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Teaching psychiatric pharmacogenomics effectively: Evaluation of a novel interprofessional online course

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Abstract

Introduction: The application of pharmacogenomic (PGx) testing to guide psychotropic use is increasing, but there is a lack of training opportunities for health care providers designed specifically around the unique issues impacting the use and interpretation of PGx in psychiatry. Furthermore, providing such education online greatly improves the accessibility of such training.

Objective: The objective was to design and evaluate a live online continuing education (CE) course on psychiatric PGx for health care providers.

Methods: A multidisciplinary team of experts in psychiatry, PGx, and medical education research designed a three-session online course to discuss key psychiatric PGx topics ranging from fundamental background material, selecting a test, and interpreting and applying results. A deliberate design of the program was to offer the course three times, in order to allow successive improvements to each iteration. To evaluate the course, pre- and post-surveys were developed with the intent of capturing change in the four Dixon levels of CE evaluation on attendee perceptions and opinions, knowledge and attitudes, and impact on clinical practice and patient outcomes.

Results: In the third course iteration, 32 health care providers registered. Among survey respondents, the course materials, speakers, organization, and online format were reviewed favorably by the majority of attendees. Perceived knowledge of PGx increased in every identified PGx topic domain and was largely reflected by improved knowledge assessment scores. A limited number of survey participants also indicated changes in clinical behavior and patient outcomes as a direct result of the material covered in this course.

Conclusions: Among survey respondents, this novel online PGx course proved effective at increasing provider understanding and confidence in key psychiatric PGx topic areas. It also demonstrated the viability of the online format, a vital characteristic to allow for future widespread dissemination.

KEYWORDS

continuing medical education, depression, online education, pharmacogenetics, pharmacogenomics, psychopharmacology, training

1 | INTRODUCTION

Pharmacogenomics (PGx) is a branch of precision medicine that utilizes genetics to improve the safety and efficacy of medications. The application of PGx in psychiatry is particularly appealing because achieving remission of depression or anxiety symptoms may take several medication trials, with each trial lasting months. The potential for PGx to reduce this trial-and-error process has led to an abundance of commercial laboratories offering PGx testing products.¹ In fact, a recent systematic review identified 37 different PGx tests offered by commercial laboratories that assess for variants in genes important to psychotropic response and metabolism.²

The majority of available psychotropic PGx products are panel tests, which means that they typically report results for a large number of genetic variants in several genes. Some products offer recommendations using proprietary algorithms, while others provide lists of genotypes and phenotypes without medication recommendations.³⁻⁷ In a comparison of four of the available commercial products designed to guide psychotropic therapy, DNA samples from five participants were sent to four commercial laboratories, and significant disagreement between products were identified in tested variants, genotype-to-phenotype conversions, and result interpretations.⁸ The current lack of standardization in PGx testing and interpretation adds complexity to result interpretation.^{9,10}

Such complexity in understanding psychiatric PGx testing and the rapidly developing nature of the field signals the need for relevant, targeted, and easily accessible training for health care providers. Recognizing this gap in training, our interdisciplinary team of experts in pharmacy, PGx, psychiatry, and education designed a PGx course with two overarching aims: (a) Focal and relevant psychiatric PGx training in a brief format, providing practical information that providers can easily implement, and (b) Use of key educational principles in the employment of an online format, to ensure widespread accessibility. We utilized key principles of effective educational design, using a needs survey and educational literature to inform course design, with careful attention to a blend of lecture and interactive case material, as detailed in the methods. Our learning objectives were to enable providers to: (a) describe basic PGx concepts; (b) distinguish which gene-drug relationships have the most evidence supporting their implementation in psychiatry; (c) factors to consider when selecting a PGx test; and (d) confidently formulate medication plans using PGx test results. Our target audience included pharmacists and all prescribers in psychiatry. Here, we describe the process we used to design our live online continuing education course (CE) on psychiatric PGx, and educational outcomes as captured by the results from surveys describing providers' perceptions of the course and PGx, as well as how they use, or intend to use, this training in practice.

2 | METHODS

2.1 | Format

The course was offered three times throughout 2019, with the first two versions serving as models used in a continuous quality 177

improvement fashion for the third and final iteration. The third iteration of the course is reported here and is also preserved as an enduring materials course on the Michigan Medicine Continuing Education website. The course consisted of three weekly lessons, with each lesson held for 90 minutes featuring a constant flow between PGx principles and case examples and illustrations. Faculty instructors used a two-person teaching model, with an expert pharmacist as the primary lecturer paired with a consistent psychiatrist as an expert provider. All pharmacist faculty had research and clinical experience in PGx, as did the psychiatrist. Faculty provided cases but invited participants to present clinical experiences or scenarios throughout.

Based on the success of previous online courses in psychopharmacology taught by members of this team,^{11,12} the course employed videoconferencing via Blue Jeans conferencing technology (BlueJeans Network, Inc., San Jose, California). Blue Jeans is a cloud-based, HIPAAcompliant audio/video/content sharing conferencing service that offers access up to 100 endpoints (eg, room telepresence system, laptop, tablet, or smartphone) to connect for a course.¹³ It supports high-resolution videoconferencing and content sharing and real-time video sharing.

2.2 | Content

Prior to the start of the course, a needs survey was distributed via email to prospective participants to allow tailoring of specific learning needs. The results of the survey led to the design of the course. Broadly, the course covered: (a) Background of PGx; (b) Introduction to the logic and philosophy of psychiatric PGx; (c) Practical considerations for PGx; (d) Ethical considerations for PGx; (e) Selecting/comparing labs; (f) Combinatorial PGx vs single-gene testing; (g) Factors influencing PGx results (specifically drug-drug-gene interaction information); and (h) Interpreting results with a mix of cases. Specific examples of patient cases, initially beginning with a simple example with one gene and then building on more complex scenarios, were a key component of the course content. The course employed both didactic and interactive learning styles, addressing unperceived needs (addressed primarily by the speaker in designing the didactic portion), as well as perceived needs identified by brief weekly needs surveys of participants for each upcoming topic. A brief portion of the start of each session included discussion of challenges participants experienced in applying any knowledge from the previous class, thus adapting the learning to actual practice scenarios and further educating faculty on the context-validity and utility of what was being taught. Consistent with standard procedures for CE events, individuals had to register, make a commitment to attend the course, complete routine needs surveys and outcome questionnaires (as a standard of evaluation, not as a formal research project) and pay a registration fee (\$45).

2.3 | Course advertising

The first round of the course was advertised locally, and the second round of the course was advertised to state mental health 178

organizations. The final round was advertised nationally to members of the College of Psychiatric and Neurologic Pharmacists (CPNP), the American Society of Clinical Psychopharmacology (ASCP), and the American Psychiatric Nurses Association (APNA) through email listservs and website listings. The course was accredited for physician, nursing, and pharmacy CE. Evaluations and outcomes measures reported below are for the final round of the course.

2.4 | Surveys

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Six surveys were designed to guide the development of the CE course, evaluation of the individual sessions, and to demonstrate how health care providers applied training from the CE sessions in practice. The surveys included a mixture of free text response, multiple choice, and Likert scales to rank degree of interest, perceived knowledge, or agreement with provided statements. These surveys were distributed through email before or after the sessions concluded. None of the surveys were required for participation in the course, and questions could be skipped. Attendees were sent reminder emails to complete the surveys in order to enable the course designers to assess the quality and impact of the CE course. The course moderator also provided verbal reminders during the sessions. These surveys were designed around the structure proposed by Dixon to capture a continuum of change in provider perceptions, knowledge, attitudes, practice, and ultimately impact on patient outcomes due to CE programs.¹⁴ Table 1 includes a summary of the four levels of CE evaluation as described by Dixon, and example guestions from our surveys that fall under each category.

The initial survey was a needs assessment administered to local health care providers at our large academic medical center to guide the development of materials and logistics. Participants were asked questions about demographics and potential course material questions that were intended to capture provider interest in 14 PGx topics. The PGx topics in this survey were formulated based on a combination of PGx teaching topics covered in our College of Pharmacy's curriculum, practical experience utilizing PGx in the clinical setting, and topics covered during ambulatory psychiatry in-services. The relative interest in the 14 topics was assessed with a 5-point Likert scale (Table 2).

In addition, a pre-survey was sent to course registrants once before the start of the course and included questions on perceived level of knowledge in the 14 PGx topics introduced in the needs survey, previous training in PGx, current application in practice, statements about perceptions of PGx, and knowledge assessment questions. A survey was administered after the conclusion of each of the three individual sessions to assess satisfaction with the presenter and material with respect to issues like clarity, relevance, quality, and to complete the post-test knowledge assessments. There were also questions specific to the overall quality of the entire course following the final session.

Finally, there were follow-up surveys at 1- and 3-months to assess changes in behavior and perception of PGx as reported by participants to be a result of the CE course. The survey also included a

TABLE 1	Dixon levels of continuing education (CE) assessment
and example survey questions	

Dixon level summary	Example survey question
1. Attendee perceptions and opinions	I would recommend this course to others
2. Knowledge and attitudes	 What is the most common terminology used for reporting pharmacogenomic variants in cytochrome P450 enzymes? a. Reference SNP cluster ID (rsID) b. Nucleotide alteration c. Amino acid alteration d. Star (*) allele
3. Impact on clinical practice	As a result of this course, have you changed anything in your prescribing (such as using psychiatric pharmacogenomics tests more regularly or acting on results by changing medication prescribing)?
4. Impact on patient outcomes	Do you feel your patients benefited (positive clinical outcomes) based on decisions you made from knowledge gained in the course?

Note: The level 1 example survey question was assessed by a Likert scale measuring agreement from 1 (strongly disagree) to 5 (strongly agree). The level 3 and 4 example survey questions were assessed with a yes/no response and a request to elaborate with a brief (1-2 sentence) explanation if the participant responded in the affirmative.

question that assessed perceived improvements in patient outcomes that the provider attributed to be a direct impact of the CE course. Results of the surveys were analyzed descriptively based on the overall low number of respondents.

3 | RESULTS

3.1 | Needs assessment

Thirteen health care providers responded to the needs assessment survey. Among them were four psychiatrists, four nurse practitioners/ physician assistants, four non-psychiatrist physicians, and one PGx researcher. With respect to the 14 PGx topic areas, detailed in Table 2, at least 50% of respondents expressed interest in every topic when defined as the cumulative number of participants who responded with a 4 or 5 on a Likert interest scale from 1 (low) to 5 (high). Table 2 highlights the percent of respondents who selected high interest (5) in each of the topics. The following three topics had over 50% (n = 8 for each) of survey participants indicate high interest: (a) "How different genetic variants affect medication response"; (b) "The evidence for using PGx testing to guide attention-deficit/ hyperactivity disorder (ADHD) or antidepressant pharmacotherapy"; and (c) "Where to go for impartial information on PGx." The area of relatively lowest interest was the topic "Why PGx is not being used more commonly in practice." Course designers took the results of this survey to build materials for the three sessions, titled: (a) Introduction

TABLE 2 Assessment of pharmacogenetic topics by interest and by perceived knowledge before and after the course

	Perceived topic knowledge: pre- and post-course ^b			
High interest in topic pre-course ^a (n = 13)	Pre-session (n = 7)	1 month follow-up (n = 6)		
%	Mean (SD)	Mean (SD)		
53.9	2.29 (1.03)	3.67 (0.75)		
61.5	2.43 (0.90)	3.83 (0.69)		
46.2	2.57 (1.59)	3.67 (0.75)		
46.2	1.86 (0.99)	3.83 (0.69)		
38.5	2.14 (0.99)	3.33 (0.75)		
38.5	1.86 (0.99)	4.00 (0.58)		
38.5	2.57 (1.18)	4.00 (0.58)		
30.8	1.86 (1.36)	4.00 (0.58)		
38.5	1.86 (1.12)	4.00 (0.58)		
38.5	1.86 (0.83)	3.67 (0.75)		
38.5	2.14 (0.99)	3.83 (0.69)		
38.5	1.71 (1.03)	3.82 (0.69)		
61.5	2.14 (0.99)	3.67 (0.75)		
61.5	1.86 (0.99)	4.17 (0.37)		
	pre-course ^a (n = 13) % 53.9 61.5 46.2 38.5 38.5 30.8 38.5 38.5 38.5 38.5 38.5 38.5 38.5 38.5 38.5 38.5 38.5 38.5 38.5 38.5 38.5 38.5 38.5 38.5 38.5 38.5 38.5	High interest in topic pre-course ^a (n = 13) Pre-session (n = 7) % Mean (SD) 53.9 2.29 (1.03) 61.5 2.43 (0.90) 46.2 2.57 (1.59) 46.2 1.86 (0.99) 38.5 2.14 (0.99) 38.5 2.57 (1.18) 38.5 2.57 (1.18) 38.5 1.86 (1.36) 38.5 1.86 (0.83) 38.5 2.14 (0.99) 38.5 1.86 (0.83) 38.5 1.101 38.5 2.14 (0.99) 38.5 2.14 (0.99) 5 3.5 38.5 2.14 (0.99)		

Abbreviation: ADHD, attention-deficit/hyperactivity disorder.

^aHigh interest in topic was determined by survey participants selecting "5" in needs survey on a Likert scale expressing level of interest from 1 (low) to 5 (high).

^bPerceived topic knowledge refers to survey participant averages on a Likert scale with levels of knowledge from 1 (low) to high (5).

to Psychiatric Pharmacogenomics (covered basics of PGx and resources); (b) An Introduction to Psychiatric Pharmacogenomic Lab and Panel Selection (considerations when selecting a PGx testing lab); and (c) Clinical Studies and Result Interpretation (a review of major clinical trials comparing pharmacogenetic-guided vs treatment as usual care, and practical considerations when applying results to assist with psychotropic prescribing). The second and third sessions were meant to build upon previous material while using a patient case that was carried through the entire course series to highlight unique concepts within each section.

3.2 | Course participants

Thirty-two individuals registered for the final iteration of the CE course. Among registrants, credentials were listed for 30 participants.

TABLE 3 Participation numbers by survey and session

Session	Participants	Survey	Participants
Registrants	32	Pre-survey	7
Session number		Post-survey	
Session 1	27	Session 1	19
Session 2	21	Session 2	15
Session 3	20	Session 3	6

Four identified as MDs, 20 as NPs or DNPs, two as RNs, two as PhDs, and many had multiple degrees and/or specialty certifications like the Psychiatric-Mental Health Nurse Practitioner (PMHNP). Despite advertising to pharmacists and offering pharmacy CE, none registered. The majority of attendees were NPs in private practice, and most had been practicing for less than 10 years, but this variable ranged from

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less than 1 to 42 years. Table 3 lists the number of participants by survey and attendees per session.

3.3 | Pre- and post-course knowledge, and perception of knowledge questions (Dixon levels 1 and 2)

To assess baseline perceptions of PGx knowledge and change after the CE course, topics from the needs survey were provided and participants were asked to measure their level of knowledge on a scale of 1 (low) to 5 (high) for all of the PGx topics. Results from the perceived knowledge section of the pre- and post-survey are included in Table 2. Notably, the average perceived gains in all PGx topics moved from averages below to above the neutral value 3. With respect to knowledge questions assessed by multiple-choice responses, among the 15 questions asked (five questions per session), the percent of correct responses increased following the course for 11 questions and decreased for four questions. This suggests a need to improve teaching in some topic areas. All knowledge questions are provided in the Supporting Information.

3.4 | Assessments of change in perceptions of PGx, clinical practice, and patient outcomes pre- and post-course survey (Dixon level 3 and 4)

In the pre-survey, 1-month, and 3-month post-course surveys, the statement, "Psychiatric pharmacogenomics testing should be more widely adopted" was assessed with a 5-point Likert scale across a spectrum of

TABLE 4 Survey questions assessing participant-reported changes in clinical practice and patient outcomes related to pharmacogenomics (PGx)

		Responses by survey timing					
Survey question	Response options	Pre-survey	1 mo	3 mo			
Questions assessing participant-reported change in PGx-related clinical practice and training							
How many patients have you ordered pharmacogenomics testing for in the last 3 months?	a. None b. 1 to 4	a = 3 b = 1	Not assessed	a = 4 b = 1			
	c. 5 to 7 d. 8+	c = 0 d = 2		c = 0 d = 1			
Which of the following sources of guidance or assistance for pharmacogenomics do you currently use (select all that apply)?	 a. Program or website for checking drug interactions b. Pharmacist c. Pharmacogenomics Knowledgebase (PharmGKB opling information recourse) 	a = 5 b = 0 c = 0	a = 3 b = 0 c = 1	a = 0 b = 1 c = 3			
	online information resource) d. Clinical Pharmacogenetics Implementation Consortium (CPIC)	d = 0	d = 0	d = 0			
	e. Mobile app	e = 1	e = 0	e = 1			
	f. Other	f = 0	f = 0	f = 0			
	g. I do not currently use any	g = 0	g = 2	g = 1			
If you have used pharmacogenomics testing, have	a. Yes	a = 4	a = 2	a = 2			
you sent it to other treatment providers for the patient/made the other providers aware of the	b. No	b = 0	b = 1	b = 2			
test results?	c.Not applicable	c = 0	c = 3	c = 0			
Have you done any additional learning on	a. Yes	Not applicable	a = 0	a = 2			
pharmacogenomics (eg, articles, podcasts, videos) since the conclusion of the course?	b. No		b = 6	b = 4			
Questions assessing participant reported change in PO	Gx-related patient outcomes (measured at the 3-month foll	low up only)					
As a result of this course, have you changed	a. Yes			a = 3			
anything in your prescribing (such as using psychiatric pharmacogenomics tests more regularly or acting on results by changing medication prescribing)? If yes, please provide a brief example (1-2 sentences)	b. No			b = 3			
Do you feel your patients benefited (positive clinical outcomes) based on decisions you made from knowledge gained in the course? If yes, please provide a brief explanation (1-2 sentences)	a. Yes b. No			a = 3 b = 3			

Note: All participant responses were recorded for each survey time point-in most instances there were six respondents.

agreement from "strongly agree" to "strongly disagree." At the time of the pre-survey, four participants strongly agreed with the statement, one agreed, and two were neutral. By the time of the 3-month follow-up survey, four still strongly agreed and two agreed. As shown in Table 4, there did not appear to be a significant change in number of tests ordered between baseline and 3 months following the CE course conclusion, although all respondents at 3 months felt better able to implement and interpret PGx tests due to the course, and felt more confident implementing PGx (either strongly agree or agree). Among the participants who responded in the affirmative that they had made changes in practice that had positively impacted patient outcomes as a result of the course, one participant described that PGx testing was ordered for a patient with treatment-resistant depression who turned out to be an ultrarapid metabolizer of "many of the meds." An additional free-text response question was used to ask participants of what other support they would need to implement PGx in their practice setting. Responses included more practice (assuming with patient cases) and more understanding of insurance coverage.

3.5 | Overall evaluation survey and assessment of course quality and content (Dixon level 1)

General statements about course quality and instructors were overwhelmingly positive for all individual sessions (either agree or strongly agree on a 5-point Likert scale), but the number of respondents decreased across the three sessions (Table 3). Among results from the overall course evaluation questions, there was general agreement (either strongly agree or agree) with statements measuring course quality, organization, ease of use for the web conference tool, impact on practice or research, and relevance (5/6 participants). However, there was generally one respondent that disagreed or selected neutral for many course measures. Assuming it was the same individual, they provided helpful feedback that the course was overly granular and detailed for their use. Interestingly, feedback about the general number of course sessions was selected as too few (3) or just right (3) from the participants who responded to this survey. Other identified strengths of the course provided as text comments include liking the "chat" function within BlueJeans to be able to ask questions without having to speak, having a better understanding of how to explain to patients the pros/cons of PGx testing, and being better able to understand PGx test results.

4 | DISCUSSION

Training opportunities in PGx have not risen at the same rate as provider and patient interest and test availability.¹⁵ Health care providers have consistently identified PGx as an area of medicine where they lack confidence and training, despite documented increases in PGx application from providers and patients alike.¹⁶⁻²⁴ Among the most recent examples, Rahawi and colleagues surveyed pediatricians in the United States (n = 210) and found that approximately 10% of

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pediatricians identified as being familiar with PGX, and only 7.2% were aware of the Clinical Pharmacogenomics Implementation Consortium (CPIC).¹⁹ The latter half of this statement is particularly relevant because CPIC is a National Institutes of Health (NIH)-funded organization of PGx experts that publishes PGx guidelines—including several pertaining to antidepressants and genetic variants in drug-metabolizing enzymes.²⁵⁻²⁷ Relatively few educational opportunities for non-pharmacist professionals have been made accessible to providers that give special consideration for the unique issues related to these psychotropic PGx.²⁸⁻³³

The goal of our course was to produce an interprofessional CE course that would enable health care providers caring for patients with mental illness to feel more confident in their knowledge and application of PGx to guide psychotropic use and improve patient outcomes. Results from participant surveys, which had response rates of 29% to 86% of attendees, were favorable for this course with respect to content, quality, and approval of the online platform. We also showed that a small number of providers reported changes in PGxrelated clinical behaviors and patient outcomes as a result of this course. It was also exciting to see a small, but steady, increase in the number of respondents who reported utilizing PharmGKB (an NIHfunded website with extensive PGx information for health care providers and researchers available at pharmgkb.org) increase over the follow-up period post-CE course series. This is particularly encouraging considering how rapidly research in PGx is evolving. When the course materials have fallen behind inevitable PGx research and guideline updates, the attendees have at least taken away from the course a professionally curated, impartial, and free database. It also reflects that we recognized the high interest in the PGx topic, "Where to go for impartial information on pharmacogenomics" and appropriately addressed it when also considering that this topic had the single largest absolute increase in perceived knowledge, as described in Table 2. Cumulatively, these positive responses to questions across the continuum of Dixon's levels of CE evaluation suggest that we have created an effective CE course, although the low number of survey participants and indirect measurements of changes to level 3 and 4 (provider practice change and improved patient outcomes) make it difficult to state this definitively.

Overall, our course does have significant limitations. Initial response to the needs survey was low, limiting our ability to carefully match lecture material with potential learner needs. However, the interactive nature of the sessions, and the fact that part of session 2 and session 3 involved asking individuals about learning and implementation challenges, allowed additional tailoring of the learning material. Despite the online nature of the course, individuals enrolling were primarily from one region of the United States, limiting generalizability. Post-session evaluations and the final post-course survey also had a low response rate, further compounding difficulties with the generalizability of the results to multiple professions and in multiple geographic regions. In the future, response rates could be improved by tying surveys to the CE session (requiring pre-surveys to be completed before entering the individual course sessions) or some other incentive. The availability of recordings that made it possible for

attendees to review the material at a later date may have also enabled some registrants to view the materials without actively participating in the live course, and may have contributed to the drop in attendees from session 1 through 3 (Table 3). Additionally, we did not have a control group of health care providers to compare changes in knowledge, skills, attitudes, or use of PGx testing. Finally, we did not collect data on the actual implementation of the course content in the practice setting, nor any data from patient outcomes as a result of this course. Instead, we asked participants to self-report these domains, inviting a positive bias. Such limitations are inherent in the evaluation process of most educational courses and can only be addressed through conduct of a rigorous, well-funded educational research project, which was beyond our scope.

A key recommendation from our course experience is that we would encourage others to also assemble a multidisciplinary team of developers when creating a PGx course. It has been recognized by several of the early adopters of PGx that it takes many disciplines to make their programs a success.³⁴⁻³⁶ These teams typically involve pharmacy, prescribers, and genetic counselors, among others. We have included pharmacy and psychiatry in the development of our materials and CE accrediting; another helpful step forward would be to include genetic counselors to improve our discussion of important topics like pre-test counseling and ancillary findings that are relevant for some PGx tests.³⁷⁻⁴⁰ We also felt it was important that this CE course was, and in any future form continues to be, easily accessible and affordable. This is particularly true as the rate of PGx test use increases with growing PGx discussion in the general media and marketing to the consumer.^{41,42} Finally, our CE course also suggests that there may be significant interest among providers in private practice settings for further PGx education, as many of our registrants identified this as their practice setting and indicated they had little-to-no onsite education in PGx. As compared with providers in large academic medical centers, individuals in private practices are also using these tests in practice but are potentially less likely to have easy access to impartial educational opportunities outside of professional meetings.

5 | CONCLUSION

Ultimately, the CE course in psychiatric PGx described here was effective in increasing provider knowledge, confidence, and ability interpreting and applying PGx results. These materials were designed with an interdisciplinary team of pharmacists and psychiatrists, with research experience in education and PGx, utilizing many best practices in education. The online nature of the program is also important both for the possibility to maintain recordings that participants can review, and for providing low-cost educational opportunities that are easy to access. With the growth in PGx, both as provider-ordered tests and with increased marketing to consumers, we feel that it will become even more important to provide easily accessible CE that will meet the needs of interdisciplinary health care teams caring for patients with mental illness.

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CONFLICT OF INTEREST

Sagar V. Parikh is a consultant for Takeda Pharmaceutical, Otsuka Pharmaceutical, Sunovion Pharmaceuticals, Inc., and Lundbeck receives grant/research support from Assurex and holds shares at Mensante Corporation. All other authors report no conflicts of interest.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

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