Building an Integrated Precision Medicine Infrastructure
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Speaker Introduction

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Conflict of Interest

John Deeken, MD
Don Rule, MBA

Have no real or apparent conflicts of interest to report.
Agenda

• Overview of Inova Health
• Review of pharmacogenomics (PGx)
• Inova’s PGx Initiative
• Challenges with genomic data
• Integrating PGx into clinical systems
• Technology infrastructure and stages of implementation
• Discussion
Learning Objectives

• Describe the implementation of pharmacogenomics (PGx) at the point of care to guide treatment decisions, achieve superior outcomes, and improve costs

• Identify strategies for leveraging technology to help capture, interpret, and use genomic data for personalized medicine

• Evaluate the technical and logistical challenges of integrating genomic data into clinical workflows to inform patient care
An Introduction of How Benefits Were Realized for the Value of Health IT

Use of pharmacogenomics-based IT solutions can help address numerous challenges faced in healthcare, including all value steps:

• Satisfaction
• Treatment/Clinical
• Electronic Secure Data
• Population Management
• Savings
About the Inova Health System

Not-for-profit healthcare system serving more than 2M people each year

Comprehensive network of hospitals, outpatient services and facilities, primary and specialty care practices, and health and wellness initiatives.

Inova’s goal is to be a global leader in the science of genomics and the new era of personalized health.

Inova By the Numbers

**KEY STATISTICS**

- Licensed Beds: 1,753
- Inpatient Admissions: 96,167
- Births: 18,477
- ER Visits: 399,692
- Home Care Visits: 95,599
- Nurses: 4,384
- Affiliated Physicians: 5,186
- Employees: ~15,000

**KEY FINANCIALS**

- Revenue: $3 billion
- S&P’s Rating: AA+

Inova By the Numbers
About the Inova Translational Medicine Institute

Goal: Research the integration of genomic information into the practice of medicine

- Applies genomic and clinical information to develop personalized healthcare
- Founded in 2011 with a team of 100 scientists, physicians, nurses, genetic counselors, and laboratory technicians
- Conducts ongoing studies to identify individual predisposition to disease, treatment, and prevention
- CLIA-certified clinical genomics laboratory performing high-complexity molecular testing
Why Pharmacogenomics?

All patients with same diagnosis

Responders and Patients not Experiencing Severe Toxicity

Non-Responders and Patients Experiencing Severe Toxicity
Personalized Medicines on the Rise

In which of the following areas are you conducting precision medicine? (please select all that apply)

- Cancer: 79.5%
- Neurology: 38.5%
- Prenatal screening: 30.8%
- Cardiology: 28.2%
- Unsure: 10.3%
- Epidemiology: 10.3%
- Other: 10.3%

Source: HIMSS Analytics 2016 Essentials Brief
CYP2D6 Enzyme

CYP2D6 is an enzyme that metabolizes many commonly prescribed medications:

- codeine, tramadol, oxycodone, hydrocodone
- amitriptyline, nortriptyline, desipramine, doxepin
- paroxetine, fluvoxamine
- haloperidol, risperidone
- metoprolol

Metabolism by CYP2D6 can either **ACTIVATE** or **INACTIVATE** a drug:

- codeine is a **prodrug** that will be **activated** to morphine
- risperidone, an **active drug**, will be inactivated by CYP2D6 to an inactive metabolite
At a regional hospital in northern Ontario, Canada, a 4-year-old (27.6 kg) First Nations’ boy underwent adenotonsillectomy (AT) - Prescribed liquid codeine at 8 mg per dose.

His parents reported him to be sedated and lethargic the day after hospital discharge.

After a total of 4 codeine doses, he was brought to hospital without vital signs.

His postmortem morphine serum concentration was 17.6 ng/mL (therapeutic morphine range 4.5 ± 2.1 ng/mL) and toxicology screen revealed a blood codeine level in the expected range.

Genotyping revealed a gene duplication and a CYP2D6 UM phenotype (CYP2D6 *1/*2AxN). Postmortem analysis revealed the cause of death to be bilateral acute bronchopneumonia.

The Lifetime Value of PGx (Pharmacogenomics) can vary across different life stages, with specific considerations for both adverse event burden and potential conditions. Here’s a breakdown:

<table>
<thead>
<tr>
<th>Infant</th>
<th>Child</th>
<th>Adolescent</th>
<th>Adult</th>
<th>Elderly</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lactation</td>
<td>Pain</td>
<td>Contraception</td>
<td>Polypharmacy</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Psychiatry</td>
<td>Cardiovascular</td>
<td>Cardiovascular</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Addiction</td>
<td>Diabetes</td>
<td>Diabetes</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Transplantation</td>
<td>Gastroenterology</td>
<td>Gastroenterology</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Cancer</td>
<td>Psychiatry</td>
<td>Psychiatry</td>
</tr>
<tr>
<td>Infections</td>
<td>Transplantation</td>
<td>Addiction</td>
<td>Addiction</td>
<td>Addiction</td>
</tr>
<tr>
<td>Infections</td>
<td>Transplantation</td>
<td>Transplantation</td>
<td>Cancer</td>
<td>Cancer</td>
</tr>
<tr>
<td>Infections</td>
<td>Transplantation</td>
<td>Autoimmune</td>
<td>Diseases</td>
<td>Diseases</td>
</tr>
<tr>
<td>Infections</td>
<td>Transplantation</td>
<td>Surgery</td>
<td></td>
<td>Surgery</td>
</tr>
</tbody>
</table>

Drug Adverse Event Burden
PGx testing may indicate how you will respond to certain prescription medications throughout your life.

PGx testing helps guide your healthcare providers to better medication choices and doses for you.

PGx testing provides information to more proactively manage your health now and in the future.
Part of Standard Package of Care for Newborns

OB Office → Hospital → Inova Genomics Laboratory → Return of Results

1. **OB Education**
   - Pre-Admit Patient Education (Marketing Materials)
   - Admit to Hospital

2. **L&D / ER**
   - Test Promotion
   - In-person Education & Counseling
     - Patient Authorization
     - White Board Check List
     - Order in Epic
     - Sample Collection & Labeling
   - White Board Communication
   - Sample Processing & Report Creation (IGL)
   - Sample Transport to Inova Genomics Laboratory (IGL)

3. **Division of Medical Genomics**
   - Report Review by Division of Medical Genomics
     - Best Practice Advisories (BPAs) in EHR

4. **Inova Genomics Laboratory**
   - Result Review & Sign-off (Inova Genomics Laboratory)

5. **Parents Share Results with MD**

6. **Return of Results to Ordering MD & Individual**

- **On Demand Genetic Counseling for MDs & Individuals**
Basic (for all ages)

1. Fill out pre-registration form & make an appointment
2. Talk to a genetic counselor
3. Complete forms
4. Get tested (painless cheek swab)
5. Sample processing in Inova Genomics Laboratory
6. Receive PGx results
7. Share test results with physician
8. Ask our genetic counselors
**PGx Program**

Postnatally, both **age and genotype** are determinant in predicting enzyme activity and the metabolizer status

<table>
<thead>
<tr>
<th>GENE</th>
<th>POST-NATAL (weeks)</th>
<th>FIRST / SECOND YEAR (months)</th>
<th>CHILDHOOD ADULTHOOD</th>
</tr>
</thead>
<tbody>
<tr>
<td>CYP2D6</td>
<td>Increases within 2 weeks</td>
<td>Constant</td>
<td>Constant (Except pregnancy when it increases)</td>
</tr>
<tr>
<td>CYP2C19</td>
<td>Constant</td>
<td>Modest increase or Constant</td>
<td>Constant</td>
</tr>
<tr>
<td>TPMT</td>
<td>Constant</td>
<td>Constant</td>
<td>Constant</td>
</tr>
<tr>
<td>CYP2C9</td>
<td>Increases</td>
<td>Increases</td>
<td>Increases until post-puberty</td>
</tr>
<tr>
<td>CYP2C19</td>
<td>Constant</td>
<td>Modest increase or Constant</td>
<td>Constant</td>
</tr>
<tr>
<td>SLCO1B1</td>
<td>Increases (liver)</td>
<td>Increases (liver-6y)</td>
<td>Liver: Constant from 7y</td>
</tr>
</tbody>
</table>

## Potentially Impacted Medications

<table>
<thead>
<tr>
<th>CLASS</th>
<th>DRUG*</th>
<th>PHARMACOGENETIC RESULTS</th>
<th>INTERACTING DRUGS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antiaddictives</td>
<td>Bupropion (Wellbutrin, Zyban, Aplenzin, Contrave)</td>
<td>![Green Check]</td>
<td>![Aripiprazole]</td>
</tr>
<tr>
<td></td>
<td>Amphetamine (Adderall)</td>
<td>![Green Check]</td>
<td>![Fluoxetine] ![Strattera]</td>
</tr>
<tr>
<td></td>
<td>Atomoxetine (Strattera)</td>
<td>![Green Check]</td>
<td>![Fluoxetine]</td>
</tr>
<tr>
<td></td>
<td>Clonidine (Kapvay)</td>
<td>![Green Check]</td>
<td>![Fluoxetine]</td>
</tr>
<tr>
<td>Anti-ADHD Agents</td>
<td>Dextroamphetamine (Dexedrine)</td>
<td>![Green Check]</td>
<td>![Fluoxetine]</td>
</tr>
<tr>
<td></td>
<td>Guanfacine (Intuniv)</td>
<td>![Green Check]</td>
<td>![Fluoxetine]</td>
</tr>
<tr>
<td></td>
<td>Lisdexamfetamine (Vyvanse)</td>
<td>![Green Check]</td>
<td>![Fluoxetine]</td>
</tr>
<tr>
<td></td>
<td>Methylphenidate (Ritalin)</td>
<td>![Green Check]</td>
<td>![Fluoxetine]</td>
</tr>
</tbody>
</table>

Source: Translational Software PGx Knowledge Base
SUMMARY OF RESULTS

RED CATEGORY
Based upon the patient's results, the medication has potentially reduced efficacy or increased toxicity. Medication change or dose adjustment with increased monitoring is highly recommended with this drug.

YELLOW CATEGORY
Based upon the patient's results, the medication has potentially reduced efficacy or increased toxicity. Dose adjustment with increased monitoring may be needed with this drug.

GREEN CATEGORY
Based upon the patient's results, the medication can be prescribed according to standard regimens.
Education is Key

• Genomics experts at the bedside postpartum to educate families

• Videos, online content, FAQs for patients and physicians

• Genetic counselors available for questions both before and after testing

• On-going education for pediatricians and other physicians who interact with patients
Technical Background
### Complexities of PGx Rules

<table>
<thead>
<tr>
<th>Type</th>
<th>Gene(s)</th>
<th>Condition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Single SNP</td>
<td>OPRM1 118A&gt;G</td>
<td>Opioid Efficacy</td>
</tr>
<tr>
<td>Multi-SNP</td>
<td>MTHFR 1298C &amp; 677T</td>
<td>Hyperhomocysteinemia</td>
</tr>
<tr>
<td>Multi-Gene</td>
<td>Factor II 20210A &amp; Factor V Leiden 1691A</td>
<td>Thrombosis Risk</td>
</tr>
<tr>
<td>Multi-Allele</td>
<td>rs16947 + rs3892097 + rs1065852</td>
<td>CYP2D6 Genotype</td>
</tr>
<tr>
<td>Mixed</td>
<td>CYP2C9 Phenotype &amp; VKORC1 -1639G&gt;A</td>
<td>Warfarin Sensitivity</td>
</tr>
</tbody>
</table>

Source: The Pharmacogenetics Knowledge Base (PharmGKB; http://www.pharmgkb.org/)
Developing Rules for PGx

• New content roughly quarterly
• Updates based upon both genetics and pharmacology
• Often need to reconcile disparate sources
## Communicating With Developers

<table>
<thead>
<tr>
<th>Case</th>
<th>C0</th>
<th>C1</th>
<th>C2+</th>
<th>R117H</th>
<th>5T</th>
<th>7T</th>
<th>9T</th>
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<tbody>
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<td>CFTR05</td>
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<td>TRUE</td>
</tr>
</tbody>
</table>
## Validating in a Rapidly Evolving Field

### Internet Model

<table>
<thead>
<tr>
<th>Application</th>
<th>Presentation</th>
<th>Session</th>
<th>Transport</th>
<th>Network</th>
<th>Data Link</th>
<th>Physical</th>
</tr>
</thead>
</table>

### Laboratory Model

<table>
<thead>
<tr>
<th>Report</th>
<th>KB Mashup</th>
<th>Phenotyping</th>
<th>Typing</th>
<th>Variant Calls</th>
<th>VCF</th>
<th>Assembly</th>
</tr>
</thead>
</table>

Source: OSI Reference Model
What we want to tell doctors
Consider alternatives to Codeine
#CYP2D6RapidMetabolizer
What Works for Reporting

- Genetic test results are useless – understanding the implications quickly is priceless
- Tailor information to the audience – e.g. implications for the cardiologist, psychiatrist, or neurologist
- Avoid gratuitous graphics
- Make sure it still works when you fax it
- Alerts are always about the consequences, not the genetic result
- Sometimes what was NOT tested is important
Easy to Misinterpret Complex Results

<table>
<thead>
<tr>
<th>Gene</th>
<th>Genotype</th>
<th>Phenotype</th>
</tr>
</thead>
<tbody>
<tr>
<td>VKORC1</td>
<td>-1639&gt;G/A G/A</td>
<td>Intermediate Sensitivity</td>
</tr>
<tr>
<td>CYP2C9</td>
<td>*1/*1</td>
<td>Normal Metabolizer</td>
</tr>
</tbody>
</table>

Warfarin Label Recommendation: 5-7 mg (Standard Dose)
Implementation Phasing

- Phase I – Message Handling
- Phase II – Alerting
- Phase III – Integration into the clinical workflow
Phase I Physical Configuration

- Patient Demographics (HL7)
- Reports & Genotypes (HL7)
- Sequencer
- Laboratory Information System
- Reports & Genotypes (HL7)
- Test Results (VCF)
- Clinical Decision Support
Where Industry Needs to Go

Reactive

Preemptive

Static

Dynamic

Just-in-Chart

Portable

Standalone

Integrated
PGx in the Clinical Workflow

• Integrated in the workflow
  – Integral to care plans
  – Prescribing CPOE alerts of potential genetic issues
  – Test order CPOE provides guidance for correct test and laboratory
  – Genetic risk surfaced during reconciliation

• On receipt of test results, alerts notify clinicians of relevant findings

• Physician (or NP or pharmacist) can find viable medications that maximize efficacy and minimize risks of gene-drug or drug-drug issues

• Future medication decisions utilize test results
Clinical Genomics Standards

CPOE

Order

Result

LIMS

Test Data

Report & Data

CDSS

Screening Request

Screening Response

PGx API
HL7V2 “Lite” for PGx

- Explicit recognition of multi-gene combinations
- Direct relationship between genetic test result, drugs, and guidance
- Reduces, but does not eliminate the burden of rules development on the recipient

Note: V2 and FHIR will be used with the same data so representation MUST be semantically equivalent
FHIR API for CDS

• REST based API
• Built on common resources (patient, medication, observation) with extensions
• Common calls
  – Is this a PGx drug and what test is relevant (i.e. which gene)
  – What is this patient’s risk of a PGx issue
  – Order a test
  – Screen a patient’s med list and genetic profile for issues
Application Level Interfaces

CDSS

SMART

FHIR®

PGx API
Many specialties are involved (lab, clinical, pharmacy, IT), important to have a solid process for resolving requirements.

It is impossible to predict all requirements a priori so plan to prototype and iterate (“build one to throw away”).

Big data is sexy but what is clinically relevant is small and messy.

ClinVar Stats

- 135,430 Records
- 121,834 With Interpretations
- 70,816 With Assertions
- 23 With Practice Guidelines

A Summary of How Benefits Were Realized for the Value of Health IT

- **Satisfaction**: A pharmacogenomics program improves satisfaction by giving physicians the tools needed to deliver the safest and most effective therapies for precision medicine.

- **Treatment**: Gene-based assessments of patients allow clinicians to launch targeted, personalized treatment interventions for better health outcomes.

- **Electronic Data**: Secure integration of genetic data into the EHR or e-prescribing system provides interactive genomic decision support within the existing clinical workflow.

- **Population Management**: Sub-optimal health outcomes can be reduced through implementation of pharmacogenomic testing.

- **Savings**: Potential for significant savings in treatment costs by getting the most effective therapy to the patient at the right time.
• Rapid technological evolution is making precision medicine attainable in clinical settings
• Use of PGx can prevent adverse drug reactions, reduce costs, and improve satisfaction along the continuum of care
• The right IT infrastructure will provide timely and accessible insights as part of routine workflows
• Inova successfully implemented a PGx program at scale and participation and satisfaction is high
Questions

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