GENESSENSE

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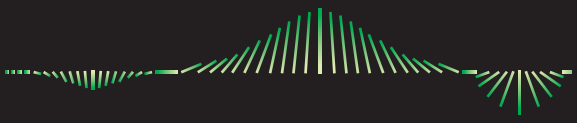
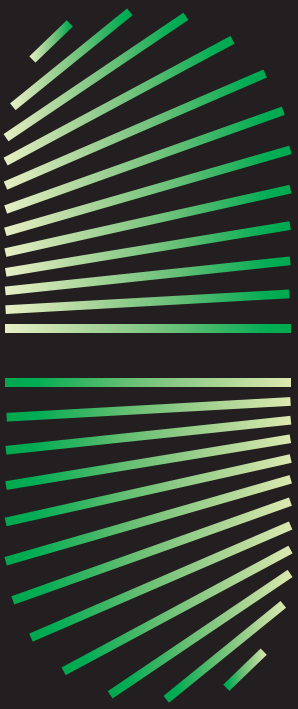
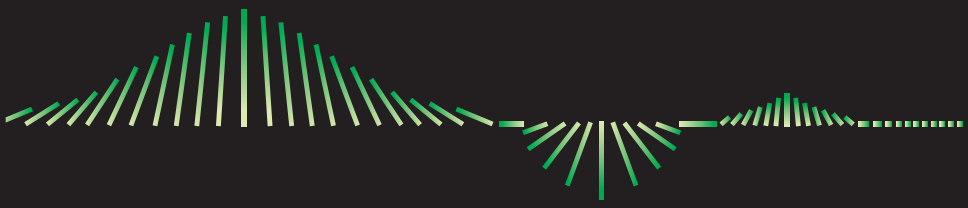




CUREGEN

Oncopharmacogenomics of Fluoropyrimidines



What are Fluoropyrimidines?

Fluoropyrimidines are an antimetabolite class of chemotherapeutic drugs. They target replicating cells.

Intended therapeutic use

Fluoropyrimidines including **5-flouorouracil** and **capecitabine** are used in treatment of cancers

- Colorectal cancer
- Pancreatic cancer
- Gastric cancer
- Breast cancer
- Head cancer
- Neck cancer

Adverse events

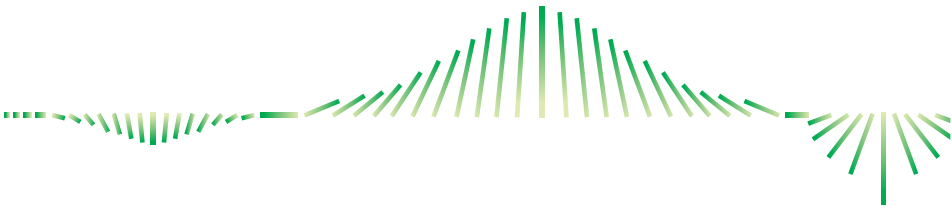
About 30% of patients on Fluoropyrimidines[1] experience adverse reactions[2] including, but not limited to

- Diarrhoea
- Nausea
- Vomiting
- Fatigue
- Hand-foot syndrome (HFS)
- Mucositis
- Neurotoxicity
- Hematological toxicity

Pharmacokinetics of Fluoropyrimidines

Fluoropyromidines are metabolised by rate limiting enzyme dihydropyrimidine dehydrogenase (DPD) encoded by gene *DPYD*.[3]

Genetic variations in *DPYD* gene have been shown to influence activity of DPD and associated with adverse effects of fluoropyrimidines.[4]



Dosing of fluoropyrimidines by DPD phenotype (CPIC guidelines)

PHENOTYPE	POSSIBLE IMPLICATION	DOSING RECOMMENDATION
DPYD normal metabolizer	Normal DPD activity and "normal" risk for fluoropyrimidine toxicity.	Based on genotype, there is no indication to change dose or therapy. Use label recommended dosage and administration.
DPYD intermediate metabolizer	Decreased DPD activity (leukocyte DPD activity at 30% to 70% that of the normal population) and increased risk for severe or even fatal drug toxicity when treated with fluoropyrimidine drugs.	Reduce starting dose based on activity score followed by titration of dose based on toxicity or therapeutic drug monitoring (if available) *Activity score 1: Reduce dose by 50% Activity score 1.5: Reduce dose by 25% to 50%
DPYD poor metabolizer	Complete DPD deficiency and increased risk for severe or even fatal drug toxicity when treated with fluoropyrimidine drugs.	Activity score 0.5: In the event, based on clinical advice, alternative agents are not considered a suitable therapeutic option, 5-fluorouracil should be administered at a strongly reduced dose with early therapeutic drug monitoring. Activity score 0: Avoid use of 5-fluorouracil or 5-fluorouracil prodrug-based regimens.

Common decreased function *DPYD* variants

GENETIC VARIATION	POSSIBLE IMPACT
*DPYD*2A* (c.1905+1G>A)	Loss of DPD enzyme activity
*DPYD*13* (c.1679T>G)	Destabilization of enzyme
DPYD c.2846A>T	Reduction in enzyme activity
DPYD HapB3 (c.1129–5923C>G)	Reduction in enzyme activity

CUREGEN advantage

Curegen, powered by MedGenome, is a precision pharmacogenomics test for individuals that checks for metabolism of more than 46 drugs/drug classes.

TEST CODE	SAMPLE TYPE	TURN AROUND TIME
GES002 - Curegen	Saliva/ Blood	14 working days
MGM1176 - *DPYD* gene analysis for 5-FU drug sensitivity	Blood	14 working days

References

1. Meta-analysis Group in Cancer, et al. Toxicity of Fluorouracil in Patients with Advanced Colorectal Cancer: Effect of Administration Schedule and Prognostic Factors. *J. Clin. Oncol*. 1998; 16: 3537–3541
2. Adrienne G. Waks, Eric P. Winer, 69 - Chemotherapy and HER2-Directed Therapy for Metastatic Breast Cancer, Editor(s): Kirby I. Bland, Edward M. Copeland, V. Suzanne Klimberg, William J. Gradishar, The Breast (Fifth Edition), Elsevier, 2018, Pages 885-906.e8, ISBN 9780323359559, https://doi.org/10.1016/B978-0-323-35955-9.00069-6.
3. Amstutz U, et al. Clinical Pharmacogenetics Implementation Consortium (CPIC) Guideline for Dihydropyrimidine Dehydrogenase Genotype and Fluoropyrimidine Dosing: 2017 Update. *Clin Pharmacol Ther*. 2018;103:210-216.
4. Thorn CF, et al.. PharmGKB summary: fluoropyrimidine pathways. *Pharmacogenet Genomics*. 2011;21:237-242.

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