A Repository for Structured Knowledge Artifacts Based on Pharmacogenomic Clinical Guidelines: Complementing the CDS-KB

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IGNITE Clinical Informatics Webinar Series
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Clinical PGx Implementation Consortium (CPIC)

• Formed in 2009 to provide guidelines that enable the translation of genetic lab results into clinical actions

• Includes over 130 clinicians and scientists, from 62 institutions and 14 countries
  • Observers from NIH and FDA

• PGx clinical guidelines
  • Authored by: domain experts
  • Target audience: clinicians, lab
  • Also used as a basis for PGx CDS rules
Clinical Pharmacogenetics Implementation Consortium Guidelines for Thiopurine Methyltransferase Genotype and Thiopurine Dosing

Thiopurine methyltransferase (TPMT) activity exhibits monogenic co-dominant inheritance, with ethnic differences in the frequency of occurrence of variant alleles. With conventional thiopurine doses, homozygous TPMT-deficient patients (+1 to 1 in 3.728 individuals with two non-functional TPMT alleles) experience severe myelosuppression, 30–40% of individuals who are heterozygotes (+1 to 1 3.728 individuals) show moderate toxicity, and homozygous wildtype individuals (+46–97% of the population) show lower active thiopurine nucleotides and less myelosuppression. We provide dosing recommendations (updates at http://www.pharmgkb.org) for azathioprine, mercaptopurine (MP), and thiopurine based on TPMT genotype.

The purpose of this guideline is to provide information with which to interpret clinical thiopurine methyltransferase (TPMT) genotype tests so that the results can be used successfully to guide the dosing of thiopurines. Although most of the dosing recommendations have been generated from clinical studies in only a few diseases, we have extrapolated recommended doses to all conditions, given the pharmacokinetic characteristics of the genotype/phenotype associations. This first guideline developed by the Clinical Pharmacogenetics Implementation Consortium, which is part of the National Institute of Health Pharmacogenomics Research Network. The consortium is a community-driven organization that is developing peer reviewed, freely available geno/drug guidelines that are available at PharmGKB (http://www.pharmgkb.org). Guidelines for the use of phenotypic tests (i.e., TPMT activity and thiopurine metabolite levels) and analysis of cost effectiveness are beyond the scope of this article.

FOCUSED REVIEW OF THE LITERATURE

The review of the literature focused on TPMT genotype and thiopurine use (Supplementary Data online), with reviews being used as summaries of earlier literature.

Gene TPMT

Background. TPMT activity is inherited as a monogenic co-dominant trait (Supplementary Figure S1 online). It metabolizes mercaptopurine (MP) and thioguanine (Figure 1), causing an inverse relationship between TPMT activity and concentrations of active thiopurine nucleotide (TPN) metabolites. With conventional doses of thiopurines, individuals (+1 to 1 in 3.728) who inherit two inactive TPMT alleles (homozygous deficient) universally experience severe myelosuppression, a high proportion of those who are heterozygotes show moderate to severe myelosuppression, and those who are homozygous for wild-type TPMT alleles have lower levels of TPN metabolites and consequently a lower risk of myelosuppression. There are substantial ethnic differences in the frequencies of low activity variant alleles (Supplementary Tables S3 and S4 online).

Three TPMT single-nucleotide polymorphisms account for >90% of inactivating alleles, and therefore genotyping tests have a high likelihood of being informative. Complementary phenotype laboratory tests can be helpful adjuncts to genotype tests (Supplementary Data online, Other Considerations).

<table>
<thead>
<tr>
<th>Genotype</th>
<th>TPMT activity</th>
</tr>
</thead>
<tbody>
<tr>
<td>WT</td>
<td>Normal activity</td>
</tr>
<tr>
<td>HET</td>
<td>Intermediate activity</td>
</tr>
<tr>
<td>HOM</td>
<td>Low activity</td>
</tr>
</tbody>
</table>

Table 2: Recommended dosing of thiopurines by Thiopurine methyltransferase (TPMT) activity

<table>
<thead>
<tr>
<th>Phenotype</th>
<th>MP concentrations of TPN metabolites</th>
<th>Dosing recommendations</th>
<th>Classification of recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>WT</td>
<td>Normal activity (0g/mL)</td>
<td>30mg/m2 daily</td>
<td>Strong</td>
</tr>
<tr>
<td>HET</td>
<td>Intermediate activity (1g/mL)</td>
<td>20mg/m2 daily</td>
<td>Moderate</td>
</tr>
<tr>
<td>HOM</td>
<td>Low activity (2g/mL)</td>
<td>10mg/m2 daily</td>
<td>Weak</td>
</tr>
</tbody>
</table>

Supplemental Table S3. Genotypes that constitute the *a* alleles for TPMT

<table>
<thead>
<tr>
<th>Allele</th>
<th>Genotype</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>a1</em></td>
<td>G&gt;A</td>
</tr>
<tr>
<td><em>a3</em></td>
<td>C&gt;T</td>
</tr>
<tr>
<td><em>a4</em></td>
<td>C&gt;T</td>
</tr>
</tbody>
</table>

ARTICLES

Table 1. Assignment of likely thiopurine methyltransferase genotypes based on phenotypes

<table>
<thead>
<tr>
<th>Likely phenotype</th>
<th>Genotypes</th>
<th>Examples of clitoraces</th>
</tr>
</thead>
<tbody>
<tr>
<td>Homozygous wild-type normal high activity (36–97% of patients)</td>
<td>An individual carrying two normal functional alleles</td>
<td>*1/*1</td>
</tr>
<tr>
<td>Homozygous intermediate activity (+1 to 1 in 3.728 of patients)</td>
<td>An individual carrying one functional allele and one non-functional allele</td>
<td>*1/*2, *1/*3, *1/*4</td>
</tr>
<tr>
<td>Homozygous varient, low, or deficient activity (+1 in 178 to 1 in 3,728 patients)</td>
<td>An individual carrying two non-functional alleles</td>
<td>*2/*2, *3/*3, *4/*4</td>
</tr>
</tbody>
</table>

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Growing interest in informatics aspects of CPIC guidelines and clinical implementation of pharmacogenetics

Goal

To support the adoption of the CPIC guidelines by identifying, and resolving where possible, potential technical barriers to the implementation of the guidelines within a clinical electronic environment.

Working group is a forum for discussion and collaboration, focused on informatics issues
CPIC Informatics WG

- Comprehensive translation tables
  - Define structure and process to efficiently develop and maintain in the most useful format(s)
  - Publish as part of CPIC guidelines
- Disseminate CPIC standardized phenotype terms
  - LOINC
- Updating implementation resources
  - Allele definition tables
  - Allele frequencies
Supplemental Table S4. Drug(s) that pertain to this guideline.

<table>
<thead>
<tr>
<th>Drug or Ingredient</th>
<th>Source</th>
<th>Code Type</th>
<th>Code</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abacavir</td>
<td>RxNorm</td>
<td>RxCUI</td>
<td>190521</td>
</tr>
<tr>
<td>Abacavir</td>
<td>DrugBank</td>
<td>Accession Number</td>
<td>DB01048</td>
</tr>
<tr>
<td>Abacavir</td>
<td>ATC</td>
<td>ATC Code</td>
<td>J05AF06</td>
</tr>
<tr>
<td>Abacavir</td>
<td>PharmGKB</td>
<td>PharmGKB ID</td>
<td>PA48004</td>
</tr>
</tbody>
</table>

Supplemental Table S5. Gene(s) that pertain to this guideline.

<table>
<thead>
<tr>
<th>Gene Symbol</th>
<th>Source</th>
<th>Code Type</th>
<th>Code</th>
</tr>
</thead>
<tbody>
<tr>
<td>HLA-B</td>
<td>HGNC</td>
<td>Symbol</td>
<td>HLA-B</td>
</tr>
<tr>
<td>HLA-B</td>
<td>HGNC</td>
<td>HGNC ID</td>
<td>HGNC-4932</td>
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<tr>
<td>HLA-B</td>
<td>NCBI</td>
<td>Gene ID</td>
<td>3106</td>
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<tr>
<td>HLA-B</td>
<td>Ensembl</td>
<td>Ensembl ID</td>
<td>ENSG00000234745</td>
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<tr>
<td>HLA-B</td>
<td>PharmGKB</td>
<td>PharmGKB ID</td>
<td>PA33056</td>
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</tbody>
</table>

Supplemental Table S7. Example Implementation of this Guideline: Pharmacogenetic Genotype/Phenotype Summary Entries

<table>
<thead>
<tr>
<th>Test Result for HLA-B*57:01</th>
<th>Coded Genotype/Phenotype Summary</th>
<th>EHR Priority Result Notation</th>
<th>Consultation (Interpretation) Text Provided with Test Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Negative</td>
<td>None</td>
<td>Normal/Low Risk</td>
<td>The HLA-B<em>57:01 allele, associated with abacavir hypersensitivity, was not detected in this patient. The patient may be prescribed abacavir. Please refer to the hospital formulary guidelines for specific dosing information. It should be noted that a negative HLA-B</em>57:01 result does not absolutely rule out the possibility of some form of abacavir hypersensitivity. Administration of abacavir therapy requires close observation including immediate discontinuation of therapy should any signs or symptoms of hypersensitivity develop.</td>
</tr>
</tbody>
</table>

| Positive                    | HLA-B*57:01Carrier              | Abnormal Priority High Risk  | The HLA-B*57:01 allele, associated with abacavir hypersensitivity, was detected in this patient. HLA-B*57:01 positive patients should NOT be prescribed abacavir. |

Supplemental Table S8. Example Implementation of this Guideline: Point of Care Clinical Decision Support

<table>
<thead>
<tr>
<th>Flow Chart Reference Point</th>
<th>CDS Context, Relative to Genetic Testing</th>
<th>Trigger Condition</th>
<th>CDS Alert Text</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Pre-Test</td>
<td>No HLA-B*57:01 result on file</td>
<td>A HLA-B<em>57:01 genotype test is recommended before prescribing abacavir per the FDA's black box warning regarding the risk of serious hypersensitivity reactions in patients that carry this allele. A HLA-B</em>57:01 genotype test does not appear to have been ordered for this patient. Please do the following to order the HLA-B<em>57:01 genotype test (insert dialogue boxes here to order clinical HLA-B</em>57:01).</td>
</tr>
<tr>
<td>2</td>
<td>Post-Test</td>
<td>HLA-B*57:01 Carrier</td>
<td>The HLA-B*57:01 allele has been detected in this patient. This allele is associated with high risk of severe hypersensitivity to abacavir. DO NOT prescribe abacavir per the FDA's black box warning. Please choose an alternate antiretroviral. For more information, please consult a clinical pharmacist.</td>
</tr>
</tbody>
</table>

*See Supplemental Figure S4
*The specific wording of the alert text may differ among sites.

Supplemental Table S9. Translation of Genotype Test Result into Interpreted Phenotype

<table>
<thead>
<tr>
<th>Test Result for HLA-B*57:01</th>
<th>Examples of Diploptypes</th>
<th>Interpreted Phenotype</th>
</tr>
</thead>
<tbody>
<tr>
<td>Negative</td>
<td>X/X</td>
<td>Low Risk of abacavir hypersensitivity</td>
</tr>
<tr>
<td>Positive</td>
<td>X:57:01 or 57:01:57:01</td>
<td>High Risk of abacavir hypersensitivity</td>
</tr>
</tbody>
</table>

*This table corresponds to the recommendations in the CPIC guideline manuscript.
### Allele Nomenclature Resources

The table defines all the single-nucleotide polymorphisms (SNPs) in *TPMT* as of January 2015.

<table>
<thead>
<tr>
<th>Haplotype Set ID</th>
<th>Haplotype Set Name</th>
<th>Allele</th>
<th>rsID</th>
<th>SNP Change</th>
<th>Gene Location</th>
<th>References</th>
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<tbody>
<tr>
<td>PA166128346</td>
<td>*1</td>
<td>C</td>
<td>rs1800462</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PA166128348</td>
<td>*15</td>
<td>C</td>
<td>rs1800462</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PA166128349</td>
<td>*2</td>
<td>G</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PA166128350</td>
<td>*3A</td>
<td>C</td>
<td>rs1142345</td>
<td></td>
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<tr>
<td>PA166128351</td>
<td>*3B</td>
<td>C</td>
<td>rs1142345</td>
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<tr>
<td>PA166128352</td>
<td>*3C</td>
<td>C</td>
<td>rs1142345</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>PA166128353</td>
<td>*4</td>
<td>C</td>
<td>rs1142345</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>PA166128354</td>
<td>*5</td>
<td>C</td>
<td>rs1142345</td>
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<td>PA166128355</td>
<td>*6</td>
<td>C</td>
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<tr>
<td>PA166128360</td>
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<td>*13</td>
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<tr>
<td>PA166128362</td>
<td>*16</td>
<td>C</td>
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<tr>
<td>PA166128363</td>
<td>*17</td>
<td>C</td>
<td>rs1142345</td>
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<tr>
<td>PA166128364</td>
<td>*18</td>
<td>C</td>
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</table>

<table>
<thead>
<tr>
<th>Allele</th>
<th>rsID</th>
<th>SNP Change</th>
<th>Gene Location</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>TPMT*1</td>
<td>rs2842934</td>
<td>allele A</td>
<td>474T</td>
<td></td>
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<tr>
<td>TPMT*1A</td>
<td>rs2842934</td>
<td>C&gt;A</td>
<td>-178C&gt;T</td>
<td>Exon I</td>
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<tr>
<td>TPMT*1S</td>
<td>rs2842934</td>
<td>A&gt;C</td>
<td>474T&gt;C</td>
<td>Exon VII</td>
</tr>
<tr>
<td>TPMT*2</td>
<td>rs1100462</td>
<td>C&gt;G</td>
<td>238G&gt;C</td>
<td>Exon V</td>
</tr>
<tr>
<td>TPMT*1A</td>
<td>rs1100462</td>
<td>C&gt;T</td>
<td>460G&gt;A</td>
<td>Exon VII</td>
</tr>
<tr>
<td>TPMT*1B</td>
<td>rs1100462</td>
<td>C&gt;A</td>
<td>719A&gt;G</td>
<td>Exon X</td>
</tr>
<tr>
<td>TPMT*1C</td>
<td>rs1100462</td>
<td>C&gt;T</td>
<td>460G&gt;A</td>
<td>Exon VII</td>
</tr>
<tr>
<td>TPMT*1D</td>
<td>rs1100462</td>
<td>C&gt;A</td>
<td>719A&gt;G</td>
<td>Exon X</td>
</tr>
<tr>
<td>TPMT*1E</td>
<td>rs1100462</td>
<td>C&gt;T</td>
<td>460G&gt;A</td>
<td>Exon VII</td>
</tr>
<tr>
<td>TPMT*1F</td>
<td>rs1100462</td>
<td>C&gt;A</td>
<td>719A&gt;G</td>
<td>Exon X</td>
</tr>
</tbody>
</table>
PGRN TPP: PGx CDS Implementations

Drug is ordered or indicated but no genotype result is on file

<table>
<thead>
<tr>
<th></th>
<th>PAAR (U Chicago)</th>
<th>PAAR4Kids (St. Jude)</th>
<th>PAPI-2 (UMB)</th>
<th>PAT (Vanderbilt)</th>
<th>PEAR (U FL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trigger Context</td>
<td>All patients</td>
<td>All orders</td>
<td>Predictive Score; Ordersets</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>(preemptive)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CDS Type</td>
<td>Passive</td>
<td>Active</td>
<td>Active + Passive</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pre-Order Genetic Testing</td>
<td>Recommended</td>
<td>Recommended</td>
<td>Recommended</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Drug is ordered, genotype test result is on file

<table>
<thead>
<tr>
<th>Phenotype</th>
<th>CDS Type</th>
<th>Recommendation(s)</th>
<th>PAAR (U Chicago)</th>
</tr>
</thead>
<tbody>
<tr>
<td>UM</td>
<td>Passive</td>
<td>No change</td>
<td></td>
</tr>
<tr>
<td>EM</td>
<td>Passive</td>
<td>No change</td>
<td></td>
</tr>
<tr>
<td>IM</td>
<td>Passive</td>
<td>Drug change</td>
<td></td>
</tr>
<tr>
<td>PM</td>
<td>Passive</td>
<td>Drug change</td>
<td></td>
</tr>
<tr>
<td>Indeterminate</td>
<td>Passive</td>
<td>No change</td>
<td></td>
</tr>
</tbody>
</table>
Lowering More Barriers to PGx Implementation

- PGx implementation resources are often targeted for human consumption
- Need more robust methods for capturing, disseminating, maintaining, and delivering knowledge
  - Computable!
- Portable, structured representations of CDS rules may
  - Remove ambiguity in guideline interpretation
  - Facilitate CDS rule authoring
  - Reduce CDS development and maintenance costs
  - Improve consistency among CDS implementations
  - Increase scalability of knowledge management
Implementing PGx CDS: Current State

Knowledge Engineering → Clinical Decision Support (CDS) → Technical Implementation → Localized Code (exe)


Implementing PGx CDS: Future State

How can we get here?
Methods and tools for representing computerised clinical guidelines

Summary information on all methods is provided below - extended details on each are provided on separate pages.

<table>
<thead>
<tr>
<th>Guideline modelling methods and tools</th>
<th>Frameworks &amp; other tools</th>
</tr>
</thead>
<tbody>
<tr>
<td>Executable methods</td>
<td></td>
</tr>
<tr>
<td>Arden Syntax</td>
<td>DeGeL - framework to support the development of a Digital electronic Guideline Library</td>
</tr>
<tr>
<td>Syntx</td>
<td>SEBASTIAN - Web service-based framework for clinical decision support</td>
</tr>
<tr>
<td>Asbru</td>
<td>Protégé - generic environment for ontology and knowledge-base development</td>
</tr>
<tr>
<td>EON</td>
<td></td>
</tr>
<tr>
<td>GASTON</td>
<td></td>
</tr>
<tr>
<td>XML methods</td>
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</tr>
<tr>
<td>CPG-RA</td>
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<td>HGML</td>
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<tr>
<td>GEM</td>
<td></td>
</tr>
<tr>
<td>Stepper</td>
<td></td>
</tr>
</tbody>
</table>
Clinical Decision Support to Health eDecisions - a brief history  continued

Barriers exist to the adoption and implementation of CDS despite research demonstrating effectiveness in improving quality and safety

Lack of widely accepted, implementable standards for importing and/or sharing proven CDS interventions (reminders, order sets, documentation templates)

ONC and AHRQ have invested in multiple research projects such as GLIDES, CDSC, ACDS and eRecs to advance CDS implementation, sharing and adoption

In April 2012, ONC and AHRQ at the April 2012 F2F stakeholders gathered from across the vendor, academic, and healthcare communities to discuss how to advance the shareability of CDS interventions and build on the research and existing standards to date from this came the Health eDecisions Initiative

Health eDecisions Project Charter and Scope

Effective CDS requires availability of computable biomedical knowledge, person-specific data, and a reasoning or inference mechanism that combines these elements to generate and present helpful information to clinicians, patients or caregivers in the right way and the right time.

In order to recognize these benefits, CDS interventions must be made more easily shareable so that anyone can easily acquire and deploy CDS interventions.

To this end, standards must be advanced to enable either the consumption of CDS via a web service or the import of CDS interventions into CDS systems.

Scope Statement:
To define standards that facilitate the emergence of systems and services whereby CDS interventions can be shared or accessed by any healthcare stakeholder via an importable format or via a CDS web service.
Health eDecisions (HeD) Interchange Format

- **HeD Schema**
  - Conditions
  - Actions (interventions)
  - Queries to EHR
  - Metadata

- **Data models, terminologies**
  - Domain-specific concepts
  - Domain-specific value sets
Creating Shareable Clinical Decision Support Rules for a Pharmacogenomics Clinical Guideline Using Structured Knowledge Representation

Margaret K. Linan, MPH\textsuperscript{1}, Davide Sottara, PhD\textsuperscript{1,2}, Robert R. Freimuth, PhD\textsuperscript{2,3}
\textsuperscript{1}Department of Biomedical Informatics, Arizona State University, Scottsdale, AZ, \textsuperscript{2}Office of Information and Knowledge Management and \textsuperscript{3}Department of Health Sciences Research, Mayo Clinic, Rochester, MN
PGx Guideline & CDS Rules in HeD Syntax

<externalData>
  <def name="Patient">
    <expression xsi:type="ClinicalRequest" dataType="vmr:Patient" />
  </def>
  <def name="ADRsToAbacavir">
    <expression xsi:type="ClinicalRequest" dataType="vmr:AdverseEvent" codeProperty="vmr:adverseEventAgent" useValueSets="true" />
    <codes xsi:type="ValueSet" id="x.y.z"/>
  </def>
  <def name="AbacavirOrders">
    <expression xsi:type="ClinicalRequest" dataType="vmr:SubstanceAdministrationOrder" codeProperty="vmr:substance.substanceCode" dateProperty="vmr:orderEventTime" />
    <codes xsi:type="ValueSet" id="x.y.z"/>
  </def>

<expressions>
  <def name="hasAdverseReaction">
    <expression xsi:type="IsNotEmpty">
      <operand xsi:type="ExpressionRef" name="ADRsToAbacavir"/>
    </def>
    <def name="currentAbacavirOrder">
      <expression xsi:type="Last">
        <source xsi:type="ExpressionRef" name="AbacavirOrder"/>
      </def>
  </expressions>

<actionGroups>
  <subElements>
    <simpleAction xsi:type="MessageAction">
      <message xsi:type="Concat" value="Consider cancelling the order..." />
    </simpleAction>
    <simpleAction xsi:type="RemoveAction">
      <actionSentence xsi:type="ExpressionRef" name="CurrentAbacavirOrder"/>
    </simpleAction>
  </subElements>
</externalData>
HL7 Standard: Clinical Decision Support Knowledge Artifact Specification, Release 1
DSTU Release 1.3

DRAFT STANDARD FOR TRIAL USE
July 2015

Sponsored by:
Clinical Decision Support in collaboration with the Health and Human Services Standards and Interoperability Framework Health eDecisions Working Group

This specification and implementation guide is developed in support of the HeD Artifact Sharing Use Case and is intended to assist implementers in the development of Clinical Decision Support (CDS) Knowledge Artifacts. The approach adopted in this specification is designed to be flexible and reusable, and to provide a baseline for CDS vendors and CDS Knowledge Artifact implementers.
CDS Consortium Knowledge Framework

Level 1
- Unstructured
- Guidelines (pdf, html)

Level 2
- Semi-structured
- Supplemental tables (xlsx)

Level 3
- Structured
- Health eDecisions (xml)

Level 4
- Executable
- Platform-dependent syntax
Objectives and Requirements

• Facilitate adoption of PGx guidelines and integration into clinical infrastructure
  • Organize disparate but related documents
  • Track revisions
  • Support a wide variety of formats

• Use same standards as clinical systems
  • Standard identifiers for genes and genetic variants
  • Standard nomenclature for genetic variants
  • Standard terminologies (RxNorm, LOINC)

• Provide implementation teams with more direct access to updated resources when knowledge evolves
  • Services for detecting and retrieving updates
Implementation

- Drupal Content Management System (CMS)
  - Open source framework
    - First release Jan 2001
    - GNU General Public License (GPL)
    - Built-in document versioning system
    - Tags support user-defined concepts
  - Very active user community
    - Long term support and maintenance

Data captured Apr 20, 2016 from www.drupal.org
Implementation

• Filedepot module
  • Extends Drupal
  • Provides hierarchical document repository

• Related extensions
  • Linkit
  • Multiupload
  • Filebuilder Service
  • Files
  • Apache Solr (search filter)

filedepot

Posted by blainelang on April 14, 2010 at 1:28am

The filedepot module is full featured Document Management module that has a google docs like feel. It fulfills the need for an integrated file management module supporting role and user based security. Documents can be saved outside the Drupal public directory to protect documents for safe access and distribution.

Checkout the filedepot_linkit module which supports browsing and inserting filedepot links from WYSIWYG editors.

Desktop Application Support

The Filebuilder desktop application is now available for Windows, Linux and Mac OS to easily upload 100's of files or very large files and manage your filedepot document repository from your desktop - a video overview is available.
Implementation

• Customized Drupal/Filedepot for PGx
  • Added structured metadata & relationships
    • Bibliographic reference
    • PubMed ID
    • Document URL (external)
  • Standard terminologies (indexing)
    • HGNC symbol
    • NCBI Gene ID
    • RxNorm CUI
    • NDR-FT NUI
  • Relationships between documents

• REST API
Workflow and Interfaces

- **PGx** Knowledge Artifacts
  - **PGx** Guideline
  - **PGx** Knowledge Engineer

- **PGx Committee**

- **Web UI**

- **REST API**
  - Detect Updates
  - Traceability

- **PGR Database**
  - MySQL
  - Drupal + File Depot
Role-Based Access Model

- Anyone can VIEW
- Registered users can DOWNLOAD
- Trusted users can UPLOAD

<table>
<thead>
<tr>
<th>role name</th>
<th>nickname</th>
<th>view folder</th>
<th>view metadata</th>
<th>download the file</th>
<th>upload direct</th>
<th>upload version</th>
<th>folder admin</th>
<th>upload admin</th>
</tr>
</thead>
<tbody>
<tr>
<td>administrator</td>
<td>power users</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>contributor</td>
<td>trusted</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>authenticated</td>
<td>any registered</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>anonymous</td>
<td>joe public</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
PGx CDS Artifacts
PGx CDS Artifacts

- Abacavir
- Azathioprine
- Clopidogrel
**PGx CDS Artifacts**

Search by tags and key words

File listings

Tags

Favorites

Users can also subscribe to notifications
# PGx CDS Artifacts

## Search Tags: guideline

<table>
<thead>
<tr>
<th>Filename</th>
<th>Folder</th>
<th>Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>CPIC CYP2C19 Clopidogrel Update 2013.pdf</td>
<td>guideline</td>
<td>09/17/15</td>
</tr>
<tr>
<td>CPIC CYP2C19 Clopidogrel 2011.pdf</td>
<td>guideline</td>
<td>09/17/15</td>
</tr>
<tr>
<td>CPIC TPMT Azathioprine 2011.pdf</td>
<td>tpmt</td>
<td>09/17/15</td>
</tr>
<tr>
<td>CPIC HLAB-Abacavir 2012.pdf</td>
<td>hlab</td>
<td>09/17/15</td>
</tr>
<tr>
<td>CPIC HLAB Abacavir Update 2014.pdf</td>
<td>hlab</td>
<td>09/17/15</td>
</tr>
</tbody>
</table>
**Document Metadata**

- **Actions**
- **Parent Document** (applies to all versions)
- **Document Version** (version-specific metadata)

**CPIC HLAB-Abacavir 2012.pdf - Details**

**Actions**
- Download
- Edit
- New Version
- Delete
- Lock

**Parent Document**
- File Name: CPIC_HLAB-Abacavir 2012.pdf
- Folder: Abacavir
- Owner: bfreimuth
- Tags: cpcic, guideline, hlab
- Description: PGx guideline for HLA-B and abacavir

**Document Version**
- Authors: Martin, Klein, Dong, Pirmohamed, Haas, Kroetz
- PubMed ID: 22378157
- HGNC Symbol: HLA-B
- NCBI Gene Id: 3106
- RxNorm RxCUI: 190521
- NDRFT: N0000022135
- Version Note: Original CPIC guideline
REST API

- Query for documents
  - Key words
  - Gene identifier (HGNC symbol or NCBI Gene)
  - Drug code (RxCUI or NDFRT NUI)
  - Tags
- Given specified document ID
  - Find all related (child) documents
  - Return document version history
- Returns document objects in JSON syntax
API: Examples of Queries

- Are there new guidelines available?
- What docs are related to <gene> and/or <drug>?
- What knowledge artifacts of type <tag> are available?
  - Submitting organization (e.g., TPP, Mayo Clinic)
  - Type of artifact (e.g., workflow)

- Are any new companion docs available for <guideline>?
- Is an updated version of <doc> available?
API: LIVE DEMO

*It worked!*
http://informatics.mayo.edu/pgx_cds/index.html

Pharmacogenomics Guideline Repository

Pharmacogenomics Guideline Repository

Services API

Resources

The resources use a data model that is supported by a set of client-side libraries that are made available on the files and libraries page.

There is a WADL document available that describes the resources API.

<table>
<thead>
<tr>
<th>name</th>
<th>path</th>
<th>methods</th>
<th>description</th>
</tr>
</thead>
<tbody>
<tr>
<td>FileRestService</td>
<td>/files</td>
<td>GET</td>
<td>Service class that handles REST requests</td>
</tr>
<tr>
<td></td>
<td>/files/children</td>
<td>GET</td>
<td></td>
</tr>
<tr>
<td></td>
<td>/files/file</td>
<td>GET</td>
<td></td>
</tr>
<tr>
<td></td>
<td>/files/parent</td>
<td>GET</td>
<td></td>
</tr>
<tr>
<td></td>
<td>/files/search</td>
<td>GET</td>
<td></td>
</tr>
</tbody>
</table>
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<td>/files/children</td>
<td>GET</td>
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</tr>
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<td>GET</td>
<td></td>
</tr>
<tr>
<td></td>
<td>/files/parent</td>
<td>GET</td>
<td></td>
</tr>
<tr>
<td></td>
<td>/files/search</td>
<td>GET</td>
<td></td>
</tr>
<tr>
<td></td>
<td>/files/tags</td>
<td>GET</td>
<td></td>
</tr>
<tr>
<td></td>
<td>/files/versions</td>
<td>GET</td>
<td></td>
</tr>
</tbody>
</table>
### GET /files/search

Find a specific file based on metadata values. May have one to many specified.

#### Request Parameters

<table>
<thead>
<tr>
<th>name</th>
<th>type</th>
<th>description</th>
</tr>
</thead>
<tbody>
<tr>
<td>HGNCsymbol</td>
<td>query</td>
<td>the HGNC code</td>
</tr>
<tr>
<td>NCBI Gene</td>
<td>query</td>
<td>the NCBI code</td>
</tr>
<tr>
<td>NDFRTNUI</td>
<td>query</td>
<td>the ndrt code</td>
</tr>
<tr>
<td>RxCUI</td>
<td>query</td>
<td>the rxNorm code</td>
</tr>
<tr>
<td>fid</td>
<td>query</td>
<td>the id assigned to all versions of a specified file</td>
</tr>
<tr>
<td>id</td>
<td>query</td>
<td>the internal id of the file</td>
</tr>
<tr>
<td>version</td>
<td>query</td>
<td>the specific version of a file</td>
</tr>
</tbody>
</table>

#### Response Body

<table>
<thead>
<tr>
<th>media type</th>
<th>data type</th>
<th>description</th>
</tr>
</thead>
<tbody>
<tr>
<td>application/json</td>
<td>array ofFileVersionModel (JSON)</td>
<td>List</td>
</tr>
</tbody>
</table>
# Data Types

## JSON

<table>
<thead>
<tr>
<th>type</th>
<th>description</th>
</tr>
</thead>
<tbody>
<tr>
<td>FileModel</td>
<td>This object contains all the metadata found in common for all versions of the file.</td>
</tr>
<tr>
<td>FileVersionModel</td>
<td>These Objects contain the metadata pertaining to a specific version of a file.</td>
</tr>
</tbody>
</table>

## FileVersionModel

These Objects contain the metadata pertaining to a specific version of a file.

### Properties

<table>
<thead>
<tr>
<th>name</th>
<th>data type</th>
<th>description</th>
</tr>
</thead>
<tbody>
<tr>
<td>id</td>
<td>string</td>
<td>The internal id of the instance. All queries are based on this value</td>
</tr>
<tr>
<td>fid</td>
<td>string</td>
<td>The file id represents all versions of that particular file</td>
</tr>
<tr>
<td>fname</td>
<td>string</td>
<td>The file's name</td>
</tr>
<tr>
<td>version</td>
<td>string</td>
<td>Identifies which version this instance represents</td>
</tr>
<tr>
<td>drupal_fid</td>
<td>string</td>
<td>Internal drupal id used to retrieve documents</td>
</tr>
<tr>
<td>size</td>
<td>number</td>
<td>The size of the instance</td>
</tr>
<tr>
<td>notes</td>
<td>string</td>
<td>Information entered regarding this specific instance</td>
</tr>
<tr>
<td>date</td>
<td>number</td>
<td>The date the instance was uploaded into the repository</td>
</tr>
<tr>
<td>uid</td>
<td>string</td>
<td>The user id</td>
</tr>
<tr>
<td>status</td>
<td>number</td>
<td>Workflow status of the document</td>
</tr>
</tbody>
</table>
Files and Libraries

C Client Library
Created March 18, 2016

The C module generates the source code for the ANSI-C-compatible data structures and (de)serialization functions that can be used in conjunction with libxml2 to (de)serialize the REST resources as they are represented as XML data.

The generated C source code depends on the XML Reader API and the XML Writer API as well as the `<time.h>`, `<string.h>`, and `<stdlib.h>` C standard libraries.

Files

<table>
<thead>
<tr>
<th>name</th>
<th>size</th>
<th>description</th>
</tr>
</thead>
<tbody>
<tr>
<td>pgx_cds.c</td>
<td>93.71K</td>
<td></td>
</tr>
<tr>
<td>enunciate-common.c</td>
<td>39.68K</td>
<td>Common code needed for all projects.</td>
</tr>
</tbody>
</table>

C# Client Library
Created March 18, 2016
null,
url_Children: http://gcds.mayo.edu:9090/pgx_cds/files/children?id=4,
url_Versions: http://gcds.mayo.edu:9090/pgx_cds/files/versions?id=4,
url_Id: http://gcds.mayo.edu:9090/pgx_cds/files/search?id=4,
url_File: http://gcds.mayo.edu:9090/pgx_cds/files/file?id=4,
date: 1438711056,
tag: null,
status: 1,
 id: "4",
size: 218509
},

null,
Get Versions for a File

```json
{
  "fid": "3",
  "fname": "CPIC_HLAB-Abacavir 2012.pdf",
  "drupal_fid": "7",
  "notes": "Original CPIC guideline",
  "uid": "2",
  "authors": "Martin, Klein, Dong, Pirmohamed, Haas, Kroetz",
  "pubmed": "22378157",
  "hgnc": "HLA-B",
  "ncbi": "3106",
  "rxnorm": "190521",
  "mdrt": "N0000022135",
  "version": "1",
  "url_Parent": "null",
  "url_Id": "http://gqs.mayo.edu:9090/pgx_cds/files/search?id=4",
}
```
Get Child Documents for a Given Parent

```json

fid: "4",
drupal_fid: "9",
notes: "Supplement to the original CPIC guideline",
```

```json

fid: "5",
fname: "CPIC_HLAB_Abacavir_Update.pdf",
drupal_fid: "10",
notes: "Updated CPIC guideline",
```

```json

fid: "6",
fname: "CPIC_Abacavir_HLAB_Supplement_Update_MA_2014.pdf",
drupal_fid: "11",
notes: "Updated CPIC guideline supplement",
```

```
Get Documents Given Coded Metadata

http://gcds.mayo.edu:9090/pgx_cds/files/search?HGNCSymbol=HLA-B&rxnorm=190521

[{
  "fid": "3",
  "fname": "CPIC_HLAB-Abacavir 2012.pdf",
  "drupal_fid": "7",
  "notes": "Original CPIC guideline",
  "uid": "2",
  "authors": "Martin, Klein, Dong, Pirmohamed, Haas, Kroetz",
  "pubmed": "22378157",
  "hgnc": "HLA-B",
  "ncbi": "3106",
  "rxnorm": "190521",
  "ndrft": "N0000022135",
  "version": "1",
  "url_Parent": null,
  "url_Id": "http://gcds.mayo.edu:9090/pgx_cds/files/search?id=4",
  "date": 1438711056,
  "tag": null,
  "status": 1,
  "id": "4",
  "size": 218509
}]}
API: Examples of Queries

- Are there new guidelines available?
- What knowledge artifacts of type <tag> are available?
  - Submitting organization (e.g., TPP, Mayo Clinic)
  - Type of artifact (e.g., workflow)
- What docs are related to <gene> and/or <drug>?
- Are any new companion docs available for <guideline>?
- Is an updated version of <doc> available?
PGR Code Repository

- All components are/will be open source
  - Drupal framework
  - FileDepot module
    - PGx extensions
  - PGx repository REST services

https://github.com/PGx-Structured-Documents
Conclusions

• First release of a public repository to host a library of documents that will facilitate the sharing of information related to PGx CDS implementations
• Stable, open source framework (customized)
• Links related files along the CDSC knowledge framework
  • May facilitate the management as knowledge evolves
  • May facilitate traceability from implementations to knowledge source(s)
• Enables the collection, organization, and dissemination of PGx knowledge
  • May help improve KM for PGx CDS as our collective knowledge base grows
Objective:
Develop a *lightweight* repository as a platform to *publicly* disseminate *unstructured* Genomic Medicine implementation artifacts from institutions with genomic medicine programs.
Four Tier Knowledge Encoding Process

- **Level 1**: Unstructured
  - Format: .jpeg, .html, .doc, .xl
  - + metadata
  - CDSKB focused on this

- **Level 2**: Semi-structured
  - Format: xml
  - + metadata

- **Level 3**: Structured
  - Format: xml
  - + metadata
  - PGR focused on this

- **Level 4**: Machine Execution
  - Format: any
  - + metadata

---

PGR: Current Status

• Framework to support PGx structured knowledge artifacts is complete
  • Web UI: Knowledge engineers, domain experts
  • REST API: CDS implementation teams

• Example content loaded
  • CPIC guidelines (not downloadable)
    • Need permission from CPT
  • TPP documents

• Exploring opportunities for integration with existing community resources
  • Avoid fragmentation!
  • CPIC, PGRN, PharmGKB, eMERGE CDSKB
Acknowledgements

• PGx Guideline Repository
  • Rick Kiefer
  • Zhonghui Lian

• Funding Sources
  • PGRN/PHONT: NIGMS U19 GM61388
  • Mayo Clinic Office of Information and Knowledge Management (OIKM)

• Knowledge Artifacts
  • CPIC
  • CPIC Informatics
  • PGRN TPP
  • PGRN PHONT
  • PharmGKB