Chapter 27
Economics of Personalized Medicine

Introduction

Personalized medicine will improve healthcare and quality of life with reduction of disease burden that will have an impact on all aspects of human life with economic benefits. A discussion of financial aspects, of personalized medicine, however, is important for two reasons: (1) pharmaceutical companies would like to know if it would be profitable; and (2) healthcare providers would like to know if it is affordable. Development of personalized medicine would also affect the pharmaceutical and molecular diagnostics markets, which change every year, and are described in detail in a special report that is regularly updated (Jain 2020a). The following sub-heading has an excerpt from this report.

Personalized Medicine and Drug Markets

Since personalized medicine as a concept is not a distinct entity, there are no markets for this except medicines developed by this approach, referred to as personalized medicines. There are only a few of these but the number will increase. Several technologies are used in the development of personalized medicine and markets for these can be calculated. No matter which way one analyzes these markets, there is considerable overlap among the components as well as related fields. Eventually introduction of personalized medicine will increase the value of both pharmaceutical and diagnostic markets although the exact value of this enhancement may not be separable in markets that were growing even prior to the concept of personalized medicine. Currently it makes no sense to detach a part of the healthcare market and label it as personalized medicine market. Even medicines that have companion diagnostics are not used exclusively in a personalized manner and diagnostics have other applications as well.

However, the current impact of personalized medicine on pharmaceutical markets can be described as contributing to ~25% of the global value of $1.4 trillion in 2019, i.e. $350 billion. This impact will increase to 35% by the year 2024, i.e., $560 billion of the total global pharmaceutical market of $1.9 trillion.

Perceived Financial Concerns

The pharmaceutical industry expects new technologies to facilitate the development and introduction of “blockbuster drugs” which are currently defined as those generating over $1 billion per year. It is common belief in the pharmaceutical industry that blockbuster drugs must target large patient populations and concern has been expressed that personalized medicine may shrink the market for a specific drug by limiting the number of those who can take it. Therefore, the pharmaceutical companies are interested in
using genetics to develop drugs for the population in general and not for a specific genotype. But the important role of genetic variability in disease and therapy revealed by pharmacogenomics suggests that smaller, genetically defined patient populations can be treated more effectively. This would require a complete rethinking and retooling of the genetics-based drug discovery and development on part of the pharmaceutical industry.

**Personalized Medicine and Orphan Drug Syndrome**

An orphan disease is a condition that affects less than 1 person per 100,000 of population. Segmentation of a common disease into subcategories on pharmacogenomic basis might create a small population for a certain drug – orphan drug syndrome. Orphan Drug Law in the US and similar laws in European Union, Japan and some other countries provide financial incentives for the pharmaceutical companies developing products for orphan diseases. Potential problems in this area, ethical and those related to cost-effectiveness, remain to be addressed.

**Commercial Aspects of Pharmacogenomics**

The commercial aspects of personalized medicine that are discussed are based on considerations of the cost of various technologies that will be used in developed such medicines. Systematic pharmacoeconomic studies of pharmacogenomics have not yet been carried out. The economic benefits can be predicted based on the current progress made in genomics and will be a sequel of reduced time for R & D and introduction of the product into the market.

**Cost of DNA Testing**

DNA tests for identifying an individual is simple and cheap. Commercial laboratories offer DNA testing for paternity and other relationships for as little as $100. Legal setting raises the costs. There are over DNA 1200 tests available, mostly for diagnosis of diseases. The cost varies from $150 to over $1000 with an average of $500. The costs are expected to drop in the future as the use increases.

**Cost of Sequencing the Human Genome**

Currently it is very expensive to sequence the 3 billion base pairs of DNA found in humans. Therefore, large scale sequencing is carried out mostly at special sequencing centers and is restricted to major expensive projects. The first human genome sequence, completed by the federally financed Human Genome Project in 2003, cost a few hundred million dollars. In 2007, the genome sequence of James D. Watson was completed at a cost of about $1 million. In 2008, the cost was ~$100,000 for sequencing alone but total charges were $350,000 that included analysis of the data and the customer service. In 2008, Life Technologies’ (now part of Thermo Fisher Scientific) latest machine could sequence a human genome for $10,000. This amount included only the cost of consumable materials, and not labor or the machinery.

The immediate goal of the NIH’s National Human Genome Research Institute (NHGRI) is to support research to lower the cost of these projects more than 100-fold to allow scientists to sequence genomes of human subjects involved in studies to find genes relevant for disease. The longer-term goal of NHGRI’s “Revolutionary Genome Sequencing Technologies” grants totaling more than $32 million is the development of breakthrough technologies that will enable a human-sized genome to be sequenced for less than $1000 so that this process can be used in routine medical tests and allow physicians to tailor diagnosis, prevention, and treatment to a patient’s individual genetic makeup. The different approaches resulted in several successful and complementary technologies and NHGRI is monitoring carefully to see how each technology progresses and which of these technologies can ultimately be used by the average researcher or health care provider.
Complete Genomics started charging $5000 in 2009 for determining the sequence of the genetic code that makes up the DNA in one set of human chromosomes. Its sequencer was not that much different from rival machines, but miniaturization enabled it to use only tiny amounts of enzymes and other materials. This price represented another step toward the long-sought goal of the “$1000 genome.” At that price point it was affordable for people to obtain their entire DNA sequences, giving them information on what diseases they might be predisposed to or what drugs would work best for them. Complete Genomics did not offer a service to consumers but provided sequencing service for consumer-oriented companies. Most of its customers were pharmaceutical companies or research laboratories that conduct studies aimed at finding genes linked to diseases.

In 2011, Illumina lowered the cost of its human whole-genome sequencing services to $5000 per genome for projects of 10 samples or more, and $4000 for projects of 50 samples or more. The services were offered through the Illumina Genome Network and compete directly with human whole-genome offerings from Complete Genomics and Life Technologies.

In 2012, Life Technologies (now part of Thermo Fisher) Benchtop Ion Proton™ Sequencer could decode a human genome in one day for $1000. From there on, the goal of various companies was to reduce the cost of WGS to $100.

In February 2020, MGI, a subsidiary of BGI launched $100 sequencing (reagents only) in China and Europe with plan to introduced it later in the US (currently on hold). The origin of this goes back to 2007, when BioNanomatrix and Complete Genomics formed a joint venture to share a grant from the US National Institute of Standards and Technology to develop technology that may be able to sequence a human genome in 8 h for <$100. Complete Genomics launched its novel DNA NanoBalls (DNB) platform in 2008 but failed and was acquired by BGI. MGI’s DNBseq technology combines DNBs—small, densely packed balls of DNA generated by rolling circle replication—and a patterned array of “sticky spots” to capture the DNBs using CoolMPS (massively parallel sequencing) technology. The Tx can sequence up to 700 genomes on a single run, a capacity that is an order of magnitude larger than any sequencer on the market today. It takes a full capacity run of 700 genomes to achieve the $100 price point for someone who owns the Tx machine.

A graph of the drop of cost per raw megabase of DNA sequence is shown in Fig. 27.1. It does not show the 2020 drop to $100 genome.

In 2015, the most common routine for sequencing an individual’s human genome involves generating a “draft” sequence and comparing it to a reference human genome sequence to catalog all sequence variants in that genome. This routine did not involve any sequence finishing. In short, nearly all human genome sequencing in 2015 yielded high-quality “draft” (but unfinished) sequence. That sequencing is typically targeted to all exons (whole-exome sequencing) or aimed at the entire ~6-billion-base genome (whole-genome sequencing), as discussed above. The quality of the resulting “draft” sequences is

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**Fig. 27.1** Cost of sequencing per genome. (Wetterstrand KA. DNA Sequencing Costs: Data from the NHGRI Genome Sequencing Program. [http://www.genome.gov/sequencingcosts](http://www.genome.gov/sequencingcosts) (accessed on 23 August 2020). Reproduced by permission)
heavily dependent on the amount of average base redundancy provided by the generated data (with higher redundancy costing more).

Emergence of commercial enterprises offering genome-sequencing services at competitive pricing has complicated the assessment of cost of sequencing. Markets for sequencing are discussed in a special report on this topic (Jain 2020b). Direct comparisons between commercial versus academic genome-sequencing operations can be particularly challenging because of the many nuances about what each includes in any cost estimates (with such details often not revealed by private companies). The cost data that NHGRI collects from its funded genome-sequencing groups includes information about a wide range of activities and components, such as: reagents, consumables, DNA-sequencing instruments, certain computer equipment, other equipment, laboratory pipeline development, laboratory information management systems, initial data processing, submission of data to public databases, project management, utilities, other indirect costs, labor, and administration. Typically, costs do not include activities such as quality assurance/quality control (QA/QC), alignment of generated sequence to a reference human genome, sequence assembly, genomic variant calling, or annotation. Almost certainly, companies vary in terms of which of the items in the above lists get included in any cost estimates, making direct cost comparisons with academic genome-sequencing groups difficult. It is thus important to consider these variables – along with the distinction between retrospective versus projected costs – when comparing genome-sequencing costs claimed by different groups. Anyone comparing costs for genome sequencing should also be aware of the distinction between “price” and “cost” – a given price may be either higher or lower than the actual cost.

The key factors to consider when assessing the “value” associated with an estimated cost for generating a human genome sequence – in particular, the amount of the genome (whole versus exome), quality, and associated data analysis (if any). With new DNA-sequencing platforms anticipated in the coming years, the nature of the generated sequence data and the associated costs will likely continue to be dynamic. As such, continued attention will need to be paid to the way in which the costs associated with genome sequencing are calculated.

**Cost of Genotyping**

Currently, it typically costs a drug company about $1 billion to develop, test, and bring to market a single drug. Pharmacogenomic data could hasten clinical drug trials, allowing researchers to design and conduct safer, more targeted trials of a certain drug. The results of such a trial would be far more conclusive and focused than those of trials that do not use pharmacogenomic data. By reducing both the time of drug development, the number of patients required and the failed clinical trials, pharmacogenomics is expected to reduce the cost of drug development. The question now is the cost of genotyping.

Genome-wide association studies require at least 100,000 SNPs to be genotyped in, for example, 500 cases and 500 controls. This represents 100,000,000 genotypes for each analysis. Using today’s technology, an amplification method is required, whether it is on an individual SNP basis using PCR or by whole genome amplification. A rapid discrimination mechanism to determine the genotype of each sample and some way of rapidly reading out and capturing the data are required. Many technologies are being developed to solve these practical issues, but they invariably require a PCR step. The miniaturization of PCR using microfluidics may provide an opportunity to reduce costs, as well as multiplexing both the amplification steps and the detection steps. Nanotechnology with nanopore DNA sequencing and single molecule detection is another promising approach.

Another problem associated with the whole genome scans in humans is that the technology platform will need to deliver between 250,000 and 1,000,000 genotypes a day to make the time frame for these studies reasonable. Current cost ranges between 10¢ and $1 per genotype. For example, using Taqman technology, 1,000,000
genotypes would cost $1 million ($1 per genotype) or oligonucleotide assay and ABI 377 technology would cost $500,000 (50¢ per genotype). Even at the level of the individual patient, to genotype 300,000 SNPs is an expensive proposition. To enable such approaches to be used widely the cost per genotype needs to come down from the current cost to 1¢ per genotype. Current genotyping arrays can reveal most of the common SNPs for $500, how much more meaningful information whole-genome sequencing can add to that remains to be seen, even though the goal of $100 genome has been reached.

Cost of Pharmacogenomics-Based Clinical Trials

The pharmaceutical companies would, therefore, have a better understanding of the cost required to complete the development of the drug and the likely economic return on their investment before proceeding to a phase III clinical trial. The cost for pharmacogenomics-based clinical trials would be less than that of conventional clinical trials because fewer patients would be required for such trials. If 5000 patients are required for current clinical trials, use of pharmacogenomics should enable all the three phases to be completed with less than 2500 patients – a saving of more than 50%. In addition, understanding the correlation between drug response and genomic differences would enable pharmaceutical companies to improve the marketing of their drugs by identifying those patients for whom certain drugs are likely to be most effective. Several pharmaceutical companies are now using genotyping in most of their clinical trials while others are not.

Business Development of Pharmacogenomic Companies

The largest segment of companies under the category of personalized medicine contains pharmacogenomic companies. This does not include all genomic companies. Among those involved in developing personalized medicines, a vast range of technologies is being used. Overall, the growth in this segment is slow but some technologies such as molecular diagnostics and SNP genotyping have a fast rate of growth that exceeds 20% per year. Companies providing toxicogenomic and pharmacogenetic services are doing well because the field is not overcrowded and there is need for these services in the pharmaceutical sector. Although some major pharmaceutical companies have various required technologies for personalized medicine in house, there are numerous collaborations with smaller companies. Smaller biotechnology companies with a strong base in molecular diagnosis or those that have pharmacogenomic collaborations with major pharmaceutical companies appear to have better prospects.

Cost of Personalized Healthcare

The Rising Healthcare Costs in the US

Overall, health care inflation continues to rise precipitously. In 2019, total health care expenditures in the US were >$4 trillion and they are continuing to increase. Hospital care, physician services, and prescription drugs account for most of this spending. The health care system in the US needs a new paradigm to change this inflation rate. Personalized medicine provides an invigorating solution for lowering the cost of health care.

It is generally recognized that drugs are the cheapest and least traumatic way of dealing with chronic illnesses. Proliferation of surgical procedures and hospitalization has raised the costs of healthcare. Refinement of surgical procedures to become minimally invasive and use of products of biotechnology to improve the results are some of the advances in surgery. Most of the surgical procedures for peptic ulcer have become obsolete by the introduction of rational anti-ulcer drugs. It is likely that essential surgery of the future will be limited to trauma, emergencies such as hemorrhages, anatomical corrections of pathology,
organ transplants (where medical therapies have failed), implantation of electronic devices, removal of benign tumors, cancer of some organs etc. Surgery will have only a subsidiary role for cancer of organs such as brain for which more effective non-surgical therapies such as gene therapy would be developed.

Currently <15% of the world's healthcare budget is spent on drugs. It is likely to increase during the next decade, depending upon what new and effective medicines emerge from the pipelines of biopharmaceutical companies. Many of the currently incurable diseases such as Alzheimer's disease will have rational therapies during the next decade. Although introduction of treatments for incurable diseases would raise the drug costs, it will reduce the total cost of healthcare such as on nursing home care and other palliative drugs, which would no longer be necessary. However, simple introduction of new medicines to the population in general may involve waste of money as some patients may not respond to these. Here, the importance of personalized medicines based on pharmacogenomics becomes obvious. These may be more expensive to develop and may cost more but will eventually lower the healthcare costs.

There are individual examples of high cost of personalized drugs of rare diseases. One example quoted by those concerned with high cost of personalized medicine is cystic fibrosis (CF) drug Kalydeco, which may help patients with certain CF gene mutations, but costs $300,000 a year. Other non-personalized biopharmaceuticals for some rare orphan diseases are also extremely expensive. No field study has been done so far to determine the overall cost of healthcare based on personalized medicine. However, overall cost of healthcare is expected to decrease with personalization due to following reasons:

- Increased efficacy of personalized medicines will offset the higher prices of drugs
- Increased safety of personalized medicines will reduce costs due to adverse reactions to conventional drugs
- Reduction of high expense of hospital stay
- Predictive medicine will reduce costs by prevention

**Genetic Testing and Cost of Healthcare**

One concern surrounding increased and widespread genetic testing is that it could lead to increased use of an already strained healthcare system in the US. However, according to one study, multiplex genetic testing may not lead to increased use of healthcare services (Reid et al. 2012). As part of the Multiplex Initiative, a NIH-funded, multidisciplinary research effort to examine how the public views genetic testing, participants were tested for 15 risk variants for several common diseases such as type 2 diabetes, coronary heart disease, and melanoma, etc. Persons offered and completing multiplex genetic susceptibility testing used more physician visits before testing, but testing was not associated with subsequent changes in use. This study supports the supposition that multiplex genetic testing offers can be provided directly to the patients in such a way that use of health services is not appropriately increased.

**Personalized Medicine for Reducing Cost of Care of Cancer**

**Lowering the High Costs of Cancer Chemotherapy**

Pharmacogenomics for cancer is being driven by the fact that treatment costs are so high and getting higher. Molecular biomarkers will enable us to decide who really needs expensive therapy. The costs will be reduced significantly as more genetic variants come into play, which are important in terms of drug response. There might be gene chips that are specifically tailored toward different types of therapy, and one could look at many different genotypes at the same time in a single patient sample. Therefore, costs should go down as discoveries are made.

Another contributor to high costs of care of cancer patients are adverse effects from chemotherapy. Identification of patients who might react adversely to a treatment could help in sav-
ing costs by avoiding administration of drugs to patients at risk of adverse reactions. Researchers are looking at sensitivity to chemotherapies within families and identifying candidate genes that contribute to susceptibility to anticancer drug toxicity. Studies of cell lines from CEPH (Centre d’Etude du Polymorphisme Humain, France) families have shown that susceptibility to the toxic effects of the anticancer drug cisplatin is significantly heritable. CEPH collects biological samples from large families which serve as reference families for genetic research. With the help of gene expression profiling, it is possible to identify the genes responsible for conferring drug susceptibility. A clinical trial by researchers at the University of Chicago has demonstrated the predictive significance of genotyping for variants that affect drug pharmacodynamics. They genotyped 20 patients, looking for variations in the promoter that controls activity of the enzyme UGT1A1, which is important for detoxification of the active metabolite of irinotecan, an effective anticancer drug that can cause diarrhea and neutropenia. One UGT1A1 variant contains a TA repeat of the TATA sequence in the promoter. The toxic effects were found only in patients who possessed at least one allele of that polymorphism.

**KRAS and BRAF Screening in CRC**

According to a study screening for KRAS and BRAF mutations can reduce the cost of anti-EGFR treatment for metastatic CRC but with small reduction in overall survival (Behl et al. 2012). Metastatic CRC patients whose tumors harbor mutations in KRAS (and to a lesser extent, in BRAF) are unlikely to respond to costly anti-EGFR therapies. Screening of patients who are candidates for these therapies for mutations in one of these genes (KRAS) has been recommended, with the goal of providing treatment to those who are likely to benefit from it while avoiding unnecessary costs and harm to those who are not likely to benefit. However, the real-world impact of mutation screening for both KRAS and BRAF is unclear. The researchers found that compared with no anti-EGFR therapy, screening for both KRAS and BRAF mutations showed high incremental cost-effectiveness ratio, i.e. it was very costly in relation to its benefits. Compared with anti-EGFR therapy without screening, screening for KRAS mutations saved approximately $7500 per patient; adding BRAF mutation screening saved another $1023, with little reduction in expected survival. In general, these results are less supportive of the use of anti-EGFR therapy than previous analyses, and they indicate lower cost savings from KRAS testing than previously reported. Although it cannot be confirmed that anti-EGFR therapy is a cost-effective use of health care resources, the results affirm that KRAS testing is cost-saving and BRAF testing may offer additional savings.

**Personalized Dose Reduction of Pembrolizumab in Cancer**

The initial FDA approval of pembrolizumab for patients with melanoma and NSCLC was based on phase III trials using a dose of 2 mg/kg every 3 weeks. Subsequent trials used a fixed dosage of 200 mg every 3 weeks, with the excuse that using a fixed dose was more convenient. Pharmacokinetic simulations performed by the manufacturer and accepted by the FDA demonstrated pharmacokinetic equivalence, and thus led to retroactive label changes for previously approved indications. However, it was noted that this dosage was higher than necessary. As the average patient with cancer weighs 75 kg, only 150 mg would be required for such a patient. It was estimated that US health care payers could save $0.8 billion annually by switching back to weight-based dosing for patients with programmed cell death ligand 1–positive NSCLC receiving pembrolizumab as monotherapy. A better solution has been proposed, i.e., dose of 4 mg/kg every 6 weeks, with a cap at 400 mg; the weight-based dosing based on pharmacokinetic data (Goldstein et al. 2020). This solution would be highly beneficial to individual patients as it would decrease their exposure to SARS-CoV-2,
maintain equivalent efficacy, and decrease financial burden for patients who bear a share of the cost. It would also provide a great benefit to society at large. In 2019, worldwide sales of pembrolizumab generated $11 billion for the manufacturer.

Reducing Healthcare Costs by Combining Diagnostics with Therapeutics

Cost-effective diagnostics are but a prelude to an era of cost-effective personalized medicine. The real potential is in better targeting expensive drugs to those who will benefit from them, thereby both cutting wasteful expenditure and decreasing adverse events associated with treating non-responders. Some examples of this are as follows.

The anticancer drug Avastin (Genentech/Roche) costs $50,000–100,000 per year of treatment but works in fewer than 50% of patients. Avastin is an approved therapy for lung cancer, kidney cancer, colorectal cancer, and brain cancer, but its approval for HER2-negative metastatic breast cancer was withdrawn by the FDA in 2010 because of lack of efficacy as well as adverse effects. Avastin may be useful in a targeted group of breast cancer patients but there is no available test that can identify such patients. Given that Avastin may generate $12 billion in peak sales, the low rate of efficacy translates into billions of dollars in misdirected healthcare spending. A test for Avastin response, such as that in development by BG Medicine, could save the healthcare system as much as $6 billion per year if all nonresponders could be removed from the treatment pool. Assuming a test of this sort is introduced at the beginning of 2021 and is 100% adopted, cumulative savings of $50 billion could be realized by 2025.

Oncotype Dx (Genomic Health) is a test with compelling cost-saving potential. It is used to predict chemotherapy benefit for patients who have node-negative, estrogen receptor positive (node-, ER+) breast cancer. By averting unnecessary chemotherapy, the test has been shown to save about $2000 per patient. Extending this cost savings to the roughly 100,000 new cases of node-, ER+ breast cancer in the US each year, this test could save the US healthcare system up to ~$200 million a year or about $2 billion over the 10-year time horizon under legislative consideration for the healthcare reform bill.

Allomap (XDx) is a noninvasive test that is used instead of biopsy in the management of heart transplant patients after surgery. The total potential cost savings is estimated at roughly $20 million per year (about $12 million for payors as well as ~$8 million for hospitals and transplant centers).

This scenario, in which a drug with high sales but low efficacy is targeted by diagnostics companies, may become a pattern in the future, multiplying cost savings.

Reducing the Cost of Treatment of Acute Myeloid Leukemia

The cost of acute myeloid leukemia (AML) treatment is substantial and increasing. Inpatient treatment costs for allogeneic hematopoietic stem cell transplant (HSCT) and intensive chemotherapy are the substantial, and may increase as new, expensive oral therapies enter the market. An overview of the healthcare costs in patients with AML treated with various methods (intensive chemotherapy, allogeneic HSCT, low-intensity treatment and supportive care only) includes the impact of the recently approved novel AML agents and an increasingly personalized treatment approach on healthcare resources (Bewersdorf et al. 2019). It remains to be seen how advances in diagnostic techniques, incorporation of novel agents, and personalized approaches will impact medical outcomes, costs and influence health policy.
Cost-Effectiveness of Personalized Medicine

Early Cost-Effectiveness Analysis of New Personalized Medicine Technologies

Development of new drugs and diagnostics is expensive including those for personalized medicine. Many diagnostic tests and biomarkers are not adopted by the healthcare system due to lack of evidence of their cost-effectiveness. A step-wise approach, decision analytic modeling, has been described for carrying out a cost-effectiveness analysis early in the development stage of a technology to reduce the potential risks of investment (Ling et al. 2019). This can identify the key drivers of cost-effectiveness and provide minimum criteria that the technology needs to meet requirements for adoption by public and private healthcare systems. Such an information analysis can provide further evidence for supporting policy decisions. These steps will also enable investors to make better decisions on their investments for maximizing the health benefits and reducing the shortcomings of suboptimal technologies.

Cost-Effectiveness of Pharmacogenetic Testing

The cost-effectiveness of pharmacogenetic testing has not been studied extensively. Although there would be added costs of genotyping, considerable unnecessary expenses can be saved in drug development. In medical practice, the cost associated with screening all individuals before drug administration can be offset by a reduction in costs associated with adverse reactions and therapeutic failures. The current empirical method of drug prescription where a doctor tries a drug and tells the patient that it may work and it does not, he will switch to another. This trial and error method is not only expensive but also harmful for the patient. Personalized medicines, which are tailored to a patient’s needs and selected on a genomic basis, are going to be more effective and safer. Therefore, there should be significant long-term cost savings for the healthcare sector in a managed care environment. An additional benefit of combining diagnostics with therapeutics would be preventive medical treatment as required to prevent the full-blown disease, which would cost more to treat. This is the concept of “Predictive Medicine” approach.

A closely watched test in this segment is AmpliChip (Roche) for pharmacogenetics, which has not been adopted as widely as expected even though its benefits have been proven. Roche sells AmpliChip for $400 but the test is offered by only four clinical reference laboratories, which charge between $600 and $1200 for the test with no evidence that it is regularly reimbursed by insurance companies.

Mayo Collaborative Services and Medco, a Pharmacy benefits management company, have studied whether using genetic tests can cut costs and improve care for patients taking the anticoagulant warfarin. The study was the first in a line of similar collaborations that will explore the financial and health benefits of genetic tests used with other drugs. This information will be important for assessing the cost-effectiveness of personalized medicine.

The cost of direct to consumer personal genetic testing, e.g., from 23andMe, is the least expensive at $399. Navigenics’ SNP-genotyping service (now part of Thermo Fisher Scientific), which uses Affymetrix arrays, costs $2500, while Decode Genetics’ program, which uses Illumina’s Human 1M BeadChips, costs $985. New Hope Medical, a clinic that provides diagnostics and therapies not readily available in conventional medicine, and charges between $475 and $900 for genomic testing for between 12 and 25 SNPs linked to certain conditions.

A global study has consolidated HLA genotypes from 3.5 to 6.4 million individuals across up to 74 countries and modeled the country-specific cost-effectiveness of genetic testing (Zhou et al. 2020). Major ethnogeographic differences were found in risk allele prevalence, which trans-
lated into pronounced differences in the number of patients needed to test to prevent one case of severe hypersensitivity reactions between countries and populations. At incremental cost-effectiveness ratio thresholds of $40,000, testing of HLA-B*57:01 in patients initiating abacavir was cost-effective in most of the countries with potential exceptions of East Asia, Saudi Arabia, Ghana, and Zimbabwe. For carbamazepine, preemptive genotyping of HLA-B*15:02 was only cost-effective across most of East and South Asia, whereas HLA-A*31:01 testing is likely to be cost-effective globally. Testing of HLA-B*58:01 is more likely to be cost-effective throughout Africa and Asia compared with Europe and the Americas. These data can serve as an important resource for clinicians and health economists to guide clinical decision making and guide public healthcare strategies.

Cost-Effectiveness of CYP Genotyping-Based Pharmacotherapy

Genetic polymorphisms of the drug-metabolizing cytochrome P-450 (CYP) enzymes CYP2C9, CYP2C19 and CYP2D6 have been characterized (see Chap. 3). This is of clinical importance mainly in patients having two non-functional alleles, phenotypically characterized as “poor metabolizers” (1–10% of Caucasians). Studies have shown that pharmacogenetic analyses will significantly contribute to reducing treatment costs for drug-induced adverse reactions and costs of sick leave, by predicting the best drug and the most effective and safest dosage. The expenses of full genotyping (CYP2C9/2C19/2D6) are less than financial loss from 1 day of sick leave of an employee. The question has been raised: are pharmacogenetic analyses coming to the point where they drive down costs incurred by illness?

Over 2 million adverse drug reactions that occur in the US per year cost approximately $25 billion. According to a study by Roche, its product AmpliChip CYP450 could cut costs in 44% of cases. Considering the current rate of growth, the US health care system could potentially save $21 billion by 2020.

CYP450 genotyping has potential to improve efficacy of 10–20% of all drug therapy and reduce incidence of ADRs by 10–15%. CYP2D6 genotyping shows mutations causing ultra-rapid metabolism leading to hugely increased levels of active compounds such as codeine, which can cause symptoms of over dosage with usually recommended doses.

Cost Effectiveness of HIV Genotyping in Treatment of AIDS

Costs of antiretroviral therapy for HIV-infected patients have increased at a time when most countries are attempting to contain health care costs. Part of this increase results from HIV drug resistance and a subsequent shift to more complex and costly therapies. Genotypic guided treatment is associated with better virologic outcome. However, it is not yet known whether it will be cost effective. Two examples show the cost-effectiveness of HIV genotyping.

VIRADAPT study, a prospective, open-label, randomized trial compared AIDS patients assigned to standard of care versus genotypic guided treatment for 6 months. Total follow-up for the extended trial was 1 year. Costs were computed from the viewpoint of the health care system in France. Genotyping using TruGene HIV-1 assay, estimated at $500 per test, resulted in yearly costs per patient of >$20,000 in the standard of care group and >$18,000 in the genotyping group. Drug costs represented 55% of total costs. There was a trend toward a decrease in drug costs in the genotyping arm, the greatest reduction being in the decreased use of protease inhibitors in the genotyping arm. The additional expense of genotyping appeared to be offset by the savings obtained in drug costs.

HIV genotyping with secondary resistance testing increases life expectancy of AIDS patients by 3 months, at a cost of ~$18,000 per quality-adjusted life-year (QALY) gained. The cost-effectiveness of primary resistance testing is $22,000 per QALY gained with a 20% prevalence of primary resistance but increases to $70,000 per QALY gained with 4% prevalence. The cost-effectiveness ratio for secondary resis-
Cost-Effectiveness of Warfarin Pharmacogenomics

Review of studies incorporating clinical efficacy data of genotype-guided dosing algorithm had shown that warfarin pharmacogenomics would improve quality-adjusted life-years gained (You 2011). However, it is unlikely to be cost-effective for patients in general. Important factors for improving the cost-effectiveness include low genotyping cost, high effectiveness in improving anticoagulation control and lowering adverse events. Application of warfarin pharmacogenomics could possibly be cost-effective in selected patient groups with high bleeding risk or practice sites with suboptimal management of anticoagulation control.

Molecular testing is as much about generating cost savings by identifying nonresponders as it is about improving survival by identifying responders, and that good modeling must account for the fact that community practice (as opposed to clinical trials) is messy. This study of an unusually accurate test raises important issues that should be considered for other molecular tests in other settings.

Overall Economic Impact of Personalized Medicine on Healthcare

Increase in treatment efficacy by individualize treatment is difficult to measure in financial terms but the savings from reduction of adverse reactions would be considerable. Adverse reactions to medicines in hospitalized patients in the US, or admissions to hospital because of an adverse event are estimated to cost over $100 billions per year to the health-care industry. A study in France found that adverse reactions to drugs accounted for 3.5% of admissions to a cancer institute and 1.8% of the hospital budget. Even if personalized medicine reduces adverse reactions by a small percentage, the resulting savings to the healthcare industry would be considerable.

References

Behl AS, Goddard KA, Flottemesch TJ, et al. Cost-effectiveness analysis of screening for KRAS and BRAF mutations in metastatic colorectal cancer. J Natl Cancer Inst. 2012;104:1785–95.

Bewersdorf JP, Shallis RM, Wang R, et al. Healthcare expenses for treatment of acute myeloid leukemia. Expert Rev Hematol. 2019;12:641–50.

Goldstein DA, Ratain MJ, Saltz LB. Weight-based dosing of pembrolizumab every 6 weeks in the time of COVID-19. JAMA Oncol. 2020; https://doi.org/10.1001/jamaoncol.2020.2493.

Jain KK. Molecular diagnostics: technologies, markets and companies. Basel: Jain Pharma Biotech; 2020a.

Jain KK. DNA sequencing: technologies, markets and companies. Basel: Jain Pharma Biotech; 2020b.

Ling DI, Lynd LD, Harrison M, et al. Early cost-effectiveness modeling for better decisions in public research investment of personalized medicine technologies. J Comp Eff Res. 2019;8:7–19.

Reid RJ, McBride CM, Alford SH, et al. Association between health-service use and multiplex genetic testing. Genet Med. 2012;14:852–9.

You A. Pharmacoeconomic evaluation of warfarin pharmacogenomics. Expert Opin Pharmacother. 2011;12:435–41.

Zhou Y, Krebs K, Milani L, Lauschke VM. Global frequencies of clinically important HLA alleles and their implications for the cost-effectiveness of preemptive pharmacogenetic testing. Clin Pharmacol Ther. 2020 Jun 14; https://doi.org/10.1002/cpt.1944. [published online ahead of print].