Educating Patients & Providers in Clinical Pharmacogenetics: Efficient and Effective Strategies

Susanne Haga, PhD
Duke University School of Medicine
Center for Applied Genomics & Precision Medicine
Disclosure

• I declare no conflicts of interest, real or apparent, and no financial interests in any company, product, or service mentioned in this program, including grants, employment, gifts, stock holdings, and honoraria.

• The University of Florida College of Pharmacy is accredited by the Accreditation Council for Pharmacy Education as a provider of continuing pharmacy education.
Overview

• Need for PGx Education
• Strategies for PGx Education (Who, What, When, How?)
• Barriers to PGx Education
• Metrics of Success for PGx Education
## PGx Educational Needs Assessment

### PROVIDERS
- Reported lack of awareness/knowledge deficit
  - Limited test utilization
  - Limited discussion with patients
  - Adverse impact on test interpretation and application of results to therapeutic decision-making

### PATIENTS
- Reported unfamiliarity with PGx testing
  - Adverse impact on informed decision-making
  - Missed opportunity to reduce anxiety about medications
  - Missed opportunity to improve adherence
Recognition of Value and Need for PGx Education from Professional Organizations

- American Association of Colleges of Pharmacy
- American College of Clinical Pharmacy
- American Society of Health System Pharmacists
Pharmacogenetics

**ABSTRACT:** Pharmacogenetics is the study of genetic variations in drug response that are determined by specific genes. It is hoped that the use of pharmacogenetics in clinical practice may improve drug safety and decrease the rate of adverse drug reactions. Given the potential applications of pharmacogenetics to women’s health care, obstetricians and gynecologists should be aware of this rapidly developing field. Currently, however, there are limited clinical indications for the use of pharmacogenetics in routine obstetric and gynecologic practice.
Multi-Disciplinary Approach to the Delivery of PGx Testing?

What preparation/training does each group need to fulfill their role in the delivery of PGx testing?

- Knowledge?
- Skills?
- Attitude?
Competencies

**Nurse**

**Physician Assistant**
- Reference: Physician Assistant Genomic Competencies (2016)

**Pharmacist**
- Reference: Pharmacogenomics Competencies in Pharmacy Practice: A Blueprint for Change (2016)

**Genetic Counselor**
- Reference: Practice-Based Competencies for Genetic Counselors (2014)

**Physician**
Physician Competencies for PGx (2014)

- Patient Treatment based on Genomic Results
  - Patient Care
  - Knowledge for Practice
  - Practice-based Learning & Improvement
  - Professionalism
  - Systems-based Practice
  - Inter-professional Collaborations
  - Personal and Professional Development

3B1. Appreciate the importance of genetic diversity of humans and the abundance of genetic variants in each individual genome

3B2. Identify single-gene disorders that may be amenable to targeted pharmacological therapy

3B3. Recognize that genomic test results may guide choice of therapy for multifactorial disorders

3B4. Recognize that there is variability in the phenotypic expression of genetic variants and in response to therapy

3B5. Recognize that the effects of some medications are strongly influenced by inherited or somatically acquired genetic variation
Nursing Competencies for PGx (2008)

• Provision of Education, Care and Support
  – Performs interventions/treatments appropriate to clients’ genetic and genomic healthcare needs
  • Pharmacogenomics, pharmacogenetics
    – Administer medications safely with consideration of pharmacogenetic test results
    – Administer prescribed genetic/genomic based therapies safely as allowed per State Practice Act
    – Teach clients about purpose, expected benefits, limitations and potential risks of genetic/genomic based interventions
Pharmacist Competencies for PGx (2016)

• **Basic Genetic Concepts (“B”)**
  3. To identify drug and disease associated genetic variations that facilitate development of prevention, diagnostic and treatment strategies; appreciate differences in testing methodologies and need to explore these differences in drug literature evaluation.
  4. To use family history (minimum of 3 generations) in assessing predisposition to disease and selection of drug treatment.

• **Genetics and Disease (“G”)**
  3. To appreciate that pharmacogenomic testing may also reveal certain genetic disease predispositions (e.g. Apo E4 polymorphism).

• **Pharmacogenetics/Pharmacogenomics (“P”)**
  1. To demonstrate an understanding of how genetic variation in a large number of proteins (e.g. drug transporters, metabolizing enzymes, receptor targets) influence pharmacokinetics and pharmacodynamics related to pharmacologic effect and drug response.
  2. To understand the influence of ethnicity in genetic polymorphisms and associations of polymorphisms with drug response.
  3. Recognize the availability of evidence based guidelines that synthesize information relevant to genomic/pharmacogenomic tests and selection of drug therapy (e.g. Clinical Pharmacogenomics Implementation Consortium).
Pharmacist Competencies for PGx

• Ethical, Legal and Social Implications (ELSI) ("E")

1. To understand the potential physical and/or psychosocial benefits, limitations and risk of pharmacogenetic/pharmacogenomics information for individuals, family members and communities, especially with pharmacogenetic/pharmacogenomic tests that may relate to predisposition to disease.

2. To understand the increased liability that accompanies access to detailed genomic patient information and maintain the confidentiality and security.

3. To adopt a culturally sensitive and ethical approach to patient counseling regarding genomic/pharmacogenomic test results.

4. To appreciate the cost, cost-effectiveness, and reimbursement by insurers relevant to genomic or pharmacogenomic tests, for patients and populations.
Other Provider Competencies

• Physician Assistants (2016)
  – Discuss the range of genetic and genomic-based approaches to treatment of disease
• Genetic Counselors (not mentioned)
• Pathology/Laboratorians (not included)
31 Flavors of Educational Strategies

**Providers**
- Medical curricula
- Residency/Training
- CE/CME
- Clinical decision support
- Peer-reviewed literature
- Drug labels
- Clinical guidelines
- Professional meetings
- Clinical decision supports/info buttons
- Test report
- Lab support (GC/pharmacist)

**Patients**
- Printed materials (brochure)
- Videos
- Consent form
- Test report
- When in doubt, Google
Strategies to Incorporate PGx in Curricula

• Add PGx content to existing lectures;
  – Integrate assignments and test questions incorporating PGx knowledge;
  – Include PGx-focused objectives;
• Create a curriculum thread focused on genetics and genomics;
• Develop an elective PGx course that can be transitioned into a required course
• Collaborate with interdisciplinary colleagues to design courses and curricula

PGx Presence in Health Curricula

• In 2009-10, 82% of US and Canadian medical (Doctor of Medicine, Doctor of Osteopathic Medicine) schools incorporated PGx into their curricula (Green et al., 2010)
  – 28% included >4 hrs of didactic coursework.
  – 76% of respondents considered PGx education to be ‘poor’ or ‘not at all adequate’ at most medical schools

• In 2009, 92% of US pharmacy schools had incorporated PGx into curricula (↑14% from 2005) (Murphy et al., 2010; Latif & McKay, 2005)
Examples in Pharmacy Curricula

• Required/Core Courses
  – Chicago State University College of Pharmacy: *Pharmaceutical Biochemistry II - Molecular Biology and Pharmacogenetics* (Year 1/Spring semester)
  – East Tennessee State University Bill Gatton College of Pharmacy: *PMSC 4134 - Pharmacokinetics and Pharmacogenomics* (Year 2/Fall semester)
  – Binghamton University - SUNY School of Pharmacy and Pharmaceutical Sciences: *PHRM 553- Pharmacy, Pharmacogenomics and Precision Medicine* (Year 3)
Preparing Pathologists for a Leading Role in Genomics

Online Genomic Pathology Modules Now Available!

GENOMICS WORKSHOPS AND COURSES

With NIH providing approximately $1.3 million in funding over five years, this grant will allow the TRIG Working Group to create workshops and courses to further assist residency programs in educating their trainees in genomic pathology.

**USCAP 2017, Annual Meeting**  
March 4-10, 2017

**Resident Workshop:**  
Genomic Medicine for Pathologists  
Saturday, March 4, 2017, 9:00 am – 5:00 pm

**ACMG 2017 Annual Meeting**  
March 21-25, 2017

**Teaching Genomic Medicine:**  
A Train-the-Trainer Workshop  
Wednesday, March 22, 2017, 1:30 pm – 3:00 pm

**American Academy of Neurology Annual Meeting**  
April 22-28, 2017

**Genomic Neurology Workshop**  
Developing Practical Knowledge of Tools and Concepts through

**Workshop Testimonials:**  
More than 95% of participants would recommend to a colleague

“[The workshop] improved my understanding of available tools for clinical evaluation.”
Continuing Education
INNOVATIONS IN TEACHING

Advancing Pharmacogenomics Education in the Core PharmD Curriculum through Student Personal Genomic Testing

Solomon M. Adams, PharmD,a Kacey B. Anderson, BS,b James C. Cody,a
Randall B. Smith, PhD,c Susan M. Meyer, PhD,c Lisa S. Parker, PhD,c
Philip E. Empey, PharmD, PhD, BCPSb

a Department of Pharmaceutical Sciences, School of Pharmacy
b Department of Pharmacy and Therapeutics, School of Pharmacy
c Department of Human Genetics, Graduate School of Public Health University
Point-of-Care Education (Interactive Clinical Support)
Point-of-Care Education (EMR-based Clinical Decision Support)

Gottesman et al. 2013

Rules for actionable gene/drug pairs

CLIPMERGE PLATFORM

CRAE

CLIPMERGE Database

CLIPMERGE PGx saliva sample from consented BioMe participant

Genome-Informed CDS

Longitudinal Clinical Data

Electronic Health Record

Mount Sinai Genetic Testing Laboratory

Reference Material

This patient has been prescribed clopidogrel (Plavix®) and is a CYP2C19 Poor Metabolizer ("2/2") according to genomic testing. Poor metabolizer status is associated with significantly diminished antiplatelet response to clopidogrel and increased risk for adverse cardiovascular events following percutaneous coronary intervention (PCI).

If no contraindication, consider alternative medication from order set below. CLICK HERE to learn more.

- PRASUGREL (Effient®)
- TICAGRELOR (Brilinta®)

If no contraindication, consider prescribing an alternative medication. Click the medication name for further information including indications, dosage and contraindications.

OK

Drug Information
Point of Care Education (Lab Reports)
### Point of Care Education (Lab Reports)

**Script Assured**

**Drug Metabolism Test Results**

**Comprehensive Pharmacogenetic Report for G**

<table>
<thead>
<tr>
<th>Gene</th>
<th>Allele</th>
<th>Pharmacogenetic Impact</th>
</tr>
</thead>
<tbody>
<tr>
<td>CYP2C19</td>
<td><em>C</em>/<em>C</em></td>
<td>No impact on metabolism</td>
</tr>
<tr>
<td>CYP2C19</td>
<td><em>C</em>/<em>T</em></td>
<td>Increased risk of adverse effects</td>
</tr>
<tr>
<td>CYP2C19</td>
<td><em>T</em>/<em>T</em></td>
<td>Increased risk of adverse effects</td>
</tr>
<tr>
<td>CYP2C19</td>
<td><em>C</em>/<em>T</em></td>
<td>Consider alternative medication</td>
</tr>
<tr>
<td>CYP2C19</td>
<td><em>T</em>/<em>T</em></td>
<td>Consider alternative medication</td>
</tr>
</tbody>
</table>

**Laboratory Director: David A. Gallegos, M.D.**

**Test Results**

<table>
<thead>
<tr>
<th>Test</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drug Metabolism</td>
<td>Normal</td>
</tr>
<tr>
<td>Renal Function</td>
<td>Normal</td>
</tr>
<tr>
<td>Liver Function</td>
<td>Normal</td>
</tr>
</tbody>
</table>

**Consider Alternatives**

- For patients with CYP2C19 *C*/*T* or *T*/*T* genotype, consider alternative medications.
- If patient has a history of CYP2C19 *C*/*T* or *T*/*T* genotype, consider alternative medications.

**Test Results**

- Consider alternative medications for patients with CYP2C19 *C*/*T* or *T*/*T* genotype.
- Consider alternative medications for patients with CYP2C19 *C*/*T* or *T*/*T* genotype.

**Conclusion**

- Patients with CYP2C19 *C*/*T* or *T*/*T* genotype may require alternative medications to avoid potential adverse effects.
- Consult with a pharmacy or healthcare provider for specific medication recommendations.

**References**

2.必备参考文献.
Patient Education
## Educating Patients – Not a Singular Event

### PRE-TESTING PHASE
- Description of test purpose, risks, limitations, alternative options, and anticipated outcomes
- Patient education should be commensurate with the risks posed by testing

### POST-TESTING PHASE
- Communication of results
- Significance to/Options for treatment
- Impact on future treatments
- Familial implications

***Extent of patient discussion may vary considerably based on several factors:***
- Preemptive or point of care test
- Degree of patient familiarity
- Provider’s training, skill, knowledge and experience
- Available resources
Patient Educational Materials vs. Decisional Aids

• Decision aids differ from usual patient health education materials
  – Intended to make explicit the decision being considered,
  – Provide detailed, specific, and personalized focus on options and outcomes for the purpose of preparing people for decision making
• Pamphlets, videos, or web-based tools
• Can be used before, during, or after a clinical encounter to enable patients to become active, informed participants

(Stacey et al., Cochrane Database Syst Rev 2014)
Educating Patients – What Should they Know about PGx?

• To answer ‘what’, need to define objective of patient education on PGx
  – To promote informed decision-making
  – To prepare patients for anticipated test outcomes
  – To promote awareness of testing and sharing of test results with other treating providers
Educating Patients – What Should they Know about PGx?

1. To promote informed decision-making
   - Purpose
   - Benefits
   - Risks
   - Limitations
   - Alternatives

2. To prepare patients for anticipated test outcomes and impact on treatment
   - Normal (Standard of care), Known variant (adjusted dose or alternative medication)

3. To promote awareness of testing and sharing of test results with other treating providers
   - Testing for one clinical indication/treatment may be relevant for another treatment since medications are sometimes processed by the same genes in the body
## Consent Forms

<table>
<thead>
<tr>
<th>Labs with accessible informed consent</th>
<th>21</th>
<th>62%</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Type of consent</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Patient-signed PGx-specific consent form</td>
<td>3</td>
<td>14%</td>
</tr>
<tr>
<td>• Patient-signed general genetic testing consent form</td>
<td>8</td>
<td>38%</td>
</tr>
<tr>
<td>• Patient-signed consent statement within requisition form</td>
<td>4</td>
<td>19%</td>
</tr>
<tr>
<td>• Provider assent only required</td>
<td>1</td>
<td>5%</td>
</tr>
<tr>
<td>• No consent/assent collected by lab</td>
<td>5</td>
<td>24%</td>
</tr>
</tbody>
</table>

Haga & Mills, 2015
Consent Forms

<table>
<thead>
<tr>
<th>Table Title</th>
<th>Word count (overall)</th>
<th>68 – 1040</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient consent embedded in test requisition</td>
<td>231.5</td>
<td>68 – 430</td>
</tr>
<tr>
<td>Patient consent as a separate form</td>
<td>680.4</td>
<td>363 – 1040</td>
</tr>
</tbody>
</table>

| Flesch-Kincaid Reading Ease score² | 39.8                | 24 – 76.1  |
| Flesch-Kincaid Reading Grade³     | 12.5                | 5.6 – 16.9 |
FAQ/Informational Sheets

GENE TEST FOR MEDICINES: PATIENT/PARENT INFORMATION

Throughout this document, references to “You” and “Your” may stand for either an adult patient or for the parents or legal guardians of a pediatric patient.

WHAT ARE GENES?
Genes are pieces of DNA that we inherit from our parents. Genes provide the instructions to make our bodies look and work as they do.

WHAT DO GENES HAVE TO DO WITH MEDICINE?
Some genes affect how medicines work in the body. When comparing a group of people, there can be slight differences in each gene’s structure. These differences can affect how people react to medicine.
1. Some gene differences might make it harder for the body to get rid of some medicines. This means that usual doses of the medicine could give some people unexpected side effects.
2. Some gene differences can cause the body to use up a medicine too fast. This means that normal doses won’t work as well and the person may need higher doses.
3. Some gene differences won’t let certain medicines work in the body at all. This means a different medicine may work better.

WHAT IS THE GENE TEST CALLED?
The gene test being considered for you is called a pharmacogenetic test. It is easier to call it a PG test.

IS THE PG TEST REQUIRED?
Most PG tests are optional. A few new medicines are designed for people with certain cancers or infectious diseases. A PG test of a tumor or a person’s blood may be needed to know if a medicine will work. Most times you can be treated with standard medicine doses without this PG test. Make sure you understand why your doctor is recommending a PG test for you.

WHAT DO YOU NEED FOR THE PG TEST?
About 1 teaspoon of your blood is needed for the PG test. It is also possible to do the test on scrapings from the inside of your cheek. Special brushes are needed to obtain the cheek scrapings.

WHY DO YOU WANT TO DO A PG TEST?
A PG test can be done before or after a medicine is given to you.
Before a medicine is given:
A PG test may help your doctor choose the medicine and dose that will work best for you.
After a medicine is given:
A PG test may help the doctor understand why you are having problems with a medicine. The test may also help your doctor decide if a different dose or different medicine should be tried.

WHAT ARE THE POTENTIAL BENEFITS OF A PG TEST?
- The test may improve the chances that the medicine will help you as intended.
- The test may lower the chance of severe side effects from the medicine.
- The PG test for the medicine may only need to be done once in a lifetime. The test looks at common gene differences. If the common gene differences are found in your blood, then the test will not need to be repeated.
- The gene tested today may be important for medicines that you need in the future.
Patient Videos

Introduction to Genome Sequencing (Animation)

About Genetics
What is Pharmacogenomics?
What is Genetic Counseling?

Testing and Drug Response
Testing and Insurance Concerns
Sharing Results with Family

Video by Site

› Boston Children's Hospital
› Children's Hospital of Philadelphia
› Columbia University Medical Center
› Geisinger Health System
› Marshfield Clinic
› Mayo Clinic
› Mount Sinai
› Northwestern University
› Vanderbilt University

Genetic Testing to Predict Responses to Medication

Genetic Testing to Predict...

Dr. Hakon Hakonarson of The Children's Hospital of Philadelphia explains that genetic testing can now be used to predict responses to certain medications. This will help to prevent negative reactions and improve healthcare.

Can Genetic Testing Improve Healthcare?

Can Genetic Testing Improve...

Dr. Dan Roden of Vanderbilt University discusses how genetic testing has begun to influence treatment of patients. As we understand more about genetics underlying human disease, we are developing increasingly sophisticated ways of managing patients' health. This is particularly true of cancer, where genetic results are increasingly used to guide patient care.

Genetic Testing to Predict Your Response to Drugs

Genetic Testing to Predict...

Dr. Murray Brilliant of Marshfield Clinic explains that genetic testing can help determine what drug is best suited to you.

Why Do Pharmacogenomic Testing?

Why Do Pharmacogenomic...

Maureen Smith, a researcher at Northwestern University explains that the goal of the pharmacogenomics projects at Northwestern University is to help patients by using genetic information about
Learn more:

Understanding the MediMap Report
Patient Educational Tools
Post-Test: Patient Results Card

John M. Doe
Lab #: 11111
CYP2D6 Normal Metabolizer *1/*2A
CYP2C19 Poor Metabolizer *4/*4
CYP2C9 Intermediate Metabolizer *1/*3
CYP3A4 Intermediate Metabolizer *22/*22
CYP3A5 Non-Expresser *1/*1

Patient:
1. Place this card in your wallet.
2. Show this card to any healthcare provider or pharmacist whenever new medications are prescribed.
3. Call Customer Support with any questions at 877-431-4362.

Healthcare providers: To access this patient’s genetic drug metabolizing profile:
1. Go to youScript.net.
2. Click “Create Account” and follow the on-screen instructions or simply login.
3. Once logged in, select “Import Patient” from the Menu at the top of the screen.
4. Enter the Lab # from the front of this card and the patient’s date of birth.
5. Enter drugs you are considering into the “Drug and Phenotype” box to see interactions.

Genelex Corporation | Seattle, WA | www.YouScript.com

Patient may be at risk for genetic-based adverse drug events. See reverse to access complete genetic drug metabolizing profile before prescribing.
A boy, 9 year old

ผลการตรวจ: CYP450 Gene: CYP2D6 *10/*10, CYP2C19 *1/*3
              HLA-B Gene:   HLA-B*5201 / 5601

วันที่ตรวจ: 24 กุมภาพันธ์ 2554

การแบ่งคลาสสิคพันธุศาสตร์:
CYP2D6 ผู้ตรวจอยู่ในกลุ่ม C (Intermediate Metabolizer)
CYP2C19 ผู้ตรวจอยู่ในกลุ่ม B (Extensive Metabolizer)

*โปรดอย่าแบ่งปันแผนที่นี้กับบุคคลอื่น

ข้อเสนอแนะ
เนื่องจากยาซัลซี่น CYP2D6 และ 2C19 ในผู้ป่วยรายนี้ มีอัตราการทิ้งผ่านของ ดังนั้นควรใช้ยาในขนาดมาตรฐาน อาจทำให้ระดับยาในกระแสเลือดไม่สมดุลในช่วงของการรักษา ซึ่งจะต้องการเกิดอาการไม่พึงประสงค์ / ประสิทธิผลจากการใช้ยาได้

ต้องการช่วยเหลือเพิ่มเติม ติดต่อ: หน่วยภาวะพันธุศาสตร์และการรักษาเฉพาะบุคคล โทรศัพท์ 02-200-4330-3, 02-201-1380, 02-201-1390

(ลายมือชื่อ: ผู้รับผิดชอบ)
What is the primary educational method that you use/plan to use to inform patients about their pharmacogenetic test results?

- A. Verbal patient counseling
- B. Written patient information
- C. Electronic educational resources (e.g., patient videos)
- D. Patient results “wallet” card
How do we know what works?
Measuring Effectiveness of Educational Interventions

- Outcomes-driven models of evaluation: an educational program is considered effective if students achieve a predetermined outcome.
- Criticisms: too narrow in scope, cannot account for unique factors related to learning, behavior change, and implementation.
Measuring Educational Effectiveness

- **Teacher Quality**
  - Knowledgeable about subject matter
  - Effective approach in teaching subject matter
    - Traditional lecture style
    - Interactive
    - Experiential

- **Outcome Measures**
  - Knowledge/Skills/Attitudes
  - Practice/Behavior

- **Quality of Measures**
- **Suitability** for multiple audiences, practice settings, specialties (no validation)
- **Comparative effectiveness**
- **Cost-effectiveness**
**Inputs vs. Outputs**

**Teacher:** Ability/extent to meet student needs (improving student performance)  
**Student:** Knowledge, performance

**Teacher:** Qualifications/training, number of years teaching  
**Student:** Number of courses taken (or hours spent) on a given topic
Impact of Decisional Aids on Patient Decision-Making

- High-quality evidence that decision aids (compared to usual care) improve people's knowledge regarding options, and reduce decisional conflict related to feeling uninformed and unclear about their personal values.
- Moderate-quality evidence that decision aids (compared to usual care) stimulate people to take a more active role in decision-making, and improve accurate risk perceptions when probabilities are included in decision aids.
- Low-quality evidence that decision aids improve congruence between the chosen option and the patient's values.

(Stacey et al., Cochrane Database Syst Rev 2014)
Impact of Patient Decision Aids

• International Patient Decision Aid Standards (IPDAS):
  – ‘Choice made' attributes
    • Conceptual and numerical knowledge
  – ‘Decision-making process' attributes
    • Decisional conflict (reduced proportions of people who remained undecided post-intervention or who were who were passive in decision making)
    • Decisional self-efficacy (preparation for decision making)
    • Patient-practitioner communication
    • Satisfaction with decision and/or decision-making process

• Patient Behavior: final decision, adherence to decision
• Health outcomes: health status, psychological impact
• Health-system effects: cost, cost-effectiveness, length of consultation
Curricula-based/Elective

Continuing Education

In-person: classroom

Experiential Learning

Clinical Decision Support

In-person: Professional meetings, Grand Rounds
Online: MOOCs, Seminars, Literature

Provider

Point of Care

Pre-emptive/Point of Care

Student

Patient

Printed Resources
Looking Ahead

- Currently, a lot of attention is focused on PGx to understand its role in drug response ..... but just a piece of the puzzle

- As evidence of clinical utility continues to be collected, the field has moved into clinical implementation
  - Facing challenges of preparing providers and patients who are largely unfamiliar with the science and application
Looking Ahead

• Uneven efforts to educate providers and patients
• Multiple educational approaches with limited evaluation of changes/impacts on practice behavior
• Potential opportunity to integrate PGx into broader educational materials/interventions on medications
Questions? Thank you.