

Title	Screening for dihydropyrimidine dehydrogenase deficiency to decrease the risk of severe toxicities related to fluoropyrimidines (5-fluorouracil or capecitabine)
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Reference	ISBN number: 978-2-37219-416-7, link to full report in French: https://www.has-sante.fr/portail/jcms/c_2891090/fr/methodes-de-recherche-d-un-deficit-en-dihydropyrimidine-deshydrogenase-visant-a-prevenir-certaines-toxicites-severes-associees-aux-traitements-incluant-une-fluoropyrimidine-5-fluorouracile-ou-capecitabine

Each year in France, almost 80,000 new patients receive fluoropyrimidines, a group of anticancer drugs including 5-Fluorouracil [5-FU] and its prodrug capecitabine (Xeloda®), used to treat various types of cancer (mainly digestive, breast and head and neck cancer). Fluoropyrimidines-based chemotherapies, can cause severe toxicities (incidence at around 20%), and rarely but sometimes lethal toxicity (incidence between 0.1 and 1%). Part of these toxicities may be related to deficiency in the activity of the main enzyme enabling elimination of 5-FU, called dihydropyrimidine dehydrogenase (DPD). This deficiency can be partial (around 3 to 8% of individuals) or complete (between 0.01 and 0.5% of individuals). Therefore, the summary of product characteristics of fluoropyrimidines includes a contraindication to treatment in patients with complete DPD loss, and the recommendation for dose adjustment and careful monitoring in partially deficient patients.

Beginning 2018, the French agency in charge of medicinal product safety ruled in favour of routine screening for DPD deficiency before treatment with fluoropyrimidine. In the absence of a previously established consensus as to the methods of implementation of the screening (detection of variants of the *DPYD* gene coding for DPD and/or determination of the activity of the DPD enzyme), the Institut National du Cancer (INCa) [French National Cancer Institute] was approached by the Ministry of Health to draw up recommendations for the said methods. Also, in order to enable reimbursement of the test selected to screen for DPD deficiency for all patients by the French health insurance system, regardless of the laboratory carrying out the test (public or private), its registration on the list of reimbursable medical biology procedures is necessary. This registration decision has to be made by the national health insurance fund, but a prior opinion from the Haute Autorité de Santé (HAS) [French

National Authority for Health] is required. For this reason, the HAS decided to refer the matter to itself and to work jointly with the INCa to be able to return an opinion without delay.

On the basis of the joint assessment carried out, which covered the various examinations on offer (genotyping, phenotyping and combined), the HAS and the INCa recommend testing for DPD deficiency by determination of uracil plasma concentration [uracilemia] where fluoropyrimidine treatment is planned. The HAS also issues a favourable opinion as to registration of the test on the list of reimbursable procedures, as it is considered to be the most likely to be able to identify at least, and as far as possible, all patients with complete DPD deficiency.

This test is recommended in the following conditions:

- pre-analytical conditions: use of blood collection tubes without separator gel and with anticoagulant, maximum delay between sample and centrifugation 1h30mins if the sample is stored at ambient temperature, and 4h if it is stored at + 4°C, centrifugation preferably at + 4°C then immediate freezing of the resulting plasma, transport respecting the cold chain,
- assay technique: by high or ultra-high performance liquid chromatography (several possible detection modalities),
- interpretation and expression of the results:
 - uracilemia \geq 150 ng/ml suggests complete DPD deficiency,
 - uracilemia \geq 16 ng/ml and $<$ 150 ng/ml suggests partial DPD deficiency,
 - interpretation of the results on the basis of these threshold values must take account the fact that uracilemia is a continuous variable and that the risk of severe toxicity increases therefore theoretically as uracilemia increases,

- results turnaround time, from prescription of the test to receipt of the result by the clinician, must ideally be seven days, or ten days maximum,
- treatment adjustment decisions associated with diagnosis of DPD deficiency must be based on discussion between clinicians and biologists.

The HAS and the INCa emphasise that regardless of the test carried out to look for DPD deficiency, not all cases of severe or even lethal toxicity can be avoided through the test. In effect, not all cases of severe toxicity occurring with fluoropyrimidines are caused by DPD deficiency, or are necessarily attributable to fluoropyrimidines in the case of cancer treatment combinations which have the potential to cause severe toxicity.

The two institutions also underline that these recommendations may be updated, according to any new available data considered to have a sufficient level of evidence

The assessment was conducted jointly by the HAS and the INCa. Their conclusions are based on the critical analysis of data available in literature, and the participation of a multidisciplinary panel of nineteen experts (clinicians, biologists, pharmacists, pharmacologists, oncogenetics specialists) brought together in a working group. The contents and conclusions of the report were reviewed nationally by fifteen experts from the specialist areas concerned, not having participated in the working group.

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