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# Pharmacogenomic tests of oncology drugs at Instituto Nacional de Câncer (INCA)

## Testes farmacogenômicos de medicamentos oncológicos no Instituto Nacional de Câncer (INCA)

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## ABSTRACT

The implementation, current status and future perspectives of the pharmacogenetics/genomics (PGx) testing program developed at Instituto Nacional de Cancer (INCA) are presented. Initial selection of drug-gene pairs for PGx testing was based on clinically-validated PGx associations and availability of international guidelines with PGx-informed dosing recommendations. The selected pairs were fluoropyrimidines-*DPYD*, irinotecan-*UGT1A1*, and thiopurines-*TPMT/NUDT15*. The aims and rationale for the implemented PGx tests, frequency of the interrogated genetic variants and assigned metabolic phenotypes, and the individual dosing recommendations are reviewed. Planned developments, such as collaboration with other cancer treatment centers, testing of additional drug-gene pairs (e.g., tamoxifen-*CYP2D6*), and inclusion of PGx testing in the routine workout of targeted patients at INCA were impacted by the outbreak of the COVID-19 pandemics. The Brazilian Society of Clinical Oncology is invited to play a leading role in the evaluation of the clinical utility of PGx tests of germline variants for oncology drugs in Brazil.


**Keywords:** DPYD; Fluoropyrimidines; Irinotecan; NUDT15; Pharmacogenomics; Thiopurines; TPMT; UGT1A1.


## RESUMO

É apresentada a implementação, o estado atual e as perspectivas futuras do programa de testes farmacogenéticos/genômicos (PGx) desenvolvido no Instituto Nacional de Câncer (INCA). A seleção inicial de pares de genes-medicamentos para testes PGx foi baseada em associações PGx clinicamente validadas e disponibilidade de diretrizes internacionais com recomendações de dosagem segundo as características PGx individuais. Os pares selecionados foram fluoropirimidinas-*DPYD*, irinotecano-*UGT1A1* e tiopurinas-*TPMT/NUDT15*. Os objetivos e a justificativa para os testes PGx implementados, a frequência das variantes genéticas interrogadas e dos fenótipos metabólicos atribuídos, e as recomendações de dosagem individuais são apresentados. Desenvolvimentos planejados, como colaboração com outros centros de tratamento de câncer, testes adicionais de pares de medicamentos-genes (por exemplo, tamoxifeno-*CYP2D6*) e inclusão de testes de PGx na rotina de pacientes-alvo no INCA foram impactados pela pandemia COVID-19. A Sociedade Brasileira de Oncologia Clínica é convidada a desempenhar um papel de liderança na avaliação da utilidade clínica dos testes PGx de variantes germinativas para medicamentos oncológicos no Brasil.


**Descritores:** DPYD; Fluoropirimidinas; Irinotecan; NUDT15; Farmacogenômica; Tiopurinas; TPMT; UGT1A1.

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## INTRODUCTION

Pharmacogenetics/pharmacogenomics (PGx) explores the role of inherited and acquired genetic variation on individual drug responses, whether beneficial or adverse. Implementation of PGx-informed drug prescription in clinical practice is based on the interpretation of results from PGx tests, that target biomarkers in pharmacogenes associated with interindividual differentiation of drug response phenotypes. The United States Food and Drug Administration (FDA) lists over 250 PGx biomarkers, of which 32% (the largest proportion) apply to oncology drugs, both targeted therapies and chemotherapeutic agents.[1] Although somatic mutations for targeted therapies have primarily been the focus of PGx profiling in the oncology setting, the use of germline genetic information to guide conventional chemotherapy has been implemented at a slower pace in oncology clinical practice worldwide. Nevertheless, a recent overview[2] identified 12 commonly used oncology drugs with germline PGx genetic information deemed clinically "actionable", i.e., variants with sufficient information to guide dose selection or dose adjustment. Six of these drugs have PGx information in the respective FDA-approved labels and/or published prescription guidelines (capecitabile, fluorouracil, irinotecan, tamoxifen, mercaptopurine, and thioguanine).

PGx testing for germline variants is offered by private clinical laboratories in Brazil, but is not routinely performed in units of the Brazilian Public Health System (SUS). However, in 2019, a PGx testing program was implemented at *Instituto Nacional de Câncer (INCA)*, as a research project approved by the institution's review board (CEP-INCA), and supported by a dedicated grant from *Decit/MS (Departamento de Ciência e Tecnologia/Ministério da Saúde)*. A comprehensive description of INCA's PGx program has been published.[3] The aims of this article are to introduce this program to readers of the Brazilian Journal of Oncology, summarize the results obtained in the implementation phase, and outline future perspectives.

### Implementation of INCA'S PGx program

### The PGx team

Assembling collaborators from various backgrounds is widely recognized as a critical factor for the successful implementation of PGx programs.[4,5] At INCA, this was accomplished by creating a task force comprising professionals from various units of the institution (Supplementary Table 1). This task force overlooked the implementation of the PGx testing program and designed the project's standard operating procedures (SOPs).

### Selection of drug-gene pairs

Selection was based on the availability of international, authoritative guidelines with clear-cut recommendations for PGx-informed drug prescription based on clinically-validated PGx associations. Two sets of guidelines fulfilled this condition, namely CPIC (Clinical Pharmacogenetics Implementation Consortium)[6] and DPWG (Dutch Pharmacogenetics Working Group)[7] guidelines. These guidelines cover four chemotherapeutic drug-gene pairs, namely:

- Fluoropyrimidines-*DPYD;*[8,9]
- Irinotecan-U*GT1A1;*[10]
- Tamoxifen-*CYP2D6;*[11,12]
- Thiopurines-*TPMT* and *NUDT15.*[13,14]

Fluoropyrimidines-*DPYD*, irinotecan-*UGT1A1* and thiopurines-*TPMT/NUDT15* were selected as initial targets of INCA's PGx program. Tamoxifen, which requires genotyping of several polymorphisms in *CYP2D6,* including copy number variation, will be eventually added to the PGx program.

### Target population

Gastrointestinal cancer patients from INCA, potential candidates for chemotherapy with inrinotecan and/or fluoropyrimidines were selected for genotyping *DPYD* and *UGT1A1* variants, whereas ALL pediatric patients from INCA and seven other cancer hospitals from Rio de Janeiro and Sao Paulo, enrolled in a project focused on genomic deletions (principal investigator: Dr. Mariana Emerenciano), were genotyped for *TPMT* and *NUDT15* polymorphisms.

### Genotyping procedures and phenotype inference

Allele discrimination Taqman assays for the selected polymorphisms in *DPYD*, *UGT1A1, TPMT* and *NUDT15* were validated at INCA's PGx lab. All genotyped polymorphisms affect the metabolism (biotransformation) of the target drugs and thereby modulate the metabolic phenotypes of the respective gene products. Assignment of metabolic phenotypes to individual diplotypes was done accordingly to the CPIC and/or DWPG guidelines.

### PGx report and prescription recommendations

The patient's genotype(s), inferred phenotype(s) and dosing recommendations according to the CPIC and/or DPWG guidelines are inserted in a brief report (2 pages). The report includes also my institutional contacts - for consultation regarding the procedures, results and interpretation of the PGx tests - and the following disclosure statements: i) the dosing recommendations are based on the CPIC and/or DPWG guidelines according to the polymorphisms genotyped; ii) the possibility of influence of other, non-interrogated genetic variants cannot be excluded; iii) adherence to the dosing recommendations is a decision of the prescribing physician. For INCA's gastrointestinal cancer patients, reports are emailed to the head of the clinical oncology service and inserted in the electronic medical records, whereas in the case LLA children, the reports are forwarded to Dr. Emerenciano (see above).

The next sections present results from the implementation phase of the project. For each drug-gene pair, the following aspects will be covered:

- Aims and rationale for the PGx tests;
- Frequency of the PGx variants genotyped;
- Distribution of the metabolic phenotypes;
- Recommendations for the initial drug dosing, according to the individual diplotypes and/or phenotypes;
- Population impact of PGx testing, estimated by the number of patients needed to be genotyped in order to avoid one additional adverse effect.

Background information on the relevant pharmacogenes/polymorphisms, respective metabolic phenotypes, and evidence for their association with drug responses are beyond the scope of this article, but may be found in the CPIC and DPWG guidelines.[8-10,13,14] An overview of Brazilian studies related to PGx in oncology is also available.[15]

## IRINOTECAN-*UGT1A1*

### Aims and rationale of the PGx test

The PGx test targets *UGT1A1* polymorphisms that encode UGT1A1 isoforms with reduced/null enzymatic activity. UGT1A1 converts the active metabolite of irinotecan (SN-38) into inactive SN-38 glucuronide; consequently, UGT1A1 isoforms with reduced/null activity, lead to accumulation of SN-38, and increased risk of irinotecan-induced adverse effects. The DPWG guidelines are based on a *UGT1A1* polymorphism (rs8173547), which modifies the number of TA repeats in the gene's promoter region, thus affecting the expression and activity of UGT1A1. The rs8173547 polymorphism is in virtual complete linkage disequilibrium with rs887829, a C>T transition,[2,16] which is genotyped at INCA in the PGx test for irinotecan. The variant T allele associates with reduced UGT1A1 expression and enzymatic activity, and consequently reduced SN-38 glucuronidation, SN-38 accumulation and increased risk of irinotecan-induced adverse effects.

### Frequency of *UGT1A1* rs887829

The minor allele frequency (MAF) of rs887829 in samples from INCA's gastrointestinal cancer patients (n=150) was 34.1% (Table 1), in excellent agreement with the MAF (35.2%) reported in the ABraOM repository of genomic variants for 1,171 unrelated Brazilians from the Southeast region.[17]

### UGT1A1 metabolic phenotypes and dosing recommendations

Based on the rs887829C>T genotypes, 40.1% (CC), 49.2% (CT), and 9.7% (TT) of tested patients were assigned to normal, intermediate and poor UGT1A1 phenotypes, respectively. According to the DPWG guidelines, which we adopted (Table 2), only poor metabolizers require adjustment of the initial irinotecan dose. The recommendation is to "start treatment with 70% of the standard dose; if the patient tolerates this initial dose, the dose can be increased, guided by the neutrophil count".

## FLUOROPYRIMIDINES-*DPYD*

### Aims and rationale for PGx testing

The PGx tests implemented at INCA target four *DPYD* polymorphisms (Table 3), which encode isoforms of the enzyme dihydropyrimidine dehydrogenase (DPD) with reduced (rs67376798 and rs75017182) or null activity (rs391820 and rs55886062). DPD accounts for ~85% of 5-fluoropyrimidine (5-FU) elimination in humans, and consequently, reduction or loss of DPD activity leads to 5-FU accumulation and increased risk of toxicity. This affects patients treated with either 5-FU or capecitabine, since 5-FU is the active metabolite of capecitabine.

### Frequency of *DPYD* variants

The targeted *DPYD* polymorphisms were rare (MAF<0.5%) or absent in gastrointestinal cancer patients from INCA (n=150; Table 3). These findings are consistent with data from the ABraOM repository,[17] as well as from previous studies of Brazilian patients with severe fluoropyrimidine-induced toxicity.[18,19]

**Table 1.** UGT1A1 target polymorphism.

| rsID | Polymorphism | Trivial name | Enzymatic activity | MAF (%) | |
|---|---|---|---|---|---|
| | | | | INCA | AbraOM |
| rs887829C>T | c.-364C>T | *UGT1A1*80* | Reduced | 34.1 | 35.2 |

rsID: Identification Hugo gene nomenclature committee; MAF: Minor allele frequency.

**Table 2.** UGT1A1 metabolic phenotypes and irinotecan dosing recommendations.

| Metabolic phenotype | Genotype rs887829C>T | Frequency (%) | Summary of dosing recommendations |
|---|---|---|---|
| Normal metabolizer | CC | 40.1 | Start treatment with usual dose |
| Intermediate metabolizer | CT | 49.2 | Start treatment with usual dose |
| Poor metabolizer | TT | 9.7 | Start treatment with 70% of standard dose; if the patient tolerates this initial dose, the dose can be increased, guided by the neutrophil count. |

**Table 3.** Genetic polymorphisms in DPYD.

| *DPYD* rsID | Polymorphism | Trivial name | Enzymatic activity | Activity Score | MAF (%) INCA | MAF (%) AbraOM |
|---|---|---|---|---|---|---|
| rs3918290 | c.1905+1G>A | *DPYD*2A* | Null | 0 | 0.33 | 0.13 |
| rs55886062 | c.1679T>G | *DPYD*13* | Null | 0 | 0 | n/a |
| rs67376798 | c.2846A>T | | Reduced | 0.5 | 0 | 0.38 |
| rs75017182 | c.1129-5923C>G | *HapB3*[#] | Reduced | 0.5 | 0.33 | 0.43 |

rsID: Identification Hugo gene nomenclature committee; MAF: Minor allele frequency. [#] HapB3 is in complete linkage disequilibrium with rs75017182.

**Table 4.** Dihydropyrimidine (DPD) metabolic phenotypes and fluoropyrimidine dosing recommendations.

| Metabolic phenotype | Examples of diplotypes | Activity Score | Frequency (%) | Summary of dosing recommendations |
|---|---|---|---|---|
| Normal metabolizer | *1/*1 (wild type) | 2 | 98.7 | Start treatment with usual dose |
| Intermediate metabolizer | *1/c.2846T, *1/HapB3 | 1.5 | 0 | Reduce initial dose by 25-50%[#] |
| Intermediate metabolizer | *1/*2A, *1/*13, HapB3/c.2846T | 1 | 1.3 | Reduce initial dose by 50%[#] |
| Poor metabolizer | *2A/c.2846T, *13/HapB3 | 0.5 | 0 | Avoid use of fluoropyrimidines[##] |
| Poor metabolizer | *2A/*2A, *2A/*13 | 0 | 0 | Avoid use of fluoropyrimidines |

[#]If no toxicity or clinically tolerable toxicity occurs in the first two cycles, the fluoropyrimidine dose may be increased in subsequent cycles; ##If alternative drugs are not a suitable therapeutic option, the initial fluoropyrimidine dosing should be strongly reduced; if no toxicity or clinically tolerable toxicity occurs in the first two cycles, the fluoropyrimidine dose may be increased in subsequent cycles.

### DPD metabolic phenotypes and dosing recommendations

The CPIC and DWPG guidelines for fluoropyrimidines attribute "activity scores" (AS) to the *DPYD* variants (Table 3) and *DPYD* diplotypes (Table 4). The DPD metabolic phenotypes – normal, intermediate and poor metabolizers - are then assigned according to this AS system. The vast majority (98.7%) of samples from INCA was assigned the normal metabolizer phenotype; poor metabolizers were not identified, whereas intermediate metabolizers ammounted to 1.3% of the samples (Table 4). The CPIC guidelines, adopted at INCA, recommend avoidance of fluoropyrimidines in DPD poor metabolizers and dose reduction (25-50%) for intermediate metabolizers; the extent of the dose reduction depends on the AS of the *DPYD* diplotypes, as shown in Table 4. It is suggested that if no, or clinically tolerable, toxicity occurs in the first two cycles, the fluoropyrimidine dose may be increased in subsequent cycles.

The combined frequency of intermediate and poor metabolizers in the INCA samples (1.3%), is considerably lower than the frequency of fluoropyrimidine-induced severe adverse effects, which may reach 35% in Brazilian patients with digestive cancer.[19] This discrepancy indicates that only a proportion of the adverse effects may be attributed to the interrogated *DPYD* variants, and has prompted adoption of phenotyping methods to assess, directly or indirectly, DPD enzymatic activity. These methods have been explored in Brazilian studies[18,19] and are listed in the DPWG guidelines as an alternative to guide fluoropyrimidine dosing when the DPD phenotype cannot be inferred from *DPYD* diplotypes.[9] The CPIC fluoropyrimidine guideline, however, does not include DPD phenotypic tests, and they are currently not implemented at INCA.

## THIOPURINES-*TPMT* AND *NUDT15*

### Aims and rationale for PGx testing

Mercaptopurine and thioguanine, commonly prescribed for lymphoid malignancies and myeloid leukemias, respectively, are prodrugs that require conversion into active metabolites to exert their clinical effects. These thiopurines and their metabolites are substrates for several enzymes, of which TPMT and NUDT15 are the most relevant for PGx testing. The PGx tests implemented at INCA target *TPMT* (rs1142345, rs1800460 and rs1800462) and *NUDT15* (rs116855232) polymorphisms, associated with reduced/null activity of the respective enzymes, leading to accumulation of active thiopurine metabolites and increased risk of toxicity.[13]

### Frequency of *TPMT* and *NUDT15* variants

Table 5 shows the frequency distribution of the *TPMT* and *NUDT15* polymorphisms in 162 pediatric LLA patients genotyped at INCA. All variant alleles were identified in the cohort, their MAF's ranging from 0.3 to 4.9%, in good agreement with the ABraOM repository[17] and a previous study from our group.[20]

**Table 5.** Genetic polymorphisms in *TPMT* and *NUDT15*.

| Gene rsID | Polymorphism | Trivial name | Enzymatic activity | MAF (%) INCA | MAF (%) AbraOM |
|---|---|---|---|---|---|
| TPMT | | | | | |
| rs1142345 | c.719A>C | *TPMT*3C (TPMT*3A)*[#] | Null | 4.9 | 3.3 |
| rs1800460 | c.460G>A | *TPMT*3B (TPMT*3A)*[#] | Null | 2.5 | 1.9 |
| rs1800462 | c.238G>C | *TPMT*2* | Null | 0.3 | 0.8 |
| NUDT15 | | | | | |
| rs116855232 | c.415C>T[##] | *NUDT15*2, NUDT15*3* | Null | 1.2 | 1.2 |

rsID: Identification Hugo gene nomenclature committee; MAF: Minor allele frequency; [#]TPMT*3A comprises both c.719A>C and c.460G>A; [##]rs116855232 is present in both NUDT15*2 and NUDT15*3.

**Table 6.** TPMT and NUDT15 metabolic phenotypes and thiopurine dosing recommendations.

| Compound metabolic phenotype | Examples of diplotypes | Frequency (%) | Summary of dosing recommendations |
|---|---|---|---|
| Normal metabolizer of both enzymes | *TPMT*1/*1* and *NUDT15*1/*1* | 87.5 | Start treatment with usual dose |
| Intermediate metabolizer of either enzyme | *TPMT*1/*1* and *NUDT15*1/*2* | 11.3 | Consider reduction of initial dose[#] |
| | *TPMT*1/*3A* and *NUDT15*1/*1* | | |
| Intermediate metabolizer of both enzymes | *TPMT*1/*2* and *NUDT15*1/*3* | 0.6 | Reduce initial dose[#] |
| Poor metabolizer of either enzyme | *TPMT*3A/*3C* and *NUDT15*1/*1* | 0.6 | Drastic reduction of the initial dose[#] |
| | *TPMT*1/*1* and *NUDT15*2/*2* | | |
| Poor metabolizer of both enzymes | *TPMT*3A/*3A* and *NUDT15*2/*2* | 0.0 | Drastic reduction of the initial dos [#] |

[#]Adjust subsequent doses based on degree of myelosuppression and disease-specific guidelines.

### Compound TPMT/NUDT15 metabolic phenotypes and dosing recommendations

Thiopurine dosing recommendations are based on TPMT and NUDT15 compound (combined) metabolic phenotypes, inferred from the respective diplotypes, as proposed in the CPIC guidelines.[13] Accordingly, there are 5 possible compound phenotypes (Table 6) with distinct dosing recommendations: i) normal metabolizer phenotype, assigned to 87.5% of the samples, no change in thiopurine initial dose is required; ii) intermediate metabolizers of either enzyme (11.3%), consider starting the treatment with reduced doses; iii) intermediate metabolizers of both enzymes ("compound intermediate metabolizers"), dose reduction is recommended in view of the considerably increased risk of toxicity; iv and v) poor metabolizers of one (0.6%) or both enzymes (none observed in the tested samples), drastic dose reduction of the initial dose and reduced frequency of administration is strongly recommended. Following the initial reduction, thiopurine doses should be adjusted based on the degree of myelosuppression and the disease-specific guidelines.

### Population impact of PGx tests

The number of patients needed to be genotyped (NNG) in order to prevent one drug-induced adverse event is a validated metric to assess the potential population impact of PGx tests.[21,22] It appears intuitive that the lower the NNG, the greater the perceived clinical utility and cost-effectiveness of the PGx test. NNG for the PGx tests are estimated from the odds ratio (OR) of PGx associations with drug-induced adverse effects, the frequency of the adverse reactions (denoted *q*) and the frequency (*p*) of the PGx variant(s) linked to the adverse effects.[21,22] Using OR and *q* values from published studies and *p*-values for the relevant metabolic phenotypes in the INCA samples, the NNG values plotted in Figure 1 are obtained.[22] The figure shows also the number of patients needed to be treated (NNT = NNG x *p*) to avoid one adverse effect. The NNG values ranged widely, from 14 for *UGT1A1*-irinotecan in high doses (>300mg.m$^2$) to 312 for *DPYD*-fluoropyrimidines, whereas the NNTs for the four gene-drug pairs varied over a considerably narrower range (2-4). Using the *TPMT/NUDT15*-thiopurines as an example, the results in Figure 1 imply that it is necessary to genotype 38 LLA patients for *TPMT* and *NUDT15* polymorphisms (NNG) and adjust the initial thiopurine dosing in four patients (NNT, i.e., those who tested positive for variants in either or both genes) in order to prevent one additional adverse effect to thiopurines.

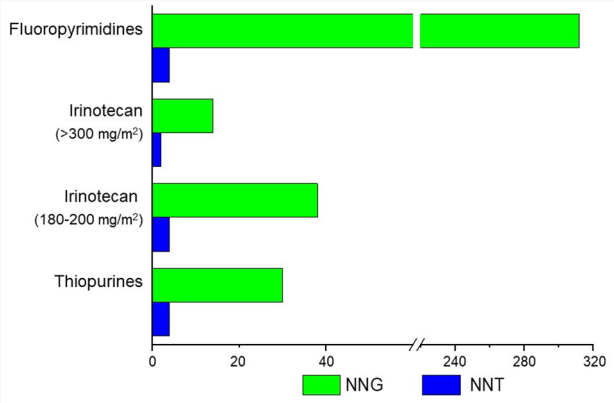


**Figure 1.** Plot of the number of patients needed to be genotyped (NNG) and to be treated (NNT) in order to avoid one additional adverse effect to fluoropyrimidines, irinotecan and thiopurines. Adapted from original data in Suarez-Kurtz et al. (2020).[2,22]

## Current status and perspectives of the PGx program

The INCA PGx testing program had been successfully implemented by the end of 2019. Early in 2020, an expansion of this program, to provide PGx tests for irinotecan and fluoropyrimidines to patients treated at three cancer centers in the states of São Paulo and Rio Grande do Sul were approved by CEP-INCA. Other developments of the PGx program were also envisaged:

- Evaluate the possibility of implementing PGx testing for tamoxifen (*CYP2D6* genotyping) in breast cancer patients from INCA.
- Inclusion of pre-emptive PGx testing for irinotecan, fluoropyrimidines, thiopurines, and possibly tamoxifen in the routine clinical laboratory workout of patients at INCA, who are potential candidates to treatment with these drugs.
- Establish INCA as a national reference center for PGx testing (germline variants) of oncology drugs.
- Assess the possibility of widening the scope of the PGx program to cover supportive care drugs commonly used in oncological patients, such as anticoagulants (warfarin), antidepressants (citalopran, escitaloran, etc.), antiemetics (ondanstron), antifungal (voriconazole) and platelet inhibitors (clopidogrel), for which there are CPIC and/or DWPG guidelines.

Unfortunately, the outbreak of the COVID-19 pandemic imposed a postponement, but certainly not suppression, of these developments; of note, testing for thiopurines-*TPMT/NUDT15* was not interrupted and a total of 278 children have been tested at the time of this writing. We are aware that continuity and, especially, expansion of the PGx program will encounter challenges not only of assuring financial support but also of availability of trained personnel, adoption of the PGx-informed prescription by the clinical staff, updating of the dosing recommendations as novel evidence of PGx associations emerge, and, ultimately, evidence of clinical utility and cost-effectiveness in a realistic scenario.

Cost-effectiveness may appear as of especial concern for fluoropyrimidines, in view of the rarity of the targeted *DPYD* polymorphisms, and, consequently the large NNG estimated from the available data (Figure 1). However, the previously mentioned overview of PGx tests in oncology[2] identified 72 published PGx studies in high-impact journals, which reported clinical associations of *DYPD* variants or DPD phenotypes with outcomes of treatment with fluoropyrimidines. Accordingly, preemptive PGx testing for fluoropyrimidines is now required by the Swiss Agency of Therapeutic Products and recommended by EMA, the European Medicines Agency (Table 7), whereas in France, health authorities recently made mandatory the routine determination of DPD deficiency prior to administration of fluoropyrimidine-based chemotherapy.[23] Other regulatory bodies, however, acknowledge the "actionability" of *DPYD* and DPD polymorphism but do not recommend or require PGx tests to guide fluoropyrimidine dosing (Table 7). Heterogeneity/discordance among international regulatory bodies with respect to PGx tests extends to the other drug/gene pairs interrogated at INCA, as shown in Table 7. To my knowledge, there are no recommendations from ANVISA (Brazilian Health Regulatory Agency) or Brazilian professional organizations, regarding PGx tests for germline variants associated with clinical response to oncology drugs. Writing for the Brazilian Journal of Oncology, I would like to challenge the SBOC (Brazilian Society of Clinical Oncology) to take a leading role in the assessment of the clinical utility

**Table 7.** Drug labels containing pharmacogenetic information.[#]

| Drugs | | EMA | FDA | Swissmedic | HCSC | PMDA |
|---|---|---|---|---|---|---|
| Fluoropyrimidines | Capecitabine | Recommended | Actionable | Actionable | Actionable | Actionable |
| | 5-fluorouracil | | Actionable | Required | Actionable | Actionable |
| Thiopurines | Azathioprine | | Recommended | Actionable | Actionable | Actionable |
| | Thioguanine | | Recommended | Actionable | Actionable | |
| Topoisomerase inhibitor | Irinotecan | Actionable | Actionable | Actionable | Actionable | Recommended |

[#]Adapted from: https://www.pharmgkb.org/labelAnnotations[24] EMA: European Medicines Agency; FDA: US Food and Drug Administration; Swiss medic: Swiss Agency of Therapeutic Products; HCSC: Health Canada Santé Canada; PMDA: Pharmaceuticals and Medical Devices Agency, Japan.

of PGx tests of germline variants for oncology drugs prescribed to Brazilians.

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## CONFLICTS OF INTEREST

None to declare.

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