

Dihydropyrimidine Dehydrogenase Gene (*DPYD*) Testing and Fluoropyrimidine Treatment in the United States – a Sentinel Distributed Database Study

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Objective

To assess whether patients received *DPYD* genetic testing before or after initiation of fluoropyrimidines.

Introduction

- The enzyme dihydropyrimidine dehydrogenase (DPD) encoded by the *DPYD* gene plays an important role in the breakdown of fluoropyrimidines.
- Fluoropyrimidines are widely used for the treatment of solid tumors.
- Individuals with certain homozygous or compound heterozygous variants of the *DPYD* gene have reduced enzyme activity and are at increased risk for acute early-onset toxicity and serious adverse reactions.
- Warnings related to DPD deficiency for fluoropyrimidine products were incrementally strengthened through multiple labeling updates since 2015. Most recently, the labeling for Xeloda (capecitabine) and fluorouracil products was updated in October 2025 and February 2026, respectively, to recommend *DPYD* testing before fluoropyrimidine administration.
- The extent of *DPYD* testing among U.S. patients, prior to the most recent updated product labeling, has not been fully characterized.
- We assessed the frequency of *DPYD* gene testing, among insured patients initiating fluoropyrimidine treatment in the United States, in the period prior to the most recent updated product labeling.

Results

Table 1. Cohort characteristics for patients initiating fluoropyrimidine treatment by any fluoropyrimidine, fluorouracil, fluorouracil excluding topical products, and capecitabine

Cohort	Any Fluoropyrimidine	Fluorouracil ¹	Non-topical fluorouracil	Capecitabine
Number of patients	1,141,786	1,091,685	268,437	77,663
Characteristics	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)
Age (years)	72.3 (9.1)	72.7 (8.9)	69.1 (9.3)	61.6 (11.2)
	n (%)	n (%)	n (%)	n (%)
Age				
0-17 years	97 (0.0)	79 (0.0)	42 (0.0)	23 (0.0)
18-24 years	287 (0.0)	227 (0.0)	181 (0.1)	98 (0.1)
25-40 years	12,315 (1.1)	8,815 (0.8)	5,495 (2.0)	4,951 (6.4)
41-64 years	211,059 (18.5)	184,556 (16.9)	70,082 (26.1)	42,260 (54.4)
≥ 65 years	918,028 (80.4)	898,008 (82.3)	192,637 (71.8)	30,331 (39.1)
Sex				
Female	525,681 (46.0)	491,332 (45.0)	127,398 (47.5)	46,395 (59.7)
Male	616,105 (54.0)	600,353 (55.0)	141,039 (52.5)	31,268 (40.3)
Race				
American Indian or Alaska Native	2,178 (0.2)	1,926 (0.2)	967 (0.4)	371 (0.5)
Asian	8,514 (0.7)	6,447 (0.6)	5,466 (2.0)	3,042 (3.9)
Black or African American	27,486 (2.4)	21,078 (1.9)	20,160 (7.5)	9,029 (11.6)
Multi-racial	4,944 (0.4)	4,380 (0.4)	1,285 (0.5)	914 (1.2)
Native Hawaiian or Other Pacific Islander	1,100 (0.1)	799 (0.1)	531 (0.2)	428 (0.6)
Unknown	155,867 (13.7)	139,714 (12.8)	46,911 (17.5)	25,875 (33.3)
White	941,697 (82.5)	917,341 (84.0)	193,117 (71.9)	38,004 (48.9)
Hispanic Origin				
Yes	15,055 (1.3)	11,322 (1.0)	7,714 (2.9)	5,233 (6.7)
No	914,506 (80.1)	886,920 (81.2)	202,497 (75.4)	41,762 (53.8)
Unknown	212,225 (18.6)	193,443 (17.7)	58,226 (21.7)	30,668 (39.5)
Number of initiators by year				
2018	151,836 (13.3)	144,174 (13.2)	34,505 (12.9)	11,438 (14.7)
2019	159,432 (14.0)	151,735 (13.9)	38,305 (14.3)	11,805 (15.2)
2020	152,179 (13.3)	143,803 (13.2)	37,533 (14.0)	12,873 (16.6)
2021	169,166 (14.8)	160,043 (14.7)	40,714 (15.2)	13,658 (17.6)
2022	150,560 (13.2)	145,333 (13.3)	35,952 (13.4)	8,382 (10.8)
2023	160,472 (14.1)	155,000 (14.2)	37,570 (14.0)	8,992 (11.6)
2024	185,112 (16.2)	179,337 (16.4)	41,284 (15.4)	9,268 (11.9)
2025	13,029 (1.1)	12,260 (1.1)	2,574 (1.0)	1,247 (1.6)
Health Characteristics				
Cancer diagnosis in 183 days prior to treatment initiation ²				
Breast Cancer	68,255 (6.0)	47,037 (4.3)	15,227 (5.7)	22,649 (29.2)
Colorectal Cancer	142,428 (12.5)	122,151 (11.2)	117,771 (43.9)	39,808 (51.3)
Esophageal Cancer	25,181 (2.2)	24,137 (2.2)	24,082 (9.0)	2,043 (2.6)
Pancreatic Cancer	56,139 (4.9)	52,711 (4.8)	53,540 (19.9)	8,139 (10.5)
Other Gastrointestinal Cancer	93,129 (8.2)	82,743 (7.6)	81,492 (30.4)	17,755 (22.9)
Basal/Squamous Cell Skin Cancer	570,508 (50.0)	568,741 (52.1)	53,995 (20.1)	2,665 (3.4)

1. Includes patients indexing on any fluorouracil (topical products and non-topical products administered intravenously).
2. Column percentages may not add to 100.

Table 2. *DPYD* testing assessment by any fluoropyrimidine, fluorouracil, non-topical fluorouracil, and capecitabine cohorts¹

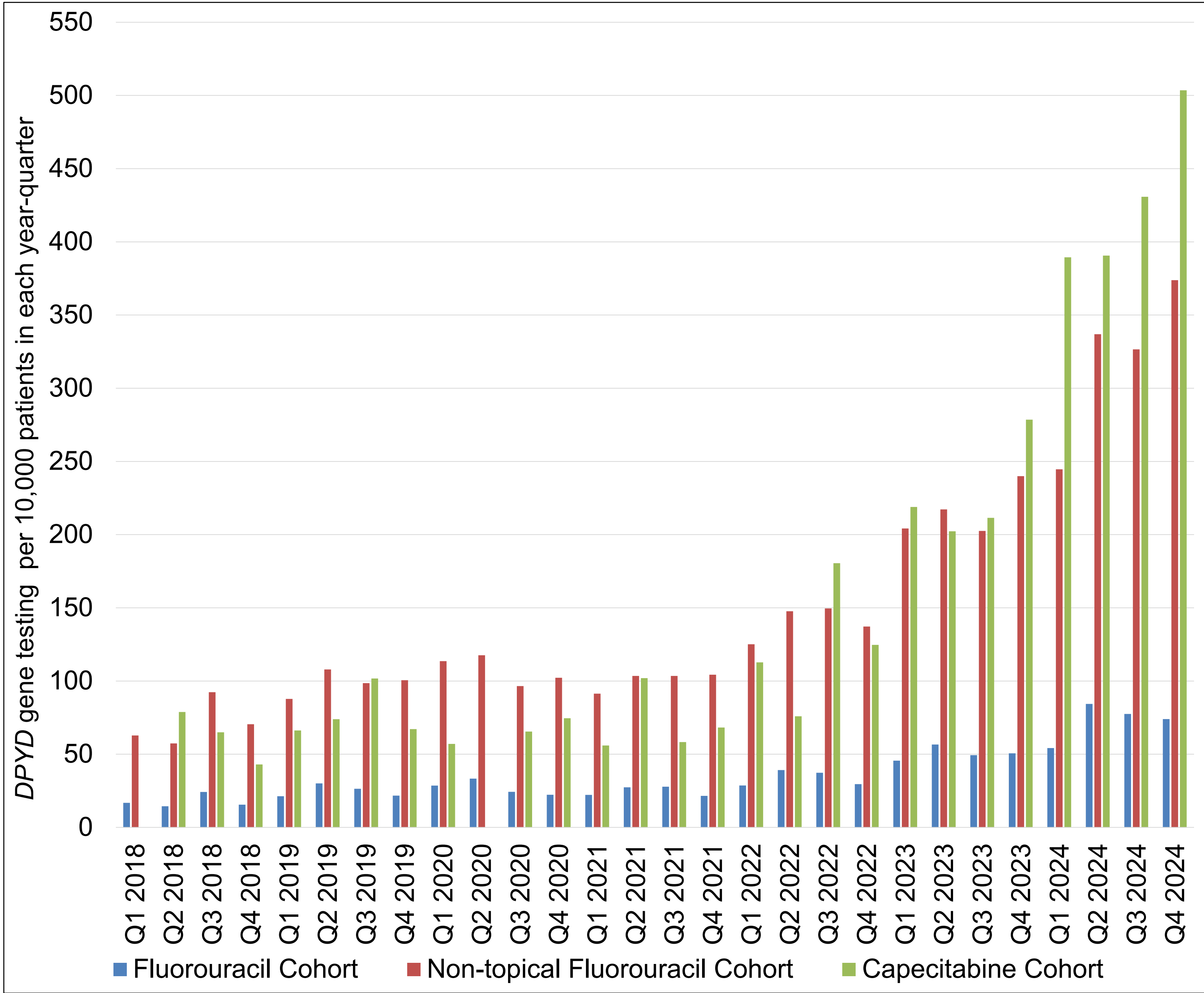
Cohort	Any Fluoropyrimidine	Fluorouracil ²	Non-topical Fluorouracil	Capecitabine
Number of patients	1,141,786	1,091,685	268,437	77,663
	n (%)	n (%)	n (%)	n (%)
<i>DPYD</i> Testing Overall ^{3,4}	5,084 (0.4)	4,258 (0.4)	4,319 (1.6)	1,089 (1.4)
60 days before fluoropyrimidine initiation	3,353 (0.3)	2,839 (0.3)	2,908 (1.1)	674 (0.9)
60 days after fluoropyrimidine initiation	1,766 (0.2)	1,442 (0.1)	1,434 (0.5)	428 (0.6)
<i>DPYD</i> Testing excluding CPT codes 0349U or 81418				
60 days before fluoropyrimidine initiation	3,010 (0.3)	2,552 (0.2)	2,616 (1.0)	608 (0.8)
60 days after fluoropyrimidine initiation	1,706 (0.1)	1,395 (0.1)	1,396 (0.5)	407 (0.5)

1. Testing numbers in the any fluoropyrimidine cohort may be lower than the sum of the testing numbers for the fluorouracil and capecitabine cohorts due to how exposure washout was applied. Testing numbers and percentages for 60 days before and 60 days after fluoropyrimidine initiation may not perfectly sum to the numbers and percentages for *DPYD* testing overall.
2. Includes patients indexing on any fluorouracil (topical products and non-topical products administered intravenously).
3. *DPYD* testing refers to CPT codes 81232, 0349U, and 81418.
4. Refers to overall *DPYD* testing in any care setting within ± 60 days of treatment initiation.

Methods

- Study design:** Retrospective cohort study, among insured patients initiating fluoropyrimidine treatment, assessing *DPYD* testing patterns.
- Study period:** January 1, 2018, to May 31, 2025.
- Data source:** Thirteen data partners in the U.S. Food and Drug Administration’s Sentinel Distributed Database.
- Inclusion criteria:** Patients with medical and drug coverage for 183 days (with gaps in coverage of up to 45 days allowed) and diagnosis of one of the following cancers: breast, colorectal, esophageal, pancreatic, other gastrointestinal, or basal/squamous cell carcinoma of the skin.
- Cohorts examined:** Patients indexing on incident use of any fluoropyrimidine and separately for fluorouracil (including topical products and non-topical products administered intravenously), fluorouracil excluding topical products (i.e., non-topical products administered intravenously), and capecitabine.
- Analysis:** We estimated the proportion of patients with a *DPYD* test, defined using Current Procedural Terminology (CPT) codes 81232, 0349U, and 81418, for each of the fluoropyrimidine cohorts. We assessed whether *DPYD* testing occurred in the 60 days before or in the 60 days after treatment initiation (i.e., within ± 60 days of treatment initiation). Additionally, we assessed *DPYD* testing for CPT code 81232 only. We also calculated the proportion of patients receiving *DPYD* testing by year-quarter per 10,000 treatment initiators.

Figure 1. *DPYD* gene testing¹ per 10,000 fluoropyrimidine treatment initiators, by year-quarter^{2,3}



1. *DPYD* gene testing refers to CPT codes 81232, 0349U, and 81418.
2. *DPYD* gene testing for the capecitabine cohort is masked for some quarters due to small cell sizes.
3. *DPYD* gene testing estimates provided through Q4 2024, which is the last full year for testing estimates.

Limitations

Observations are limited to insured patient populations in which a medical billing code could be captured for *DPYD* testing. *DPYD* testing percentages provided do not include some patient populations (e.g., special or other vulnerable patient populations such as uninsured patients) and may not be generalizable. This study was not designed to report the presence or absence of DPD deficiency. We cannot definitively state whether these patients had partial or complete DPD deficiency or any resulting adverse reaction.

Conclusion

DPYD testing was ≤ 1.6% across cohorts of patients initiating fluoropyrimidine treatment; however, testing began to increase among patients initiating non-topical fluorouracil and capecitabine in quarter 1 of 2023. The percentages provided (0.4% to 1.6%) offer a baseline ascertainment of *DPYD* testing in the U.S. insured patient population. Additional studies are needed to determine whether *DPYD* testing in the United States (overall and prior to fluoropyrimidine treatment initiation) increased following labeling changes to fluorouracil and capecitabine products. *DPYD* testing observed after treatment initiation, in this study, is consistent with complete DPD deficiency prevalence in the general population and may indicate testing conducted in response to severe fluoropyrimidine toxicity.

Disclaimers

The contents are those of the authors and do not necessarily represent the official views of, nor an endorsement by, the U.S. Food and Drug Administration (FDA), Centers for Disease Control and Prevention/the Agency for Toxic Substances and Disease Registry (CDC/ATSDR), or the U.S. Department of Health and Human Services (HHS). Use of trade names and commercial sources is for identification only and does not imply endorsement by the FDA, CDC/ATSDR, or HHS. This project was supported by Task Order 75F40125F19015 under Master Agreement 75F40119D10037 from the U.S. Food and Drug Administration. A.R., A.T., and D.E. are employees of Harvard Pilgrim Health Care Institute, an organization which conducts work for government and private organizations, including pharmaceutical companies. Many thanks are due to the Sentinel Data Partners who provided data used in this analysis.