# Connection

**BMIR**
**Stanford Center for Biomedical Informatics Research**

| Winter 2021 | *We Connect Data to Health* |

## A Commitment to Building Durable Technologies

As you will read below and on the next page of this issue of *Connection*, BMIR is engaged in building technologies that endure. In the case of Mary Goldstein's work from the 1990s on a knowledge-based clinical decision support (CDS) system, that CDS system is still serving the VA Palo Alto Health Care System. In another case, Samson Tu's current work for the World Health Organization builds on the WebProtégé tool, which WHO uses for editing ICD-11 disease-related information. WebProtégé was developed by BMIR more than a decade ago.

Our commitment to building truly useable software presents us with opportunities to perform research that distinguishes BMIR from other organizations.

While the technologies built by BMIR have been well chronicled in the literature, they are so much more than software engineered for peer review. We have built numerous durable technologies that can be a basis for ongoing experimentation. Protégé, for example, has provided the foundation for research in decision support, data abstraction and visualization, knowledge graphs,

and knowledge management. A further advantage to building these robust systems is the opportunity to deploy them so that collaborators can use them in multiple ways. That capability allows us to study the durable effects of technologies that otherwise would be ephemeral.

*Mark Musen, MD, PhD*
Director, Stanford Center for Biomedical Informatics Research

## CLINICAL CARE     Early BMIR Work Is Still Helping CDS at the VA



A knowledge-based clinical decision support (CDS) system that was built upon software tools developed by BMIR remains in use after nearly a quarter century at VA Palo Alto Health Care System.

Mary K. Goldstein, MD (above), with Stanford's Center for Health Policy/Center for Primary Care and Outcomes Research and the Office of Geriatrics and Extended Care in the Veterans Health Administration, said the system was developed to support pri-

mary-care staff in providing evidence-based treatment for patients with hypertension, one of the most prevalent diagnoses in adult medicine.

In the late 1990s, Dr. Goldstein collaborated with fellow Stanford faculty member Brian B. Hoffman, MD, at VA Palo Alto and Mark Musen, MD, PhD, and his group in BMIR. They initially encoded a computable knowledge base of hypertension clinical knowledge using Protégé, the knowledge-acquisition software that BMIR developed.

There was further work in knowledge representation with BMIR academic staff, including the internationally recognized expertise of Samson Tu, MS, and with VA Palo Alto, whose health informatics staff understood the importance of providing evidence-based CDS for clinical providers.

Those innovative approaches to implementing technologies led to development of an architecture for extracting patient data, processing it with the knowledge base, generating recommendations, and displaying recommendations to primary care pro-

viders (PCPs) in a computer window that displayed on top of the patient's electronic health record and could be viewed on the screen in real time.

The original system was created to help PCPs in managing hypertension. Over time, the VA Palo Alto-based team has built on that system so that today it has evolved into a new CDS system that can be displayed within a clinical dashboard for additional diseases including diabetes. The current program, known as Med Safe CDS, still uses Protégé and a lot of the concepts—and program code—from the original work.

"Many decision support systems are based on simple rules with branching logic that reach a limit of how much complexity they can handle. At the VA, we wanted to be able to take account of more patient complexity so that multiple patient clinical characteristics would be processed at the same time. The underlying system for doing this has allowed us to generate much more complex recommendations than could be done with a rule-based branching logic system," Dr. Goldstein said.

Laying the Foundation for New WHO Controlled Terminologies
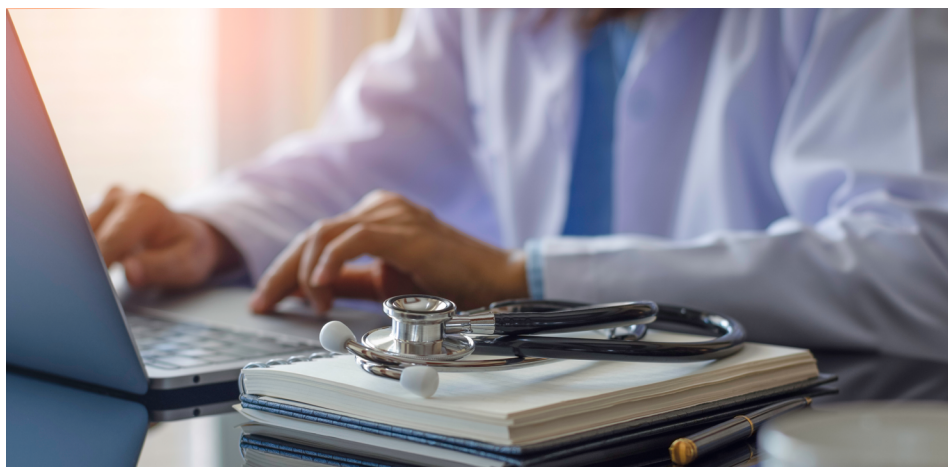


Samson Tu, MS, senior research scientist, emeritus, at BMIR, is playing a leading role as the World Health Organization (WHO) develops a new system for producing future versions of international classifications that are consistent with each other and that may span across diseases, interventions, and functional assessment.

These capabilities stem from activities of the World Health Organization Family of International Classifications (WHO-FIC) Network.

Tu, who co-chairs the WHO-FIC Network Informatics and Terminology Committee, explained that the WHO-FIC is a set of classifications that can be used to support the production of health information nationally and internationally to assess the health of individuals and populations and to inform health system financing and resource allocation, evidence-based practice, monitoring of health outcomes, and access to services.

"The WHO-FIC provides a standardized common language for coding a wide range of information about health and wellbeing,

and about interventions delivered to individuals and populations," Tu said.

The WHO-FIC includes three core classifications: the International Statistical Classification of Diseases and Related Health Problems (ICD), the International Classification of Functioning, Disability and Health (ICF), and the emerging International Classification of Health Interventions (ICHI).

ICD is used to categorize diseases and other related health problems, such as symptoms and injury. ICF categorizes functional status, health, and wellness, and ICHI categorizes health interventions.

The three classifications cover the main parameters of health and the health system, such as death, disease, functioning, disability, health, and health interventions. While ICD and ICF have already gained wide acceptance, ICHI is a new classification that awaits endorsement of the World Health Assembly. In addition, they may be used as models for the development or revision of other classifications, with respect to the

structure, the character and definition of the categories.

"Our job is to place all the WHO's core classifications within the same framework, and we are doing that by developing a harmonized content model for the WHO-FIC classifications," Tu said.

That work builds on the ICD Collaborative Authoring Tool (iCAT), a WebProtégé tool for editing ICD-11 information that was developed by Tania Tudorache, PhD, and software engineer Csongor Nyulas when they were research scientists in the Protégé group at BMIR.

Dr. Tudorache and Nyulas, who now reside in Romania, continue to maintain the iCAT software for the WHO. In addition to serving as the curation platform for ICD-11, iCAT will become the curation platform for the other two WHO-FIC core classifications.

Future development of iCAT means modernizing the software that's currently being used in the iCAT platform. The current software is based on an earlier version of Protégé.

"There are a number of differences in the current and previous versions of the Web Ontology Language that Protégé supports. So another area of the work that I am pursuing is how to migrate this modeling and software from the earlier version of Protégé to the current version," Tu explained.

He expects to be involved not only in the modeling but also in the content alignment in areas where these classifications overlap and said that he hopes to use techniques from ontological modeling to express the relationships among aligned entities more precisely.

Division Hosts Research Colloquia

Continuing a practice that began more than 30 years ago, BMIR hosts weekly research colloquia as an open scientific forum for sharing ideas on high stakes issues related to informatics, data, statistics, and health care in general.

Recent colloquia have addressed controversial topics such as "Reconsidering the Use

of Race Correction in Clinical Algorithms" and "COVID-19 Antibody Seroprevalence," featuring high profile speakers, including David Jones, MD, PhD; Eran Bendavid, MD; Jay Bhattacharya, MD, PhD; Frank Harrell, PhD; Graham Walker, MD; and Joseph Ross, MD, MHS.

Upcoming programs include Dan Riskin, MD, addressing "Real-World Evidence: State of the Industry" and Gary Collins, PhD, speaking on "(Lack of) Quality of Prediction Research."

Complete details of all upcoming colloquia and recordings of past programs are available here.

The Stanford Center for Biomedical Informatics Research is expanding its clinical engagement by recruiting for a clinically active faculty member.

"This is a unique opportunity for someone with demonstrated expertise in informatics as well as board eligibility in internal medicine," said Nigam Shah, MBBS, PhD, who is chairing the search committee.

Dr. Shah said the ideal candidate might be a clinically trained health services researcher who is skilled at evaluating algorithm-guided care delivery. Alternatively, the candidate might be a practicing clinician who is primarily motivated to use informatics for quality improvement.

"No matter where they land on the spectrum, the successful candidate would have a thorough understanding of how information can be used as well as a deep understanding of informatics. They will also be expected to conduct a vigorous, independent research program, and to advise students in a graduate program in biomedical informatics" Dr. Shah said.

BMIR connects data to health. The interest in recruiting a clinically active faculty member ties directly to the division's mission of using data and computation to improve patient care.

"From a practical standpoint, the new faculty member can bring pressing clinical problems to our attention. Likewise, after we develop a proposed solution to the problem, that person can help bring the solution back to the clinic," Dr. Shah noted.

"For the practicing clinician who sees the potential in the use of data and algorithms to improve care, this is their opportunity to work with some of the top people in data science and to shape how data are used to improve care," Dr. Shah added.

BMIR expects to welcome its new faculty member as soon as fall 2021, but the position will be open until the right candidate fills it.

Those interested in the position should contact BMIR at contact-BMIR@stanford.edu.

## FACULTY FOCUS  Andrew Gentles, PhD

On a broad level, Andrew Gentles, Ph.D, uses computational systems biology to study human health and disease. To do this, his group integrates high-throughput data sets with each other and with phenotypic information and clinical outcomes.

A member of the Quantitative Sciences Unit (QSU), he collaborates with colleagues in his lab and other clinical and basic research scientists from Hematology, Pathology, and other divisions and departments throughout the School of Medicine. One thread is to identify biomarkers from data such as those from gene-expression studies to try to understand why some patients respond to therapy and others don't, why some patients survive longer than others, and what specific mechanisms occurring in the tumor drive those things.

The ultimate goal is to determine that particular patients will respond positively to particular treatments, and to identify new therapeutic targets through understanding disease mechanisms. There is currently particular focus around immune therapies, with spectacular results in some patients

who have previously incurable disease, such as metastatic melanoma.

The complicated computational analytics work depends on having access to large data sets, which become available whenever published studies include data collected from hundreds of thousands of patients. Using that information, Gentles's team can carefully examine a population with a known variation in which patients received which treatment, along with natural variation in gene expression, and distill their analysis

down to what is happening at the individual patient level.

The Gentles Lab, in collaboration with the labs of Sylvia Plevritis, PhD, and Maximilian Diehn, MD, PhD, developed a publicly available resource called the Lung Tumor Microenvironment Interactome that allows interrogation of potential interactions among cell subpopulations within human lung tumors. A recent paper in *Genome Biology* describes how that resource complements certain gene-sequencing analyses to facilitate future studies of lung-cancer biology.

On occasion, Dr. Gentles turns to colleagues in the QSU, who are known for their expertise in biostatistics, for answers to specific questions about how to analyze types of data in particular trial contexts. Likewise, the Gentles Lab, with its knowledge of genomic data, adds to the breadth of the QSU.

Gentles also has a strong motivation in teaching. "It's not just about research, it's about training and helping people to go out and achieve the goals they have," he said.

Lance Downing, MD, an active clinician and a BMIR faculty member, is connecting data to health through his work on the Care Itinerary (CARE-IT) Advanced Care Planning project.

With less than 40 percent of Americans having documented advanced care directives, there is a great need for people in the U.S. to learn about, document, and share their wishes for end-of-life care. Yet insufficient bandwidth, lack of incentives, and fear of removing hope create barriers for healthcare providers to begin discussing this topic. For patients, the primary barriers are lack of awareness of the topic at all and waiting for their provider to initiate the conversation at the right time.

"Fundamentally, the CARE-IT project has focused on how to empower patients to address this important topic on their own so they don't need to depend on the healthcare system and their physician to initiate these discussions," Dr. Downing said.

What began as a course through the Stanford Byers Center for Biodesign evolved into a digital health app-based intervention that allows patients to learn about, record, and share advanced care planning wishes.

Project collaborators now include researchers in palliative care such as VJ Periyakoil, MD, Winnie Teuteberg, MD, and Stephanie Harman, MD and primary care physician Anu Phadke, MD. Dr. Periyakoil has identified best practices around how to have
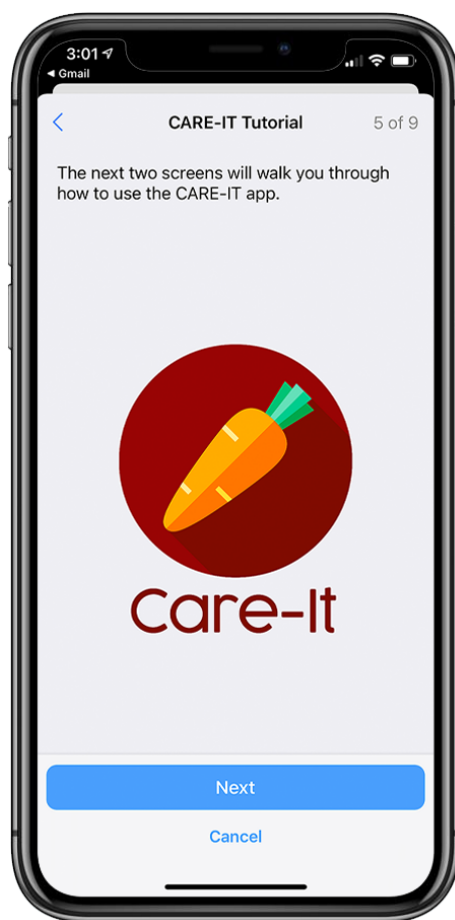


these conversations, which are captured in the Stanford Letter Project.

"One of the most critical elements of the project is the data that address patients' wishes, but those data are too often missing," Dr. Downing said.

After recognizing that unmet need, he and his fellow researchers found a mature technology that they thought might be helpful. The team used Apple Health application programming interfaces and software development kits to build a mobile app with a user-friendly interface to lead patients through advanced care planning. Downing's team used best practices in software engineering when creating the app.

"While this is a little bit different approach than many more data-intense BMIR faculty projects, I think it is the correct approach because it gets at the root cause of the problems. In fact, we are helping patients generate the important data of their advanced-care-planning wishes and then building a platform to ensure that it's shared with other stakeholders such as family members and care teams. It's far more applied than much of what we do in BMIR, but as a practicing physician, this falls more in line with my personal interests," he said.

The team expects the app to be stabilized, with all content in place, so it can be studied with 100 Stanford primary care patients in a clinical trial that will take place in early 2021.

Pending positive results, the researchers hope to be able to offer the CARE-IT Advanced Care Planning program to other Stanford patients and eventually to those outside the Stanford Health system, with the ultimate goal of expanding it nationally.



**BMIR**
**Stanford Center for Biomedical Informatics Research**

**WE CONNECT DATA TO HEALTH**

The Stanford Center for Biomedical Informatics Research (BMIR) uses advanced research techniques to discover, apply, translate, and organize data that make a difference for health and health care. With its expertise in clinical and translational informatics research and biostatistics, the division works to uncover new ways to advance personalized medicine and to enhance human health and wellness.

Collaboration is in our DNA. We are excited about the prospect of working with other experts who share our goal to connect data to health and medicine. We encourage you to contact Mark Musen, Director of BMIR (musen@stanford.edu), to learn more.

Stanford Center for Biomedical Informatics Research
1265 Welch Road, Stanford, California 94305-5479
https://bmir.stanford.edu