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A patient-centered approach to the development and pilot of a warfarin pharmacogenomics patient education tool for health professionals

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Abstract

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Objective—To describe an exploratory project to develop and pilot a novel patient educational tool that explains the concept of pharmacogenomics and its impact on warfarin dosing that can be utilized by health professionals providing patient counseling.

Methods—A pharmacogenomics educational tool prototype was developed by an interdisciplinary team. During the pilot of the tool, focus group methodology was used to elicit input from patients based upon their perspectives and experiences with warfarin. Focus group sessions were audio-recorded and transcribed, and the data was analyzed through consensus coding in NVivo.

Results—The focus group participants were generally unfamiliar with the concept of pharmacogenomics but were receptive to the information. They thought the patient education tool was informative and would provide the most benefit to patients newly initiated on warfarin therapy.

Conclusions—Preliminary results from this exploratory project suggest that implementation and further feasibility testing of this pharmacogenomics patient education tool should be performed in a population of newly initiated patients taking warfarin.

Keywords

Pharmacogenomics; patient education; warfarin; individualized medicine

Introduction

Warfarin is an oral anticoagulant medication commonly used for the treatment or prevention of thromboembolic disorders. Management of patients on warfarin can be challenging due to the need for long-term therapy and frequent laboratory monitoring to maintain a therapeutic INR (international normalized ratio). Significant patient counseling efforts are expended and health care resources utilized to educate patients and their families about warfarin medication compliance, drug-food interactions, drug interactions, and laboratory follow-up. As part of the Joint Commission National Patient Safety Goals for hospitals, such education is initiated in the inpatient setting.^{1,2} Well-informed patients taking warfarin demonstrate enhanced medication adherence that may result in increased efficacy of the drug and enhanced patient safety.^{3,4}

Patients often have unpredictable responses to medications including warfarin. Patients' warfarin doses frequently require multiple adjustments to reach their individual target INR range. It can be a time-consuming and frustrating process to identify an appropriate warfarin dose for a patient. For example, a warfarin dose for one individual may result in a high INR that leads to an increased risk of bleeding events, but for another individual, the same warfarin dose results in a low INR that may lead to a thrombotic event. Adverse drug events due to warfarin are a leading cause for emergency room visits and hospital admissions in older adults.⁵ Genetic variants are now known to be a major factor in determining the inter-individual variation in the response to warfarin.⁶⁻⁸

The “era of the genome” commenced with the sequencing of the human genome in 2003. This genetic revolution created the field of pharmacogenomics, the study of the relationship

between an individual's genetics and its effect on drug therapy.⁹ Warfarin has a narrow therapeutic index that has been shown to have wide patient variability in the anticoagulant dose needed to achieve target therapeutic goals. A patient's response to warfarin has been shown to be impacted by genetic variants in the hepatic enzyme Cytochrome P450 2C9 (CYP2C9) and the vitamin K-epoxide reductase complex enzyme (VKORC1), among other factors.^{10,11} The importance of CYP2C9 is due to its primary drug metabolism role for the active drug enantiomer *s*-warfarin while VKORC1 is the enzyme that catalyzes the rate-limiting step of vitamin K recycling in the vitamin K-associated blood coagulation pathway.¹² In 2010, the FDA updated warfarin labeling to include dose initiation recommendations for patients with known genetic variations of the *CYP2C9* or *VKORC1* genes.

Currently, integration of genetics into warfarin dosing and patient education is a novel and unfamiliar practice for most pharmacists and other health professionals. Lack of confidence, lack of genetic education in training programs, and need for continuing education for practicing clinicians are obstacles in implementing warfarin pharmacogenomics in the clinical setting and in patient counseling interactions.^{13–17} Recent direct-to-consumer genomic testing has put genetic information directly into the hands of consumers, which they may take to their health care providers and increasingly expect genetic results to inform clinical decision making.¹⁸ There is an emerging need for patient education to be developed to encourage open discussions about drug-gene interactions between patients and health professionals.

Treatment decision aids incorporating illustrations have been shown to increase patient involvement and improve knowledge retention of complex health issues.^{19–23} Decision aids benefit from incorporation of simple language to increase knowledge and comprehension by writing for the average reader, organizing the information to serve patients' needs, using short sentences and sections, using active voice, and using "you" and other pronouns that speak to the patient.²⁴ A systematic approach to development of treatment decision aids may include user-centered observations, multi-disciplinary synthesis, and iterative development.^{20,22,25,26} Importantly, incorporating elements of adult learning theory into the development and pilot process of new patient education tools aids delivery of information that adult patients need to know, in the capacity that they can learn, and at the time they need to know it.²⁷

This article describes the preliminary results obtained from the development and pilot of a patient education tool for warfarin pharmacogenomics using a patient focus group approach.

Materials and methods

The interdisciplinary research team, including pharmacists, physicians, a bioethicist, research assistants, and an illustration and design specialist, developed content, established goals, constructed a timeline, and established data collection methods for the project. The prototype was developed in collaboration with an illustration and design specialist through four iterations before piloting the pictograph prototype in focus groups of patients taking warfarin.

Prototype development was based on previous models used for developing health treatment decision aids and creating health communication using pictures.^{19–23,25,26} To increase patient comprehension and knowledge retention on the complex topic of pharmacogenomics, the research team incorporated plain-language elements and adult learning theory.^{24,27}

The final prototype format was one page in layout and included 10 panels. Each panel included text as well as an accompanying illustration that pictorially represented the written information. We selected a 10 panel-format to allow sufficient space for written text and the illustrations to enhance communication of a complex educational topic. The colors of the panels were blue, green, black, and white, which the interdisciplinary team selected due to their complementary nature and ease of reading. The information was presented in a question and answer format to explain how genetic variants may impact warfarin dosing. The prototype used in the pilot is shown in Figure 1.

Based on professional experience in prescribing, counseling, and providing warfarin patient education, the research team decided that the prototype would focus solely on warfarin as it relates to genetics as adjunct to currently used warfarin patient education resources at our institution. In addition, the research team felt a brief introduction on warfarin (what it is, why it is prescribed, how it works) was appropriate to include. The prototype introduced warfarin, the concept of genetics, and the impact of genetic variance on warfarin dosing. The evolution of three key panels from versions 2 and 4 are shown in Figures 2 and 3.

Three focus groups each consisting of 5–7 patients taking warfarin were engaged. The focus group participants were taken from a convenience sample of patients receiving care from a thrombophilia anticoagulation clinic. The participants were offered \$20 remuneration for their time and a light meal. The study was approved by the institutional review board. Patients taking warfarin provided oral consent prior to focus group participation. The focus groups were facilitated by a skilled moderator using a semi-structured guide of open-ended questions developed by the research team. The moderator adapted questions as needed to facilitate a robust discussion among focus group participants, while making sure specific topic areas were addressed. Themes from the moderator's guide included discussion on the participants' experience when initially learning about warfarin; education materials used during participants' own warfarin education or counseling session(s); participants' knowledge and attitudes about pharmacogenomics and individualized medicine to explore health literacy; and feedback on the initial prototype, specifically the participants' thoughts on the language, graphics, and content.

Focus group discussions during the group sessions were audio recorded and transcribed. Participants were de-identified in the transcripts to protect patient confidentiality. Three members of the research team who were present took field-notes during the focus group sessions. Together, the transcriptions and notes from the researchers were used for data analysis.

For analysis of the data, focus group transcripts were read by a subset of the research team. Concepts of grounded theory were used to identify the emerging themes. The final codebook

used for coding the data was developed using an iterative and collaborative process.^{28,29} Two members of the research team independently coded the transcript. NVivo 8 software (QSR International Pty Ltd, Doncaster, Victoria, Australia) was used to facilitate the process. Any disagreements were discussed and resolved through consensus, involving a third research team member when necessary.

Results

Seventeen patients taking warfarin participated in the focus groups: 7 patients in the first focus group, 5 patients in the second focus group, and 5 patients in the third focus group. There were three focus groups in total. Approximately half of the focus group participants were male, and the average age was 68.6 years. The average number of years participants had been on warfarin drug therapy was 6.6 years. Eighty-seven percent (13 participants) of participants identified using health care information given to them from their health care providers followed by books/pamphlets (47%, 7 participants). Focus group participant characteristics are shown in Table 1.

The focus group participants provided informative feedback on the patient education prototype. Overall, the participants thought that the prototype generally contained useful information. Some thought that the overall content was “easily understood” and that information in it “makes sense” (Focus group #1). They also generally liked the layout, with one participant stating specifically, “I like the question and answer format; that is very good.” (Focus group #2) Another participant commented similarly saying, “I like the idea of giving the information in a brochure, which is very good.” (Focus group #2)

We heard mixed views about the pictures. Some thought they were helpful while others thought that they distracted from the overall message because the pictures didn’t match up with the text. For example, we realized that the concept of metabolism and being a fast or slow metabolizer in the context of having a high or low INR (the most familiar measure for these patients as to how well they are doing) was not conveyed as clearly as we had thought in the pictures or text. This was noted most succinctly by this participant who said, “Well, if you are talking about INR it’s ‘high’ or ‘low’ it is not necessarily ‘slow’ or ‘fast’.” (Focus group #1) There was some confusion as to what it meant to be “fast” in the context of a low or high INR.

One of the aims of the patient education prototype was to convey basic knowledge about pharmacogenomics, which is a complicated topic. Some participants thought that the prototype did this, for example one noted, “I guess not knowing anything about genetics really as it pertains [to] what we are talking about – this explained it and I understood what it was talking about,” (Focus group #1) indicating that the prototype was able to convey some basic concepts as it relates to participants taking warfarin who generally did not have a good understanding of genetics. Another individual echoed this saying, “It [the patient education prototype] has some good detail about what genetic variation is actually causing the high metabolism, versus the low metabolism, and how your genetic makeup affects this medication and the dosage.” (Focus group #2)

Some participants questioned the value of their needing to know this kind of information. One participant summed it up saying, “The emphasis of this brochure is actually more on the lines of how your genetic variation is going to affect the dosage of the Coumadin or warfarin you are going to take. And it also describes about which exact variation is actually causing the slow processing versus the faster processing of the Coumadin, as I understand...Other than that it is not giving me any other information.” (Focus group #2) Others made similar statements, “It does not really describe [why I am on warfarin], and I think people will say, well, I don't know for sure what I need that for,” (Focus group #1) suggesting that for some participants learning about pharmacogenomics and drug-gene relationships was not a priority. However, they appeared to like the idea of having the test done, as one participant noted, so as to “avoid all of that monkey business,” referring to the challenges associated with dose adjustment (Focus group #1).

What we heard commonly was that the patient education prototype would probably be most helpful to patients who are being initiated on warfarin therapy. Many made statements similar to this: “It is the most beneficial when you are just starting out [on warfarin]” (Focus group #1). One participant expressed that she could see the value in the relationship of genetics and warfarin metabolism explained to her before starting the drug. Another echoed this sentiment, saying, “It would have been nice to have this when I started...instead of asking questions, constantly to the doctors” (Focus group #3).

Finally, we heard that using a simple approach to developing and communicating pharmacogenomics patient education is key: “Simplicity ... is very important...just don't make it [the educational tool] for a country bumpkin that just fell off the wagon, make it for a person that has got a little bit of intelligence ... [but] don't get it all wrapped up in ... compound chemical theories,” (Focus group #2).

Discussion

This article describes the exploratory project to develop and pilot a warfarin pharmacogenomics patient education tool. The method to utilize patient focus groups was innovative for this subject matter, and clinical translation of pharmacogenomics to patient care has the potential to positively impact the patient-health professional encounter and improve comprehension and adoption of complex drug-gene concepts. To our knowledge, this is the first report of a patient education tool comprised of warfarin pharmacogenomic information that has been developed and piloted in focus groups of patients taking warfarin.

Pharmacogenomics is a complex and challenging topic for health professionals to learn and incorporate into their daily practices, and this study provides evidence that it is also a challenging topic to convey through a pictograph to patients.¹³⁻¹⁷ Through the focus groups, the participants communicated their limited knowledge of the concepts of pharmacogenomics, but once the warfarin-genetic link was described in further detail, they provided actionable feedback for the next iteration of the patient education prototype. They generally welcomed the introduction of pharmacogenomics concepts into patient education, although a few questioned the need for this particular information. Reflecting on their own warfarin experiences, participants who had been on warfarin therapy for an average of 6.6

years felt that the information would be most beneficial for patients being newly initiated on warfarin therapy in the context of drug dose variability. They also felt that a simple approach would be the most effective way of delivering the pharmacogenomics education to patients beginning warfarin therapy. The focus group feedback reinforced that simply designed warfarin patient education was the best direction for the next iteration of the prototype.

With regard to the patient education prototype, the focus group participants thought that removing confusing pictures and descriptions would be helpful, but not simplifying it to the point of ‘insulting’ a person’s intelligence. Some pictures and descriptions were unhelpful in communicating the concepts that were being conveyed and will be modified or removed in the next iteration of the patient education prototype.

In this study, a prototype developed through a pictograph approach was piloted in patients taking warfarin. A pictograph is a tool that health professionals can employ to educate patients and to facilitate health care decision-making. Pictographs are visual decision aids that may enhance retention of health education, improve comprehension, and create an emotional adoption of a behavioral target.^{19–21} Improved patient education has been shown to increase patient involvement in their health care decision-making.^{20,22} Using pictures in educational materials also has been shown to positively impact health communication in terms of comprehension, attention, recall, and adherence.^{21,23}

Based on work by Houts et al.,²¹ the research team’s approach to creating the pharmacogenomics patient education prototype organically developed through collaboration with an illustration designer and resulted in an approach that focused on key pharmacogenomics concepts, used simple language, supported concepts with pictures, and included patients from the intended education audience. We evaluated previously developed decision aids.^{19–23,25,26} We focused on the needs of the adult learner initiating warfarin therapy and worked with the assumption that the learner would be engaged and prepared to participate in the learning process of this difficult to manage drug and the lifestyle changes that it would require.²⁷ There are six elements of Knowles’ adult learning theory, and we aimed to address the learner’s needs using these elements including: the need to know, self-concept, previous experiences, readiness to learn, orientation to learning, and motivation to learn.²⁷ Based on these tenets, we aimed to develop understandable and relevant pharmacogenomic educational material that focused on what patients newly initiated on warfarin therapy needed to know at the time of warfarin patient counseling.

Similar to development of diabetes and osteoporosis decision aids,^{20,22,25,26} we formed an interdisciplinary team that included clinicians and health professionals that provide care for patients taking warfarin. A review of available institutional warfarin patient counseling documents and search of the literature found no warfarin pharmacogenomic patient education materials. Thus, based on clinical experience, pharmacogenomics knowledge, adult learning theory, and simple language, we proceeded to design a pharmacogenomics patient education tool for patients taking warfarin. Once the interdisciplinary development was completed after multiple iterations, the patient education prototype was piloted in focus groups of patients taking warfarin to begin the initial step of iterative development.^{20,22,25,26}

Other groups have demonstrated multiple iterations and enhancements to the prototype subsequently occur and based on patients' input, guide further development of aids^{20,22,25,26}; however, our exploratory project reports preliminary results after one iteration with patients currently taking warfarin. Additional research involving iterative development is warranted to further tailor the patient education tool.

Our study had a number of limitations. First, participants were recruited from one anticoagulation clinic, which may limit generalizability. It is anticipated that participation will be expanded in the future to include patients in diverse anticoagulation clinics. Second, participants were offered remuneration that may have introduced social desirability bias. Third, we did not formally assess the reading levels of focus group participants but we did collect "highest level of education" attained as part of the demographics collection; 69 percent (11/16) of the focus group participants had completed community/junior college or higher levels of education.

The next steps for testing of the pharmacogenomics education tool include: refining the tool in collaboration with the Mayo Clinic Patient Education Development Center and an education specialist, iterative enhancements of the educational tool, and conducting a trial utilizing the tool loaded on mobile devices in newly-initiated patients taking warfarin through different anticoagulation clinics.

Conclusion

A patient education prototype was created to actively engage patients in the genetic aspects of their warfarin therapy in a meaningful and approachable manner. The implication of genetics on warfarin dosing is not currently part of patient education; however, this novel tool paves the path to incorporation of genetic language in patient counseling to ensure that patients are fully informed on all aspects of their warfarin therapy. This patient education tool will be valuable as warfarin genetic testing becomes more accepted and is adopted by health care consumers. Importantly, the development and pilot process can be extrapolated to other drug and gene combinations to enhance discussions between patients, pharmacists, and other health professionals for active health care engagement.

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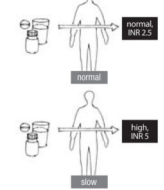
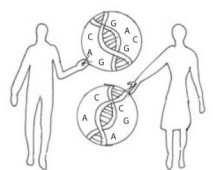
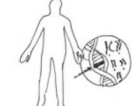
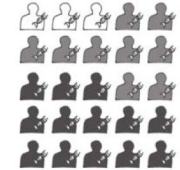
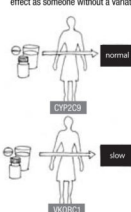
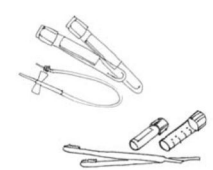
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Medication Information

A tool for understanding how genetics may impact warfarin metabolism

| | | | | |
|---|---|---|--|---|
| <p>1 What is warfarin and why is this drug prescribed?</p> <p>Warfarin is in a class of medications called anticoagulants. It is often referred to as a "blood thinner". It works by decreasing the clotting ability of the blood so the blood clots slower.</p> <p>Warfarin is used to treat or prevent venous thrombosis (blood clot in a vein) and pulmonary embolism (a blood clot in the lungs). Warfarin is also prescribed for people with certain types of irregular heartbeat, people with artificial heart valves, and people who have suffered a heart attack or stroke.</p>  | <p>2 Why do people need different doses of warfarin to have the same effect?</p> <p>Pharmacogenetics is a growing area of research in understanding how people respond to medications. Pharmacogenetics is part of individualized medicine (for example, tailoring therapy to each patient).</p> <p>When a person takes warfarin, the time it takes the body to process the drug depends on their genetics. Some people's genetics cause them to process warfarin slower than others. Those who process warfarin slower require smaller doses to have the same effect as someone who processes warfarin at a normal rate.</p> <p>Other reasons why people require different doses of warfarin include age, sex, weight, ethnicity, race, diets containing vitamin K, compliance with warfarin, liver disease and other disorders, and other medications. In addition, variation in a person's genes has been identified as a factor that determines a patient's warfarin dose.</p>  | <p>3 How will I know if my body will process warfarin at a slow or normal rate? Why is this important?</p> <p>Your health care provider can request a genetic test that looks at your body's ability to process warfarin – patients process warfarin at a slow, fast, or normal rate. People who process warfarin slowly are more sensitive to warfarin and require a lower dose than patients who process warfarin normally. Knowing that your body processes warfarin more slowly or more quickly can help your health care provider adjust your dose appropriately.</p>  | <p>4 Will my family history and genetics impact the processing of warfarin in my body?</p> <p>Yes, family history and genetics can impact how your body processes warfarin. If you have a family member who needed a small dose of warfarin, it is possible that you will need a small dose of warfarin as well. This can be determined by a genetic test.</p>  | <p>5 What are genetic variations and why do they cause patients to require varying doses of warfarin?</p> <p>Genes are like an instruction manual for your body that tells it how to work. For example, gene variants explain why some people have blue eyes and some people have brown eyes. Genetic variants can also influence your response to a medication, how quickly a drug is metabolized, how well the drug works, or the likelihood of side effects. Genes that are responsible for processing warfarin include CYP2C9 and VKORC1.</p> <p>For some patients, their CYP2C9 gene variation determines the rate your body processes warfarin. In a slow processor, warfarin stays in the body longer. The longer warfarin is in the body, the more effect it can have on thinning your blood and may cause side effects. To prevent unwanted side effects from warfarin, "slow processors" need a lower dose than most patients.</p>  |
| <p>6 How does my DNA affect my response to warfarin?</p> <p>DNA is hereditary building blocks of life that create a unique blueprint for every individual. Your DNA is made up of many different genes that are inherited from one's mother and father. If your DNA has a certain variation in the genes CYP2C9 or VKORC1 then you will process warfarin differently.</p>  | <p>7 How do the variations in the genes affect my warfarin therapy?</p> <p>Paired with other non-genetic factors (age, weight, diet, medications, etc.), variations in the following genes can cause patients to process warfarin slower than a patient without these variations.</p> <p>Thus, if a patient has "slow" processing of warfarin, they will require a smaller dose to achieve the same blood thinning effect as someone without a variation in these genes.</p>  | <p>8 What types of testing can be done to determine if my genetic variance will affect my processing of warfarin?</p> <p>A genetic test using saliva or blood may be ordered by your health care provider. A small amount of saliva or blood is tested to find out if you have a genetic variation that processes warfarin differently. You should contact your health insurance provider about coverage of genetic testing expenses. It takes 5 to 10 days for the results of your genetic test to come back.</p>  | <p>9 Are there possible downsides to genetic testing?</p> <p>Possible downsides to a warfarin genetic test include burden of genetic knowledge, cost of the test (especially if it is not covered by your insurance and you have to pay out-of-pocket), and the wait time for genetic testing results. The results may take days to receive which is too long if warfarin must be started as soon as possible; the genetic test would be less useful. Once a person has started warfarin and has reached a stable (not changing) warfarin dose, a genetic test generally is not useful.</p> | <p>10 For more information:</p> <ul style="list-style-type: none"> <input type="checkbox"/> Discuss further with your health care provider(s) and work together to make sure you are taking the right dose of warfarin. <input type="checkbox"/> Request genetic variation testing if you are interested <input type="checkbox"/> Visit www.MayoClinic.com and search under "warfarin" for online resources |

This information reflects the best available research studies. It was prepared by Mayo Clinic researchers without funding from makers of warfarin medication. ©2012 Mayo Foundation for Medical Education and Research. All rights reserved. Revised 3/6/12

Figure 1. Patient education prototype

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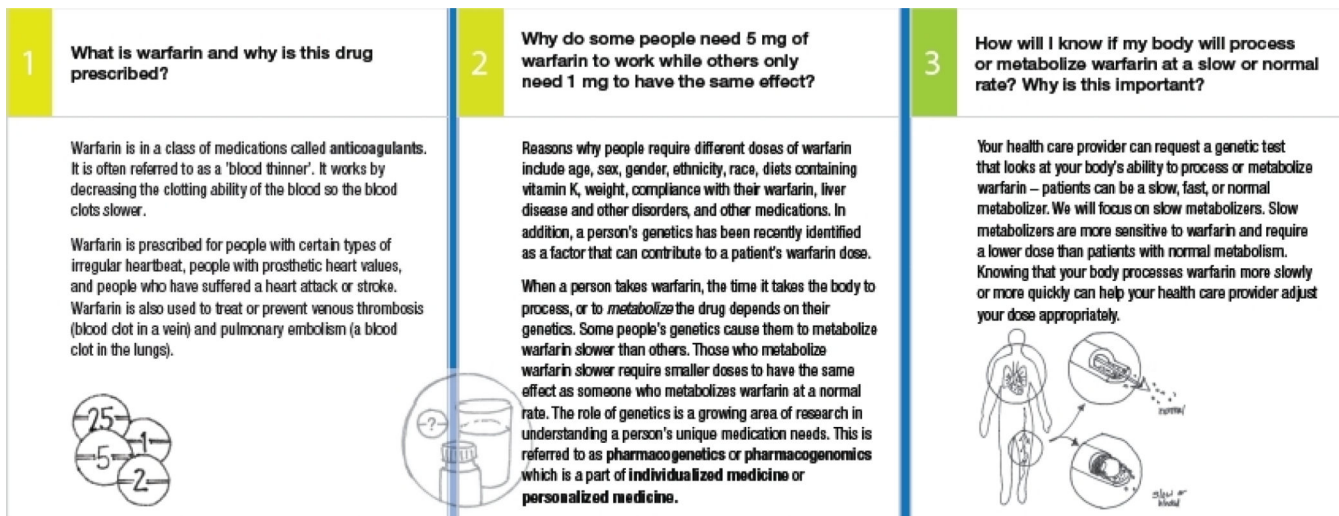


Figure 2. First three panels of version Two

The aim of the graphics was to visually represent the language contained in each panel.

Warfarin tablets were depicted with various strengths. The concepts of pharmacogenomics and individualized medicine were introduced in this version as well as other factors that can impact a patient's INR. Copyright Mayo Foundation for Medical Education and Research; used with permission.

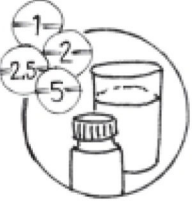

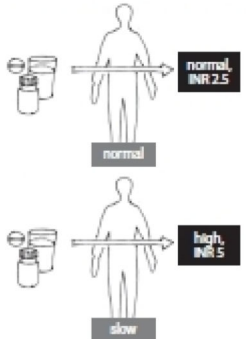
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Figure 3. First three panels of version Four

The terms 'normal' and 'slow' was added to the third panel in the final version to demonstrate the implications of a normal or slow metabolizer on a patient's INR. Additionally, the question in the second panel was changed from "Why do some people need 5 mg of warfarin to work while others only need 1 mg to have the same effect?" to "Why do people need different doses of warfarin to have the same effect?" The research team felt that including specific doses of warfarin may falsely generalize that patients take 5 mg or 2.5 mg of warfarin. Copyright Mayo Foundation for Medical Education and Research; used with permission.

Table 1

Focus group participant characteristics (n=17)

| Demographics | Response (#) |
|--|--------------------|
| Sex | |
| Male | 53% (9) |
| Female | 47% (8) |
| Mean age (range, years) | 68.6 (48–85) |
| Mean years on warfarin (range) | 6.6 (3 mo – 28 yr) |
| Race | |
| White | 88% (15) |
| Black or African American | 6% (1) |
| Asian | 6% (1) |
| Highest level of education* | |
| High School or GED | 31% (5) |
| Community or Jr. College | 25% (4) |
| Four Year College | 6% (1) |
| Graduate School | 19% (3) |
| Professional School | 19% (3) |
| Have you participated in research before?* | |
| Yes | 50% (8) |
| No | 50% (8) |
| What sources of health care information do you use?+ | |
| My health care providers | 87% (13) |
| Books/pamphlets | 47% (7) |
| Internet | 33% (5) |
| Family/friends | 27% (4) |

* 1 participant did not respond to the question

+ participants could select more than 1 choice