Mobilizing Computable Biomedical Knowledge: An Imperative for Learning Health Systems

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M SPH

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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

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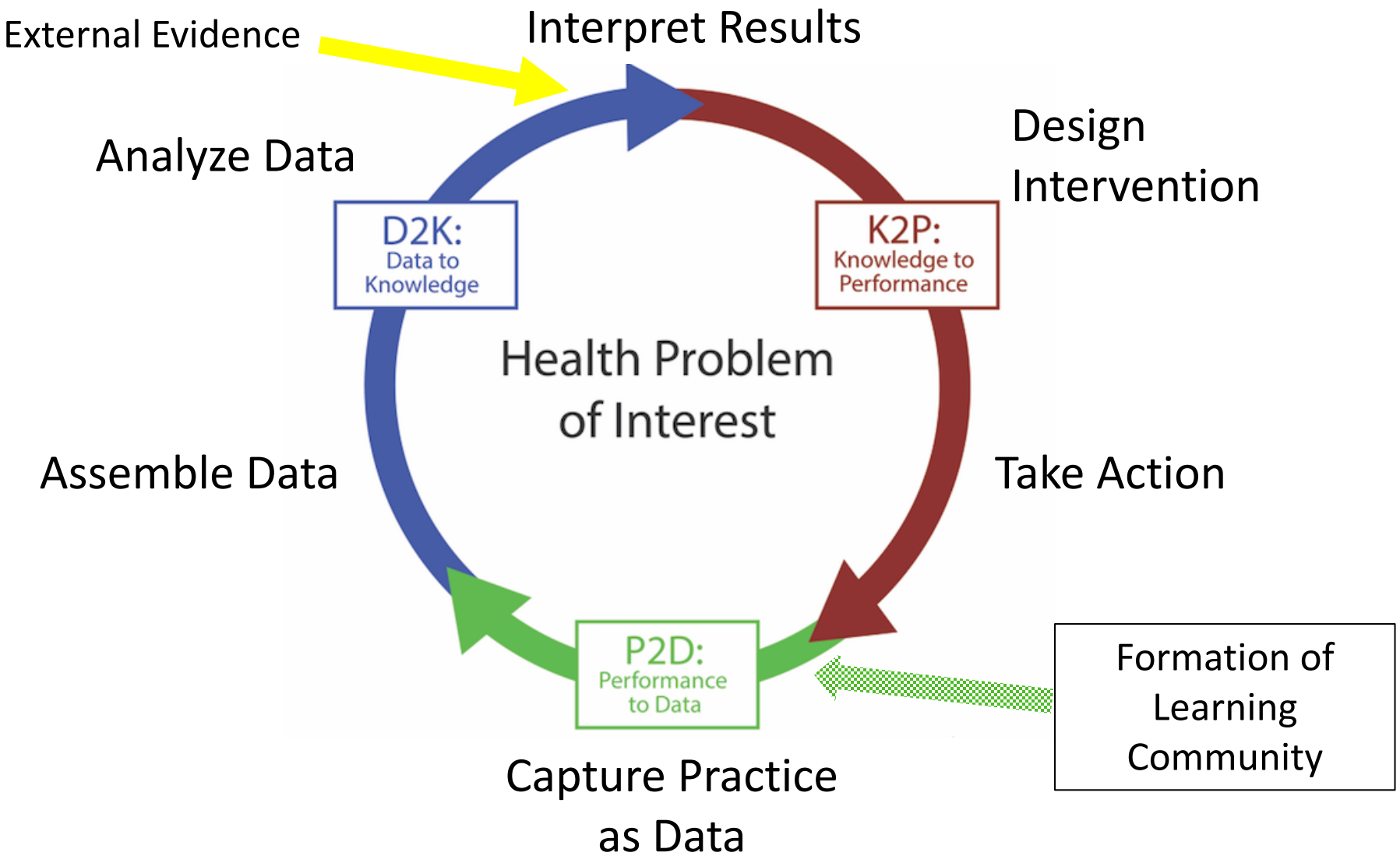
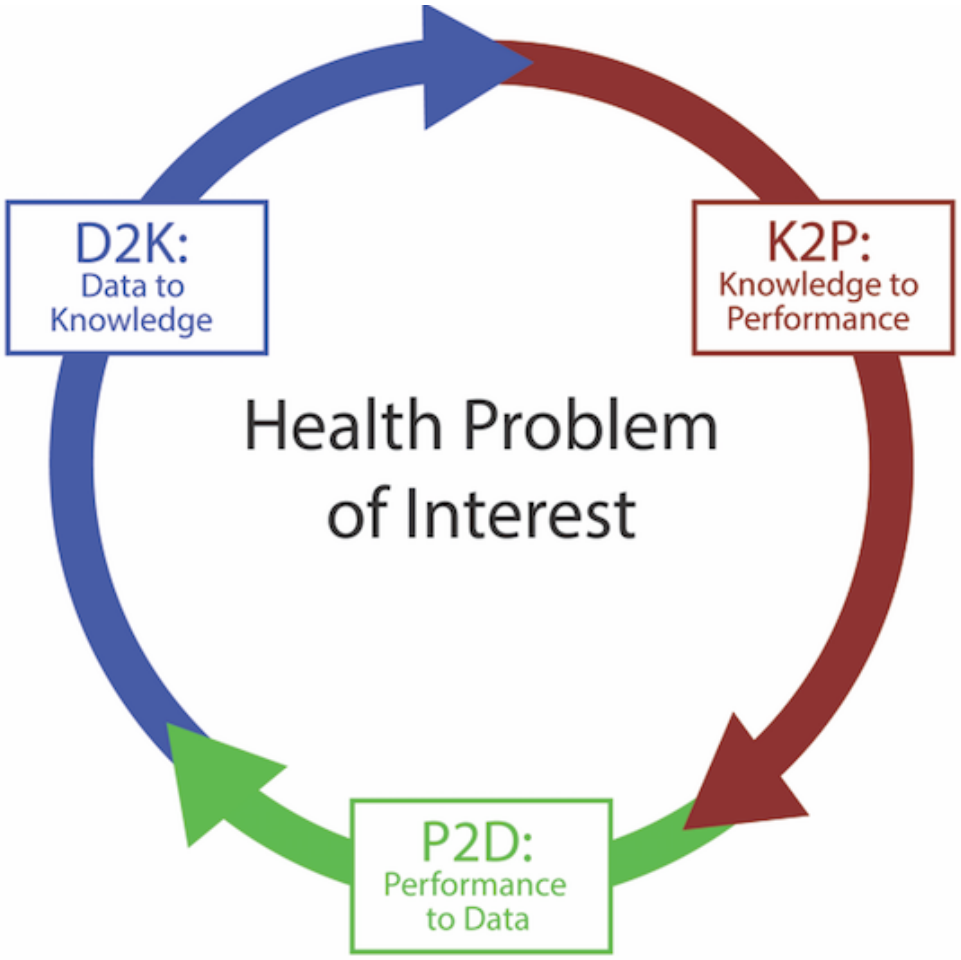
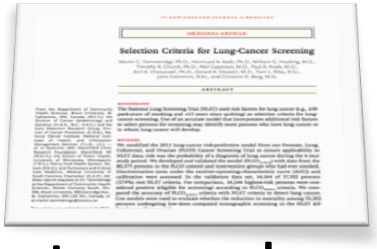
Learning Health Systems: Continuous Cycles of Study and Change



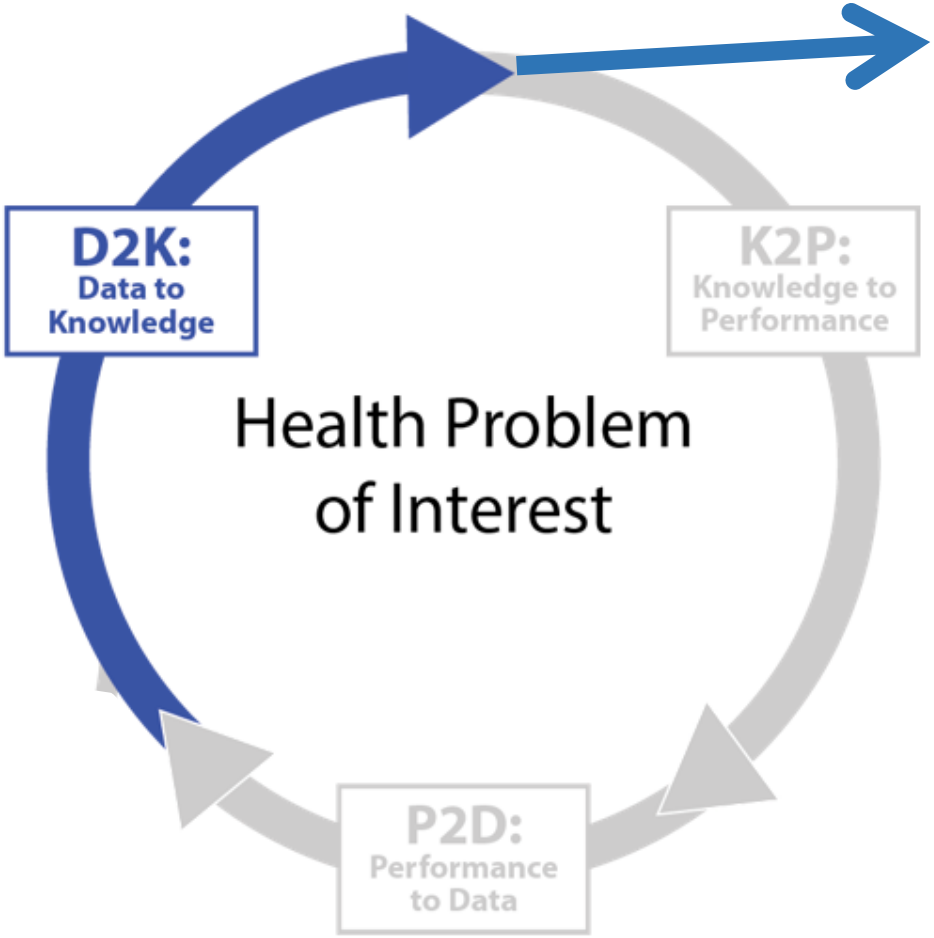
Better Health Requires This



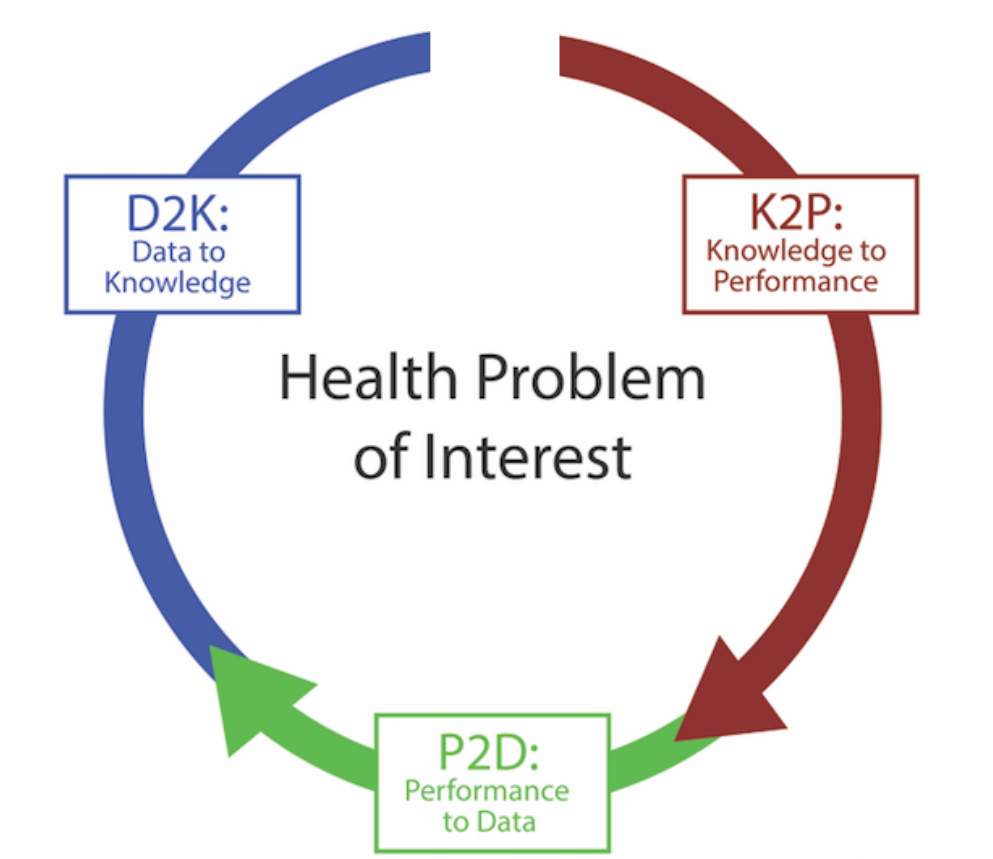
Not This…



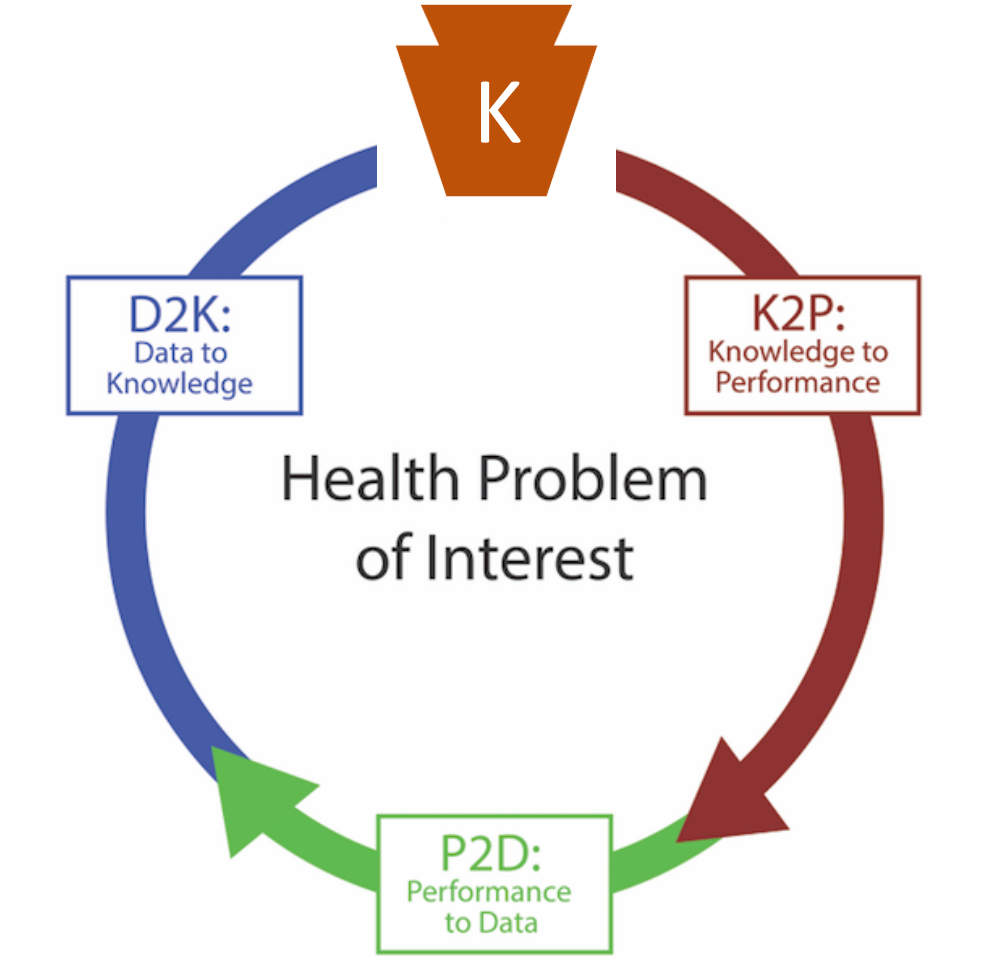
Journals



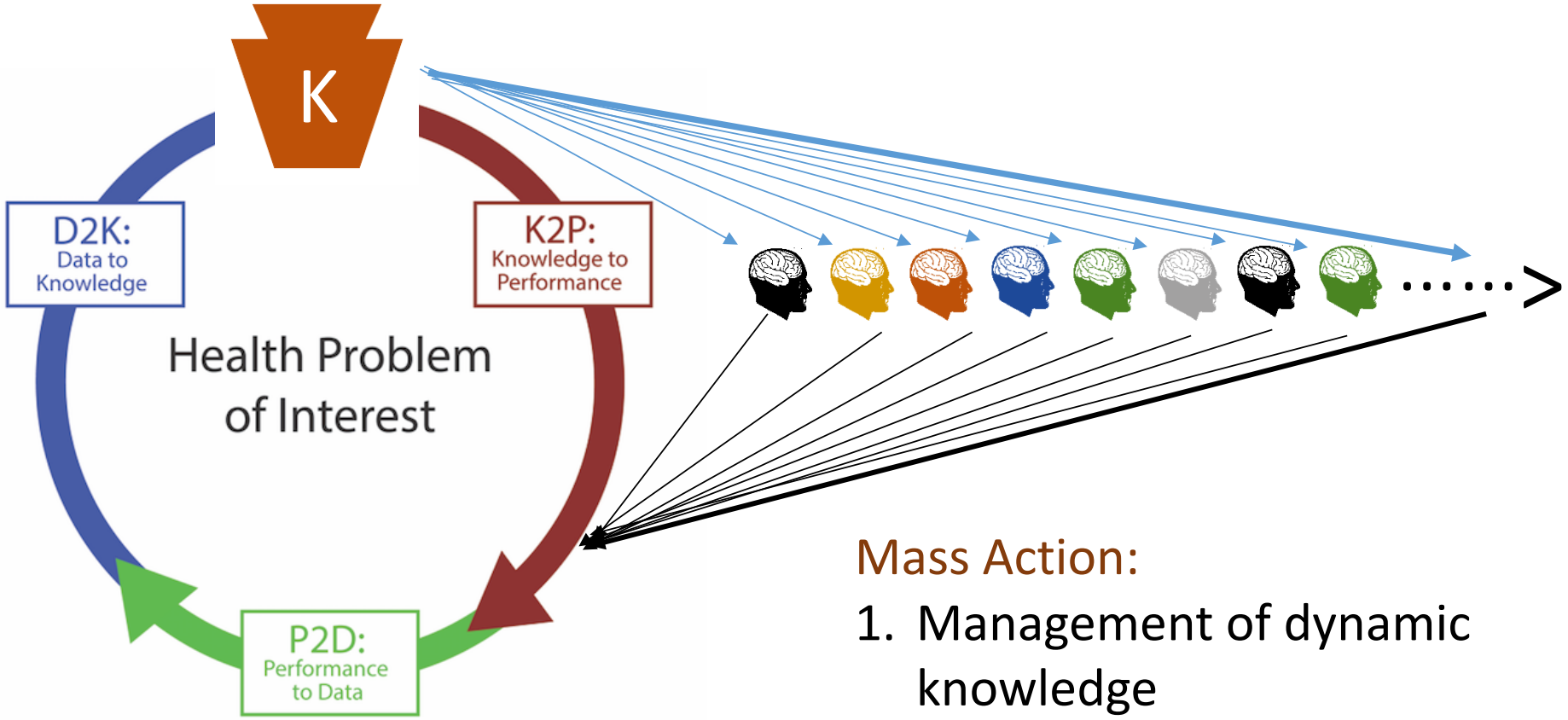
And Not This…
The "Gap" as a Major Problem



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

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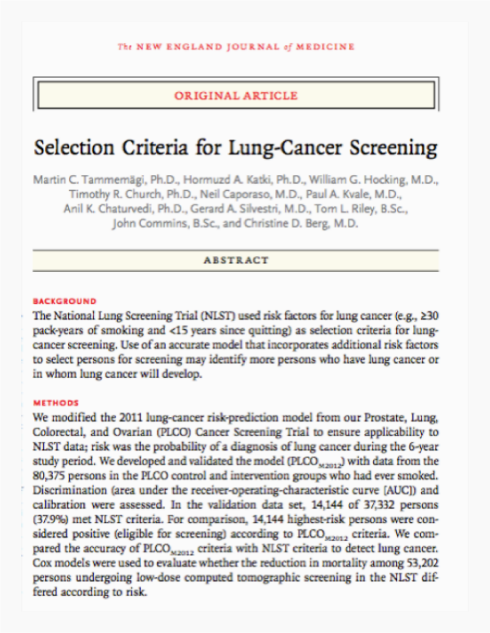
Two Complementary Ways to Represent Knowledge

Human readable in words, pictures, equations



The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Selection Criteria for Lung-Cancer Screening

Martin C. Tammemägi, Ph.D., Hormuzd A. Katki, Ph.D., William G. Hocking, M.D., Timothy R. Church, Ph.D., Neil Caporaso, M.D., Paul A. Kvale, M.D., Anil K. Chaturvedi, Ph.D., Gerard A. Silvestri, M.D., Tom L. Riley, B.Sc., John Commins, B.Sc., and Christine D. Berg, M.D.

ABSTRACT

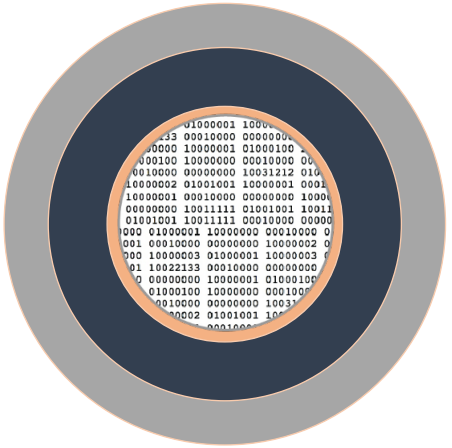
BACKGROUND

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.

Computable (machine-executable) in code



Example: Human Readable Knowledge

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From the Department of Community Health Sciences, Brock University, St. Catharines, ON, Canada (M.C.T.); the Division of Cancer Epidemiology and Genetics (H.A.K., N.C., A.K.C.) and the Early Detection Research Group, Division of Cancer Prevention (C.D.B.), National Cancer Institute, National Institutes of Health, and Information Management Services (T.L.R., J.C.) — all in Rockville, MD; Marshfield Clinic Research Foundation, Marshfield, WI (W.G.H.); the School of Public Health, University of Minnesota, Minneapolis (T.R.C.); Henry Ford Health System, Detroit (P.A.K.); and Pulmonary and Critical Care Medicine, Medical University of South Carolina, Charleston (G.A.S.). Address reprint requests to Dr. Tammemägi at the Department of Community Health Sciences, Walker Complex South, Rm. 306, Brock University, 500 Glenridge Ave., St. Catharines, ON L2S 3A1, Canada, or at martin.tammemagi@brocku.ca.

This article was updated on July 3, 2013, at NEJM.org.

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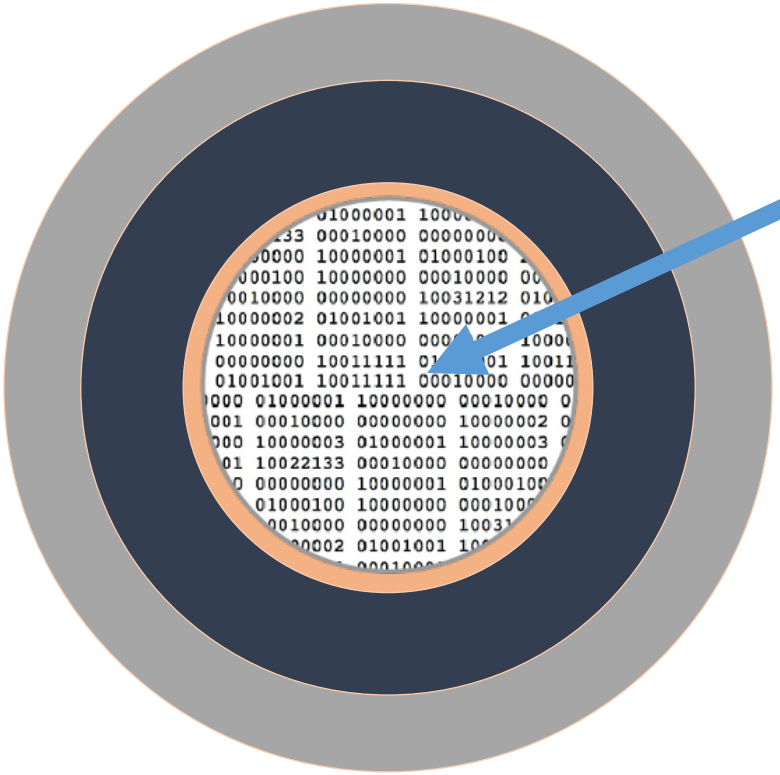
The New Knowledge (the "Result") is Expressed in a Model

Table 2. Modified Logistic-Regression Prediction Model ($PLCO_{M2012}$) of Cancer Risk for 36,286 Control Participants Who Had Ever Smoked.*

Variable	Odds Ratio (95% CI)	P Value	Beta Coefficient
Age, per 1–yr increase†	1.081 (1.057–1.105)	<0.001	0.0778868
Race or ethnic group‡			
White	1.000		Reference group
Black	1.484 (1.083–2.033)	0.01	0.3944778
Hispanic	0.475 (0.195–1.160)	0.10	−0.7434744
Asian	0.627 (0.332–1.185)	0.15	−0.466585
American Indian or Alaskan Native	1		0
Native Hawaiian or Pacific Islander	2.793 (0.992–7.862)	0.05	1.027152
Education, per increase of 1 level†§	0.922 (0.874–0.972)	0.003	−0.0812744
Body-mass index, per 1-unit increase†	0.973 (0.955–0.991)	0.003	−0.0274194
Chronic obstructive pulmonary disease (yes vs. no)	1.427 (1.162–1.751)	0.001	0.3553063
Personal history of cancer (yes vs. no)	1.582 (1.172–2.128)	0.003	0.4589971
Family history of lung cancer (yes vs. no)	1.799 (1.471–2.200)	<0.001	0.587185
Smoking status (current vs. former)	1.297 (1.047–1.605)	0.02	0.2597431
Smoking intensity¶			−1.822606
Duration of smoking, per 1-yr increase†	1.032 (1.014–1.051)	0.001	0.0317321
Smoking quit time, per 1-yr increase†	0.970 (0.950–0.990)	0.003	−0.0308572
Model constant			−4.532506

* 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 $e^{logit}/(1+e^{logit})$. CI denotes confidence interval.

And the Knowledge Can be Made Computable by Representing It as Code



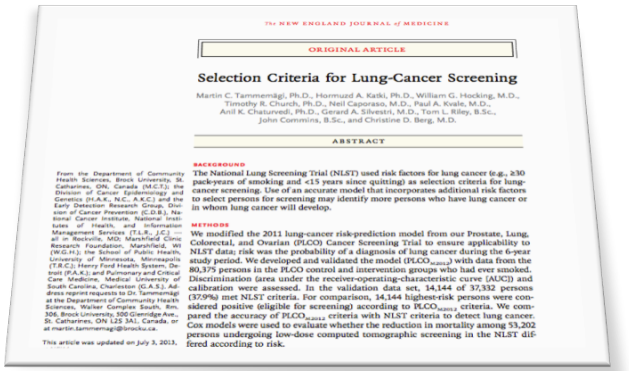
A Knowledge Object

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

Computable Knowledge Extends the Publication Pipeline

Extraction

Programming



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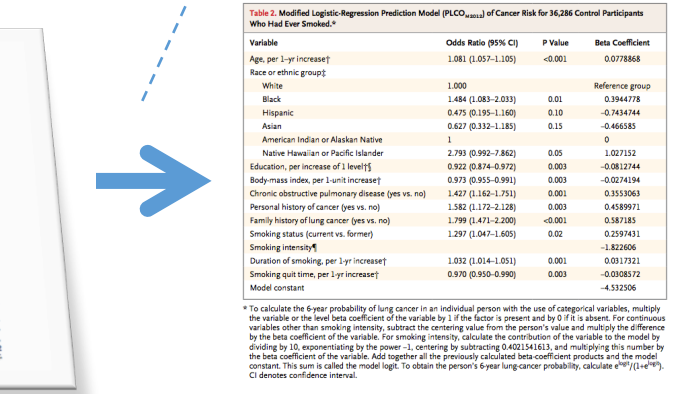
This article was updated on July 3, 2013.

Human Readable: Article



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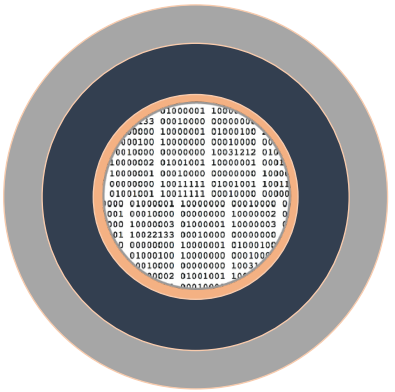
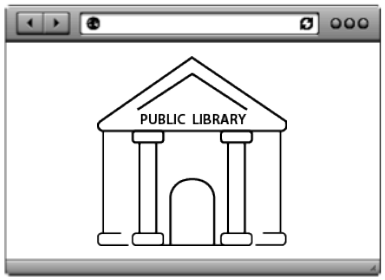
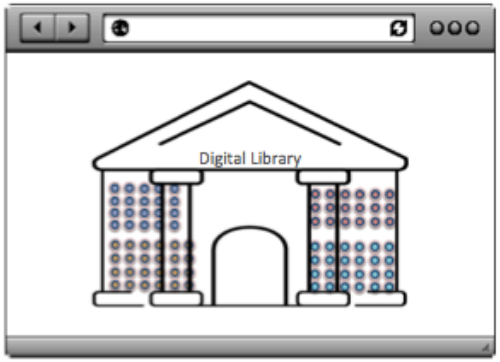
Encodable: Model



Computable: Code



Library



Expanded Library

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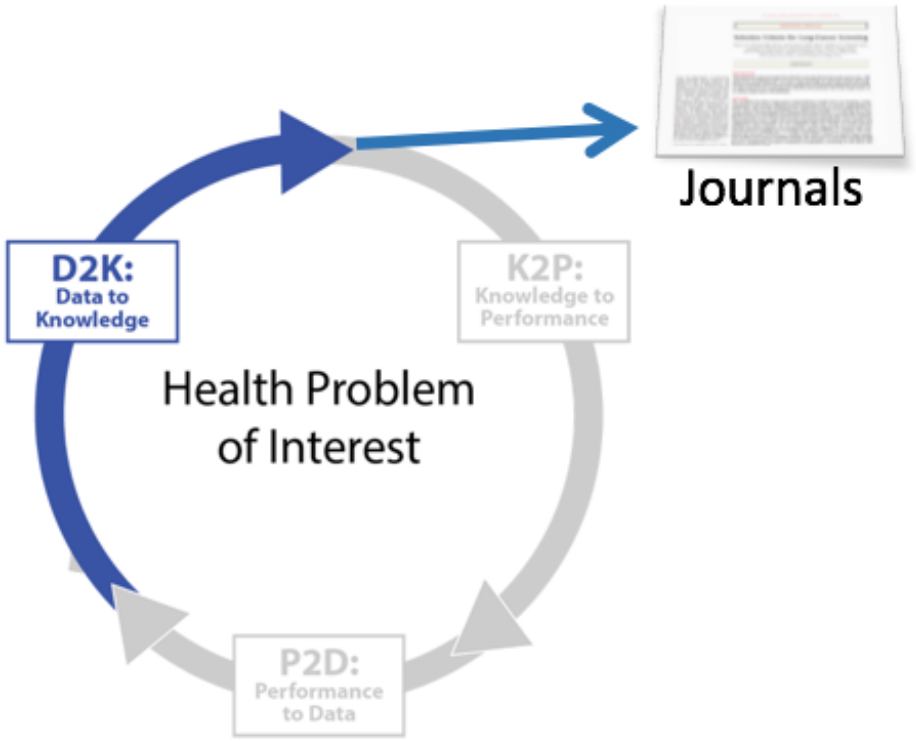
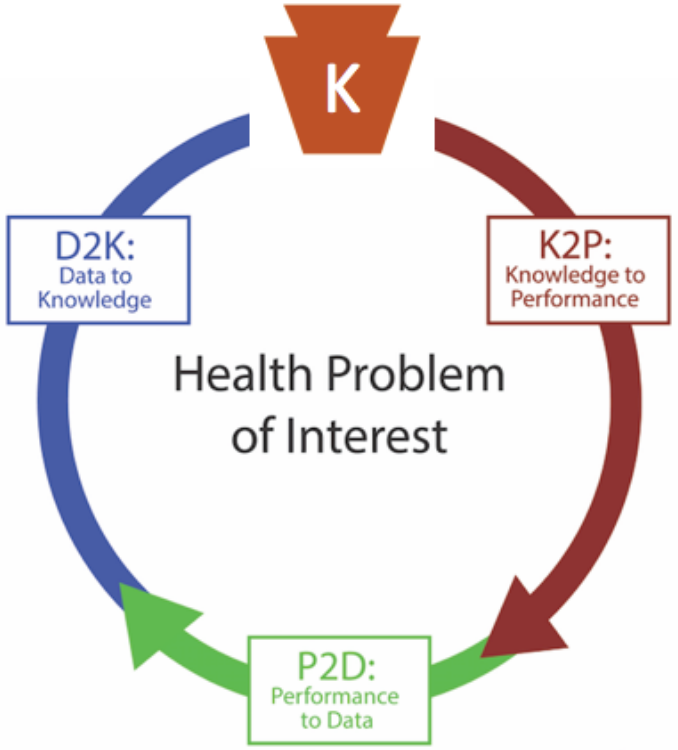
Discovery Systems vs. Learning Systems

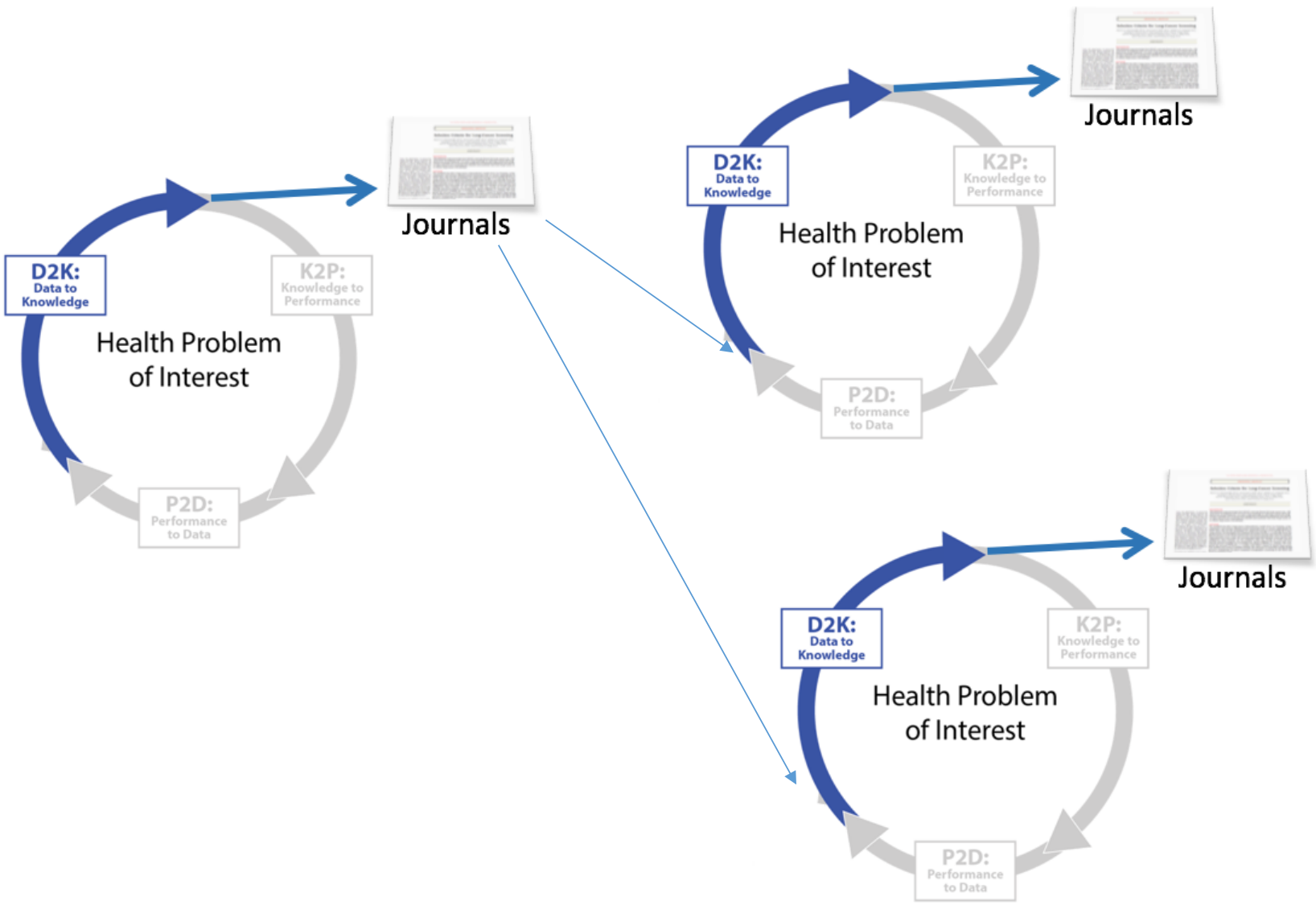


Discovery Systems

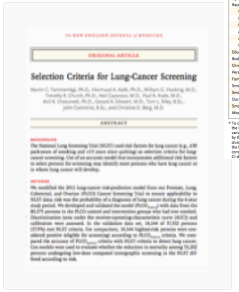


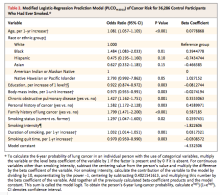
Learning Systems

Discovery Systems Require Only *Mass Access*: Human-Readable Knowledge Suffices



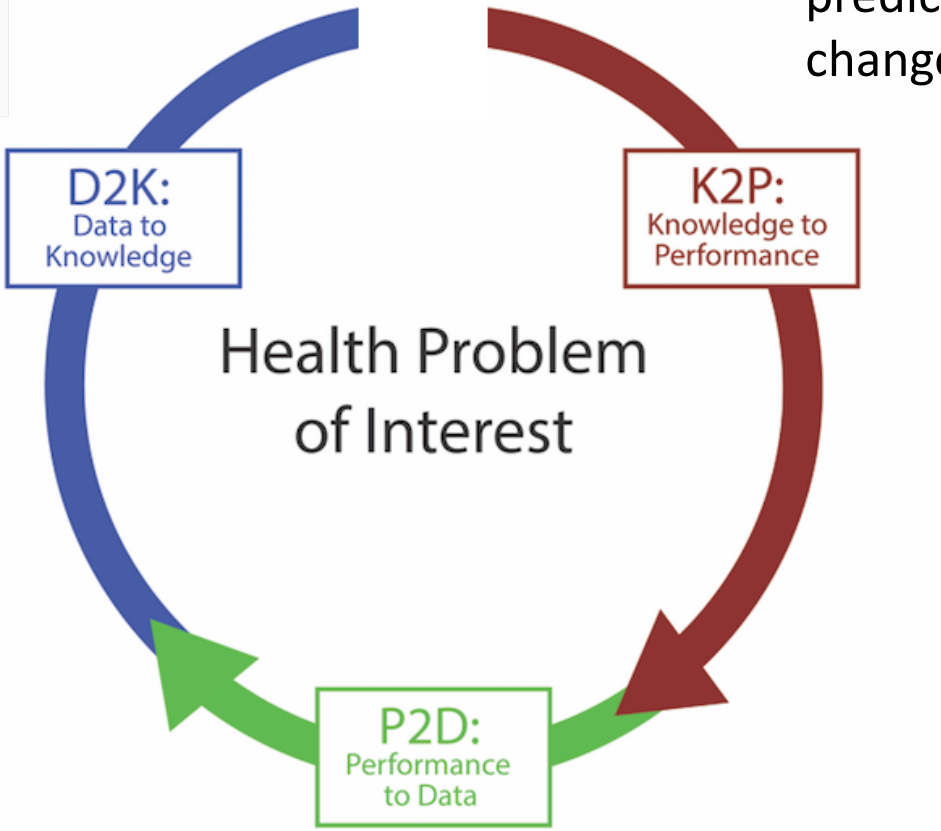
But Human-Readable Knowledge Can't Work for Learning Systems



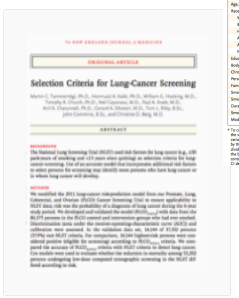


17 Year Gap

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



LHSs Need Computable Biomedical Knowledge to Bridge the Gap



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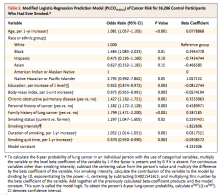

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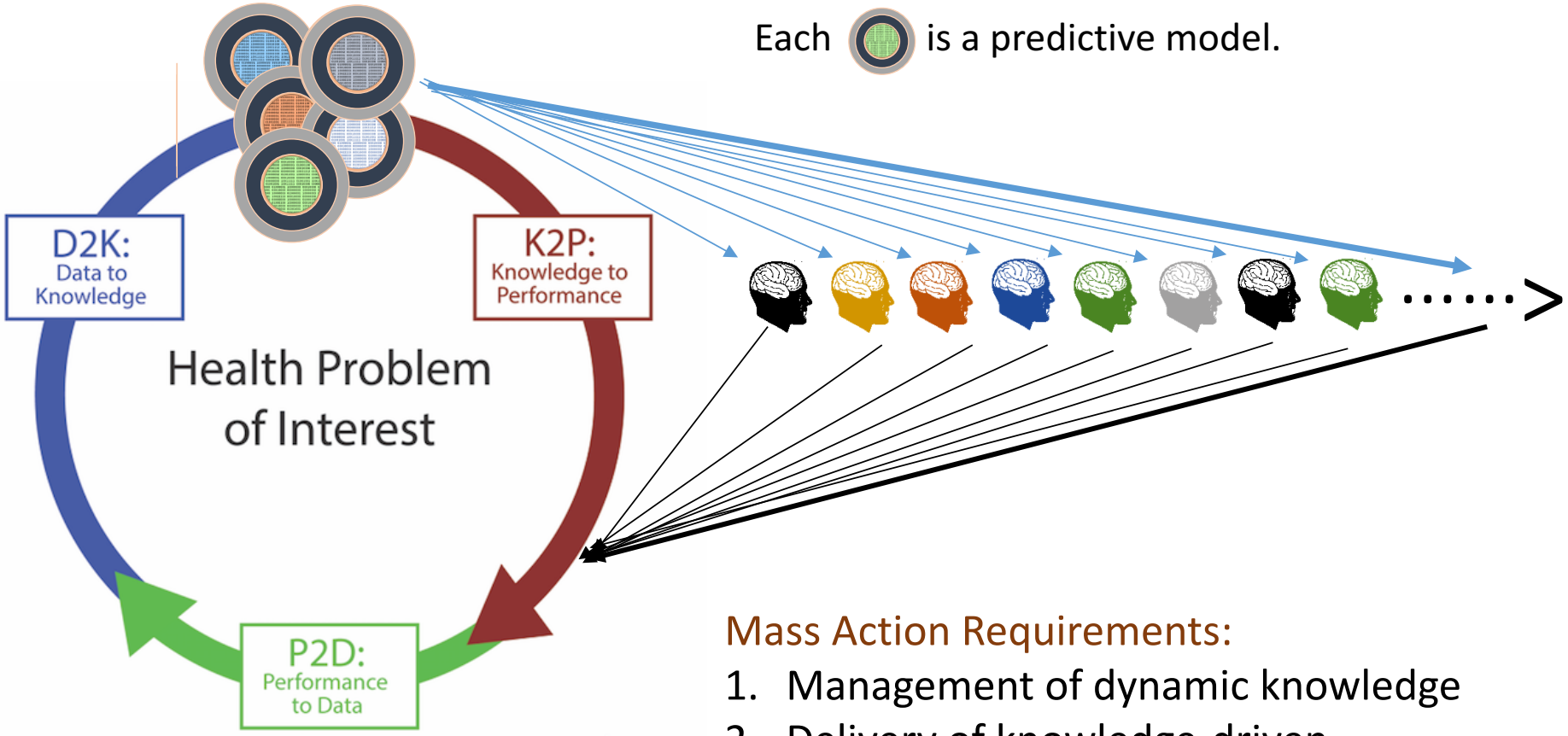
LHSs Also Need Computable Knowledge to Surpass *Mass Access*, Enabling *Mass Action*



Mass Action Requirements:

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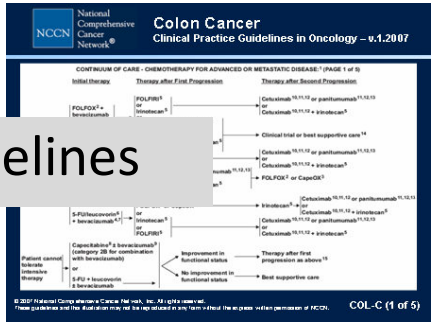
- Examples and Demos: Taking Prevention & Clinical Pharmacogenomics to Mass Action
- A Increasingly Global Movement to "Mobilize" Computable Biomedical Knowledge

Building Mass Action Infrastructure

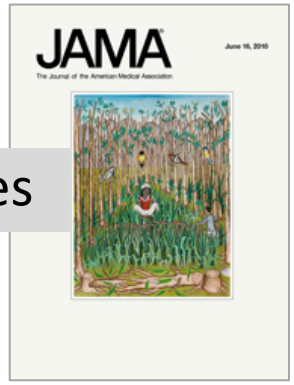
1. Represent knowledge in computable form as Knowledge Objects
2. Establish a library that holds Knowledge Objects
3. Create an “activator” to generate an intervention
4. Enable messages/advice to be delivered

1. Representing Knowledge: Machine-executable Knowledge Objects

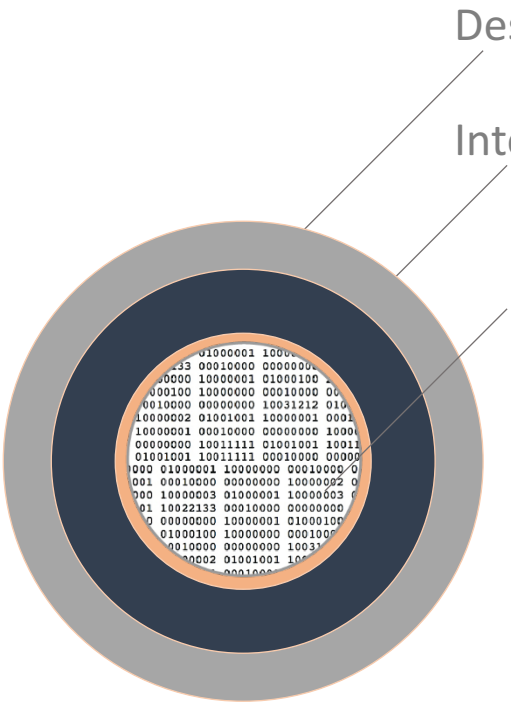
Guidelines



Articles



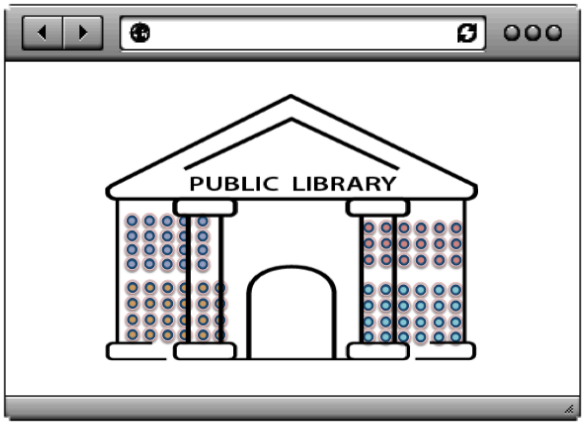
Local Analytical Results



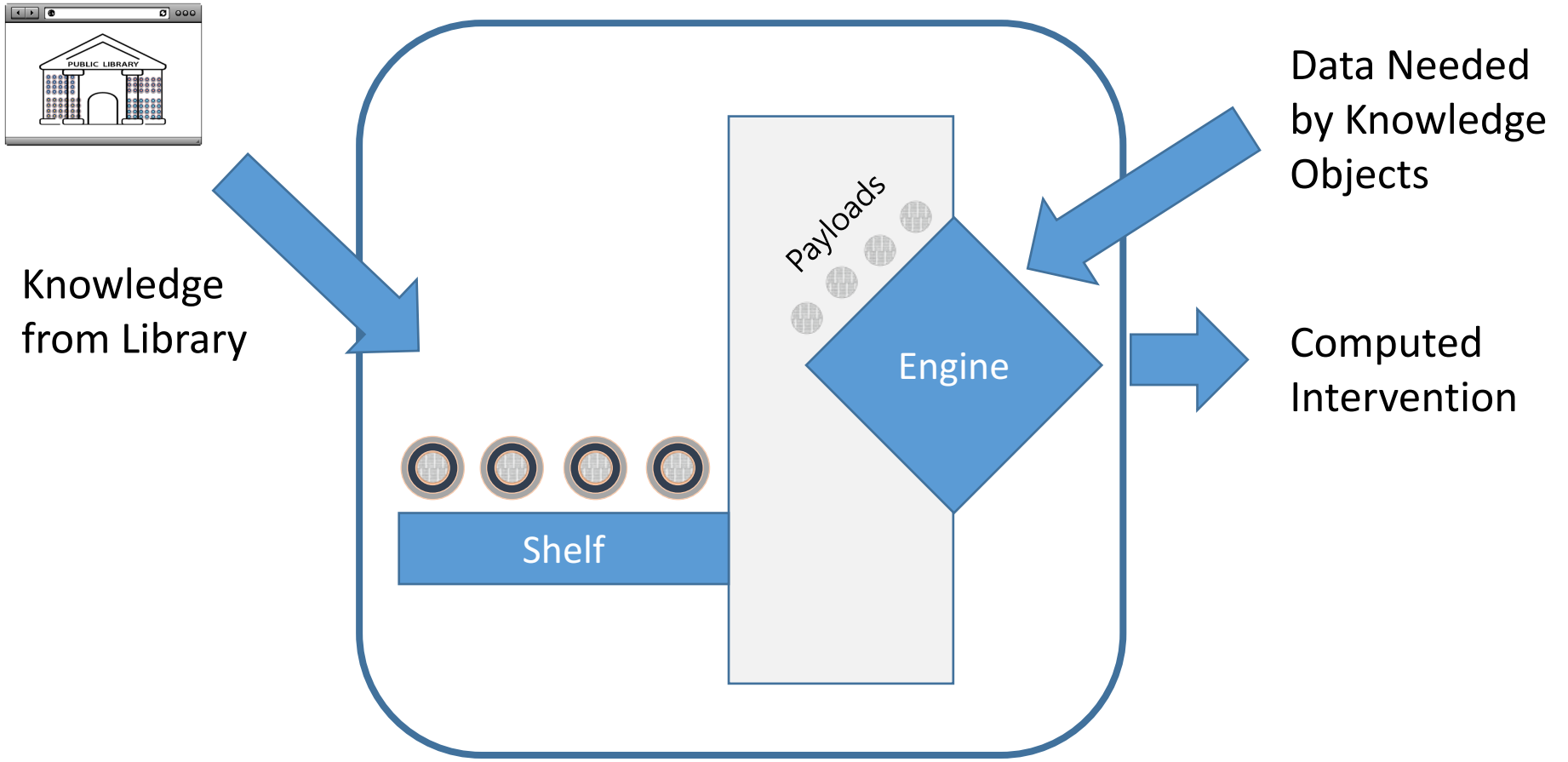
Knowledge Objects

2. A Digital Library

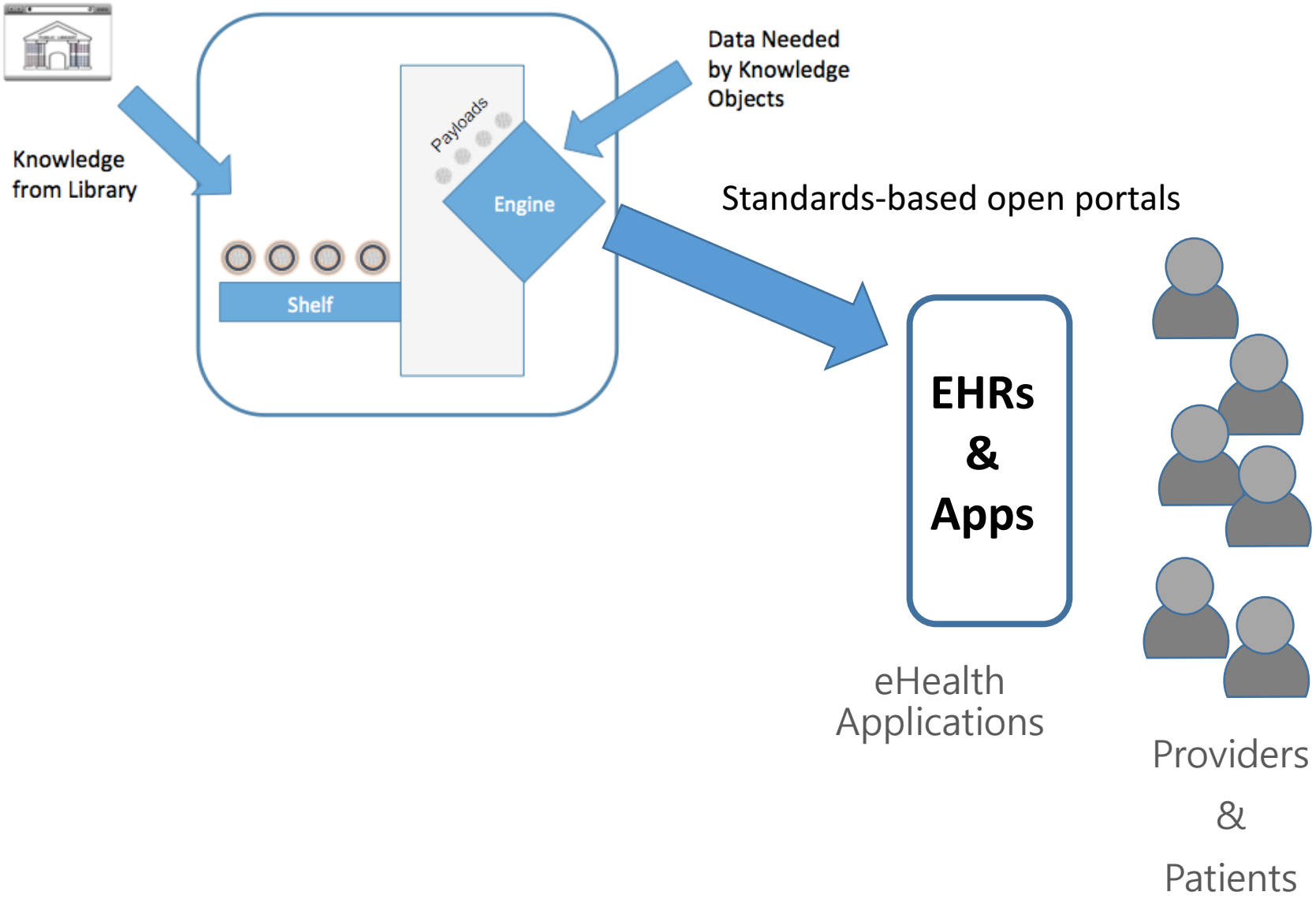
- Just like the libraries you know, except that it stores collections of computable knowledge objects
- Maintains and protects knowledge objects
- Enables them to be shared and returned



3. An "Activator" to Generate Messages



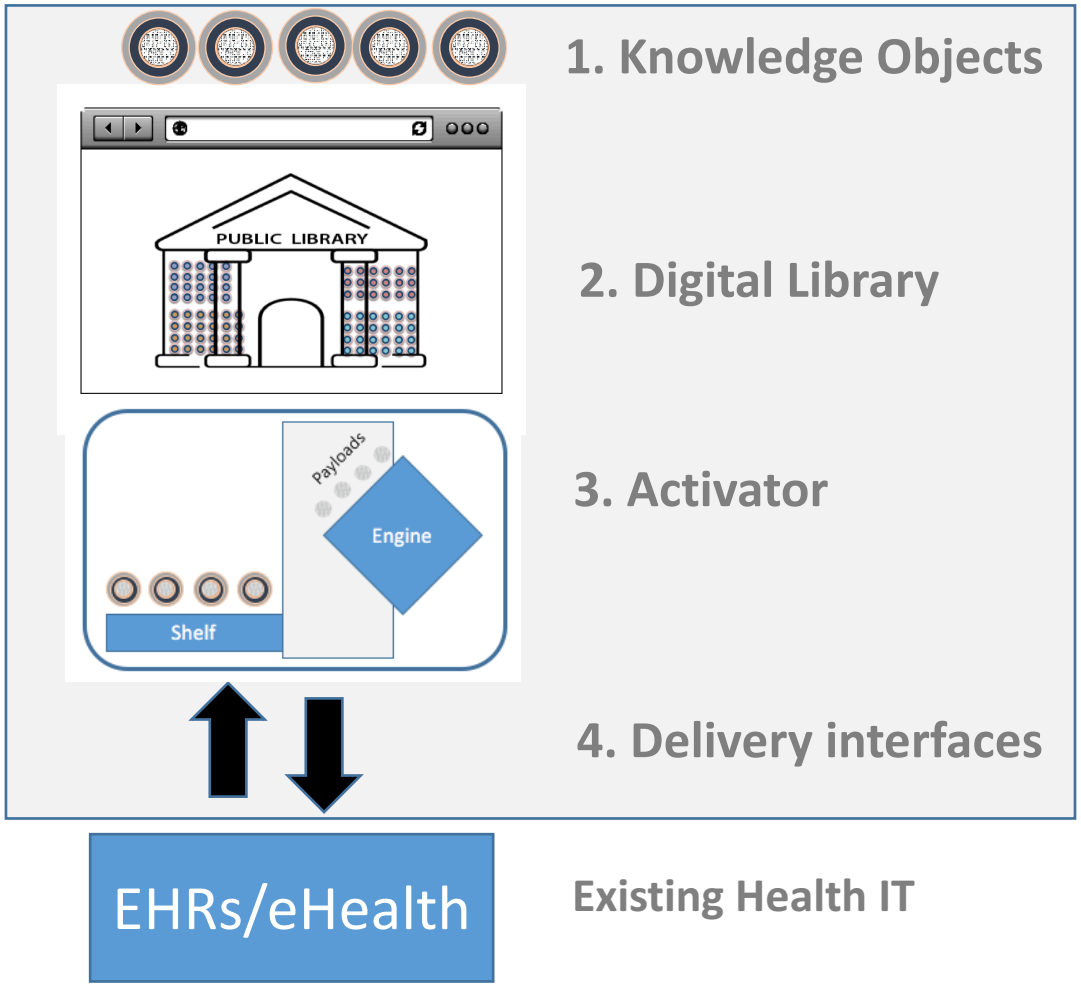
4. Delivering the Intervention



We Have Built an Infrastructure that Supports Mass Action

Knowledge Grid

Kgrid.org



Continuing the Journey

- Knowledge…
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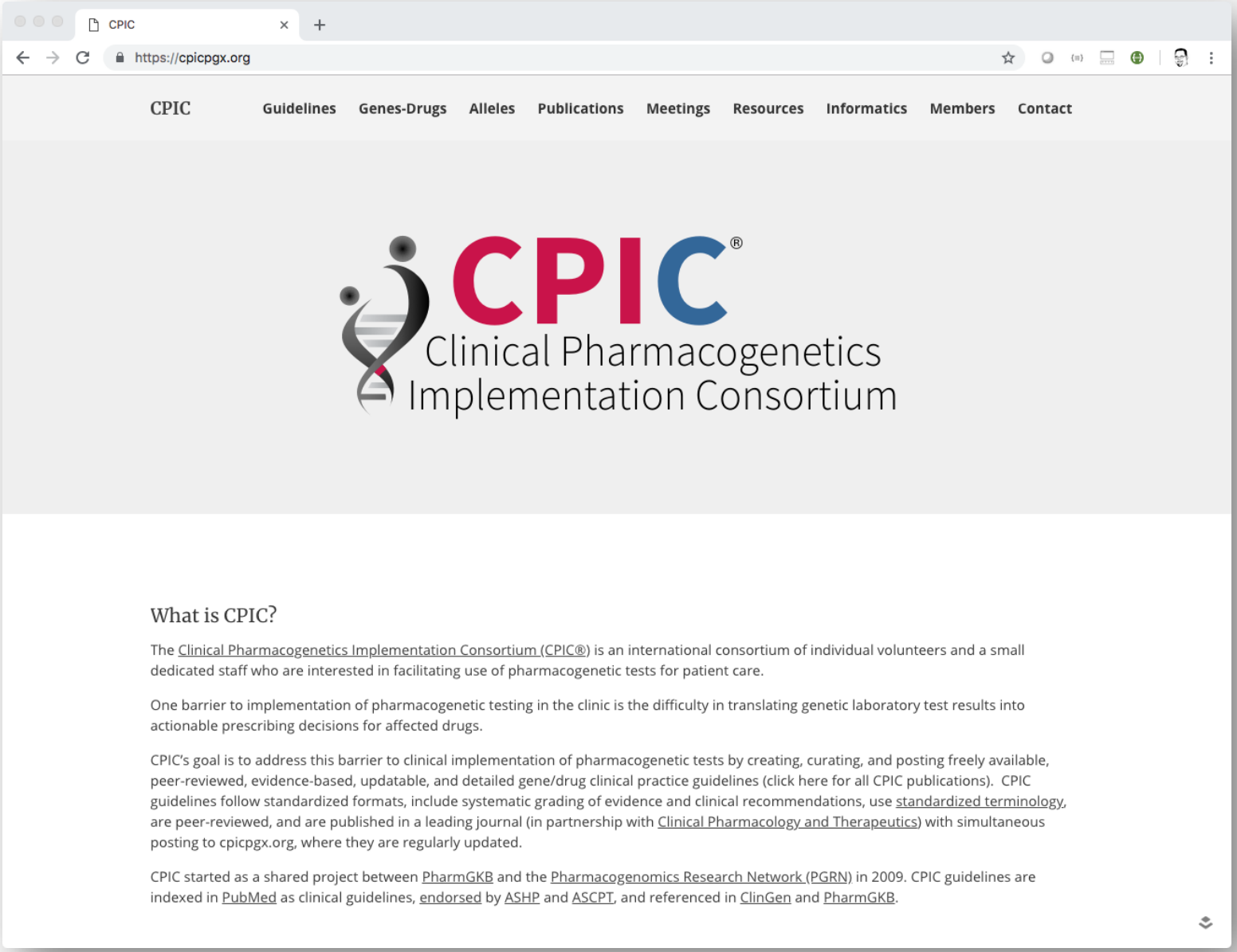
CPIC
https://cpicpgx.org
CPIC
Guidelines
Genes-Drugs
Alleles
Publications
Meetings
Resources
Informatics
Members
Contact
CPIC®
Clinical Pharmacogenetics
Implementation Consortium
What is CPIC?
The Clinical Pharmacogenetics Implementation Consortium (CPIC®) is an international consortium of individual 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 cpicpgx.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.

CPIC Recommendations in Human Readable Form (Mass Access Only!)

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

Phenotype	Implications for codeine metabolism	Recommendations for codeine therapy	Classification of recommendation for codeine therapy[a]	Considerations for alternative opioids
Ultrarapid metabolizer	Increased formation of morphine following codeine administration, leading to higher risk of toxicity	Avoid codeine use due to potential for toxicity.	Strong	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]
Extensive metabolizer	Normal morphine formation	Use label-recommended age- or weight-specific dosing.	Strong	—
Intermediate metabolizer	Reduced morphine formation	Use label-recommended age- or weight-specific dosing. If no response, consider alternative analgesics such as morphine or a nonopioid.	Moderate	Monitor tramadol use for response.
Poor metabolizer	Greatly reduced morphine formation following codeine administration, leading to insufficient pain relief	Avoid codeine use due to lack of efficacy.	Strong	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]

[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 postsurgery. Use of other analgesics in CYP2D6 poor and ultrarapid metabolizers may therefore be preferable.[18,20,21] [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.

Crews KR, Gaedigk A, Dunnenberger HM, Leeder JS, Klein TE, Caudle KE, Haidar CE, Shen DD, Callaghan JT, Sadhasivam S, Prows CA. Clinical Pharmacogenetics Implementation Consortium guidelines for cytochrome P450 2D6 genotype and codeine therapy: 2014 update. Clinical Pharmacology & Therapeutics. 2014 Apr 1;95(4):376-82.

From Human Readable Knowledge to a Computable Object

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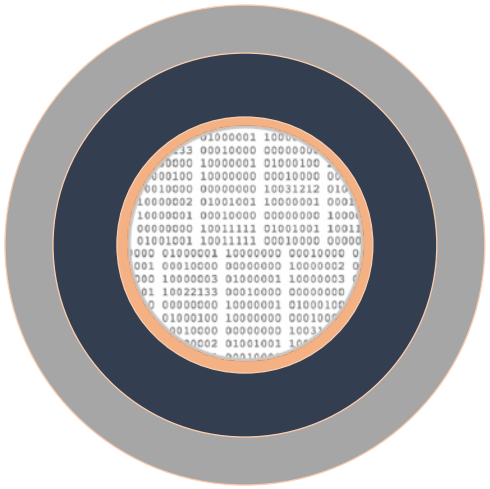

https://cpicpgx.org/guidelines/guideline-for-codeine-and-cyp2d6/

CYP2D6_Diplotype_Phenotype...

Search Sheet

Home Insert Page Layout Formulas Data Review View

Normal Page Layout Custom Views Show Zoom 100% Zoom to 100% Unfreeze Panes Freeze Top Row Freeze First Column Split View Macros Record Macro

A1 CYP2D6 Diplotype

GENOTYPE → PHENOTYPE → DOSING ADVICE

	A	B	C	D
1	CYP2D6 Diplotype	Gaedigk Activity Score (formula)	Coded Diplotype/Phenotype Summary[a]	EHR Priority Result Notation[b]
695	*3/*4xN	0	CYP2D6 Poor Metabolizer	Abnormal/Priority/High Risk
696	*3/*5	0	CYP2D6 Poor Metabolizer	Abnormal/Priority/High Risk
697	*3/*6	0	CYP2D6 Poor Metabolizer	Abnormal/Priority/High Risk
698	*3/*6xN	0	CYP2D6 Poor Metabolizer	Abnormal/Priority/High Risk
699	*3/*7	0	CYP2D6 Poor Metabolizer	Abnormal/Priority/High Risk
700	*3/*8	0	CYP2D6 Poor Metabolizer	Abnormal/Priority/High Risk
701	*3/*9	0.5	CYP2D6 Intermediate Metabolizer	Abnormal/Priority/High Risk
702	*3/*9x2	1	CYP2D6 Normal Metabolizer	Normal/Routine/ Low Risk
703	*3/*10	0.5	CYP2D6 Intermediate Metabolizer	Abnormal/Priority/High Risk
704	*3/*10x2	1	CYP2D6 Normal Metabolizer	Normal/Routine/ Low Risk
705	*3/*11	0	CYP2D6 Poor Metabolizer	Abnormal/Priority/High Risk
706	*3/*12	0	CYP2D6 Poor Metabolizer	Abnormal/Priority/High Risk
707	*3/*13	0	CYP2D6 Poor Metabolizer	Abnormal/Priority/High Risk
708	*3/*14A	0	CYP2D6 Poor Metabolizer	Abnormal/Priority/High Risk
709	*3/*14B	0.5	CYP2D6 Intermediate Metabolizer	Abnormal/Priority/High Risk
710	*3/*15	0	CYP2D6 Poor Metabolizer	Abnormal/Priority/High Risk
711	*3/*17	0.5	CYP2D6 Intermediate Metabolizer	Abnormal/Priority/High Risk

Possible CYP2D6 Diplotypes | 2D6 Interpretation consult note

Ready Count: 4 100%

Codeine-CYP2D6 Table

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

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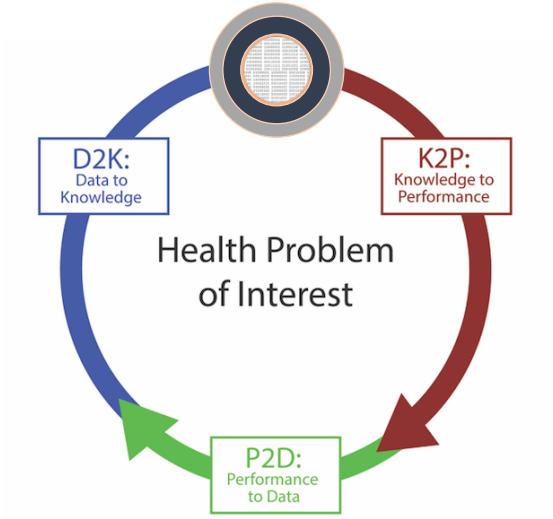
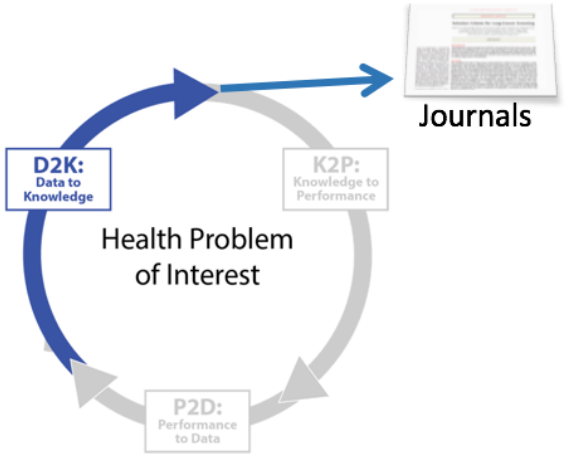
Join the Movement!

MCBK
Mobilizing Computable Biomedical Knowledge

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

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lhs.medicine.umich.edu