ORIGINAL ARTICLE

Attitudes of clinicians following large-scale pharmacogenomics implementation

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Clinician attitudes toward multiplexed genomic testing may be vital to the success of translational programs. We surveyed clinicians at an academic medical center about their views on a large pharmacogenomics implementation, the PREDICT (Pharmacogenomic Resource for Enhanced Decisions in Care and Treatment) program. Participants were asked about test ordering, major factors influencing use of results, expectations of efficacy and responsibility for applying results to patient care. Virtually all respondents (99%) agreed that pharmacogenomics variants influence patients’ response to drug therapy. The majority (92%) favored immediate, active notification when a clinically significant drug–genome interaction was present. However, clinicians were divided on whether providers were responsible for acting on a result when a prescription change was indicated and whether patients should be directly notified of a significant result. We concluded genotype results were valued for tailoring prescriptions, but clinicians do not agree on how to appropriately assign clinical responsibility for actionable results from a multiplexed panel.

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INTRODUCTION

The introduction of pharmacogenomics into clinical settings is accelerating as academic medical centers and integrated health systems have implemented pharmacogenomics testing, encouraged routine use within prescribing and placed results within electronic health records.1–7 Many programs have adopted multiplexed, panel testing—in which multiple variants are tested simultaneously to inform prescribing—to leverage economies of scale and the potential for reuse of panel data over time.7–9 However, multiplexed testing may present challenges as clinicians may be expected to apply pharmacogenomics test results that were ordered in an unrelated clinical context and to consider genomic risks that are not relevant to their usual scope of practice.

Concerns about the ability of front-line clinicians to manage genomic data are highlighted by surveys and qualitative studies of likely users.10–14 Nationally, fewer than one in eight primary-care physicians has ordered a pharmacogenomics test or felt adequately informed to use the result. Within implementation programs, significant new educational efforts and clinical-decision-support strategies are designed to bridge this knowledge gap.1,2 However, little has been reported on the views of clinicians working in these new programs.

Education and implementation assistance from medical geneticists and knowledgeable pharmacists has been anticipated from the onset of genomic medicine.15 Even with the assistance of sophisticated electronic health record tools, clinicians’ understanding of pharmacogenomics and active engagement with pharmacogenomics testing is critical for test adoption and utilization. We report the outcomes of a survey administered to clinicians participating in a large pharmacogenomics program within an academic medical center. Those solicited had either requested or received results from a multiplexed pharmacogenomics panel performed for primary-care and cardiovascular patient populations between 2010 and 2013 (ref. 1). The present analysis focuses on clinicians’ perceptions of clinical utility, preparedness to effectively use pharmacogenomics test results, and questions of responsibility for disclosure and clinical use of multiplexed results over the course of patients’ care.

MATERIALS AND METHODS

Pharmacogenomics implementation

Clinicians solicited for this study participated in an institutional pharmacogenomics program launched in 2010. The program was designed to pre-emptively genotype patients, store actionable results as determined by the local pharmacy and therapeutics committee and provide program interpretations and recommendations at the point of care. During the initial implementation, program leaders gave educational seminars, distributed informational brochures and conducted direct communications with clinicians through email and in-person meetings. The program created a website summarizing the evidence for applying the tested variants to clinical care and linked pharmacogenomics results to the relevant page.1 Inpatient and outpatient clinical decision support provided guidance at the point of medication prescribing for five drugs, including clopidogrel and warfarin, during the survey period.1 A pharmacist-led active surveillance program focused on CYP2C19 and clopidogrel ensured key results were delivered to the cardiology-attending physicians following coronary stent placement.16 As part of program development, members of the patient population served by the institution gave feedback and guidance to program development as part of focus groups. Pharmacogenomics testing was performed under the terms of treatment consent similar to other laboratory testing within a health-care environment.

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Development of survey
Investigators conducting pharmacogenomics research developed the survey. Questions were based on a prior publication by Stanek et al., and contributions from authors. Two clinicians piloted the survey for clarity and completeness of the potential responses. The survey was designed to address the following domains: perception of clinical utility; preparedness to receive results; and assignment of clinical responsibility for communicating results and adjusting medications as warranted over the course of the patient’s care.

Sampling method
The survey was distributed by email between November 2012 and March 2013 to all clinicians within cardiology, primary care and endocrinology who met the following criteria: (1) had ordered a panel-based test via the pharmacogenomics implementation or cared for a patient with a pharmacogenomics result in the previous year; and (2) held a position as an attending physician, specialty fellow physician or nurse practitioner position with active prescribing privileges.

Collection of survey responses
Survey items were entered into REDCap that features a secure environment for building and managing online surveys for research. A unique access code was created for each solicited subject, allowing the responses to be collected anonymously. After the initial email solicitation, nonresponders were solicited with two additional emails. A modest incentive was provided for completing the survey. The Vanderbilt Institutional Research Board approved the study.

Data analysis
Responses were included in the analysis if the majority of coded questions were answered including the key questions related to the responsibility for results. Responses were tabulated as numeric counts and frequencies. Respondents were stratified by cardiology and noncardiology specialty for the analysis related to questions about clinical responsibility for acting on pharmacogenomics results where a prescription change was indicated. All analyses were conducted in R version 3.0.1 (R Foundation for Statistical Computing, Vienna, Austria, http://www.R-project.org).

RESULTS
Of 156 surveys distributed, 80 (52%) were returned with a complete response and 4 (3%) were returned incomplete. Respondents were evenly split between clinicians practicing cardiology (51%) and those practicing primary care or endocrinology (49%). Survey respondents were predominantly young with <15 years of practice (71%) and female (63%). Approximately half were attending faculty while the remainder consisted of nurse practitioners and fellows (Table 1).

Preparedness to order pharmacogenomics testing
As expected based on study inclusion criteria, two-thirds (63%) had ordered or recommended a pharmacogenomics test in the prior 6 months. A high proportion of respondents (95%) were familiar with the institutional pharmacogenomics program. Nearly all (94%) prescribed at least one of the three drugs targeted by the program at the time of survey: simvastatin, clopidogrel and warfarin. When deciding whether to order a pharmacogenomics test, the most important considerations reported were strength of evidence for the drug–gene interaction and patients’ out-of-pocket costs for testing (Figure 1).

Perception of clinical utility
All but one respondent (99%) agreed that pharmacogenomics variants influence patients’ response to drug therapy. The majority agreed or strongly agreed with the clinical utility of CYP2C19 variants to tailor antplatelet therapy following percutaneous coronary interventions (80%) and VKORC1 and CYP2C9 variants to tailor initial warfarin dosing (86%). The majority also agreed or

Table 1. Characteristics of survey respondents

| Age (years) | Cardiology, N (%) | Noncardiology, N (%) | Total, N (%) |
|------------|------------------|----------------------|--------------|
| 20–30      | 0 (0)            | 0 (0)                | 0 (0)        |
| 31–40      | 22 (54)          | 20 (51)              | 42 (52)      |
| 41–50      | 7 (17)           | 12 (31)              | 19 (24)      |
| 51–60      | 7 (17)           | 4 (10)               | 11 (14)      |
| 61–70      | 3 (7)            | 2 (5)                | 5 (6)        |
| > 71       | 2 (5)            | 1 (3)                | 3 (4)        |

| Gender     | Cardiology, N (%) | Noncardiology, N (%) | Total, N (%) |
|------------|------------------|----------------------|--------------|
| Male       | 11 (27)          | 19 (49)              | 30 (38)      |
| Female     | 30 (73)          | 20 (51)              | 50 (63)      |

| Years of clinical practice | Cardiology, N (%) | Noncardiology, N (%) | Total, N (%) |
|---------------------------|------------------|----------------------|--------------|
| < 5                       | 9 (22)           | 6 (15)               | 15 (19)      |
| 5–10                      | 13 (32)          | 14 (36)              | 27 (34)      |
| 11–15                     | 5 (12)           | 10 (26)              | 15 (19)      |
| 16–20                     | 3 (7)            | 5 (13)               | 8 (10)       |
| 21–25                     | 0 (0)            | 0 (0)                | 0 (0)        |
| > 25                      | 11 (27)          | 4 (10)               | 15 (19)      |

| Practice specialty     | Cardiology, N (%) | Noncardiology, N (%) | Total, N (%) |
|------------------------|------------------|----------------------|--------------|
| Internal medicine:     |                  |                      |              |
| primary-care physician | 0 (0)            | 21 (54)              | 21 (26)      |
| Internal medicine:     |                  |                      |              |
| hospitalist            | 0 (0)            | 0 (0)                | 0 (0)        |
| Medical specialty:     |                  |                      |              |
| interventional cardiology | 11 (27)       | 0 (0)                | 11 (14)      |
| Medical specialty:     |                  |                      |              |
| general cardiology     | 30 (73)          | 0 (0)                | 30 (38)      |
| Medical specialty:     |                  |                      |              |
| endocrinologist        | 0 (0)            | 7 (18)               | 7 (9)        |
| Pediatrics             | 0 (0)            | 1 (3)                | 1 (1)        |
| Other                  | 0 (0)            | 10 (26)              | 10 (13)      |

| Position               | Cardiology, N (%) | Noncardiology, N (%) | Total, N (%) |
|------------------------|------------------|----------------------|--------------|
| Physician              | 19 (46)          | 32 (82)              | 51 (64)      |
| Fellow                 | 12 (29)          | 1 (3)                | 13 (16)      |
| Resident physician     | 0 (0)            | 0 (0)                | 0 (0)        |
| Nurse practitioner      | 8 (20)           | 6 (15)               | 14 (18)      |
| Physician assistant    | 0 (0)            | 0 (0)                | 0 (0)        |
| Other                  | 2 (5)            | 0 (0)                | 2 (5)        |

| Number of half-day outpatient sessions per week | Cardiology, N (%) | Noncardiology, N (%) | Total, N (%) |
|-----------------------------------------------|------------------|----------------------|--------------|
| 0–2                                           | 30 (73)          | 18 (46)              | 48 (60)      |
| 3–4                                           | 8 (20)           | 6 (15)               | 14 (18)      |
| 5–6                                           | 0 (0)            | 4 (10)               | 4 (5)        |
| 7–8                                           | 0 (0)            | 9 (23)               | 9 (11)       |
| 9–10                                          | 3 (7)            | 2 (5)                | 5 (6)        |

strongly agreed that the variants affected patient outcomes, such as stent thrombosis and warfarin-related bleeding (Figure 2).

We asked participants to indicate which sources of information were of major, minor or no importance to their perception of pharmacogenomics clinical utility. As indicated in Figure 3, respondents ranked published literature including systematic reviews and specialty society guidelines higher than guidance from the implementing institution, from a third-party laboratory or from the Food and Drug Administration-approved medication labels.

Preparedness to receive results
A minority of the respondents (19%) reported no prior instruction in pharmacogenomics; the remainder had completed undergraduate courses (11%), professional school instruction (31%), postgraduate
Being prompted by an alert within the Electronic Medical Record

My patient's interest in knowing their genetic susceptibility for drug response

Knowing that pharmacogenomic testing is an institutional priority

Inclusion of pharmacogenomic test with an order set

My interest in knowing my patients' genetic susceptibility for drug response

Recommendations by thought leaders or respected colleagues

Recommendations by guidelines or the Food and Drug Administration

Absence of out-of-pocket cost to the patient

Strength of evidence that genetic test results could affect my patients' drug selection dose

Figure 1. Influential factors reported by clinicians when deciding whether to order a pharmacogenomics panel test.

A patient's genetic profile may influence his/her response to drug therapy

Pharmacogenomic testing prior to prescribing clopidogrel assists with anti-platelet therapy decisions

Pharmacogenomic-guided antiplatelet therapy will reduce the likelihood in-stent thrombosis

Pharmacogenomic testing is useful for directing the dose of warfarin therapy

Pharmacogenomic testing prior to warfarin prescription will reduce the likelihood of an adverse drug event

Figure 2. Attitudes toward clinical utility of genomic variants to tailor prescriptions. Likert scale responses indicating strongly agree and strongly disagree are collapsed into agree and disagree categories.

Guidance from national standards-setting organizations

Systematic review of peer-reviewed literature

Original research article in peer-reviewed literature

Guidance from your local institution

Information included on an FDA-approved drug label

Guidance from third-party pharmacogenomic testing laboratory

Figure 3. Influential factors reported by clinicians when deciding to use pharmacogenomics variants to tailor therapy.
coursework (23%), continuing medical education seminars (52%) or self-instruction by reading peer reviewed literature (51%). Overall, 70% of respondents felt they had adequate educational resources in the clinic to support clinical decision making related to pharmacogenomics, a proportion that did not significantly differ between cardiology and noncardiology providers \((P = 0.63)\). Many who did not feel adequate resources were available submitted free text responses requesting more point-of-care guidance with links to primary sources in the literature. In addition, providers requested supplemental information geared toward patients to reduce the time required to educate patients about genomic variants and the rationale for tailoring therapy.

Responsibility for results

Survey subjects were asked to respond to two clinical scenarios applying pharmacogenomics results to clinical decision making and to select which providers were responsible for clinical action (Table 2). The first scenario was modeled after the most common drug–genome interaction encountered at the time of the survey:

### Table 2. Clinician attitudes regarding notification and responsibility for acting on a pharmacogenomics result

| Clinical scenario: A 65-year-old patient with diabetes and hypertension experiences angina with brisk walking. Nuclear stress testing reveals evidence of cardiac ischemia. Upon referral to an interventional cardiologist, he is scheduled for elective angiography the following day and receives pharmacogenomics testing. He is prescribed aspirin and clopidogrel after successful placement of a drug-eluting stent and is discharged. One week later, the result of the pharmacogenomics test is returned and indicates that the patient is homozygous for the **CYP2C19**\(^*2\) variant and thus is a poor metabolizer of clopidogrel. |
|---|

| In addition to including the results in the EMR, who should be individually notified of the new pharmacogenomics result? (check all that apply) | Cardiology, N (%) | Noncardiology, N (%) |
|---|---|---|
| Not necessary to notify any provider directly | 0 (0) | 0 (0) |
| Primary-care provider | 22 (54) | 27 (69) |
| Specialist treating medical condition affected by test result | 37 (90) | 35 (90) |
| Provider who ordered pharmacogenomics test | 31 (76) | 27 (69) |
| Provider who prescribed drug therapy affected by test | 33 (80) | 37 (95) |
| Patient should be notified directly | 18 (44) | 19 (49) |

| Which of the patient’s providers is responsible for acting on a pharmacogenomics result if a prescription change is indicated? (check all that apply) | Cardiology, N (%) | Noncardiology, N (%) |
|---|---|---|
| Primary-care provider | 3 (7) | 7 (18) |
| Specialist treating medical condition affected by test result | 33 (80) | 29 (74) |
| Provider who ordered pharmacogenomics test | 23 (56) | 20 (51) |
| Provider who previously prescribed drug therapy affected by test | 20 (49) | 23 (59) |

| When should providers be actively notified (e.g., with a reminder or prompt) if a prescription change based on the pharmacogenomics results is indicated? | Cardiology, N (%) | Noncardiology, N (%) |
|---|---|---|
| As soon as results are available in the EMR | 37 (92) | 36 (92) |
| During the next appointment at Vanderbilt | 1 (2) | 1 (3) |
| Only when selecting antiplatelet medication using e-script | 2 (5) | 1 (3) |
| No reminder or prompt necessary | 0 (0) | 1 (3) |

Continued scenario: Six months following the patient’s stent placement, the program begins reporting genetic results to guide warfarin therapy. On the basis of genetic and clinical variables, the patient is expected to have a stable therapeutic INR on a low dose of warfarin (\(\leq 2.1\) mg per week) and increased risk of bleeding on standard or high doses of warfarin. Since his stent implantation, the patient has resumed care with his primary-care provider and cardiologist in his hometown.

| Who should be notified of the pharmacogenomics result? (check all that apply) | Cardiology, N (%) | Noncardiology, N (%) |
|---|---|---|
| Vanderbilt provider who has seen the patient most recently | 11 (27) | 8 (21) |
| Primary-care provider | 27 (66) | 30 (77) |
| Specialist treating medical condition affected by test result | 31 (76) | 28 (72) |
| Provider who ordered the pharmacogenomics test | 24 (59) | 22 (56) |
| Provider who will prescribe drug therapy affected by test | 35 (85) | 30 (77) |
| Patient should be notified directly | 19 (46) | 21 (54) |

| Who, within Vanderbilt, should take responsibility for following up with the patient or outside providers? (check all that apply) | Cardiology, N (%) | Noncardiology, N (%) |
|---|---|---|
| Vanderbilt provider who has seen the patient most recently | 9 (22) | 4 (10) |
| Vanderbilt provider who ordered the pharmacogenomics test | 21 (51) | 24 (62) |
| PREDICT staff should contact the providers | 28 (68) | 28 (72) |
| PREDICT staff should contact the patient directly | 11 (27) | 12 (31) |

| What are your preferred methods of receiving notification of a pharmacogenomics result that may require you to take clinical action? | Cardiology, N (%) | Noncardiology, N (%) |
|---|---|---|
| Standard laboratory reporting in EMR | 15 (37) | 19 (49) |
| Phone call from PREDICT staff | 4 (10) | 3 (8) |
| Electronic clinical message from PREDICT staff | 33 (80) | 27 (69) |
| Clinical decision support via e-prescribing and computerized physician order entry | 15 (37) | 16 (41) |
| Message to nursing staff or pharmacy directly | 1 (2) | 0 (0) |

Abbreviations: EMR, electronic medical record; INR, international normalized ratio; PREDICT, Pharmacogenomic Resource for Enhanced Decisions in Care and Treatment.
prescribing clopidogrel in the setting of an intermediate or poor metabolism phenotype for CYP2C19. In the second scenario, new pharmacogenomics information pertinent to warfarin dosing became available months after the patient was initially tested. In both cases, respondents were asked to identify who should be notified and who should be responsible for acting on this result. Respondents could choose multiple selections.

No agreement emerged about which group of providers should be notified or who should take responsibility for clinical action when necessary. In the first scenario of an actionable result for clopidogrel and CYP2C19, most agreed that multiple providers should be notified; however, only 44–49% agreed that the patient should also be directly notified (Table 1). The clinician most commonly selected by cardiologists for direct notification was the specialist treating the medical condition (90%), whereas non-cardiologists chose the provider who prescribed the drug affected by the result (95%). There was less agreement about which provider is responsible for acting on the result, but both groups most commonly chose the specialist treating the medical condition affected by the result (74–80%). Nearly all (92% in each group) wanted active notification as soon as the results were reported.

The second scenario also gave an actionable result, but this pharmacogenomics result for guiding initial warfarin dosing became available 6 months following the original testing. Again, about half of the respondents (46–54%) felt that the patient should be notified directly and the majority of respondents indicated that multiple clinicians should also be notified. While cardiologists most commonly selected the provider who would prescribe warfarin (85%), non-cardiologists selected both this option (77%) and the primary-care provider (77%). Both cardiologists and non-cardiologists most commonly assigned responsibility for follow-up for this delayed result to the implementation program staff, to the provider who initially ordered the pharmacogenomics panel or to both.

**DISCUSSION**

Within an institutionally supported pharmacogenomics implementation program, clinicians expressed support for the concept that pharmacogenomics variants affect drug responses and more than 80% agreed that common drug–genome interactions for clopidogrel and warfarin reported by the program had clinical utility. The majority reported prior instruction in pharmacogenomics and felt adequately supported to use the results in clinical practice. National guidelines and published literature were favored as sources of guidance over local initiatives such as computerized prompts and institutional recommendations.

Several of these findings are distinct from those obtained from prior studies of physicians who practiced outside an implementation program. In one national survey, physicians reported near-universal acceptance of the concept of pharmacogenomics, but had infrequently been educated on the topic and felt unprepared for test ordering and using the results. A second regional survey of primary-care physicians and family practitioners yielded similar results. The differences highlight the importance of implementation programs to prepare end users for ordering and interpreting pharmacogenomics results.

Our survey identified a lack of agreement regarding which clinician should be responsible for results with either immediate or potentially persistent value. Respondents assigned responsibility for long-term follow-up of genomic test results to an inconsistent array of providers, ranging from specialists to primary-care providers to the administrative staff of the implementation program. In retrospect, this was not surprising as pharmacogenomics results can apply to a wide variety of clinical scenarios and survey respondents may not have felt comfortable with genetic information not directly related to their specialty. Nonetheless, this lack of agreement about who should act on pharmacogenomics results raises the risk that some patients may fall through the cracks. As a result, more work is needed to create systems for return of results that clearly assign responsibility for clinical action related to genomic variants.

Our study has several limitations. Subjects were selected within a tertiary-care academic medical center program and survey responses may not be representative of the general practitioner population. Given the rapid changes in the evidence base for drug–genome interactions, survey responses related to specific clinical scenarios are expected to change over time. For example, the survey was performed before the publication of several large-scale studies of pharmacogenomics-guided dosing for warfarin, and thus, the physician responses presented here may not be fully indicative of current attitudes and practices related to that particular drug–gene interaction. Finally, clinicians may be influenced by a broader array of information sources than those indicated in the survey, and attitudes and preferences expressed by survey respondents may not always correspond with information-seeking behavior in the clinic.

The growth of multiplexed pharmacogenomics testing is anticipated to occur both within and outside of the context of institutional implementation programs. Physicians operating within an implementation program report greater prior knowledge and educational support to order and use pharmacogenomics results than previously published results from a national sample. However, even in the context of a single health system, dilemmas persist related to assigning responsibility for pharmacogenomics results and require new strategies to ensure that patients receive the benefits of high-quality genome-informed care.

**CONFLICT OF INTEREST**

The authors declare no conflict of interest.

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