# P4 Medicine Could Transform Healthcare, but Payers and Physicians Are Not Yet Convinced

BY BOB CARLSON, MHA, Senior Contributing Editor

Edward Abrahams, PhD, president of the Personalized Medicine Coalition (PMC), calls it "personalized medicine."

Leroy Hood, MD, PhD, co-founder and president of the Institute for Systems Biology (ISB), in Seattle, calls it "P4 medicine."

Clayton Christensen, PhD, Harvard Business School professor and co-author of *The Innovator's Prescription: A Disruptive Solution for Healthcare*, calls it "precision medicine."

Still others like the term "stratified medicine."

Confusing, isn't it?

"I think we're all talking about the same thing," says Abrahams. "Our challenge is to join forces to remove the barriers to the advancement of personalized medicine, or P4 medicine, so that we're no longer just talking about personalized medicine but about medicine as it's practiced."

Then again, maybe it's terminology catching up with technology.

For example, when Hood co-founded the ISB in 2000, and the implications of a systems approach to health and disease became apparent, he realized that personalized medicine could be both *predictive* and *preventive*.

By 2002, Hood was thinking in terms of P3 medicine: predictive, preventive, and personalized. Then P3 medicine came up in conversation with Google co-founder and president Larry Page.

"Larry said people participating in their own care is just as important as the other three Ps, and I immediately realized that's true," Hood recalls.

And that's how, with a little help from his friends, Lee Hood came up with the fourth "P" of P4 medicine.

"Not everybody sees the same thing when they use these different terms," chimes in Clay B. Marsh, MD, who is on the PMC board of directors and is director of the Center for Personalized Health Care, Ohio State University Medical Center (OSUMC), in Columbus. "Each center has a bit of a different take on what this means and what the details of the programs are."

## P4 medicine is transformational

Marsh's take on personalized medicine is to lead the OSUMC in collaborating with the ISB in P4 medicine pilot projects on chronic disease (including cancer) and on wellness.

Clay B. Marsh, MD

ISB provides cutting-edge systems biology technology, and OSUMC supplies 55,000 covered lives, a 1,400-bed multihospital system, healthcare providers, and $200 million in annual research funding. OSUMC, where Marsh also is senior associate vice president and vice dean for research at the College of Medicine, is the largest health science center in the United States.

"Ohio State has an integrated, closed system," Marsh explains. "We are the employer, payer, and provider of healthcare to our employee base. This gives us an opportunity to test whether different types of approaches to healthcare and wellness-based care can lower costs and improve outcomes."

The ISB/OSUMC deal became official when the OSU Board of Trustees approved it on May 13, 2010. The P4 Medicine Institute, co-founded by OSUMC and ISB and headed by executive director Frederick Lee, MD, MPH, is dedicated to accelerating the emergence and adoption of P4 medicine.

As P4 medicine is successfully implemented, Hood and Marsh envision a radical transformation of our "healthcare ecosystem." They hope to demonstrate that ISB-developed technologies, such as genomics, wellness, and chronic disease biomarkers, will make it possible not only to intervene in disease presymptomatically, but also to maintain wellness in the first place.

"The reason we're doing the pilot projects is to show in a friendly environment how transformational these applications of P4 medicine are going to be," says Hood.

Among the transformational outcomes Hood expects is a decline in healthcare costs.

"I'll guarantee you that the escalating costs of medical care will at some point, as P4 medicine becomes a reality, turn around and drop to the point where we can export P4 medicine to the developing world and make it the basis of the global health initiatives that the [Bill and Melinda] Gates Foundation and others are pushing," Hood asserts.

In 2008, The Grand Duchy of Luxembourg invested $100 million with the ISB in a bid to become the

European leader in systems biology. Two ISB-led research projects — commercialization of joint ISB and Luxembourg research, and development of the Luxembourg ISB — are included in the deal.

### P4 medicine is systems biology

If the human genome is the parts list, systems biology is about how these parts interact. That's a tall order, because about 25,000 genes make up the human genome, and each gene may not be fully expressed. Additionally, multiple genes share multiple responsibilities, and each gene encodes multiple proteins, all of which interact in complex ways.

This kind of complexity is where supercomputers like the IBM Blue Gene come in to model biological networks (formerly known as pathways) and to simulate how these networks function. An *in silico* model validated by *in vitro* or *in vivo* experiments can then be used to identify the key nodes involved in network perturbations (i.e., disease) and the therapies most likely to return the network to normal function.

Instead of PhD molecular biologists and post-docs working in isolation, the ISB in Seattle teems with biologists, chemists, computer scientists, engineers, mathematicians, and physicists, all working together. Hood calls it "integrated cross-disciplinary biology."

Right now, most systems biology research is aimed at understanding how organ networks, such as the brain and the liver, work. It turns out that certain proteins in the blood are specific to perturbations in organ networks long before symptoms appear. These organ-specific "protein signatures" are potentially inexpensive and reliable biomarkers in predicting, preventing, and treating disease. So are whole-genome sequences of patients, especially in combination with those of blood relatives.

"We're transforming medicine from a descriptive science into an informational science," says Hood. "In the next 5 to 10 years, every patient will be surrounded with a cloud of billions of data points, and the challenge is going to be to reduce this enormous data dimensionality to simple hypotheses about health and disease for the individual."

P4 medicine is systems biology translated into practice, but it's not how medicine is currently practiced. In Hood's opinion, medicine as we know it today is never going to be very effective, and healthcare costs will continue to increase. If all goes according to plan, P4 medicine will be a real horse pill for the medical–industrial complex to swallow.

"Within the next 5 to 10 years, we're going to see the beginning of an absolutely transformational revolution in medicine, and it won't be incremental," Hood predicts. "It's going to be revolutionary, and the business plan of every single sector of the healthcare industry is going to be transformed."

### Overcoming the barriers

But the wheels of regulatory bureaucracies grind slowly, and whether you call it personalized medicine or P4 medicine, the U.S. Food and Drug Administration and the Centers for Medicare and Medicaid Services are not yet fully on board. Abrahams mentions three barriers that PMC faces.

First, the FDA regulates diagnostics and therapeutics separately. That makes the process of bringing companion diagnostics to market needlessly complex. FDA commissioner Margaret A. Hamburg, MD, has promised to issue a new Draft Guidance on this topic by the end of 2010.

Second, Abrahams faults CMS for "no clear understanding of the uses of evidence to evaluate products" for coverage. He cites a 2009 decision by CMS to deny reimbursement for the pharmacogenomic testing of warfarin response. This contrasts with a 2007 FDA label change recommending such testing prior to dosing warfarin, and a three-year study (released in March) by the Mayo Clinic and pharmacy benefits manager Medco Health Solutions that shows that patients whose warfarin therapy included genetic testing were 28 percent less likely to be hospitalized for a bleeding episode or thromboembolism.

### Physician acceptance

A third barrier is slow physician uptake of molecular diagnostics. It may be a lack of education about genetic testing, inadequate marketing, or time constraints, but doctors are not ordering pharmacogenetic assays when indicated.

Hood speculates that physicians may simply not understand the opportunities offered by the new medicine. He then cites the all-important issue of reimbursement, which is still based on an archaic methodology that has little in common with the utility and value of genomic and proteomic diagnostics. Then there's the conservatism and skepticism common to all scientists and physicians.

The way to overcome the barriers to widespread adoption of P4 medicine, Hood and Marsh believe, is with data from demonstration projects like those now under way at the OSUMC.

As for that terminology issue, Marsh thinks that whoever comes up with the most compelling demonstration project data will influence whether we'll be talking about P4 medicine, personalized medicine, or something else entirely in 2020.

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