Dihydropyrimidine Dehydrogenase Deficiency, a Pharmacogenetic Syndrome Associated with Potentially Life-Threatening Toxicity Following 5-Fluorouracil Administration

Hany Ezzeldin, Robert Diasio

Abstract

Dihydropyrimidine dehydrogenase (DPD) deficiency is a pharmacogenetic syndrome associated with potentially life-threatening toxicity following the administration of standard doses of 5-fluorouracil. This syndrome derives its importance from the fact that approximately 2 million patients receive the drug worldwide each year. Population studies have suggested that 4%-7% of the American population exhibit dose-limiting toxicity that might be associated with a genetic defect in the DPYD gene that encodes for the DPD enzyme. During the past several years it has become increasingly clear that genetics is a major determinant of the variability in drug response, accounting for the probability of drug efficacy and the likelihood of toxic drug reactions. This article briefly discusses the clinical presentation, laboratory diagnosis, pharmacokinetics, inheritance, and the clinical management options of DPD deficiency. The variability of DPD enzyme activity in population studies and the different DPYD alleles together with new phenotypic and genotypic methods of screening for DPD deficiency will also be reviewed.

Introduction

Adverse drug reactions account for more than 100,000 deaths in the United States per year and have been reported as the fourth leading cause of death after heart diseases, cancer, and stroke.1 Genetics is a major determinant of the variability in drug response, accounting for drug efficacy and toxicity. Although 5-fluorouracil (5-FU) remains one of the most widely prescribed cancer chemotherapy drugs and is generally well tolerated, a recent population study suggested that 31%-34% of treated patients exhibit dose-limiting toxicity.2 Approximately 40%-50% of patients with grade 3/4 toxicity to 5-FU displayed partial or profound dihydropyrimidine dehydrogenase (DPD) deficiency3,4 as a result of a genetic defect.

Pharmacokinetic studies have shown that the catabolic pathway of 5-FU metabolism is important in the systemic toxicity and the antitumor efficacy of 5-FU-based treatment.5-7 Like many other cancer chemotherapy drugs, 5-FU has a relatively narrow therapeutic window, with a small difference between the median therapeutic efficacious dose and the median toxic dose. Some examples of chemotherapy drugs with efficacy and/or toxicity are known to be affected by gene expression levels of enzymes involved in their metabolic pathway. Three examples are now being recognized in cancer chemotherapy and metabolizing enzymes associated with pharmacogenetic syndromes: the DPD enzyme involved in the metabolism of 5-FU, 5-fluoro-2'-deoxyuridine, and capecitabine; the uridine diphosphate glucuronosyltransferase enzyme implicated in the metabolism of irinotecan; and the thiopurine methyltransferase enzyme responsible for the metabolism of 6-mercaptopurine, azathioprine, and 6-thioguanine.

The importance of DPD in 5-FU catabolism has been dramatically illustrated by a pharmacogenetic syndrome caused by molecular defects in the DPYD gene that can result in a
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Figure 1 Anabolic and Catabolic Pathways of 5-FU Metabolism^5

The activity of the DPD enzyme regulates the bioavailability of 5-FU. The anabolic pathway is responsible for the incorporation of the active metabolites into RNA and DNA. The 5-FU generates FUdUMP, which competes with deoxyuridine monophosphate (e.g., FUMP, the natural substrate of thymidylate synthase), on the active catalytic site, preventing the formation of thymidylate, which is essential for DNA synthesis. The catabolic pathway is essentially responsible for approximately 85% of 5-FU metabolism. Activations: CFBAL = carboxy-fluoro-β-alanine; DHFU = dihydrofluorouracil; dR-1-P = deoxyribose-1-phosphate; FBAL = α-fluoro-β-alanine; FdUDP = fluorodeoxyuridine diphosphate; FdUTP = fluorodeoxyuridine triphosphate; FdUMP = fluorouridine diphosphate; FUMP = fluorouridine monophosphate; Furd = fluorouridine; FUTP = fluorouridine triphosphate; OPRT = orotate phosphoribosyltransferase; PDPK = pyrimidine diphosphate kinase; PMPK = pyrimidine monophosphate kinase; PRPP = phosphoribosyl pyrophosphate; R-1-P = ribose-1-phosphate; TP = thymidine phosphorylase; TK = thymidine kinase; UK = uridine kinase; UP = uridine phosphorylase.

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Complete (profound) or partial loss of DPD enzyme activity.5-11 Pharmacogenetics refers to the influence of genetic differences on patients’ response to drugs.12

Most of the pharmacogenetic syndromes that were first identified were monogenic, having a common allele or alleles responsible for the variable response among individuals sharing the same phenotype.13 However, in drugs that are metabolized by several different enzymes in a multistep metabolic pathway, the possibility of a genetic variation in any or all of the metabolizing enzymes (polygenic) will result in a multimodal overlapping frequency distribution, and the relatively simple one-to-one relation observed, for example, with thiopurine methyltransferase enzyme or the cytochrome P450 enzyme, would not be observed.13

Since the late 1980s, there has been an increasing number of case reports describing severe toxicity (including death) to patients receiving 5-FU. Excessive availability of 5-FU metabolites11 affects the primary target sites in both cases, leading to increased side effects and toxicity.20 Nausea, vomiting, rectal bleeding, fever (associated with neutropenia), mucositis, stomatitis, and diarrhea,21-23 which is similar to that of an accidental overdose of 5-FU. Excessive availability of 5-FU metabolites11 affect the primary target sites in both cases, leading to increased side effects and toxicity.20 Nausea, vomiting, rectal bleeding, and/or skin changes may also occur. Neurologic abnormalities include cerebellar ataxia, a broad-based gait, and changes in cognitive function, and are often subtle, but when these symptoms occur, there should be increased suspicion of DPD deficiency. Changes in the level of consciousness, reaching a coma state, is mostly encountered in cases with profound DPD deficiency.2,11 Initially at the time of presentation, routine chemistry tests and urine analysis show no abnormalities secondary to DPD deficiency. However, abnormal blood counts, with leukopenia, a decrease in the absolute neutrophil count (often near 0), and possibly thrombocytopenia and anemia, are most typically seen when 5-FU is administered as a bolus with or without leucovorin.11,21,23

Clinical Presentation of Dihydropyrimidine Dehydrogenase Deficiency

The typical clinical presentation of DPD deficiency includes fever (associated with neutropenia), mucositis, stomatitis, and diarrhea,21-23 which is similar to that of an accidental overdose of 5-FU. Excessive availability of 5-FU metabolites affect the primary target sites in both cases, leading to increased side effects and toxicity.20 Nausea, vomiting, rectal bleeding, and/or skin changes may also occur. Neurologic abnormalities include cerebellar ataxia, a broad-based gait, and changes in cognitive function, and are often subtle, but when these symptoms occur, there should be increased suspicion of DPD deficiency. Changes in the level of consciousness, reaching a coma state, is mostly encountered in cases with profound DPD deficiency.2,11 Initially at the time of presentation, routine chemistry tests and urine analysis show no abnormalities secondary to DPD deficiency. However, abnormal blood counts, with leukopenia, a decrease in the absolute neutrophil count (often near 0), and possibly thrombocytopenia and anemia, are most typically seen when 5-FU is administered as a bolus with or without leucovorin.11,21,23

Laboratory Diagnosis of Dihydropyrimidine Dehydrogenase Deficiency

In general, the clinical diagnosis of DPD deficiency remains difficult because the appearance of life-threatening toxicity secondary to treatment with 5-FU is typically the first symptom
of this pharmacogenetic syndrome. Elevated levels of uracil and/or thymine (the natural substrates for DPD) in plasma or urine were the basis for laboratory diagnosis of complete or profound DPD deficiency.11,24 In the past, diagnostic laboratory methods have included mass spectrometry (mainly for confirmation), thin-layer chromatography, and high-performance liquid chromatography (HPLC) to assay for thymine and uracil. Partial DPD deficiency is more difficult to detect with the aforementioned methods. This has led to the development of a radioenzymatic assay for the DPD enzyme.16 This radiometric assay remains the gold standard for diagnosing DPD deficiency, even after the development of genotypic assays, because of the presence of the multiple heterozygous sequence variations detected in most DPD-deficient patients. Various cells and tissues can be examined with this assay. Peripheral blood mononuclear (PBM) cells have been particularly useful because the DPD is present without the subsequent enzymes of the pyrimidine catabolic pathway, making the assessment of DPD activity in PBM cells more suitable.

There have been many attempts to develop genotypic tests for the identification of DPD-deficient patients.24-26 The complexity of the DPYD gene (with 23 exons), combined with the large number of reported sequence variations (>30; Table 1) and the fact that DPD enzyme assays are often not possible in patients who experience lethal toxicity, has resulted in limited usefulness of single-mutation genotyping tests such as restriction fragment length polymorphism or single strand conformation polymorphism.

In addition, the sequence variations reported in previous studies have not always been correlated with a specific phenotype (eg, DPD enzyme activity).27-29 This has resulted in confusion over which sequence variations result in decreased DPD activity. Earlier studies of DPD-deficient patients have reported homozygote mutations resulting in complete (profound) DPD deficiency.4,9,14,30,31 More recently, our laboratory described the characterization of a profoundly DPD-deficient patient having a complex compound heterozygote genotype.24 In addition to confirming a codominant pattern of inheritance for this pharmacogenetic disease, this study demonstrated the utility of a familial approach to examine genotype and phenotype. However, many of the reported sequence variations, as mentioned later in this review, are of questionable importance or impact on DPD enzyme activity.

### Pharmacokinetics of Dihydropyrimidine Dehydrogenase Deficiency

The disposition and pharmacokinetics of 5-FU were evaluated in one of the first reported DPD-deficient patients, who had been shown to have no detectable DPD enzyme activity.11 A test dose of 5-FU (25 mg/m², 600 µCi [³H-6]-5-FU) was administered as an intravenous bolus, after which plasma, urine, and cerebrospinal fluid were sampled at specified times. The 5-FU was detected in the plasma at unusually high levels for ≥8 hours, demonstrating a markedly altered pharmacokinetic pattern for this patient. In this patient, the biological half-life was 159 minutes, with a clearance of 70 mL/min/m², and 89.7% of the administered [³H]-5-FU was excreted unchanged in the 24 hours after administration of the drug. This is in contrast to a group of 10 normal control patients who were given a typical dose of 5-FU (450 mg/m²), in which the half-life was 13 minutes ± 7, clearance was 594 mL/min/m² ± 198, and 9.8% ± 1.6% of the administered 5-FU was excreted in the initial 24 hours.
Inheritance of Dihydropyrimidine Dehydrogenase Deficiency

The pattern of inheritance of DPD deficiency was investigated in a family study of one of the initial patients who developed severe toxicity after 5-FU administration and who was subsequently shown to have DPD deficiency. The patient’s father, daughter, and son had enzyme levels intermediate between the patient’s level (essentially 0) and the level observed in the normal population, suggesting that the patient’s relatives were partially deficient as a result of a heterozygous mutant gene, whereas the patient may have inherited 2 copies of a mutant gene (homozygous). These data, together with a history of consanguinity in this family, initially suggested an autosomal recessive pattern of inheritance. Although earlier studies reported a single homozygous mutation in the DYPD gene associated with DPD deficiency, subsequent reports demonstrated that multiple heterozygous mutations could occur in the same patient. A recent report from our laboratory that characterized a profoundly DPD-deficient patient and family members demonstrated that profound DPD deficiency can result from a complex compound heterozygote genotype. This same patient was previously thought to have an autosomal recessive pattern of inheritance.

Also, a recent study of patients who experienced lethal toxicity after administration of a standard dose of 5-FU showed that lethal toxicity can occur in partially DPD-deficient individuals (ie, heterozygote for a mutant gene) after administration of 5-FU and is not exclusive to profoundly DPD-deficient individuals (ie, homozygous for a mutant gene) as previously suggested. Therefore, population studies show that partial DPD deficiency is more common than profound deficiency, and lethal toxicity to treatment with 5-FU may be more common than originally thought. The complicated heterozygote genotype seen in these patients combined with DPD deficiency being an autosomal codominant inherited syndrome preclude the use of simple genotypic assays that identify 1 or 2 mutations as a method for identifying DPD-deficient individuals. These multiple heterozygote genotypes (which are more difficult to accurately characterize) may be responsible for some of the conflicting reports that suggested a lack of correlation between phenotype and genotype.

Clinical Management of Dihydropyrimidine Dehydrogenase Deficiency

Currently, most cases of DPD deficiency are diagnosed long after the administration of 5-FU because of the lack of a user-friendly test that permits rapid screening for DPD deficiency. Despite the limited options in managing patients’ toxicities, several approaches have been suggested as follows.15

Termination of Further Administration of 5-FU

Termination of any further administration of 5-FU (or related drug) if the clinical manifestation suggests DPD deficiency. Hemodialysis and Hemoperfusion

Hemodialysis and hemoperfusion were suggested to rapidly remove any drug remaining in the body of a patient who has already finished receiving 5-FU and is suspected of having a DPD deficiency. However, in the presence of normal renal function, neither is likely to be effective, particularly because 5-FU, even in the presence of complete DPD deficiency, is rapidly cleared via the urine.11

Alternative methods used to manage the increased risk of 5-FU toxicity include:

Administration of the Pyrimidine Nucleosides. Administration of the pyrimidine nucleosides (thymidine or uridine) can be undertaken as soon as possible (within a few hours) after 5-FU administration to overcome the block in thymidylate synthesis resulting from the inhibition of thymidylate synthase by the 5-FU nucleotide FdUMP. This has been used in few patients, with questionable results. As with hemodialysis and hemoperfusion, this would have to be performed soon after the administration of 5-FU. In addition, the unavailability of the thymidine and uridine nucleosides has made this option less feasible.

Administration of a Colony-Stimulating Growth Factor. Administration of a colony-stimulating growth factor (eg, granulocyte colony-stimulating factor) for the granulocytic precursors has been proposed because life-threatening toxicity caused by DPD deficiency is often accompanied by febrile neutropenia or agranulocytosis. Although this line of treatment has been used in the management of several cases, its benefit is still unproven and the timing of administration is likely critical.

Aggressive Supportive Care. Appropriate antibiotic coverage for bacterial infections as well as antimicrobial coverage for potential nonbacterial infections may be necessary. For example, in cases of fungal infections, fluid and electrolyte support with hospitalization in the intensive care unit (eg, for sepsis with the additional need for hemodynamic support) should be used as necessary.

Variability of Dihydropyrimidine Dehydrogenase Enzyme Activity in Population Studies

To better understand the extent of DPD variability, studies were undertaken to test for DPD activity in different populations. It became apparent that this activity was variable even within otherwise healthy “normal” individuals. In a population study of 124 healthy individuals (45% men and 55% women), DPD activities followed a normal distribution, with an approximate 6-fold range in DPD enzyme activity. Although low DPD activity was observed in some female patients, no significant differences in DPD activity by sex or age were demonstrated in subsequent studies. These studies of healthy adult populations and of cancer patient populations consisting of men and women 20-70 years of age demonstrated no obvious age-related variation in DPD activity.
Although population studies of DPD activity have not been comprehensively performed in all racial groups, initial studies in the United States suggested that there was no difference in DPD activity between white and black patients. However, the frequency of DPD deficiency seems to vary among racial groups, being much less common in Japanese and Chinese patients than in white and black patients. Population studies of healthy individuals permitted the establishment of a statistical cutoff point for the normal enzyme activity with use of the radioenzymatic assay described earlier.

**Human Dihydropyrimidine Dehydrogenase Enzyme**

In the late 1980s, when DPD deficiency was first reported or suspected in patients with cancer, there was little knowledge of the human enzyme.\(^{11,40}\) The recognition of the increasingly important role of DPD as a critical step in 5-FU metabolism and pharmacology provided the impetus for undertaking the earlier studies.\(^{41}\) Initial approaches focused on human liver because animal study results and clinical experience with 5-FU administered intraperitoneally and by hepatic artery infusion suggested that this catabolic enzyme was in abundance in the liver. Human liver DPD was purified to homogeneity in a 5-step purification scheme that permitted characterization of the protein, including its substrate kinetics; the location of functional domains; and the preparation of a polyclonal antibody. The determination of the N-terminal amino acid sequence in this protein contributed to the elucidation of the complementary DNA (cDNA) sequence and the subsequent isolation and characterization of the DPD gene known as DPYD.\(^{19}\) Additionally, these studies have proven that 5-FU has a similar affinity to human DPD enzyme as the natural substrate uracil.\(^{19,42}\)

Further insight into the DPD protein was provided by the determination of the cDNA sequence, wherein various functional domains within the translated amino acid sequence could be predicted.\(^{43,44}\) Several potentially important regions within the linear sequence of amino acids were identified, including flavin-binding regions, NADPH-binding regions, iron/sulfur domains, and the uracil-binding site. Awareness of these critical regions was made possible by studies of the conservation of the amino acid sequence during evolution of the DPD protein, which helped in predicting the possible functional consequences for DPD activity resulting from various mutations in the coding region of the DPYD gene.\(^{45}\)

Studies of the 3-dimensional structure of the protein were initiated by the isolation of the pure protein in sufficient quantities. These studies demonstrated that porcine DPD shares approximately 99% homology with human DPD. The radiographic diffraction studies have permitted the 3-dimensional modeling of the DPD protein dimer with its 2 identical polypeptide chains.\(^{46,47}\) Subsequently, software programs were developed to illustrate the 3-dimensional structure of the human DPD protein (Figure 2). The 3-dimensional structure of the DPD protein offered the possibility of predicting influence of different mutations or sequence variations on the functional domains of the protein, and consequently its activity.

![Figure 2 Three-Dimensional Structure of DPD Protein](image)

Stereo view of the DPD protein showing the different functional domains and their locations (FMN-1030; FAD-1031; NDP [NADPH]-1032; 4 iron sulfur motifs (FS4 [1026-1029]). Also shown is the location of 26 amino acid sequence variants of the total 32 sequence variants reported in the literature. The 3-dimensional structure of the molecule offers a better view of the proximity between the different amino acid residues and functional domains. This figure was produced using the free macromolecular Visualization software program (Protein Explorer) developed by Eric Martz.\(^{70}\)

However, it does not replace recombinant studies that involve expression systems that experimentally determine the effect of the different mutations on the enzyme activity.

**DPYD Alleles**

The determination of the complete cDNA sequence and the use of fluorescence in situ hybridization has permitted the assignment of the DPYD gene to the region of chromosome 1p22.\(^{48}\) The DPYD gene consists of 23 exons with exon length that varies from 50 base pairs to >1550 base pairs.\(^{49,50}\) More recently, the promoter for the DPYD gene has been cloned with initial characterization, permitting examination of its possible role in regulating expression of the DPYD gene through its regulatory elements detected in the 5′UTR.\(^{51}\)

The cDNA from individuals with DPD deficiency was examined to determine any obvious structural abnormalities that could explain the apparent dysfunctional DPD protein. A G-to-A mutation in the 5′ splicing recognition sequence of intron 14 was the first mutation to be described in the DPYD gene. This mutation resulted in deletion of the 165 base pair corresponding to exon 14,\(^{51}\) and, according to established nomenclature, it is known as DPYD*2A, (IVS14+1G>A).\(^{52}\) Further population studies demonstrated that it is the most frequently detected mutation to be associated with DPD deficiency.\(^{3,14,25,26,33,53}\) During the past 7 years, >30 sequence variants have been reported in the literature.\(^{4,24,28,30,32,33,35,54}\)
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Table 1 shows the exon location of many of these sequence variants. Although many were initially thought to be alleles with functional significance for DPD activity, it has become increasingly clear that many are polymorphisms with little or no obvious functional effect. In addition, if the frame shifts reported in the literature truly occur, their quantitative importance in DPD enzyme activity remains to be clarified in the population. In our own experience over 15 years with DPD deficiency, we have not observed frame shifts in any patient with DPD enzyme deficiency.

Expression systems were used to evaluate the effect of these sequence variants on protein function (ie, activity). This approach includes the examination of the cDNA sequence containing the sequence variant after formation of sufficient protein in an expression system to perform an assay of protein function (ie, assessment of DPD activity). Additional insight into the potential functional consequence of sequence variant can be obtained by determining whether the location of the amino acid change is a highly conserved area or a potentially critical region of the molecule (eg, active site, critical binding regions), which could be easily performed with a comparative amino acid sequence alignment of the protein in different species to examine the conservation of the critical functional domains, binding sites, and important contact residues.

The confusion in identifying the molecular basis for DPD deficiency in some individuals might be attributed to the complicated heterozygote genotype pattern for DPD deficiency detected in some patients. Family studies of normal and deficient members can provide valuable insight into the molecular basis of DPD deficiency and 5-FU toxicity.

New Phenotypic Methods for Screening of Dihydropyrimidine Dehydrogenase Deficiency

The radioenzymatic assay described earlier has remained the gold standard for making the diagnosis of DPD deficiency. This assay offers the capability of identifying individuals who are completely deficient in DPD activity and those who are partially deficient; it can also differentiate within a population with activity in the normal range (low normal, mid-normal, and high normal). However, it is time-consuming and unsuitable for screening patients before the administration of 5-FU. More user-friendly assays were developed to determine plasma (or urine) levels of uracil or thymine. Recently, monoclonal antibodies to DPD were developed. These assays could typically permit diagnosis of completely DPD-deficient individuals; however, they are somewhat less accurate in assessing partially DPD-deficient individuals (typically individuals with a heterozygous mutation), who represent the vast majority of DPD-deficient indi-
individuals. In an alternative approach, a limited sampling model was developed to detect abnormalities of DPD metabolism and 5-FU/5-di-hydro-FU disposition in poor metabolizers. In this model, a 2-time point (45 and 180 minutes) assessment allowed the evaluation of drug exposure, suggesting that this approach could potentially improve therapeutic drug monitoring for treatment optimization of 5-FU in patients with cancer.66

Recently, a rapid (≤ 90 minutes), noninvasive, and cost-effective breath test has been developed. This test is suitable for use in a clinical laboratory and permits the evaluation of DPD activity (normal activity and partial or profound deficiency) before the administration of 5-FU.67 In this assay, an administered dose of stable isotope 13C-uracil is released as 13CO2 after a 3-step catabolism (Figure 3). With this breath test, partially DPD-deficient individuals have demonstrated very different breath patterns compared with those of individuals with normal DPD activity (Figure 4).

New Genotypic Methods for Screening of Dihydropyrimidine Dehydrogenase Deficiency

Allele-Specific Polymerase Chain Reaction and Denaturing High-Performance Liquid Chromatography

Allele-specific polymerase chain reaction (ASPCR) and denaturing HPLC (DHPLC) are 2 new approaches that were developed for the rapid detection of sequence variants in complicated genes like the DPYD gene. In ASPCR, specific primers and fluorogenic probes are used to detect specific known mutations in a specific fragment of the gene, such as DPYD*2A.14 However, this method is not suitable for the detection of unknown mutations. Although DPYD*2A is thought to be the most common sequence variant, thereby justifying the development of a specific assay, multiple sequence variants are associated with DPD deficiency, which complicated the identification of the molecular basis of DPD deficiency. Therefore, it would be desirable to rapidly screen the entire coding region and potentially additional regions responsible for regulating the expression of DPD messenger RNA (eg, promoter).

Advantages of the DHPLC over other methods include the rapid examination of DNA fragments (< 1000 bp), for known and unknown sequence variations, using programmed melting temperature and optimized buffer gradients. With use of DHPLC, chromatographic patterns generated by DNA fragments different from normal wild-type DNA sequence can be detected.68 By using this method, the entire coding sequence of the DPYD gene, including the promoter region, can be scanned within 12.5 hours. In GC-rich genes such as the DPYD gene, usually characterized by the presence of multiple melting domains, the use of multiple screening temperatures ensures the detection of all sequence variations inherent in a DNA fragment.

Conclusion

Dihydropyrimidine dehydrogenase deficiency is an example that illustrates the impact of pharmacogenetics on cancer chemotherapy. In DPD enzyme deficiency, death can occur as a result of the presence of excessive drug, prolonged exposure caused by the increase in elimination half-life, and the typically narrow therapeutic window for most cancer chemotherapy drugs. Other drug-metabolizing enzymes, with detected sequence variants in coding and noncoding regions of their genes, have been associated with abnormal patterns of drug metabolism, altered drug pharmacokinetics, and severe, often life-threatening toxicity.

With the completion of sequencing of the human genome and the potential to rapidly screen individuals with use of powerful pharmacogenetic research tools, a new era in cancer chemotherapy is likely to emerge. Although pharmacogenetics will remain important, there will be an increasing emphasis on pharmacogenomics, wherein the alteration in sequence or a difference in the expression of critical genes might provide insights in future clinical therapeutic decisions.59

References

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determination of dihydropyrimidine dehydrogenase (DPD) activity.


