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The New Era of Personalized Medicine



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Introduction to Personalized Medicine



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In the 20th century, and even now, medicine was largely reactive: the patient visited a doctor, a symptom-based diagnosis of an illness was made, treatment was prescribed, and the patient might recover or revisit the physician for further investigation. This approach ignored the natural history of disease (*Figure 1*). Genetic background for the disease went uninvestigated, and preclinical manifestations of disease at the molecular level were not detected in early to midlife. Symptoms of disease were almost always necessary before seeking medical attention.

In addition, this is an important opportunity to improve health and reduce premature death by

changing personal behavior. Personal behavior accounts for nearly 40% of preventable deaths in the United States^{1,2,3} with obesity, smoking, and physical inactivity as the top causes. Fifty percent of people will still die after their first heart attack, and COPD, which in the vast majority of cases results from smoking, is an emerging epidemic. Genetic predisposition is responsible for another 30% of preventable deaths in the United States.^{1,2,3} One in 3 will develop cancer in his or her lifetime, and 25% of people aged 75 to 84 will suffer from Alzheimer's disease. A medical paradigm that is reactive, rather than proactive, is still used in many diseases, regardless of whether they are behavioral or genetic in origin.

The era of personalized medicine will present a change in the way physicians treat their patients. Medical practice will become increasingly preventive rather than reactive (*Figure 2*), and this approach promises to reduce the number of deaths due to genetic disposition and personal behavior. Formerly, pooled data from many people with average responses were used in clinical trials. Now, the traditional "one size fits all" model is being abandoned. Genetic information is being used to customize detection, treatment and prevention at the individual level, and in some cases, is even used to segregate patients to determine who is likely to respond best in a clinical trial. Previously, it was unusual for physicians to modify treatment strategies according to a particular patient's response. Now, treatment strategies are being designed based on an individual's unique genetic makeup. The former approach lacks precision, while the new one reduces uncertainty and error in both diagnosis and treatment.

Early work in medical genetics was focused on monogenic disorders, but with the sequencing of the Human Genome, it is now possible, with an extraordinary amount of innovation and practical application, to understand genetic disorders caused by environment-gene interaction with more than 1 genetic variant. The

The New Era of Personalized Medicine

Learning Objectives

1. Compare and contrast 20th century medicine with the new paradigm of personalized medicine.
2. Discuss the concept of 'omics, and relate how it is transforming the use of biomarkers in therapeutics and imaging.
3. Describe new genotyping tools that are being used to prescribe and dose drugs.
4. Explain how individual biomarkers are used to predict, prevent, diagnose, and track disease status.

Target Audience:

This activity was developed for Family Physicians, Allergists/ Immunologists, Registered Nurses, Pediatricians, Pulmonologists, Physician Assistants, and Nurse Practitioners.

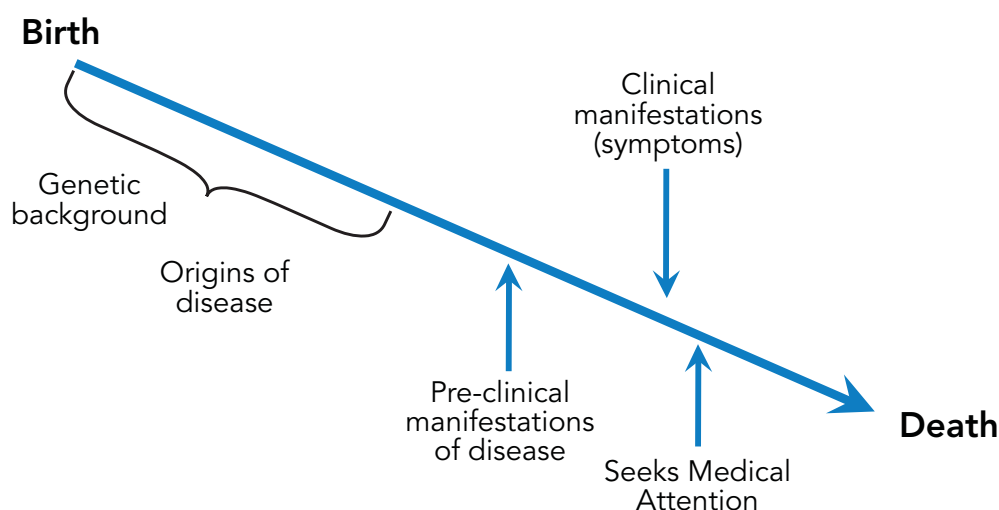
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Figure 1. The traditional approach to medicine.

Traditional Approach is Reactive Ignores the Natural History of the Disease



combination of these natural variations across several genes influences risk for developing certain diseases and explains why some patients respond to some drugs while others do not. It also offers the possibility of promoting lifestyle changes or using chemoprevention or nutrigenomics to delay or prevent onset of a disease. We have always tried to personalize medicine, but we now have much more powerful tools: genomics, proteomics, metabolomics, and lipidomics. These core tools are referred to collectively as 'omics. The field of 'omics is currently dominated by proteomics, which is at the forefront of biomarker discovery for disease diagnosis, particularly cancer.⁴ Epigenetics seeks to evaluate nongenomic changes such as gene methylation, which cause changes in expression. Epigenetics helps to diagnose disease and provide targets for drugs.

In anticipation of rapid changes in 'omics, the Personalized Medicine Coalition (www.personalizedmedicinecoalition.org) has been established by more than 20 leading companies, academic institutions, and government agencies to facilitate education and consensus among providers, payers, and policymakers regarding the evolution and adoption of personalized medicine.⁵ Ultimately, the new paradigm of

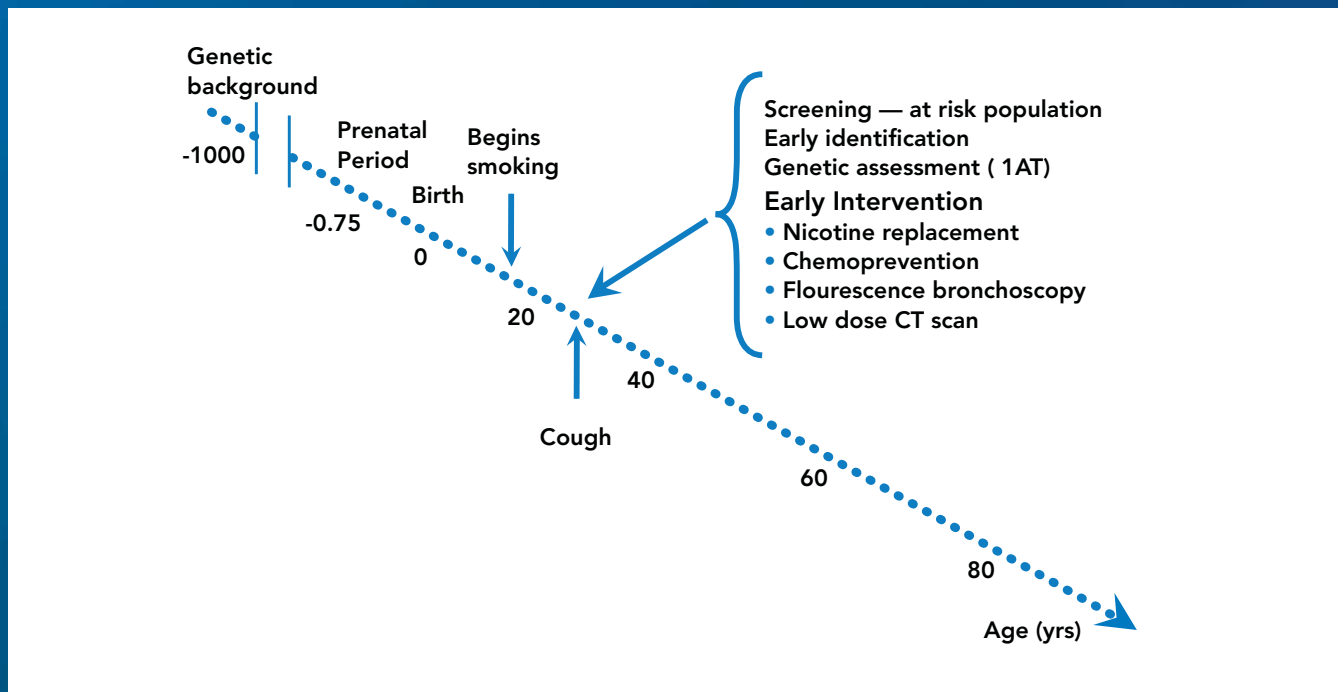
personalized medicine will consist of predicting, preventing, finding, profiling, treating, and tracking disease using biomarkers, epigenetic modification, and pharmacogenetics. While personalized medicine is often discussed in the future tense, it is already having an impact on treatment and is an unavoidable trend in medicine that is enabled by technology and knowledge of 'omics and is spurred by economics and consumerism. It is currently delivering better diagnoses, earlier interventions, more efficient drug development, and better therapies, and it is promising more for the future.

Personalized Drug Prescription and Dosing Based on Individual Drug Metabolism

Each year, 117,000 people are hospitalized for adverse drug reactions⁶ and 100,000 die from them.⁷ Current dose recommendations are often vague and are based on factors such as age, gender, and body weight. A substantial amount of the population also does not respond to a given drug. A review of patient response to 5 different drug classes (angiotensin-converting enzyme inhibitors, beta blockers, antidepressants, statins and beta agonists) found absent or incomplete

Figure 2. The new paradigm of personalized medicine.

Personalized Healthcare for COPD Proactive vs Reactive



efficacy in 10 to 70% of cases. The highest rates of inefficacy were for antidepressants, statins, and beta agonists, which were between 50 to 70% inefficient, in the upper range for inefficacy.⁸ That so many drugs are ineffective in such a large portion of the population is evidence of both the inherent genetic complexity of humans and the need of the healthcare industry to do better. As such, biomarker discovery and the personalized medicine industry have sought an alternative strategy to the “one size fits all” drug model. That strategy is to exploit rather than avoid genetic diversity by tailoring drug treatment to the individual. Whether or not a drug is efficacious and whether the patient has resistance or toxicity is dependent on how well a particular patient metabolizes a drug and whether the drug is inactivated or activated by the metabolic enzyme in question.⁹

Cytochrome P450 represents a family of enzymes expressed in the liver and gastrointestinal (GI) tract that metabolize most medications, such as anticoagulants, antidepressants, proton pump inhibitors, selective serotonin reuptake inhibitors, antipsychotics, codeine, anticancer medications, and other drugs such as lidocaine, oxycodone, fentanyl, and warfarin. In January 2005, the FDA approved Roche’s Amplichip

(Indianapolis, IN) CYP450 test for the genotyping of more than 30 pharmacogenetically relevant CYP2D6 and CYP2C19 variants that are involved in the metabolism of 25% of all prescription drugs. This is the first FDA- approved microarray screening test to search for mutations in enzymes affecting drug metabolism. It allows an examination of a patient’s genetic capacity to metabolize certain drugs, thus allowing drug prescription and dosing according to an individual’s genotype.

Such information on drug metabolism has already proven useful in a variety of medical disciplines from oncology to psychotherapy. In fact, an FDA advisory committee has already recommended the genotyping of all patients receiving warfarin. Warfarin is the most frequently prescribed anticoagulant and is used in more than 2 million new patients per year in the United States alone. Initiation of warfarin therapy is largely a trial-and-error process, with potential life-threatening bleeding.¹⁰ Two genes greatly affect the warfarin dose: cytochrome P450 2C9 (CYP2C9) and vitamin K epoxide reductase (VKORC1). Preprescription genotyping and individualized therapy based upon an individual’s capacity to metabolize warfarin represent the best way to minimize the risk of hemorrhage.¹¹

The cytochrome P450 CYP2B6 genotype also determines smoking abstinence rates with bupropion.¹² Among smokers in the CYP2B6*6 group (CYP2B6*1/*6 or CYP2B6*6/*6 genotype), bupropion resulted in significantly higher abstinence rates than placebo: 32.5% vs. 14.3% at the end of treatment, respectively. Polymorphisms in the dopamine D2 receptor also influence treatment response to bupropion.¹³ A current personalized medicine approach to smoking would be to conduct dual genotyping to determine the chemoprevention mechanism for an individual's smoking cessation plan.

Many groups are developing preclinical assays for drug metabolism. Gene polymorphisms also influence responses to antiasthma therapy, including B₂-agonists, glucocorticosteroids, and leukotriene modifier drugs. The majority of asthmatics are treated with antileukotriene modifiers (e.g. montelukast), but only 50% or less of patients respond to this medication. If known in advance, inappropriate use could be avoided. A personalized medicine approach would test for polymorphisms in the leukotriene pathway and measure for metabolites in the urine or breath. Many genotyping methods are still in the development stage, and although gaps in knowledge still remain, future work will enable the application of clinical phenotyping.¹⁴

Furthermore, the CYP450 test is not the only FDA-approved molecular assay. Genzyme's molecular assay, Invader (Cambridge, MA) detects variation in UGT1A1, an enzyme that metabolizes irinotecan therapy for metastatic colorectal cancer. About 10% of white Americans cannot metabolize irinotecan: it builds to toxic levels resulting in bone marrow suppression, infection, and possibly death. If the UGT1A1 genotype is known in advance, the chemotherapy dose can be customized and adverse reactions avoided. Identifying nonresponders to particular drugs saves time, money, and a patient's exposure to an ineffective and potentially toxic drug (*see Case Studies*). Also, clinical trials may preselect those likely to respond to treatment, increasing the likelihood that a useful drug will come to market.

Personalized Medicine Based on Individual Biomarkers

Biomarkers can be classified as predictive, diagnostic, and prognostic in their utility. In their structure, they may be proteins, antigens, viruses, genes, genetic and epigenetic variations, differences in mRNA and protein expression, posttranslational modifications of proteins, or metabolite levels. They are already used in risk assessment, prevention, and early detection of disease and are also being put to use in treatment and monitoring.⁴ Researchers in oncology have led the way in providing biomarkers for disease, because in cancer, changes in genes and gene expression are the disease. While the particular biomarkers are different for each disease, the essential aspects of personalized medicine remain the same: prediction, prevention, diagnosis, treatment, and tracking. Breast cancer serves as a model displaying the current integration of all of these aspects of personalized medicine. While development of breast cancer biomarkers and treatment strategies continue to advance, many other diseases will march to the current stage of development at which breast cancer is now.

During the pregenetic era, breast cancer was histologically defined, graded, and predicted for recurrence. Following that, treatment by surgery, hormonal therapy, and/or chemotherapy was chosen. Now, women may be genotyped for mutations in the BRCA1 and BRCA2 genes, which partially determine susceptibility to breast cancer. Mutations in these genes increase risk greater than 100 fold, with an accompanying 50% to 80% lifetime risk of developing breast cancer. Women with altered versions of BRCA1 or BRCA2 are advised for increased monitoring for any sign of cancer, and may benefit from chemoprevention treatment with tamoxifen. Tamoxifen is metabolized by the CYP2D6 enzyme (which may be genotyped with the Roche Amplichip) to produce endoxifen, an antiestrogen. Women with a specific genotype, CYP2D6*4/*4, metabolize tamoxifen poorly, producing less endoxifen.

Once breast cancer has been diagnosed, gene expression analysis (Oncotype, Genomic Health, Inc. [Redwood City, CA]) on tissue samples predicts the likelihood of cancer recurrence based on 21 genes and predicts adjuvant treatment benefits for hormonal therapy and chemotherapy. This test determines a Recurrence Score (Genomic Health, Inc.) which corresponds to the likelihood of cancer recurrence within the first 10 years of diagnosis.

HER2 is a proto-oncogene coding for a transmembrane receptor tyrosine kinase involved in signal transduction pathways regulating cell growth and differentiation. Approximately 25% to 30% of breast cancers overexpress HER2: these tumors grow faster, are more likely to recur, and respond poorly to standard therapies.⁴ A predictive assay for HER2/neu overexpression allows patients to be selected for Trastuzumab treatment. Trastuzumab is a monoclonal antibody treating (HER2)/neu positive breast cancer. By binding to the extracellular domain of the receptor, Trastuzumab blocks its activity, reducing the recurrence rate by 50% and increasing survival by 30%. The first FDA-approved test identifying those who should receive Trastuzumab was DakoCytomation's HercepTest (Glostrup, Denmark), measuring the HER2/neu protein, available since 1998. In January 2002, Abbott/Vysis introduced the first genomic test, PathVision (Downer's Grove, Illinois), to detect the HER2/neu gene, which is more accurate.¹⁵

The Near Future of Cancer Treatment with Personalized Medicine

Drug response to cancer drugs is typically low, and biomarkers hold promise in stratifying patients for treatment. Sixty-two genes are potentially associated with the onset or severity of breast cancer. Specific roles played by these genes are yet to be elucidated at the protein level.¹⁶ DNA methylation as a prediction, prognostic, and monitoring marker has also been shown to be promising for individualization of breast cancer treatment. With regard to ease of discovery, methylation compares favorably to mutations and gene expression measurements but it is not yet sufficiently validated for clinical use.¹⁷

In the near future it may be possible to test for cancer at very early stages using the presence of auto-antibodies in the blood.¹⁸ Over-expressed or abnormal proteins produced by cancer cells are recognized by the immune system as foreign antigens. The immune system responds by producing high numbers of antibodies against them. In the future, we may be able to use this “signal amplification” to our advantage.⁴ Nowhere is such an approach more needed than in lung cancer, where a mortality rate almost equivalent to its incidence makes early detection particularly critical.

Gefitinib has been approved by the FDA to treat non-small-cell lung cancer. This drug competes with adenosine triphosphate for binding to the extracellular domain of tyrosine kinases, inhibiting their activity. A subset of patients significantly benefit from treatment with this drug, particularly patients with increased levels of epidermal growth factor receptor (EGFR) or somatic mutations in EGFR. Patients can be tested for EGFR mutations prior to gefitinib treatment. Gefitinib is a small molecule inhibitor of EGFR that affects a mutated form of the EGFR causing the cancer. When the drug advanced to phase III trials, there was no survival benefit, but there was a benefit in subpopulations, which were patients of Asian origin, females, nonsmokers, and those with adenocarcinoma histology. Successfully identifying these subpopulations earlier in the development of a drug may save companies costs in clinical trials and save the drugs for use by identifying a specific market. Erlotinib is another small molecule that inhibits tyrosine kinase activity of EGFR. It was approved by the FDA in 2004 to treat patients with advanced or metastatic non-small-cell lung cancer after chemotherapy failure.

Advances have been made not only in industry, but also in academia, highlighting the importance of linking industry, academic, and governmental partners to advance personalized medicine. A recently developed metagene model by academic scientists predicted recurrence of non-small-cell lung cancer significantly better than clinical prognostic factors, identifying a subgroup of patients with stage IA disease who were at high risk for recurrence and might be treated with adjuvant chemotherapy. This is an important finding, as clinical trials have not identified a benefit of adjuvant chemotherapy for patients with stage IA non-small-cell lung cancer.¹⁹

Biomedical Imaging Tied to Reference Laboratories in Personalized Medicine

The concept of advanced diagnostics in personalized medicine includes both the latest imaging modalities seamlessly tied to clinical reference laboratories. Creation of an Institute for Advanced Biomedical

Imaging™ is specific to this concept. Genomics, proteomics, and metabolomics are now inter-related with imaging. Molecular imaging based on ‘omics is an important new diagnostic and therapeutic tool, and provides noninvasive, real-time information. Antibodies to protein receptors have led to antibody-guided in vivo imaging. In vivo imaging for cancer detection or therapy can be performed by applying radiolabeled antibodies using positron emission tomography (PET). Metabolomic profiling with nuclear magnetic resonance spectroscopy (NMRS) can also be applied to detect biomarkers. Metabolite profiles can be generated with magnetic resonance imaging (MRI) in different cells, tissues, and organisms. Another relatively new application is the monitoring of transgene expression. This can be done by cotransfer of reporter genes imaged using bioluminescence, positron emission, or magnetic resonance, and this application gives qualitative as well as quantitative information about the effectiveness of gene transfer in gene therapy.²⁰

COPD as a Personalized Medicine Program

One example of the inadequacy of the current reactive medical practice is the emerging epidemic of chronic obstructive pulmonary disease (COPD). COPD is strongly influenced by the interaction between environment (smoking, occupational exposure to asbestos, etc.) and an individual’s genetic makeup. Only 1% of COPD patients have a purely genetic component to their disease. Not all smokers develop COPD. Certain smokers with specific genotypes are less likely to develop COPD, but roughly 15 to 20 percent will develop the disease. When an individual begins smoking and starts to develop mild symptoms of COPD such as cough, a window of opportunity exists to halt the disease through lifestyle change. By the time symptoms worsen and the patient develops dyspnea and seeks medical attention, the decline is almost always irreversible. Under a personalized medicine program, a physician would be able to predict COPD based on personal lifestyle, family history, and an “omics” assessment (*Figure 2*). With more specific knowledge, a patient would be encouraged to take preventive action by altering smoking lifestyle and using chemoprevention treatment suited to his/her individual genetics. The patient would continue to be monitored by advanced diagnostics, with emerging problems targeted by a new means of treatment, such as protein replacement therapy or leukocyte elastase inhibitors. The patient would have an opportunity to participate in National Institutes of Health trials or other investigator-sponsored trials to obtain targeted therapies. A multidisciplinary approach includes rehabilitative psychiatry, nutrition, and smoking cessation, in addition to the measure described above, is critical. After initial therapies, disease tracking and management are the keys to future success.

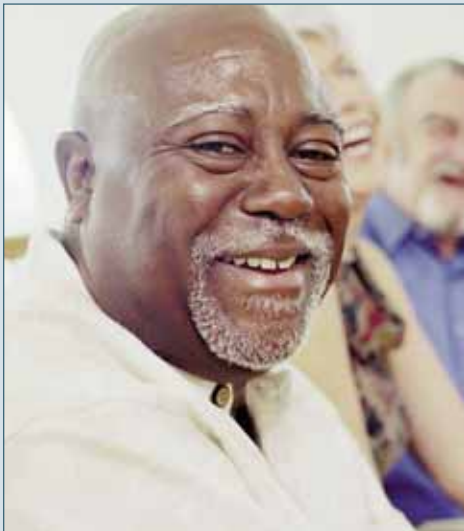
Case studies. Past and present: how genotyping affects outcomes



Hypothetical case #1

In 2000, Jane Doe is diagnosed with depression, one of 20 million such individuals per year in the United States. She's placed on a standard dose of a tricyclic antidepressant but still shows signs of confusion and difficulty concentrating. The physician interprets this as further signs of depression and increases the dose of the medication. In response, Jane develops agitation, nausea, and vomiting. She's switched by her physician to an alternative tricyclic antidepressant.

In 2007, Jane can be genotyped for 30 pharmacogenetically relevant variants in 2 genes in the gene family cytochrome P450. Jane is found to be deficient in CYP2D6 and is placed on a selective serotonin reuptake inhibitor. This genotype also explains how she will respond to other drugs, such as codeine. The information is placed in her electronic medical record. As a result, other physicians of Jane's who consult the medical record will be alerted to potential problems when attempting to prescribe drugs that may be contraindicated based on Jane's predetermined genotype.



Hypothetical case #2

In 2002, John Doe is diagnosed with hypertension and placed on his first beta blocker. He experiences shortness of breath and wheezing, with the hypertension remaining unresolved. He's switched to another beta blocker by his physician. His hypertension is eased, but he experiences dizziness at the effective dose. John speaks to a friend and sees his friend's physician as a new patient and receives a third beta blocker. The hypertension is controlled without significant side effects.

In 2009, the same patient is diagnosed with hypertension. The physician orders a cytochrome P450 genotype test. The test identifies him as a poor metabolizer for a class of drugs requiring the enzyme CYP2D6. The physician selects a beta blocker not metabolized by CYP2D6. The hypertension is controlled without significant side effects, in one visit, with one drug.

Summary

Personalized medicine consists of detecting diseases and risk for disease at earlier stages, shifting medicine from reactive to preventive. It reduces trial-and-error drug prescriptions and adverse drug reactions, enables the selection of optimal therapy, and improves the process of drug discovery by decreasing the failure rate of clinical trials. Personalized medicine enhances collaborative medicine and promises to decrease the overall cost of healthcare. Genotyping for determination of drug metabolic capabilities and diagnostic genotypic tests for therapy in oncology, cardiology and psychiatry have led the way, with genotypic tests shortly to come in pulmonary medicine.

Challenges for personalized medicine will include the technology of individual whole-genome sequencing and the realization that the phenotype reflects a complex interaction of genes and the environment. The most significant technological gap we need to fill is in bringing information technology together with the discovery and

care modalities. Some patients will choose not to know their future, and that may stem from issues of privacy and genetic discrimination. Finally, it will remain a challenge to educate providers about recent developments in personalized medicine. Although there will be much to determine with regard to industry collaboration; medical practice conventions; and ethical issues surrounding electronic medical records and personal genomic data, intellectual property, and regulatory policy,⁵ personalized medicine has already proven clinically efficacious within the current healthcare infrastructure and is quickly becoming a reality for many other diseases, such as asthma, cardiovascular disease, colorectal cancer, and leukemia. Despite the fact that these new challenges are different in the details, concerns of a technological, personal, and social nature have always been a part of medicine. Once the new personalized medicine paradigm becomes fully accepted by physicians and expected by patients, we will be closer to the vision of total healthcare for the patients we treat.

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References

- McGinnis JM, Williams-Russo P, Knickman JR. The case for more active policy attention to health promotion. *Health Aff (Millwood)*. 2002;21(2): 78–93.
- McGinnis JM, Foege WH. Actual causes of death in the United States. *JAMA*. 1993; 270:2207–2212.
- Mokdad AH, Marks JS, Stroup JS, Gerberding JL. Actual causes of death in the United States, 2000. *JAMA*. 2004; 291:1238–1245. [Errata, *JAMA*. 2005; 293:293–294, 298.]
- Srivastava S, Wagner PD. Risk-based and diagnostics-linked personalized medicine for cancer. *Personalized Medicine*. 2007;4(1):33–43.
- Munroe JB. A coalition to drive personalized medicine forward. *Personalized Medicine*. 2004;1(1):9–13.
- Budnitz DS, Pollock DA, Weidenbach KN, Mendelsohn AB, Schroeder TJ, Annett JL. National surveillance of emergency department visits for outpatient adverse drug events. *JAMA*. 2006;296(15):1858–1866.
- Pirmohamed M, James S, Meakin S et al. Adverse drug reactions as a cause of admission to hospital: prospective analysis of 18820 patients. *BMJ*. 2004;329(7456):15–19.
- Ross JS, Ginsburg GS. The integration of molecular diagnostics with therapeutics. *Am J Clin Pathol*. 2003;119(1):26–36.
- Xie H-G, Frueh FW. Pharmacogenomics steps toward personalized medicine. *Personalized Medicine*. 2007;4(1):45–58.
- Buckaveckas BL. Pharma, clinicians and the lab come together over personalized medicine. *Personalized Medicine*. 2005;2(4):325–337.
- Wadelius M, Pirmohamed M. Pharmacogenetics of warfarin: current status and future challenges. *Pharmacogenomics J*. 2007; 7(2): 99–111.
- Lee AM, Jepson C, Hofmann E et al. CYP2B6 genotype alters abstinence rates in a bupropion smoking cessation trial. *Biol Psychiatry*. 2007;62(6):635–641.
- David SP, Brown RA, Papandonatos GD et al. Pharmacogenetic clinical trial of sustained-release bupropion for smoking cessation. *Nic Tob Res*. 2007;9(8):821–833.
- Bhatnagar P, Guleria R, Kukreti R. Variable therapeutic response in asthma: a genetic perspective. *Personalized Medicine*. 2006;3(1):61–78.
- Mattingly S. Really personal medicine. *TechComm Magazine*. 2004; Oct-Nov.:26–28.
- Balgley BM, Wang W, DeVoe DL, Lee CS. Mass spectrometry-based tissue proteomics for cancer biomarker discovery. *Personalized Medicine*. 2007;4(1):45–58.
- Maier S, Lesche R, Nimmrich I, Eckhardt F, Dahlstroem C, Plum A. DNA methylation markers— an opportunity to further individualize breast cancer? *Personalized Medicine*. 2005;2(4):339–347.
- Wang X, Yu J, Sreekumar A et al. Autoantibody signatures in prostate cancer. *N Engl J Med*. 2005;353(12):1224–1235.
- Potti A, Mukherjee S, Petersen R et al. 2007. A genomic strategy to refine prognosis in early-stage non-small-cell lung cancer. *N Engl J Med*. 2006;355(6):570–580.
- Oehr P. 'Omics-based imaging in cancer detection and therapy. *Personalized Medicine*. 2006;3(1):19–32.

The New Era of Personalized Medicine CME Exam

Select the best answer from the following choices.

- The 20th century paradigm of reactive medicine consisted of predicting, preventing, finding, profiling, treating, and tracking disease using biomarkers, epigenetic modification, and pharmacogenetics.
 - True
 - False
- Which of the following is a likely "personalized medicine" approach to delaying or preventing the onset of a disease?
 - chemoprevention
 - nutrigenomics
 - lifestyle changes
 - all of the above
- Whether or not a drug is efficacious and whether the patient has resistance or toxicity to a drug is dependent on how well a particular patient metabolizes a drug and whether the drug is inactivated or activated by the enzyme in question.
 - True
 - False
- Which gene or family of genes is responsible for the metabolism of the majority of drugs?
 - UGT1A1
 - CYP450
 - VKORC1
 - BRCA
- Which of the following does not represent a biomarker?
 - HER2/neu
 - BRCA1
 - VKORC1
 - EGFR
- Because so many drugs are ineffective in such a large portion of the population, a personalized medicine approach to drug discovery is in finding drugs that are not metabolized by genes with common polymorphisms, thus ensuring uniform metabolism by most patients.
 - True
 - False
- Reporter genes give information about the effectiveness of gene transfer and gene therapy, and are imaged using:
 - bioluminescence
 - magnetic resonance
 - radiolabeled antibodies
 - A and B
 - A, B, and C
- The most personalized therapies and diagnostic tests are currently found for which disease?
 - asthma
 - cardiovascular disease
 - breast cancer
 - COPD
 - diabetes
- Which of the following was not discussed as a biomarker for cancer?
 - auto-antibodies
 - vitamin K epoxide reductase
 - DNA methylation
 - growth factor receptors

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