The Future of Precision Medicine

Harry Glorikian, Founder and Managing Partner

September 12th, 2013
Agenda

• Overview of Precision Medicine
• Implications
Healthcare is undergoing major changes across the world with increasing pressure to control costs while improving quality of care.

**GLOBAL HEALTHCARE* SPENDING (TRILLION USD)**

- **Unsustainable growth**
- Pressure from regulators and payers to improve efficiency

- Radical reforms expected globally to control healthcare costs
- Increased demand for innovative healthcare solutions that are cost effective and improve quality of care

Source: Scientia Analysis, Datamonitor, SG Cowen Therapeutics Outlook 2007, Frost & Sullivan, Bain & Company, Center for Medicare and Medicaid Services

* Includes hospital/physician/dental services, home health services, non durable medical products, prescription drugs, durable medical equipment, nursing care and continuing care retirement services, total other healthcare, residential and personal care expenditures, total admin and net cost of health insurance expenditures, public health activity, research, structures and equipment, functional foods/nutrition
The healthcare systems around the world are increasingly demanding “Precision Healthcare Solutions”, i.e. solutions that improve quality of care while demonstrating cost and comparative effectiveness.

- **“EVIDENCE BASED”**
  - Increased Accuracy And Precision (Quality)*
  - “One size fits all”
  - Low-moderate accuracy and precision*
  - Lack of cost and comparative effectiveness evidence

- **“TRIAL & ERROR BASED”**
  - “BROAD-BASED”
  - “TARGETED SUB-POPULATIONS”

* For therapeutics oriented business (Pharma/biotech and devices) this could mean improved efficacy and safety. For diagnostics and monitoring businesses, this could mean improved sensitivity and specificity.
What is Personalized Medicine?

**Personalized Medicine** is the custom design and implementation of health care for every individual.

It is a function of an increase in:

- **Upfront Information**
  - Novel tests provide data that can segment populations by into an ever increasing number of sub-categories

- **Targeted Therapy Development**
  - Therapeutic (or preventative) options are being developed that can specifically treat ever more specific sub-categories

*The Right Therapy for the Right Patient, at the Right Time, with the Right Dose*
The evolution towards Personalized Medicine is exemplified by the development of Companion Diagnostics (CDx) for Targeted Therapies

Companion Diagnostics (CDx) provide information about an individual patient that is essential for the safe and effective use of a corresponding Targeted Therapy.

Sources:
ScienAa Analysis

HER2 Tests/Kits:
DAKO, Abbott, Sigma, Invitrogen, Oncogene etc.
Vysis ALK Break Apart FISH Probe Kit

All materials copyrighted and cannot be used without explicit permission
The history of Rx-CDx approvals demonstrates the take-off of CDx in the past decade and the likelihood of a strong upward trend.

2010 appears to be an inflection point in Rx & CDx approvals.*

*A growing divide is seen between CDx and Rx approvals, as multiple tests for a single marker are released due to the competition among CDx developers.

Sources: Scientia analysis; FDA.gov

7 | Scientia Advisors | 2013 |
Providers see the potential for more targeted, more efficacious and safer therapy selection when using Rx-CDx pairs.

**Companion Diagnostics (CDx)**

Tests that provides clinically actionable information regarding use of a specific drug or class of drugs, usually through evaluation of a biomarker.

<table>
<thead>
<tr>
<th>Likelihood of Response</th>
<th>Likelihood of Adverse Event</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dako HercepTest™</td>
<td>Roche BCR/ABL</td>
</tr>
<tr>
<td>genzyme BCR/ABL</td>
<td>Nanosphere Verigene®</td>
</tr>
<tr>
<td>meningom trofile</td>
<td>Hologic Invader® UGT1A1</td>
</tr>
</tbody>
</table>

↑ Efficacy

Identify patients who are most likely to benefit from a therapeutic product.

Monitoring

Monitor change in disease characteristics for the purpose of adjusting treatment to achieve improved safety or effectiveness.

↑ Safety

Identify patients who are likely to be at increased risk for serious adverse reactions as a result of treatment with a particular therapeutic product.

Sources: Scientia Analysis, Company Websites
Payers see the potential for Rx-CDx to provide significant overall cost savings due to correct treatment of patients

<table>
<thead>
<tr>
<th>HER2</th>
<th>EGFR</th>
<th>BRAF</th>
<th>ALK</th>
<th>BCR-ABL</th>
</tr>
</thead>
<tbody>
<tr>
<td>$40,000</td>
<td>$40,000</td>
<td>$80,000</td>
<td>$80,000</td>
<td>$80,000</td>
</tr>
</tbody>
</table>

Savings from changed decision (US$)

Probability that diagnostic changes treatment decision

<table>
<thead>
<tr>
<th>HER2</th>
<th>EGFR</th>
<th>BRAF</th>
<th>ALK</th>
<th>BCR-ABL</th>
</tr>
</thead>
<tbody>
<tr>
<td>70%</td>
<td>85%</td>
<td>50%</td>
<td>5%</td>
<td>5%</td>
</tr>
</tbody>
</table>

Cost of test (US$)

<table>
<thead>
<tr>
<th>HER2</th>
<th>EGFR</th>
<th>BRAF</th>
<th>ALK</th>
<th>BCR-ABL</th>
</tr>
</thead>
<tbody>
<tr>
<td>$100</td>
<td>$1,000</td>
<td>$700</td>
<td>$1,000</td>
<td>$1,000</td>
</tr>
</tbody>
</table>

Cost savings for the payers?

Potential cost saved per test can be considered broadly as the cost of a round of associated treatment that would have been wasted on a patient who is a non-responder

Sources: Scientia analysis; Nature Reviews Drug Discovery 8, 279–286; Delaware BioScience Association; Roche
Why Now? Several factors are making precision healthcare all the more important

**Comparative Effectiveness (CE):**

*Pressure from payers and health technology assessment programs (HTA) to demonstrate their products are not only efficacious, but also effective relative to the standard of care*

**Convergence and Maturity of Measurement Technologies:**

*The rise of novel Dx has allowed smaller sub-populations of patients to be identified and administered specialized treatment right way*

**Electronic Health Records and Clinical Decision Support Systems:**

*The capturing and sorting of patient data enables better sub-categorization and treatment selection*

**Healthcare Reform:**

*In the US, realignment of incentives for healthcare service providers (hospitals, doctors, etc) is moving from fee for service to payment for outcomes, recognizing current alignment does not serve patients properly*

**Targeted Therapeutic Design:**

*Evolved cellular and molecular understanding of healthy and disease states has enabled the targeting of therapies to sub-categories of diseased (and pre-diseased) patients*

**IT/Internet, Computing, Connectivity:**

*Infrastructure investments and pervasive high technology enables unprecedented capture and management of medical information*

**Societal Drivers**

*Enablers*
Precision medicine is seeing a dramatic increase in the number of stakeholders actively engaging in promoting and furthering its use in the delivery of healthcare.

<table>
<thead>
<tr>
<th>PRECISION MEDICINE STAKEHOLDERS</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>RESEARCH TOOLS</strong></td>
</tr>
<tr>
<td>Genomics companies</td>
</tr>
<tr>
<td>Bioinformatics companies</td>
</tr>
<tr>
<td><strong>PRODUCT DEVELOPMENT</strong></td>
</tr>
<tr>
<td>Pharma companies</td>
</tr>
<tr>
<td>Medical device companies</td>
</tr>
<tr>
<td>Diagnostic companies</td>
</tr>
<tr>
<td><strong>REG. APPROVAL &amp; REIMBURSEMENT</strong></td>
</tr>
<tr>
<td>Regulators</td>
</tr>
<tr>
<td>Payors</td>
</tr>
<tr>
<td>Pharmacy benefit managers</td>
</tr>
<tr>
<td><strong>HEALTHCARE DELIVERY</strong></td>
</tr>
<tr>
<td>Hospitals</td>
</tr>
<tr>
<td>Physicians</td>
</tr>
<tr>
<td>Patients</td>
</tr>
</tbody>
</table>
These stakeholders are now being inundated with an abundance of information and this has created the need for systems capable of producing the “right information at the right time”

**Precision Healthcare:**
The systematic use of information to optimize the individual patient’s medical care

Notes: EHR=Electronic health records, LIMS=laboratory information management systems, PACS=picture archiving and communication systems, PBM=pharmacy benefits manager, PIMS=pharmacy information management systems, RCM=revenue cycle management (e.g., billing)

1Surgeons, radiation oncologists, etc.;
2Includes academic genetic databases;
3Hematologist, oncologist, urologist, palliative care specialist, etc.
In response, healthcare solution providers are increasingly launching novel solutions that indicate a move towards precision healthcare, although we are in the early stages.

### TRADITIONAL VERSUS PRECISION HEALTHCARE EXAMPLES

#### Traditional Healthcare

- **Pharma/ Biotech**
  - Chemotherapy (e.g., cisplatin)
  - Non-small cell lung cancer
  - Efficacy: ~15-35%
  - Safety: Severe adverse reactions
  - Cost/ Comparative effectiveness: Moderate\(^1\)

- **Medical Devices**
  - Traditional colposcopy
  - Cervical cancer
  - Efficacy: Manually and subjectively assess the aceto-whitening process in cervical cancer
  - Sensitivity: 49%-55%
  - Cost/ Comparative effectiveness: Moderate\(^1\)

- **Diagnostics**
  - PSA test
  - Prostate cancer
  - Sensitivity: 40-80%; Specificity: 80-94%
  - Cost/ Comparative effectiveness: Low
  - Impact on therapy selection: Low-Moderate*\(^\)

#### Precision Healthcare

- **Pharma/ Biotech**
  - Xalkori (Crizotinib)/ Pfizer
  - Non-small cell lung cancer
  - Efficacy: ~80%
  - Safety: Mild to Moderate adverse reactions
  - Cost/ Comparative effectiveness: High\(^2\) based on advanced ALK+ NSCLC efficacy

- **Medical Devices**
  - DySIS colposcopy/ DySIS Medical
  - Cervical cancer
  - Efficacy: Objective, dynamic mapping of aceto-whitening effect in cervical cancer
  - Sensitivity: 79%-88%
  - Cost/ Comparative effectiveness: High\(^2\); NICE recommended device

- **Diagnostics**
  - Oncotype DX/ Genomic Health
  - Breast cancer
  - Sensitivity/ Specificity: >90%^\(^\)
  - Cost/ Comparative effectiveness: High for Oncotype Dx for breast cancer
  - **Impact on therapy selection: High**
    (Distinguish aggressive breast cancer)

---

1: Current stand of care 2. Ability to cause a paradigm shift 3. Controversy among organization

* Disagreement among United States Preventive Task Force (USPTF) and American Urology Association(AUA)
^ real time PCR

Source: Scientia Analysis, company news release, publications, research papers
Business models for diagnostics are evolving as stakeholders find new ways to bring value to healthcare

**Players will require new business models to participate across the disease care paradigm**

- Business models for precision medicine are likely to evolve as players look to add value to core products through new products, services, and information offerings that span care cycles.
- Pharma/Biotech business models are extending beyond companion diagnostics and adding novel information management services (e.g., Sanofi expansion into glucose monitoring).
Precision medicine approaches impacts the pharmaceutical development process at almost every stage of a drug’s lifespan

Precision medicine approaches have the potential to de-risk development projects, shorten development timeframes, accelerate new product adoption, and generate additional revenue streams

Sources: Scientia Analysis
15 | Scientia Advisors | 2013 |
Several collaborations have recently been established where diagnostics are used to aid in the discovery process and identify disease-specific targets.

- **Foundation Medicine and AstraZeneca announce genomic profiling collaboration (Nov 2012)**
  - A multi-year collaboration to identify alterations found in cancer-related tumor genes that may predict a person’s response or resistance to targeted medicines
  - Working with Foundation Medicine to reveal these genomic alterations may help AstraZeneca to research new medicines for people with cancer

- **GlaskoSmithKline enters into companion program with diaDexus for heart disease drug**
  - LpPLA2 immunoassay, developed by diaDexus and approved for predicting the risk of heart disease and ischemic stroke
  - GlaxoSmithKline is developing a small molecule designed to inhibit this enzyme, thus reducing the risk of adverse cardiovascular events

Sources: Scientia Analysis; Company literature and press releases

All materials copyrighted and can not be used without explicit permission
...with additional collaborations occurring more frequently

- **Abbott and Merck Collaborate to Develop Companion Diagnostic Test for Investigational Cancer Therapy**
  (March 2012)
  - Collaboration to evaluate the use of a FISH-based companion diagnostic test to aid in the development of a Merck investigational cancer therapy
  - Abbott will develop a test to identify deletions of the TP53 gene in cancer patients and evaluated in clinical trials to help identify patients more likely to respond favorably to Merck's investigational cancer therapy

- **Foundation Medicine, Novartis Ink New Deal for Clinical Oncology Programs**
  (June 2012)
  - The use of Foundation Medicine's molecular information platform will be used across many of Novartis' Phase 1 and Phase 2 oncology clinical programs
  - Tumor genomic profiling has become an important part of Novartis' clinical trials

Sources: Scientia Analysis; Company literature and press releases
Several other partnerships are being established between pharma and diagnostic companies for companion diagnostics initiatives

- **MDxHealth**, Merck KGaA Partner to Develop Companion Dx for Glioblastoma Drug (July 2012)
- **Eli Lilly** collaborates with PrimeraDx for Companion Diagnostics Development (June 2012)
- **Ventana** to Collaborate with Bayer on Companion Diagnostic Test for new cancer biological cancer therapy (Jan 2012)
- **Takeda** and Zinfandel Pharmaceuticals Sign Licensing Agreement for Alzheimer’s Disease Biomarker in Combination with Pioglitazone (Jan 2011)

Sources: Scientia Analysis; Company literature and press releases
The number of companion diagnostic deals between pharmaceutical companies & diagnostic manufacturers is on the rise and this will have an impact on the healthcare supply chain

<table>
<thead>
<tr>
<th>NUMBER OF COMPANION DIAGNOSTIC DEALS SINCE 2009</th>
</tr>
</thead>
<tbody>
<tr>
<td>2009 H1</td>
</tr>
<tr>
<td>5</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>IMPACTED HEALTHCARE SUPPLY CHAIN STAKEHOLDERS</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Hospitals</td>
</tr>
<tr>
<td>• Wholesale Distributors</td>
</tr>
<tr>
<td>• Group Purchasing Organizations</td>
</tr>
<tr>
<td>• Manufacturers</td>
</tr>
<tr>
<td>• Pharmacies</td>
</tr>
<tr>
<td>• Payors/PBMs</td>
</tr>
<tr>
<td>• Physicians</td>
</tr>
<tr>
<td>• Patients</td>
</tr>
</tbody>
</table>

Sources: Scientia analysis; Seeking Alpha, Coming Wave of Companion Diagnostics July 26, 2012
Agenda

• Overview of Precision Medicine
• Implications
Historically, physicians determined which therapy would be the best option to treat a patient’s illness in the traditional healthcare supply chain model.
However, with the rise of personalized medicine, diagnostics will be introduced into the healthcare supply chain and they will determine whether or not a therapy is appropriate for a patient (1 of 2)
However, with the rise of personalized medicine, diagnostics will be introduced into the healthcare supply chain and they will determine whether or not a therapy is appropriate for a patient (2 of 2)

**EXAMPLE PM CLINICAL DECISION SUPPORT RULE**

*Partners Healthcare’s EHR contains a PM CDSS component which will remind a physician of a contraindication between TARCEVA and certain genetic mutations when the physician tries to prescribe this drug to a patient with the mutation*

**KEY TAKEAWAYS**

- By reminding physicians of “easy to learn, easy to forget” information, CDSS tools can decrease variation in the use of various tests and interventions
- A CDSS will also be able to suggest options of published or guideline suggested therapeutic options allowing physicians to stay on top of the latest research and guideline changes

Sources: Scientia analysis, ScientiaNet, Partners’ Healthcare

23 | Scientia Advisors | 2013 |
The use of diagnostics such as Genomic Health’s Oncotype is an example of how the treatment paradigm for early stage breast cancer is shifting away from most patients receiving chemotherapy to a more targeted approach.

Oncotype DX Penetration/Chemotherapy Usage

Sources: Scientia analysis; Genomic Health OncoReport ICI T2 2009
Due to the progression of personalized medicine, what will be the implications for healthcare supply chain stakeholders?

**PRECISION HEALTHCARE SUPPLY CHAIN MODEL**

- **Patient**
- **Hospital or Physician**
- **Diagnosis**
- **Group Purchasing Organization**
- **Manufacturer**
- **Wholesale Distributor**
- **Therapy? Yes or No**
- **Retail/Hosp Pharmacy**
- **Payor/PBM**
- **Employer**

**KEY:**
- Stakeholder
- Decision

**Decision Tree:**
- **No**
  - Manufacturer
  - Wholesale Distributor
- **Yes**
  - Retail/Hosp Pharmacy
  - Payor/PBM
  - Employer
Precision Healthcare Implications for Hospitals

**MASS GENERAL starts Personalized Cancer Program**

*Genome Web March 6, 2009*
MGH, a member of Partners Healthcare, is one of the premier hospitals that are utilizing knowledge management initiatives for data stored in EMR and CDSS to enable better outcomes through the adoption of personalized medicine.

**IMPLICATIONS TO PERSONALIZED MEDICINE**

- This portal has revolutionary potential to translate the promise of personalized medicine into reality.
- The portal when expanded into an enterprise wide application across several labs/hospitals can be used to educate physicians, increase awareness of emerging high value MDx tests and accelerate adoption of these tests.
- IVD/MDx companies can use this portal to streamline their internal biomarker mining efforts to identify biomarkers with most clinical validity and utility for physician.

Sources: Scientia analysis, the Harvard Medical School Partners Healthcare Center for Genetics and Genomics

| 27 | Scientia Advisors | 2013 |

All materials copyrighted and can not be used without explicit permission.
Other members of Partners Healthcare, Dana-Farber and Brigham & Women's Hospital, have joined to launch PROFILE for genetic research, one of the most extensive national level research projects in cancer genomics yet.

Dana-Farber, Brigham and Women's launch PROFILE, a large-scale research program to scan tumors for mutations, establish extensive genomic database (Oct 2011)

• **Goal of PROFILE**
  » To leverage access to patients’ tumor samples and genetic testing tools to scan tumor tissue for hundreds of gene mutations linked to cancer

• **Advantages of PROFILE**
  » Enable clinicians to treat more cancers with mutation-specific targeted therapies in the future
  » Expand with the discovery of additional cancer-related mutations
  » Develop more advanced screening technologies
  » Patient eligibility for clinical trials
So traditional healthcare supply chain stakeholders have to ask themselves, not if they will be impacted by the growth of precision medicine but how they have prepared to be impacted.
YouScript®
Applying Pharmacogenetics in Pharmacy Practice

• Brian Hocum, PharmD
• Personalized Prescribing Clinical Pharmacist
• February 25th, 2014
Disclosure

• Personalized Prescribing Clinical Pharmacist, Genelex Corporation
• Adjunct Faculty Member Washington State University College of Pharmacy
DNA and adverse drug events?

• Michael died from a seizure caused by chronic fluoxetine (Prozac®) overdose
• A common genetic defect made him a CYP2D6 poor metabolizer
• CYP2D6 is the major metabolizing pathway for fluoxetine
• His doctor would have changed Michael’s medication or dose had he known

Sallee et al.
Without genetics

Advertised dose

With genetics

Personalized dose
Cytochrome P450’s Metabolize Drugs

Major drug metabolizers: 2D6, 2C9, 2C19, 3A4/5

Minor drug metabolizers: 2B6, 1A2, 2A6, 2C8, 2E1

Location:
- Hepatocytes
- Intestinal lumen
- Other sites: blood brain barrier, brain, placenta, etc.
Drug metabolism phenotypes

- **Poor Metabolizer (PM)**
  - CYP2D6: 5.1%
  - CYP2C9: 3.4%
  - CYP2C19: 2.3%*

- **Intermediate Metabolizer (IM)**
  - CYP2D6: 36%
  - CYP2C9: 28.2%
  - CYP2C19: 25.4%*
  - CYP3A4: 9.4%

- **Normal Metabolizer (NM)**
  - <15% normal for all three enzymes

- **Ultra Rapid Metabolizer (UM)**
  - CYP2D6: 3.5%
  - CYP2C9: N/A
  - CYP2C19: 27.7%
  - CYP3A5: 20.8%*
CYP2D6 phenotype effects on nortriptyline pharmacokinetics

The YouScript® difference

Drug Interaction Software

Drug A vs. Drug B
Drug B vs. Drug C
Drug C vs. Drug A

- 1:1 drug-drug interactions

Multi-drug interactions
Drug-gene interactions
Multi-drug-gene interactions
YouScript® software is the most advanced medication management software available

Most comprehensive drug-gene and drug-drug interaction software
- 2,500 drugs & metabolites
- 15,000 PubMed links & notes
- Data updated daily; published monthly

Incorporates herbals, over-the-counter and recreational drugs

Genotype-based drug and dosage recommendations

Only solution to factor multi-drug and cumulative effects
## Drug-gene interaction

<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>metoprolol</td>
<td>76-200%</td>
<td></td>
<td>CYP2D6 Intermediate Metabolizer</td>
</tr>
</tbody>
</table>
Cumulative drug-drug-gene interaction

<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>metoprolol</td>
<td>≥200%</td>
<td>Some</td>
<td>CYP2D6 Intermediate Metabolizer, paroxetine</td>
</tr>
<tr>
<td></td>
<td>paroxetinene</td>
<td>26-75%</td>
<td></td>
<td>CYP2D6 Intermediate Metabolizer</td>
</tr>
</tbody>
</table>
**Alternatives selection**

![Interaction Report](image)

**Patient Factors**

<table>
<thead>
<tr>
<th>CYP2D6 Poor Metabolizer</th>
<th>Known</th>
<th>Potential</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>2</td>
<td>2</td>
</tr>
</tbody>
</table>

**Codeine**

- **Notes**
  - Metabolism
  - Select Drug Class

**Causative Agents**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Prodrug</th>
<th>Clinical Effect</th>
<th>CYP2D6 Poor Metabolizer</th>
</tr>
</thead>
<tbody>
<tr>
<td>codeine</td>
<td>Prodrug</td>
<td>Major</td>
<td>CYP2D6 Poor Metabolizer</td>
</tr>
<tr>
<td>metabolite morphine</td>
<td>81-100%</td>
<td>Major</td>
<td>CYP2D6 Poor Metabolizer</td>
</tr>
</tbody>
</table>

**Analgesics - Opioid Agonist**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Rank</th>
</tr>
</thead>
<tbody>
<tr>
<td>morphine *</td>
<td>1</td>
</tr>
<tr>
<td>hydromorphone *</td>
<td>1</td>
</tr>
<tr>
<td>oxymorphone *</td>
<td>1</td>
</tr>
</tbody>
</table>
YouScript® partnered with a large health system for a pilot study to validate predictive technology.

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

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

<table>
<thead>
<tr>
<th></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>
Validation study results

Total savings to 700,000 member health plan estimated at $25,000,000 to $57,000,000 per year

In Israel $4,000 per diem

<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>

In Israel $4,000 per diem
YouScript® Clinical Study
Preliminary Data

Study background:
- 2 arms dividing a 700,000 patient, ~200 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>Vs. Control Arm</th>
</tr>
</thead>
<tbody>
<tr>
<td>Imaging Procedures</td>
</tr>
<tr>
<td>Hospitalizations</td>
</tr>
<tr>
<td>DRT Procedures</td>
</tr>
</tbody>
</table>

- MDs changed prescribing habits in 71% 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
Clinical relevance

- Active patient sample from Dr. David Durham, a neuropsychiatrist in New Mexico
- Clinical Asst. Professor of Psychiatry, Un. of New Mexico School of Medicine
- Current Chair, Board of Governors, The American College of Neuropsychiatry & Neurocognitive Medicine
- Total patients evaluated = 296
- Testing revealed 101 previously unknown significant interaction risks in 82 (27.7%) of patients
YouScript® testing process

- Doctor orders the test
- Pharmacogenetics is fully covered by Medicare and usually by private insurance
- Cheek swab
- Send the swab and a medication list to Genelex in prepaid mailer
- Information is loaded into the YouScript® interaction software. Pharmacists review and provide a summary report of interactions
Confusion – Alzheimer’s like symptoms

- Chlor-Trimeton® (chlorpheniramine)
- Major CYP2D6 substrate
- CYP2D6 Poor Metabolizer
- Study shows 200% increase in CYP2D6 Poor Metabolizers (2002 Blackwell Science Ltd Br J Clin Pharmacol, 53, 519–525)
- Advised pt to stop chlorpheniramine and discussed alternative options
- 3 days later she called to say she had been in a drug induced haze and could now think clearly again
<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>chlorpheniramine</td>
<td>&gt;200% ↑</td>
<td>Major</td>
<td>65 years or older, CYP2D6 Poor Metabolizer</td>
</tr>
</tbody>
</table>
THANK YOU

Brian Hocum, PharmD
Personalized Prescribing Clinical Pharmacist
bhocum@genelex.com
Recommended reading

- Clinical Manual of Drug Interaction Principles for Medical Practice
  - Gary H. Wynn, M.D.
  - Jessica R. Oesterheld, M.D.
  - Kelly L. Cozza, M.D.
  - Scott C. Armstrong, M.D.

- Drug Interactions Casebook
  - The Cytochrome P450 System and Beyond
  - Neil B. Sandson, M.D.