Neurology Asia 2023; 28(4) : 943 – 949

Pharmacogenomics knowledge within Neurology: A brief survey amongst physicians

[1]Kaavya NARASIMHALU *MRCP*, [2]Joel SOO *BSc (Pharmacy)*, [3]Jia Yi SHEN *MRCP (UK)*, [2]Pei Shieen WONG *PharmD*

[1]Department of Neurology, National Neuroscience Institute, Singapore General Hospital Campus, Singapore; [2]Department of Pharmacy, Singapore General Hospital, Singapore; [3]Department of Neurology, National Neuroscience Institute, Tan Tock Seng Hospital Campus, Singapore

Abstract

Pharmacogenomics has emerged as a tool to optimise treatment. Many neurologists encounter drugs with pharmacogenomic associations with unclear guidelines. We therefore aimed to determine the knowledge, attitudes, and barriers to implementing pharmacogenomics in clinical practice within a neurology unit. We developed and administered a survey on pharmacogenomics to physicians working in a neurology unit. Three drug-gene pairs clinically relevant to neurology were presented as case scenarios to assess physicians' perceived competency, attitudes, and risks towards pharmacogenomics. Thirty-two (27.4%) physicians responded to the survey. Respondents were most confident about activities involving the HLA-B*15:02 test, followed by the *CYP2C19* test, and lastly the *CYP2C9* test. However, perceived competency in drug-drug-gene interactions was consistently low for all three tests. Referring to the product information leaflet ranked highest in usefulness, followed by local practice guidelines. In conclusion, local clinical guidelines and training on the clinical applications of pharmacogenomics are important to facilitate the implementation of pharmacogenomics.

Keywords: Pharmacogenomics, genotype-guided treatment, neurology, clinical guidelines

INTRODUCTION

Precision medicine is an emerging approach to disease treatment and prevention that considers an individual's gene variability, environment and lifestyle. Pharmacogenomics, the study of how DNA and RNA variation relate to drug response, is a core element of precision medicine. Pharmacogenomics helps to guide drug prescription and dosing decisions with the overall aim of improving clinical outcomes and reducing adverse effects.[1] Concerns about the clinical validity and utility of pharmacogenomics, lack of clear clinical guidelines, perceived lack of self-competency, and contradictory results from pharmacogenomic studies are some of the macro-level barriers to clinical implementation of pharmacogenomics.[2,3] Turnaround time to receive results, accuracy and cost of pharmacogenomic testing, and lack of clarity on how test results affect patient's insurability are some of the micro-level barriers to clinical implementation of pharmacogenomics.[4]

The United States Food and Drug Administration recommendations on pharmacogenomics can be classified into three groups[5]: 1. Associations for which the data support therapeutic management recommendations; 2. Associations for which the data indicate a potential impact on safety or response; 3. Associations for which the data indicate a potential impact on pharmacokinetic properties only. Neurologists have several drug-gene associations for which the data support therapeutic management recommendations, including HLA-B*15:02 genotyping before initiation of carbamazepine in new patients of Asian ancestry, *CYP2C19* genotyping to assess treatment efficacy of clopidogrel, and recently *CYP2C9* genotyping before initiation of siponimod. At present, little is known about neurologists' concerns about the practical aspects of incorporating pharmacogenomics into clinical decision-making.

As such, we developed a survey to determine the knowledge, attitudes, and practice towards the

Address correspondence to: Dr Kaavya Narasimhalu, Consultant Neurologist, National Neuroscience Institute (Singapore General Hospital Campus), Outram Road, Singapore 169608. Email: nkaavya@gmail.com

Date of Submission: 27 June 2023; Date of acceptance: 8 October 2023

https://doi.org/10.54029/2023xfs

clinical application of pharmacogenomics within a tertiary neurology centre.

METHODS

Study design and participants

This cross-sectional study was conducted using a voluntary, self-administered questionnaire using the online survey tool Qualtrics (UT, USA) between 28th March 2022 and 30th June 2022. The target population for this survey was all 117 physicians engaged in the clinical practice of neurology from the National Neuroscience Institute campuses at Singapore General Hospital and Tan Tock Seng Hospital. This included non-specialists (general medicine medical officers who were doing a rotation in Neurology, Neurology trainees) and Neurologists registered with the Singapore Medical Council. Study invitation was disseminated through the principal investigator via department e-mails to all prospective participants. Reminder e-mails were sent on Day 4, Day 22, and 1 week prior to the end of the survey to increase response rates. All participants provided electronic consent before starting the survey. Institutional review board exemption was granted as this was an anonymous survey, and no identifiable information was collected.

Questionnaire

A 27-item questionnaire was developed for this study in consultation with the principal investigator and study collaborators who have experience with pharmacogenomics. The questionnaire was checked for face and content validity, with pre-testing done with a group of six individuals comprising two neurologists who were study collaborators, two internal medicine residents and two neurology trainees. Their feedback on the relevance, clarity, order, and time taken to complete the survey was collected. Construct validity was not performed due to the exploratory nature of the study and the limited number of potential participants.

The questionnaire (Supplementary Figure 1) contained three sections, requiring approximately 15 minutes to complete. The first section comprised seven multiple-choice questions on demographics. The second section comprised three case scenarios regarding the clinical application of pharmacogenomics on the use of carbamazepine, clopidogrel, and siponimod. Case scenarios were formulated based on guidelines recommendations and clinical information reflecting the current standard of practice.[5,6]

Each case scenario contained four to five main questions evaluating perceived competency and perceived attitudes. Questions on perceived competency required participants to rank confidence levels when performing clinical tasks, using a 5-point Likert scale. It also included a multiple-choice question on pharmacotherapeutic choice. Questions on perceived attitudes included two multiple-choice questions to understand if the information provided along with the test result was adequate in providing guidance in clinical decision-making and whether genetic testing is a useful tool in various scenarios.

The last section was on training, and perceived risks and barriers. The former involved two multiple-choice questions on whether participants had received formal training in pharmacogenomics and their preferred learning modality. A question requiring participants to rank the usefulness levels of various resources in incorporating pharmacogenomics in their practice was included. The question on perceived barriers required participants to rank what they felt was the most important barrier in utilising pharmacogenomic testing in clinical practice.

Statistical analysis

Anonymised survey responses were collated electronically on Qualtrics, and summarised using descriptive statistics. Analysis was performed using IBM SPSS Statistics for Windows, Version 21.0 (Armonk, NY). Categorical variables were presented as frequencies and percentages. Ordinal variables were presented as median (interquartile range) or number (percentage). For ranking questions on the usefulness level of information sources and importance levels of barriers, responses were assigned numerical scores, and means were compared between subgroups. The correlation between confidence levels in performing clinical activities and demographics was evaluated using Spearman's. Statistical significance was set at $p < 0.05$. Narrative comments were extracted and analysed thematically.

RESULTS

Thirty-two of 117 (27%) of invited doctors responded to the survey. Majority of the respondents were male (75.0%), had between 11 and 20 years of experience (43.8%), and were specialists (68.7%). Around half of respondents ordered more than 20 pharmacogenomic tests in the past year (Table 1).

Perceived attitudes and competency

Thirty-one respondents (96.9%) agreed that the application of pre-emptive pharmacogenomic testing for actionable drug-gene pairs in neurology likely improves clinical outcomes. Respondents were more confident about activities involving the HLA-B*15:02 test, *CYP2C19* test, than the *CYP2C9* test (Table 2). Confidence in knowing how the test result affects the patient's other drugs was consistently ranked low.

Correlational analysis found perceived competency in interpreting various test results, choosing an appropriate drug, and knowing how test results affect other drugs have a statistically significant positive correlation with perceived competency providing pre- and post-test counselling, and answering patient's queries for all three tests (Table 3). No statistically significant correlation was found between demographic characteristics and the confidence level of various activities.

*Carbamazepine-HLA-B*15:02 scenario*

An HLA-B*15:02 positive male patient with newly diagnosed focal onset seizure was presented and participants had to select an alternative anti-seizure medication. Participants were allowed to select more than one option. Levetiracetam was the most selected option (90.6%, $n = 29$), followed by sodium valproate (50.0%, $n = 16$), lamotrigine (31.3%, $n = 10$), and phenytoin (12.5%, $n = 4$). Both specialists (26%) and non-specialists (55%) chose lamotrigine or phenytoin as alternatives to carbamazepine in the HLA-B*15:02 positive patient. All respondents viewed pre-emptive HLA-B*15:02 genotyping as a useful tool to prevent severe adverse effects when choosing anti-seizure medications.

Clopidogrel-CYP2C19 scenario

A patient started on dual anti-platelet therapy (DAPT) consisting of clopidogrel and aspirin for secondary prevention of stroke was presented. Given her *CYP2C19* *2/*2 genotype, 50% of respondents indicated they would switch to ticagrelor/aspirin for 3 weeks, then aspirin lifelong. A quarter however indicated they would continue clopidogrel/aspirin for 3 weeks, then aspirin lifelong, and 9.4% of respondents indicated switching to aspirin/dipyridamole. Overall, 96.9% of respondents viewed *CYP2C19* genotyping useful to guide the choice of anti-platelet in secondary stroke prevention.

Table 1: Baseline demographic of respondents ($n = 32$)

Characteristics	Respondents, *n* (%)
Sex	
Male	24 (75.0)
Female	8 (25.0)
Years of experience	
1 – 5	5 (15.6)
6 – 10	10 (31.2)
11 – 20	14 (43.8)
> 20	3 (9.4)
Job Title	
Non-specialists	10 (32.3)
Specialists[1]	22 (68.7)
Experience ordering PGx tests	
Yes	32 (100.0)
No	0 (0.0)
PGx tests ordered/requested in last one year	
< 5	1 (3.1)
5 – 20	13 (40.6)
> 20	18 (56.3)

PGx: Pharmacogenomics

Table 2: Median [interquartile range] confidence levels performing various activities stratified by pharmacogenomic test

Activities	HLA-B*15:02	*CYP2C19*	*CYP2C9*
Deciding when to order the pharmacogenomic test	5 (4 – 5)	4 (4 – 5)	2 (1 – 3)
Interpreting test result	5 (4 – 5)	4 (4 – 5)	2 (2 – 3)
Providing pre- and post-test counselling	4 (3 – 5)	4 (3 – 5)	2 (1 – 3)
Choosing the appropriate drug[a] in view of test result	5 (4 – 5)	4 (4 – 5)	NA[b]
Knowing how test result affects patient's other drugs	4 (3 – 5)	3 (2 – 4)	2 (1 – 2)
Answering patient's queries	4 (3 – 5)	4 (3 – 4.75)	2 (1 – 3)

Measurement made using 5-point Likert scale with 1 being the least confident and 5 being the most confident. NA: not applicable.

[a] Refers to anti-seizure drug for HLA-B*15:02 test and anti-platelet drug for *CYP2C19* test.

[b] Not applicable as the siponimod-*CYP2C9* involves a genotype-guided dosing change rather than a change in drug selection

Siponimod-CYP2C9 scenario

The case involved a *CYP2C9* *1/*1 individual recently started on siponimod. Respondents were least confident in navigating the use of siponimod (Table 2). Overall, 87.5% of respondents agreed that pharmacogenomic-guided therapy for specialty drugs such as siponimod can be safely implemented if clear guidance was available.

Information sources

Most agreed that pharmacogenomic test results were adequately visible in the electronic medical records (71.9%, n = 23). Almost all respondents agreed the information provided along with all three test results were adequate in providing guidance in the clinical decision-making.

Table 3: Spearman correlational analysis of factors including perceived competency interpreting genotype test result, knowing how test results affect patient's other drugs, providing pre- and post-test counselling, and answering patient's queries (n = 32)

Activities	Providing pre- and post-test counselling		Answering patient's queries	
	Correlation coefficient	*P* value	Correlation coefficient	*P* value
Deciding when to order test				
HLA-B*15:02	0.255	0.158	0.406	0.021
CYP2C19	0.461	0.008	0.541	0.001
CYP2C9	0.746	<0.001	0.769	<0.001
Interpreting test result				
HLA-B*15:02	0.466	0.007	0.590	<0.001
CYP2C19	0.589	< 0.001	0.557	<0.001
CYP2C9	0.707	<0.001	0.719	<0.001
Choosing appropriate drug in view of test result				
HLA-B*15:02	0.601	<0.001	0.604	<0.001
CYP2C19	0.491	0.004	0.641	<0.001
CYP2C9[a]	NA	NA	NA	NA
Knowing how test result affects patient's other drugs				
HLA-B*15:02	0.670	<0.001	0.705	<0.001
CYP2C19	0.504	0.003	0.708	<0.001
CYP2C9	0.880	<0.001	0.918	<0.001

NA: not applicable.

[a] Not applicable as the siponimod-*CYP2C9* involves a genotype-guided dosing change rather than a change in drug selection

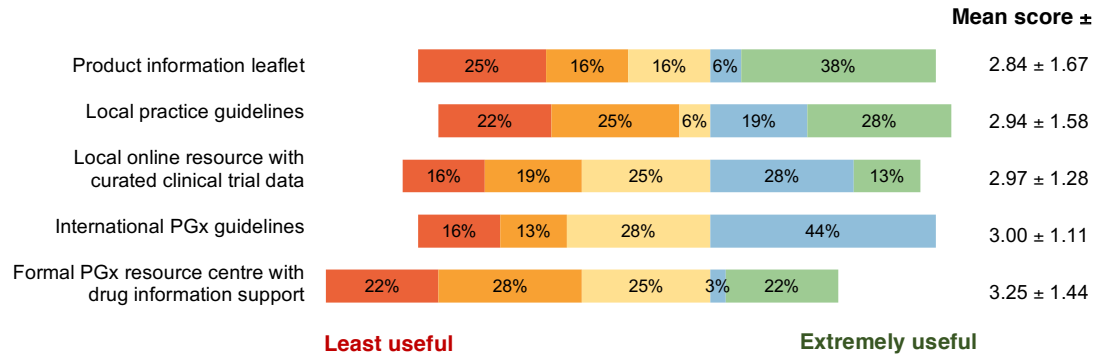

Figure 1. Usefulness levels of information sources when making clinical decisions (n = 32). Data represented as percentages of respondents within each category. Percentages may not add up to 100% due to rounding. Data sorted in ascending order according to a weighted average by assigning scores of 1, 2, …, or 5 to its respective ranks 1 to 5. A lower average score implies a more favourable attitude towards the usefulness of the resource. Rank 1 (green), extremely useful; Rank 2 (blue), moderately useful; Rank 3 (yellow), somewhat useful; Rank 4 (orange), slightly useful; Rank 5 (red), least useful. PGx: Pharmacogenomics.

Product information leaflets and local practice guidelines were the two resources (Figure 1) that participants found most useful. International pharmacogenomic guidelines ranked fourth.

Perceived risks and barriers and training

Lack of clear clinical guidelines was the most important barrier to integrating pharmacogenomics into clinical practice, followed by lack of information technology (IT) infrastructure to integrate pharmacogenomic information systematically (Figure 2). Of respondents with experience ordering pharmacogenomic tests, 18.7% found it difficult to order them in their institutions.

Three-quarters of respondents did not receive formal training on pharmacogenomics, 12.5% were unsure and the rest felt training was inadequate. For desired training modalities, e-learning was top (71.9%, n = 23), followed by lecture (53.1%, n = 17), and workshop (15.6%, n = 5).

DISCUSSION

In this study, we surveyed a group of physicians in the neurology unit of two major hospitals on their opinions on pharmacogenomics. While physicians found pharmacogenomic testing was useful in the three clinical scenarios, they found that lack of clear clinical guidelines was the biggest

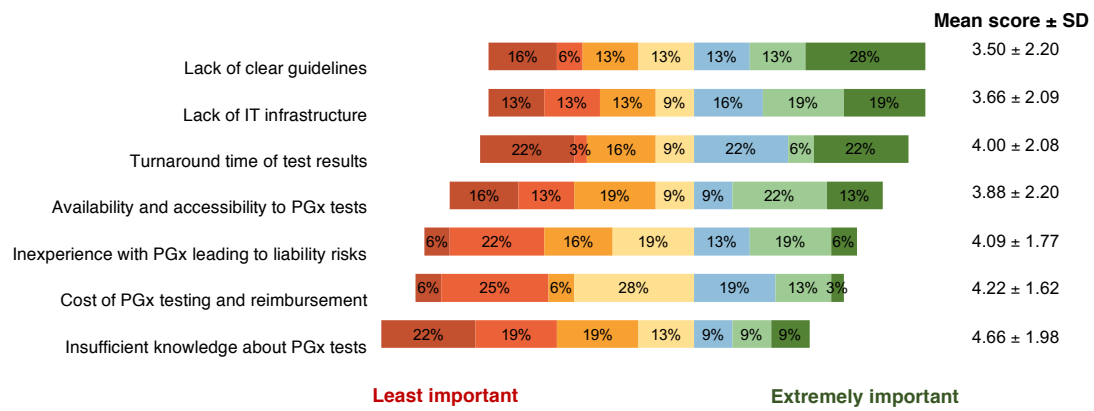

Figure 2. Importance levels of barriers to integrating pharmacogenomics into practice (n = 32). Data represented as percentages of respondents within each category. Percentages may not add up to 100% due to rounding. Data sorted in ascending order according to a weighted average by assigning scores of 1, 2, …, or 7 to its respective ranks 1 to 7. A lower average implies a more favourable attitude towards the importance of the resource. Rank 1 (dark green), extremely important; Rank 7 (dark red), least important. PGx: Pharmacogenomics.

barrier to the implantation of pharmacogenomics. Physicians valued the product information leaflets and local practice guidelines as the two most useful sources of information when making clinical decisions.

The case scenarios in our survey highlight the complexities of the interpretation of pharmacogenomic guidelines. In the carbamazepine example, 55% of non-specialists and 26% of specialists chose phenytoin or lamotrigine despite a positive HLA-B*15:02 result.[7] In the Asian context, the cost-effectiveness of screening HLA-B*15:02 before prescribing carbamazepine has been established, while for lamotrigine and phenytoin, while positive patients are at an increased risk of Stevens-Johnson syndrome/toxic epidermal necrolysis, screening has not been shown to be cost-effective. This has resulted in local guidelines requiring the testing of HLA-B*15:02 prior to the initiation of carbamazepine[6] while phenytoin and lamotrigine do not have similar guidelines. The large proportion of physicians who have chosen either phenytoin or lamotrigine reflects the complexities of interpreting guidelines. Similarly, a quarter of physicians continued aspirin and clopidogrel in a poor metaboliser of *CYP2C19*, reflecting the complexities of prescribing when there are no clear local guidelines despite the availability of international recommendations.[5]

We found an increased perceived competency in interpreting test results, choosing an appropriate drug, and knowledge in drug-drug-gene interactions were associated with increased perceived competency in providing pre- and post-test counselling and answering patients' queries. We also found that despite all participants ordering pharmacogenomics tests, three-quarters received no formal training to do so. A recent survey of American medical programs suggests that most do not have formal education programs in pharmacogenomics, a majority (85%) have at least 10 hours' worth of didactic lectures on pharmacogenomics. However, despite this time, the majority of medical programs do not find that physicians have sufficient knowledge to address pharmacogenomics.[8]

A limitation of this study was the non-response bias due to the low response rate. Some subgroups (non-specialists and senior consultants) were not well-represented. This inherently limited the statistical tests performed. There were also limitations to using a self-administered online questionnaire like difficulty in eliciting nuanced responses and tendency to leave open-ended questions blank. Given that this study was conducted in two tertiary centres, the results of this study may not be generalizable. The strength is that this is the first study assessing the knowledge, attitudes, and concerns about pharmacogenomics within multiple subspecialties within neurology.

In conclusion, in this study, while pharmacogenomic testing was perceived as useful in physicians working in a neurology ward, the lack of clear clinical guidelines was the biggest barrier to the implantation of pharmacogenomics. Physicians valued the product information leaflets and local practice guidelines as the two most useful sources of information when making clinical decisions.

DISCLOSURE

Availability of data: The datasets generated during and/or analysed during the current study are not publicly available due to lack of consent during the waiver of consent application but are available from the corresponding author on reasonable request.

Financial support: None

Conflict of interest: None

REFERENCES

1. Cecchin E, Stocco G. Pharmacogenomics and personalized medicine. *Genes (Basel)* 2020;11(6):679. doi:10.3390/genes11060679
2. Chan CYW, Chua BY, Subramaniam M, Suen ELK, Lee J. Clinicians' perceptions of pharmacogenomics use in psychiatry. *Pharmacogenomics* 2017;18(6):531-8. doi:10.2217/pgs-2016-0164
3. Mrazek DA, Lerman C. Facilitating clinical implementation of pharmacogenomics. *JAMA* 2011;306(3):304-5. doi:10.1001/jama.2011.1010
4. Jameson A, Fylan B, Bristow GC, *et al*. What Are the barriers and enablers to the implementation of pharmacogenetic testing in mental health care settings? *Front Genet* 2021;12:740216. doi:10.3389/fgene.2021.740216
5. Administration F and D. Table of Pharmacogenetic Associations. https://www.fda.gov/medical-devices/precision-medicine/table-pharmacogenetic-associations. Published 2022. Accessed September 3, 2023.
6. Authority HS. HLA-B*1502 genotyping and carbamazepine-induced severe cutaneous adverse reactions. Drug Safety Alerts. https://www.hsa.gov.sg/announcements/safety-alert/hla-b-1502-genotyping-and-carbamazepine-induced-severe-cutaneous-adverse-reactions. Published 2016. Accessed September 3, 2023.
7. Zheng Z, Zhong H, Zhang Q, Huang Q, Wu H. HLA-B*1502 is associated with aromatic

anticonvulsant drug-induced cutaneous adverse drug reactions among the Hakka population in China. *J Int Med Res*. 2020;48(3):300060520911276. doi:10.1177/0300060520911276

8. Basyouni D, Shatnawi A. Pharmacogenomics instruction depth, extent, and perception in US medical curricula. *J Med Educ Curric Dev* 2020;7: 2382120520930772. doi:10.1177/2382120520930772.

Supplementary Figure 1. Online questionnaire hosted on Qualtrics

Job Title

- Medical officer
- Registrar / Senior resident
- Associate consultant / Consultant
- Senior consultant

Do you have experience ordering pharmacogenomic tests (eg. HLA-B*15:02, CYP2C9, CYP2C19)?

- Yes
- No

If answered "Yes" to previous question, the following three questions will appear. Otherwise, the survey will skip to section 2A.

How many pharmacogenomic tests have you ordered/requested in the last one year?

- Less than 5
- 5 - 20
- More than 20

Do you agree with the following statement:

"Pharmacogenomic tests are easy to order in my institution."

- Agree
- Disagree

Do you agree with the following statement:

"Pharmacogenomic test results that may influence my therapeutic decision is adequately visible in the electronic medical records."

- Agree
- Disagree

Section 2A: Clopidogrel case scenario

Please read the following case and answer the following questions.

Background: A 40-year old woman is admitted for an acute ischemic stroke (NIHSS 3
week ago and started on a dual antiplatelet therapy consisting of clopidogrel and asp
for secondary prevention of stroke. Prior to her clinic visit today, a CYP2C19 genotyp
was ordered and the results are out today.

The following is the report of the results:

```
Received Date/Time: 14/03/2022 0845
CYP2C19 diplotype: *2/*2
Predicted phenotype: Poor Metaboliser

Note:
1. This test may be used to aid drug selection and dose
alteration for drugs metabolised by CYP2C19. These drugs
include but are not limited to clopidogrel, voriconazole,
selective serotonin reuptake inhibitors, tricyclic
antidepressants, and proton pump inhibitors.
2. Diplotype-phenotype predictions are based on Clinical
Pharmacogenetics Implementation Consortium (CPIC) guideline
3. Prodrugs that are activated by CYP2C19 (such as clopidog
are likely to show reduced effectiveness in patients who ar
intermediate or poor metabolisers. Some drugs metabolised b
CYP2C19 (such as voriconazole) will have delayed achievemen
target blood concentrations in rapid or ultrarapid metaboli
and increased risk of adverse drug events in poor metabolis
Dose adjustments or alternative therapeutic agents may be
necessary in these situations. Please refer to the relevant
management guidelines for therapeutic recommendation.
4. This test does not detect all variants of the gene teste
Non-detected variants, other genetic or clinical factors ma
affect drug metabolism. Clinical correlation is recommended
```

Q1. On a scale of 1-5 (with 1 being the **least** confident, and 5 being the **most** confident), how confident are you in:

1 2 3 4 5

Deciding when to order the CYP2C19 test

Interpreting the CYP2C19 test result

Providing pre and post-test counselling

Choosing the appropriate anti-platelet(s) for this patient in view of the test result

Knowing how the test result may affect other drugs that patient may be taking

Answering patient's queries

Q2. Do you agree with the following statement: "The information provided along with the test results was adequate in providing guidance in the decision-making process."

Agree

Disagree

Q3. Do you agree with the following statement: "CYP2C19 genetic testing is a useful tool to guide choice of anti-platelet in secondary stroke prevention."

Agree

Disagree

Q4. What will be your next course of action for this patient?

- Continue aspirin and clopidogrel for 3 weeks, then aspirin lifelong
- Switch to aspirin and ticagrelor for 3 weeks, then aspirin lifelong
- Not sure
- Others (please specify)

Q5. Any other comments on the application of CYP2C19 pharmacogenomics testing for clopidogrel?

Section 2B: Carbamazepine case scenario

Please read the following case and answer the following questions.

Background: A 27 year-old man has been newly diagnosed with focal-onset epilepsy HLA-B*15:02 genotype test was done one week ago and the results are out today.

The following is the report of the results:

Received Date/Time: 16/03/2022 1120
Clinical Diagnosis: Epilepsy
HLA-B*15:02 Genotyping: Positive

Note:
Clinical studies have demonstrated a strong association bet HLA-B*1502 allele, which has a higher frequency in Asian population, and risk of carbamazepine (CBZ)-induced Stevens Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) The Ministry of Health (MOH) recommends that genotyping for HLA-B*1502 allele prior to the initiation of carbamazepine (CBZ) therapy in new patients of Asian ancestry to be a standard of care.

Method: Polymerase Chain Reaction (PCR) using One Lambda Mi SSP HLA Class I B Locus Specific kit (SSP1B)

Q1. On a scale of 1-5 (with 1 being the **least** confident, and 5 being the **most** confident), how confident are you in:

1 2 3 4 5

Deciding when to order the HLA-B*15:02 test

Interpreting the HLA-B*15:02 test result

Choosing the appropriate anti-seizure medication in view of the test result

Knowing how the test result may affect other drugs that patient may be taking

Providing pre and post-test counselling

Answering patient's queries

Q2. Do you agree with the following statement: "The information provided along with the test results was adequate in providing guidance in the decision-making process."

Agree

Disagree

Q3. Do you agree with the following statement: "HLA-B*15:02 testing is a useful tool to prevent severe adverse effects when choosing anti-seizure medications."

Agree

Disagree

Q4. Which anti-seizure medication(s) would you consider switching this patient to? (choose all possible options)

- Levetiracetam
- Lamotrigine
- Phenytoin
- Sodium valproate
- Not sure
- Others (please specify)

Q5. Any other comments on the application of HLA-B*15:02 pharmacogenomics testing for carbamazepine?

Section 2C: Siponimod case scenario

Please read the following case and answer the following questions.

Background: A 33 year-old female has been recently diagnosed with secondary progressive multiple sclerosis (SPMS) and decision is made to initiate siponimod. CYP2C9 genetic test was ordered.

The following is the dose report of the results:

```
Received Date/Time: 15/03/2022 1330
Clinical Diagnosis: SPMS
CYP2C9 Genotyping: CYP2C9 *1/*1

Note: Siponimod is a sphingosine-1-phosphate receptor modulator
indicated for the treatment of relapsing forms of multiple
sclerosis and is contraindicated in patients with a CYP2C9*3/*3
genotype.
```

Recommendations from the product insert:

Genotype	**Recommendations**
CYP2C9 genotype *1/*1, *1/*2 or *2/*2	Initial: 0.25mg once daily on day 1 and 2, then 0.5mg once daily on day 3, then 0.75mg once daily on day 4, then 1.25mg once daily on day 5 Maintenance: 2mg once daily, beginning on day 6
CYP2C9 genotype *1/*3 or *2/*3	Initial: 0.25mg once daily on day 1 and 2, then 0.5mg once daily on day 3, then 0.75mg once daily on day 4 Maintenance: 1mg once daily, beginning on day 5

Q1. On a scale of 1-5 (with 1 being the **least** confident and 5 being the **most** confident), how confident are you in:

1 2 3 4 5

Deciding when to order the CYP2C9 test

Interpreting the CYP2C9 test result

Knowing how the test result may affect other drug(s) that patient may be taking

Providing pre and post-test counselling

Answering patient's queries

Q2. Do you agree with the following statement: "The information provided along with the test results was adequate in providing guidance in the decision-making process."

Agree

Disagree

Q3. Do you agree with the following statement: "Pharmacogenomics-guided therapy for specialty drugs, such as siponimod, can be safely implemented if clear guidance is available."

Agree

Disagree

Q4. Any other comments on the application of CYP2C9 pharmacogenomic testing for siponimod?

Section 3: Final questions: Training and perceived barriers

Have you received formal training in *pharmacogenomics?

(*Pharmacogenomics is the study of variations of DNA and RNA characteristics as related to drug response. Eg. HLA-B*15:02 and carbamazepine-induced SJS/TEN association)

- Yes
- Yes, but it is not adequate
- No
- Not sure

Which mode of learning would you prefer to guide your learning of pharmacogenomics? (you may select more than one option)

- Lecture
- E-learning
- Workshop
- Others (please specify)

What resources will be useful to help support you in incorporating pharmacogenomics in your practice?

Please **RANK** the following resources (1 being the **most** useful, and 5 being the **least** useful).

	1	2	3	4	5
Product information leaflet	○	○	○	○	○
Local practice guidelines	○	○	○	○	○
Local online resource with curated clinical trial data on relevant drug-gene pairs	○	○	○	○	○
International pharmacogenomics guidelines (e.g. CPIC, PharmGKB)	○	○	○	○	○
A formal Pharmacogenomics Resource Centre with drug information support	○	○	○	○	○

Do you agree with the following statement:

"Application of *pre-emptive pharmacogenomics testing for actionable drug-gene pairs in Neurology is likely to improve clinical outcomes."

(*testing of relevant pharmacogenes that impact a number of high-risk drugs before the time of prescription consideration)

- Agree
- Disagree

What are the BARRIERS to integrating pharmacogenomics into your practice?

Please **RANK** the following (1 being the **most** important, and 7 being the **least** important) in order of importance to you.

	1	2	3	4	5	6	7
Availability and accessibility to pharmacogenomic tests	○	○	○	○	○	○	○
Cost of pharmacogenomic testing and reimbursement	○	○	○	○	○	○	○
Turnaround time of test results	○	○	○	○	○	○	○
Lack of clear clinical guidelines on application	○	○	○	○	○	○	○
Lack of awareness and inexperience with integrating pharmacogenomics into decision making may lead to liability risks	○	○	○	○	○	○	○
Lack of information technology (IT) infrastructure to integrate pharmacogenomic information systematically and provide decision support	○	○	○	○	○	○	○
Insufficient knowledge about pharmacogenomic test interpretation and drug therapy	○	○	○	○	○	○	○

Do have any further comments on the clinical implementation of pharmacogenomics in Neurology?

End of survey