Value of Genetics-informed Drug Dosing Guidance in Pregnant Women: A Needs Assessment with Obstetric Healthcare Providers at Johns Hopkins

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Abstract

In order to better understand the potential value of genetics-informed drug dose guidance to obstetric healthcare providers at Johns Hopkins we administered a web-based needs assessment survey. The survey included questions about: 1) experience with adjusting drug doses during pregnancy; 2) comfort prescribing medications to pregnant women with chronic conditions; 3) awareness and use of genetics-informed dosing guidance; and 4) perceived value of access to services to provide genetics-informed dosing guidance. Among thirty-one respondents, 81% indicated an interest in access to genetics-informed drug dose guidance, particularly a mobile or electronic health record (EHR) application. It was indicated, however, that genetics is one of many characteristics that influence dose adjustments during pregnancy. This study motivates future research to help obstetric healthcare providers tailor drug dose to individual patients based upon models integrating multiple patient characteristics, including genetics.

Introduction

While obstetric healthcare providers counsel pregnant women to limit medication use during pregnancy unless clinical necessity warrants, prescription drug use during pregnancy is on the rise. Mitchell et al[1] conducted a 33-year study finding that nearly half of women between 1997 and 2003 used prescription medications and less than 5% took four or more. Use increased from 2003 to 70% of pregnant women using any medication, and the use of four or more medications rose to over 15%. Women today are delaying pregnancy[2] resulting in older women with higher rates of obesity and chronic medical conditions becoming pregnant. This increase in chronic medical conditions often requiring medications has highlighted the need for more research on medication use and safety in pregnancy[3].

Despite these challenges, there is a growing body of pharmacogenomics data on medications in general that can be used to find the most effective and safe doses for pregnant women. In addition, the Food and Drug Administration (FDA) has included pharmacogenomics information in the labeling of several medications that are commonly prescribed in pregnant women[4]. Thus, the development of clinical dosing models that bring together clinical characteristics, physiologic parameters in pregnancy, and pharmacogenomics measures has been proposed as a way forward to eventually guide obstetric healthcare providers to individualize drug therapy in pregnant patients[5,6].

The first stage of designing a new software product is to specify the needs for a setting and the intended users of that product[7]. One common way to complete this evaluation and to establish design requirements is to use a needs assessment survey. Given our interests in understanding the needs of obstetric health care providers, we conducted a needs assessment survey. The primary goal for this survey was to understand the value of genetics-informed dosing guidance to obstetric healthcare providers.

Methods

Recruitment

An initial recruitment email containing a link to a web-based survey was sent to approximately 80 obstetric healthcare providers associated with the Johns Hopkins Hospital (JHH). Two follow-up emails were sent to the distribution list in subsequent weeks. Survey responses were collected anonymously, and participants who agreed to be contacted about future research were entered into a contest to win $100 USD.

Survey development

Four co-authors developed a twenty-four-item survey instrument with the primary goal of understanding the potential value of genetics-informed drug dose guidance to obstetric healthcare providers (CO, HL, CC, JS). The survey included questions about: experiences with adjusting drug doses in pregnant women (five multiple choice, and one free response question, e.g., "How often do you have to seek consultation to confirm drug doses in pregnant women?");

comfort in prescribing nine antiretroviral, four antihypertensive, and fourteen antidepressant drugs to pregnant women (Likert scale questions e.g., "How comfortable are you in treating pregnant women with the following antihypertensive medications?"); awareness and use of genetics-informed dosing guidance (five Likert scale and one free response questions, e.g., "Do you know of and use any resources for clinical guidance on genetics-informed dose use in pregnancy?"); perceived value of tools and consult services to provide genetics-informed drug dosing guidance for pregnant women (two multiple choice questions, e.g., "Would it be valuable to have access to a tool that considers genetics in drug dose use in pregnancy?"); and demographic information such as gender, years practicing, and clinical caregiver status (six questions) (see **Appendix 1**). For questions about comfort with prescribing, one co-author (CO) selected an initial list of medications used to treat HIV, hypertension, and depression for which drug exposure is known to be influenced by genetics according to PharmGKB[8]. Another co-author with expertise in obstetrics (JS), then narrowed down that list of medications to those prescribed in pregnant women.

Data analysis

Survey data was collected using Qualtrics (Qualtrics, Provo, UT) and analyzed using Stata (StataCorp, 2013. *Stata Statistical Software: Release 13.* College Station, TX: StataCorp LP). We estimated the proportion of respondents indicating that genetics-informed drug dose guidance was of high importance by gender, experience, specialty, and years since completing training. We then evaluated factors that may influence the perceived value of accessing guidance including experiences with adjusting drug dose in pregnant women, comfort with adjusting drug doses in pregnant women taking antiretroviral, antihypertensive and antidepressant medications, the perceived importance of genetics-informed dosing guidance in prescribing those medications, and awareness and access to existing guidance for genetics-informed drug dosing. Furthermore, we identified which modalities obstetric healthcare providers would like to use when seeking guidance in prescribing. Only descriptive statistics are reported given that our population is relatively small (obstetric healthcare providers from one institution).

Results

Data collection initiated on October 11, 2016 and concluded on December 23, 2016. Thirty-one out of 80 obstetric healthcare providers completed the survey for a response rate was 39%. The results of this survey are accurate at the 90% confidence level plus or minus 12%. All survey respondents were employed by Johns Hopkins University, Johns Hopkins Hospital, and/or Johns Hopkins Community Physicians. In response to questions about the value of accessing genetics-informed dosing guidance, with one exception, 50% or more of the respondents indicated that they would value access to genetics-informed drug dose guidance across all demographic categories (for more details see "Value of Genetics-Informed Dosing Guidance for Obstetric Healthcare Providers"). The one exception was that one male respondent indicated that it a consult service would be valuable. **Table 1** summarizes the demographic data of our study sample.

Table 1. Obstetric healthcare providers that value access to genetics-informed drug dose guidance, according to demographic data

Characteristics	**Healthcare Providers (N=31) N (%)**	**% Value access to genetics-informed drug dose guidance**	
		Yes, as an app	Yes, as a consult service
Gender			
Female	27 (87%)	78%	59%
Male	4 (13%)	100%	25%
Experience			
Resident	10 (32%)	90%	50%
Attending	17 (55%)	76%	53%
Other	4 (13%)	75%	75%
Specialty			
Obstetrics Healthcare Provider	29 (94%)	83%	55%
Gynecology practice only	2 (6%)	50%	50%
Years since completing training	Median 10 (1-36)	Median 5 (1-36)	Median 10 (1-36)

Experiences with Adjusting Drug Dose in Pregnant Populations

Survey respondents indicated several patient characteristics that they have considered when making dose adjustments: twenty-six (81%) indicated that they use body weight, ten (31%) use height, fifteen (47%) use body surface area, twenty-seven (84%) use organ system function, five (16%) use genetics, and five (16%) indicated use of other characteristics. Among the twenty-seven respondents indicating that they use organ system function to adjust drug dose, free-text descriptions of specific organs included: kidney, liver, GI, respiratory (e.g., h/o asthma), blood volume, and brain/cognitive function. For the five respondents indicating that they have used other patient characteristics, free-text descriptions included: patient history, blood levels for some medications (e.g., anti-epileptics), medical co-morbidities and other medication use.

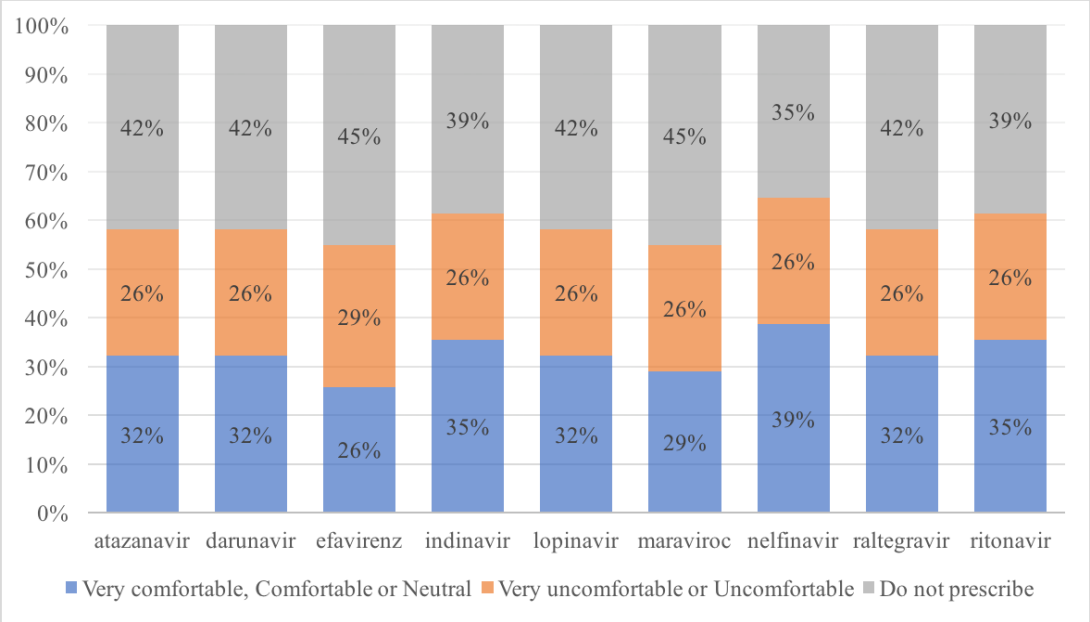
Dose adjustments are relatively common in pregnant women with nine (30%) of survey respondents indicating that dose adjustments occurred greater than or equal to 50% of the time when including changes due to pregnancy progression. When excluding dose changes due to pregnancy progression, only two (7%) indicated that that dose adjustments occurred greater than or equal to 50%. In instances where drug dose adjustments do occur, it is uncommon for drug does to be modified beyond normal ranges, with twenty-three (74%) of respondents indicating that they modified drug dose beyond normal ranges less than 10% of the time (45%, or fourteen, indicated that they did so less than 1% of the time). However, in the instances where drug dose changes are made, seeking outside consultation is modest, with twenty-six (84%) of respondents indicating that they sought consultation less than 25% of the time (10%, or three, indicated that they never seek consultation).

Comfort in Prescribing Medications and Opinions about Using Genetics when Prescribing Medications

Obstetric healthcare providers were asked about their comfort in prescribing medications used to treat HIV, hypertension, and depression in pregnant women for which drug exposure is known to be influenced by genetics. For those who prescribe those medications, comfort in prescribing was split with more respondents indicating high comfort levels across all three categories of medications.

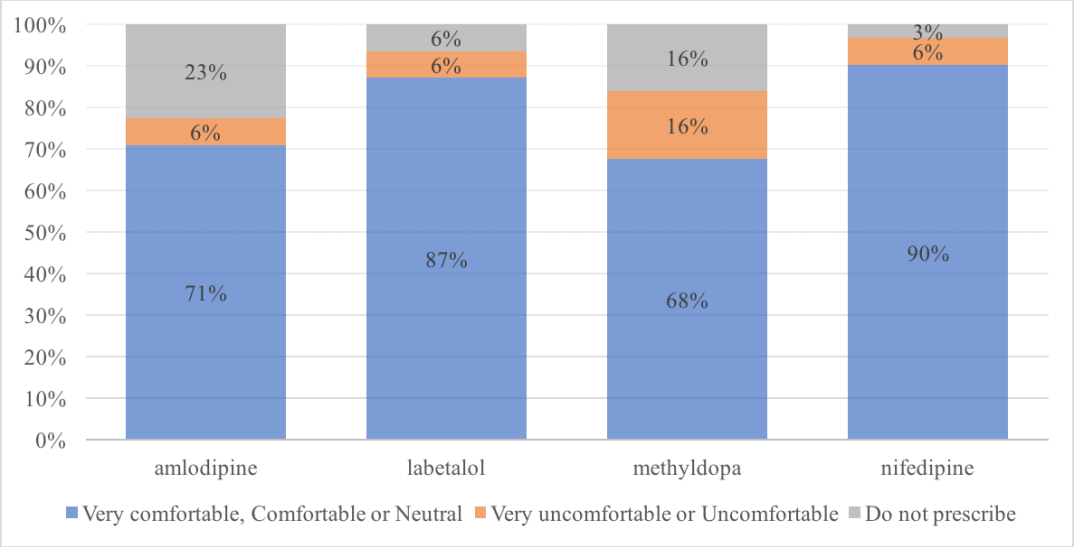
For nine antiretroviral medications, 35-45% do not prescribe, 26-29% are very uncomfortable or uncomfortable prescribing, and 26-39% are very comfortable, comfortable, or neither comfortable or uncomfortable with prescribing those medications (See **Figure 1**). The majority of survey respondents (58%, eighteen) also indicated a belief that genetics-informed dose adjustments was important or very important to achieve good outcomes when treating pregnant women with HIV. Thirteen (42%) respondents indicated that genetics-informed dose adjustments were moderately important, slightly important or not at all important.

Figure 1. Comfort in Prescribing Antiretroviral Drugs



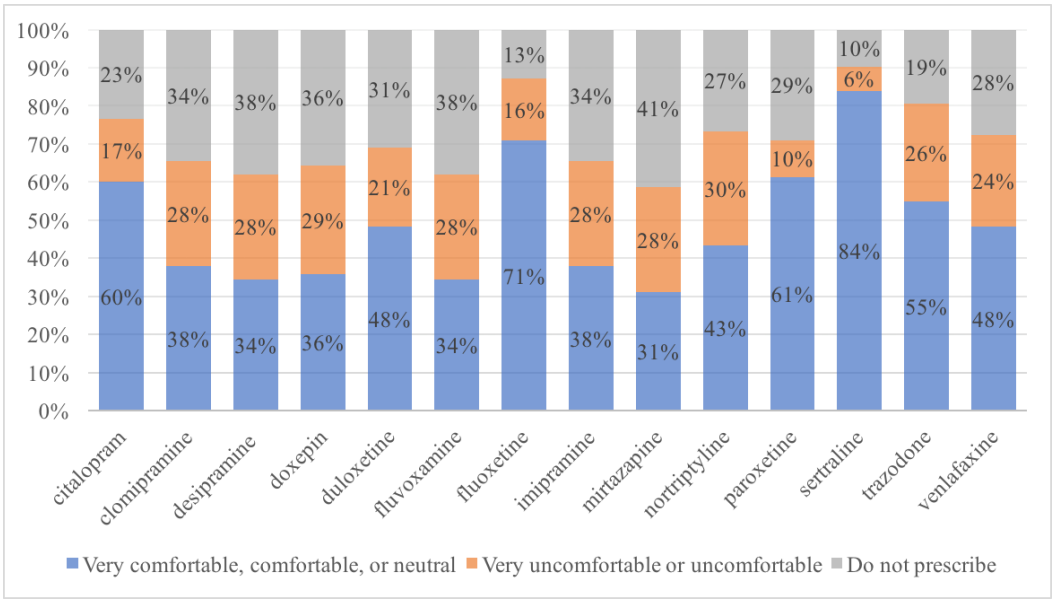
For four antihypertensive medications, survey respondents indicated that 3-23% do not prescribe, 6-16% are very uncomfortable or uncomfortable prescribing, and 68-90% are very comfortable, comfortable, or neither comfortable or uncomfortable with prescribing those medications (See **Figure 2**). Slightly fewer than half of survey respondents (48%, fifteen) indicated a belief that genetics-informed dose adjustments was important or very important to achieve good outcomes when treating pregnant women with hypertension. Sixteen (52%) respondents indicated that genetics-informed dose adjustments were moderately important, slightly important or not at all important.

Figure 2. Comfort in Prescribing Antihypertensive Drugs



For fourteen antidepressant medications, among obstetric healthcare provider survey respondents 10-41% do not prescribe, 6-30% are very uncomfortable or uncomfortable prescribing, and 31-84% are very comfortable, comfortable, or neither comfortable or uncomfortable with prescribing those medications (See **Figure 3**). Slightly fewer than half of survey respondents (48%, fifteen) indicated a belief that genetics-informed dose adjustments was important or very important to achieve good outcomes when treating pregnant women with depression. Sixteen (52%) respondents indicated that genetics-informed dose adjustments were moderately important, slightly important or not at all important.

Figure 3. Comfort in Prescribing Antidepressant Drugs



Awareness of and Access to Genetics-Informed Dosing Guidance

Few survey respondents, ten (37%), were aware of any existing resources for clinical guidance on genetics-informed drug dosing. Of those indicating an awareness of any existing resources, only four indicated that they had used any. One respondent indicated as a free-text response that they had used FDA resources. For the six respondents indicating that they were aware of resources for guidance on genetics-informed dosing guidance, but that they had not used any, the following resources were listed as free-text responses: Micromedex®[9], REPROTOX®[10], UpToDate®[11], OMIM[12], and PubMed[13]. One respondent indicated that a patient's lab report can contain guidance. Another respondent indicated that genetics-informed dosing guidance can be provided by genetic counselors.

Among ten respondents indicating an awareness of resources for genetics-informed dosing guidance, seven indicated a belief that guidance on genetics-informed drug dose use in pregnancy was moderately or slightly convenient to obtain. Three indicated that such guidance was not at all convenient. One respondent indicated resources for genetics-informed guidance in pregnancy are very useful, seven indicated that the resources are moderately or slightly useful, and two indicated that the resources are not at all useful.

Value of Genetics-Informed Dosing Guidance for Obstetric Healthcare Providers

In response to questions about access to genetics-informed dosing guidance, twenty-five (81%) indicated that they would like to have access to an app when seeking such guidance, four (13%) indicated that they may like to have access to an app, and two (6%) indicated that they would not like to have access to an app. Among twenty-five respondents indicating that they would like to have access to an app, they also indicated preferred modalities (they were able to select more than one): nine (36%) as an app that can be installed on a computer, seventeen (68%) as an app that is embedded in the EHR, and sixteen (64%) as a mobile app that can be installed on a tablet or cell phone.

Approximately one-half (48%-58%) of respondents perceived genetics-informed dose guidance to be important to achieve good outcomes when treating pregnant women with depression, hypertension or HIV (see **Table 2**). Regardless of the perceived importance, with one exception, 50% or more of the respondents indicated an interest in having access to genetics-informed drug dose guidance as an app or as a consult service. The one exception was that 44% healthcare providers perceiving genetics-informed drug dose guidance to be of low importance for anti-hypertensive medications indicated that it a consult service would be valuable (see **Table 2**).

Table 2. Obstetric healthcare providers that value access to genetics-informed drug dose guidance, according to perceived importance

Perceived importance of genetics-informed dosing guidance	Healthcare Providers (N=31) N (%)	% Value access to genetics-informed drug dose guidance	
		Yes, as an app	Yes, as a consult service
Anti-depressant medications			
High	15 (48%)	93%	60%
Low	16 (52%)	69%	50%
Anti-hypertensive medications			
High	15 (48%)	93%	67%
Low	16 (52%)	69%	44%
Anti-microbial medications			
High	18 (58%)	94%	55%
Low	13 (42%)	61%	54%

The interest in having access to an app was higher among respondents indicating that genetics-informed dosing guidance was of high importance (important or very important) compared those indicating a low importance (moderate importance to not at all important, see **Table 2** and **Figure 4**). When asked about interest in being able to access a consult service when seeking genetics-informed dosing guidance for pregnant women, sixteen (52%) indicated that they would like to have access and thirteen (42%) may like to have access. One respondent indicated that (s)he would not like to have access, and another indicated that (s)he already has access to a consult service. The interest in having access to a consult service is similar to or slightly higher than among respondents indicating that genetics-informed dosing guidance was of high importance compared to those indicating a low importance (see **Table 2** and **Figure 5**).

Figure 4. Percent of Obstetric Healthcare Providers Indicating An Interest in Having Access to an App

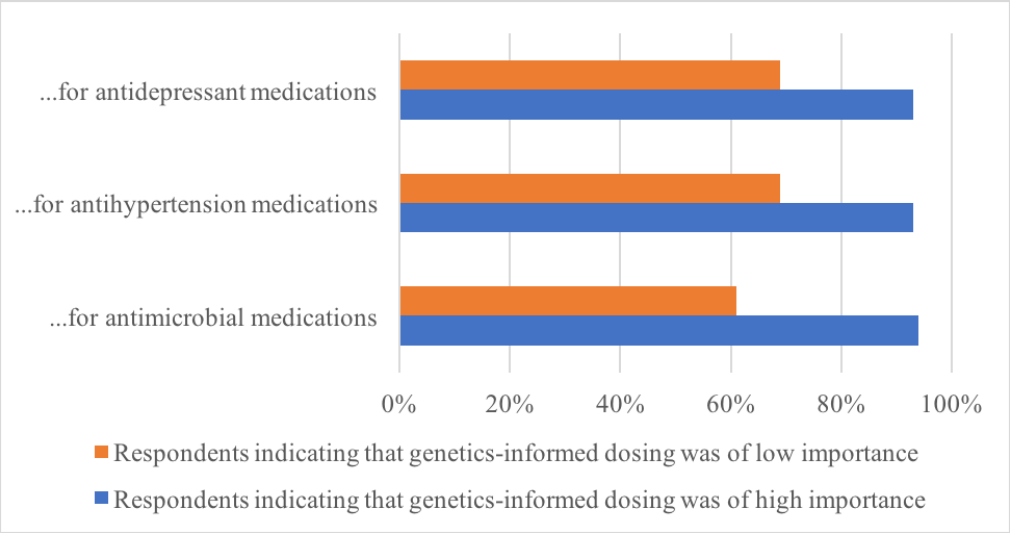
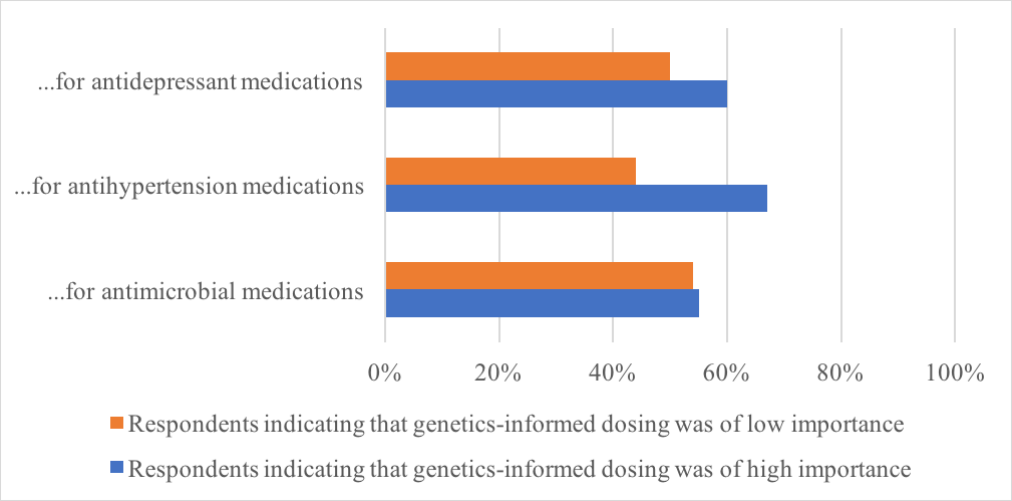


Figure 5. Percent of Obstetric Healthcare Providers Indicating an Interest in Having Access to Consult Services



Discussion and Conclusion

This study obtained feedback from a sample of thirty-one Johns Hopkins obstetric healthcare providers. We found that dose adjustments are relatively common in pregnant women, and they are made using a combination of factors. Most obstetric healthcare providers use body weight and organ system function. Height and body surface area are used less often, and genetic data is rarely used. Also, obstetric healthcare providers who report making dose adjustments, infrequently report using outside consultation. We believe that as more evidence to support the use of genetics becomes available and readily accessible as clinical decision support, physician education will improve and genetic information use will increase.

When asked about comfort in prescribing medications for which drug exposure is known to be influenced by genetics, obstetric healthcare providers indicated that they do not prescribe many of the medications we asked about. For those indicating that they do use the medications, around half were uncomfortable with prescribing antiretroviral medications. The majority of those indicating that they used the antidepressants and antihypertensive medications were comfortable with prescribing them. However, over a quarter of respondents were uncomfortable with prescribing many antidepressant medications. While the first and second line therapies are widely used, and may be working well at the time a patient becomes pregnant, dosing adjustments may still be needed. Furthermore, even those physicians that are comfortable with individual drugs, may need assistance with prescribing specific drug combinations. Genetics-informed dose adjustments may help guide dose adjustments for individual drugs and combination regimens.

When asked about clinical guidance on genetics-informed dosing, few respondents indicated that they were aware of or had ever used any. Most would, however, indicated an interest in having access to genetics-informed dosing information as an app embedded in an EHR and as an app that can be installed on a tablet or cell phone. In addition, around half of respondents indicated an interest in having access to a consultation service for guidance on genetics-informed dosing.

Findings from this study on genetics-informed drug dose guidance are concordant with other studies in identifying a need for more clinical guidance on using pharmacogenomics data[14-16]. One study indicated that healthcare providers had a preference for a pharmacogenomics educational resource to be electronic and to include information on how to interpret pharmacogenomic test results, recommendations for prescribing, population subgroups most likely to be affected, and contact information for laboratories offering pharmacogenomic testing[16]. Similarly, obstetric healthcare providers also had a preference for guidance to be made available electronically. Though it is not yet standard of practice, several institutions have established programs to perform prospective pharmacogenomics testing and also provide the results of those tests in the medication treatment context with clinical decision support[17-22]. The current study provides insights into the clinical decision support needs of obstetric healthcare providers that use pharmacogenomics testing.

Our finding that dose adjustments are relatively common and most often occur due to pregnancy progression, suggests that pharmacogenomics should be considered secondarily to other more common characteristics that also influence drug exposure in pregnant patients (e.g., physiological changes). However, there may be some uncertainty to what will be the added value of presenting pharmacogenomics in the context of other characteristics given that this rarely occurs today. While there remains a lack of research on pharmacogenetics changes during pregnancy[23], pharmacogenomic testing developed in other populations can potentially help guide its use in pregnant women. There are already a few clinical decision support tools to consider patient genetics that are targeted to obstetrics healthcare providers[24]. None of these tools to these authors knowledge, however, provide drug dosing guidance based upon models that consider pharmacogenomics. Thus, there is a particular need for dosing models that integrate multiple patient characteristics in this special population.

A large number of pregnant women who take medications could potentially benefit from improved drug dosing guidance. One study conducted in 2004 indicated that 49.9% of their sample of 152,531 pregnant women used medications from Food and Drug Administration (FDA) categories C, D, or X at some point during their pregnancy[25]. Categories C, D, and X were previously used to denote potential or unknown risks to a human fetus. Another study examining the use of medications during pregnancy in a sample of 578 women found that 59.7% used prescription medications, 92.6% used at least one over-the-counter medication, and 45.2% used at least one herbal medication[4]. Further indicating a need for improved guidance, in 2014 the letter-based category system was retired in favor of the Pregnancy and Lactation Labeling (PLL) Rule[26,27]. The PLL rule summarizes risks and provides information about testing, contraception, and infertility to be used by the health care providers. The new labels, however, do not provide the detailed information needed to make prescribing decisions, which "will require focused efforts on the part of multiple stakeholders."

The safety of medications is an even greater concern for pregnant women given the potential risks that some medications pose to the fetus. Research by Adam et al[28] found that, of 172 drugs tested for teratogenicity (harmfulness for a fetus), 168 (97.7%) could not be definitively determined to pose a risk for the fetus, and 126 (73.3%) of those drugs did not even have enough data to begin assessment. While outside of the scope of our survey focusing on maternal pharmacogenomics, prenatal pharmacogenomics studies are on the rise. As the influence of pharmacogenomics on fetal exposure to medications is better understood, that data could also begin to be made available to obstetric healthcare providers for use to manage their patients[29].

We found that obstetric healthcare providers at Johns Hopkins would find access to genetics-informed dosing guidance to be valuable. This work thus motivates future work to develop electronically accessible software to offer drug dosing guidance targeted to obstetric healthcare providers (or designated parties that provide consultation) based upon a range of patient characteristics, including genetics. The work of others has also indicated that pharmacogenomics data alone is not always sufficient to change test ordering and prescriber decisions[30,31], further supporting this need to consider multiple patient characteristics.

Despite the perceived value of access to genetics-informed dosing guidance, there is also the potential for confidence in prescribing decisions to be impacted. Previous research of one co-author, for example, found that physicians indicated a lowered confidence in prescribing decisions with access to pharmacogenomics clinical decision support[32]. This finding was also reflected in the proportion of physicians who changed doses toward doses supported by

published evidence. Thus, another area for future research will be to monitor prescribing patterns to see what is the impact of providing access to genetics-informed dosing guidance. Findings from self-reports of comfort prescribing in this work have potential to provide some insight into prescribing pattern observations. However, we believe that ultimately new approaches to enable assessing the clinical utility of having a more complete patient picture in drug dosing decisions are needed. Indeed, there are circumstances where pharmacogenomics differences become more critical for prescribing decisions (when pregnancy significantly changes pharmacokinetics), and other circumstances where factors having nothing to do with the pharmacogenomics of these drugs influence those decisions (e.g., weight gain as a drug side effect).

Furthermore, like many needs assessment studies, the generalizability of findings is limited to the group studied. Our goal, however, was to understand the value of genetics-informed dosing guidance to obstetric healthcare providers at Hopkins so that in follow-up work we can design clinical decision support with potential to support obstetric healthcare practices more broadly. There are some parallels from our previous work investigating opinions of junior physicians (cardiology and oncology fellows)[32]. Work here, however, includes physicians with a range of experience (obstetrics residents and attending physicians). Differences in responses and prescribing patterns between the residents and the attending physicians in the obstetrics clinical domain will be another interesting area to explore.

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Appendix A. Survey questions

1. Which of the following do you take into account in modifying drug doses for pregnant women?
2. How often do you have to seek consultation to confirm drug doses in pregnant women?
3. How often do you modify doses beyond the norm in pregnant women?
4. How often do you need to make dose adjustment in patients due to pregnant progress?
5. How often do you need to make dose adjustment in pregnant patients (excluding reasons due to pregnancy progress)?
6. Any other comments about experience and need for dose adjustment in pregnant patients?
7. How comfortable are you in treating pregnant women with the following antimicrobial drugs known to be influenced by genetics?
8. To what degree do you think genetics-informed dose adjustment is critical for good outcomes for the treatment of pregnant women with HIV in your practice?
9. How comfortable are you in treating pregnant women with the following antihypertensive drugs known to be influenced by genetics?
10. To what degree do you think genetics-informed dose adjustment is critical for good outcomes for the treatment of pregnant women with hypertension in your practice?
11. How comfortable are you in treating pregnant women with the following antidepressants known to be influenced by genetics?
12. To what degree do you think genetics-informed dose adjustment is critical for good outcomes for the treatment of pregnant women with depression in your practice?
13. Do you know of and use any resources for clinical guidance on genetics-informed drug dose use in pregnancy?
14. How convenient is it to obtain guidance on genetics-informed drug dose use in pregnancy? (Select one)
15. How useful are currently available information resources and tools on genetics-informed drug dose use in pregnancy?
16. Would it be valuable to have access to a tool that considers genetics in drug dose use in pregnancy?
17. Would it be valuable to have access to a consult service to provide genetics-informed dosing guidance for pregnant women?
18. Any other comments about available pharmacotherapy resources for genetics-informed drug dose use?
19. What is your gender?
20. What is your status as a clinical caregiver?
21. How many years since completing your training?
22. What is your specialty?
23. Where are you located?
24. What is your institution?