Lives at Risk from Below Standard Guidelines for Genomic Testing

Dr V.S. Kapoor - October 29, 2024

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Disclosures

None

Interventions for preventing ophthalmia neonatorum

Vimal Scott Kapoor, Jennifer R Evans, S Swaroop Vedula Authors' declarations of interest

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Abstract

Available in English | Español | فارسی | Français | ภาษาไทย | 简体中文

Background

Ophthalmia neonatorum is an infection of the eyes in newborns that can lead to blindness, particularly by *Neisseria gonorrhoeae.* Antiseptic or antibiotic medication is dispensed into the eyes of newborns, o soon after delivery to prevent neonatal conjunctivitis and potential vision impairment.

Objectives

1. To determine if any type of systemic or topical eye medication is better than placebo or no prophylaxi ophthalmia neonatorum.

2. To determine if any one systemic or topical eye medication is better than any other medication in pre neonatorum.

Search methods

We searched CENTRAL, MEDLINE, Embase, LILACS, and three trials registers, date of last search 4 Octobe references of included studies and contacted pharmaceutical companies.

Selection criteria

We included randomised and quasi-randomised controlled trials of any topical, systemic, or combinatic used to prevent ophthalmia neonatorum in newborns compared with placebo, no prophylaxis, or with e

Data collection and analysis

We used standard methods expected by Cochrane. Outcomes were: blindness or any adverse visual out months, conjunctivitis at 1 month (gonococcal (GC), chlamydial (CC), bacterial (BC), any aetiology (ACAE (CUE)), and adverse effects.

Main results

Outline

- DPYD gene testing to reduce risk of death from fluoropyrimidines
- Case of my brother, Dr Anil Kapoor
- Global variation of Guidelines
- Critique of the American NCCN Guidelines
- Gold standard of Guideline development
- Equity aspects of my Guideline development
- Hope and Solutions

- What if I told you that I was giving you a drug which had a risk of death of 1 in 500, would you be concerned with that risk of death of the drug?

- What if I did NOT tell you that there were 5 ways to significantly reduce this risk of death of this drug from 1 in 500 to 1 in 1000 or less, would it bother you?

- What if I told you the cost for any one of these methods/tests to reduce your risk of death was between $50 to $300? Would you pay for one or more of these tests/ methods ?

Let me share **one** of those **five** ways to reduce your risk of death from this drug:

- What if I told you that you could have a genetic variant in your enzyme that is supposed breakdown the drug, causing toxic metabolites, present in **2-8%** of the population, that would **increase your risk of dying** from this drug to **as high as 1 in 30** depending on the variant you have?

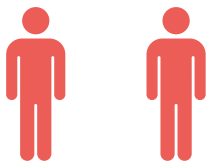
- What if I told you by doing a **simple blood test** to see if you have one of these genetic variants, that costs no more than **$300** you could reduce your risk to **less than 1 in 1000**? Would you want the test?

NO SCREENING TEST

GIVEN SCREENING TEST

1000 PEOPLE GIVEN FLUOROPYRIMIDINES

1 IN 500 RISK OF DEATH FOR GENERAL POPULATION



NUMBER OF DEATHS

1000 PEOPLE GIVEN FLUOROPYRIMIDINES

1 IN 1000 RISK OF DEATH

NUMBER OF DEATHS

NO SCREENING TEST

GIVEN SCREENING TEST

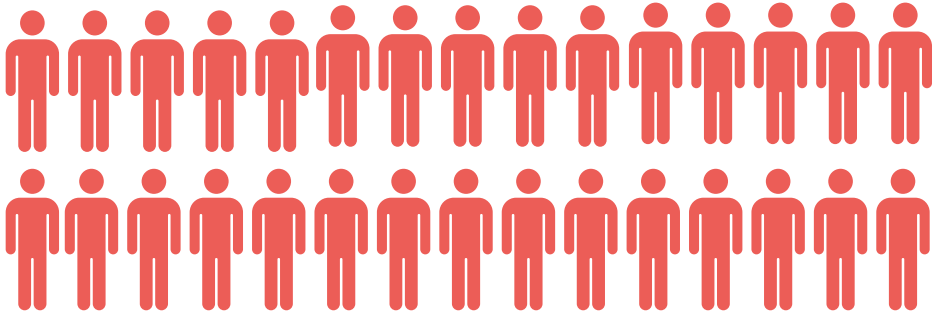
1000 PEOPLE GIVEN FLUOROPYRIMIDINES

1 IN 30 RISK OF DEATH FOR THOSE WITH VARIANT

1 IN 1000 RISK OF DEATH

1000 PEOPLE GIVEN FLUOROPYRIMIDINES

NUMBER OF DEATHS



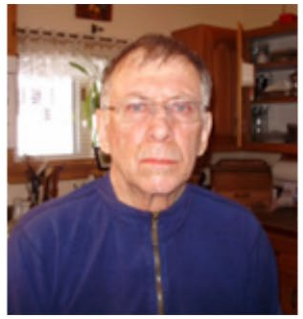
NUMBER OF DEATHS

What if you or a loved one died from this drug and no one told you any of this information in the past slides ?

Kathy
Rectal Cancer

Kerrie
Colon Cancer

Linda
Rectal Cancer



Paul
Colon Cancer

Gerri
Colon Cancer

Jane
Colon Cancer

Anil
Colon Cancer

David
Bile Duct Cancer

Carol
Breast Cancer

Gary
Colon Cancer

Susan
Colon Cancer

Dr. Anil Kapoor

Dr. Anil Kapoor, MD, FRCSC

Urologist

Renal Transplant Surgeon

Uro-Oncologist

Academic Rank of Full Professor of Surgery (Urology), McMaster University

Published over 350 papers

Director, Urologic Cancer Centre for Research & Innovation (UCCRI)

President, Urologic Society of Transplantation and Renal Surgery (USTRS) An Affiliate Society of the American Urologic Association (AUA)

Surgical Director, Renal Transplantation, McMaster University, Hamilton, Ontario

Chair, Kidney Cancer Research Network of Canada (KCRNC)

President, Canadian Academy of Urological Surgeons (CAUS)

Chair, Genito-Urinary (GU) Oncology Program, Juravinski Cancer Centre, McMaster University, Hamilton, Ontario

Director, Urological Laparoscopy, Centre for Minimal Access Surgery (CMAS) McMaster University, Hamilton, Ontario

Associate Oncology Editor, Canadian Urological Association Journal (CUAJ)


News from ASCO 2018 - Dr. Anil Kapoor, Uro-Oncolgist
DR. ANIL KAPOOR
URO-ONCOLOGIST
0:28 / 8:04 • Intro ›
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DESIGNS


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JANUARY 2023

SUN	MON	TUES	WED	THURS	FRI	SAT
1	2	3	4	5	6	7
8	9	10	11	12	13	14
15	16	17	18	19	20	21
22	23	24	25	26	27	28
29	30	31				

KEY FINAL DAYS DR. ANIL KAPOOR

- Colonoscopy – Diagnosis of Colon Cancer
- CT Scan
- Raptor's Basketball Game
- Oncology Appointment

FEBRUARY 2023

SUN	MON	TUES	WED	THURS	FRI	SAT
			1	2	3	4
5	6	7	8	9	10	11
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KEY FINAL DAYS DR. ANIL KAPOOR

- 5-FU Infusion Begins for 48 hours
- Overdose Signs and Symptoms
- Proceeds to Emergency Room
- Proceeds to Emergency Again- Admitted
- Admitted to ICU
- Intubated
- Death

HAMILTON REGION

Dr. Anil Kapoor was ‘fun-loving’ and ‘a rock star’ in medical profession

He broadened use of minimally invasive surgery in operating room

Updated Dec. 25, 2023 at 2:43 p.m. | March 20, 2023 | 2 min read

Dr. Anil Kapoor was a groundbreaking surgeon at St. Joseph’s Hospital.

Courtesy of St. Joseph's Hospital

By **Daniel Nolan** Contributor

Dr. Anil Kapoor is being remembered as “a gifted surgeon” who was a “rock star” in the medical profession.

LIVES LIVED

Anil Kapoor was a gifted surgeon with a bedside manner that put everyone at ease

SUNIL KAPOOR, **VIMAL KAPOOR**, **AKSHAY KAPOOR** AND **JEEVAN KAPOOR**
CONTRIBUTED TO THE GLOBE AND MAIL
PUBLISHED NOVEMBER 1, 2023
UPDATED NOVEMBER 2, 2023

This article was published more than 6 months ago. Some information may no longer be current.

33 COMMENTS SHARE BOOKMARK

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Anil “Monty” Kapoor: *Surgeon. Father. Partner. Friend. Born April 30, 1964, in Montreal; died Feb. 28, 2023, in Toronto; of a chemotherapy medication dosing error; aged 58.*

Anil (Monty) Kapoor.
MIKE BEATTIE/COURTESY OF FAMILY

From a young age, Anil Kapoor was a trailblazer. He followed his interests fully, exploring new opportunities and meeting people of all stripes.

He was the eldest child of immigrant parents (both professors at St. Mary’s University in Halifax) who gave their three sons nicknames based on where they were born. Since Anil was born in Montreal, he went by “Monty.” In high school, Monty showed exceptional hand-eye co-ordination and made intricate models. This talent set the stage for his career as a gifted surgeon.

Anil attended Dalhousie University for his BSc in mathematics and engineering. In 1985, while continuing engineering at McGill, he switched to medicine and went

Hamilton Philharmonic. He also accompanied many artists, including the Jackson 5 and Glenn Gould.

Dr. Anil Kapoor A groundbreaking surgeon at St. Joseph's Hospital, Kapoor helped expand the use of minimally invasive laparoscopic surgery and conducted Canada's first laparoscopic renal donor transplant and the first laparoscopic renal aneurysm repair. He died from colon cancer Feb. 28.

Phil Lind Lind helped entrepreneur Ted Rogers build a small company with two radio stations and fewer than 10,000 cable subscribers into Rogers Communications Inc. Lind was also instrumental in Rog-

PETER POWER · ST. JOSEPH'S HEALTHCARE HAMILTON

Dr. Anil Kapoor, a surgeon at St. Joseph's Hospital, helped expand the use of minimally invasive laparoscopic surgery.

ers' acquisition of th
Jays in 2000. Th
longtime chair of C
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of Commons and
fairs programming
20, his 80th birthda

Lloyd McKell The
social justice activi
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dela at the forme
1998, an event now
dela and the Chil
who began his 35-y
the Toronto Board
a school commu
worker, died June 1

Joyce Mongeon T
er of the Royal C
Mongeon was a pa
fundraiser and a m
overseeing the H
Opera Hamilton,
us, Art Gallery of
Brott's National A
tra and Hope Ha
died June 20.

Martin McSkim
ming, who came
New Zealand in t
an accountant, fo

CBC National News

This commonly prescribed cancer drug was supposed to help save this doctor's life. Instead, it killed him

Some provinces pre-screen patients at risk of toxic reactions, but experts say tests don't go far enough

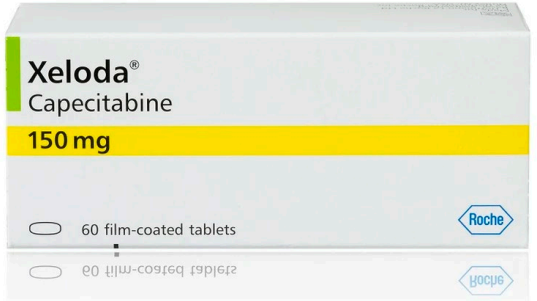
Rosa Marchitelli, Jenn Blair · CBC News ·
Posted: Nov 27, 2023 4:00 AM EST | Last Updated: November 27, 2023

Drug is called

5-FU or Fluorouracil in IV form

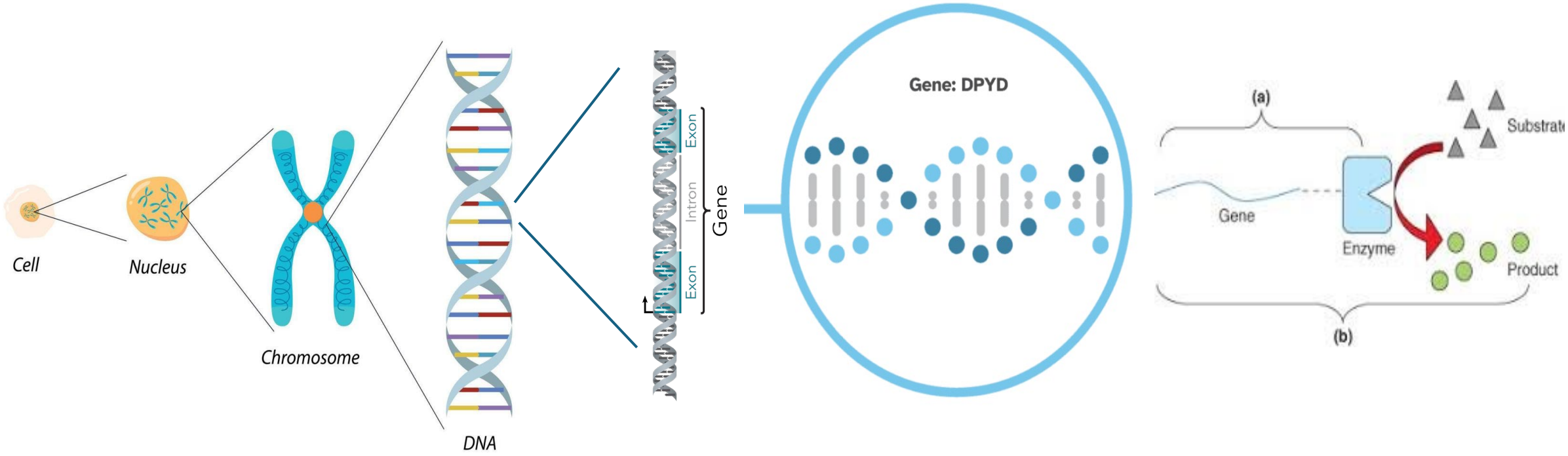
or

Capecitabine in pill form



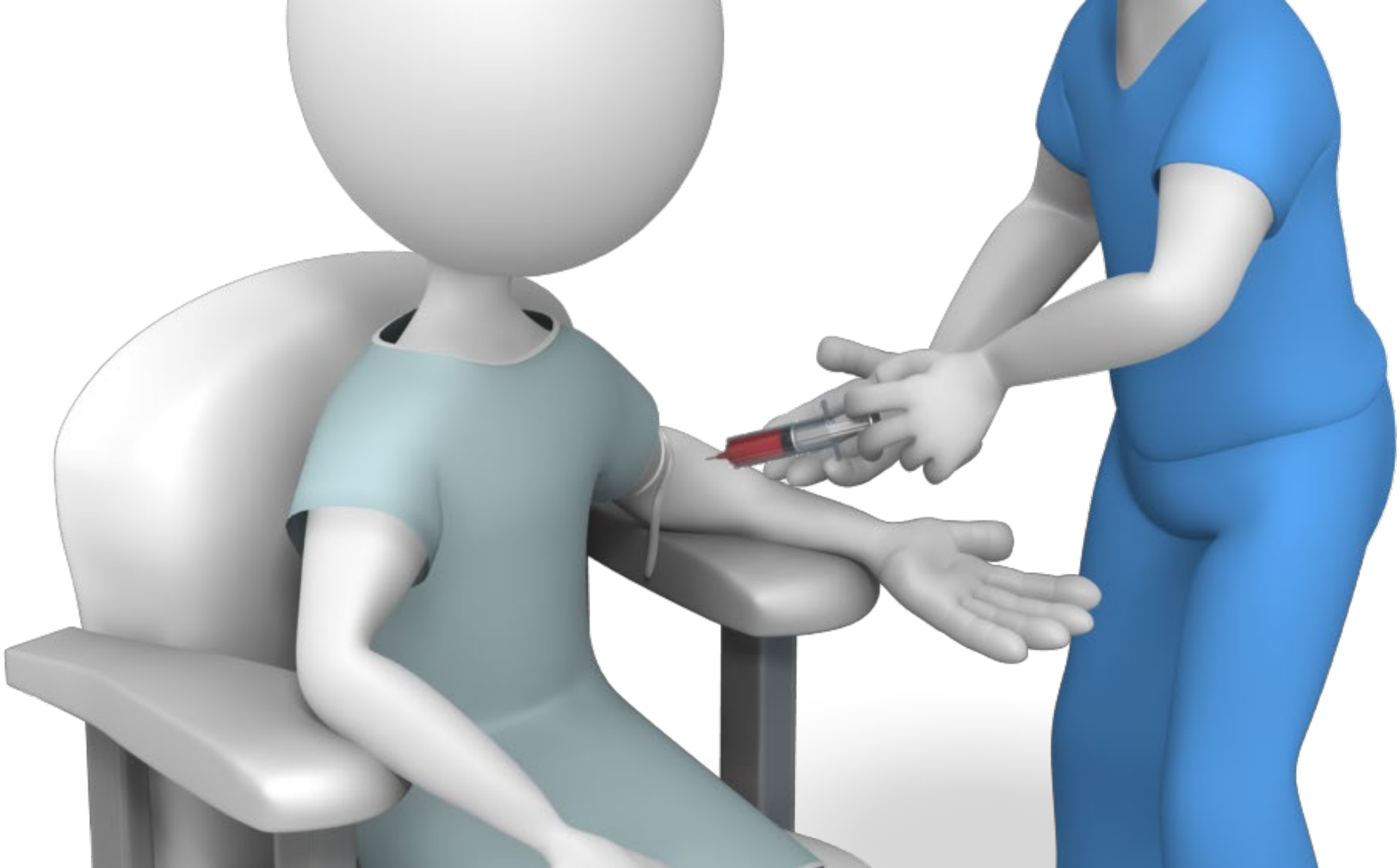
Together these 2 drugs are classified as fluoropyrimidines

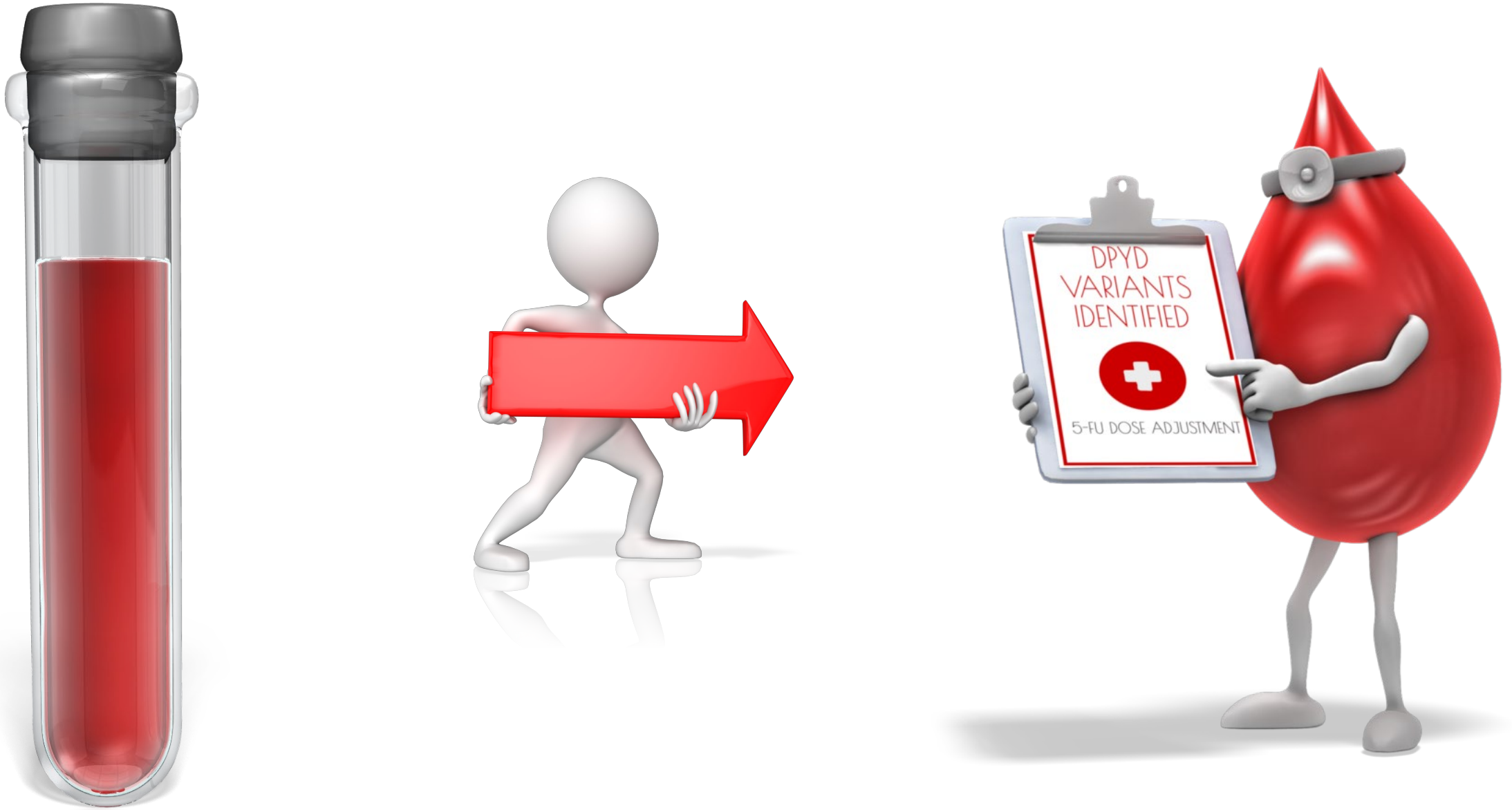
Used in head and neck cancers, breast cancer, and gastrointestinal cancers

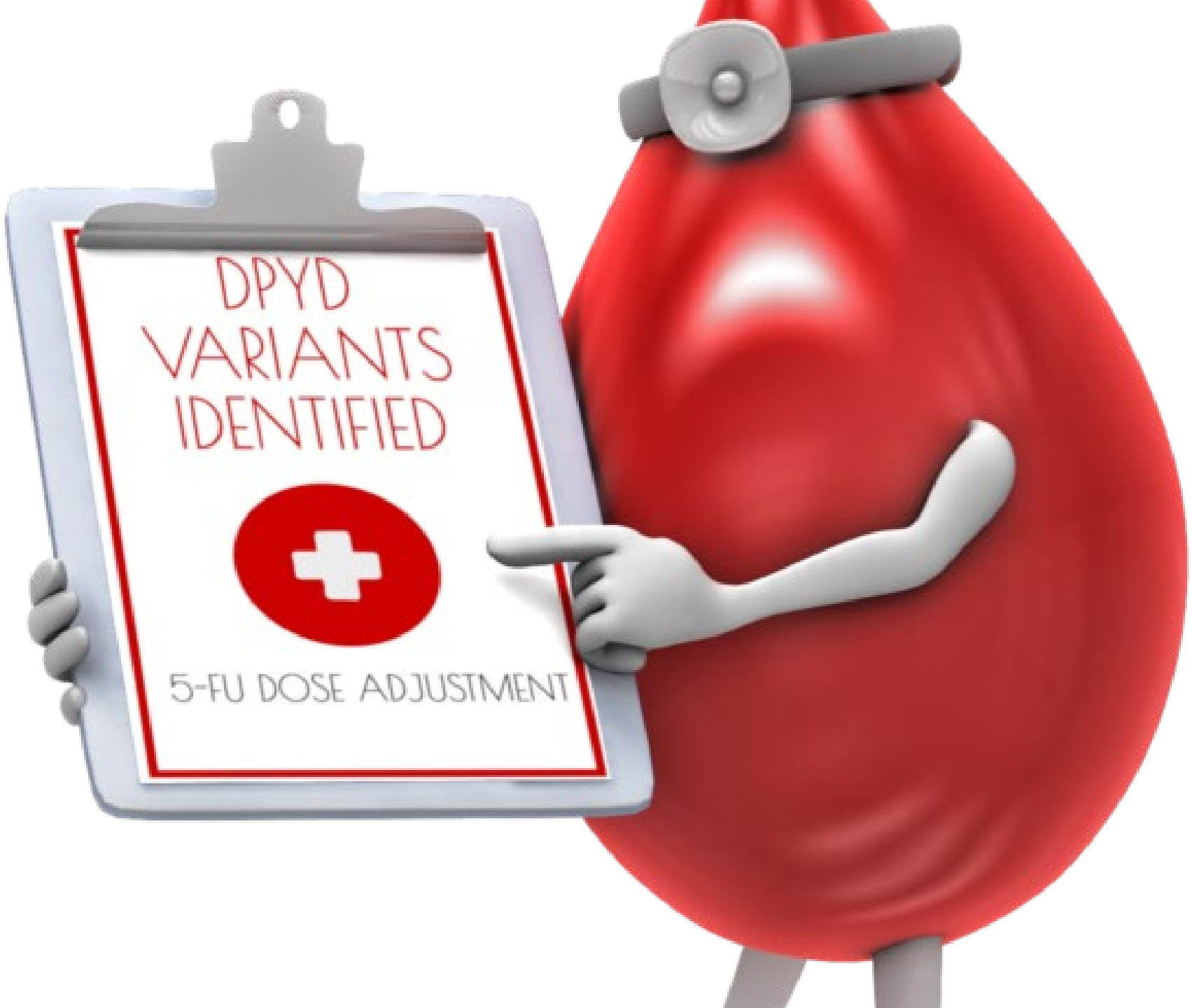


The **DPYD gene** encodes dihydropyrimidine dehydrogenase (DPD), an enzyme that **breaks down fluorouracil**. Genetic variants in the *DPYD* gene can lead to **enzymes with reduced or absent activity**. These with reduced or absent activity DPD enzymes are at risk of potentially **life-threatening fluorouracil overdose**

How easy would it have been to save these lives ?

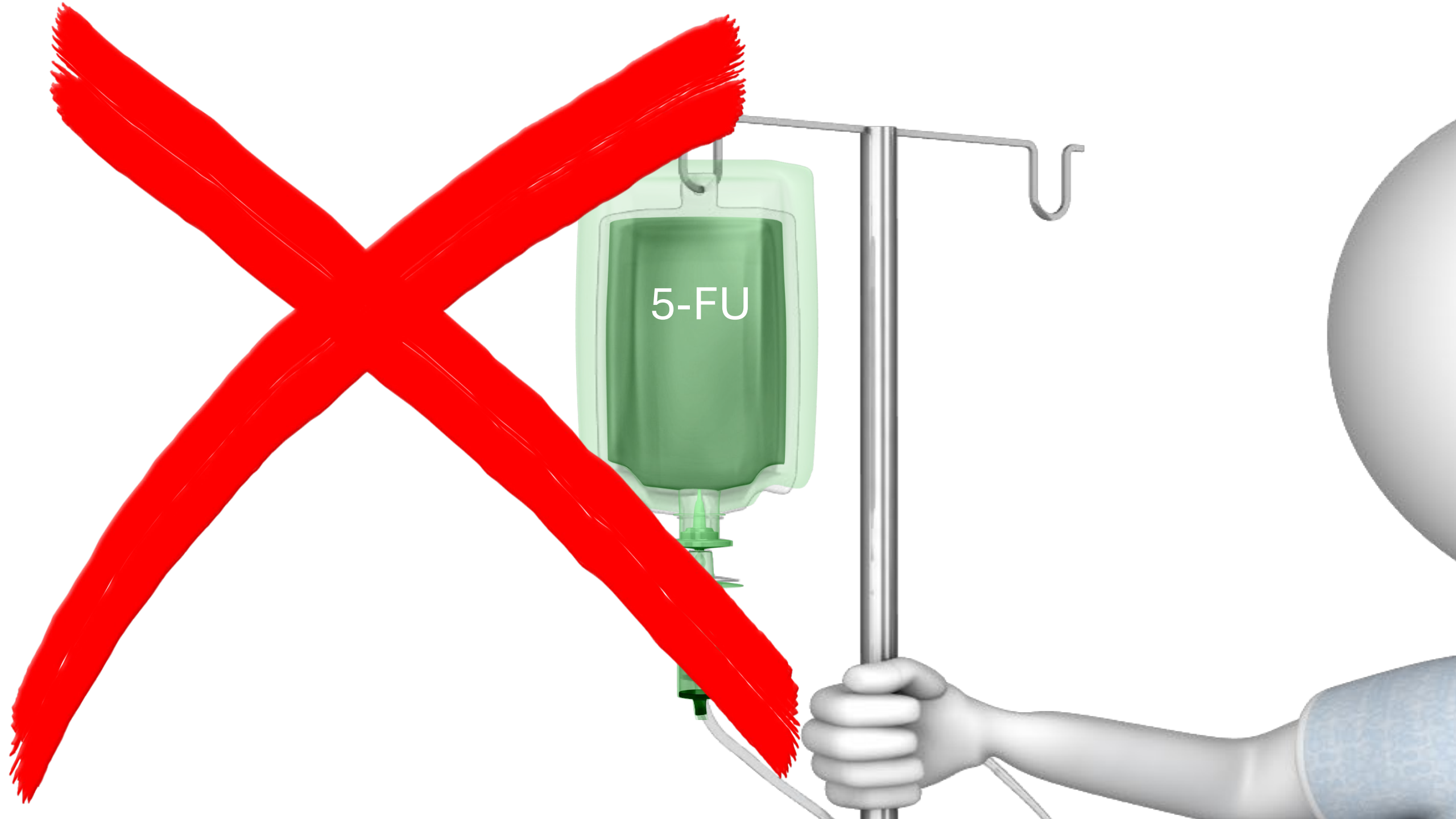



DPYD
VARIANTS
IDENTIFIED
5-FU DOSE ADJUSTMENT

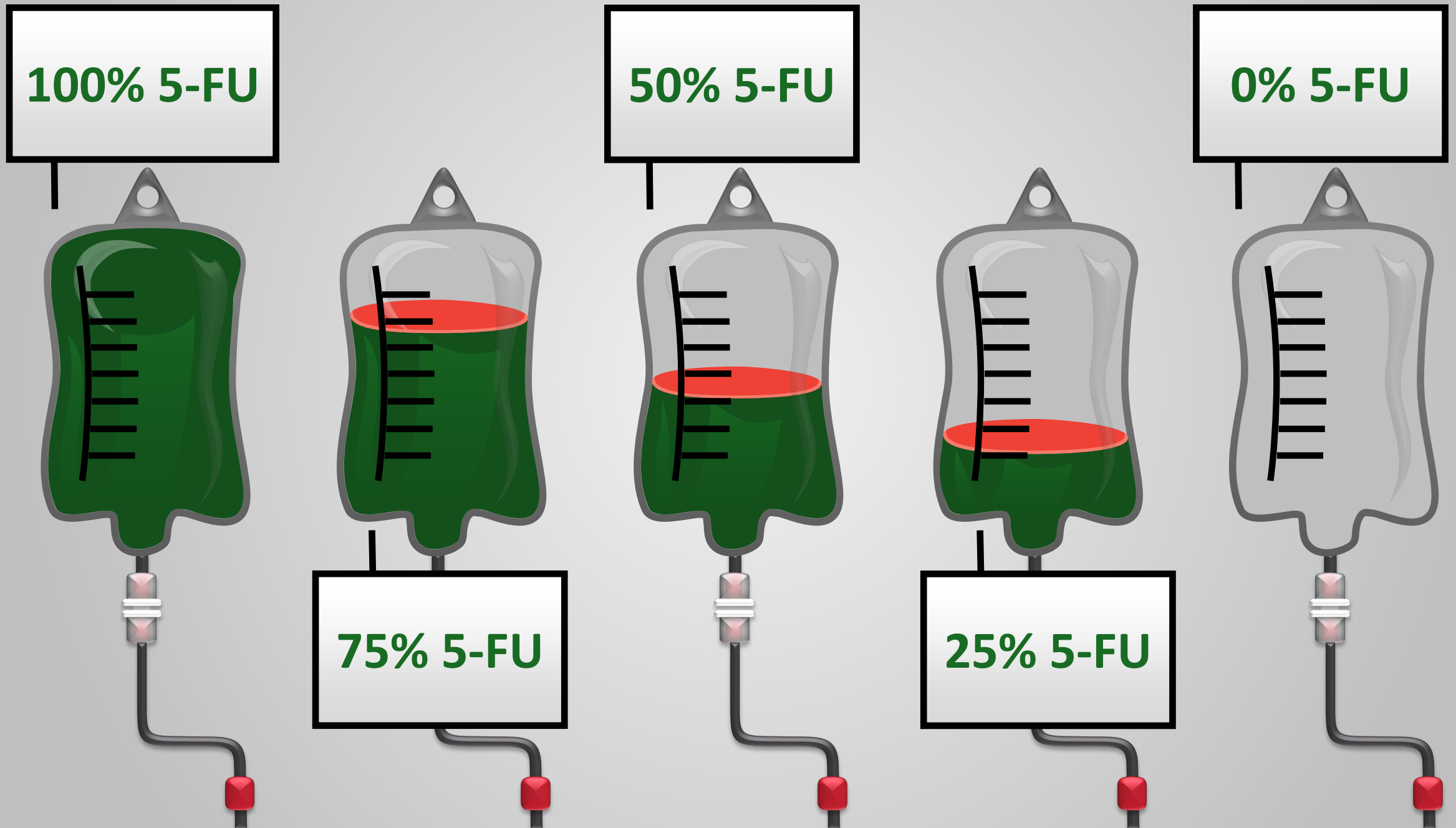

DPYD
VARIANTS
IDENTIFIED
5-FU DOSE ADJUSTMENT

Predicted activity score	Genotype	Likely *DPYD* phenotype	Dosing Guidelines for Fluoropyrimidines
0	Homozygous (or compound heterozygous) for a non-functional variant	Poor metabolizer	Do not use
0.5	One non-functional + one reduced function variant		Use not recommended. If alternative agents are not a suitable therapeutic option, administer at a strongly reduced dose (at least 75% reduction) with early therapeutic drug monitoring
1.0	Heterozygous for a non-functional variant Homozygous for a reduced function variant*	Intermediate metabolizer	A 50% lower starting dose is recommended. Titrate future doses based on clinical judgement
1.5	Heterozygous for a reduced function variant		A 25%–50% lower starting dose is recommended. Titrate future doses based on clinical judgement
2.0	Variant negative	Normal metabolizer	No indication for changing dose

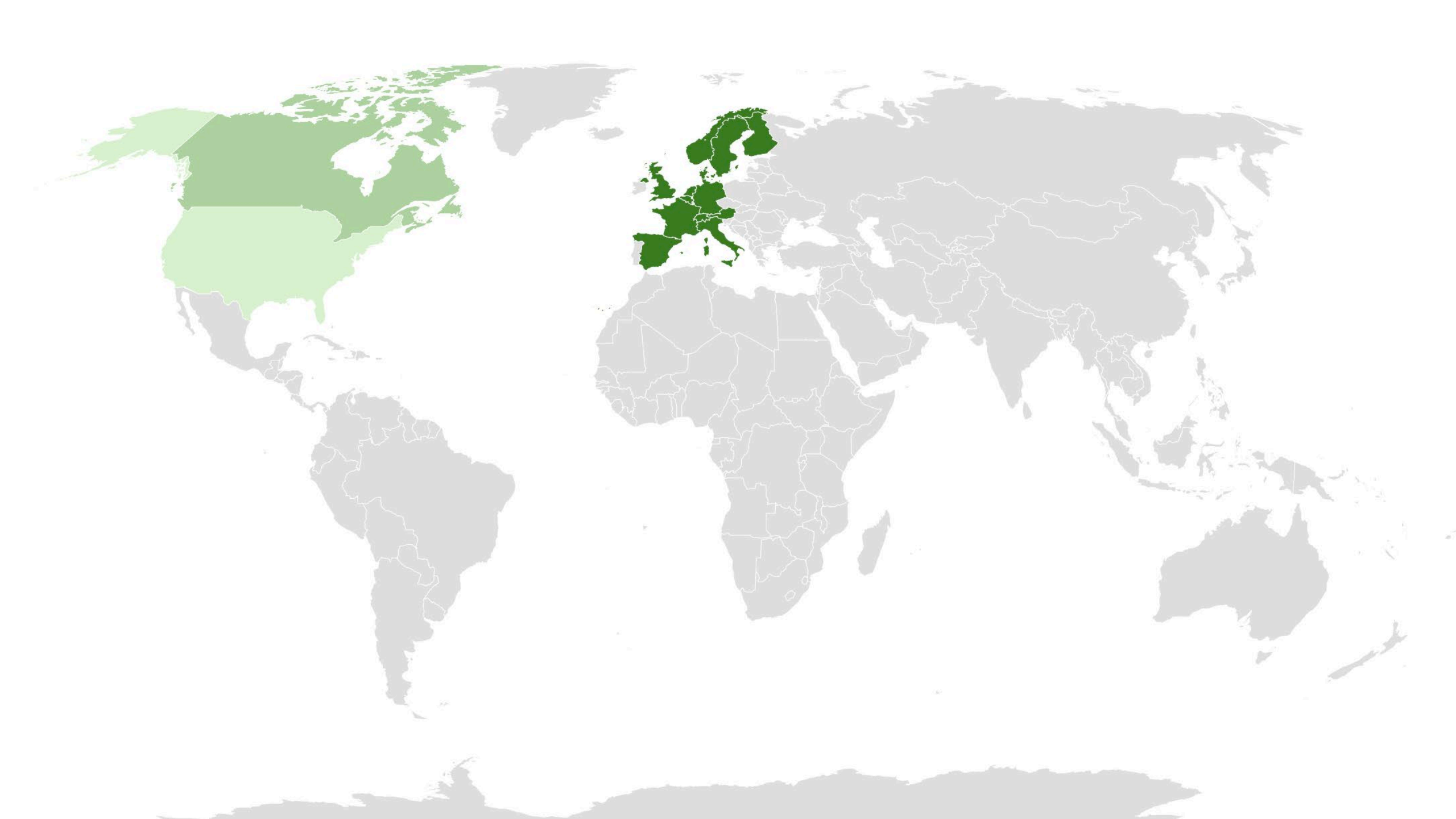

5-FU


5-FU

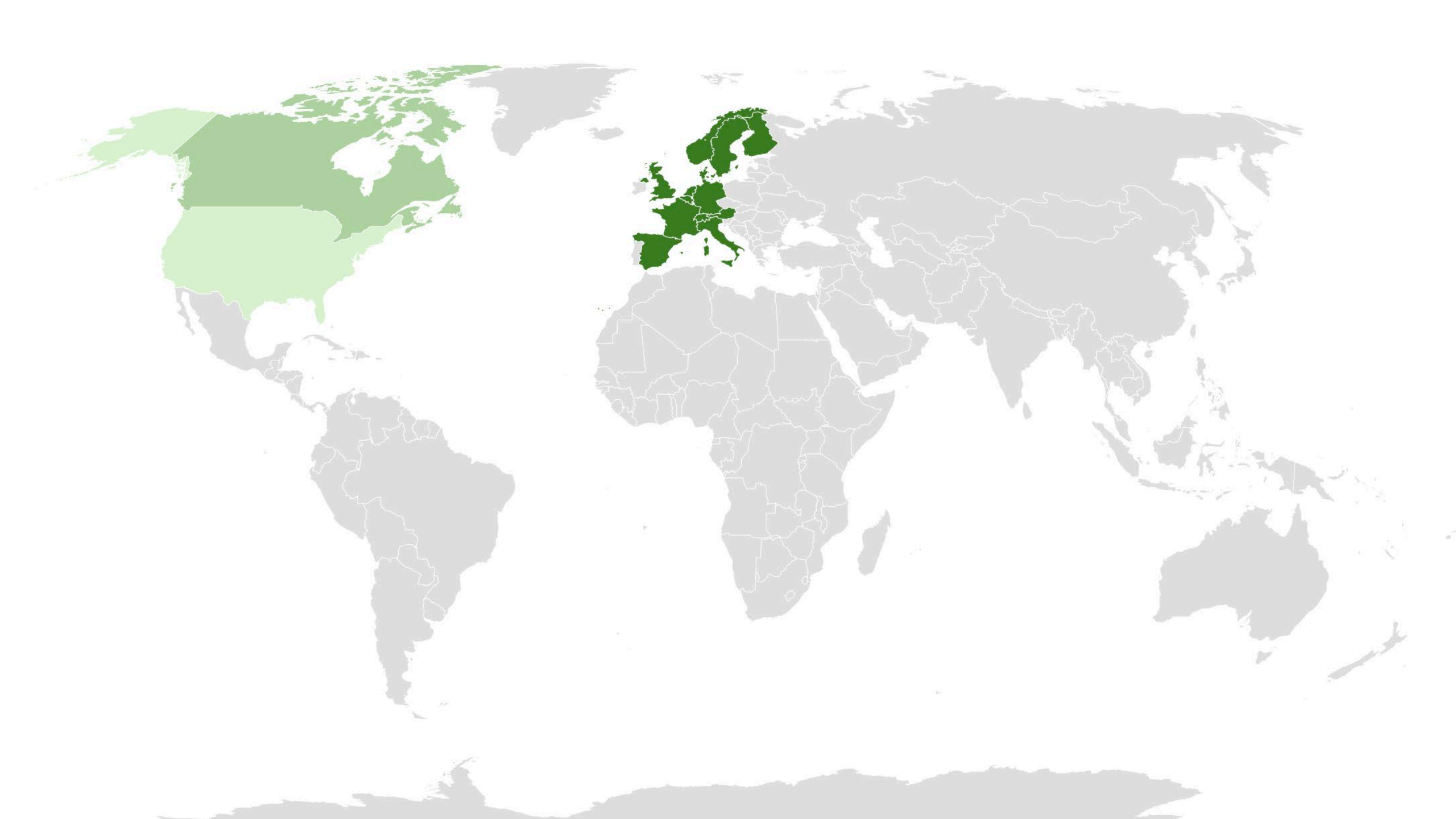
Adjust Dose of 5-FU Based on Blood Test DPYD

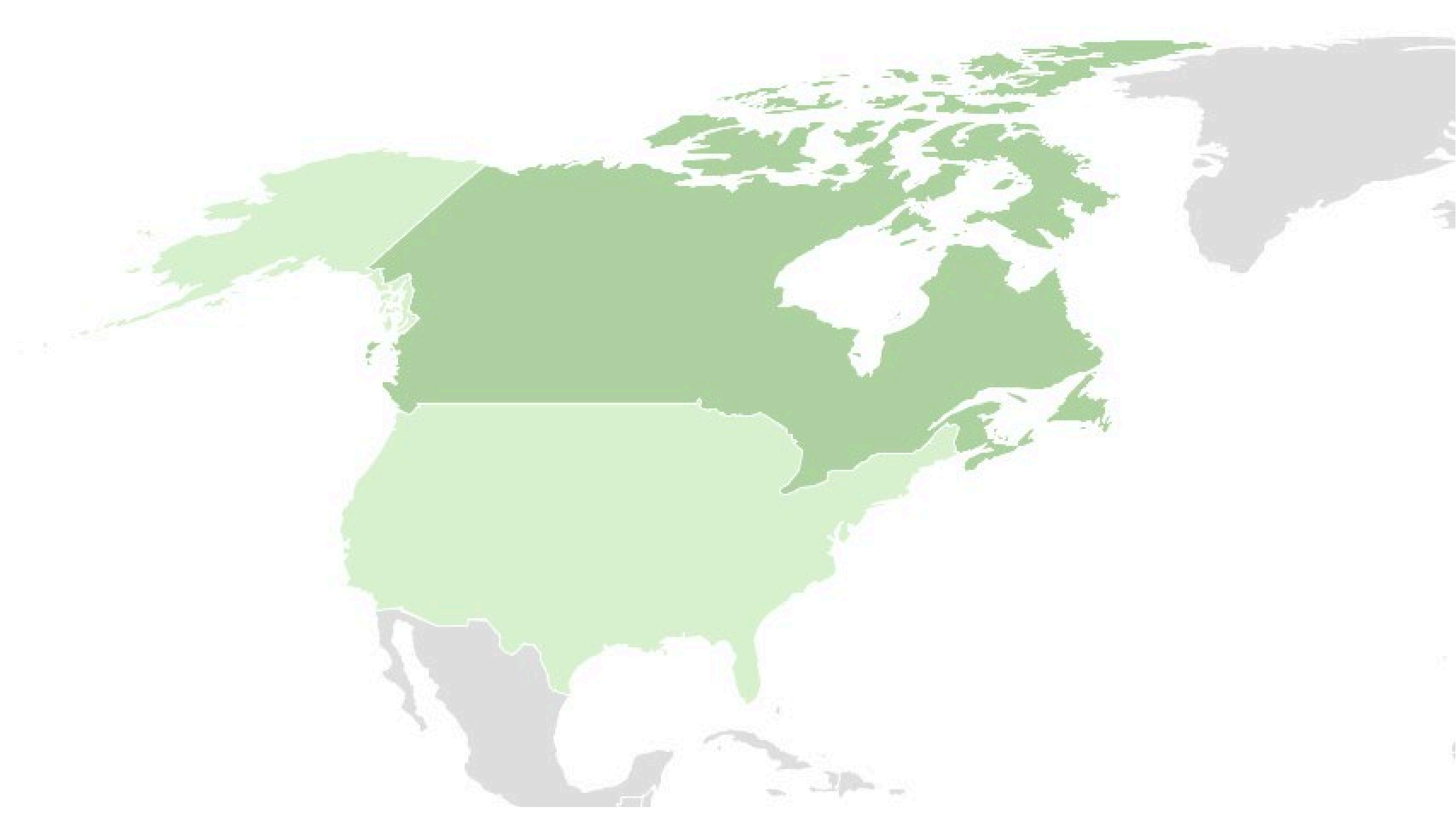


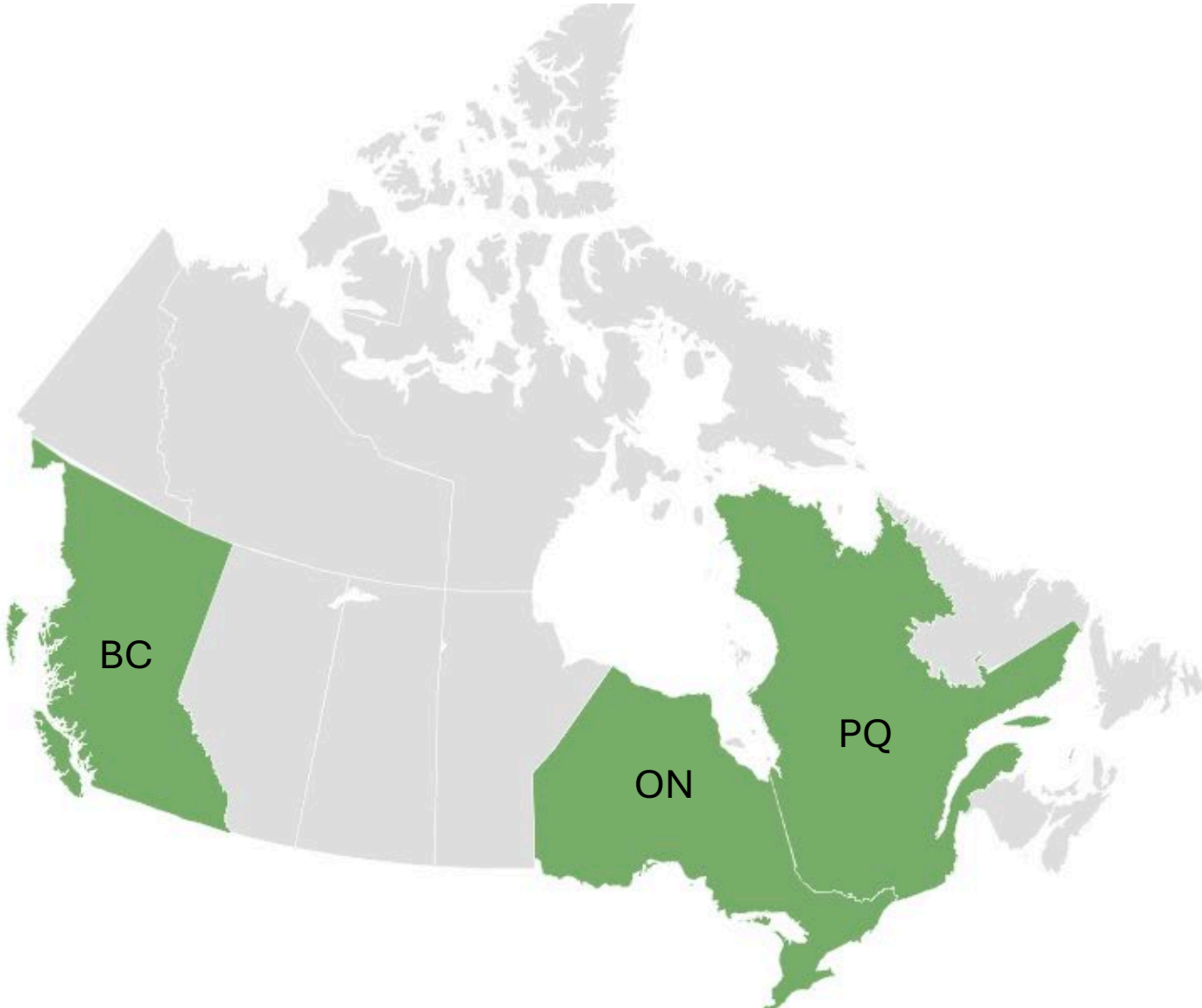
Feasible ?



The European Medicines Agency, the French National Agency for the Safety of Medicines and Health Products, and the UK Medicines and Healthcare Products Regulatory Agency have approved guidelines for pre-emptive \DPD activity testing for patients treated with fluoropyrimidines



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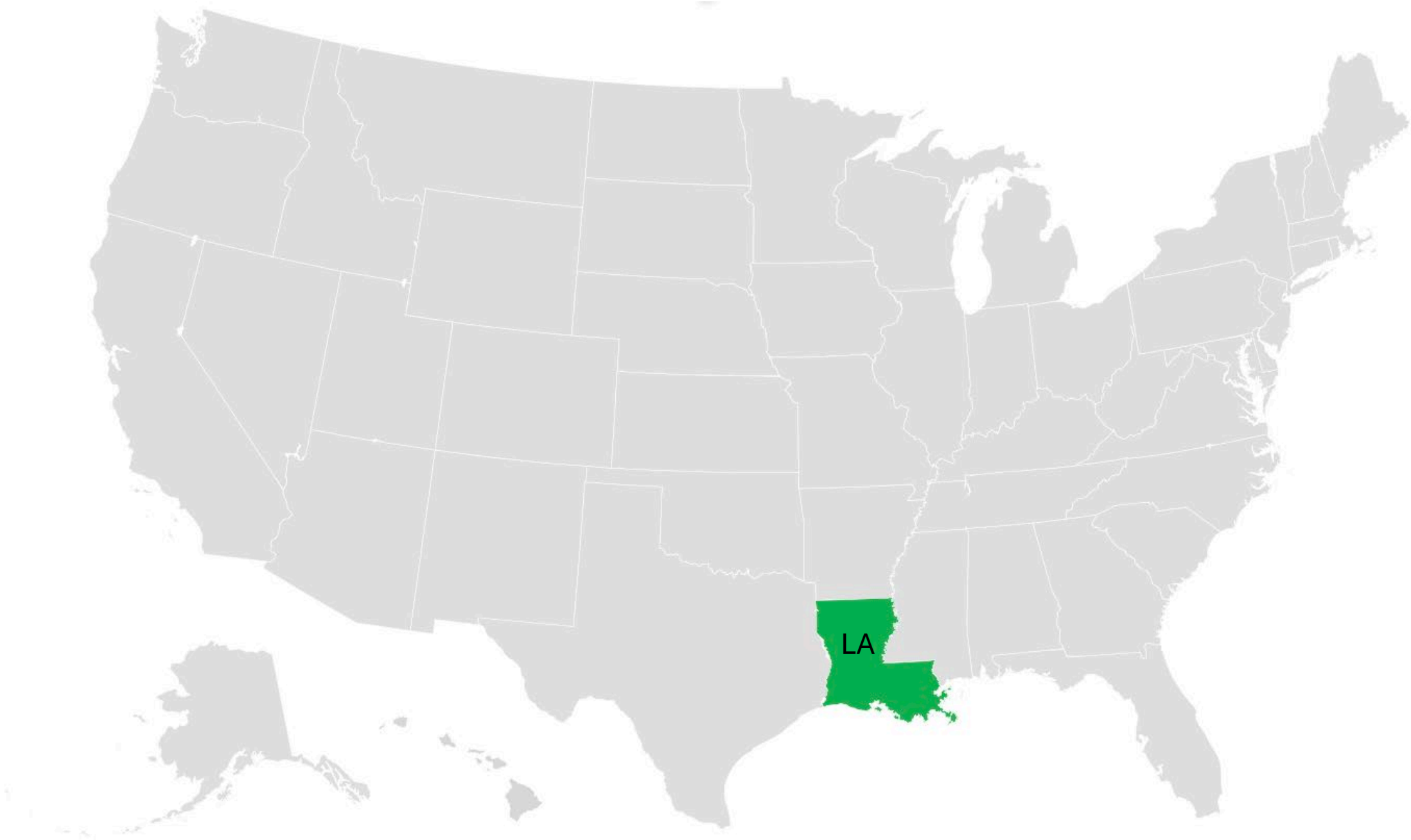
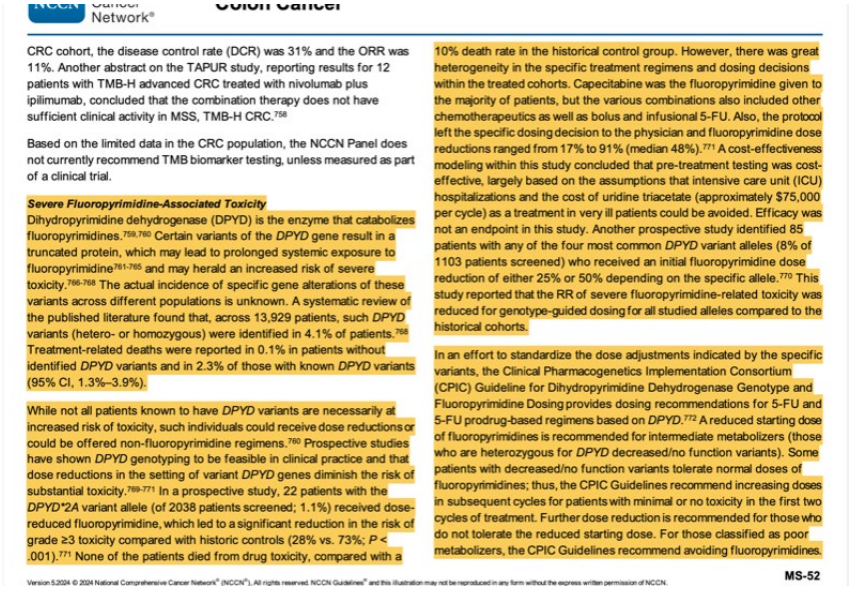

LA

Why not the USA, but most of Europe ?

National Comprehensive Cancer Network®

NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®)

Colon Cancer



Network®

Colon Cancer

CRC cohort, the disease control rate (DCR) was 31% and the ORR was 11%. Another abstract on the TAPUR study, reporting results for 12 patients with TMB-H advanced CRC treated with nivolumab plus ipilimumab, concluded that the combination therapy does not have sufficient clinical activity in MSS, TMB-H CRC.[758]

Based on the limited data in the CRC population, the NCCN Panel does not currently recommend TMB biomarker testing, unless measured as part of a clinical trial.

Severe Fluoropyrimidine-Associated Toxicity

Dihydropyrimidine dehydrogenase (DPYD) is the enzyme that catabolizes fluoropyrimidines.[759,760] Certain variants of the *DPYD* gene result in a truncated protein, which may lead to prolonged systemic exposure to fluoropyrimidine[761-765] and may herald an increased risk of severe toxicity.[766-768] The actual incidence of specific gene alterations of these variants across different populations is unknown. A systematic review of the published literature found that, across 13,929 patients, such *DPYD* variants (hetero- or homozygous) were identified in 4.1% of patients.[768] Treatment-related deaths were reported in 0.1% in patients without identified *DPYD* variants and in 2.3% of those with known *DPYD* variants (95% CI, 1.3%–3.9%).

While not all patients known to have *DPYD* variants are necessarily at increased risk of toxicity, such individuals could receive dose reductions or could be offered non-fluoropyrimidine regimens.[760] Prospective studies have shown *DPYD* genotyping to be feasible in clinical practice and that dose reductions in the setting of variant *DPYD* genes diminish the risk of substantial toxicity.[769-771] In a prospective study, 22 patients with the *DPYD*2A* variant allele (of 2038 patients screened; 1.1%) received dose-reduced fluoropyrimidine, which led to a significant reduction in the risk of grade ≥3 toxicity compared with historic controls (28% vs. 73%; $P < .001$).[771] None of the patients died from drug toxicity, compared with a 10% death rate in the historical control group. However, there was great heterogeneity in the specific treatment regimens and dosing decisions within the treated cohorts. Capecitabine was the fluoropyrimidine given to the majority of patients, but the various combinations also included other chemotherapeutics as well as bolus and infusional 5-FU. Also, the protocol left the specific dosing decision to the physician and fluoropyrimidine dose reductions ranged from 17% to 91% (median 48%).[771] A cost-effectiveness modeling within this study concluded that pre-treatment testing was cost-effective, largely based on the assumptions that intensive care unit (ICU) hospitalizations and the cost of uridine triacetate (approximately $75,000 per cycle) as a treatment in very ill patients could be avoided. Efficacy was not an endpoint in this study. Another prospective study identified 85 patients with any of the four most common *DPYD* variant alleles (8% of 1103 patients screened) who received an initial fluoropyrimidine dose reduction of either 25% or 50% depending on the specific allele.[770] This study reported that the RR of severe fluoropyrimidine-related toxicity was reduced for genotype-guided dosing for all studied alleles compared to the historical cohorts.

In an effort to standardize the dose adjustments indicated by the specific variants, the Clinical Pharmacogenetics Implementation Consortium (CPIC) Guideline for Dihydropyrimidine Dehydrogenase Genotype and Fluoropyrimidine Dosing provides dosing recommendations for 5-FU and 5-FU prodrug-based regimens based on *DPYD*.[772] A reduced starting dose of fluoropyrimidines is recommended for intermediate metabolizers (those who are heterozygous for *DPYD* decreased/no function variants). Some patients with decreased/no function variants tolerate normal doses of fluoropyrimidines; thus, the CPIC Guidelines recommend increasing doses in subsequent cycles for patients with minimal or no toxicity in the first two cycles of treatment. Further dose reduction is recommended for those who do not tolerate the reduced starting dose. For those classified as poor metabolizers, the CPIC Guidelines recommend avoiding fluoropyrimidines.

These guidelines reflect common sense dose adjustments rather than methodically derived dosing based on actual pharmacokinetics. Also, the dose adjustment paradigm does not distinguish between IV bolus or infusional 5-FU or the pro-drug capecitabine. The pharmacokinetics of IV 5-FU vary greatly based on the rate of infusion and there are many more factors involved in determining an individual's tolerance of capecitabine, which is uniformly used at reduced dose in the United States compared to Europe.[773]

While dose adjustment of fluoropyrimidines based on *DPYD* genotype has been shown to diminish toxicity, it is not certain that dose reductions do not result in inferior efficacy. A prospective multicenter study of 156 *DPYD* variant carriers and 775 *DPYD* wild-type controls, most with advanced or metastatic disease, sought to test this.[774] In this study, *DPYD* variant carriers received either a 25% or 50% fluoropyrimidine dose reduction, depending on the exact variant. Each *DPYD* variant carrier was matched to three wild-type controls treated with the standard dose. For pooled *DPYD* variant carriers, PFS and OS were not significantly affected by these lower fluoropyrimidine doses, although a shorter PFS (HR, 1.43; 95% CI, 1.10–1.86; $P = .007$) was found in the 61 carriers of the c.1236G>A variant who were treated with the reduced dose. These findings raise the possibility that dose reduction may diminish the efficacy of the fluoropyrimidine with at least this variant of *DPYD*. While the impact in patients with advanced CRC may not be significant, reduced efficacy of fluoropyrimidines when used in the adjuvant setting could be very meaningful.[775] Because fluoropyrimidines are a pillar of therapy in CRC and it is not known with certainty that given *DPYD* variants are associated with this risk and/or that dose adjustments do not impact efficacy, the NCCN Panel does not recommend universal pretreatment *DPYD* genotyping at this time. However, as with all guideline decisions, the Panel reviews all new data and considers input from stakeholders in real time

Uridine triacetate is an orally administered pyrimidine analog that is believed to compete for receptors on normal cells and, as such, decreases the toxic effects of excessive fluoropyrimidines. It is FDA approved for the emergency treatment of both adult and pediatric patients exhibiting early-onset, severe or life-threatening toxicity within 96 hours of the completion of 5-FU or capecitabine administration.[776] Uridine triacetate was evaluated in two single-arm, multicenter open-label trials in which a total of 135 patients were treated with uridine triacetate following 5-FU or capecitabine overdose or upon early onset of severe toxicities.[777,778] In these studies, a total of 96% of the patients treated with uridine triacetate survived and exhibited rapid reversal of severe cardiac and neurologic toxicities. Thirty-eight percent of these patients were able to resume chemotherapy within 30 days, with a mean time to resumption of chemotherapy of 19.6 days.[777] The importance of administration of uridine triacetate within the first 96 hours must be noted. While most patients on these trials were treated within the first 96 hours, 50% of the four patients who were treated beyond 96 hours died.[778]

Regimens Not Recommended

The consensus of the Panel is that infusional 5-FU regimens seem to be less toxic than bolus regimens and that any bolus regimen of 5-FU is inappropriate when administered with either irinotecan or oxaliplatin. Therefore, the Panel no longer recommends using the IFL regimen (which was shown to be associated with increased mortality and decreased efficacy relative to FOLFIRI in the BICC-C trial[614,779] and inferior to FOLFOX in the Intergroup trial[780]) at any point in the therapy continuum. 5-FU in combination with irinotecan or oxaliplatin should be administered via an infusional biweekly regimen,[312] or capecitabine can be used with oxaliplatin.[781]

The Dutch CAIRO trial showed promising results for the use of

19 references

1000 words

2 pages

“…the NCCN Panel does not recommend universal pretreatment DPYD genotyping at this time.”

PubMed®

(DPYD or DPD) and "fluoro*

Search

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Save Email Send to Sort by: Best match Display options

RESULTS BY YEAR

1,475 results

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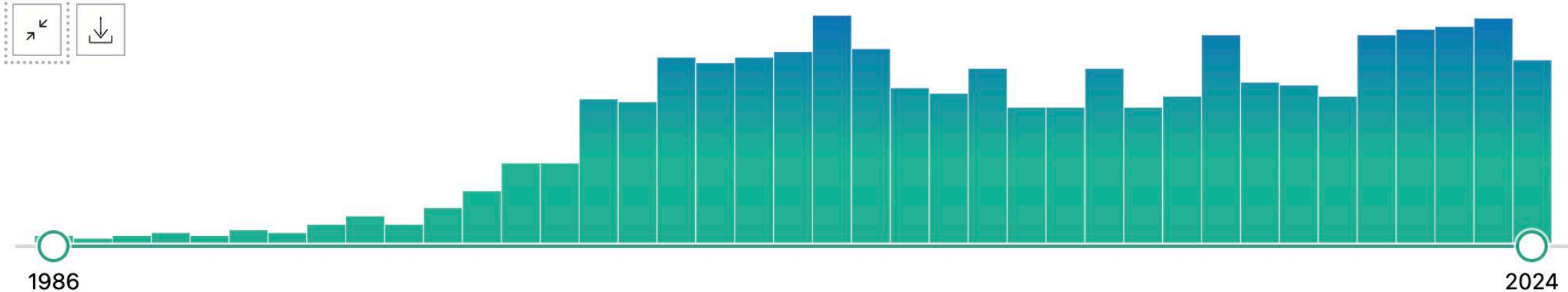

1,475 results

literature in the field of CRC published since the previous Guidelines update, using the following search terms: colon cancer, colorectal cancer, and rectal cancer. The PubMed database was chosen as it remains the most widely used resource for medical literature and indexes peer-reviewed biomedical literature.[8]

The search results were narrowed by selecting studies in humans published in English. Results were confined to the following article types: Clinical Trial, Phase II; Clinical Trial, Phase III; Clinical Trial, Phase IV; Guideline; Practice Guideline; Randomized Controlled Trial; Meta-Analysis; Systematic Reviews; and Validation Studies. The data from key PubMed articles as well as articles from additional sources deemed as relevant to these Guidelines as discussed by the Panel during the Guidelines update have been included in this version of the Discussion section. Recommendations for which high-level evidence is lacking are based on the Panel's review of lower-level evidence and expert opinion.

The data from key PubMed articles as well as articles from additional sources deemed as relevant to these Guidelines as discussed by the Panel during the Guidelines update have been included in this version of the Discussion section. Recommendations for which high-level evidence is lacking are based on the Panel's review of lower-level evidence and expert opinion.

These guidelines reflect common sense dose adjustments rather than methodically derived dosing based on actual pharmacokinetics. Also, the dose adjustment paradigm does not distinguish between IV bolus or infusional 5-FU or the pro-drug capecitabine. The pharmacokinetics of IV 5-FU vary greatly based on the rate of infusion and there are many more factors involved in determining an individual's tolerance of capecitabine, which is uniformly used at reduced dose in the United States compared to Europe.[773]

While dose adjustment of fluoropyrimidines based on *DPYD* genotype has been shown to diminish toxicity, it is not certain that dose reductions do not result in inferior efficacy. A prospective multicenter study of 156 *DPYD* variant carriers and 775 *DPYD* wild-type controls, most with advanced or metastatic disease, sought to test this.[774] In this study, *DPYD* variant carriers received either a 25% or 50% fluoropyrimidine dose reduction, depending on the exact variant. Each *DPYD* variant carrier was matched to three wild-type controls treated with the standard dose. For pooled *DPYD* variant carriers, PFS and OS were not significantly affected by these lower fluoropyrimidine doses, although a shorter PFS (HR, 1.43; 95% CI, 1.10–1.86; *P* = .007) was found in the 61 carriers of the c.1236G>A variant who were treated with the reduced dose. These findings raise the possibility that dose reduction may diminish the efficacy of the fluoropyrimidine with at least this variant of *DPYD*. While the impact in patients with advanced CRC may not be significant, reduced efficacy of fluoropyrimidines when used in the adjuvant setting could be very meaningful.[775] Because fluoropyrimidines are a pillar of therapy in CRC and it is not known with certainty that given *DPYD* variants are associated with this risk and/or that dose adjustments do not impact efficacy, the NCCN Panel does not recommend universal pretreatment *DPYD* genotyping at this time. However, as with all guideline decisions, the Panel reviews all new data and considers input from stakeholders in real time and guidelines are continuously reassessed.

Uridine triacetate is an orally administered pyrimidine analog that is believed to compete for receptors on normal cells and, as such, decreases the toxic effects of excessive fluoropyrimidines. It is FDA approved for the emergency treatment of both adult and pediatric patients exhibiting early-onset, severe or life-threatening toxicity within 96 hours of the completion of 5-FU or capecitabine administration.[776] Uridine triacetate was evaluated in two single-arm, multicenter open-label trials in which a total of 135 patients were treated with uridine triacetate following 5-FU or capecitabine overdose or upon early onset of severe toxicities.[777,778] In these studies, a total of 96% of the patients treated with uridine triacetate survived and exhibited rapid reversal of severe cardiac and neurologic toxicities. Thirty-eight percent of these patients were able to resume chemotherapy within 30 days, with a mean time to resumption of chemotherapy of 19.6 days.[777] The importance of administration of uridine triacetate within the first 96 hours must be noted. While most patients on these trials were treated within the first 96 hours, 50% of the four patients who were treated beyond 96 hours died.[778]

Regimens Not Recommended

The consensus of the Panel is that infusional 5-FU regimens seem to be less toxic than bolus regimens and that any bolus regimen of 5-FU is inappropriate when administered with either irinotecan or oxaliplatin. Therefore, the Panel no longer recommends using the IFL regimen (which was shown to be associated with increased mortality and decreased efficacy relative to FOLFIRI in the BICC-C trial[614,779] and inferior to FOLFOX in the Intergroup trial[780]) at any point in the therapy continuum. 5-FU in combination with irinotecan or oxaliplatin should be administered via an infusional biweekly regimen,[312] or capecitabine can be used with oxaliplatin.[781]

The Dutch CAIRO trial showed promising results for the use of capecitabine/irinotecan (CapeIRI) in the first-line treatment of mCRC.[650]

Guideline Chair Cites Own Editorial

of the fluoropyrimidine with at least this variant of *DPYD*. While the impact in patients with advanced CRC may not be significant, reduced efficacy of fluoropyrimidines when used in the adjuvant setting could be very meaningful.[775] Because fluoropyrimidines are a pillar of therapy in CRC and it is not known with certainty that given *DPYD* variants are associated

775. Tamraz B, Venook AP. DPYD Pharmacogenetics: To Opt-in or to Opt-out. JCO Oncol Pract 2024:OP2400255. Available at: https://www.ncbi.nlm.nih.gov/pubmed/38743915.

Hochster HS.: Routine DPYD genetic testing. J Clin Oncol 41:2119-2120, 2023

”the cost of genetic testing….is likely to be a minimum of $1,500 US dollars (USD)”

“This cost estimate also does not include the costs of delaying treatment by 2 weeks to obtain such results..”

Cost in $300 or less

Time to test is 3 days

NCCN Guidelines

How is the Chair selected ?

"The Panel Chair is nominated and selected by NCCN Guidelines Senior Staff in consultation with the Chair of the Guidelines Steering Committee".

How are the committee members selected?

"The Guidelines Steering Committee member of each institution appoints one of their institution's members to each Guidelines Panel, typically in consultation with the Panel Chair and NCCN Headquarters Senior Staff".

Is there a term limit of the Chair? - "No"

Is there a term limit on the committee members? - "No"

NCCN Categories of Evidence and Consensus	
Category 1	Based upon high-level evidence (≥1 randomized phase 3 trials or high-quality, robust meta-analyses), there is uniform NCCN consensus (≥85% support of the Panel) that the intervention is appropriate.
Category 2A	Based upon lower-level evidence, there is uniform NCCN consensus (≥85% support of the Panel) that the intervention is appropriate.
Category 2B	Based upon lower-level evidence, there is NCCN consensus (≥50%, but <85% support of the Panel) that the intervention is appropriate.
Category 3	Based upon any level of evidence, there is major NCCN disagreement that the intervention is appropriate.

All recommendations are category 2A unless otherwise indicated.

Basically, levels of evidence is based on a VOTE count of the Committee

NCCN Guidelines Committee :

The Chair basically chooses his Committee members, where they all stay on for unlimited periods of time, where they get to arbitrarily select what papers they want to cite as a basis for the guidelines, (including the Chair’s own), and their level of evidence is based on a vote count of the committee

J Clin Epidemiol. 2022 Sep:149:206-216. doi: 10.1016/j.jclinepi.2022.06.005. Epub 2022 Jun 17.

Analytical frameworks in colorectal cancer guidelines: development of methods for systematic reviews, their application and practical guidance for their use

Samer G Karam [1], Andrea J Darzi [1], Antonio Bognanni [1], Rami Z Morsi [2], Elie E Tannous [3], Rana Charide [4], Se-In Choe [5], Rosa Stalteri [1], Yung Lee [5], Thomas Piggott [1], Laura Jewell [6], Finn Schünemann [7], Miranda Langendam [8], Elena Parmelli [9], Zuleika Saz-Parkinson [9], Annett Roi [9], Nadia Vilahur [9], Yasaman Vali [8], Siw Waffenschmidt [10], Douglas K Owens [11], Grigorios I Leontiadis [12], Paul Moayyedi [12], Jan L Brozek [13], Holger J Schünemann [14]

	utilized
NCCN(38)	No analytical framework, clinical questions are identified during the annual Institutional Review process
SEOM (39, 40)	No analytical framework, methods for question

assessed the quality of the guidelines using the Appraisal of Guidelines for Research and Evaluation II tool. The systematic review was registered in International Prospective Register of Systematic Reviews, registration CRD42020172117.

Results: We screened 34,505 records and identified 1,166 guidelines and 3,127 systematic reviews on CRC of which five met our inclusion criteria. These five publications included four analytical frameworks in colorectal cancer (one update). We also describe our methodological approach to systematic reviews for analytical frameworks and underlying concepts for developing analytical framework using a bottom-up or top-down approach.

Conclusion: Few guidelines and systematic reviews are utilizing analytical frameworks in the development of recommendations. Development of analytical frameworks should begin with a systematic search for existing analytical frameworks and follow a structured conceptual approach for their development to support guideline recommendations. Our methods may be helpful in achieving these objectives.

Quality Assessment AGREE II Total Score

Author, Year	Domain 1: Scope and Purpose	Domain 2: Stakeholder Involvement	Domain 3: Rigour of Development	Domain 4: Clarity of Presentation	Domain 5: Applicability	Domain 6: Editorial Independence	Total % score
Canadian Task Force, 2016 **(2)** Bacchus,	94.4%	72.2%	70.8%	97.2%	66.7%	100.0%	**84%**
Leddin, 2018(37)	100.0%	97.2%	83.3%	100.0%	79.2%	100.0%	**93%**
Benson Venook, 2017(88)	**41.7%**	**69.4%**	**37.5%**	**55.6%**	**37.5%**	**58.3%**	**50%**
Tinmouth, 2016(89)	91.7%	63.9%	80.2%	88.9%	52.1%	62.5%	**73%**

What is the solution to higher quality, objective Guidelines?

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GIN-McMaster Guideline Development Checklist

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This page allows users to read and learn about the topics and items included in the GIN-McMaster Guideline Development Checklist (GDC) as well as to provide feedback and suggestions. The GDC is organized into 18 topics for the guideline development process, with corresponding items to consider for each topic. Users of the checklist should review all topics and items before applying them as they are not necessarily sequential and many are interconnected.

The overall guideline development process is outlined in the diagram below, which portrays the relationships between the various topics in guideline development and the groups involved. Please also see the online glossary for definitions of terms and acronyms appearing throughout the checklist.

Dr Anil Kapoor

DPYD Variant

c.704G>A

Severe Capecitabine Toxicity Associated With a Rare *DPYD* Variant Identified Through Whole-Genome Sequencing

Reynold C. Ly, PhD[1]; Remington E. Schmidt, BS[2]; Patrick J. Kiel, PharmD[1]; Victoria M. Pratt, PhD[3]; Bryan P. Schneider, MD[4]; Milan Radovich, PhD[4]; Steven M. Offer, PhD[2]; Robert B. Diasio, MD[2]; and Todd C. Skaar, PhD[1]

INTRODUCTION

Fluoropyrimidine drugs, both fluorouracil (FU) and its prodrug capecitabine, are widely used in the treatment of solid tumors such as breast, colorectal, and gastric cancers.[1] Over 2 million patients newly diagnosed with cancer are treated each year with fluoropyrimidines.[2] Between 10% and 40% of these patients develop severe, sometimes life-threatening toxicities, which may include mucositis, neutropenia, nausea, severe diarrhea, vomiting, stomatitis, and hand-foot syndrome.[2] These toxicities can be caused by genetic variants in *DPYD*, the gene that encodes for dihydropyrimidine dehydrogenase (DPD), the rate-limiting enzyme responsible for FU catabolism.[1,2]

the Appendix for WGS and Sanger sequencing. Targeted genotyping was performed in the following Clinical Laboratory Improvement Amendments–certified laboratories: ARUP Laboratories (Salt Lake City, UT) and the Indiana University Pharmacogenomics Laboratory (Indianapolis, IN).

Integrated Genomics Viewer Version 2.4.10 (Broad Institute, Cambridge, MA)[11] was used to visualize WGS data, and Ingenuity Variant Analysis (Qiagen, Germantown, MD) was used for variant identification and annotation. DPYD-Varifier[10] was used to evaluate the functional impact of p.R235Q on DPD function. The effect of p.R235Q on DPD enzyme activity was determined in vitro as previously described.[10]

Heterozygous rare missense variant in DPYD:

Rs755416212

NM_000110.3 : c.704G.A;

NP_000101.2 : p.Arg235Gln;

referred to as

p.R235Q

Equity Aspects

c.704G>A DPYD variant:

- Paper: “…variant has a minor allele frequency of 0.00001”

gnomAD 21 v4.1.0 data:

- ”Found in 2 of 60,366 alleles in people of South Asian ethnicity”
- “Found in 10 of 1,111,732 alleles of NonFinnish European ethnicity”

At least 1.5 billion people of South Asian ethnicity

Ontario Health

ONTARIO HEALTH TECHNOLOGY ASSESSMENT SERIES

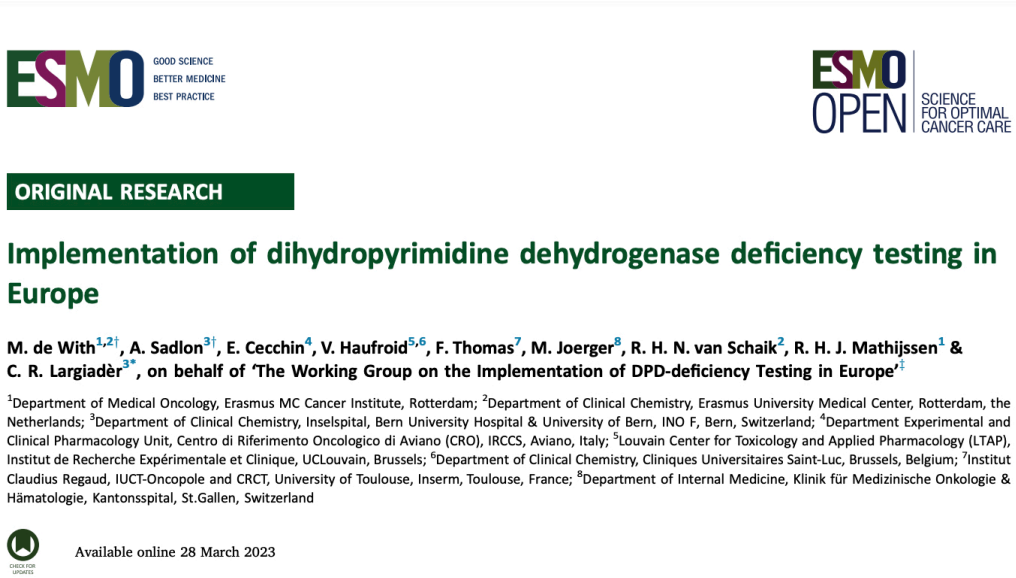
DPYD Genotyping in Patients Who Have Planned Cancer Treatment With Fluoropyrimidines: A Health Technology Assessment

"*The Ontario Health Technology Advisory Committee* ***recognized that the DPYD variants listed in the recommendation are more common in White populations*** *and that DPYD variants that are more prevalent in other racial/ethnic groups have not been studied as extensively.*

The committee advises the Ministry of Health that implementation strategies for DPYD genotyping in Ontario ***should include the collection of data on race/ethnicity to inform care for all patients***"

Dr. Anil Kapoor’s son and one brother has the same variant

Frequency just doubled !



ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

ESMO OPEN SCIENCE FOR OPTIMAL CANCER CARE

ORIGINAL RESEARCH

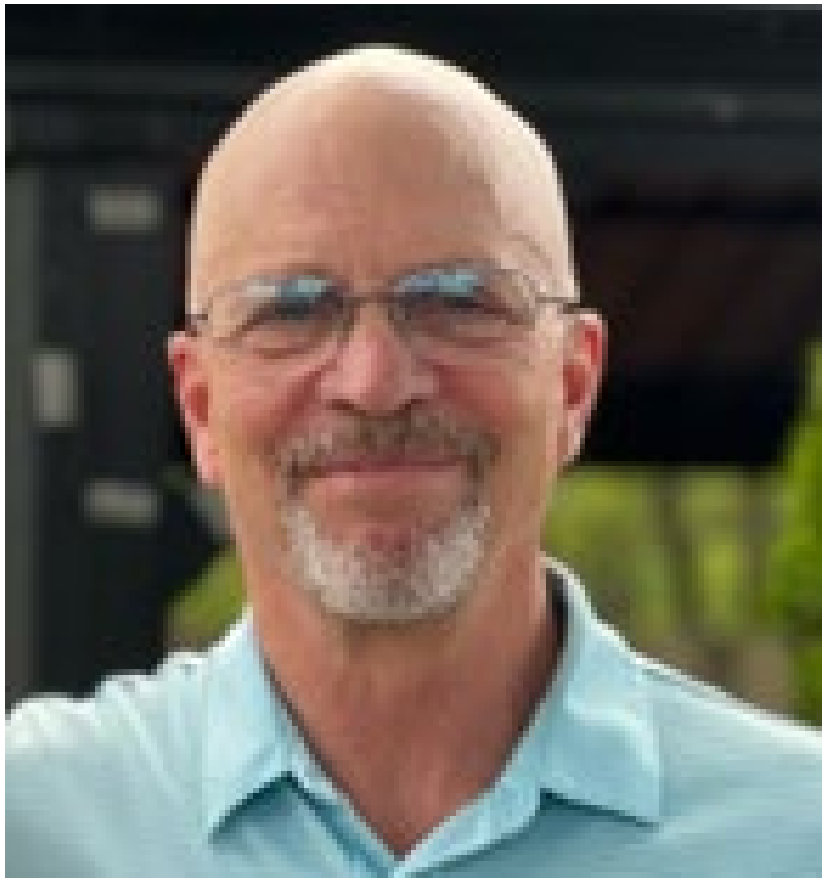
Implementation of dihydropyrimidine dehydrogenase deficiency testing in Europe

M. de With[1,2†], A. Sadlon[3†], E. Cecchin[4], V. Haufroid[5,6], F. Thomas[7], M. Joerger[8], R. H. N. van Schaik[2], R. H. J. Mathijssen[1] & C. R. Largiadèr[3*], on behalf of 'The Working Group on the Implementation of DPD-deficiency Testing in Europe'[‡]

[1]Department of Medical Oncology, Erasmus MC Cancer Institute, Rotterdam; [2]Department of Clinical Chemistry, Erasmus University Medical Center, Rotterdam, the Netherlands; [3]Department of Clinical Chemistry, Inselspital, Bern University Hospital & University of Bern, INO F, Bern, Switzerland; [4]Department Experimental and Clinical Pharmacology Unit, Centro di Riferimento Oncologico di Aviano (CRO), IRCCS, Aviano, Italy; [5]Louvain Center for Toxicology and Applied Pharmacology (LTAP), Institut de Recherche Expérimentale et Clinique, UCLouvain, Brussels; [6]Department of Clinical Chemistry, Cliniques Universitaires Saint-Luc, Brussels, Belgium; [7]Institut Claudius Regaud, IUCT-Oncopole and CRCT, University of Toulouse, Inserm, Toulouse, France; [8]Department of Internal Medicine, Klinik für Medizinische Onkologie & Hämatologie, Kantonsspital, St.Gallen, Switzerland

Available online 28 March 2023

Some European centres do PCR and NGS Whole Genome DPYD sequencing



ADVOCATES FOR UNIVERSAL DPD/DPYD TESTING

www.Test4DPD.org

Hope

Name of Individual or Institute	City	State
Dana Farber Cancer Institute	Boston	MA
Dartmouth Cancer Center	Lebanon	NH
Atrium Health	Charlotte	NC
University of Michigan	Ann Arbor	MI
Indiana University	Bloomington	IN
St Jude Children's Hospital	Memphis	TN
St Elizabeth Healthcare (Cincinnati region)	Edgewood	KY
Ochsner Health	New Orleans	LA
Northshore -- Edwards Elmhurst Health	Evanston	IL
Cleveland Clinic	Cleveland	OH
Moffitt Cancer Center	Tampa	FL
Sanford Imagenetics	Sioux Falls	SD
University of Colorado	Aurora	CO
Wentworth-Douglass Hospital Seacoast Cancer Center	Dover	NH
Christ Hospital Health Network	Cincinnati	OH
Yale New Haven Health	New Haven	CN
Johns Hopkins University	Baltimore	MD
Geisinger Medical Center	Danville	PA
University of Minnesota	Minneapolis	MN
Georgetown Lombardi Cancer Center	Washington	DC
University of Pennsylvania Health System	Philadelphia	PA

Key Takeaways

- Guidelines need to be objective, evidence-based
- Feasible to apply Gold standard to development of Guidelines
- Reconcile disparate recommendations from various jurisdictions
- Truly recognize the diversity of populations
- Lives depend on high quality, objective, equitable, comprehensive Guidelines

END

Thanks to Ken Suprenant, Karen Merritt, Dr. Steven Offer, Dr. Jai Patel, Dr. CB Allard, Dr. Peter Nygren, Kris Gregory

Dedicated to my brother, Dr. Anil Kapoor