A collection-spanning view of computable CPIC guidelines

Presentation for CPIC Informatics
September 17, 2018

Allen Flynn, PharmD, PhD
Assistant Professor of Learning and Knowledge Systems
University of Michigan Medical School
Department of Learning Health Sciences

Our ongoing PGx projects

- **NHRI Taiwan + Northshore Health System + Michigan**
  (a) Make CPIC guidelines computable (machine-executable)
  (b) Apply computable PGx knowledge in research & in practice in Taiwan as part of a larger learning health system and precision medicine initiative

- **Michigan Pharmacy**
  (a) Study the current state and the population in Michigan to identify PGx implementation opportunities
  (b) Do basic PGx research
  (c) Implement PGx in clinical practice at Michigan

<u>And in the future we hope to</u>:

Participate in helpful ways toward the dissemination of CPIC guidelines in computable formats on a widespread, global basis.

What is a collection-spanning view?

DRUGS	GENES	GUIDELINES
abacavir	HLA-B	guideline
allopurinol	HLA-B	guideline
amitriptyline	CYP2C19 CYP2D6	guideline
atazanavir	UGT1A1	guideline
azathioprine	TPMT	guideline
capecitabine	DPYD	guideline
carbamazepine	HLA-B	guideline
citalopram escitalopram	CYP2C19	guideline
clomipramine	CYP2C19 CYP2D6	guideline
clopidogrel	CYP2C19	guideline
codeine	CYP2D6	guideline
desipramine	CYP2D6	guideline
doxepin	CYP2C19 CYP2D6	guideline
fluorouracil	DPYD	guideline
fluvoxamine	CYP2D6	guideline
imipramine	CYP2C19 CYP2D6	guideline
ivacaftor	CFTR	guideline
mercaptopurine	TPMT	guideline
nortriptyline	CYP2D6	guideline
ondansetron	CYP2D6	guideline
oxcarbazepine	HLA-B	guideline
paroxetine	CYP2D6	guideline
peginterferon alfa-2a peginterferon alfa-2b ribavirin	IFNL3	guideline
phenytoin	CYP2C9 HLA-B	guideline
rasburicase	G6PD	guideline
sertraline	CYP2C19	guideline
simvastatin	SLCO1B1	guideline
tacrolimus	CYP3A5	guideline
tamoxifen	CYP2D6	guideline
tegafur	DPYD	guideline
thioguanine	TPMT	guideline
trimipramine	CYP2C19 CYP2D6	guideline
tropisetron	CYP2D6	guideline
voriconazole	CYP2C19	guideline
warfarin	CYP2C9 CYP4F2 VKORC1	guideline

To us, “computable guidelines” means machine-executable guidelines

CYP2D6 Diplotype	Gaedigk Activity Score (formula)	Coded Genotype/Phenotype Summary	EHR Priority Result Notat
*3/*3	0	CYP2D6 Poor Metabolizer	Abnormal/Priority/High Ri
*3/*3xN	0	CYP2D6 Poor Metabolizer	Abnormal/Priority/High Ri
*3/*4	0	CYP2D6 Poor Metabolizer	Abnormal/Priority/High Ri

Programming

IF (diplotype = ___)

THEN

Phenotype = _____

Table Dosing recom ations for tricyclic antidepressants based on cyp2d6 phenotype

Phenotype	Implication	Therapeutic recommendation[a,b]	Classification of recommendation for amitriptyline and nortriptyline[c]	Classification of recommendation for other TCAs[c,d]
CYP2D6 ultrarapid metabolizer	Increased metabolism of TCAs to less active compounds compared to normal metabolizers Lower plasma concentrations of active drug will increase probability of pharmacotherapy failure	Avoid tricyclic use due to potential lack of efficacy. Consider alternative drug not metabolized by CYP2D6. If a TCA is warranted, consider titrating to a higher target dose (compared to normal metabolizers).[e] Utilize therapeutic drug monitoring to guide dose adjustments.	Strong	Optional
CYP2D6 normal metabolizer	Normal metabolism of TCAs	Initiate therapy with recommended starting dose.[f]	Strong	Strong
CYP2D6 intermediate metabolizer	Reduced metabolism of TCAs to less active compounds compared to normal metabolizers Higher plasma concentrations of active drug will increase the probability of side effects	Consider a 25% reduction of recommended starting dose.[f] Utilize therapeutic drug monitoring to guide dose adjustments.[e]	Moderate	Optional
CYP2D6 poor metabolizer	Greatly reduced metabolism of TCAs to less active compounds compared to normal metabolizers Higher plasma concentrations of active drug will increase the probability of side effects	Avoid tricyclic use due to potential for side effects. Consider alternative drug not metabolized by CYP2D6. If a TCA is warranted, consider a 50% reduction of recommended starting dose.[f] Utilize therapeutic drug monitoring to guide dose adjustments.[e]	Strong	Optional

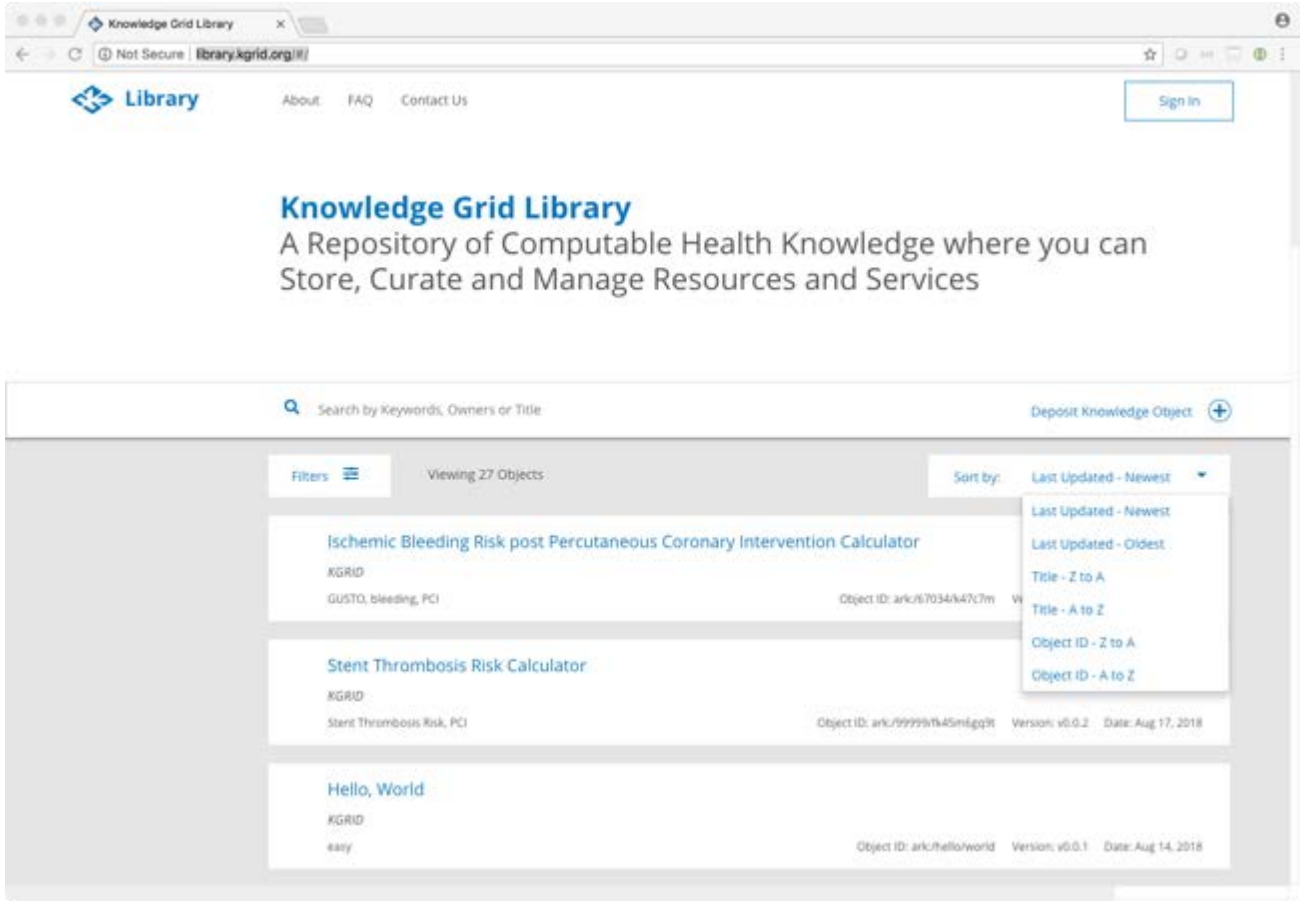
Programming

IF (phenotype = ___)

THEN

Recommendation = “Do This”

We study how to scale-up infrastructure to manage & deploy ***computable knowledge***



library.kgrid.org kgrid.org

Our goal this month is to develop a computable CPIC Guideline "Kit"

- Contains computable CPIC guidelines in a convenient file and folder format
- Makes it easy to see computable CPIC guidelines in action
- Download, run, and try on any Mac or PC with Java installed in only 5 minutes
- It also has:
    - Knowledge Grid components with APIs
    - A command line interface tool
    - An easy-to-use, browser-based web application
    - Automated tests to let users see that the "Kit" is working
    - Online documentation of all these things!

In the future, we would like a CPIC Computable Guideline Kit to also contain:

- **A realistic but fake patient data set as a 'gold standard' to test and confirm reliability of the "Kit" once it's been downloaded by someone**

Three issues from our work to make the whole CPIC collection computable

1

Variance related to Diplotype to Phenotype Conversions:

(a) "Singlets", as in the case of HLA-B (*57:01)
(b) diplotype-to-phenotype tables, like the one for CYP2D6
(c) allele definition tables only, like the one for TPMT
(d) sometimes star alleles are not used (?), as for DPYD variants

2

Variance in Phenotype Definitions:

Normal, Intermediate, Likely Intermediate, Poor, Likely Poor, etc.

3

Variance in the Format of Drug-specific Recommendations:

Mostly Tables & a Tree (warfarin)

And then there's the issue of multiple interacting genes too . . .

Summary & some planned next steps

- We plan to begin analyzing some real-world patient data sets using the CPIC computable guidelines Kit over the next 4 months at Michigan and in Taiwan
- When the CPIC computable guidelines Kit is ready to try, we'll announce it
- We are starting a dialog with our EHR teams at Michigan to see what it will take to integrate the shareable versions computable CPIC guidelines we area developing with our Epic EHR install called "MiChart"

*** If we don't have time for Q&A today… email me with questions*!* ***

Allen Flynn: ajflynn@umich.edu