Right drug. Right dose. Right now.

Delivering on the promise and value of personalized prescribing
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*requires scheduling ahead of time
Part One

Pharmacogenetics 101
ADEX: Avoidable medical problem

2.2 MILLION severe adverse drug events per year

FOURTH leading cause of death in the U.S.

100,000 deaths per year by properly prescribed drugs
80,000 deaths per year by improperly prescribed drugs

COST LEADER for malpractice payouts

Gurwitz JH. Et al. Incidence and preventability of adverse drug events among older persons in the ambulatory setting. JAMA 2003;189(9):1107-16
Treatment failures also increase the cost of healthcare and are very common in prevalent disease states. 

<table>
<thead>
<tr>
<th>Disease Type</th>
<th>Percentage Ineffective</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cancer Drugs</td>
<td>75%</td>
</tr>
<tr>
<td>Alzheimer's Drugs</td>
<td>70%</td>
</tr>
<tr>
<td>Arthritis Drugs</td>
<td>50%</td>
</tr>
<tr>
<td>Diabetes Drugs</td>
<td>43%</td>
</tr>
<tr>
<td>Asthma Drugs</td>
<td>40%</td>
</tr>
<tr>
<td>Anti-depressants (SSRIs)</td>
<td>38%</td>
</tr>
</tbody>
</table>

**Percentage of patient population for whom drug is ineffective on average.**

A large contributor of treatment failure rates are driven by genetic differences in metabolism.

DNA & Pharmaceuticals

- **50%** of all medicines are processed by genetic-specific enzymes
- More than **75%** of the population have genetic variations that increase their risk for ADEs
- Medicines most commonly associated with ADEs are **8X** more likely to go through pathways with genetic variants
- Exacerbated by polypharmacy:
  - **40%** of individuals over 65 take **five or more** medications
The Answer: Personalized Prescribing

Without Genetics

Advertised Dose

With Genetics

Personalized Dose
<table>
<thead>
<tr>
<th>CYP 2D6</th>
<th>CYP 2C9</th>
<th>CYP 2C19</th>
<th>CYP 3A4/5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Beta blocker’s</td>
<td>Warfarin</td>
<td>Plavix</td>
<td>Benzodiazepines</td>
</tr>
<tr>
<td>Antiarrhythmic’s</td>
<td>Phenytoin &amp; Valproic acid</td>
<td>Carisoprodol</td>
<td>Fluticasone</td>
</tr>
<tr>
<td>SSRI’s &amp; TCA’s</td>
<td>Fluoxetine</td>
<td>Diazepam</td>
<td>Cyclosporine and Tacrolimus</td>
</tr>
<tr>
<td>Antipsychotic’s</td>
<td>Sulfonylurea’s</td>
<td>Proton pump inhibitor’s</td>
<td>Statins</td>
</tr>
<tr>
<td>Opioid’s</td>
<td>NSAID’s</td>
<td>SSRI’s &amp; TCA’s</td>
<td>Combined Oral Contraceptives</td>
</tr>
</tbody>
</table>

More than 100 medications have drug-gene interactions identified by FDA in package insert
Inhibition

CYP2D6 inhibitor

HEME CYP

CYP2D6 substrate

Drug D

Drug C

CYP2D6
**Induction**

Drug D (inducer) sends message to nucleus to make more CYP protein—induction of 2C9 → lower concentration of Drug C
Drug Metabolism Phenotypes

**Poor Metabolizer**
- CYP2D6: 10%
- CYP2C9: 5%
- CYP2C19: 5-20%

**Intermediate Metabolizer**
- CYP2D6: 30%
- CYP2C9: 30%
- CYP2C19: 2-30%
- CYP3A4

**Ultra Metabolizer**
- CYP2D6: 5%
- CYP2C9: N/A
- CYP2C19: 30%

**Normal Metabolizer**
- <15% normal for 2D6, 2C9 & 2C19
- CYP3A4
CYP3A5 Phenotypes

- *3/*3 = Normal Metabolizer
- *1/*3 = Rapid Metabolizer
- *1/*1 = Ultra Rapid Metabolizer
Sink and Drain Analogy

- Normal
- IM
- Ultra Rapid
Drug response: Active drugs

Genetics affects drug clearance

Drug Response

PM: Poor Metabolizer  IM: Intermediate Metabolizer  NM: Normal Metabolizer  UM: Ultra Metabolizer

PM
IM
NM
UM

Toxic level
Therapeutic level

Drug Levels vs. Day

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Active drug

- Parent
- Metabolism
- Metabolite

Prodrug

- Inactive parent
- Metabolism
- Active metabolite
- Metabolism
- Metabolite
Drug response: Prodrugs

Genetics affects drug clearance

PM: Poor Metabolizer  IM: Intermediate Metabolizer  NM: Normal Metabolizer  UM: Ultra Metabolizer
Part Two

YouScript Background
YouScript software is the most advanced medication management software available

- Most comprehensive drug-gene and drug-drug interaction software
  - 2,700 drugs & metabolites
  - 11,500 clinical interaction notes
  - 12,000 PubMed references & product inserts
  - New data updated daily

- Population Risk Analysis

- Ranked Alternate Selector

- Incorporates herbals, over-the-counter and recreational drugs

- Genotype-based drug and dosage recommendations

- Only solution to factor multi-drug and cumulative effects

- EHR integration

Allscripts™ Open App Challenge Winner

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Select safer and more effective medications

<table>
<thead>
<tr>
<th>Overall Impact</th>
<th>Affected Drug</th>
<th>Drug Exposure (PK)</th>
<th>Clinical Effect (PD)</th>
<th>Causative Agents</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Seroquel</td>
<td>81-100% ↓</td>
<td>Some</td>
<td>Tegretol</td>
</tr>
<tr>
<td></td>
<td>n-desalkylquetiapine</td>
<td>51-80% ↓</td>
<td></td>
<td>Tegretol</td>
</tr>
<tr>
<td></td>
<td>Tegretol</td>
<td>26-75% ↑</td>
<td>Some</td>
<td>Seroquel</td>
</tr>
<tr>
<td></td>
<td>carbamazepine epoxide</td>
<td>26-75% ↑</td>
<td>Some</td>
<td>Seroquel</td>
</tr>
<tr>
<td></td>
<td>Crestor</td>
<td>Some</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>asenapine</td>
<td>Some</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Seroquel**

ANTIPSYCHOTIC - ATYPICAL

<table>
<thead>
<tr>
<th>Drug</th>
<th>Rank</th>
</tr>
</thead>
<tbody>
<tr>
<td>asenapine *</td>
<td>1</td>
</tr>
<tr>
<td>ziprasidone *</td>
<td>2</td>
</tr>
<tr>
<td>olanzapine *</td>
<td>2</td>
</tr>
<tr>
<td>amisulpride</td>
<td>2</td>
</tr>
<tr>
<td>clozapine</td>
<td>2</td>
</tr>
<tr>
<td>zotepine</td>
<td>2</td>
</tr>
<tr>
<td>tiospirone</td>
<td>2</td>
</tr>
<tr>
<td>iloperidone *</td>
<td>2</td>
</tr>
<tr>
<td>serindole</td>
<td>2</td>
</tr>
<tr>
<td>ramoxipride</td>
<td>2</td>
</tr>
<tr>
<td>melperone</td>
<td>2</td>
</tr>
<tr>
<td>risperidone *</td>
<td>2</td>
</tr>
</tbody>
</table>
DDI software solutions do not adequately address the ADE & treatment failure problem

Typical Drug Interaction Software

DDI software and clinical decision support have shown to reduce ADEs, but have well-established shortcomings

- Lack of usability / incomplete training
- "Alert fatigue"
- Do not incorporate pharmacogenetics
- May not address polypharmacy, OTC or supplements
- Often not integrated across all points of care
YouScript makes it easy to factor pharmacogenetics into prescribing decisions

YouScript comprehensive medication management:

• Systems approach to multidrug interactions
• Addresses the cumulative impact of Drug B, C, D on Drug A
• Predicts drug-gene interactions
• Provides what-if scenarios and simplifies alternative selection
YouScript partnered with a large health system for a pilot study to validate predictive technology.

**Study background:**
- Patient drug lists provided, no genetic testing.
- YouScript stratified patients into “Warned” or “Unwarned” – no intervention or changes made to drug regimen.
- Patients followed for one year to assess healthcare resource utilization.

Ambulatory polypharmacy treated patients followed for one year (N = 111) without intervention.

**Baseline demographics**

<table>
<thead>
<tr>
<th>Condition</th>
<th>Drug Interaction Warned N = 77</th>
<th>Drug Interaction Unwarned N = 34</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drugs</td>
<td>8.9</td>
<td>8.2</td>
</tr>
<tr>
<td>Age</td>
<td>69.6</td>
<td>72.8</td>
</tr>
<tr>
<td>IHD</td>
<td>36.4%</td>
<td>32.3%</td>
</tr>
<tr>
<td>Hypertension</td>
<td>90.0%</td>
<td>91.1%</td>
</tr>
<tr>
<td>Diabetes</td>
<td>72.7%</td>
<td>70.6%</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>62.3%</td>
<td>64.7%</td>
</tr>
</tbody>
</table>
YouScript validation study results

Total savings to 700,000 member health plan estimated at

$25,000,000 – $57,000,000 per year

Ambulatory polypharmacy treated patients followed for one year (N = 111)

<table>
<thead>
<tr>
<th></th>
<th>Drug Interaction Warned N = 77</th>
<th>Drug Interaction Unwarned N = 34</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Total</td>
<td>Avg. per person</td>
</tr>
<tr>
<td>ER Visits</td>
<td>50</td>
<td>0.66</td>
</tr>
<tr>
<td>Hospitalizations</td>
<td>96</td>
<td>1.25</td>
</tr>
<tr>
<td>Days in Hospital</td>
<td>477</td>
<td>6.19</td>
</tr>
<tr>
<td>Imaging Procedures</td>
<td>659</td>
<td>8.56</td>
</tr>
</tbody>
</table>
YouScript Clinical Study Preliminary Data

*1st 6 months*

**Study background:**

- 2 arms dividing a 700,000 patient, ~2000 physician plan, 1000 patient genetic testing subarm
- Patients stratified into “Warned” or “Unwarned”
- Physician response to warnings was voluntary
- Patients 65+ on 5+ meds compared in 2 arms to assess healthcare resource utilization

<table>
<thead>
<tr>
<th></th>
<th>vs. Control arm</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hospitalizations</td>
<td>-2.9%</td>
</tr>
<tr>
<td>Total number of drugs used**</td>
<td>-2.0%</td>
</tr>
<tr>
<td>Imaging Procedures (MRI, CT, U/S, X-ray)</td>
<td>-3.0%</td>
</tr>
</tbody>
</table>

- MDs changed prescribing habits in 40% of accessed warnings
- **$530 USD per patient savings** seen although only 15% of MDs accessed warnings
- In high healthcare resource consuming patients, savings was **$2400 USD**
Part Three

Report Interpretation
# Report Interpretation: Example Report

## Patient Information

<table>
<thead>
<tr>
<th>PATIENT:</th>
<th>RESULTS:</th>
<th>LAB INFO:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient: John Doe (Primary Care)</td>
<td>Test: CYP2D6&lt;br&gt;Phenotype: Intermediate Metabolizer&lt;br&gt;Genotype: *1/*4</td>
<td>Lab#: 12348</td>
</tr>
<tr>
<td>DOB: 11/1/1945</td>
<td>Test: CYP2C19&lt;br&gt;Phenotype: Poor Metabolizer&lt;br&gt;Genotype: *2/*2</td>
<td>Sample: Buccal Swab</td>
</tr>
<tr>
<td>Acct: Doe Primary Care</td>
<td>Test: CYP2C9&lt;br&gt;Phenotype: Normal Metabolizer&lt;br&gt;Genotype: *1/*1</td>
<td>Collected: 08/05/2013</td>
</tr>
<tr>
<td>Ref: Dr. Doe</td>
<td>Test: VKORC1&lt;br&gt;Phenotype: Intermediate sensitivity to warfarin&lt;br&gt;Genotype: G/A</td>
<td>Received: 08/06/2013</td>
</tr>
<tr>
<td></td>
<td>Test: CYP3A4&lt;br&gt;Phenotype: Intermediate Metabolizer&lt;br&gt;Genotype: *22/*22</td>
<td>Reported: 08/07/2013</td>
</tr>
<tr>
<td></td>
<td>Test: CYP3A5&lt;br&gt;Phenotype: Normal Metabolizer&lt;br&gt;Genotype: *3/*3</td>
<td></td>
</tr>
</tbody>
</table>

### Patient's genotype will never change.
Login to YouScript to identify possible interaction risks when making medication changes.

---

### Advisory Note to Treating Practitioner:

The prescribing suggestions below are based on standard doses of the medications listed on the patient test requisition we received from you, do not take into account the full clinical picture, and do not supersede your clinical judgment. Please review the medication list for accuracy before proceeding. If you would like to share more information about the patient's history, I may be able to provide more specific guidance regarding potential interactions of prescribed medications with your patient's genotype. If you would like to discuss this case, I can be reached Monday - Friday between 8 a.m. and 4:30 p.m. PST.

Consultation by: Sample PharmD/RPh | (877) 796-4362

---

### Medications:
citalopram, clopidogrel, hydroxyzine, simvastatin
### MEDICATIONS:

citalopram, clopidogrel, hydroxyzine, simvastatin

### PRESCRIBING SUGGESTIONS:

<table>
<thead>
<tr>
<th>Action</th>
<th>Drug Impacted</th>
<th>Type</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>clopidogrel</td>
<td>Drug / Gene</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
**Effect:** Clopidogrel's (Plavix) risk for cardiovascular events may increase in CYP2C19 poor metabolizers.

**Management:** For acute coronary syndrome: Consider prescribing prasugrel (Effient) or ticagrelor (Brilinta) [per CPIC]. For secondary stroke prevention or peripheral artery disease: Consider aspirin/dipyridamole (Aggrenox) or aspirin.

<table>
<thead>
<tr>
<th>Action</th>
<th>Drug Impacted</th>
<th>Type</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>citalopram</td>
<td>Drug / Gene</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
**Effect:** Citalopram (Celexa) exposure and QTc prolongation risk increases in CYP2C19 poor metabolizers.

**Management:** Monitor EKG and anticholinergic effects. Use a maximum of 20 mg daily. When necessary, prescribe sertraline (Zoloft), mirtazapine (Remeron) or vilazodone (Viibryd).

<table>
<thead>
<tr>
<th>Action</th>
<th>Drug Impacted</th>
<th>Type</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>hydroxyzine</td>
<td>Drug / Gene</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
**Effect:** Hydroxyzine (Vistaril) exposure may increase in CYP2D6 intermediate metabolizers.

**Management:** Monitor for anticholinergic effects, sedation and dizziness. When necessary, decrease dose or prescribe doxylamine (Unisom), cetirizine (Zyrtec), fexofenadine (Allegra) or fluticasone nasal spray (Flonase).
LABORATORY RESULTS INTERPRETATION:

CYP2D6 Intermediate Metabolizers exhibit less than normal enzyme activity. Their genotype consists of either one active and one inactive, one partially active and one inactive, or two partially active CYP2D6 alleles. For CYP2D6 inactivated drugs, consider less than standard dosage to prevent adverse effects. For prodrugs that require activation by CYP2D6, consider increased dosage or an alternative treatment for optimal therapeutic response.

CYP2C19 Poor Metabolizers exhibit greatly decreased enzyme activity. Their genotype consists of two inactive CYP2C19 alleles. For CYP2C19 inactivated drugs, consider alternative treatments or less than standard dosage to prevent adverse effects. For prodrugs that require activation by CYP2C19, consider increased dosage or alternative treatment for optimal therapeutic response.

CYP2C9 Normal Metabolizers are the common phenotype for CYP2C9 enzyme activity. Their genotype consists of two fully active CYP2C9 alleles. May prescribe CYP2C9 metabolized drugs following standard dosing practices.

Patients with the VKORC1 (-1639 GA) genotype exhibit intermediate sensitivity to warfarin. Results may be used for initial warfarin dose titration along with CYP2C9. Consult lab or www.warfarindosing.org for dosing advice and adjust warfarin dose based on INR and concurrent medications.

CYP3A4 Intermediate Metabolizers exhibit less than normal enzyme activity. Their genotype consists of one or two decreased activity alleles (*22). For CYP3A4 inactivated drugs, consider less than standard dosage to prevent adverse effects.

CYP3A5 Normal Metabolizers are the common phenotype for CYP3A5 enzyme activity. Their genotype consists of two severely reduced CYP3A5 alleles (*3). Prescribe CYP3A5 metabolized drugs following standard dosing practices. This phenotype may also be known as CYP3A5 non-expressers.

Legend:

- Clinical Impact:
  - Major
  - Substantial
  - Some
  - Insignificant

Clinical Indication for Testing: Patient taking medications metabolized by the cytochrome P450s or other enzymes, has a personal or family history of adverse reactions including treatment failure, or to confirm the presence or absence of relevant genotypes and as an aid to dosing and co-medication administration. DNA testing does not replace the need for clinical and therapeutic drug monitoring.

Methodologies: PCR based assays detect listed alleles, including all common and most rare variants with known clinical significance at analytical sensitivity and specificity >99%. Variants tested may include: CYP2C19: active *1, inactive *2, *3, *4, *5, *6, *7, *8, *8r, *9, *10, *11, *12, *13, *14, *15, partially active *9, *17, *41, gene duplications *1, *2, *4, *10, *41, CYP2C9: active *1, inactive *2, *3, *4, *5, *6, *8, *11, *13, VKORC1: high sensitivity 1639G>A, CYP3A4: active *1, partially active *22, CYP3A5: active *1, inactive *3. Rare variants may not have been observed at Genelex. Other known variants not listed are not detected. Assays developed and performance characteristics determined by Genelex. Rare false negative or false positive results may occur. These tests have not been cleared or approved by the US Food and Drug Administration. FDA does not require these tests to go through premarket FDA review. These tests are used for clinical purposes and should not be regarded as investigational or for research. Genelex Corporation is certified under the Clinical Laboratory Improvement Amendments (CLIA No. 5006800569), Washington State Medical Test Site No. MT-3019, New York State Department of Health license no. PFI 8201 and is licensed to perform high complexity clinical testing in all US states.

Liability Disclaimer: This report is based solely on the medications and other information provided to Genelex and does not take all factors of the patient’s care into account. Genelex is neither responsible nor liable for the accuracy of the information supplied to Genelex by the treating healthcare professional. The treating healthcare professional has ultimate responsibility for all treatment decisions made with regard to the patient, including any made on the basis of the patient’s genotype. Therefore, neither Genelex nor its employees, shall have any liability to any person or entity with regard to claims, loss, damage arising, or alleged to arise, directly or indirectly, from the use of information contained in this report.

References: Available at www.YouScript.com/healthcare-professionals or by request. Drug-gene tables with dosing considerations for commonly prescribed medicines can be accessed from the YouScript software at www.YouScript.net. Log in credentials are the patient’s Genelex lab number and date of birth.
# Report Interpretation: Action Items

## Recommended Protocol

<table>
<thead>
<tr>
<th>Action</th>
<th>If medication is prescribed by referring physician</th>
<th>If medication is prescribed by another physician</th>
</tr>
</thead>
<tbody>
<tr>
<td>![Change Icon]</td>
<td>Have physician review the report immediately.</td>
<td>Have physician review the report, contact patient to determine prescribing physician then fax report to prescriber, or fax back to Genelex at 206-219-4000 with “Did not prescribe” written at top.</td>
</tr>
<tr>
<td>![Consider Icon]</td>
<td>Contact patient if change is implemented.</td>
<td></td>
</tr>
<tr>
<td>![Consider Icon]</td>
<td>Have the physician review the report at his next earliest convenience.</td>
<td>Have physician review the report, contact patient to determine prescribing physician then fax report to prescriber or fax back to Genelex at 206-219-4000 with “Did not prescribe” written at top.</td>
</tr>
<tr>
<td>![Monitor Icon]</td>
<td>Have the provider review prior to the next patient visit.</td>
<td>Fax to prescribing physician or fax to Genelex at 206-219-4000 with “Did not prescribe?” written at top.</td>
</tr>
<tr>
<td>![No Change Icon]</td>
<td>Put report in patient’s file and explain to the patient that no significant drug-drug or drug-gene interactions currently exist.</td>
<td>Put report in patient’s file and explain to the patient that no significant drug-drug or drug-gene interactions currently exist.</td>
</tr>
</tbody>
</table>
“With YouScript, its no longer a trial and error proposition as to what drug and dose to prescribe; we can now do it more scientifically and with a much better outcome for the patient.”

Dr. J.E. Block
FACP Internal Medicine
Questions?

Training and Support

Matthew Berry

support@genelex.com

Toll Free- 1-877-431-4362

Direct: 206-826-1969

YouScript® Personalized Prescribing System