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Risk vs Prevalence: Weighing Routine DPYD Variant Testing Prior to Fluoropyrimidine-Based Chemotherapy

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Guest: Dr. Nicholas Larkey is a clinical chemist and an assistant professor of pathology at the University of Virginia in Charlottesville, Virginia.

Bob Barrett: This is a podcast from *Clinical Chemistry*, a production of the Association for Diagnostics & Laboratory Medicine. I'm Bob Barrett.

More than 100,000 new cases of colon cancer will be diagnosed in the United States in 2025, and most of these patients will be treated with fluoropyrimidine chemotherapy. These drugs are metabolized by the DPD enzyme, which is encoded by the *DPYD* gene. For many years, it's been known that certain *DPYD* variants reduce enzyme activity leading to adverse reactions, including treatment-related death when a standard dose of chemotherapy is administered.

As a result, many labs have begun offering *DPYD* genetic testing, allowing the identification of poor metabolizers who would benefit from a reduced dose or a different treatment altogether. Prior to April 2025, laboratorians largely had to chart their own path by determining which variant should be evaluated and how testing should be performed. This changed with the release of the updated National Comprehensive Cancer Network's clinical practice guidelines for colon cancer.

A News & Views article, appearing in the October 2025 issue of *Clinical Chemistry*, highlights these new guidelines and describes efforts to improve the care of patients with colon cancer through optimal laboratory testing. In this podcast, we're joined by the article's lead author. Dr. Nicholas Larkey is a clinical chemist and an assistant professor of pathology at the University of Virginia. He is the director of point-of-care testing and associate director of the clinical chemistry core laboratory. So Dr. Larkey, let's get to the basics. First, just what is *DPYD*?

Nicholas Larkey: Thank you for your question and thank you so much for having me on your podcast. *DPYD* is a gene that encodes the enzyme dihydropyrimidine dehydrogenase, or DPD. If we remember our introductory biochemistry, DNA and RNA are made up of purine and pyrimidine nucleotide bases. The purines include adenine and guanine, and the pyrimidines include cytosine, thymine, and uracil.

The enzyme DPD is responsible for the first catabolic step in the breakdown of uracil and thymine. Some individuals have different variants of the *DPYD* gene leading to variants of the DPD protein, which can potentially cause DPD deficiency if the protein is dysfunctional. This can lead to a buildup of pyrimidines in the body of these individuals as the catabolic pathway is diminished.

Bob Barrett: So different *DPYD* variants can potentially lead to DPD deficiency. What does DPD deficiency have to do with chemotherapy?

Nicholas Larkey: That's a great question. Many solid tumors, including colon cancer, are treated with fluoropyrimidine chemotherapy drugs such as 5-fluorouracil, or capecitabine. The breakdown of these drugs in the body relies on the DPD enzyme, just like other pyrimidines. For individuals receiving fluoropyrimidine chemotherapy that have a DPD deficiency, the fluoropyrimidine drugs are not broken down as effectively, potentially leading to toxic effects and even treatment-related death as the drug stays in the body for longer.

This falls in the realm of personalized medicine, specifically pharmacogenomics, or PGx, where a person's genetic makeup can affect how they metabolize different medications. In the case of DPD deficiency and other enzymatic deficiencies, pharmacogenetic testing can be performed before drugs are administered, so the drug treatment plan can be tailored to the patient. A recent meta-analysis of 35 studies, including 13,929 patients that were treated with standard dose fluoropyrimidines, found that carriers of *DPYD* variants had a 25.6-fold increased risk of treatment-related death when compared to patients without *DPYD* variants.

Therefore, there is great benefit to those with *DPYD* variants to have pharmacogenetic testing performed before receiving fluoropyrimidine chemotherapy.

Bob Barrett: Of course, personalized medicine and pharmacogenomics are hot topics in the laboratory field, and it seems from what you've indicated that *DPYD* pharmacogenetic testing is not new. So, what is the change here?

Nicholas Larkey: As I stated earlier, pharmacogenomic testing can be performed before drugs are administered so that the drug treatment plan can be tailored to the patient. However, before the recent guideline changes, *DPYD* testing in colon cancer was not a routine practice. Prior to April 2025, multiple practice groups had been asking agencies such as the National Comprehensive Cancer Network, or NCCN, or the American Society of Clinical Oncology, ASCO, to update their

practice guidelines to make this testing routine for patients who would receive fluoropyrimidine therapy.

Finally in 2025 in April, the NCCN clinical practice guidelines in oncology for colon cancer updated its guidance for *DPYD* variant testing and now recommend routine pharmacogenomic testing for this gene.

Bob Barrett: You've talked about pharmacogenomic testing for *DPYD* variants. Are these tests standardized and are there any specific alleles that should be tested for?

Nicholas Larkey: So that's a great question. A consensus document pertaining to the standardization of *DPYD* genotyping was published in October 2024 by a joint consensus clinical pharmacogenomics working group of six organizations, led by the Association for Molecular Pathology, or AMP. The AMP working group recommended a minimum set of seven Tier 1 *DPYD* alleles that should be tested based on clinical impact, allele frequency, availability of reference materials, and technical feasibility.

There are also six Tier 2 alleles that were recommended as well with these alleles meeting at least one, but not all four of the Tier 1 criteria. They stated that in the future, Tier 2 alleles may be reclassified as Tier 1 alleles if they satisfy the other requirements. The new NCCN guidelines only include recommendations for testing for four of the most common and best characterized of the seven Tier 1 alleles that are included in the AMP document.

Bob Barrett: The title of your paper mentions "Risk vs Prevalence." How does this play a role in this testing?

Nicholas Larkey: So, when thinking about any type of laboratory test used for screening purposes, the topic of prevalence must be discussed when using a screening test in the population. The percentage of the population that have the disease in question here would be the variant alleles in question. It's important to know in most populations the prevalence of the Tier 1 *DPYD* variance is less than 1%. While this prevalence is very low, the risk potential for toxicity and treatment-related death is high in individuals who are DPD deficient. Therefore, routine screening will have a great impact on this small population of patients, but no impact on the majority of patients.

The risk benefit analysis for making pharmacogenomic testing routine becomes a risk prevalence analysis when the benefit of the small population of patients is well documented, even with the prevalence of Tier 1 *DPYD* variants being less than 1% multiple practice groups and finally, the NCCN advocate

for routine testing in colon cancer patients to prevent fluorine toxicity.

Bob Barrett: Finally, Dr. Larkey, what can be done for these individuals who need chemotherapy but are DPD-deficient?

Nicholas Larkey: The Clinical Pharmacogenetics Implementation Consortium, or CPIC, guideline for dihydropyrimidine dehydrogenase genotype and fluoropyrimidine dosing provides dose reduction protocols based on whether patients are categorized as normal, intermediate, or poor metabolizers of pyrimidines. These dose reduction protocols have been shown to decrease both the likelihood and degree of toxicity in these patients. For poor metabolizers, CPIC recommends avoiding fluoropyrimidine chemotherapy altogether if possible. In patients who have experienced fluoropyrimidine toxicity, uridine triacetate, a uridine analog and competitive inhibitor to the fluoropyrimidines, is used as an emergency treatment and has been proven to be effective within the first 96 hours of exhibited toxicity.

Bob Barrett: That was Dr. Nicholas Larkey from the University of Virginia in Charlottesville, Virginia. He wrote a News & Views article in the October 2025 issue of *Clinical Chemistry,* highlighting recommendations for pharmacogenomics testing in patients with colon cancer and he's been our guest in this podcast on that topic. I'm Bob Barrett, thanks for listening.