

Lessons for the future of personalized health care

The Ohio State University Medical Center's Personalized Health Care National Conference provides a roadmap for realizing the promise of genetically-based medical treatment

Realizing the potential of personalized health care depends on the collaborative interactions of its stakeholders. As home to the Center of Personalized Health Care (CPHC), The Ohio State University Medical Center in October 2008 hosted its first Personalized Health Care National Conference: Translating Science into Personalized Health Care. The event brought together representatives of the diverse sectors of the health care industry to discuss convergent viewpoints of how genetically-based medical diagnosis and treatment will transform health care.

Personalized health care is rapidly moving beyond theoretical application into real-world medicine. Advances in understanding how genetic differences influence treatment and prevention of disease have leapt forward based on the understanding of the human genome. DNA sequencing and genetic profiles that used to take many years to generate can now be defined in a short period of time. At this rate of discovery, achieving the X-Prize goal of sequencing a person's whole genome at a price lower than \$10,000 is probably just months away.

However, despite these advances in understanding the genetic basis of disease, the post-genome era will need to focus on understanding how gene and protein networks interact with environmental stimuli to create complex human diseases. Prominent U.S. leaders have recognized the importance of this next stage in personalized health care development: Health and Human Services Secretary Michael Leavitt has created a national platform through the Personalized Health Care Initiative. Immediate past Director of the National Institutes for Health Elias Zerhouni has emphasized the importance of predictive, preventive and personalized health care for Americans. The American health care system is positioning to leverage advances in personalized health care from both an application and organizational standpoint. Greater understanding of the immediate application and future potential of these tools is necessary to affect the transformational benefit for patients receiving individualized genetically-based medical care.

There is a need for comprehensive understanding and integration of personalized health care among research principals as well as stakeholders beyond the scientific research community. The Center of Personalized Health Care at The Ohio State University Medical Center reacted to this need by reaching beyond the scope of previous conferences on the subject. The implicit goal of the conference was to advance the discussion and understanding of personalized health care beyond research to focus on real-world implications.

Establishing the Personalized Health Care National Conference

The creation of a Personalized Health Care National Conference has been a top priority for The Ohio State University Medical Center since the 2005 launch of its Center of Personalized Healthcare. Since its inception, the CPHC has focused on educating health care industry sectors on the promise of genetically-based disease prediction, prevention and treatment, and has the goal of transitioning medical care systems from disease- to wellness-based. To accomplish this goal, Medical Center leadership is committed to being a driver of reengineering medical care delivery at Ohio State and beyond. Since it is still rare among academic institutions to embrace personalized health care, the CPHC serves as a test site to define how to best convey its message to health care practitioners and educators. Even with a commitment to incorporating personalized health care into all levels of the organization, it has taken time to transition the culture from disease- to wellness-focus and position the Medical Center as a key stakeholder in the personalized health care movement.

Key to Medical Center organizational understanding of personalized health care is the realization that many of the systems for its delivery are already in place. Under the direction of CPHC, the Medical Center has grouped its programs into four aligned areas:

- Discovery – basic science, systems biology and systems medicine
- Translation – experimental therapeutics and device design
- Application and implementation – health care delivery
- Dissemination – personalized medicine at the community and individual user level.

To realize the potential of personalized medicine, the academic community is just one of many components necessary to bring personalized health care practice to reality. This is why the Personalized Health Care National Conference engaged participation by scientific research, medical practitioner, pharmaceutical development, government regulatory and health insurance communities to establish a framework for ongoing and future collaborations.

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Conference structure

The Personalized Health Care National Conference amassed a who's who list in the subject field. The conference began with a keynote address by Edison Liu, MD, executive director of the Genome Institute of Singapore. The need for collaboration was set by Liu's presentation on Genome-to-Systems Strategies in Personalized Cancer Medicine. Following a robust discussion on genetic research offering major insights into his findings on cancer therapy successes based on genetic markers, Liu called for wholesale change in the American health care system, noting that 17 percent of U.S. gross domestic product spending is allocated toward health care costs, an unsustainable trend.

The first day of the conference continued emphasizing scientific research, including a presentation by Geoffrey Ginsburg, MD, PhD, director of the Center of Genomic Medicine at Duke University and a panel discussion of Ohio State University medical professors joined by Michael Christman, PhD, president and CEO of the Coriell Institute for Medical Research and David Twardy, MD, interim chair of the Baylor College of Medicine Department of Medicine. Jeffrey Trent, PhD, president and scientific director of the Translational Genomics Research Institute, concluded with his keynote presentation on integrating genetics, genomics and biology toward personalized medicine.

The conference then transitioned into industry-academia applications of personalized health care. A panel discussion on Industry Perspectives on Personalized Health Care, moderated by Caroline Kovac, PhD, managing director of Burrill & Company, brought together the leaders of the Translational Genomics Research Institute and deCODE Genetics, alongside executives from Pfizer Global Research and Development, Navigenics and BioOhio. The first day ended with a series of presentations on the use of genetic and genomic approaches to personalize the treatment and prevention of cancer, chaired by Dr. Clara Bloomfield, cancer scholar and former director of The Ohio State University Comprehensive Cancer Center.

The conference's second day began with remarks from Lawrence Lesko, PhD, FCP, director of the Office of Clinical Pharmacology for the Food and Drug Administration's Center for Drug Evaluation and Research, establishing an obvious diversification within the conference agenda. Many conference participants, including featured speakers, commented on the unique distinction of gaining government regulatory insight into personalized health care directly from a high-ranking FDA representative. 23andMe, Inc.'s Rajiv Mahadevan, director of business development for the TIME Magazine Invention of the Year-award-winning genetic information research repository, joined Lesko for the

panel discussion Challenges of Moving Personalized Health Care Forward: Public Policy, Regulatory, Consumers, and Payer. This panel discussion was led by Edward Abrahams, Executive Director of the Personalized Medicine Coalition.

The list of participants attending the Personalized Health Care Conference also reflected the diversity of the subject matter presented. The conference served as a useful training tool for physicians and hospital administrators, and also attracted representatives from drug companies, health care industry, and institutional and corporate research organizations.

Research advances discussed at conference

As mentioned, the Personalized Health Care National Conference was distinguished by the presence of Edison Liu as keynote speaker. Liu, whose titles also include professor of medicine at the National University of Singapore and executive director of the Singapore Cancer Syndicate, spoke about the dramatic increase in speed of personalized health care scientific research. Liu said his involvement in leukemia research on the impact of Ras protein mutations on therapy success, based on the discovery of Ras as a genetic biomarker likely to be associated with cancer outcomes, took nine years from conception to publication. This groundbreaking study determined that individuals with leukemia with Ras mutations treated by Ara-C chemotherapy drugs experienced a four-to-tenfold increase in effective killing of cancer cells vs. Ras-negative individuals. Furthermore, Ras-positive individuals treated with the highest doses of Ara-C experienced the longest remissions, whereas no correlation in dosage to remission length was found in Ras-negative individuals. Liu also detailed a similar breast cancer study determining the impact of chemotherapy treatment on HER2 protein-positive individuals and the need for more aggressive doses based on the protein presence.

Now, genomic medicine is enabling more rapid interrogating systems to identify gene networks and molecular pathways that contribute to disease (thereby building on all of the available data), instead of studying the effects of a single gene on disease and human phenotype, Liu said. Using this approach, Liu focused on the impact of p53 mutations, HDAC inhibitors and DZNep on cancer treatment outcomes. Knowing that the p53 protein is a key check point that commits cells with DNA damage to apoptosis, or programmed cell death, Liu set out to determine cancer treatments for individuals with p53 mutations. He determined that the presence of p53 activates another protein, bax, an apoptosis-inducing protein. In further exploration searching for a pathway leading to apoptosis independent of p53 status, the protein E2F1 was identified.

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Liu found anti-cancer activity using existing treatment therapies with HDAC inhibitors and DZNep. Screening a compound library of drugs bearing similarities to HDAC inhibitors, the study has found a series of drug therapy combinations in vitro that predict novel drug treatments for these same tumors in vivo. This targeted strategy allows effective and safer ways of killing transformed cells. Liu said he expects future research to eventually lead to cancer treatments determined by patient cancer genotype allowing individualized, less toxic and more specific treatments.

The Ohio State University perspective

A panel of Ohio State University professors presented a series of short sessions by subject area based on their areas of expertise, serving as a springboard for a Q&A-based discussion on how scientific breakthroughs in genomic medicine will translate to health care practice.

Rebecca Jackson, MD, professor of endocrinology, diabetes and metabolism, said personalized health care has the potential to reduce fractures in individuals with genetic predispositions to bone density loss, detailing a five-year hip fracture study designed to measure clinical risk factors that resulted in a fracture risk calculator (www.hipcalculator.fhrc.org). Jackson says she envisions the addition of phenotyping to standard clinical risk factors for fracture, citing the understanding of current biomarker associations such as risk decrease in the presence of higher levels of the hormones estradiol and testosterone, and risk increase in the presence of higher levels of SHBG and Cystatin C.

Wolfgang Sadée, Dr.rer.nat., professor of pharmacology, said the bottleneck to progress in personalized health care research has been finding functional genetic variants hidden in the vast amount of data represented by the human genome. Echoing Liu's comments, Sadée says establishing computational tools to determine whether a gene has a regulatory polymorphism on disease outcome, which has already generated success in speeding the research progress. Current studies of techniques to investigate 100 genes simultaneously would generate findings in six months instead of six years, Sadée said. However, he said testing costs must be controlled to create efficiencies so that personalized health care reduces instead of increases care costs.

Brad Rovin, MD, professor and director of the Division of Nephrology, said nephrology is "light years behind" in the field of personalized health care. However, Rovin said lab work is focusing on the identification of more meaningful biomarkers associated with lupus. While there are several well-accepted lupus

biomarkers that change at the time of renal flare, most of the markers do not change before the flare, so there is insufficient data to predict it, he said. Rovin said study has created working predictive equations for C3 and ESR, but that they are only able to increase prediction of chance of flare to 10.6 percent, only slightly better than the existing benchmark clinical data that predicts a 6 percent chance. His study is focusing on hep-20 as a possible marker of impending flare, which may be useful in following the response of flare to therapy.

Related external perspectives

Baylor College of Medicine Department of Medicine Interim Chair David Twardy provided an overview of that institution's progress toward advancing personalized health care, detailing the development of the Baylor Chip that conducts 10,000 genetic tests to determine a personal genomic profile. The chip detects pharmacogenetic variations in 32 genes, SNPs associated with increased risks for common diseases, HLA transplantation antigens and single gene disorders that contribute to disease. Following implementation and training on the testing system, results have been 100 percent accurate to date, Twardy said. Testing was scheduled to go live in the Center for Women's Health Research Clinic in January, he said.

Similar to Ohio State, Baylor has created creating organizational movement toward a vision of personalized health care, through the Baylor College of Medicine Personalized Medicine Alliance, which will include a genomic leadership residency and genomic medicine education program in the future, Twardy said. The new Baylor Clinic and Hospital planned for completion in 2011 will represent a personalized medicine Center of Excellence, he said.

Coriell Institute for Medical Research President and CEO Michael Christman discussed the value of engaging individuals in genetic study and monitoring how they use the information the institute provides back to them. Dr. Christman is planning a 100,000 person Coriell Personalized Medicine Collaborative that will evaluate how individuals view their risk of disease through analysis of functional single nucleotide polymorphisms in their individual DNA. Because health care payers want to see evidence-based studies that genetic testing has a direct benefit on patient health, collecting this information is crucial to understand what data is clinically useful, Christman said. To encourage understanding and use of testing results, Coriell provides secure access online that study participants can share with their physicians, and also offers free genetic counseling at no cost by phone or in person, he said. Christman said he is confident the Human Genome Center project will reach its goal of enrolling 10,000 participants by the end of 2009 – more than 3,000 people were enrolled at the time of the conference.

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Translational Genomics Research Institute President Jeffrey Trent likened recent advances in personalized health care research to putting together the pieces of a puzzle, even if they don't fit perfectly, and without knowing the overall image to work toward – simply to see what happens and to build knowledge of the big picture of the human genome. Trent cited as an example the identification of a candidate gene that may contribute to Alzheimer's Disease, determined from running genetic data through 500,000 SNPs tests. Following the determination of a KIBRA association with Alzheimer's Disease, research set out to demonstrate change to memory performance based on modifications to its inhibitor pathway, that have generated remarkable results, Trent said. A similar process has generated success in treating a rare melanoma, he said. Conducting genetic testing on pooled data has generated efficiencies in cost with the same results as conducting tests solely on individual genetic matter, Trent said.

Trent said he envisions future personalized health care treatment following a process of:

- Identification of a new diagnostic test
- Definition of performance criteria
- Payer support of research on test performance
- Lab development of test
- Clinician use of test
- Clinician alteration of treatment based on test
- Payer reimbursement for test

Trent said the Translational Genomics Research Institute is already working with single payer nation health care models, including Luxembourg, on the institution of such a process. The nation has already begun testing and treatment for lung cancer based on the model, he said.

Business and regulatory perspectives

Lawrence Lesko, director of the FDA's Office of Clinical Pharmacology, said genomics is creating a new drug trial model that will improve both efficiency and efficacy in the research process. The reigning standard of the randomized clinical trial is the worst method to determine what population will benefit from a drug therapy, Lesko said. Instead of entering clinical trials with no insight into response rates, future processes will need to increasingly rely on genetic testing data to establish populations with built-in likelihood to respond to the therapy being tested.

More than 50 percent of Phase III trials in drug development fail to meet their primary endpoints, and some trials have

contradictory results; however, these failings may have more to do with the study structure than whether the drug does or does not work, Lesko said. The HIV-1 treatment Maraviroc (brand name Selzentry) that the FDA has just approved provides a recent example of a genomics-enriched trial design that demonstrates greater rates of success than among a random sample because the therapeutic response is dependent on blocking the CCR5 co-receptor and the Maraviroc trial only included individuals possessing that genetic trait. By doing so, the trial demonstrated efficacy rates of 55 to 60 percent vs. 26 percent if it had enrolled a random population. Genomically based trials can reverse the failure rate for approval without the ramping up of sample size that is contributing to the high cost of drug development today, he said.

Lesko also spoke to the fact that genomic testing provides greater insight into the successful use of existing medicines. Since 2002, FDA has pursued relabeling of drugs approved over the last 20 years that would benefit from genetic testing, he said, citing the atrial fibrillation and deep venous thrombosis treatment Warfarin. Because of the risk of bleeding in some patients, patient compliance in taking Warfarin is as low as 20 percent within one year of prescription. Testing determined that two genetic factors contributed to 43 percent of variability in patient response to Warfarin, which resulted in the FDA approving four different tests that physicians can use prior to prescribing the drug (www.warfarindosing.org). The response stakeholder groups provided to Centers for Medicaid & Medicare Services inquiry on whether this testing should be Medicaid/Medicare reimbursable illuminates future challenges. Lesko also said that while response among most groups was mixed, with negative responses from health care plans, patients and caregivers overwhelmingly supported reimbursement.

Science and technology is always going to outpace society's ability to catch up with it, said Rajiv Mahadevan, director of business development for 23andMe. According to Mahadevan, 23andMe, which is compiling a genetic database through submitted saliva samples screened for indicators of traits and conditions, has already faced regulatory concerns at the state government level in its nationwide collection process. The amount of time and resources 23andMe has to spend navigating uncharted regulatory authority as each state considers policy on genomics business practice represents a detriment to forward progress in the field, he said. Mahadevan said the benefit 23andMe and other genetic data collection business models will provide is the engagement of consumers in participating in the research process. By amassing a database of shared information and creating social networking tools for its customers, 23andMe can help identify shared genetic

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characteristics individuals with the same disease possess. The 23andMe model can provide a valuable social networking tool to help stimulate research, particularly in generating a critical mass among individuals who share a rare disease or condition, and among individuals for whom a common medical treatment does not work, Mahadevan said.

Currently, Mahadevan said, the performance incentives for academic medical research are inconsistent with advancing personalized health care, because institutional collaboration is not part of the process from the beginning. Mahadevan praised the Medical Center for pursuing institutional expertise and collaboration in personalized health care simultaneously, because for patient care to be improved consistent with research advances in personalized health care, research institutions are going to have to share data and study together.

Conference outcomes and next steps

By gathering all representative intellectual capital in the emerging personalized health care system in one place, the Personalized Health Care National Conference at The Ohio State University Medical Center created an environment for greater understanding of the current and near-term advances in personalized health care, as well as the systematic challenges it faces. Beyond greater understanding of the capabilities of genetically based medical treatments, the conference sought the beginning of a roadmap to transition American health care from its disease treatment and management model to a proactive health maintenance and disease prevention system.

Predictive findings for individual genetically-based responses to medical treatment have the potential to improve outcomes, but will require support by all pillars of the health care system to achieve maximum success. The current health care system's substantial misalignment between the best possible care outcomes and care reimbursement by private and public payers must be addressed to provide for more and wider-reaching preventative care, and genetically guided outcomes can help effect this change. There is already global movement toward pay-for-performance measures in public health systems, so that drug companies would only receive compensation for dosage based on outcome in the individual patient. This payment model transition will require internal and inter-system collaboration to ensure that all patients receive effective treatment, not just a select group of them. Establishing a regulated tracking system of patient genetic information will also be necessary to personalized health care's future, and will require a resolution of the debate on how this information is stored and who has access to it. If there

are negative consequences to testing for genetic markers for predispositions to diseases and conditions, personalized health care will not be able to advance. Speaking during a conference panel discussion on the challenges to forward movement in the field, Lisa Salberg, president of the Hypertrophic Cardiomyopathy Association, called for the elimination of pre-existing conditions in U.S. health insurance policies, and said that genetic testing will need to be covered by insurance in the future, the same way routine tests such as blood work and echocardiograms are covered now. From a care practitioner perspective, the U.S. will need to create a portable electronic medical records access system so a patient's care record, including genetically-based findings and care applications, are accessible to all care providers, instead of only residing with a single provider.

The Medical Center is already working with conference participants to continue forward momentum in the spirit of collaboration. Working with 23andMe, the Coriell Institute and academic partners, the institution is seeking ways to engage the medical care practitioner community in greater understanding of personal genetic information among students and physicians. Having this population directly interact with the testing process will increase understanding of relevance and provide a personal stake in the outcome for translation to the patient care perspective. Educating current and future physicians about their personal genetics is a valuable first step in gaining buy-in from this important population.

The Ohio State University Medical Center's predictions for personalized health care

Personalized health care will both rapidly and over the long term create drastic changes to the health care system. Health care for the general public will soon begin to resemble the preventative executive health care model currently only servicing the very wealthy, as genetic testing identifies an increasing number of risk factors for possible future disease to combat with lifestyle and pharmacological measures. As the cost of total genome sequencing drops from \$60,000 to around \$5,000 – probably in 2009 – it will quickly push forward increased testing leading to further medical care advances that force more rapid change in the overall health care model.

In the immediate term, the blockbuster business model that has served drug developers for so long will cease to exist, in favor of a rapid transition to clinical trials with enrollment criteria based on genetic predisposition to treatment success to the drugs being tested. This change will happen simultaneously with payer

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reimbursement based on treatment effectiveness, so that drug developers simply won't be able to afford to create drugs that are only effective for a small percentage of the population they are designed to serve. The existing model for breast cancer patients receiving diagnostic tests for the biomarker Herceptin before obtaining a treatment prescription will become increasingly common across a wide spectrum of diseases and conditions.

Advances in information technology supporting the housing and mobility of personalized health care data will also occur rapidly. IT solutions to increase comfort in information privacy will be critical to the successful implementation of the Genetic Information Nondisclosure Act as well as general public acceptance of the concept of portable, lifelong medical records kept housed securely for individuals and accessible online. As technology evolves to protect this information in the hands of consumers, they will have control over with whom they share it, effectively acting as the gatekeepers of disclosing their own information.

Conclusion

No one person or organization can make effective changes in personalized health care, but it will happen faster through the support of early-stage stakeholders committed to realizing the promise and potential of personalized health care. While The Ohio State University Medical Center does not have all the answers, its mission will strive to ask the questions necessary to continue an active public dialogue keeping personalized health care at the forefront of social issues. And whenever possible, the Medical Center will contribute to the collaborative research and policy development that provides the building blocks for personalized health care's bright tomorrow.

Personalized health care will usher in a new age of medicine that we can only now begin to envision. It won't happen over night – in fact, its full impact will only be realized over decades – but it will drive a series of small and large changes that eventually add to up to completely transform the health care system from what we know today.



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