# DPD Deficiency

## General Overview

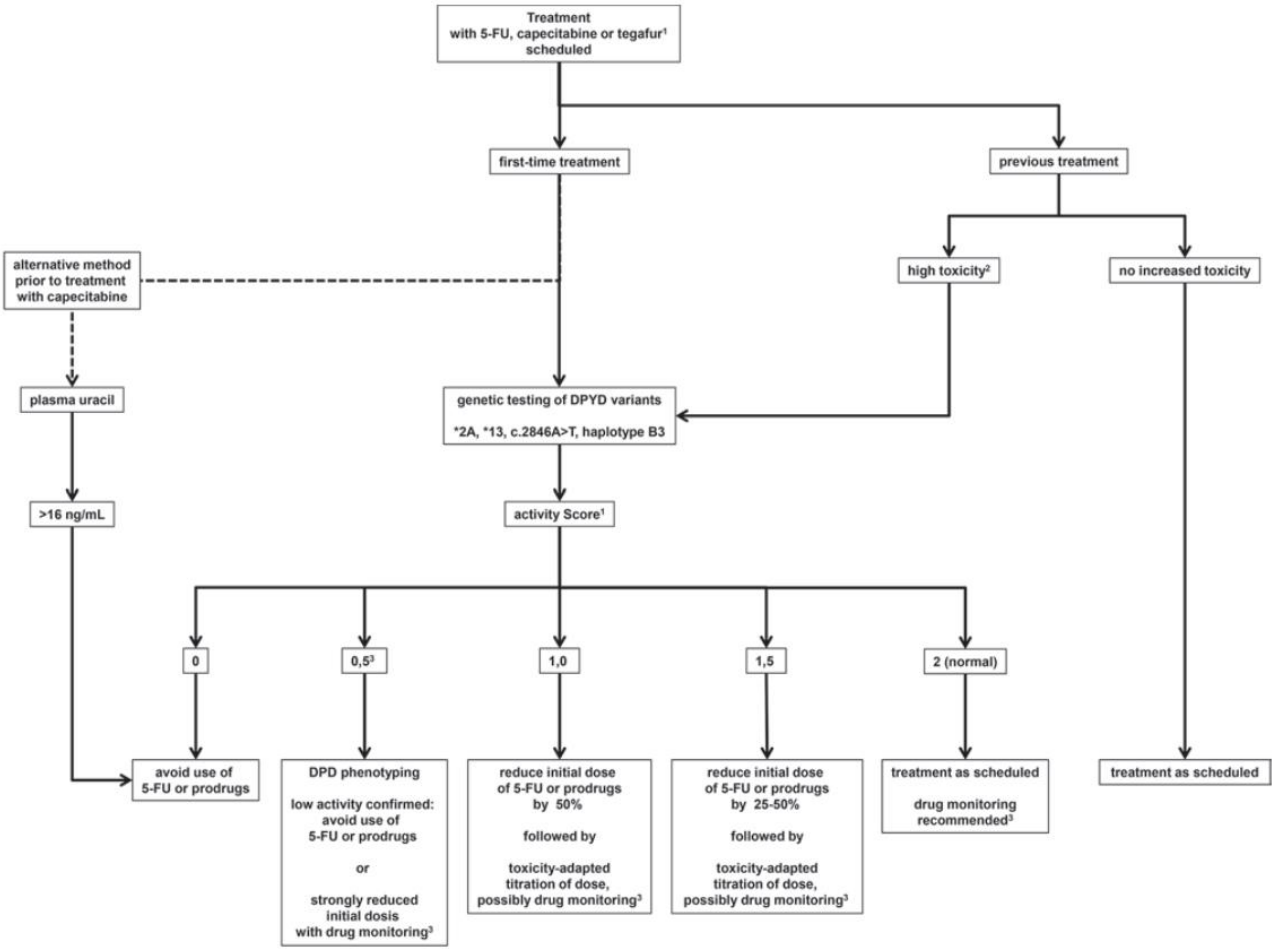
- Dihydropyrimidine dehydrogenase (DPD), the first of three enzymes in the fluoropyrimidine metabolic pathway is the rate-limiting enzyme in the FU catabolism
- Patients who are partially or totally deficient in DPD activity cannot adequately degrade fluoropyrimidine, leading to increased toxicity, sometimes fatal.
- Molecular analysis of patients with DPD deficiency has identified over 128 mutations and polymorphisms in the *DPYD* gene that may result in partial or total loss of DPD activity.
- Only 4 have been consistently associated with enhanced 5-FU toxicity
    - ***DPYD*2A* SNP**
    - ***DPYD*13* SNP (c.1679T>G)**
    - ***DPYD*9B* SNP (c.2846A>T)**
    - **HapB3** (3 intronic variants and one synonymous variant)
- Complete DPD deficiency is rare. Partial deficiency occurs in 3.5% of women and 1.9% of men
- Inheritance of one of these high risk alleles does not account for all cases of DPD deficiency (sometimes epigenetic mechanisms).
- Other potential genotypes that cause toxicity: *DPYD*4* and *DPYD*5*
- Preemptive testing for *DPYD* variants is recommended by the EMA (but not the FDA)
- Phenotypic testing (enzymatic function) may be an alternative
- More information: All You Need to Know About DPYD Genetic Testing for Patients Treated With Fluorouracil and Capecitabine: A Practitioner-Friendly Guide | JCO Oncology Practice (ascopubs.org)
- Implementation of dihydropyrimidine dehydrogenase deficiency testing in Europe (nih.gov)
- Dihydropyrimidine Dehydrogenase Testing prior to Treatment with 5-Fluorouracil, Capecitabine, and Tegafur: A Consensus Paper (karger.com)

## Guidelines for treatment

| Genotype | Activity score |
|---|---|
| Not carrier of decreased function/no function *DPYD* variant (**1/*1*) | 2.0 |
| Heterozygous carrier of decreased function *DPYD* variant (**1/c.1236G>A or *1/c.2846A>T*) | 1.5 |
| Heterozygous carrier of no function *DPYD* variant (**1/*2A or *1/*13*) | 1 |
| Carrier of two decreased function *DPYD* variants (e.g., **1/c.1236G>A* and **1/c.2846A>T*) or Carrier of one reduced function *DYPD* variant and one no function variant (combination of *c.1236G>A* or **1/c.2846A>T* with **2A* or **13*, such as *c.2846A>T*) | 0.5* |
| Homozygous carrier of no function *DPYD* variant (**2A/*2A; *13/*13*) or Heterozygous carrier of two no function *DPYD* variants (**2A/*13*) | 0 |

The activity score of 0.5 is not always reliable and requires additional phenotyping [24].

Update: December 2023


Treatment with 5-FU, capecitabine or tegafur[1] scheduled
first-time treatment
previous treatment
high toxicity[2]
no increased toxicity
alternative method prior to treatment with capecitabine
plasma uracil
genetic testing of DPYD variants
*2A, *13, c.2846A>T, haplotype B3
>16 ng/mL
activity Score[1]
0
0,5[3]
1,0
1,5
2 (normal)
avoid use of 5-FU or prodrugs
DPD phenotyping
low activity confirmed: avoid use of 5-FU or prodrugs
or
strongly reduced initial dosis with drug monitoring[3]
reduce initial dose of 5-FU or prodrugs by 50%
followed by
toxicity-adapted titration of dose, possibly drug monitoring[3]
reduce initial dose of 5-FU or prodrugs by 25-50%
followed by
toxicity-adapted titration of dose, possibly drug monitoring[3]
treatment as scheduled
drug monitoring recommended[3]
treatment as scheduled