Web-Based Phenotyping for Pharmacogenomics Research

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Introduction

Significant barriers to the progress of pharmacogenomics research include the cost and time required to assemble, phenotype, and genotype an appropriately-sized cohort. 23andMe's research program uses web-based surveys to gather a broad range of phenotype data from an expanding cohort of genotyped individuals. The primary goal of this study is to develop, assess, and implement web-based surveys for the rapid, efficient collection of drug response and toxicity data across three classes of medication: warfarin, proton pump inhibitors (PPIs), and non-steroidal anti-inflammatory drugs (NSAIDs). Results and conclusions presented here are from the initial phase of a two-part study.

Methods

Phase I: To develop valid questions on drug response and side effects, we conducted online and semi-structured phone interviews to assess test-retest reliability and to receive qualitative feedback on survey questions.

- Consenting customers who gave prior indication of warfarin or NSAIDs use were sent link to online survey
- Option to participate in a follow up phone interview was presented at end of online survey
- Warfarin: 86 people took initial web-based survey, 41 of them completed follow up phone interview
- NSAIDs: 107 people took initial web-based survey, 40 of them completed follow up phone interview
- Scored identical web-based and phone responses as a "match" and different answers between each method as a "mismatch"
- Calculated percent agreement between the 41 (warfarin) and 40 (NSAIDs) web-based and phone responses for each question

Results

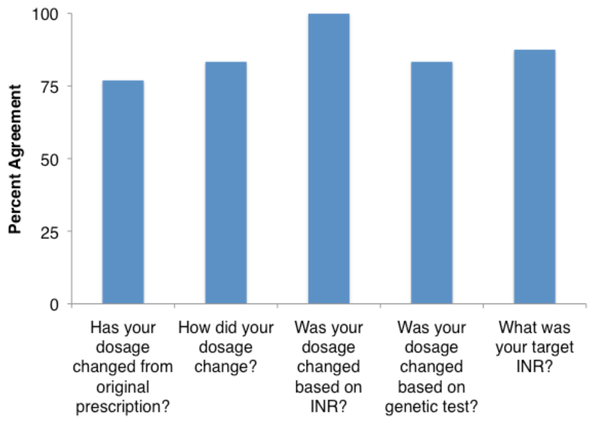

Figure 1. Percent agreement between online self-report and phone interview responses for warfarin dosing information

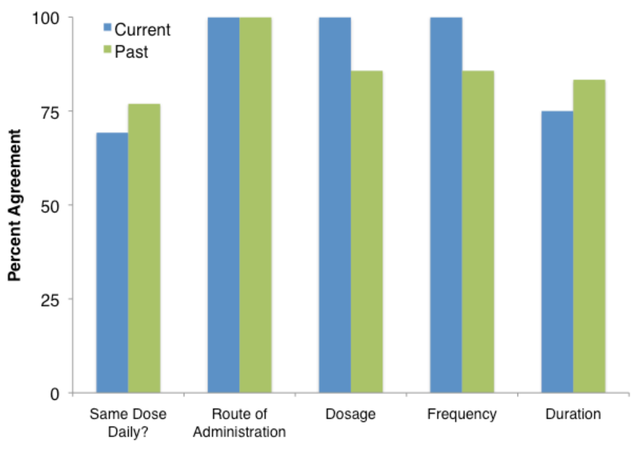

Figure 2. Concordance between web-based and phone responses for current and past warfarin usage

Warfarin Results Summary:

- Agreement about warfarin specifics (dosage and frequency of administration) higher for current medications (85% matching) than for past regular use (71% matching)
- Strong overall agreement between web and phone responses for side effects reported by past and current warfarin users (89% for both)

Side effect	Current % Agmt (N = 13)	Past % Agmt (N = 26)
Blood clot	100	92
Blood in stool	100	88
Blood in urine	85	96
Bleeding in brain	100	96
Bleeding in joints	100	96
Bleeding in kidneys	100	88
Bleeding in muscles	100	92
Bleeding in spinal cord	100	96
Bleeding in stomach	100	92
Bleeding in organ	100	92
Back Pain	N/A	88
Bruising	77	69
Chest Pain	85	88
Diarrhea	92	85
Difficulty moving	69	N/A
Fever	92	85
Gangrene	100	100
Heart Attack	100	100
Joint Pain	62	85
Nausea	85	88
Numbness	77	65
Pain	92	81
Priapism	100	100
Purple toes	100	85
Rash	54	92
Skin sores	92	88
Stroke	92	100
Bone thinning	85	88

Table 1. Concordance between web-based and phone responses for current and past warfarin side effects

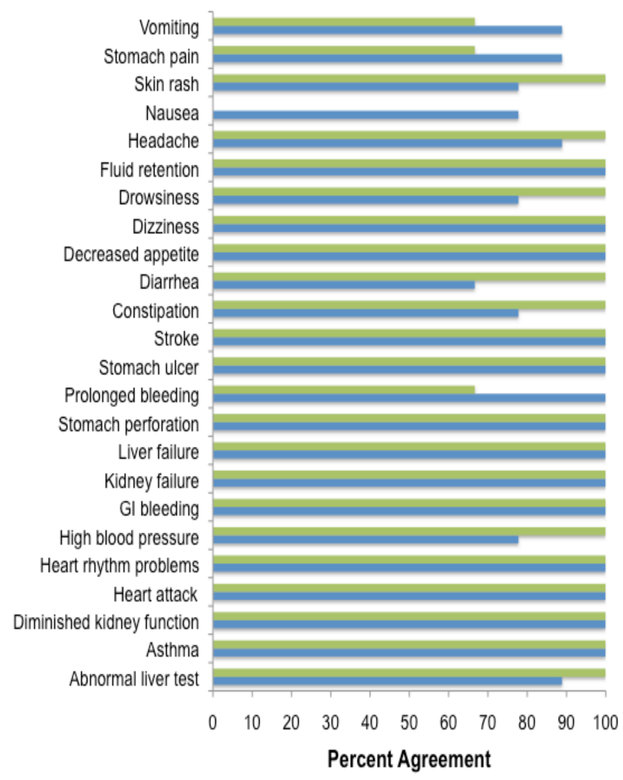

Figure 3. Percent agreement for side effects in (■) current (N=9) and (■) past (N=3) aspirin users between online data and phone interview responses. (Note: nausea not reported in past aspirin users)

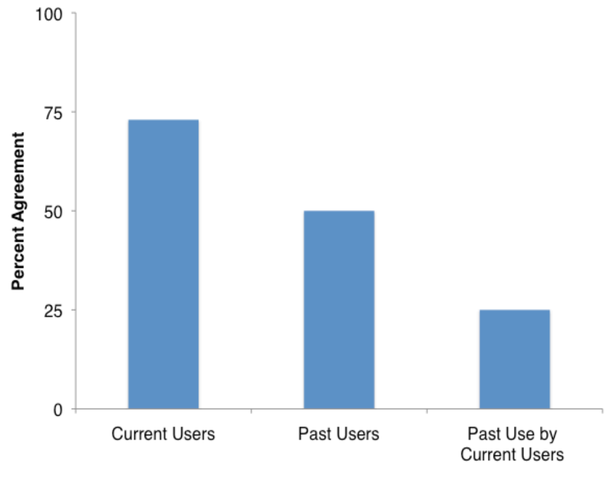

Figure 4. Overall NSAIDs test-retest reliability

NSAIDs Results Summary:

- Strong agreement between web and phone responses for side effects from current NSAIDs use (92% matching) and side effects reported for NSAIDs stopped some time in the past (94% matching)
- Test-retest reliability for current NSAIDs use was good, but reliability for past NSAIDs use was poor
- Efficacy data for improvement of inflammation and pain symptoms showed reasonable agreement, but a larger sample size is needed before making any conclusions

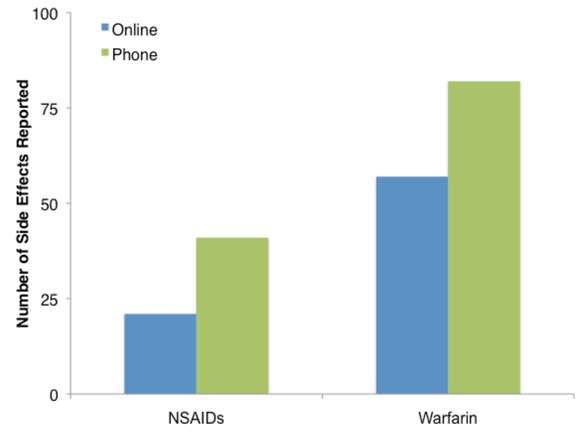

Figure 5. Number of side effects reported online and via phone interview for NSAIDs and warfarin

Phase I Conclusions

- Web-based surveys performed well in terms of getting medication response and side effects information
- Test-retest reliability for most questions was high (>70%)
- Reporting for past medications and medications taken as needed proved less reliable than for prescription medications (as expected)
- Low rates of agreement for some questions with commonly experienced symptoms may have stemmed from confusion about whether or not to mention symptoms unrelated to the medication
- Providing accurate date and dosage information often presented a challenge for many people
- Data were more reliable when questions focused on most recent use of over the counter drugs that may be taken for multiple indications (i.e. NSAIDs)
- Data were more reliable for side effects that led to cessation of use for over the counter drugs that may be taken for multiple indications (i.e. NSAIDs)
- Online surveys must clarify potentially ambiguous terms (i.e. "regular use", "frequently", and "current")
- Increased reports of side effects over the phone may be due to additional familiarity with questions (all phone interviews followed completion of web-based surveys) and the fact that participants could ask for additional clarification during the interview

Future Plans

Phase II: To leverage 23andMe's customized genotyping chip and incorporate data from tens of thousands of customers to validate known genetic associations (PPIs and CYP2C19; warfarin/NSAIDs and CYP2C9), and to search for novel associations of SNPs with drug efficacy and toxicity.

Based on findings and participant feedback from Phase I:

- Revise warfarin and NSAIDs surveys to re-release to larger subset (up to tens of thousands) of 23andMe customers
- Draft initial PPIs survey and send link to small subset of 23andMe customers for Phase I web and phone response comparisons

Since web-based surveys can be administered efficiently to millions of individuals, validation of this method of assessing drug response would remove traditional cost and time barriers and lead to significant acceleration of pharmacogenomics research.

Acknowledgments

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