Genomics in the Consumer World

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We stand on the brink of a fast moving scientific, technological, and marketplace revolution.

The completion of the Human Genome Project is an historic event that will produce a tidal wave of new drug and biological research projects. The biologically based genomics, protoeomics, and bioinformatics technologies driving this revolution will be integrated with all kinds of pharmaceutical, agricultural, health maintenance, and eventually consumer products.

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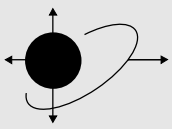


Introduction

Within the next 20 years, virtually everything in the $3 trillion healthcare and wellness industry will change. In economic terms, this tsunami will translate into a multi-billion dollar spending spree for new products based on the new technologies.

The revolution will begin in the arena of health care:

- Diseases that were not treatable will be cured with new drugs.
- Drugs that uniquely treat a disease and a person's genetic response to the disease, as well as to the drug itself, will be developed.
- Drug development will become rational and predictable.
- Adverse side effects will be eliminated.
- Patients will be screened early in life to ascertain their predisposition to disease.
- Genetically modified foods will be incorporated into customized diets that ensure the delivery of nutrients or even drugs needed by a specific individual.
- Life-threatening childhood diseases will be treatable at the embryo stage.
- Eventually preventive medicine will dominate therapy

These advances in medicine will simultaneously create innovations in the marketplace as the individualized drug replaces the blockbuster drug. But the innovations will have impacts far beyond the field of medicine and health care, and the entire marketplace will begin to reorient itself around the concept of "right product, right person, right time."

This report examines the likely path toward this new marketplace. In particular, it focuses on the stepwise co-evolution of technology and markets over the next decade. What steps need to occur at each critical stage in order for the revolution to proceed? What opportunities will present themselves for companies and for consumers? And what societal issues are likely to become "hot buttons" at each stage?

For a quick answer to these questions, review the executive summary. For a more detailed portrait of each stage of transformation, see the "Timeline of a Revolution." This section of the report provides an overview of the four stages, plus concise discussions of the major opportunities and issues in each stage. The conclusion draws some final inferences about the impacts of genomics in the broader marketplace. A final glossary of terms gives a brief overview of the language of genomics and bioinformatics.

Executive Summary

Three Premises

The starting place for this report is a set of three basic premises. From these premises, we can go on to forecast a sequence of developments over the next decade, starting with major changes in the pharmaceuticals industry and ending with a new paradigm for consumer products.

Premise 1

The mapping of the human genome is an information revolution that will ultimately change the basic paradigm for consumer products of all kinds.

While the information technologies involved in this revolution to date are unremarkable—no breakthroughs in processing or computer science here—the application of these technologies in the world of biology will lead to new ways of managing life from the molecular level to the level of human populations.

Central to this new paradigm will be personalized products, based on an individual's genetic makeup. Think of the right product, for you as an individual, just at the time you find you need it most, or, in short, right product, right person, right time.

Premise 2

The infrastructure for this genomic information revolution will be underwritten primarily by the pharmaceuticals industry.

The pharmaceuticals industry stands to gain—and lose—the most from the genomic revolution in the near term. On one hand, the costs to develop new drugs—and to clinically test them—can be slashed. Treatments for previously intractable diseases will generate new markets. On the other hand, genome-based individualized therapy spells the possible end of the blockbuster drug model, in which entire populations take the same drug with varying degrees of therapeutic success. Small upstart biotechnology companies are likely to drive the innovation in both technology and clinical trial models here if pharmaceutical companies don't aggressively obsolete their own successful business models.

Two key thresholds will need to be crossed before this infrastructure is ready for the broader consumer market:

1) The cost per genotype test must drop from 50¢ to less than 1¢.

2) Sufficient data to correlate therapeutic choices and later consumer purchase decisions to genetic information must be available and accessible in public and/or private databases.

Premise 3

This infrastructure will shape the way the revolution plays out in the consumer marketplace—culminating in the "genotyped consumer."

The pharmaceuticals industry is part of a larger health care delivery system, and it will develop the genomic information infrastucture in this context. The companies that can adapt this infrastructure to broader consumer products will take the lead in reaching the genotyped consumer.

Four Stages of Transformation

Stage 1 – 2001 to 2003: The New Pharma Industry Model

In this period, the pharmaceuticals and diagnostics industries are the big winners with higher productivity, new business model opportunities, and perhaps higher profit margins. The challenge will be overcoming the "blockbuster drug" business model.

The technology will focus on developing new drug targets and new models of clinical trial management, as well as drug rescue.

The social debate will center around constraints: should the technology be limited? The flashpoints will be GMOs, cloning, privacy of medical information, embryo testing, and the meaning of "consent" to use genetic samples in drug development.

Stage 2 – 2003 to 2006: Early Genome Therapy Market

In the second stage of this transformation, patients with knowledge and connections reap the benefits. They have better disease outcomes for serious disease and suffer less toxic side effects of the therapies. But this is a small and exclusive group of early adopters who can afford the high cost of subsidizing development.

The technological goals in this timeframe will include predetermining which drug will be most effective for an individual, providing therapies for previously untreatable diseases, and deploying a model of rational drug development. Genome-targeted food research will also explode.

Social issues will arise around the question of access: Who pays for the therapies, who profits from them, and who gets the drugs? The sometimes contradictory goals of cost-effective care and best outcome will continue to drive policy debates and personal health care choices. The concerns about genomics in agriculture will escalate, focusing on allergies, eco-disasters, and bad business models.

Stage 3 – 2007 to 2010: High-End Wellness Market

The beneficiary in the third stage of the genomics revolution is the new health consumer. Like other new consumers (who generally make more than $50,000 per year, have some college education, and use information technology in their home and workplace), the new health consumer will take advantage of individualized therapies, over-the-counter health maintenance productions, and individualized wellness & beauty products.

At this point, technology will make it possible to screen for predispositions to many diseases and to intervene to prevent early onset of those diseases. Nutraceuticals and cosmeceuticals will crowd the shelves of stores. Law enforcement will also begin to use genomic tools as crime deterrents.

Privacy will loom as the big social debate: Who gets to know your genetic profile? These privacy issues will play out in the medical system, the workplace, and law enforcement. Embryo screening will also become a highly charged social issue in this stage.

Stage 4 – After 2010: The Genotyped Consumer

At some point, the general consumer will become the genotyped consumer. The market for genotyped products will extend beyond the health and wellness offerings. The model will be "Right Product, Right Person, Right Time" Health care will shift from treatment models to prevention and postponement of disease. The nutritional profiles of people worldwide will improve.

The technology of the genotyped consumer will be point-of-use tools and tests based on genome databases. Food producers and manufacturers will follow in the footsteps of the pharmaceuticals industry, focusing on genotype-targeted foods and the niche markets they represent. DNA-based identity products will enter the marketplace, creating a second or third-generation of biometric technologies. Embryo screening tools will be generally available.

The social issues will focus on defining a new ethics of genetic design. Instead of arguments about the basic concept of genetic design, the debate will shift to the process of genetic design: Who does it? Who regulates it? Who can't or shouldn't we fix?

Gating Factors

A host of factors will ultimately determine whether and how quickly the future evolves through the stages outlined here. These factors include:

- Near-term incentives for the paradigm shift from blockbuster drugs to niche drugs
- New business models, particularly in the pharmaceutical industry
- Enlightened regulatory changes
- A knowledgeable consuming public
- Cost reduction for genotyping
- Creation of a database and broadband transmission infrastructure
- The social dialog

Timeline of a Revolution

The next decade will see the progressive integration of genomic therapies, technologies, and market strategies into the broader consumer marketplace. This market revolution will have a distinctive form, starting with highly sophisticated research products sold to pharmaceutical industry professionals and evolving into ever more broadly adopted consumer products in which the technologies are invisibly integrated.

The revolution begins in the field of health care, and one effect of it will be to create a wave of new health care products and markets. These markets will come to represent a much larger percentage of GDP, and few industries will be immune to their effects. But the market transformation will expand beyond the bounds of healthcare to include other consumer and even industrial applications. Early new markets will be safety and security products, for example. Cosmetics, clothing, and even learning and testing tools could be adapted to genotypes, once genotyping is easy and inexpensive.

This diffusion of technology will occur in four major stages. Each stage defines the prerequisites for what is to come next. These prerequisites include technological developments, market benefits, and the resolution of social issues. While the actual timeframes for each stage may be shorter or longer than we forecast here, the four stages describe the likely path to an integrated consumer genomics marketplace.

In the pages that follow, we examine the four stages in detail. We provide an overview of each stage, and then we identify the key market opportunities and social issues that will give shape and character to each stage. For still more detail on each stage, please see our online Forum2020 website, accessible through the Outlook Program website at www.iftf.org.

Stage 1: Overview

This first stage of the genomics revolution is all about improvements in drug discovery. Bioinformatics and genomics will be used extensively in-house by large and small pharmaceutical development companies to improve the success rates and lower the costs of drug development. A large contingent of companies, with many differing business models, will compete aggressively to define the new treatment breakthroughs and new business models necessary to realize their benefits. Society will grapple with if, where to, and how to place constraints on the science to reconcile the industry to a collective societal morality. Consumers will largely be bystanders in the process.

The new bioinformatics and genomics technologies have already been widely adopted by sophisticated research organizations in their industry of origin—that is, biologically based drug discovery.

Broadly speaking, these technologies allow massively parallel collecting, processing, warehousing, and flexible mining of biological sequence and other raw data needed for therapeutic and diagnostic products. As beneficiaries of the genomics revolution, the pharmaceutical industry hopes to be able to make better decisions regarding investment in new drugs through the use of genomics:

- Clinical trials will be more focused, cost less and be successful more often.
- Unsuccessful drugs with adverse side-effects in a small portion of the population will be "rescued" and benefit the larger majority of patients with no side-effects.
- Toxic drugs in which the toxicity typically appears late in clinical development will be dropped from costly development earlier.

The technology to support these and future applications is far from developed, however. The completion of the human genome has produced a misconception that genomics technology is finite and largely complete. This is not the case. Most of the genes identified by sequencing efforts have no known function, and specific functions in disease processes are rare indeed. Rapid technology development beyond inexpensive sequencing and genotyping will continue.

Stage 1: Opportunities and Issues

New Drug Discovery

The search for new and more powerful drugs for previously untreated conditions is speeding up. All pharmaceuticals on the market today and at all times in the past rely on fewer than 500 molecular targets. Genomic companies are already forecasting that the number of attractive targets will be increased to thousands of validated targets within a few years. This rapid increase is straining the traditional drug discovery process, which is also relying on genomic and bioinformatics technologies to relieve some of the congestion.

Opportunities for drug discovery include:

- *Making Better Investment Decisions*. Initially the most compelling and immediate entries into the market for genomic technologies will be products that allow pharmaceutical companies to make better bets on which compounds to take into later stage development. Overall, genomic methods improve drug investment decisions by eliminating candidate drugs likely to have bad clinical profiles earlier in the process; identifying and validating new clinical target possibilities that make use of new genetic pathways discovered through informatics investigation; and understanding how patients might be genotypically segmented into groups that are more effectively treated by a certain drug than those not in the groups
- *Lowering Costs to Approval*. Once the research on disease pathways yields genetics related to a clinical phenomenon, a large business will ensue in which contract research organizations (CROs) and clinical development departments of the pharmaceutical companies themselves incorporate the new information as an integral design of much more effective clinical trials. In these clinical trials, emphasis would shift from advancing the most potent drug for the "average" patient to testing a much broader range of drug candidates for both disease-specific pathways and individual response to the drug. In such trials, therapeutic benefit might be demonstrated with 200 patients instead of 5000.
- *Drug Rescue*. Drug rescue is another highly economic use of genomic methods. Here, genotype or gene expression data for patients is collected initially in a clinical trial as insurance against non-response or toxic effects in a certain population. Once the undesirable effects are observed, the pharmaceutical company can determine if the strength of the good therapeutic results of the drug justify a de post-facto effort to use the genetic data to eliminate patients who will not be helped by the drug. In other words, drugs with serious adverse effects on a small portion of the population would not necessarily have to be pulled from the market.

Stage 1: Opportunities and Issues (cont.)

Constraints on Research

The big issue in the current societal debate about genomics is about constraints on research. While it is hard to argue with technologies that cure horrible diseases, others areas of application of genomic technologies are already under public scrutiny with potential bans in the works. The pharmaceutical industry has evolved by working largely in secrecy on the development of drugs, but other industries will be subject to more public review. Even big pharmaceutical companies already face public outcries and restrictions on its use of animals in pre-clinical trials. Working out these concerns will be important and may slow the diffusion of genomics tools and technologies.

Two areas of research are currently at the center of the "constraints" debate:

• *Cloning.* Recently cloning of higher animals—which is not a central technology to most biotechnology work—has garnered much attention and even moved legislative bodies around the world to rapidly ban various types of cloning experiments. Bacterial level cloning is the very basis of most molecular biology and gene discovery. If one must allow cloning in bacteria for some level of research, and yet cloning of higher animals is ethically unacceptable, at what level of organism evolution does one draw the line between acceptable and unacceptable cloning—and why?

• *DNA Samples and Privacy of Medical Information.* Due to past abuses and some current practices related to private medical information, the public at large is wary of providing DNA samples to participate in the broad clinical research trials that are needed to determine initial correlations of disease and family history to genotype. Indeed, access to high quality samples with a good medical history attached to them is such a concern that one company—DNA Sciences—has recently undertaken an Internet strategy to recruit the general public to provide DNA samples for analysis and correlation with medical records with absolute anomymity. A major component of its business model relates to the value of such a store of samples in the face of more and more regulatory restrictions and a largely untrusting public.

Stage 2: Overview

Within the next six years, a new golden age of effectiveness of pharmaceuticals will begin. Diseases that were not treatable will be cured with new drugs. Drugs will become uniquely effective for a particular disease and an individual's genetic response to both the disease and the drug. Drug development will become rational and predictable. It will be possible to eliminate adverse side effects of drugs. The big problem will be how to pay for the new wonder medicines. Also, the very foundations of the way in which drugs and health care are delivered will begin to change.

As increasingly complex queries are possible using the new bioinformatics technologies, new products based on these technologies will become available. Initially such products will be largely in the high-technology drug discovery and diagnostic arenas. But they will also begin to impact the consumers of health care—solving big problems for those who have access.

For example, pathway analysis of certain complex and serious diseases will be more fully understood, and diagnostics related to full evaluation of, say, cancer metastasis or cardiac risks, will be possible. However, the technology will not be easily accessible. It will be available to the public only through very specialized and restricted clinical research protocols in highly expert institutions. Health products such as advanced diagnosis and prognostic capability will most likely not be reimbursed by health insurance plans, but will be demanded by those consumers who know of the power of the technology and are willing to pay for it. Access will be by prescription from state-of-the-art physicians participating in trials.

If these new treatment paradigms are successful, the main societal concern will be the considerable pressure on employers and health care funding organizations to develop funding models for the new technologies. That pressure will drive efforts to measure and prove the cost effectiveness of new diagnostic and therapeutic paradigms—that is, proving that the new technologies lower overall health care cost while improving quality.

Stage 2: Opportunities and Issues

Targeted Molecular Medicine

The new molecular medicine drug treatment paradigm enabled by genomics creates a more efficient health care delivery system in which, ultimately, each patient receives the right drug at the right time in the right dose tailored to the genetic makeup of that individual patient. This new paradigm will begin to be developed in the next three to six years, with an initial focus on cancer and chemotherapy.

Targeted molecular medicine is not consistent with the current blockbuster drug paradigm. Most current drugs work in a statistical fashion. Over an entire population exposed to the drug, there must be a statistically significant improvement. For most drugs, the statistics are achieved by producing large improvement in a significant portion of the population, little improvement in an embarrassingly large portion, and few fatal or severe side effects in a tiny portion. By contrast, genotype-based therapy will target the specific molecular characteristics of the patient.

This era will thus begin the total remaking of the health care delivery system. However, by year six, only those drugs with serious side effects in serious disease settings will be prescribed by genotype. For example, the daunting side-effects of cancer chemotherapy treatment could be minimized by identifying—through genotyping—those patient/drug combinations that are effective and well-tolerated by patients. Knowing that certain chemotherapy agents are likely to be toxic or ineffective in patients with certain known genotypes drives use of genotype information in three ways:

- Patients with diseases that need to be treated early will demand the best drug for them to avoid the treatment time lost to a potentially ineffective drug.
- Reduction or elimination of toxic side effects will better assist patients in maintaining compliance with difficult drug courses.
- Outcomes will be better with immediately effective treatment.

Previously Untreatable Diseases

Genomics promises to understand the true molecular basis of disease. Indeed, the molecular study of many poorly understood diseases such as cancers, arthritis, and coronary artery disease, will most likely elucidate many subcategories of disease that will become treatable when diagnosed. The method of diagnosis will be genomics-based genotyping, gene expression, or monoclonal antibodies discovered from genomic methods.

Curing previously untreatable diseases poses no challenge to the pharmaceutical industry's established-blockbuster model. The dilemma here is how to pay the huge cost of new drug development as each disease becomes a smaller subset of the population and each disease subpopulation reacts differently to treatments.

How the FDA conducts itself will be central to success here. If the FDA moves quickly to embrace genomic methods and data in the regulatory process and understands the impact of the methods on effective treatment of a population, it can become the enlightened driver of rapid change. Some key decisions the FDA may make well or badly include:

- How quickly the FDA sets standards for use of genomic methods and data in toxicology and clinical trials
- How aggressively the FDA requires companies to link analysis of side-effects to genotypic markers for the side-effects
- Whether or not the FDA creates easy routes to, or even mandates, approval of drugs with diagnostic tests that can limit serious side effects
- How quickly the FDA specifies acceptable formats for genotype-driven clinical trials in which genotype diagnosis is required to direct effective therapy (for example, genotype-guided cancer therapy).

Stage 2: Opportunities and Issues (cont.)

Rational Drug Development

In the next three to six years, genomics promises rationality in drug discovery. However, the road to rational drug design is not straightforward, and the issues have to do with the basic underlying biology as well as the technical challenges in testing, manufacturing, and delivering genetically targeted drugs. The use of computer simulations for target validation may the most promising developments in this area.

Theoretically genetically-based drug development could be totally rational once three conditions are met:

- There is a finite set of genetic factors that can positively or negatively affect the disease
- The levels of those genetic factors are known
- The levels can be modified by well known rules

Unfortunately, such simplicity is deceptive. While genomic experiments can elucidate differences in genetic materials between normal and disease states, they cannot tell us whether such differences are causes of the disease, the effects of it, or artifacts of the experiment. Even if we can prove that an overabundance or absence of certain genetic materials causes disease, it may not be possible to properly modify the amount of such material in the right tissue at the right time.

Target validation research sidesteps some of the problems of rational drug development, with a focus on two tools: antisense and ribozyme-based down-regulation of genes. Isis Pharmaceuticals and Ribozyme Pharmaceuticals are leaders in this area. If successful, their methods could change the trial-and error method of small molecule development to a verification and validation of computer-driven algorithms. Such computer simulation may be the only way in which the drug discovery machine can scale up sufficiently to address the thousands of new target possibilities emerging from genomics.

AGRICULTURAL GENOMICS RESEARCH

Between 2004 and 2007, genomic methods applied to agricultural targets are likely to take off. Important long-standing needs in plant and animal breeding can be met by genetic manipulation—higher yields, resistance to adverse conditions such as drought and freezing, pest resistance, better nutrition, better taste, and many others. Beyond breeding improved characteristics into plants and animals, the integration of genomics into food could change everything about how food is used. Commercialization of these new food products could be much further away and will depend on how the industry addresses real and serious risk factors.

Some of the opportunities include:

- Different people in the population might receive different plant supplements grown in food to enhance their health based on their genotype
- Plants could be used to produce and deliver difficult to manufacture drugs
- Waste plant material, after cash crops were harvested, could be harvested again for biotech drugs
- Crops in third world countries could be enhanced to deliver more key nutritional components in one food

The risk factors include:

- Safety—especially allergic reactions and the potential for local or widespread ecological disruptions
- Technological development risks—including the challenges of reliable, cost-effective benefits in the low-cost structure of agricultural markets
- Improper business decisions—benefitting parochial interests of the large suppliers or even Machiavellian in their conception (such as pesticide resistant plants sold to increase sales of pesticides)

Stage 2: Opportunites and Issues (cont.)

New Business Models

In addition to major changes in the way patients and payors interact with the health care system, genomics-based therapy will introduce a new model for pharmaceuticals. This new business model will be a major cultural shift for pharmaceuticals because the new definition of success will be almost the converse of the old "blockbuster" drug model.

Pharmaceutical companies have to find a way to maintain their large margins and growth rates with smaller and smaller target patient populations for each drug. Rather than target the largest possible patient population, pharmaceutical companies will need to create more value per customer. In an environment of already high drug prices and spiraling health care costs, the industry will be challenged to convince patients and payors alike of the increased value of more focused and customized care.

Drugs that have already been approved may also be forced to include genotype testing or face withdrawal because of toxic events in a small number of patients. Insurance companies may even force tests to ensure that the prescribed drug will work in the individual before the first prescription.

In this treatment paradigm, there will be collateral opportunities for sales. Each therapeutic will be accompanied by at least an initial genetic diagnostic test and possibly repeated monitoring tests.

Pharmaceutical companies are also quietly preparing for such a future. Nearly every new clinical trial by a major pharmaceutical company now includes the collection of patient DNA samples, anticipating future use of such samples to sort out toxic responders and non-responders later in the life of the drug.

Access to Health Benefits

The period from 2004-2007 will see the beginning of a rapid change in health care delivery systems. This rapid change will trigger social concerns about how the population at large begins to access better therapy choices. More specifically, society will need to answer questions of who pays and what standard of care will be supported.

A combination of reimbursement providers (Medicare plus insurance companies) will likely begin to set standards, limiting physician and hospital choices to only those therapies that are documented to save costs. But while genomics-based therapies hold the promise of better healthcare for less cost, initially the cost savings will not be documented, and the newer treatments will cost more in a system that cannot afford more.

Simply defining the timeframe for calculating costs will be a challenge. For example, should the current insurance company be responsible for an expensive genotyping of a patient with a history of cancer so that preventive therapy can be initiated to avoid expensive cancer hospitalization ten years hence? HMOs, as profit-making entities, are predisposed to pursue only the most cost-effective therapy solutions. With quarterly pressure on corporate profits, it will be hard for HMOs to link their cost-effectiveness timeframes with the long-term best outcome for the patient.

Certain minimum standard levels of therapy may become covered under insurance, and those seeking both disease and preventive therapies with better outcomes will simply do so by paying for the extra care themselves. Indeed such systems are beginning to emerge even now. But this approach—which allows those with more money to access better health care and presumably better therapy options—has consistently been rejected by a political process that favors a transfer from the wealthy to subsidize those less well off to receive the same uniform level of care.

Stage 2: Opportunites and Issues (cont.)

Consumer Information

The overriding consumer issue in this stage will be the demand for access to the new technology and the best possible therapies before it is in widespread use. Starting with individuals highly motivated by serious personal or family disease, consumers will use information sources now available through the Internet to search out the most successful new tests and treatments.

Unfortunately, there will be a great deal of misunderstanding by non-expert consumers attempting to determine the effect of published scientific results on their individual situations. The doctor will therefore remain the primary expert on which the consumer must rely. But it is unclear whether doctors will have enough time to research the latest genomic diagnostic and treatment methods for each patient condition. As with many issues, those "in the know" will thrive and benefit most.

For those genomics-based therapies that truly provide major new treatment routes, adoption will be "viral," starting with doctors and healthcare professionals demanding the better therapies for themselves, their families, and their friends. The therapies will then spread until the medical, regulatory, and reimbursement authorities "catch up" with controlled studies documenting the improvements.

Stage 3: Overview

In the third stage of the genomics revolution, the new health care paradigm begins to bloom. Individualized medicine begins to take a recognizable form in the world of health care and high-end wellness products based on genotype start to show up on store shelves. This is not yet a mass market movement, but rather a high-end wellness movement. Those consumers who have led the way with alternative therapies, nutritional awareness, and wellness lifestyles will be the "fast followers" at this stage of technology diffusion.

The foundation for this new era will be distributed access to medical data—not just for medical professionals but for consumer purchases, too.

New companies will appear to provide this access, distinguishing themselves by their expertise in handling certain types of queries. Genotype database information and tools to query such data will become widely available outside the health care industry.

Within the industry, individualized pharmaceutical prescriptions (to maximize effectiveness and minimize side effects) will be common for top-tier health care organizations. Such technology will also begin to move into over-the-counter health maintenance and cosmetic products, nutraceuticals, and biologically engineered food products.

Nutraceuticals will earn a much better scientific reputation. For example, spas that recommend important changes in nutrient, diet, and supplement intake will be supported by convincing clinical studies of benefits accruing to correct prescription of a wide variety of consumer products and customized-by-genotype nutraceuticals or pharmaceuticals.

As individual genomics data becomes ubiquitously available, the key societal concerns are likely to focus on standards of consent and privacy related to one's genetic information. For example, if genotype data can allow early treatment of disease, who has access to the data to generate the treatment and how is that data kept private?

Stage 3: Opportunities and Issues

Toward Prevention

The health care mantra of towards the end of the decade will be: "Treat disease early." Each person will be screened regularly throughout life for predisposition to diseases, early onset of the disease itself, and prognosis and best therapy for a disease once it has taken place.

Each person's genetic profile will be used, in conjunction with user-friendly database access, to guide a physician's treatment of a patient almost from birth onward. Predisposition to disease will be treated aggressively so that disease onset will be avoided, delayed, or otherwise mitigated in severity.

For example, those patients at high risk for coronary artery disease can be treated with drugs having minimal side-effects before the onset of diagnosable disease. Someone predisposed to certain types of cancers which are best treated at an early stage will receive preventive diagnostic procedures more frequently than someone who is not so predisposed.

Such markets will move genomic analysis out of the research lab and into regular clinical use in what is expected to become the largest single market in the world in this timeframe—that is, healthcare delivery. With regular improvements in genetic understanding and ease of use of genetic information, this combination of genomic therapies and genomic database technologies can follow the market and scale to these ultimate end uses.

The Wellness Industry

The end of the decade will see the flowering of the "wellness" industry, as well, with an emphasis on good food and good looks. Nutraceuticals and cosmeceuticals will proliferate. Full genomic understanding of the individual will make it easier to maintain good health, secure in the knowledge of one's own genotypic strengths and weaknesses.

The nutrition industry is likely to produce an abundance of pleasant dietary supplements to help counter one's genetic predisposition to disease. For example:

- High-level antioxidant shakes will allow elevated levels of cancer protection in those susceptible to disease
- A diet high in refined sugar, which plays an important role in inducing cells to become resistant to insulin over a period of years, can be managed from birth, and the onset of Type II diabetes can be avoided
- Dietary additives can increase cardioprotective agents (e.g., good cholesterol) in individuals prone to coronary artery disease
- People susceptible to skin defects linked to genetic characteristics may find relief in cosmetics that help prevent those defects developing either in puberty or in old age

Virtual certainty of a pending disease, based on genotype prognosis, can create powerful motivation to take countermeasures to preserve health. Such motivation can be tapped by numerous dietary and other products designed to mitigate the potential problem. These products will eventually create a continuum with more powerful pharmaceutical and cosmeceutical products.

Next 7 to 10 Years: Opportunities and Issues (cont.)

Genotyping and Privacy

As individual genotyping becomes routine, a key societal concern is likely to be the development and applications of standards of consent and privacy related to one's genetic information. The process by which these standards emerge may not be left to any single group, but must include informed social dialog among technical experts, politicians, and religious leaders—as well as individuals facing these questions on a personal level.

The following questions will come to the forefront during this third stage of the genomics revolution:

- If genotype data can allow early treatment of disease, who has access to the data to generate the treatment, and how is that data kept private?
- Will healthcare funding organizations, who have it in their interest and yours to keep you healthy, be allowed to peruse data and encourage or require someone to seek treatment?
- Will employers be able to screen potential employees' genotype data to screen out employees predisposed to violent behavior, kleptomania, or other genetically-based personality disorders?
- What will be the level of law enforcement access to genotype databases—and legal use of genetic information from crime scenes?
- Will genomics be enlisted in crimes against society, such as a terrorism, and will the same standards apply in those crimes as in crimes against individuals?

Stage 4: Overview

This is the brave new world of genomics integrated into the marketplace. With instant genotyping for consumer purchases, it is a world in which preventive medicine dominates health care purchases. Individualized medicine dominates disease treatment with pharmaceuticals. Food, nutritional, and wellness products are all integrated with genomics. DNA identity products are ubiquitous. What's more, the infrastructure for genomic-based products can now be tapped for many secondary applications and product offerings, changing the basic way that companies think about marketing products to individual consumers.

The holy grail of genomics is point-of-use, instant analysis of genotype for individualized purchases of all types. However, several early-stage technologies need to converge in order to realize this vision:

- Fast, inexpensive, automated collection of large amounts of genotype (DNA sequence) information
- Fast broadband transmission (preferably wireless) of large amounts of data
- Easy access to new levels of bioinformatics tools to concisely query accessible databases of genetic information
- Sophisticated algorithms to assemble all the data into purchase recommendations

Initially, the technology will be adopted for real-time, individualized, bedside analysis of disease, driven by the goal to determine the most effective treatment of only the target disease for that specific individual subject. Based on the proper amount of genotype data, such individualized medical treatment has been summarized as "Right drug, Right person, Right time, Right dose". Over-the-counter pharmaceuticalls with different levels of effectiveness and side effects in different genetic groups will be chosen based on the drug's performance profile in the individual subject's genetic category.

As humans, we're born with the genome that will accompany us throughout our lives. Theoretically, then, it would be possible to do a once-at-birth analysis in an imbedded chip. Practically, however, new information about ever more powerful associations between genotype, environmental factors, and protein interactions will be streaming into databases continuously over the next 50 or more years. Regular upgrading of the analysis and recommendations will thus be necessary for up-to-date medical diagnosis in the foreseeable future.

Stage 4: Opportunities and Issues

Preventive Medicine

Once the complete human genome—or genome-wide markers for most important diseases and predispositions to disease—have been analyzed, the most effective medicine will be preventive medicine. Preventive health care means proactively avoiding, postponing, or providing early diagnosis of the onset of disease, through understanding of the individual's genetic make-up.

It is well documented even today that treatment costs escalate exponentially for diseases that are allowed to progress untreated for periods of time. Costs also increase when risk of a disease spills over into active management of the disease.

Postponing such events will become the prime goal of healthcare in the new world. It is hard to understand the full impact today, but one thing is certain: the way doctors interact with patients must change. Instead of seeking medical help for disease symptoms, consumers will be highly motivated to focus on regular health maintenance, monitoring their overall health and adjusting everything from drug therapy to nutrition to lifestyle.

If truly preventive medicine prevails in the medical community, natural diets, supplements, and other wellness products could be prescribed by physicians knowledgeable about these products. Traditional medicine and homeopathy could merge into a more effective whole. Homeopathy, in genomic terms, is merely the accumulated observation that certain low-dosage natural cures work well in certain segments of the population. Those cures and preventative supplements could be incorporated into approaches that have been more rigorously tested in the scientific community.

Individualized Medicine

In the new medical paradigm, once a person is diagnosed with a disease, the next step will be to conduct a series of definitive tests to determine the prognosis for the patient and the best course of therapy for success. At the same time, difficult therapies that can be determined ahead of time to be ineffective will be avoided.

Examples of this model exist even now in the determination of an AIDS patient's resistance to drug combinations before treatment. Also, Bristol-Myers Squibb has inked a deal with Millennium Pharmaceuticals to develop a test that will determine which women at high risk for breast cancer should take the powerful anti-cancer drug Taxol. In the genetic test, they will try to determine:

- which women will likely experience unacceptable side-effects
- which women will suffer liver toxicity based on variations they possess in liver metabolism enzymes
- which women will benefit the most from the treatment

Once the pharmaceutical industry embraces the new model for disease treatment, development of new treatment test/therapy combinations will come rapidly. The new model will prove economically sound because demonstration of a drug's effectiveness and safety in a small population pre-selected for its response will be much less expensive than today's approvals.

Stage 4: Opportunities and Issues (cont.)

DNA-Based Identity Products

While huge cultural hurdles exist for universal DNA identity, it is one of the simplest applications of genomic science and is bound to find application well beyond the bounds of the health care and even criminal justice industries. We can expect that the costs and capabilities will undergo exponential improvement in the coming decade, with rapid Moore's Law-style growth.

Assuming that this scenario plays out as expected, DNA identity products will show up in everything from credit card encryption strategies to car key security. All manner of personal products could be secured with DNA evidence. Even collectibles and other valuables could be authenticated with DNA samples. Just this year, the NFL decided to encrypt footballs used in the SuperBowl with DNA security so that they could not be forged.

DNA identity products, of course, raise basic questions for our legal and criminal justice system:

- Will DNA evidence from a crime scene be entered anonymously into a national database to identify perpetrators? Or will such a data search be illegal search and seizure of private property?
- Will genomics be enlisted in crimes against society, such as a terrorism and will the same standards apply in those crimes as in crimes against individuals?

Genome-Based Selection

As we enter the next decade, beginning around 2010, perhaps the most pervasive social issue will be whether or not we, as a race, explicity engage in genome-based selection of our offspring. This is the so-called "designer baby" issue. There is no question that certain levels of individual trait selection will be technically possible in in-vitro fertilization. However, it will be many decades before the technology is likely to be sufficiently low-cost and widespread to envision elective genetic manipulation.

The good news is that most genomics research initiated is and will continue to be funded by the pharmaceutical and healthcare industries. Those industries' prime goals and economic incentives are to avoid and eliminate disease. Hence, for many years to come, the most studied aspects of the human genome will be surrounding disease and wellness.

While disease mechanisms can be enormously complex, they may be simple cases compared to the development of longevity, pigmentation, or an aptitude for mathematical, musical, or sports, for example. In addition, modification of genes and genomes in pre-differentiated cells remains a nascent technology.

The bad news is that every major technology breakthrough in history that has been used, has also been abused. Think of the long history of dynamite and explosives as applied to constructive versus destructive purposes. In-vitro fertilization was once considered an abomination; now it is an accepted cure for widespread and growing infertility. One cannot forecast a vibrant new technology without acknowledging the likelihood that such technology will be abused.

Conclusion: Right Product, Right Person

The next decade will see the progressive integration of genomic therapies, technologies, and market strategies into the broader consumer marketplace. This market revolution will have a distinctive form, starting with highly sophisticated research products sold to pharmaceutical industry professionals and evolving into ever more broadly adopted consumer products in which the technologies are invisibly integrated.

The genomics revolution is at the intersection of two technological worlds: information technology and biotechnology. It's as much about information as it is about biology, and the trends in information technology will drive its development.

For the past 20 years, information technology has been driving markets toward a more direct connection with individual consumers—and toward customization of products and services for those individual customers. Genomics, combined with the tools of the infomated marketplace, takes this customization to the level of biology. It defines the consumer in terms of their molecular make-up. So any product that interacts with the human biology becomes a candidate for the "right product, right person" paradigm that is currently being worked out in the pharmaceutical and health care industries.

At the same time, information technology is entering a new phase of development in which the accumulation and management of global stores of data will lead to a kind of worldwide data infrastructure. Over the next ten years, we will see this data infrastructure become a robust foundation for personal and business applications that have yet to be imagined. Among these applications will certainly be those that link individual genetic information to knowledge about the significance of that genetic information—as well as products and services designed for their individual genetic characteristics.

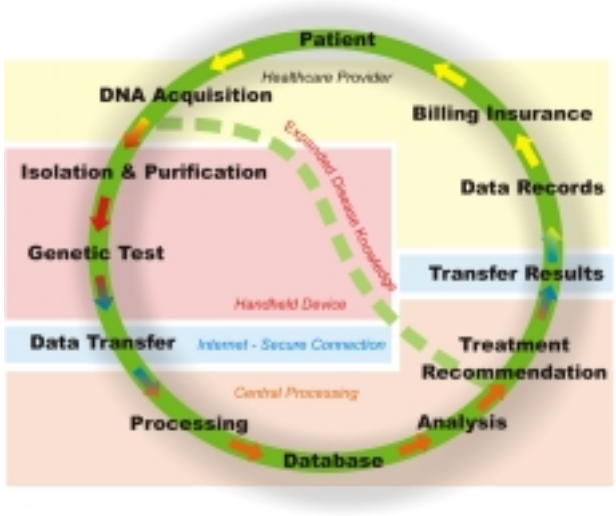
The exact form that this infrastructure will take is uncertain, but we can speculate how it might evolve out of the pharmaceutical model. In this model, the infrastructure for matching the genotyped patient with the right therapy develops as shown in Figure 1.

This infrastructure is then expanded to match the genotyped consumer with the right product or service as shown in Figure 2.

These technologies thus continue a long-term general trend toward increasing individualization and customization. However, society always requires a balance of individual and social identities, and we can expect that countervailing trends will emerge to maintain this balance. Even as individuals seek personalized medicine and genetically-tailored products, will they also turn to genomics as a basis for new communities? For example, will people with shared genetic diseases coalesce into communities to influence policy and research in those diseases? Will those with other shared genetic traits find each other and find reasons to act as a group in addition to acting as individuals?

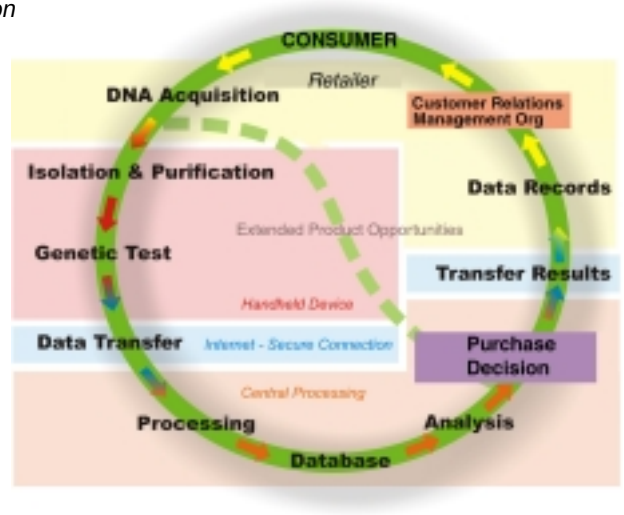
Understanding the future of genomics in the marketplace will require an understanding of both of these trends.

Figure 1
Right Patient, Right Drug Therapy



Source: Bob Molinari/Medstar

Figure 2
Right Product, Right Person



Source: Bob Molinari/Medstar

Glossary

amino acids: small molecules that form a protein when linked together.

bases: the building block of DNA; often used interchangeably with nucleotide.

chromosome: a structure in a cell nucleus composed of genes; human genes are organized into 46 chromosomes.

cDNA: DNA that is made by assembling a strand of bases complementary to a messenger RNA and has almost the same sequence as the gene from which the messenger RNA was originally made.

cloning: a laboratory technique used to produce multiple copies of a piece of DNA.

coding region: the portion of the genome that codes for protein.

codon: a piece of DNA comprising 3 base units which codes for a unique amino acid.

complementarity: the property of attraction between the nucleotides adenine and thymine and guanine and cytosine.

DNA (deoxyribonucleic acid): a molecule composed of four nucleotides that contain the genetic instructions for living organisms.

DNA sequence: the ordering of the four bases (A, T, C, and G) that comprise DNA. The ordering of the bases is the basis of all genetic variability. The sequence gives rise to the classic inherited traits, as well as variations in the coding sequence which can cause disease or predisposition to genetically linked diseases.

drug targets: molecules which are believed to be important in biochemical pathways which pharmaceutical companies may want to up- or down-regulate with drugs. A drug is designed to associate with and change the activity of the target.

electrophoresis: a process of separating large molecules by passing an electrical current though a medium containing a mixture of molecules; molecules separate by size and charge.

enzyme: a protein that acts as a catalyst to induce chemical change in other substances.

functional analysis: the process of determining the function of a gene.

gene: a segment of DNA that codes for the manufacture of one protein.

gene expression: Although all genes are present in the DNA of every cell, each type of differentiated cell produces (expresses) different proteins from its DNA. Those genes that are highly expressed (i.e. lots of protein is made) are 'turned on' in that type of cell, and those that are not are 'turned off'.

gene expression profiling: When tissues become diseased, certain genes may not be functioning properly, and are more or less expressed than in normal tissue. Hence, detecting changes in expression of genes has become important in identifying genes (and hence proteins) that malfunction in a disease. Identification of the genes and proteins implicated in a disease is a critical part of current genomics efforts and can immediately give rise to validated targets for drug screening and intervention.

genome: all the genetic information present in a particular organism.

genomics: the study of genomes.

gene sequence: the order of nucleotides present in a piece of DNA.

homologous: the property of being genetically equivalent.

hybridization (stringent and astringent): the process whereby complementary strands of single stranded DNA come together to form double-stranded DNA. Hybridization conditions can be tailored such that hybridization occurs only when the complementary strands contain no mismatches whatsoever (stringent) or such that hybridization occurs readily when small mismatches (e.g. <4 bases) are present (astringent).

linkage: the property of being in close physical proximity on a chromosome.

mapping: a determination of the positions of genes and the distances between them on a chromosome.

marker: a specific location on a chromosome whose inheritance can be tracked.

mass spectroscopy: a physical method used to analyze compounds by the respective weights of their components.

megabase: a million bases.

messenger RNA (mRNA): RNA that is made from a gene and directs the construction of a specific protein.

motifs: a pattern of DNA sequence that is similar for genes of similar function.

mutation: a change in a base.

nucleotide: the basic building block of DNA. adenine (A), thymine (T), cytosine (C) and guanine (G) are nucleotides.

polymorphism: the difference or variation in nucleotide sequence between genes that code for the same protein.

positional cloning: a collection of techniques used to locate specific genes.

prevalence: the degree to which a specific genetic sequence occurs in a population.

protein: a large molecule consisting of amino acids arranged in a specific sequence.

PCR (Polymerase Chain Reaction): a Nobel-prize winning technology to copy exponentially only specific DNA of interest to a researcher. It is used throughout molecular biology and allows sufficient DNA for analysis to be created from very small amounts of DNA present in samples. Only the specific region of DNA between two 'primer sites' defined by a given DNA sequence is amplified.

sequencing (DNA): the process of determining the order of nucleotides contained in a strand of DNA.

SNP (single nucleotide polymorphism): a single base change in a region of DNA sequence which is different from that deemed to be the normal sequence broadly prevalent in the population. A mutation is a type of SNP in a coding region of a gene; a silent polymorphism is a base change that gives rise to no change in amino acid during transcription; and an informative SNP is one in which its presence or absence can be indicative of some other trait, e.g. inheritance of a disease.

validated drug target: a target that has been proven through some set of experiments to be important to a disease pathway. For example, dramatic changes in the expression level of a certain mRNA between diseased tissue and normal tissue would validate the mRNA as a potential drug target.