, some of the science that's happening, you know, our oncologists are already they've been practicing for some of them for 30 years, and maybe aren't as up or aware about the science that is out there, and it does take, as we're seeing, a long time, to get it into practice. And that's why we've put in submissions, or we call them petitions to the NCCN to change guidelines, because we want more clinicians to be aware. And even if it's in the labeling, if it's not in the guidelines, they are not following labeling. One oncologist said, “as a community oncologist, I'm married to the NCCN guidelines, and so is insurance coverage. “

And the second question, lawsuits. Thank you for bringing that up. There was a lawsuit filed in 2019 by a widow against Oregon Health Sciences University, and this was before the labeling changes, but they were successful. Well, they settled that lawsuit two days before going to trial. The lawsuit was for $6 million. The settlement was $1 million, and it was all for lack of informed consent. They did not tell the patient. And this man had bile duct cancer. He had a whipple surgery, and from what I understand, that's a really complex surgery, he recovered from that beautifully. And this is what the surgeon said, “You're cured. You have no cancer. Go enjoy your life”. Then he went and met with his medical oncologist, who wanted to do cleanup chemo His wife said by day seven on capecitabine, things weren't going well, and just like my mom, once he went into the hospital, he never came home. And it was, and, it's like torture.

Cindy Ness 29:44
Did you think of suing with your mom? Or is there a statute of limitations? Because it sounds like there really needs to be more lawsuits.

Karen Merritt 29:53
Yes, there do need to be more lawsuits. We did think of it. We should have, in hindsight. Especially with the note in my mom's chart that said there was no way to know of this before she died. There are lawsuits going on. It's just the legal system like the medical system, it takes time. There are some individuals in different states looking for attorneys, because we have an attorney that we know in Washington state that has a case that will go to trial in February of 2026, 42 year old man, six month old son, capecitabine for colon cancer, very sad, and a couple other cases in in different states, we had a patient that reached out to us from our website, and so this is also a stage one bile duct cancer. She had a second opinion, and she also had at a NCCN member institution second opinion oncologist, and she also had a Community Oncology colleges. She asked them for a DPYD test because she had read about it, and she saw our website, and they both told her, Oh, we don't do that testing in the United States. And she said, look at this list right here. Yes, we do. So she pushed. They finally conceded to her request. She

got the test. She has the most common variant, she needs a 50% dose reduction, and she called to let us know that if she hadn't been tested, she and her husband and kids know or they feel that she would have died.

Cindy Ness 31:31
Sounds like you need a class action suit?

Karen Merritt 31:35
Yeah, what we've been told is we need to get some wins before we can go to like that big battle, right? We need to win a few little wars before the big one. But it takes time, and unfortunately, 1000 patients die every year. That's like 10,000 patients since my mom passed in 2014 alone.

Brad Power 32:10
Question from the chat from Bill Passman: How much has the cost changed for the DPD test over time?

Karen Merritt 32:16
Oh, significantly. I mean, in 2014 for my mom, it was probably going to be if they had tested $1,000 you can get it through some lab companies for $200 and one of the lab companies, I know I was just at a conference that they were there also one ohm, They have their test is $199 and they have a if you can't pay that, they have a patient assistance program. Mayo Clinic. There are eight variant panels, 285, full gene at Mayo Clinic. $585 and then I mentioned earlier, color genomics, when I had that done, my last child had that done last year was $288 and that wasn't just for DPYD,

Brad Power 33:13
The patient assistance program is an interesting avenue. Brian, you know we were talking about how you get access to drugs. We should check into that, because the price for some of these treatments is very high, and then the insurance company may deny it, but if you go to the manufacturer, they might have a way around that. So it's worth checking.

Karen Merritt 33:34
it's great to ask. Call those companies. I was just talking to somebody else, and they this was a different it wasn't cancer, but she had this huge expense, and she's like these drug companies want the drugs to stay out there, right? So she called the drug company, and they're paying her co pay. She couldn't afford the co pay. The drug company is going to pay her co pay.

Brad Power 34:04
Question from Dennis Watson: Is the test included in any of the broad germline hereditary panels from companies like Myriad?

Karen Merritt 34:14

I don't know about Myriad. I do know that Tempus has a panel where they are testing your tumor, I believe, but you can do an add on for DPYD. I'm trying to get Tempus to if they're testing you for your tumor, why not just include DPYD and UGT1A1.

Rick Davis 34:45
I'm looking at the Color panels right now, and not all the Color panels include DPYD, so just because you had a Color test may not necessarily mean you tested for it.

Karen Merritt 35:07
Yes, you have their extended panel, right?

Rick Davis 35:11
I just wanted to point that out to everybody, because I just got a Color test and I didn't see anything about that.

Karen Merritt 35:20
I and if that's the case, Rick, I would call them and ask them, as it's my understanding. Sometimes, when they get something for like a test from somebody, they're gonna or a sample, they're gonna test it all, because that's what they do on their panel, but they're only gonna report out to you on what you requested. So I would ask, call back and ask,

Rick Davis 35:47
I would this was part of a large clinical trial called promise for people who have prostate cancer, and I suspect they just use a very basic thing for the trial, but it's a good that's a very good suggestion. But I just want to be sure people think just because they got a color test, they got tested. That's that may not be the case.

Karen Merritt 36:12
I appreciate you saying that, and I should remember to say the expanded test. But I would call, if you were in that trial, I would call and ask they have they have that information, I

David Plunkett 36:30
DPD deficiency is something entirely new to me. So my question is, are there consequences to it other than this intolerance for certain chemotherapies there,

Karen Merritt 36:43
there is a, I don't know what the term is, so most people with DPD deficiency have no outward signs. There is one type of DPD deficiency that's super rare that you do have signs as as a youth. And I am not educated on that at all.

David Plunkett 37:02
Well, should anything prompt a request for the test, other than upcoming chemotherapy?

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Karen Merritt 37:09
I don't, I don't believe so, not for an adult. I think the the other form of DPD deficiency would be evident as a young child.

Brad Power 37:25
Question from Dennis Watson in the chat: Do patients with this have different response rates? IE, if you have to lower the dose to reduce adverse events, does that mean lower response rates and outcomes? If so, it seemed trying an alternate drug path may be more valuable than a reduced dose of the frontline drug.

Karen Merritt 37:49
That is one of the concerns of the NCCN, and why they have said they won't reduce the dose. But first off, there are studies that show that it does not reduce the efficacy, if by reducing the dose. And like Kristine Ashcraft shared with this group, if you are RA for instance, my metabolizer status is like 1.0 so I have a half functioning DPYD gene. So that means that my body can only process half the dose. So in effect, I am getting the full dose for my genes and our response to NCCN when they say, reducing the dose might not cure the cancer. Well, in the case of most of the loved ones in our group, there is no curing the cancer if you've killed the patient because they have an overdose of 5-FU or capecitabine.

Brad Power 38:52
We’ve had conversations about minimum effective dose and maximum tolerated dose, and most of the drugs have been approved at a level of maximum tolerated dose, and then that's the way they go into the guidelines. And so the notion of personalized dosing is, is a reasonable thought process that people could be getting the minimum effective dose personalized based on their metabolism, metabolization of that drug.

Karen Merritt 39:19
It seems like clinical trials too for new drugs are having to include or look for the lowest effective dose, right? And pharmacogenomics, personalized precision medicine.

Brad Power 39:33
Chris Apfel has put a couple things in the chat. Maybe, Chris, you could also comment on this, because I know that when you are running your functional tests, you also do them at different dose levels.

Chris Apfel 40:00
First of all, I'm very saddened to hear about the loss of your mother. When I listened to that, it made me really, really angry, and in particular, because this is known. Every oncologist knows that, and so that the fact that this was for a long time, not in the guidelines, actually shows that there are other aspects than patient safety that play a role, how, how practice, how oncology practice is, is practice? In reality, which are health economic considerations. And I think that's behind it. There is, there are a few other mutations as well, actually, variants, polymorphisms. I've put a little table in there, but the one that you are hitting on is by far, well, clearly the most

important one, or the most frequent one with fatal outcomes. In regards to the dose adjustments, the effectiveness on a tumor is is clearly dependent on the dosage that the tumor gets. And if we think about met metabolism, and you are low metabolizers, and therefore with, let's say, a third of the dose, you still have twice the concentration in the blood. If you, if you would reduce the dose to a level that you actually have effective blood concentrations, there is no reason not to make the argument it would be less effective. I actually think it's pretty clear cut. And if, if we are doing our functional profiling, we can actually see which tumor is responding to which drug, and we can actually see those response curves that are often fairly flat. And it means, what I mean with that is sometimes you need an order of magnitude difference to get from 70% kill to to 90% kill, and it's 1010, fold difference in drug dosage. So you should always consider toxicology. And the argument that this would be less effective is, is, is a very weak argument, and especially when you're a slow metabolizer, when you because you, if you give, if you're if you only metabolize it 1/5 let's say, fifth of the speed, and you give 1/5 of the dose, you still have the full effective plasma concentration for which the clinical trials were designed. So that argument, those adjustments would make it less effective. That's scientifically not right, sorry, right.

Karen Merritt 42:48
So I have two things, Doctor, thank you for that. I'm looking at your chart of DPYD. How many variants is that? Is that four?

Chris Apfel 43:15
I listed three, but those are just examples. What I missed listed here are four of them, but there are some more. There is a Cy, p2, 2d, six, which is a very common one. There is this argument tamoxifen, for example. That's one part. There are a few others. They're not as common. And also a little bit more controversial. But CYP, 2d, six, which I didn't list on on that table, I believe that's another one that also could easily be tested for. Yes.

Karen Merritt 43:52
When the NCCN just updated those guidelines, they said that there's no concrete evidence on how to reduce dose which, as an advocate, I disagree with. I think those CPIC guidelines would be great for dose adjustment, and that's exactly what the institutions that have implemented testing are using. And I believe CPIC has guidelines for CYP2D6 also,

Chris Apfel 44:27
so, good, good. So, so, so the argument there is no evidence, is really a I hear this very often and and what they what this is actually it's in different form to say there are no prospective, randomized control trials with 5 million patients that have actually shown that it makes a 1% difference. And and, and evidence is not a binary parameter, right there? There are different levels of evidence. If you look at the Bradford Hill criteria, there are eight criteria for level of evidence, or for for what is, what distinguishes a correlation with causality, or what makes a causality likely, and, and, and it. And there are many arguments for the there is a lot of evidence for that. What, what they often say is, well, there, there aren't sufficient prospective clinical trials for that particular individual case, and then to really to prove it, to find the ultimate proof, but, but

the evidence is there. There's no question on that. So they, they should not be. I think one should push back on that, and I'm happy to help you and communicate with you offline. I think this is outrageous, and one really needs to do something about it.

Karen Merritt 45:50
Yes, thank you. I woke up in the middle of the night trying to figure out, oh my gosh. I thought that this year going to ASCO annual meeting, we would be celebrating a change of guidelines. But yet, I wake up in the middle of the night figuring, how can we use this patient who got her testing? It was DPD deficient, and then I read you can't use case reports as an abstract at ASCO.

Roger Royse 46:23
This might be a little off topic, but it kind of reminds me so, by the way, so I was at Stanford, I had all of the chemo drugs you mentioned, and some more. And I do believe I had that test, because I remember to start, as a patient, I'm on a need to know basis, and I guess I didn't need to know what tests they were running, but they told me I was okay to take the chemo. So I think that institution uses it. But there's so much more they don't tell you about chemotherapy drugs than they do and and I'm hearing a lot more about metronomic dosing, or this, which you're saying minimum effective dose, dosing of chemo, and maybe spreading it out over a longer period of time, because I got the maximum tolerable dose and then some. And what I'm starting to worry about now is what I've learned now that Nope, because they gave me a long list of side effects, and it was like two pages long, and I had all of them, but they didn't tell me everything, and I understand now there's, there's quite a bit of evidence that the chemotherapies that I had, almost every one of them, results in probably a 10 fold increase in leukemia risk. And I don't know if I'd have done the same thing if I'd have known that then, and this is sort of the tip of the iceberg of things that patients don't know and are not informed about and don't really have a have much of a say in, because we just don't get the information. And, and, and I really feel like it's, it's just, it's standard of care, and I think it's, it almost starts with FDA guidance. I think you're on the right track on that. This might sound odd for an attorney to say, but I'm not sure litigation is the right way to get there in this case, because it's hard to sue a doctor. Just look at the way you know some of the things they do. On the other hand, every one of them knows about you know what standard of care is and what the FDA is approved and, oh, what your insurance is going to cover? Fact, a lot of times I feel like my, you know, the insurance company was deciding what treatment I get more than anybody else, so I feel like that's probably the right path. So, like, I say it's a little off topic, but if you got any comments on that, I'd love to hear them.

Karen Merritt 48:39
I just went to this interesting and very unique cancer conference in Louisiana. So in Louisiana, they have the cancer advocacy group of Louisiana. They call it cagla. It's a non profit to make cancer care better in the Gulf South and State of Louisiana. And they, they, I at one of the exhibit booths, a drug company, somebody, they told me about the saltz regimen. S, a, l, t, z, it's a doctor. I believe he's at Memorial Sloan Kettering. I asked the guy, is he still practicing? I don't think so. Well, I think he still is. And it was like, I think, I think the regimen that he does, and he, I

read about it just yesterday for healthy patients, or patients other than their cancer, right, that are strong. I think it's FOLFIRINOX. He's like, he just, like, gives them a really strong dose all up front, because it's that's 5-FU, irinotecan and oxaliplatin. I can't find the research, but a lot of patients did not do well in that regimen. Because you're right. You're giving so much, why not have a reduced dose over a longer period of time, so that you actually want to stick with your treatment too Right? Like, if you're not testing patients, or you're giving them too much for them, and then they don't want to stay on their treatment, because that was so horrific, or right? But if you could give them a lower effective dose over a long period of time, right? And Richard Pazdur, the director of the Oncology Center of Excellence here, had a paper out in 2020 about when less is more when it comes to chemotherapy.

Roger Royse 50:45
It's an economic issue, because I've been thinking about this a lot over the last three years, and I know when I walked into that chemo room, they were packed. They were oversubscribed, and I was only there one day a week, like everybody else, if I had to go back every day and, you know, get a smaller dose, but every day, there's no way that facility could handle that much, you know, that much, that many patients. So I almost could kind of think that maybe that's the reason that's the protocol, but that's just my cynical mind at work.

Karen Merritt 51:20
I think what I've heard too, is that's why a lot of people would prefer capecitabine-an oral pill where they could take it at home, versus in an infusion center like that. But there are complications with that too, like you have to be well hydrated. You need to drink it with something that isn't going to automatically inflame your esophagus, and yeah, it definitely seems like patient safety and patients and families are demanding this now, right? Like, how can we want to cure the cancer, but we want to make sure that the patient has quality of life and will stay on the treatment and is safe?

Brad Power 52:05
You're onto something big there: the first thing was to make sure the patient lives. Then the second one was the treatments are getting good enough, and then people are having a long life and living with the side effects of the drugs that they took. Let's look at those. Could we swap out a more toxic drug for a less toxic drug? We just had a session which I should plug you can see the notes in the learning sessions with Javid Moslehy, who was looking at a number of chemotherapies and their effect on the heart and downstream heart and cardiovascular issues. So that's emerging as a more common topic, where keeping the patient alive was the first thing, but now it's more of a chronic disease. How do we have a good quality of life, living with the treatments that we're getting?

Rick Davis 53:14
This raises an idea for another session to talk about dosage and toxicities. We right now are about to go to a pharmaceutical company that we work with who has a phase one phase two trial in process for a radionuclide and the benefit of this radionuclide is you can deliver treatment in two weeks rather than 36 weeks, which makes a huge difference for a patient. Problem is

when you look at the toxicities, they're much, much greater. So the question then is, well, is there some spot between two weeks and 36 weeks where there is a benefit? However, maybe, maybe we can go a little bit longer and we don't have so many AES and so it just, it seems it's right on point, and what, soon as I hang up, I'm going to talk to one of my doctor advisory board members and figure out how we go back. So just a thought. But I think this happens in a lot of places. Karen, looks like you want to say something on that.

Karen Merritt 54:39
Oh, no. I was just shaking my head, and I, you know, sometimes I'll I meet oncologist, and they're, they're not a fan of testing. this one doctor-he said I'm retiring next year, but I would never start a patient on full dose 5-FU. I start them at 50% dose, and I give them my mobile number, and I say. Right? If your symptoms are any worse than this, this and this, yeah, call me something's wrong, right? But that's not, that's not the oncologist that's just starting to practice on their own and is looking for the recipe book of the NCCN guidelines, right? He was a community oncologist here in the state of Washington in a small town. It's nuanced, but patients need to be made aware. And I, yes, I agree. Like, why? How can we get less toxicity? But I like, the timing is probably better. But this woman I was telling you about Emily, the patient who had to push back to get her testing she's doing really well on the low dose and she's able to to work and play with her kids.

Rick Davis 56:00
Patients should always be prepared to go back to their oncologists and talk to them about lowering the dose and maybe increasing the frequency if they're having comorbidities and side effects. Patients don't feel empowered to do that.,

Karen Merritt 56:21
that's important, right there? Patient empowerment, because we trust our doctors, right? My mom, we wanted her to get a second opinion. She wouldn't hear of it. She loved her oncologist she was super comfortable and confident in her doctor. So asking for more and empowering patients with information, right? Saying, No, this is look at all these places where they're doing this testing, whether it's DPYD, UGT1A1.,I think Dr Chris Apfel put in the chat. There are some other genes to be on the lookout for, and I've heard of them,Very important for patients to be empowered. And we need to do what you are all doing and empowering patients is super, passing all this information along and sharing with I mean, I look at the different people from different places just here on the screen. Very important. Thank you so much for what you guys are all doing. And ladies, thank you for watching.

“Getting a Better Diagnostic (DPYD) into the Standard of Care” (Karen Merritt) [#137]

CHAT DISCUSSION

00:30:11 Rick Davis, AnCan Foundation: Is DPYD a risk for gemcitabine use?
00:34:14 Bill Paseman: how’s much has the cost changed over time?
00:35:05 Mike Camara: Where do pharmacists or Oncologist go to find out how to adjust the dose of 5-FU or Capecetabine
00:36:48 Dennis Watson: Is it included in any of the broad germline hereditary panels from companies like myriad
00:41:20 David Plunkett: Are there consequences to DPD deficiency beyond chemotherapy tolerance?
00:42:50 Dennis Watson: Do pts with this have different response rates (i.e. if you have to lower the dose to reduce adverse events - does that mean lower response rates/outcomes? If so, it would seem trying an alternate drug path may be more valuable than a reduced dose of the front line drug. Thoughts?
00:53:54 Rick Davis, AnCan Foundation: From COLOR.... ;Medication Response Genetic Test: Analyzes 20 genes that affect how your body
processes medications, helping guide safer, more effective treatments. These genes include:
ABCG2, CACNA1S, CYP1A2, CYP2C cluster, CYP2C19, CYP2C9, CYP2D6, CYP3A4, CYP3A5,
CYP4F2, DPYD, F5, G6PD, IFNL3, NUDT15, RYR1, SLCO1B1, TPMT, UGT1A1, VKORC
01:05:22 Rick Davis, AnCan Foundation: Thanks so much for putting this on our radar, Karen - you too Brad. We will ensure our pancreas cancer participants are made aware of DPYD. Please do not hesitate to reach out rd@ancan.org https://ancan.org
01:12:08 Dr. Chris Apfel: Karen, thank you so much for your wonderful presentation and thank you for your initiative and how you are changing clinical practice. Would love to support you wherever I can. Patients need to know!!!
And need to understand that they have to advocate for themselves.