

The Ohio State University
Personalized Health Care National Conference

Collection of Speaker Abstracts
(In alphabetical order)



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Christman

Collaborative Approach in Personalized Medicine Development

**Michael Christman,
PhD, President and CEO
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The Coriell Personalized Medicine Collaborative (CPMC) is a research study that employs an evidence-based approach to determine the utility of using personal genome information in health management and clinical decision-making. The CPMC also aims to build a cohort with rich genotypic and phenotypic data with which to discover genetic variants that affect drug toxicity and efficacy, as well as to discover presently unknown gene variants that elevate a person's risk of cancer and other complex diseases. This forward-looking, collaborative effort involves physicians, scientists, ethicists, genetic counselors, volunteer study participants, and information technology experts. Its goal is to better understand the impact of personalized or genome-informed, medicine and guide its ethical, legal and responsible implementation. The study will enroll 10,000 individuals by the end of 2009 with an ultimate goal of 100,000 participants. As of September 2008, there were 3,500 participants enrolled in the study. There is no charge to study participants.

De la Chapelle

Population-wide screening for genes predisposing to colorectal cancer

Albert de la Chapelle, MD, PhD
Distinguished University Professor
Human Cancer Genetics Program
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Colorectal cancer (CRC) is preventable by clinical surveillance and curable if diagnosed early. Therefore, identifying individuals at high genetic risk of CRC is desirable. The major high-risk conditions are: 1. Lynch syndrome due to mutations in the mismatch repair genes and 2. genetic predisposition associated with reduced allele-specific expression of the *TGFBR1* gene. Both of these conditions are presently seriously underdiagnosed. It is argued that screening for Lynch syndrome among *all patients* with CRC and endometrial cancer is already feasible, sensitive, and relatively simple. Large-scale screening for *TGFBR1* related CRC is not yet a simple procedure and will need to await further research results. It is proposed that large scale screening for Lynch syndrome be initiated immediately, and methods be developed to screen for aberrant *TGFBR1* expression. Taken together, the two conditions may account for some 15% of all CRC. Assessing individuals for these risk parameters should be part of personalized health care.

Dennis

Ohio's investments in the biosciences and their implications for personalized medicine

Anthony Dennis, PhD

President and CEO

BioOhio

Ohio has made significant investments in bioscience projects and programs through the Third Frontier and other programs. Many of these investments, ranging from Wright Centers of Innovation to Edison Centers and Incubators will either directly or indirectly advance the fundamentals of personalized medicine. The presentation will review the range and depth of these efforts and relate them to the emerging field of personalized medicine.

Gillison

HPV as a biomarker for treatment response and prognosis for head and neck cancer

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There is an ongoing paradigm shift in concepts of risk and pathogenesis of head and neck cancer, due to the recent recognition of HPV as a major cause of these cancers. Tumor HPV status is the most important biomarker of response to therapy and prognosis for head and neck cancers. Recent data indicate that much of the recent improvements in treatment outcome for head and neck cancers may be due to a shift in the underlying etiology of the disease and its inherent biological responsiveness, rather than to therapeutic advances. It is clear that the risks and benefits of combined modality therapy for head and neck cancer differ for the HPV-positive and HPV-negative patient, however, whether and how therapeutic decision making should be altered to personalize therapy by disease etiology is not currently established.

Ginsburg

Transforming the Practice of Medicine Using Genomics

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Recent studies have demonstrated the use of genomic data, particularly gene expression signatures, as clinical prognostic factors in complex diseases. Such studies herald the future for genomic medicine and the opportunity for personalized prognosis in a variety of clinical contexts that utilize genome-scale molecular information. Several key areas represent logical and critical next steps in the use of complex genomic profiling data towards the goal of personalized medicine. First, analyses should be geared toward the development of molecular profiles that predict future events - such as major clinical events or the response, resistance, or adverse reactions to therapy. Secondly, these must move into actual clinical practice by forming the basis for the “next generation” clinical trials that employ these methodologies to stratify patients or predict outcomes. Several design features of these trials are unique and must be undertaken both by academia and industry in order to establish the clinical utility of the molecular profiles to predict health outcomes that will inform clinical guidelines and potentially product labeling. Third is the delivery of information such that healthcare providers can seamlessly incorporate it into risk assessment. This last step will necessarily involve a number of policy strategies that include educating the public and healthcare workforce as well as reducing the barriers to participating in the research. Creating a multidisciplinary environment that supports and fosters collaboration and commercial partnerships will move us closer to fulfilling the promise of personalized medical care.

Gulcher

Genetic risk tests already available for the common diseases

Jeffrey Gulcher, MD, PhD
Chief Scientific Officer and Co-Founder
deCode Genetics

Over the last few years we have applied cost-effective large scale genotyping using about 1 million markers together with large collections of well-characterized patients and controls leading to the discovery and wide replication of genetic variants contributing significant risk to common diseases such as myocardial infarction, atrial fibrillation/stroke, prostate cancer, breast cancer, and type 2 diabetes. We have made 7 genetic risk tests based on some of these discoveries clinically available through our CLIA laboratory and these tests are being used by physicians to reclassify, as higher risk, many patients who otherwise would have been considered as average risk based on conventional risk factors. This offers the patient and their physician an opportunity to be attentive to prevention strategies or earlier detection of disease.

For example, the prostate cancer risk test measures 8 SNP markers that have been widely confirmed in over 20 different populations totaling tens of thousands of patients and controls, and appear to account for about 70% of the risk for prostate cancer. Multiplying the risks of these markers together define overall risk ranging from 0.4 fold to over 6 fold compared to the general population. About 10% of the white male population have an average 2 fold risk and 1% have 3 fold risk. The risk is independent of family history of early prostate cancer which is the only other risk factor for prostate cancer in Caucasians. Therefore, this test reclassifies a significant portion of the 95% of Caucasian men who are normally considered to be of “average-risk” as having a risk that is equivalent or greater in magnitude than the higher risk due to family history. Men at higher risk may benefit from earlier PSA and digital examination screening. Higher risk men who have borderline PSA levels may benefit from more aggressive evaluation. The test may improve the specificity of PSA, perhaps decreasing the proportion of negative prostatic biopsies.

The breast cancer risk test measures 7 SNP markers, widely confirmed by us and other groups in almost 100,000 patients and controls. The markers define risk for the common forms of breast cancer ranging from 0.4 to 4 fold compared to the general population. A subset of the markers defines likelihood of ER positive versus ER negative tumors in the event the patient develops cancer. Patients at higher risk for the common forms of breast cancer may benefit from more sensitive screening for early breast cancer with breast MRI as well as preventive strategies with tamoxifen and other similar drugs, especially in those predicted to be at higher risk for ER positive tumors.

The genetic risk test for myocardial infarction (deCODE MI) contain markers on the chromosome 9p21 region that have been widely replicated in numerous prospective and retrospective studies including over 20,000 patients and 50,000 controls. About 25% of the population carry the higher risk genotypes and this common genetic risk factor is independent of conventional risk factors including family history. Prospective studies have shown that a significant portion of patients are reclassified into higher and more accurate risk categories using this test and may benefit from more aggressive LDL cholesterol and blood pressure targets.

Jackson

Predicting Risk for Fracture
Rebecca D Jackson MD
The Ohio State University Medical Center

Each year in the United States, there are 1.5 million fractures attributable to osteoporosis including 329,000 hip fractures, one of the most disabling consequences of aging in women. Approximately 16% of non-Hispanic white women and 3-5% of Hispanic and African-American women will suffer a hip fracture during their lifetime. Estimates in European white women suggest that the one in six lifetime risk for hip fracture exceeds the one in nine lifetime risk for breast cancer. To successfully reduce the impact of osteoporosis, it is necessary to identify the populations at risk for fracture where treatments can be cost-effectively targeted. Although bone density measurements have been advocated as a means for stratification of fracture risk, it is imperfect as more than 50% of fractures occur in women whose BMD levels are above the diagnostic threshold established by the World Health Organization for osteoporosis. Recent work by our collaborative group in the Women's Health Initiative has extended our ability to predict fracture risk based upon clinical risk factors and biomarkers in postmenopausal women. Based upon 11 clinically available risk factors (age, race/ethnicity, self-reported health, weight, height, physical activity, parental hip fracture, fracture history after 54, current smoking, corticosteroid use and history of treated diabetes), an algorithm has been developed to predict 5-year hip fracture risk. Biomarkers including low vitamin D or bioavailable testosterone and/or high Cystatin-C or sex hormone binding globulin also predict risk for hip fracture independent of clinical risk factors. A genome-wide association study of hip fracture is in progress and should identify genetic associations of hip fracture. These data will also allow for pharmacogenomic studies to identify populations who might benefit from specific interventions for fracture reduction such as hormone therapy or calcium plus vitamin D. The data from these and other studies in progress shall help us to meet the goals of healthy People 2010 to reduce the magnitude of osteoporosis.

Jasinski

The Role of IT on the Road to Personalized Medicine

Dr. Joseph M. Jasinski

Distinguished Engineer and Program Director Healthcare and Life Sciences Institute

IBM Research

Information technology has been and will continue to be a key enabler in the drive towards personalized, information based, medicine. We will examine the state of progress in two distinct areas where IT plays a key role: basic and translational research and clinical care. In the area of basic and translational research there is much evidence that IT systems have allowed the community to advance the state of our understanding of fundamental biology, genomics and systems biology. In the area of clinical care, the evidence so far is less compelling, although national scale examples of the effective use of clinical IT to deliver increasingly personalized care are beginning to emerge.

Keckley

Challenges in the Pursuit of Personalized Medicine

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Deloitte Center for Health Solutions
Washington DC

Personalized medicine promises to improve the quality of medical care, but faces three major challenges to which investigators, innovators and policy-makers must be attentive: (1) public understanding of the relative value of personalized diagnostics and therapeutics over conventional methods, (2) health plan integration of personalized medicine in coverage schemes, and (3) regulatory support for the pursuit of personalized medicine in the context of global economic turmoil and industry uncertainty.

In this session, Dr. Keckley will discuss findings of Deloitte Center for Health Solutions studies relative to these challenges, and possible solutions that would stimulate increased pursuit of personalized medicine.

Lesko

DNA-Guided Medicine - Successes to Date and Challenges to Overcome

Lawrence Lesko, PhD, FCP

Director, Office of Clinical Pharmacology

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Uncertainty and variability between patients in medicine is an age-old problem. These problems have been addressed in many ways over the years in an attempt to "personalized medicine". Testing DNA for genomic biomarkers provides a new approach to understanding the molecular basis for inter-patient variability in disease and drug response. While there are many opportunities for improved therapeutics, there are relatively few successes to date in translating genomic information to clinical decision-making by healthcare providers. This presentation will focus on the successes in DNA-guided medicine and several of the major challenges that are preventing more widespread adoption of DNA testing

Liu

Genomic and systems strategies for personalized cancer medicine

Edison T. Liu, M.D.
Genome Institute of Singapore

The power of genomic technologies is its comprehensiveness and speed. The range of genomic strategies allow us now to link experimental systems to maximize the translation of fundamental findings to the clinic.

We present work in predictive pharmacology using p53 as the model system. We explored divergent aspects of the p53 transcriptional response. First, we identified a clinically embedded 32-gene expression signature that distinguishes p53-mutant and wild-type tumors of different histologies from 251 primary breast cancers. The class determination of this 32 gene cassette outperforms sequence-based assessments of p53 in predicting prognosis and therapeutic response.

Second, we identified a unique role for glycogen synthesis kinase-3beta (GSK-3beta) in regulating p53 functions in human colorectal cancer cells. Pharmacologic modulation of GSK-3beta markedly impaired p53-dependent transactivation of targets including p21 and Puma but promoted p53-dependent conformational activation of Bax resulting in cytochrome c release, and apoptosis. Thus, p53-mediated damage response is converted from cell cycle arrest to apoptosis following exposure to chemotherapeutic agents.

Since 50% of tumors have p53 mutations, this GSK3beta inhibition strategy will not in these tumors. To this end, we sought approaches to the treatment of cancers with alternative mutations such as the p16/pRB pathway. Activation of E2F1 is akin to depletion of pRB and/or p16 which are common events in human tumors. This system was used to screen compounds that would induce apoptosis upon activation of E2F1. This approach revealed that histone deacetylase inhibitors augmented programmed cell death in cells perturbed in the E2F1/Rb/p16 pathway. We found that HDAC inhibition augmented E2F1 binding and activation of *bim* promoter which is a key factor in the induction of apoptosis arising after combined HDAC inhibition and E2F1 activation. Extension of this system allowed us to find a compound with a HDAC-like effect, but is distinct from HDAC inhibitors. This compound, 3-Deazaneplanocin A (DZNep), is an S-adenosylhomocysteine hydrolase inhibitor that induces efficient apoptotic cell death in cancer cells but not in normal cells. Our systems approach directed us to the mechanism of action of this drug which is to deplete cellular levels of components of the polycomb repressive complex 2 (EZH2, SUZ12, and EED, which are often upregulated in human cancers. This permits the overexpression of key genes contributing to cell death.

Quinn

Challenges of moving Personalized Health Care forward: Public policy, regulatory, consumers, and payer

Bruce Quinn, MD, PhD
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Personalized medicine offers great promise for more accurate and effective treatments for many illnesses. However, there are additional challenges beyond those usually recognized in the PM literature (e.g. Roden et al., 2006, *Annals Intern Med* 145:749). Healthcare payors have an uneasy relationship with innovation. Innovation is risky and requires high investment. To recoup investment, prices must be well above the marginal cost of the product. However, the profit margin raises concern about overutilization in healthcare (much more than for direct-pay consumer purchases). In addition, the cost margin for diagnostics is very high, and particularly in the Medicare system, regulations tend to force diagnostic chemistry prices to marginal cost. Given the huge scale of our healthcare system (\$2 trillion dollars) the coverage decision process is very underdeveloped, and the claims system (called CPT codes and ICD9 codes) is cryptic and telegraphic compared to the complexity of patients and services. Diagnostics also face the same challenges as the drug pipeline without the same rewards; elaborate diagnostics development costs before Phase II trials, but only a modest chance of reaching a marketplace, and only years in the future, and at uncertain and perhaps low price. There are also many aspects of decision-making for clinical diagnostic tests (beyond the simplified metrics of sensitivity and specificity) that are not widely understood by policy makers.

Rovin

Can We Personalize Therapy for Kidney Disease?

Brad H. Rovin, MD
The Ohio State University Medical Center

Microarray analysis clearly demonstrates the molecular heterogeneity of kidney diseases that appear phenotypically similar. Using the glomerulonephritis of systemic lupus erythematosus (SLE) as a model, we found that biomarkers commonly used to follow the clinical course of the disease, such as serum complement levels, have very poor sensitivity and specificity when applied to individuals. Longitudinal analysis of complement in individuals with lupus nephritis demonstrated several patterns of expression. This suggested that SLE nephritis could be modeled by measuring these biomarkers over time, and by combining biomarkers. Using multivariate logistic regression analyses in a generalized estimating equation framework, measurements of complement and other biomarkers taken prospectively from a large cohort of SLE patients were used to build a complement-oriented model to forecast impending renal flare, and to mark concurrent renal flare. These prediction equations proved to be better than chance alone at forecasting or marking flares, but were not very powerful. To build better models, better biomarkers are needed. Therefore, we examined the feasibility of longitudinal proteomics to monitor changes in the urine proteome of patients during renal flare cycles to determine if biomarkers could be identified that may be useful in prediction modeling. SELDI-TOF mass spectrometry analysis led to the discovery of several candidate biomarkers. Using peptide sequencing one candidate was positively identified as hepcidin. Although the relevance of hepcidin needs to be verified in an independent population, this result demonstrates the potential of urine proteomics in identifying biomarkers to model kidney disease in individuals.

Sadee

Wolfgang Sadee, OSU

Pharmacogenetic Biomarkers as Guides in Drug Therapy

The use of genetic biomarkers in drug therapy has the promise to improve treatment outcomes significantly. However, clinical implementation is emerging rather slowly. On the one hand, the link between genotype and phenotype – such as drug response or toxicity – is often tenuous, and multiple genes may contribute to a complex phenotype. On the other, we often do not have accurate information on the relevant polymorphisms in candidate genes, and their clinical penetrance. Frequently, marker SNPs are used in lieu of the true functional SNPs, and this could introduce additional uncertainty and reduce predictive power of the test. Our research has focused on finding the relevant functional variants in strong candidate genes and testing their impact on clinical outcomes. Recent examples include polymorphisms in *DRD2*, *TPH2*, *VKORC1*, and *CYP3A4*, each with demonstrated clinical implications.

Salberg

Hypertrophic Cardiomyopathy and Genetic Testing – 2008

By Lisa Salberg

Hypertrophic cardiomyopathy is an autosomal dominant disease affecting one in 500 people in the general population¹. The Hypertrophic Cardiomyopathy Association currently maintains a database of over 4000 families (representing approximately 30,000 individuals) with the condition. Our database is comprised of 55% males and 45% female with an average age of diagnosis at 34 years.

At the current time there are 13 genes with over 450 mutations identified to cause hypertrophic cardiomyopathy². Approximately 50% of all disease causing mutations are found in cardiac myosin-binding protein-C (MyBP-C) and myosin heavy chains (MyHC). In the past four years genetic testing has moved from the research laboratory into a clinical environment. Currently, laboratories are reporting the ability to identify genetic mutations in between 60 to 70% of tests conducted. It does appear that when an HCM genetic test is ordered from any HCMA recognized center of excellence the chance of locating a genetic mutation that is pathogenic or possibly pathogenic is nearly 70%; when testing is ordered from a general cardiologist the positive predictive value is much lower. The availability of clinical genetic testing for hypertrophic cardiomyopathy has enabled thousands of families to access critical genetic information about the status of the disease within their family.

Historically patients with hypertrophic cardiomyopathy have been counseled to have all first-degree relatives screened with an echocardiogram, electrocardiogram and a consult with a cardiologist³. In some cases additional evaluation with magnetic resonating imaging is required. The frequency of these evaluations is based upon age. Children from the onset of puberty until 20 years of age are to be screened annually and the current recommendation is for adults to be screened every five years or upon the onset of symptoms. This process requires a great deal of financial expenditure, anxiety on the part of the family and in most cases needs to be repeated multiple times in one's lifetime. Based on national averages the cost associated with one screening is approximately \$2,800.00, without MRI. Without adjustments for inflation the cost to screen a child from age 12 to 20 is approximately \$22,400.00. Based on the average age of diagnosis within the HCMA database an additional 3 screenings may be required to identify a person presenting the phenotype of HCM, costing an additional \$8,400.00 (a total of nearly \$31,000.00). Insurance reimbursement of this testing has uniformly been standard practice in the past 15 years, in the rare occasion reimbursement was not made an appeal has been submitted for reconsideration and the problem resolved nearly every time.

In the current era of genetic testing it is now a reasonable course of action to perform genetic testing on the index patient within a family. The cost for genotyping an index case will range between \$2500 and \$5600. Once a mutation has been discovered in the index patient the remainder of the family may choose to have genetic testing performed. The cost of confirmation testing ranges between \$250 and \$960 per person. Reimbursement from insurance providers has been inconsistent but is trending toward paying between 50 and 80%.

As HCM is an autosomal disease 50% of first-degree relatives will not have the genetic marker. For those with out the genetic marker there is no clinical value to serial echocardiogram, electrocardiogram and consultation with a cardiologist for the detection of hypertrophic cardiomyopathy. For those with an identified mutation continued surveillance and serial

¹ Maron et al, [Circulation](#). 1995 Aug 15;92(4):785-9

² Alcalai R et al, [J Cardiovasc Electrophysiol](#). 2008 Jan;19(1):104-10. Epub 2007 Oct 4

³ Maron et al, [J Am Coll Cardiol](#). 2003 Nov 5;42(9):1687-713.

evaluation should continue throughout life. With the passage of the Genetic Information Nondiscrimination Act in May of 2008 many patients feel secure enough to embark upon accessing genetic testing; the numbers are growing every day.

In addition to the identification of those carrying a gene mutation the value of genetic testing expands beyond identification of those with the disease. There is current human subject research underway evaluating the utilization of a calcium channel blocker given to those who carry a genetic mutation who have yet to show phenotypic expression of hypertrophic cardiomyopathy (Principal Investigator, Carolyn Ho, MD, Brigham and Woman's Hospital, Boston MA). This study originated from research conducted on mouse models proving that the use of diltiazem limited the development of hypertrophy⁴. We hope this study is simply the beginning of the realization of personalized medicine in treatment, management and potentially the eradication of hypertrophic cardiomyopathy.

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¹ Maron et al, [Circulation](#). 1995 Aug 15;92(4):785-9

² Alcalai R et al, [J Cardiovasc Electrophysiol](#). 2008 Jan;19(1):104-10. Epub 2007 Oct 4

³ Maron et al, *J Am Coll Cardiol*. 2003 Nov 5;42(9):1687-713.

⁴ [Semsarian C](#), et al, *J Clin Invest*. 2002 Apr;109(8):1013-20.

⁴ [Semsarian C](#), et al, *J Clin Invest*. 2002 Apr;109(8):1013-20.

Shapiro

Selecting Treatment for Women with Breast Cancer: One size does not fit all.

Charles L. Shapiro MD
Professor of Internal Medicine
Director of Breast Medical Oncology
Director of the Survivorship Center of Excellence

The most important discovery during past ten years is the recognition that breast cancer is not one disease, but at least 5 different subtypes based on gene expression profiling.¹ These subtypes, including luminal A, B, HER2-*neu*, basal and normal-type, serve as prognostic factors affecting clinical outcomes (i.e. disease-free and overall survival) and predictive factors that determine sensitivity or resistance to treatment.^{2,3} The best example is HER2-*neu*, a member of epidermal growth factor receptor (EGFR) family. HER2-*neu* encodes a transmembrane protein tyrosine kinase that is overexpressed in about 20% of breast cancers.⁴ Trastuzumab is a monoclonal antibody that binds to extracellular domain of HER2-*neu* and when combined with standard chemotherapy improves the outcome for women with advanced,⁵ and early stage breast cancer.^{6,7} Lapatinib is a small molecule dual tyrosine kinase inhibitor that targets the intracellular domain of the HER2-*neu* protein and prevents dimerization with itself or with HER1 the EFGR.⁸ Lapatinib combined with chemotherapy inhibits EGFR and HER2 signal transduction pathways and improves the outcome for HER2-*neu* overexpressing women with advanced stage breast cancer.⁹

Gene profiles of breast cancers can identify women who will or will not benefit from adjuvant chemotherapy. The *Oncotype DX*TM assay is a 21-gene profile performed on a standard paraffin tissue block in women diagnosed with axillary node-negative, estrogen receptor positive breast cancers.^{10,11} The results of this assay are either low, intermediate or high-risk of 10 year distant-disease free survival. The low risk group, which constitutes about 50% of breast cancers, does not benefit from adjuvant chemotherapy whereas in the high-risk group there is an absolute improvement in distant-disease free survival at 10 years from 60% with tamoxifen alone versus 88% in women who received both tamoxifen and adjuvant chemotherapy. The *Oncotype DX*TM assay is currently being evaluated in a large prospective validation trial,¹² and other gene profiles are similarly being validated.

The examples above illustrate that gene profiling leads to a deeper understanding of the relevant molecular pathways and the identification of the relevant targets which in turn leads to the development of new drugs. Importantly, adjuvant chemotherapy is used more selectively in women that stand to benefit most and avoided in those that will not benefit. However, this “revolution” is incomplete without consideration of host factors or pharmacogenetics. The best example is tamoxifen and its’ cytochrome P450 2D6 metabolizing enzymes.¹³ About 7% of white women inherit 2 variant 2D6 alleles and do not metabolize tamoxifen;¹⁴ retrospective studies suggest that these women who are “poor metabolizers” have worse disease-free survival than women who have normal 2D6 alleles and are “extensive metabolizers” of tamoxifen.^{15,16} In addition, the selective serotonin reuptake inhibitors (SSRIs) are potent inhibitors of the 2D6 metabolizing enzymes and concurrent use of tamoxifen and SSRIs decrease the active metabolite of tamoxifen and should be avoided.¹³

Winston Churchill once said “it is not the beginning of end; it is the end of the beginning.” This quote describes the current state of using gene profiling and pharmacogenetics to tailor individual

treatments for breast cancer. Already much progress has been made to improve the outcome of women with breast cancer and in the near term future more will be forthcoming.

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Trent

INTEGRATING GENETICS, GENOMICS, AND BIOLOGY TOWARDS A MORE PERSONALIZED MEDICINE

Jeffrey Trent, PhD

President and Scientific Director

Translational Genomics Research Institute

Genome wide profiling of gene states (structure, expression, et cetera) has emerged as a means for molecularly defining disease. The next challenge is to match the specific molecular context of disease with the most appropriate therapy. Systems medicine is emerging as a new field of research, which seeks to identify contextual vulnerabilities that arise in disease context. Towards this end, TGen has developed and applied a number of genome wide and genome compatible technologies and strategies to both profile the disease context (structural and functional genomics), as well as profile context selective drug targeting (cellular genomics). Our group has focused primarily on cellular genomics using very high throughput RNAi to systematically knockdown genes, and determine the functional role of each gene in various cellular processes including cell growth, survival, molecular end points, and drug response. The computational ‘fusion’ of multidimensional data sets to integrate structural, functional, and cellular genomic information has proven to be a very powerful strategy for generating new predictive models of context dependent targeting. In oncology, this research has led to the discovery of context specific vulnerabilities, enabling us to prioritize pharmacologically and clinically relevant drug targets and support more personalized medicine oriented drug discovery. Additionally, we have shown that this approach can lead to the discovery of genes that are casually involved in determining specific response to cancer drugs. These genes are currently being advanced as candidate predictive markers to select patient populations that would respond to specific cancer drugs, and as putative combination targets to enhance response in patients that are not responding. Such information can improve and accelerate the clinical development of emerging cancer therapies. This strategy represents a new paradigm for both drug discovery and drug development, and has the potential to some day impact on how therapeutic decisions are made.

Tweardy

Translating science into personalized health care at Baylor College of Medicine

David J. Tweardy, M.D.

Professor of Medicine and Molecular and Cellular Biology

Chief, Section of Infectious Diseases

Chair, *ad interim*, Department of Medicine

Baylor College of Medicine (BCM), by history and institutional inclination, is destined to become a hub of personalized medicine. Home to the nation's top genetics department and one of the nation's three NIH-funded human genome-sequencing centers, BCM is leading the way in genetic diagnostics. BCM scientists have recently created the Baylor Chip—a microarray encompassing much of adult genetic testing now available. This chip provides a unique platform for individual adult genetic analysis because it incorporates over 6,000 assays including: 1) 2,300 assays devoted to pharmacogenetics, which involves detection of variations in 32 gene that affect the way individuals respond to different drugs; 2) 800 tests for single nucleotide polymorphisms (SNPs) that are associated with increased risk of 24 common diseases such as breast and prostate cancer, coronary artery disease and type 2 diabetes; 3) 400 tests for SNPs used for human leukocyte antigen (HLA) typing; 4) 3,000 tests for 99 genes to detect predispositions for 260 adult-onset diseases including Alzheimer's disease, Parkinson's disease, cancer and cardiovascular disorders and 5) 574 ancestry information markers to control for the effect of race and ethnic background in interpretation of genetic testing. The Baylor Chip will soon be in clinical use in the Baylor Clinic Women's Health Center with the goal of expanding its use to all patients cared for at the new BCM Clinic and Hospital opening in 2011. One advantage of the Baylor Chip over commercial microarray platforms will be dynamic versioning of the Baylor Chip based on clinician-laboratory interaction.

BCM has established the Personalized Medicine Alliance chaired by the College President, Peter Traber MD, to provide the organizational framework for personalized medicine at the College since the changes that personalized medicine will entail sweep across all departments, centers, institutions as well as all of the College's core missions—clinical care, research and education. At the vanguard of educational initiatives is the BCM Genomics Leadership Residency Program that will be open to all BCM trainees. This innovative program being developed with ACGME input will function as a multi-year graduate medical education experience with a fully integrated research component designed to train future leaders in personalized medicine.

Van Liew

Dennis Van Liew
Senior Director
Strategic Management Group
Pfizer Global Research and Development

Great opportunity exists for the adoption of personalized medicine products and services, but barriers involving provider delivery and a sustaining financial underpinning value framework need to be addressed. An outline of the key questions and emerging thinking on the resulting barriers and issues which need resolution will be presented. Challenges covered include:

- How can we align various stakeholder incentives to move PM forward?
- Developing sustainable reimbursement models to accelerate adoption of PM
- How to get consumers prepared for personalized medicine?
- How to facilitate training/education of clinicians, allied health professionals and others (e.g. MDs, Genetic Counselors)?
- Supporting the widespread adoption of EMR for successful implementation of PM

Vanier

Vance Vanier, MD, MBA
Chief Medical Officer
Navigenics

In 1953, Watson and Crick, in a two page letter published in the journal *Nature*, wrote their brief and understated description of the DNA double helix, and gave medical science a first glimpse of its future. Fifty-five years and hundreds of publications later the field of preventive genomic medicine finally stands poised to move off the pages of journals and into the daily lives of patients and physicians. The impressive scientific achievements of our predecessors now demand an equal level of clinical leadership from ourselves as we seek to understand the use of these new tools with our patients. This brief presentation will discuss the components that have formed the foundation of the advent of preventive genomic medicine and the further work to be done to make it a standard of care.