Toward effective knowledge delivery: a proposed framework

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What is **effective** delivery of (pharmaco)(genomic) knowledge?

### Genomics data

- **Patient A**
  - CYP2C19 *1/*1 (normal)
  - **IF prescribed clopidogrel** THEN prescribe clopidogrel at standard dose

- **Patient B**
  - CYP2C19 *1/*2 (intermediate metabolizer)
  - **IF prescribed clopidogrel** THEN suggest alternative treatment (e.g., prasugrel, ticagrelor)

- **Patient C**
  - CYP2C19 *2/*2 (poor metabolizer)
  - **IF prescribed clopidogrel** THEN suggest alternative treatment (e.g., prasugrel, ticagrelor)

**Effective communication**

- Standard dose OK for clopidogrel (No Message)
- "Alternative therapies to clopidogrel recommended"
- No Message

**NOTE:** The FDA does not offer any specific guidance on drug dosing in CYP2C19 variant allele carriers
Effective communication of genomics knowledge is challenging

– Scarcity of genomics education in medical school curricula (*SACGHS Education Report 2011*)

– Physicians perceive existing guidance to be inadequate (*Barrett JS et al. BMC Pediatr 2011, Klitzman et al. J Genet Couns 2013*)
Efforts to improve the effective communication of genomic knowledge

- Information resource creation
- Guidelines for using genetic/genomic test results

- Once accessible, we need to implement approaches to delivery these resources effectively
EHR-linked decision support tools to deliver genomic knowledge

Electronic Health Record (EHR)

Education & Guidance

- Making appropriate treatment decisions
- Interpretation of test results
- Discussion points for explaining test results to patients
- Drawing accurate conclusions

Alternative therapies to clopidogrel recommended for CYP2C19 intermediate metabolizers

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Main channels for clinical decision support (CDS)

• Consulting service
  – Librarian consultation (McGowan et al., 2010, Health Info Libr J), Pharmacy consultation (Donovan et al., 2006, J Thromb Thrombolysis; Zaidan et al., 2011, J Multidiscip Healthc)

• External online resources
  – UpToDate (www.uptodate.com; Sayyah Ensan et al., 2011, PLoS One), BMJ Clinical Evidence (www.clinicalevidence.bmj.com; Buchan et al., 2009, Implement Sci), Cochrane Reviews (www.cochrane.org/cochrane-reviews; Cipriani et al., 2011, Epidemiol Psychiatr Sci), MD on Tap (Demner-Fushman et al., 2006, AMIA Annu Symp Proc)
  – For genomics, what? (GeneTests, PharmGKB?, FDA?, CPIC?, EGAPP?)

• Integrated with electronic health records (EHRs)
  – For genomics, what? (OpenInfobutton, HL7 Clinical Genomics)
Different EHR clinical decision support design configurations can be applied to present genomics knowledge in a clinical context

- **Passive CDS ("knowledge resources")**: Manual submission of patient data & manual retrieval of patient-specific knowledge
- **Semi-active CDS ("Information retrieval tool")**: Automated submission of patient data & manual retrieval of patient-specific knowledge
- **Active CDS ("classic clinical decision support")**: Automated submission of patient data & automated retrieval of patient-specific knowledge

*(Enabling Health Care Decision Making through Decision Support and Knowledge Management, AHRQ, 2012)*

Example: **Warfarin dose calculation for a patient initiating anticoagulation and with CYP2C9 & VKORC1 genetic test results**

*(Jonas & McLeod, 2009)*
Semi-active CDS

- OpenInfobutton testing tool to generate websites for semi-active CDS
  - 3 resources for lab review context; 9 resources for the medication order entry context

VHA CHIO Innovation project: "CPRS Decision Support enhanced by Context-Sensitive Infobuttons"

*Requesting Organization: University of Washington
*Task context: Medication order entry
*Main search criteria: Code: 904162 Display name: irinotecan Code system: RxNorm
Age: Value: __ Unit: __
Age group: __
Gender: __
Care setting: __
Performer: __ language: __ discipline: __
Information recipient: __ language: __ discipline: __
Output: HTML – University of Washington layout

Semi-active CDS

- OpenInfobutton testing tool to generate websites for semi-active CDS
  - 3 resources for lab review context; 9 resources for the medication order entry context

CPOE Scenario - Irinotecan

A 48 year old Caucasian male with a 40 pack year history of smoking is diagnosed with extensive stage small cell lung cancer. Past medical history is noncontributory and all laboratory values are within normal limits. He will be treated with cisplatin and irinotecan for 4-6 cycles.

Laboratory value(s):

<table>
<thead>
<tr>
<th>Gene name</th>
<th>Variant(s)</th>
<th>Genotype Common Name</th>
<th>Assigned Phenotype classification (Source: e-PKgene)</th>
</tr>
</thead>
<tbody>
<tr>
<td>UGT1A1</td>
<td>(TA)(^7)TAA</td>
<td>UGT1A1*1/28</td>
<td>Slow Extensive Metabolizer</td>
</tr>
</tbody>
</table>

**Note:** This is 1 of 11 clinical case scenarios
PGx CDS in the medication order entry context
ONC promotes adoption of CDS through specifying criteria for ‘meaningful use’ of EHRs to be eligible for the HITECH Act incentive payments through Medicare and Medicaid

- Stage 1 (2011), specifies implementation of CDS
- Stage 2 (2013), specifies use of CDS to improve performance
  - Record family history as structured data
  - Adopt the HL7 Context Aware Knowledge Retrieval Standard
- Stage 3 (2015), requires demonstrated use of CDS in ways that improves the outcomes of care

*(Fed Regist. 2012 Dec 7;77(236):72985-91.)*
There is a need for more work evaluating interventions to deliver genomic knowledge


<table>
<thead>
<tr>
<th></th>
<th>Discovery, characterization, and development (T0/T1)</th>
<th>Evaluation of tests and interventions (T2)</th>
<th>Implementation in practice and programs (T3/T4)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Original studies</td>
<td>GWAS, biomarkers, and proposed new applications</td>
<td>Clinical trials, clinical cohorts, and new data on analytic or clinical validity</td>
<td>Studies generating new process or outcome data from clinical populations; surveillance</td>
</tr>
<tr>
<td>Knowledge synthesis</td>
<td>Meta-analysis and systematic reviews of gene-disease associations</td>
<td>Evidence Reports</td>
<td>Cost-effectiveness analyses and national program evaluation</td>
</tr>
<tr>
<td>Guidelines/policies/recommendations</td>
<td>New nomenclature, data sharing and publication standards</td>
<td>Clinical practice and professional guidelines</td>
<td>Electronic health standards, reporting requirements, and ethical standards</td>
</tr>
<tr>
<td>Tools/methods/training/education/decision support</td>
<td>Research road maps, databases, software, and training tools</td>
<td>Modeling methods, databases, and methods for systematic review</td>
<td>Clinical algorithms; provider and patient education materials</td>
</tr>
</tbody>
</table>

*Table 1 from Clyne et al. “Horizon scanning for translational genomic research beyond bench to bedside” Gent Med 2014*
T1-T4 Translational research

T1 From Gene Discovery to Health Application
T2 From Health Application to Evidence-based Guideline
T3 From Guideline to Health Practice
T4 From Practice to Health Impact

Evaluation of tests and interventions
Clinical Guidelines
Implementation research
Dissemination research
Precision Medicine
Outcomes research

Promising application
Evidence-based recommendation or policy
Other translational research projects
Scientific discovery
Practice and control programs
Population health/disease burden

Example method for evaluating interventions (T2)

• A framework for discussing genomic clinical decision support for genetic testing workflow

Opportunities for genomic clinical decision support interventions

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Efforts to conceptualize genomic clinical decision support

- Exchange of genomic data within clinical systems (*AHIC Personalized Healthcare Detailed Use Case, 2008*)

- Technical desiderata for managing genomic data in clinical systems (*Masys et al. JBI 2012*)

- Genomic results handling pathways (*Starren et al. JAMA 2013*)

- Wanted to characterize delivery of genomic CDS to facilitate genetic testing workflow and communication processes

(Figure from *Starren et al. JAMA 2013*)
A framework for the delivery of genomic CDS

Stakeholders

- Clinical-care provider
- Health-care consumer or family

Transactions

- What are relevant transactions for this activity?
- When should this activity occur (i.e., what phases)?
- How should this activity be initiated and by who?
- Where should data be pushed to or pulled from?

Clinical systems

- Display “field-of-view” genetic/genomic test results
- Retrieve genetic/genomic test results
- Retrieve personal data, family history and pedigree
- Order genetic/genomic test
- Report personal data, family history and pedigree

EHR

PHR
Use Case: The Personalized Diabetes Medicine Program (PDMP)

- PI: Dr. Toni Pollin (University of Maryland, Baltimore)

- Diabetes mellitus (and monogenic diabetes)
  - Affects >25 million people in the U.S.
  - At least 1% (>250,000 diabetes cases) caused by mutations in one of several genes
  - Most cases of genetic diabetes misdiagnosed as T1DM or T2DM

- Benefits to personalizing treatment:
  - Improved glucose control
  - Better prediction of prognosis
  - Enhanced familial risk assessment
A framework for the delivery of CDS: PDMP screening

- What are relevant transactions for this activity?
  - Report personal data, family history and pedigree

- When should this activity occur (i.e., what phases)?

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A framework for the delivery of CDS: PDMP screening

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  - Pre-analytic phase

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A framework for the delivery of CDS:
**PDMP screening**

- What are relevant transactions for this activity?
  - Report personal data, family history and pedigree

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- How should this activity be initiated and by who?
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A framework for the delivery of CDS:

**PDMP screening**

- What are relevant transactions for this activity?
  - Report personal data, family history and pedigree

- When should this activity occur (i.e., what phases)?
  - Pre-analytic phase

- How should this activity be initiated and by who?
  - Human-initiated by the health-care consumer

- Where should data be pushed to or pulled from?
  - PHR -> EHR
PDMP Patient Screening

• What are relevant transactions for this activity?
  – Report personal data, family history and pedigree
    • CDS content: Documentation template for data collection

• When should this activity occur (i.e., what phases)?
  – Pre-analytic phase
    • Setting: Outpatient
    • Workflow context: Between visits

• How should this activity be initiated and by who?
  – Human-initiated by the health-care consumer
    • Target user: Diabetes patient

• Where should data be pushed to or pulled from?
  – PHR
    • CDS technologies: internal off-the-shelf functionality
    • CDS capabilities: active CDS
    • CDS features:
      – trigger – time (e.g., 24 hrs after visit);
      – input data element – prior visit type;
      – intervention – email link to data entry template;
      – offered choice – defer/complete data entry

Note: Some features are included in CDS taxonomies proposed by Wright et al. JAMIA 2007 & Wright et al. JAMIA 2011
Summary

• Genomic CDS can be characterized using common frameworks for CDS

• Characterizing implementation from the perspective of genetic testing workflow and communication processes helps determine effective approaches to deliver and exchange genomic knowledge

• Proposed a framework that may help with this characterization
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