Mobilizing Computable Biomedical Knowledge: An Imperative for Learning Health Systems

Charles P. Friedman, PhD
Josiah Macy, Jr. Professor
Chair, Department of Learning Health Sciences
Professor of Information and Public Health
University of Michigan
December 3, 2020
Disclosure

I serve on the Board of Directors of the Learning Health Community, a non-profit corporation promoting Learning Health Systems.
Today’s Journey

• Knowledge...

• Learning Health Systems (LHS) and “Mass Action”

• The Concept of Computable Biomedical Knowledge

• Why Computable Knowledge is Essential for Mass Action

• Building Mass Action Infrastructure

• Examples and Demos: Taking Prevention & Clinical Pharmacogenomics to Mass Action

• A Increasingly Global Movement to “Mobilize” Computable Biomedical Knowledge
A Way to Think About Knowledge

The *result* of an analytical and/or deliberative process that holds significance for an identified community.
Examples of Biomedical Knowledge (Viewing Knowledge As a “Result”)

*From primarily analytical to primarily deliberative in origin:*

- Predictive/explanatory models
- Computable phenotypes
- Causal/propositional networks
- Best practices (guidelines)
- Decision Trees
- Policies
Continuing the Journey

• Knowledge...

• Learning Health Systems (LHS) and “Mass Action”

• The Concept of Computable Biomedical Knowledge

• Why Computable Knowledge is Essential for Mass Action

• Building Mass Action Infrastructure

• Examples and Demos: Taking Prevention & Clinical Pharmacogenomics to Mass Action

• A Increasingly Global Movement to “Mobilize” Computable Biomedical Knowledge
Learning Health Systems:
Continuous Cycles of Study and Change

External Evidence → Interpret Results → Design Intervention

Analyze Data

Assemble Data

Capture Practice as Data

Formation of Learning Community

D2K: Data to Knowledge

K2P: Knowledge to Performance

P2D: Performance to Data

Health Problem of Interest
Better Health Requires This

D2K: Data to Knowledge

K2P: Knowledge to Performance

Health Problem of Interest

P2D: Performance to Data
Not This...

Health Problem of Interest

D2K: Data to Knowledge
K2P: Knowledge to Performance
P2D: Performance to Data

Journals
And Not This…
The “Gap” as a Major Problem

Health Problem of Interest

D2K: Data to Knowledge

K2P: Knowledge to Performance

P2D: Performance to Data
Bridging the Gap: Knowledge is the “Keystone” Holding the LHS Cycle Together
To Bridge the Gap Routinely, LHSs Need Mass Action Capability

**Mass Action:**
1. Management of dynamic knowledge
2. Delivery of knowledge-driven interventions at unlimited scale
Continuing the Journey

• Knowledge...

• Learning Health Systems (LHS) and “Mass Action”

• The Concept of Computable Biomedical Knowledge

• Why Computable Knowledge is Essential for Mass Action

• Building Mass Action Infrastructure

• Examples and Demos: Taking Prevention & Clinical Pharmacogenomics to Mass Action

• A Increasingly Global Movement to “Mobilize” Computable Biomedical Knowledge
Two Complementary Ways to Represent Knowledge

Human readable in words, pictures, equations

Computable (machine-executable) in code
Selection Criteria for Lung-Cancer Screening


ABSTRACT

BACKGROUND

The National Lung Screening Trial (NLST) used risk factors for lung cancer (e.g., ≥30 pack-years of smoking and ≤15 years since quitting) as selection criteria for lung-cancer screening. Use of an accurate model that incorporates additional risk factors to select persons for screening may identify more persons who have lung cancer or in whom lung cancer will develop.

METHODS

We modified the 2011 lung-cancer risk-prediction model from our Prostate, Lung, Colorectal, and Ovarian (PLCO) Cancer Screening Trial to ensure applicability to NLST data; risk was the probability of a diagnosis of lung cancer during the 6-year study period. We developed and validated the model (PLCO_{M2012}) with data from the 80,375 persons in the PLCO control and intervention groups who had ever smoked. Discrimination (area under the receiver-operating-characteristic curve [AUC]) and calibration were assessed. In the validation data set, 14,144 of 37,332 persons (37.9%) met NLST criteria. For comparison, 14,144 highest-risk persons were considered positive (eligible for screening) according to PLCO_{M2012} criteria. We compared the accuracy of PLCO_{M2012} criteria with NLST criteria to detect lung cancer. Cox models were used to evaluate whether the reduction in mortality among 53,202 persons undergoing low-dose computed tomographic screening in the NLST differed according to risk.
The New Knowledge (the “Result”) is Expressed in a Model

Table 2. Modified Logistic-Regression Prediction Model (PLCO_M2012) of Cancer Risk for 36,286 Control Participants Who Had Ever Smoked.*

<table>
<thead>
<tr>
<th>Variable</th>
<th>Odds Ratio (95% CI)</th>
<th>P Value</th>
<th>Beta Coefficient</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, per 1-yr increase†</td>
<td>1.081 (1.057–1.105)</td>
<td>&lt;0.001</td>
<td>0.0778868</td>
</tr>
<tr>
<td>Race or ethnic group‡</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>1.000</td>
<td></td>
<td>Reference group</td>
</tr>
<tr>
<td>Black</td>
<td>1.484 (1.083–2.033)</td>
<td>0.01</td>
<td>0.3944778</td>
</tr>
<tr>
<td>Hispanic</td>
<td>0.475 (0.195–1.160)</td>
<td>0.10</td>
<td>-0.7434744</td>
</tr>
<tr>
<td>Asian</td>
<td>0.627 (0.332–1.185)</td>
<td>0.15</td>
<td>-0.466585</td>
</tr>
<tr>
<td>American Indian or Alaskan Native</td>
<td>1.000</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Native Hawaiian or Pacific Islander</td>
<td>2.793 (0.992–7.862)</td>
<td>0.05</td>
<td>1.027152</td>
</tr>
<tr>
<td>Education, per increase of 1 level†‡</td>
<td>0.922 (0.874–0.972)</td>
<td>0.003</td>
<td>-0.0812744</td>
</tr>
<tr>
<td>Body-mass index, per 1-unit increase†</td>
<td>0.973 (0.955–0.991)</td>
<td>0.003</td>
<td>-0.0274194</td>
</tr>
<tr>
<td>Chronic obstructive pulmonary disease (yes vs. no)</td>
<td>1.427 (1.162–1.751)</td>
<td>0.001</td>
<td>0.3553063</td>
</tr>
<tr>
<td>Personal history of cancer (yes vs. no)</td>
<td>1.582 (1.172–2.128)</td>
<td>0.003</td>
<td>0.4589971</td>
</tr>
<tr>
<td>Family history of lung cancer (yes vs. no)</td>
<td>1.799 (1.471–2.200)</td>
<td>&lt;0.001</td>
<td>0.587185</td>
</tr>
<tr>
<td>Smoking status (current vs. former)</td>
<td>1.297 (1.047–1.605)</td>
<td>0.02</td>
<td>0.2597431</td>
</tr>
<tr>
<td>Smoking intensity¶</td>
<td></td>
<td></td>
<td>-1.822606</td>
</tr>
<tr>
<td>Duration of smoking, per 1-yr increase†</td>
<td>1.032 (1.014–1.051)</td>
<td>0.001</td>
<td>0.0317321</td>
</tr>
<tr>
<td>Smoking quit time, per 1-yr increase†</td>
<td>0.970 (0.950–0.990)</td>
<td>0.003</td>
<td>-0.0308572</td>
</tr>
<tr>
<td>Model constant</td>
<td></td>
<td></td>
<td>-4.532506</td>
</tr>
</tbody>
</table>

* To calculate the 6-year probability of lung cancer in an individual person with the use of categorical variables, multiply the variable or the level beta coefficient of the variable by 1 if the factor is present and by 0 if it is absent. For continuous variables other than smoking intensity, subtract the centering value from the person’s value and multiply the difference by the beta coefficient of the variable. For smoking intensity, calculate the contribution of the variable to the model by dividing by 10, exponentiating by the power –1, centering by subtracting 0.4021541613, and multiplying this number by the beta coefficient of the variable. Add together all the previously calculated beta-coefficient products and the model constant. This sum is called the model logit. To obtain the person’s 6-year lung-cancer probability, calculate $e^{\text{logit}}/(1+e^{\text{logit}})$. CI denotes confidence interval.
And the Knowledge Can be Made Computable by Representing It as Code

Example: Code that takes in characteristics of a person and computes a risk score

A Knowledge Object
Computable Knowledge Extends the Publication Pipeline


Library → Expanded Library
Continuing the Journey

• Knowledge...
• Learning Health Systems (LHS) and “Mass Action”
• The Concept of Computable Biomedical Knowledge
• Why Computable Knowledge is Essential for Mass Action
• Building Mass Action Infrastructure
• Examples and Demos: Taking Prevention & Clinical Pharmacogenomics to Mass Action
• A Increasingly Global Movement to “Mobilize” Computable Biomedical Knowledge
Discovery Systems vs. Learning Systems
Discovery Systems Require Only *Mass Access*: Human-Readable Knowledge Suffices
But Human-Readable Knowledge Can’t Work for Learning Systems

17 Year Gap

How does a paper offering a useful prediction model enable changed practice?

D2K: Data to Knowledge

K2P: Knowledge to Performance

Health Problem of Interest

P2D: Performance to Data
LHSs Need Computable Biomedical Knowledge to Bridge the Gap
LHSs Also Need Computable Knowledge to Surpass *Mass Access*, Enabling *Mass Action*

**Mass Action Requirements:**
1. Management of dynamic knowledge
2. Delivery of knowledge-driven interventions at unlimited scale
Continuing the Journey

• Knowledge...
• Learning Health Systems (LHS) and “Mass Action”
• The Concept of Computable Biomedical Knowledge
• Why Computable Knowledge is Essential for Mass Action
• Building Mass Action Infrastructure
• Examples and Demos: Taking Prevention & Clinical Pharmacogenomics to Mass Action
• A Increasingly Global Movement to “Mobilize” Computable Biomedical Knowledge
Building Mass Action Infrastructure

1. Represent knowledge in computable form as Knowledge Objects
2. Establish a library that holds Knowledge Objects
3. Create an “activator” to generate an intervention
4. Enable messages/advice to be delivered
1. Representing Knowledge: Machine-executable Knowledge Objects

- Guidelines
- Articles
- Local Analytical Results

Knowledge Objects

Description

Interface

Computer-processable Knowledge ‘Payload’
2. A Digital Library

- Just like the libraries you know, except that it stores collections of computable knowledge objects
- Maintains and protects knowledge objects
- Enables them to be shared and returned
3. An “Activator” to Generate Messages

- Knowledge from Library
- Shelf
- Engine
- Payloads

- Data Needed by Knowledge Objects
- Computed Intervention
4. Delivering the Intervention

Knowledge from Library

Data Needed by Knowledge Objects

Standards-based open portals

EHRs & Apps

eHealth Applications

Providers & Patients
We Have Built an Infrastructure that Supports Mass Action

Knowledge Grid
Kgrid.org
Continuing the Journey

- Knowledge...
- Learning Health Systems (LHS) and “Mass Action”
- The Concept of Computable Biomedical Knowledge
- Why Computable Knowledge is Essential for Mass Action
- Building Mass Action Infrastructure
- Examples and Demos: Taking Prevention & Clinical Pharmacogenomics to Mass Action
- A Increasingly Global Movement to “Mobilize” Computable Biomedical Knowledge
What is CPIC?

The Clinical Pharmacogenetics Implementation Consortium (CPIC®) is an international consortium of individual volunteers and a small dedicated staff who are interested in facilitating use of pharmacogenetic tests for patient care.

One barrier to implementation of pharmacogenetic testing in the clinic is the difficulty in translating genetic laboratory test results into actionable prescribing decisions for affected drugs.

CPIC’s goal is to address this barrier to clinical implementation of pharmacogenetic tests by creating, curating, and posting freely available, peer-reviewed, evidence-based, updatable, and detailed gene/drug clinical practice guidelines (click here for all CPIC publications). CPIC guidelines follow standardized formats, include systematic grading of evidence and clinical recommendations, use standardized terminology, are peer-reviewed, and are published in a leading journal (in partnership with Clinical Pharmacology and Therapeutics) with simultaneous posting to cpcpgx.org, where they are regularly updated.

CPIC started as a shared project between PharmGKB and the Pharmacogenomics Research Network (PGRN) in 2009. CPIC guidelines are indexed in PubMed as clinical guidelines, endorsed by ASHP and ASCPT, and referenced in ClinGen and PharmGKB.
<table>
<thead>
<tr>
<th>Phenotype</th>
<th>Implications for codeine metabolism</th>
<th>Recommendations for codeine therapy</th>
<th>Classification of recommendation for codeine therapya</th>
<th>Considerations for alternative opioids</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ultrarapid metabolizer</td>
<td>Increased formation of morphine following codeine administration, leading to higher risk of toxicity</td>
<td>Avoid codeine use due to potential for toxicity.</td>
<td>Strong</td>
<td>Alternatives that are not affected by this CYP2D6 phenotype include morphine and nonopioid analgesics. Tramadol and, to a lesser extent, hydrocodone and oxycodone are not good alternatives because their metabolism is affected by CYP2D6 activity.b,c</td>
</tr>
<tr>
<td>Extensive metabolizer</td>
<td>Normal morphine formation</td>
<td>Use label-recommended age-or weight-specific dosing.</td>
<td>Strong</td>
<td>—</td>
</tr>
<tr>
<td>Intermediate metabolizer</td>
<td>Reduced morphine formation</td>
<td>Use label-recommended age-or weight-specific dosing. If no response, consider alternative analgesics such as morphine or a nonopioid.</td>
<td>Moderate</td>
<td>Monitor tramadol use for response.</td>
</tr>
<tr>
<td>Poor metabolizer</td>
<td>Greatly reduced morphine formation following codeine administration, leading to insufficient pain relief</td>
<td>Avoid codeine use due to lack of efficacy.</td>
<td>Strong</td>
<td>Alternatives that are not affected by this CYP2D6 phenotype include morphine and nonopioid analgesics. Tramadol and, to a lesser extent, hydrocodone and oxycodone are not good alternatives because their metabolism is affected by CYP2D6 activity; these agents should be avoided.b,c</td>
</tr>
</tbody>
</table>

a Rating scheme is described in Supplementary Data online. b There is substantial evidence for decreased efficacy of tramadol in poor metabolizers and a single case report of toxicity in an ultrarapid metabolizer with renal impairment following tramadol use post-surgery. Use of other analgesics in CYP2D6 poor and ultrarapid metabolizers may therefore be preferable. c Some other opioid analgesics, such as hydrocodone and oxycodone, are metabolized by CYP2D6. To avoid treatment complications, opioids that are not metabolized by CYP2D6, including morphine, oxymorphone, buprenorphine, fentanyl, methadone, and hydromorphone, along with nonopioid analgesics, may be considered as alternatives for use in CYP2D6 poor and ultrarapid metabolizers.

From Human Readable Knowledge to a Computable Object

Table 2: Codeine therapy recommendations based on cytochrome P450 2D6 (CYP2D6) phenotype

<table>
<thead>
<tr>
<th>Phenotype</th>
<th>ImPLICATIONS FOR PHARMACODYNAMICS</th>
<th>RECOMMENDATIONS FOR CODEINE THERAPY</th>
<th>CONSIDERATIONS FOR ALTERNATIVE OPIOIDS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ultrafast metabolizer</td>
<td>Increased formation of morphine following codeine administration, leading to higher risk of toxicity.</td>
<td>Avoid codeine use due to potential for toxicity.</td>
<td>Alternatives that are not affected by this genotype include oxycodone and tramadol, however use with caution as these agents may be metabolized by CYP2D6.</td>
</tr>
<tr>
<td>Extensive metabolizer</td>
<td>Normal or decreased morphine formation following codeine administration, leading to less frequent pain relief.</td>
<td>Use label recommended age-weight-specific dosing.</td>
<td>Use label recommended age-weight-specific dosing.</td>
</tr>
<tr>
<td>Intermediate metabolizer</td>
<td>Normal or decreased morphine formation following codeine administration, leading to less frequent pain relief.</td>
<td>Use label recommended age-weight-specific dosing.</td>
<td>Use label recommended age-weight-specific dosing.</td>
</tr>
<tr>
<td>Poor metabolizer</td>
<td>Greatly reduced morphine formation following codeine administration, leading to less frequent pain relief.</td>
<td>Avoid codeine use due to lack of efficacy.</td>
<td>Alternatives that are not affected by this genotype include oxycodone and tramadol, however use with caution as these agents may be metabolized by CYP2D6.</td>
</tr>
</tbody>
</table>

https://cpicpgx.org/guidelines/guideline-for-codeine-and-cyp2d6/

GENOTYPE → PHENOTYPE → DOSING ADVICE

Programming to represent the table as executable code
Taking Clinical Pharmacogenomics to Mass Action

Current State (Mass Access): CPIC’s guidelines are currently in human readable form in tables

Future State Enabling Mass Action:

1. Guidelines in fully computable form as knowledge objects
2. Computable objects publicly available through a trusted digital library
3. "Activation" services that use the objects to generate advice
4. Delivery of advice through apps or EHRs
Last Stop on the Journey

• Knowledge…

• Learning Health Systems (LHS) and “Mass Action”

• The Concept of Computable Biomedical Knowledge

• Why Computable Knowledge is Essential for Mass Action

• Building Mass Action Infrastructure

• Examples and Demos: Taking Prevention & Clinical Pharmacogenomics to Mass Action

• A Increasingly Global Movement to “Mobilize” Computable Biomedical Knowledge
Join the Movement!

**A multi-stakeholder effort to mobilize computable knowledge**

- Annual U.S. Meetings beginning in 2018
  - 240 participants in virtual 2020 meeting
- Now Going Global!
  - MCBK-UK inaugural meeting: October 29, 2019
- Four workgroups producing key deliverables
- All materials at mobilizecbk.org.
- To join, write to mcbk-info@umich.edu
- More about MCBK later today
Thanks and Write to Me

cpfried@umich.edu
lhs.medicine.umich.edu