DETECTION OF DPYD*2A ALLELE IN DIHYDROPYRIMIDINE
DEHYDROGENASE GENE: PERSPECTIVE
FOR FLUOROPYRIMIDINE-TREATED PATIENTS

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ABSTRACT – Dihydropyrimidine dehydrogenase is a key enzyme involved in the metabolism
of fluoropyrimidine anticancer drugs. Several studies have demonstrated that diminished DPD
activity as a consequence of genetic variations in the DPYD gene limits carrier’s ability to fully
metabolize the drug, resulting in toxicity and adverse events. DPYD*2A (IVS14+1G>A)
represents the most abundant variant allele in the European Caucasian population. Cancer
patients with this gene variant represent a subgroup with higher risk of toxicity when treated
with fluoropyrimidines. Therefore, we have implemented a method for DPYD*2A allele
genotyping. In our pilot study performed in a group of individuals derived from our regional
reference population, we found that none out of 47 subjects was a carrier of the DPYD*2A
variant allele.

INTRODUCTION

Dihydropyrimidine dehydrogenase (DPD; EC 1.3.1.2) is the initial and rate-limiting
enzyme of pyrimidine bases (uracil and thymine) catabolic pathway. DPD is also the key
enzyme involved in metabolism of pyrimidine analog drugs including 5-fluorouracil (5-FU)
and its derivates (e. g. capecitabine) (Amstutz et al., 2011) (Fig. 1). Fluoropyrimidine
drugs are widely used as chemotherapeutic agents in the treatment of solid carcinomas
including gastrointestinal (CRC – colorectal cancer) and breast cancer. The human gene
encoding DPD (DPYD; OMIM 612779) maps to chromosome 1p21.3 and consists of 23
exons (Wei et al., 1998). Polymorphisms or mutations in genes encoding drug-
metabolizing enzymes are responsible for wide variability in individual response to
standard doses of anticancer drugs. In up to 40% of patients, the use of 5-fluorouracil
therapy is compromised by development of severe gastrointestinal and hematological
toxicity and neurotoxicity (Caudle et al., 2013). As DPD is the main enzyme involved in
fluoropyrimidine metabolism it is assumed that genotyping of DPYD gene helps to identify
individuals predisposed to high risk of adverse events related to fluoropyrimidine toxicity.