Agenda

11:45 AM  |  Lunch and Networking
12:15 PM  |  Welcome Remarks – Chuck Friedman
12:20 PM  |  Computable Biomedical Knowledge: A Really Big Idea
               - Chuck Friedman
12:35 PM  |  Continuing the Story and MCBK in Translational Research – Chuck Friedman and Rachel Richesson
1:10 PM   |  Q&A
1:30 PM   |  Adjourn
Upcoming Seminar Series

**LHS Collaboratory**

About the Learning Health System (LHS) Collaboratory: Across the U-M campus, many faculty, students, and staff share interest in the concept of an LHS. By creating a campus-wide hub for these interests, the LHS Collaboratory advances interdisciplinary research and promotes the development of learning health systems. Through collaboration, U-M could become the world-wide academic epicenter for the LHS, and the Collaboratory seeks to realize that potential.

Join peers, thought leaders, LHS subject matter experts, and others interested in Learning Health Systems at one of these informative events for the Winter 2019 LHS Collaboratory Seminar Series.

**Location:**
Palmer Commons, Great Lakes North Central

**Nancy Kass, ScD, Johns Hopkins**
*Ethics for a Learning Health System: The “Common Purpose” Framework*
Tuesday, February 12 - 12:00 - 1:30pm

**Peter Margolis, MD, PhD, Cincinnati Children’s Hospital**
*Healthier Together: Collaborative Networks of Patients, Clinicians and Researchers Working Together to Transform Care*
Tuesday, March 19 - 12:00 - 1:30pm

**LHS Spring Symposium**
*Action-oriented event connecting researchers and others across campus with an interest in Learning Health Systems*
Thursday, April 18 - 8am - 12pm

For more information or to register, contact LHSCollaboratory-info@umich.edu or visit ghna-umi.ch/lhs-collaboratory.
Computable Biomedical Knowledge: A Really Big Idea

Charles P. Friedman, PhD
Josiah Macy, Jr. Professor
Chair, Department of Learning Health Sciences
Professor of Information and Public Health
University of Michigan
January 15, 2019
A Way to Think About Knowledge

The result of an analytical and/or deliberative process that holds significance for an identified community.

Analysis makes data into “proto-knowledge”. To become knowledge, it must be reviewed and endorsed.
Examples of Biomedical Knowledge

• Predictive models

• Best practices (guidelines)

• Decision Trees

• Policies governing research conduct
Persistent Knowledge in Two Forms

• **Persistent Knowledge:** An explicit representation exists at any point in time

• Persistent knowledge can be represented in two ways:
  – Human readable (words, pictures, equations)
  – Computable (machine code)

• Persistent knowledge ≠ Static knowledge
Two Complementary Ways to Represent Knowledge

Human readable in words, pictures, equations

Computable (machine-executable) in code

Library Holdings: Books & Journals

Library Holdings: Will add Digital Knowledge Objects
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_{2012}) 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_{2012} criteria. We compared the accuracy of PLCO_{2012} 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 is Expressed in a Model

Table 2. Modified Logistic-Regression Prediction Model (PLCO\text{m2012}) of Cancer Risk for 36,286 Control Participants Who Had Ever Smoked.\textsuperscript{a}

<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\textsuperscript{†}</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\textsuperscript{‡}</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>1.000</td>
<td>Reference group</td>
<td></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</td>
<td>0</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\textsuperscript{†\‡}</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\textsuperscript{†}</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\textsuperscript{‡}</td>
<td></td>
<td></td>
<td>–1.822606</td>
</tr>
<tr>
<td>Duration of smoking, per 1-yr increase\textsuperscript{†}</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\textsuperscript{†}</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>

\textsuperscript{a} 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 Coded “Knowledge Objects”

Example: A computer program that takes in characteristics of a person and computes a risk score for that person
What the LHS Requires: Discovery Systems vs. Learning Systems

Discovery Systems

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

Journals
(Human-Readable)

Learning Systems

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

Knowledge Objects
(Machine readable)
Serial Discovery Systems Require Only Mass Access to Knowledge

To enable **mass access**, persistent human-readable knowledge is sufficient.
Parallel Learning Systems Require Mass Action Supporting Learning Communities at Any Level of Scale

To enable mass action, persistent computable knowledge is essential.
An Extended Publication Pipeline to Support Mass Action and Learning Systems

Human Readable: Article

Extraction

Computable: Code

Programming

Encodable: Model

Library

Expanded Library
Libraries of Computable Knowledge Can be Linked
Imagine a Global Computable Knowledge Ecosystem
The Importance of This Idea

The Atlantic, 2018


U.S. National Library of Medicine, 2017

Mobilizing Computable Biomedical Knowledge in Translational Research

Rachel Richesson, PhD, MPH,
Duke University

January 15, 2019
Outline

• MCBK – Continuing the story

• MCBK in Translational Research: Perspective from NIH Collaboratory

• Discussion
MCBK - Inaugural Public Meeting

July 10-11, 2018

Lister Hill National Center for Biomedical Communications

National Library of Medicine
Meeting Components

• Federal guest speakers
  • Dr. Don Rucker (ONC)
  • Dr. Patti Brennan (NLM)
  • Dr. Eric Dishman (NIH, *All of Us*)

• Manifesto Review and Reactor Panel
• Panel - State of the Art for CBK
• Poster Session, System Demos, & Reception
• Breakout Discussions – Developing Action Plans
  • Report & Synthesis
• “Open Mic”
Outcomes of Meeting

• Advance MCBK agenda with theme-based workgroups
• Develop supportive infrastructure (website, communications)
• Create webinar series
• Plan for 2nd public meeting for summer 2019
• Interim “governance”
  • Meeting Planning Committee ➔ Steering Committee
  • University of Michigan interim home/resource hub
Workgroups Leading the Charge

- **Standards for MCBK**
  - Bob Greenes, MD, PhD

- **Technical Infrastructure for MCBK**
  - Leslie McIntosh, PhD, MPH
  - Chris Shaffer, MS

- **Policy & Coordination to Ensure Quality & Trust**
  - Blackford Middleton, MD, MPH, MSc
  - Jody Platt, PhD, MPH

- **Sustainability for Mobilization and Inclusion**
  - Chris Dymek, Ed.D.
  - Jerry Perry, MLS
Standards for MCBK

• Standardize descriptions for characterizing CBK
  • Identify axes for metadata,
    • e.g., domain, type of knowledge, derivation, users, and context-situation attributes

• Develop a spanning set of use cases for CBK and knowledge-sharing scenarios

• Standardize knowledge representation for different CBK types
Technical Infrastructure

- Identify the landscape of infrastructure stakeholders
- Describe the framework components necessary to move CBK from generation to practice by facilitating testing, versioning, use, evaluation, scalability, interoperability, and dissemination of CBK
- Develop use cases connecting stakeholders to framework components
- Act as a clearinghouse for news and events of interest to infrastructure stakeholders
# Policy and Coordination to Ensure Quality and Trust

**How do we ensure quality and trust in CBK?**

<table>
<thead>
<tr>
<th>Components:</th>
<th>Characteristics:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Validity</td>
<td>Transparency</td>
</tr>
<tr>
<td>Authorship/ Review/ Publication criteria</td>
<td>Reliability</td>
</tr>
<tr>
<td>Evidence</td>
<td>Reproducibility</td>
</tr>
<tr>
<td>Currency (up-to-date)</td>
<td>Consistency</td>
</tr>
<tr>
<td>Audit</td>
<td>Provenance</td>
</tr>
<tr>
<td>Credentialing</td>
<td>Accessibility</td>
</tr>
<tr>
<td>Software</td>
<td>Relevancy</td>
</tr>
<tr>
<td>Interoperability</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Challenges:</th>
<th>Characters:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Governance</td>
<td>Users (patients, providers, payors, communities)</td>
</tr>
<tr>
<td>Adjudication of knowledge/ Prioritization</td>
<td>Engineers</td>
</tr>
<tr>
<td>Aligning incentives (Buy-in, acceptability)</td>
<td>Vendors</td>
</tr>
<tr>
<td>Validity/ Validation</td>
<td>System administrators</td>
</tr>
</tbody>
</table>

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Policy and Coordination to Ensure Quality and Trust

- Identify policy gaps and issues that impact quality and trustworthiness of the data and knowledge.

- Coordinate efforts to apply, evaluate, and build upon the Trust Framework to ensure that all stakeholders can participate as trusted and trustworthy agents.

- Ensure robust and unbiased methods to support
  - transparency
  - FAIRness, and
  - currency, validity, and provenance of CBK
Policy and Coordination to Ensure Quality and Trust

Next Steps

• Understand the current landscape for governance and policies for CBK (to ensure trust)

• Define attributes for CBK “product information labels” that would promote transparency and trust

• Develop and test model governance structures
Sustainability for Mobilization and Inclusion

• Mobilize diverse stakeholders around value proposition of CBK
• Communications and engagement with stakeholders are essential to equitable and FAIR* CBK ecosystem
• Seek engagement through diverse and active communication with stakeholder communities:
  • creator
  • hosting and dissemination
  • consumer
  • funding communities
Outline

• MCBK – Continuing the story

• MCBK in Translational Research: Perspective from NIH Collaboratory

• Discussion
Background: Research Networks

- NIH Rare Diseases Clinical Research Network
- The Environmental Determinants of Diabetes in the Young (TEDDY)
- Type 1 Diabetes TrialNet
- Cystic Fibrosis TDN
- PCORnet
- NIH Distributed Research Network
- SCD Implementation Consortium
- NIH Health Systems Research Collaboratory
NIH Health Care Systems Research Collaboratory
Enabling pragmatic clinical trials embedded in health care systems

Initiated through the NIH Common Fund in 2012

Goal: Strengthen the national capacity to implement cost-effective large-scale research studies that engage health care delivery organizations as research partners

Vision: Support the design and execution of innovative pragmatic clinical trial Demonstration Projects to establish best practices and proof of concept
Definition

• Pragmatic clinical trials (PCTs) are research investigations embedded in healthcare settings designed to increase the efficiency of research and relevance to clinical practice.
Embedded PCTs Bridge Research into Clinical Care

- Study designed with input from health system stakeholders
- Intervention incorporated into routine clinical workflow
- Data collected through EHR in health care settings
- Diverse, representative study populations
- Outcomes important to decision makers
Demonstration Projects

- PCTs conducted within health care systems to address questions of major public health importance
- Span multiple Institutes & Centers
- 1-year planning phase (UH3)
- Implementation phase (UG3)
LIRE Lumbar Imaging with Reporting of Epidemiology

• Cluster trial evaluating whether **inserting epidemiologic benchmarks** into lumbar spine imaging reports reduces subsequent tests and treatments
• 98 clinical sites
• 246,289 patients
TSOS  *Trauma Survivors Outcomes and Support*

- Stepped-wedge cluster trial testing innovative intervention for patients with PTSD and comorbidity
- 25 level 1 trauma centers
- 960 expected patients
Nudge  Personalized Patient Data and Behavioral Nudges to Improve Adherence to Chronic Cardiovascular Medications

• Patient-level randomized pragmatic trial comparing the effects of digital interventions (text messages and chat bot) on medication adherence in patients with chronic cardiovascular conditions

• 3 health systems
PRIM-ER Primary Palliative Care for Emergency Medicine

• Cluster trial testing the effects of implementing primary palliative care in emergency medicine on healthcare utilization and survival

• 35 emergency departments across 18 health systems
Sharing Challenges & Solutions

The Living Textbook of Pragmatic Clinical Trials

www.rethinkingclinicaltrials.org

The National Institutes of Health (NIH) Health Care Systems Research Collaboratory Coordinating Center is supported by the NIH Common Fund, through a cooperative agreement from the Office of Strategic Coordination within the Office of the NIH Director (Grant # 1U24AT009676-01). The views presented here are solely the responsibility of the authors and do not necessarily represent the official views of the National Institutes of Health.
Common Themes

- Plan for broad roll-out of successful interventions
- Design trial with dissemination in mind
- Sustainability plans
- Data & resource sharing requirements
CBK in Pragmatic Trials

• Can be the intervention
• Can support the intervention
• Can facilitate the assessment of implementation, conduct of trial, or analysis
CBK in LHS and PCTs

- Interpret Results
- Assemble Data
- Analyze Data
- Capture Practice as Data
- Design Intervention
- Take Action

“FAIR” CBK

Health Problem of Interest

D2K: Data to Knowledge

K2P: Knowledge to Performance

P2D: Performance to Data
Thank you!

The National Institutes of Health (NIH) Health Care Systems Research Collaboratory Coordinating Center is supported by the NIH Common Fund, through a cooperative agreement from the Office of Strategic Coordination within the Office of the NIH Director (Grant # 1U24AT009676-01). The views presented here are solely the responsibility of the authors and do not necessarily represent the official views of the National Institutes of Health.
Get involved!

• Website – www.MobilizeCBK.org
• General Email – MCBK-Info@umich.edu
• Join a workgroup – complete the survey or email us! http://bit.ly/MCBKweb2
• Promote and attend webinars
• Plan to attend next MCBK meeting July 18-19, 2019