Review

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Pharmacogenomics

Implementation of a pharmacogenomic program in a Brazilian public institution

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This narrative review describes implementation, current status and perspectives of a pharmacogenomic (PGx) program at the Brazilian National Cancer Institute (INCA), targeting the cancer chemotherapeutic drugs – fluoropyrimidines, irinotecan and thiopurines. This initiative, designed as a research project, was supported by a grant from the Brazilian Ministry of Health. A dedicated task force developed standard operational procedures from recruitment of patients to creating PGx reports with dosing recommendations, which were successfully applied to test 100 gastrointestinal cancer INCA outpatients and 162 acute lymphoblastic leukemia pediatric patients from INCA and seven other hospitals. The program has been subsequently expanded to include gastrointestinal cancer patients from three additional cancer treatment centers. We anticipate implementation of routine pre-emptive PGx testing at INCA but acknowledge challenges associated with this transition, such as continuous financing support, availability of trained personnel, adoption of the PGx-informed prescription by the clinical staff and, ultimately, evidence of cost–effectiveness.

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Brazil is the 5th largest country in the world, occupying an area of 8.5 million km^2. The Brazilian population, currently in excess of 210 million people, is highly heterogeneous and admixed, a fact that has far-reaching pharmacogenetic/genomic (PGx) implications [1,2,3] and prompted the creation of a nation-wide network, the Rede Nacional de Farmacogenética or Refargen [4,5]. Studies carried out by Refargen investigators described the influence of individual biogeographical ancestry (Native American, European and sub-Saharan African) on the distribution of PGx polymorphisms among Brazilians [6,7,8], leading to the following conclusions: (i) the distribution of PGx polymorphisms varies across the self-reported 'race/color' categories adopted by the Brazilian census, and is best modeled as continuous functions of individual proportions of European and African ancestry; (ii) the differential frequency of polymorphisms across population strata impacts the calculations of sample sizes required for adequate statistical power in clinical trials; (iii) extrapolation of PGx data from well-defined ethnic groups to Brazilians is plagued with uncertainty. As a corollary to these conclusions, implementation of PGx-informed prescription in Brazil must be based on data from the various strata of the Brazilian population.

This review covers the implementation of PGx tests at Instituto Nacional de Câncer (INCA), which is the organization of the Brazilian Ministry of Health responsible for the development and coordination of integrated actions in the prevention and control of cancer in Brazil [9]. In keeping with INCA's mission, the PGx testing initiative focused on cancer chemotherapy drugs for which there are PGx guidelines published by the Clinical Pharmacogenetics Implementation Consortium (CPIC) and/or Dutch Pharmacogenetics Working Group (DPWG). Our initial targets were thiopurines, irinotecan and fluoropyrimidines; tamoxifen a highly effective agent in estrogen receptor-positive breast cancer, with CPIC and DPWG guidelines based on *CYP2D6* genotyping was not

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included in the implementation of the PGx program. Comprehensive information on the PGx of the targeted drugs and respective paired gene(s) is publicly available through the CPIC [10] and PharmGKB [11] websites. In this review, published PGx data from Brazilian studies pertinent to fluoropyrimidines, irinotecan and thiopurines will be initially highlighted, and then the development, current status and future perspectives of INCA's PGx program will be presented.

Fluoropyrimidines & *DPYD*

Fluoropyrimidines are antimetabolites widely used in the treatment of solid tumors including colorectal, gastric, breast and lung cancer. 5-Fluorouracil (5-FU) and its oral prodrug, capecitabine, are the commonly used fluoropyrimidines in Brazil. DPD, encoded by the *DPYD* gene, is the rate-limiting enzyme of 5-FU catabolism. The CPIC and DPWG recommendations for fluoropyrimides dosing are based on four *DPYD* polymorphisms, namely rs3918290 (c.1905+1G>A), also known as *DPYD*2A*, rs55886062 (c.1679T>G, *DPYP*13*), rs67376798 (c.2846A>T) and rs75017182 (c.1129-5923C>G), a biomarker of the *DPYD* HapB3 haplotype [12,13,14]. The guidelines apply the *DPYD* gene activity score (AS) system to predict DPD metabolizer phenotypes, which in turn are used to optimize the individual fluoropyrimidine-starting dose.

The *DYPD*2A* and **13* SNPs, which have the most deleterious impact on DPD activity, were not detected in a cohort of 270 self-reported white, brown (*Pardo* in Brazilian Portuguese) and black healthy subjects from the southeast region of Brazil [8]; the other two variants (2646A>T and HapB3) were not investigated in this cohort. Rodrigues *et al.* [15] reported minor allele frequencies (MAFs) of 1, 2 and 4% for *DPYD*2A*, *DPYP*13* and rs67376798A, respectively, in 146 individuals from three Amazonian Amerindian populations. An additional functional *DPYD* variant, rs115232898 (c.557A>G, Y186C), first reported in African–Americans [16] was detected at a frequency of 2.6% in healthy Brazilians of predominantly African ancestry or self-reported as black [17]. Two groups examined the association of *DPYD* polymorphisms with toxicity during 5-FU-based chemotherapy of gastrointestinal tumors. Cunha-Junior *et al.* [18] reported that three out of 13 patients with grade 3–4 toxicity were carriers of either *DPYD*2A* or the 2846A>T SNP, whereas Galarza *et al.* [19] failed to detect the *DPYD*2A*, *DPYD*13* and rs115232898 (Y186C) SNPs in 21 patients with severe toxicity. These studies explored also the use of phenotypic indices of DPD activity, such as the plasma and saliva uracil (U) to dihydrouracil (UH_2) metabolic ratio, to predict 5-FU toxicity, and suggested that these ratios, especially in saliva, may be promising functional tests for the toxicity of fluroropyrimidines.

Irinotecan & *UGT1A1*

The topoisomerase-I inhibitor irinotecan is widely used in the treatment of metastatic colorectal cancer, in combination with 5-FU/leucovorin (FOLFIRI) and bevacizumab. Irinotecan is a prodrug that requires *in vivo* conversion into the active metabolite 7-ethyl-10-hydroxycamptothecin (SN-38), to exert its pharmacological effects. SN-38 is cleared by the biliary route after glucuronidation by UGT1A1. UGT1A1 activity exhibits a wide intersubject variability, in part due to *UGT1A1* polymorphisms, notably a variable number of TA base repeats in the gene's promoter region (reviewed in [20]). The wild-type allele (*UGT1A1*1*) has six TA repeats [$(TA)_6$], whereas a common variant allele (*UGT1A1*28*) has seven TA repeats [$(TA)_7$]. Other rarer variants at this locus are *UGT1A1*36* [$(TA)_5$] and *UGT1A1*37* [$(TA)_8$]. The gene transcription level is reduced by the $(TA)_7$ and $(TA)_8$ alleles, and consequently, carriers of these alleles catabolize SN-38 less efficiently than patients with the wild-type genotype, and are subjected to greater exposure to SN-38.

Frequency data for the *UGT1A1*28* allele in Brazilians were first reported by Fertrin *et al.* [21]. Suarez-Kurtz and colleagues subsequently extended this analysis to *UGT1A1*36* and **37* [22,23]. Collectively, these data indicate that the *UGT1A1*28* allele is quite common (32–40%) among self-reported white, brown and black Brazilians, whereas the alleles *36 and *37 are rare (0.4–1.1%). Accordingly, 10–15% of Brazilians would be categorized as poor UGT1A1 metabolizers. *UGT1A1*6*, an exonic SNP (rs4148323), associated with reduced UGT1A1 metabolic activity, common in Asian populations, but rare or absent in people of European or African descent, was not detected in a Refargen cohort of 270 healthy, self-reported white, brown or black Brazilians [8]. However, it occurred at 0.6% in a larger cohort (n = 614) of elderly Brazilians, which included Japanese descendants [24].

A PubMed search using the terms 'irinotecan AND Brazil* AND UGT1A1' disclosed no studies on the PGx of irinotecan. In a different PGx context, the *UGT1A1* tata-box polymorphism was reported to associate with the *L*-thyroxine (T_4) doses required for thyrotropin suppression following thyroid ablation in patients with

differentiated thyroid cancer. The effect size, however, accounted for only 2% of the total variability in T_4 dosage and recommendation of pre-emptive *UGT1A1* genotyping was deemed not warranted [22,23].

Thiopurines, *TPMT* & *NUDT15*

The thiopurines, mercaptopurine (MP), thioguanine (TG) and azathioprine, share most pharmacological effects, but MP and azathioprine are commonly used for nonmalignant conditions (e.g., inflammatory bowel disease), while MP is prescribed for lymphoid malignancies and TG for myeloid leukemias. Thiopurines are prodrugs that require conversion into active TG nucleotide metabolites to exert their clinical effects. Thiopurines and their metabolites are substrates for several enzymes, of which TPMT and NUDT15 are the most relevant for PGx testing. Accordingly, the recently updated CPIC thiopurine guideline is based on *TPMT* and *NUDT15* genotypes and inferred phenotypes [25].

A number of studies investigated the frequency distribution among Brazilians of commonly reported SNPs in *TPMT* (rs1142345, rs1800460 and rs1800462; Supplementary Table 1), which define the nonfunctional *TPMT*2*, **3A*, **3B* and **3C* haplotypes [26,27,28]. The combined frequency of these haplotypes was 4.5% in the overall Refargen cohort (n = 1034, healthy individuals), with similar distribution in self-reported white, brown and black subjects [5]. These data are consistent with previously published studies in Brazilian healthy individuals [26,27] and children with acute lymphoblastic leukemia (ALL) [28]. Reis *et al.* [26] quantified the TPMT enzymatic activity in 306 Brazilians and observed a trimodal distribution of normal (89.9% of individuals), intermediate (9.8%) and poor (0.3%) TPMT metabolizer phenotypes.

Regarding *NUDT15*, a search in the PubMed database disclosed only one study in Brazilians [29], focused on the first identified and most extensively studied *NUDT15* polymorphism linked to thiopurine cytotoxicity, namely c.415C>T (rs116855232). Haplotypes comprising this SNP are associated with a dramatic loss of NUDT15 enzymatic activity [30]. The variant c.415T allele has been reported as most common in East Asians and in Hispanics with high Native American ancestry, but rare in Europeans and Africans [30,31]. Suarez-Kurtz *et al.* [29] reported MAF of c.415C>T ranging between 5.2 and 31.7% among Native American groups living in reservation areas in Brazil. The top MAF values are the highest reported so far for any population worldwide. For comparison, in a large admixed Brazilian cohort (n = 614), the MAF at c.415C>T was reported at 1.1% [24]. Collectively, the available data for *TPMT* and *NUDT15* indicate that approximately 0.3% of Brazilians are at very high risk of severe toxicity when exposed to the standard doses of thiopurines and approximately 10% are at increased risk of toxicity with such doses.

Implementation of PGx testing at INCA

Financial support for this initiative was provided by a grant from the Brazilian Ministry of Health. Because PGx testing is not a routine procedure at INCA, implementation of the tests required approval by the Institutional Ethics Committee (CEP-INCA). For the drug/gene pairs, irinotecan/*UGT1A1* and fluoropyrimidines/*DPYD*, an original project was designed (CAAE 05787219.3.0000.5274), whereas for thiopurines/*TPMT*/*NUDT15* an amendment was added to an ongoing study of molecular aspects of ALL in children (CAAE 33709814.7.1001.5274). Both submissions were approved, having as primary objective the implementation of standard operation procedures (SOPs) for PGx tests in our institute. The projects were carried out in accordance with the ethical principles from the Declaration of Helsinki and with Good Clinical Practice as defined by the International Conference on Harmonization. All participating patients gave written informed consent. The development and current status of the two projects will be presented separately.

PGx testing for *UGT1A1* & *DPYD* polymorphisms

The initial step of this project was the creation of a task force comprising professionals from five units of INCA, namely the Division of Clinical Research and Technological Development, the Clinical Oncology Service and the Clinical Pathology Service of Cancer Hospital I, the National Tumor Bank and the Technology Information Service. This task force overlooked the implementation of the PGx testing program, and designed SOPs for:

- Access to, and use of DNA samples stored at the National Tumor Bank;
- Recruitment of gastrointestinal cancer outpatients at the Clinical Oncology Service;
- Obtaining clinical and demographical data of the recruited patients;
- Collection, transport and storage of blood samples from the outpatients;

- DNA extraction and storage;
- Genotyping selected polymorphisms in *UGT1A1* and *DPYD* using TaqMan allele discrimination assays (Supplementary Table 1);
- Inference of UGT1A1 and DMD metabolic phenotypes based on *UGT1A1* and *DPYD* genotypes and metabolic phenotypes, as described in the CPIC and/or DPWG guidelines [12,13,14];
- Recommendations for the initial doses of fluoropyrimidines or irinotecan, according to the CPIC and/or DPWG guidelines;
- Informing the individual genotyping results, inferred phenotypes and dosing recommendations to the clinical staff in charge of the patients.

The study protocol, comprising these SOPs, received approval from CEP-INCA for genotyping 50 DNA samples from the National Tumor Bank and from 120 INCA outpatients. The DNA samples provided by the National Tumor Bank were used for development and validation of genotyping procedures for *UGT1A1* and *DPYD*. The target *UGT1A1* polymorphism, namely, variable $TA_{(n)}$ repeats in the promoter region, had been previously investigated in our lab using Sanger sequencing [22,23]. For the present purposes, however, we explored the use of a TaqMan allele discrimination assay for the rs887829 SNP (c.-364C>T, *UGT1A1*80*; Supplementary Table 1) as a proxy for the $TA_{(n)}$ polymorphism, based on the very strong linkage disequilibrium (LD) of the -364C allele with $(TA)_5$ and $(TA)_6$, and of the -364T allele with $(TA)_7$ and $(TA)_8$ [32,33]. To verify this LD in Brazilians, we compared sequencing data available from 90 thyroid cancer patients, comprising $TA_{(6)}$ homozygous, $TA_{(5)}$, $TA_{(7)}$ and $TA_{(8)}$ heterozygous and $TA_{(7)}$ homozygous genotypes (16) with TaqMan results and obtained a pairwise R^2 value of 0.94. We then assayed the DNA samples from the Tumor Bank for the *UGT1A1*80* and detected a MAF of 41%; the genotype distribution did not deviate from Hardy–Weinberg equilibrium. We found no data on *UGT1A1*80* from other Brazilian cohorts for comparison, but the MAF in the Tumor Bank samples was not significantly different from the combined frequency of the *UGT1A1* $TA_{(7)}$ and $TA_{(8)}$ variants (35%) in Brazilian thyroid cancer patients [23].

Regarding the four *DPYD* polymorphisms covered in the CPIC and DPWG guidelines, one Tumor Bank sample was heterozygous for rs67376798 and another for rs5603487, but the nonfunctional *DPYD*2A* and *DPYD*13* alleles were absent.

Next, recruitment of gastrointestinal cancer patients, who were potential candidates for chemotherapy with irinotecan and/or floropyrimidines was initiated and completed within 5 weeks. This relatively short time may be attributed, in part, to the fact that INCA is a reference center for cancer care in Brazil; indeed, nearly 500 patients received chemotherapy with irinotecan and/or fluoropyrimidine at INCA in 2019. The MAF of the *UGT1A1*80* SNP was 34% in the recruited patients, and the distribution of genotypes did not deviate from HWE. Based on individual *UGT1A1*80* genotypes, 41, 49 and 10 patients were inferred as normal (extensive), intermediate and poor DPD metabolizers (Table 1). The following dosing recommendations were proposed, according to the DPWG guidelines: normal and intermediate metabolizers, no action required, in other words, start treatment with the usual dose; poor metabolizers, start with 70% of the standard dose and if the patient tolerates this initial dose, the dose can be increased, guided by the neutrophil count [13].

Regarding *DPYD*, the four SNPs interrogated were not detected in the gastrointestinal cancer patients. This cannot be attributed to genotyping failure since heterozygosis for each polymorphism was verified in control DNA samples. On the basis of AS applied to *DPYD* genotypes [14], the normal DPD metabolizer phenotype (AS = 2) was assigned to all patients, with the recommendation to start treatment with the usual fluoropyrimidine dose. For other phenotypes, not detected in this cohort, the recommendations would have been: intermediate metabolizers (AS = 1 or 1.5), reduce starting dose based on AS, followed by titration of dose based on toxicity. If AS = 1, reduce initial dose by 50%; if AS = 1.5, reduce initial dose by 25–50%. Poor metabolizers, if AS = 0, avoid the use of fluoropyrimidines, if AS = 0.5, avoid the use of fluoropyrimidines, but if alternative drugs are not considered a suitable therapeutic option, the initial fluoropyrimidine dosing should be strongly reduced.

The *UGT1A1* or *DPYD* genotypes, the inferred UGT1A1 or DPD metabolic phenotypes, and the recommendations for initial dosing of irinotecan or fluoropyrimidines were included in separate, concise reports, which were conveyed by institutional email to the Head of the Clinical Oncology Service and inserted in the electronic medical record of the patient. The reports contained the following disclosure statements: the dosing recommendations were based on the CPIC and/or DPWG guidelines according to the polymorphisms genotyped; the possibility of

Table 1. Distribution of TPMT and NUDT15 alleles, diplotypes and metabolic phenotypes†.

TPMT			NUDT15		
Alleles	**wt**	**var**	**Alleles**	**wt**	**var**
rs1142345	95.1	4.9	rs116855232	98.8	1.2
rs1800460	97.5	2.5			
rs1800462	99.7	0.3			
Diplotypes			**Diplotypes**		
*1/*1	90.1		wt/wt	97.6	
*1/*2	0.6		wt/var	2.4	
*1/*3A	4.3				
*1/*3C	4.3				
*3A/*3C	0.6				
Phenotypes			**Phenotypes**		
Normal	90.1		Normal	7.6	
Intermediate	9.2		Intermediate	2.4	
Poor	0.6				

†Data from 162 pediatric acute lymphoblastic leukemia patients; frequency expressed in %.
var: Variant; wt: Wild-type.

influence of other, not interrogated, PGx variants cannot be excluded; adherence to the dosing recommendations is a decision of the prescribing physician.

Publication of the reports for all enrolled patients concluded successfully the process of implementation of SOPs for performing PGx tests at INCA and providing dosing recommendations for irinotecan and fluoropyrimidines. This led us to offer these PGx tests to gastrointestinal cancer patients from other cancer centers in Brazil. A multicenter study protocol was designed (CAAE 23358719.3.1001.5274), comprising INCA and three other institutions, namely Instituto de Câncer do Estado de São Paulo (ICESP), Hospital AC Camargo (HACC), both located in the city of São Paulo, and Hospital de Clínicas, Universidade Federal do Rio Grande do Sul (HC-UFRGS) in Porto Alegre, the capital city of Rio Grande do Sul state. Approval from CEP-INCA was granted in January 2020, with the primary goal of enrolling 400 patients from the four institutions within 6 months, in a competitive process. Genotyping will be performed at INCA, using the previously approved SOPs plus additional SOPs for collection, storage and shipment of blood or DNA samples from the collaborating institutions, and for conveying the PGx test reports to the Principal Investigator in each collaborating institution. The turn-around time from receiving the samples (blood or DNA) in our lab to providing the PGx reports including dosing recommendations has been set to 1 week.

PGx testing for *TPMT* & *NUDT15* polymorphisms

This initiative was designed as an extension of an ongoing project focused on genomic deletions found in pediatric patients diagnosed with ALL, receiving treatment at INCA and seven other cancer hospitals in the states of Rio de Janeiro and São Paulo. Routine procedures for receiving the DNA samples at our institute were already established and genotyping assays for *TPMT* and NUDT15 polymorphisms have been previously validated at INCA [25,29]. Thus, the required SOPs for the implementation of the PGx tests referred to:

- Inference of TPMT and NUDT15 metabolic phenotypes based on *TPMT* and *NUDT15* genotypes, respectively, as described in the updated CPIC guideline [25];
- Proposing recommendations for the initial thiopurine dosing, according to the CPIC guideline;
- Informing the individual genotyping results, inferred phenotypes and dosing recommendations to the clinical staff in charge of the patients.

The polymorphisms selected for genotyping were rs1142345, rs1800460 and rs1800462 (Supplementary Table 1), which identify the *TPMT*2*, **3A*, **3B* and **3C* haplotypes, and rs116855232 present in the *NUDT15*2* and **3* haplotypes. Table 1 shows the distribution of TPMT and NUDT15 alleles, diplotypes and assigned metabolic phenotypes in 162 ALL patients, available for genotyping between May and December 2019.

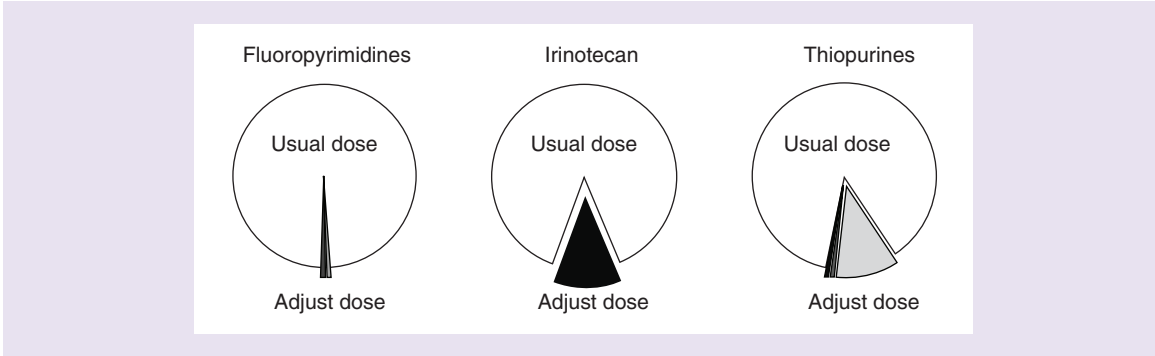

Figure 1. Distribution of Clinical Pharmacogenetics Implementation Consortium and/or Dutch Pharmacogenetics Working Group recommendations for adjustment of initial dose or fluoropyrimidines, irinotecan and thiopurines in the study cohorts. The pie graphs for irinotecan and fluoropyrimidines are based on combined data from the Tumor Bank samples (n = 50) and recruited gastrointestinal cancer patients (n = 100). The thiopurine plot is based on 162 samples from acute lymphoblastic leukemia patients. The colors in the plots correspond to: 'use standard (usual) dose' (white); 'consider dose reduction' (gray); 'dose reduction recommended' (black). The shades in gray in the fluoropyrimidines' plot distinguish DMP intermediate metabolizers with activity score of either 1.0 or 1.5. The dark gray wedge in the thiopurines' plot refers to the compound intermediate metabolizer.

The observed frequencies are consistent with data from previous studies in Brazilians: the metabolic phenotypes showed a trimodal distribution for TPMT, with 90.1% normal, 9.2% intermediate and 0.6% poor metabolizers, whereas NUDT15 phenotypes were restricted to normal (97.6%) and intermediate (2.4%) metabolizers. Of note, one patient was a compound intermediate metabolizer, in other words, with intermediate metabolizer status for both TPMT and NUDT15, a condition associated with lower thiopurine tolerance compared with intermediate metabolizers for either TPMT or NUDT15 [25].

The individual genotyping results for *TMPT* and *NUDT15*, inferred TMPT and NUDT15 metabolic phenotypes and recommendations for initial dosing of thiopurines according to the CPIC guideline [25], were included in a concise report, which was conveyed by institutional email to the Principal Investigator of the ALL genomic deletions project. For INCA patients enrolled in this project, the PGx reports were also added to their electronic medical data. The turnaround time from receiving the DNA samples to providing the PGx reports averaged 10 days. The reports contained the same disclosure statements, described above for irinotecan and fluoropyrimidines, namely: that the dosing recommendations were based on the CPIC guidelines according to the polymorphisms genotyped; the possibility of influence of other, not interrogated, PGx variants cannot be excluded; adherence to the dosing recommendations is a decision of the prescribing physician.

Conclusion

PGx tests targeting cancer chemotherapeutic drugs was successfully implemented as a research project at the Brazilian National Cancer Institute, and subsequently extended to patients from other cancer institutions in the country. This is to be followed by the addition of pre-emptive PGx testing, when appropriate, to the routine clinical laboratory workout of patients at our institution. However, we are aware that this development 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 and, ultimately, evidence of cost–effectiveness.

Future perspective

PGx testing to inform prescription of irinotecan, fluoropyrimidines and thiopurines is offered by private clinical laboratories in Brazil, but not routinely performed in the Brazilian Public Health System. From this perspective, the implementation of the PGx program at INCA is a pioneer and successful initiative, which hopefully will prompt similar programs in other medical centers in Brazil, whether public or private. The pilot project has now been expanded to provide PGx tests for irinotecan and fluoropyrimidines to patients from INCA and three other cancer treatment centers, whereas PGx tests for thiopurines will continue to be available to pediatric ALL patients from INCA and seven other hospitals. Providing PGx testing for *CYP2D6*-tamoxifen gene–drug interaction is the next goal of the program.

A decisive factor for the positive results obtained in this program was the commitment of INCA's PGx task force, which carried out the multiple steps of the project, such as recruitment of patients, generation and interpretation of PGx data, provision of concise reports including dosing recommendations and migration of the reports into the patient's electronic medical at our institution. Importantly, the implementation and current status of PGx testing at INCA were made possible by a dedicated grant from the Brazilian Ministry of Health. The successful outcome of the ongoing project will lead to inclusion of pre-emptive PGx testing, when appropriate, in the routine clinical laboratory workout of patients at INCA. However, we are aware that this development 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 and, ultimately, evidence of cost–effectiveness. The latter is of special concern for fluoropyrimidines in view of the absence and/or rarity of the targeted *DPYD* polymorphisms in the gastrointestinal cancer patients and Tumor Bank samples. In the case of irinotecan and thiopurines, however, recommendation to reduce the starting dose and/or consider dose reduction applies to approximately 10% of the gastrointestinal cancer and LLA patients, respectively (Figure 1).

Executive summary

Scope of the review

- The review covers the implementation and current status of pharmacogenomic (PGx) tests at the Brazilian National Cancer Institute (INCA), which is the organization of the Ministry of Health responsible for the development and coordination of integrated actions in the prevention and control of cancer in Brazil.
- The PGx program focused on cancer chemotherapy drugs included in the Clinical Pharmacogenetics Implementation Consortium and/or Dutch Pharmacogenetics Working Group, namely thiopurines, irinotecan and fluoropyrimidines.

Implementation of PGx tests at INCA

- Because PGx tests are not routinely performed at INCA, implementation required approval by the institutional Ethics Committee (CEP-INCA).
- A task force of INCA's staff oversighted the project, whereas financial support was provided by a dedicated grant from the Brazilian Ministry of Health.
- Standard operational procedures were designed for each step, from the recruitment of patients to migration of the test results and dosing recommendations to the patients' electronic medical recordings.
- TaqMan allele discrimination assays for selected *DPYD*, *UGT1A1*, *TPMT* and *NUDT15* polymorphisms were validated in samples from INCA's Tumor Bank and subsequently applied to genotype 100 gastrointestinal cancer patients and 162 acute lymphoblastic leukemia patients.
- Based on the individual genotypes and inferred metabolic phenotypes, recommendation of dosing adjustment applied to 10% of patients receiving or being candidates to receive irinotecan of thiopurines, but to only 0.3% of patients under treatment or candidate to treatment with a fluoropyrimidine.
- This initiative has now been expanded to provide PGx tests for irinotecan and fluoropyrimidines to patients from INCA and three other cancer treatment centers, whereas PGx tests for thiopurines will continue to be available to pediatric acute lymphoblastic leukemia patients from INCA and seven other hospitals.

Conclusion & future perspective

- The successful development of the ongoing project will, hopefully, lead to inclusion of pre-emptive PGx testing, when appropriate, in the routine clinical laboratory workout of patients at our institution. However, we are aware that this development 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 and, ultimately, evidence of cost–effectiveness.

Supplementary data

To view the supplementary data that accompany this paper please visit the journal website at: www.futuremedicine.com/doi/suppl/10.2217/pgs-2020-0016

Author contributions

G Suarez-Kurtz was the principal investigator of the project, designed the study protocol, analyzed data and wrote the original manuscript. G Kovalevski contributed to the design of the study protocol, recruited patients and collected clinical and demographical data. VLA Motta recruited patients and collected clinical and demographical data. ABR Elias and K Wolch performed polymorphism genotyping. A Palladino contributed to the design of the study protocol and provided patients for recruitment. M Emerenciano and MB Mansur recruited patients, designed and coordinated the ALL molecular study. MT Accioly provided the Tu-

mor Bank samples. M Ferreira and AA Gonçalves integrated the PGx reports into INCA's intranet system. AC de Melo contributed to the design of the study protocol. All the authors critically reviewed and approved the final manuscript.

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Financial & competing interests disclosure

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No writing assistance was utilized in the production of this manuscript.

Ethical conduct of research

The authors state that they have obtained appropriate institutional review board approval or have followed the principles outlined in the Declaration of Helsinki for all human or animal experimental investigations. In addition, for investigations involving human subjects, informed consent has been obtained from the participants involved.

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