Chapter 28
Future of Personalized Medicine

Introduction

Personalized medicine is already in use in practice and expanding. Several studies of the human genome are still going on and some are planned. Although molecular diagnostics has already made considerable advances, the technologies have not been fully exploited to understanding the genetic basis of disease, which is important for developing personalized medicine. Future of personalized medicine in various therapeutic areas is described in the corresponding chapters. Further progress in personalized medicine will require extensive research on highly identifiable, integrated datasets of genomic and health information.

Personal Genome Project

A Personal Genome Project (PGP) was launched as a sequel of the Human Genome project and volunteers were recruited to make their own genomic and phenomic data available. Participants in the PGP chose to forgo privacy via institutional review board-approved “open consent” process. These resources included full (46-chromosome) genome sequences, digital medical records and other medical information that became a part of personal health profile. It also includes comprehensive data about RNA and protein, body and facial measurements and imaging such as MRI. Human cell lines representing each subject were deposited in a repository at the National Institute of Genome Medical Sciences. The findings after enrollment of >1800 participants, including WGS of 10 pilot participant genomes (the PGP-10), have been published (Ball et al. 2012). The Genome-Environment-Trait Evidence (GET-Evidence) system, which automatically processes genomes and prioritizes both published and novel variants for interpretation, was introduced. In the process of reviewing the presumed healthy PGP-10 genomes, the authors found numerous literature references implying serious disease. Although it is sometimes impossible to rule out a late-onset effect, stringent evidence requirements can address the high rate of incidental findings. To that end the team developed a peer production system for recording and organizing variant evaluations according to standard evidence guidelines, creating a public forum for reaching consensus on interpretation of clinically relevant variants. Genome analysis becomes a 2-step process: using a prioritized list to record variant evaluations, then automatically sorting reviewed variants using these annotations. Genome data, health and trait information, participant samples, and variant interpretations are all shared in the public domain. There is an open invitation to others to review the results using participant samples and contribute to interpretations. This public resource and methods are offered to further research in personalized medicine. In the ongoing project, the organizers hope to enroll 100,000 participants.
Genome-Wide Association Studies

The NIH is seeking public input on the policy designed to facilitate the research community’s access to data resulting from NIH-funded, genome-wide association studies (GWAS), which would lead to the development of a centralized NIH data repository. GWAS rely on the newly available research tools and technologies to rapidly and cost-effectively analyze genetic differences among persons with specific illnesses, such as diabetes or heart disease, compared to healthy individuals. The differences may point to genetic risk factors for the development or progression of disease. Several NIH institutes were launched, or are planning, GWAS initiatives with the expectation that the results will accelerate the development of better diagnostic tools and the design of new, safe, and highly effective treatments. This will be an important contribution to genomics-based health care and personalized medicine.

As numerous GWAS programs get underway, NIH seeks to harmonize the policies by which the results will be made available to researchers. The proposed GWAS Policy calls on NIH-funded GWAS investigators to quickly submit genetic data (genotypes) along with relevant health information (phenotypes) about individuals to a centralized NIH data repository. Data will be submitted in a form that protects the privacy and confidentiality of research participants. The data will be made freely available to all approved researchers to accelerate their studies. The draft policy also proposes terms and conditions for investigators to access GWAS data for research purposes. Data will be released in a manner that preserves the privacy and confidentiality of research participants.

NIH encourages patenting of intellectual property that addresses public need, such as creating new treatments that can be brought to the clinic but seeks to prevent premature or inappropriate patents that impede future research. Because publication credit is critical to academic promotion, the proposed NIH policy also defines a grace period during which GWAS data will be available for access, but principal investigators submitting the data would be the only ones allowed to publish analyses in scientific journals. The policy also asks that recipients of GWAS data acknowledge the submitting investigator in any published works.

Beyond the direct implications for the 1000 Genomes Project, the effort has spurred researchers to pioneer and evaluate methods that benefit other research efforts as well. For example, researchers have been working with high-throughput sequencing, developed new approaches for exchanging and analyzing data, discovering SNPs and CNVs, and making imputations based on next-generation sequence data. One study from this project shows how structural variants are implicated in numerous diseases and make up most of varying nucleotides among human genomes. The authors describe an integrated set of eight structural variant classes comprising both balanced and unbalanced variants, which they constructed using short-read DNA sequencing data and statistically phased onto haplotype blocks in 26 human populations (Sudmant et al. 2015). Analyzing this set, they identified numerous gene-intersecting structural variants exhibiting population stratification and describe naturally occurring homozygous gene knockouts that suggest the dispensability of a variety of human genes. They demonstrated that structural variants are enriched on haplotypes identified by GWAS and exhibit enrichment for expression quantitative trait loci. Their catalogue will enhance future studies into structural variant demography, functional impact, and disease association.

There is a need, however, for developing shared data formats for different stages of the analysis. In the absence of standard formats or a clear framework for such analysis, efforts to decipher the genetic information would be delayed. Consequently, team members are working to develop draft formats to aid this analysis. The International Genome Sample Resource was established to ensure the ongoing usability of data generated by the 1000 Genomes Project and to extend the data set.

NHGRI’s genomics Vision for 2020

In 2018, NHGRI embarked on a thorough, community-driven program to collect ideas for the Institute’s next strategic plan to be formally presented in October 2020 on the 15th
anniversary of the completion of the HGP, which is also the 30th anniversary of the launch of the HGP. Because following a strategic plan that is >10 years old is no longer productive, the most recent plan has charted an ambitious course beyond genomics to understand disease, apply genomics to medical science, and shape healthcare. The new plan will be published in October 2020. A key question remains whether the strategic plan will focus more narrowly on NHGRI’s funding priorities or whether it should chart a broader vision for the genomics community. NHGRI will continue to maintain its established leadership role in many areas including technology development, genome function, epigenomics, genetic-environment interactions, genomic medicine, workforce development, policy development, and ethical/legal issues. Other important areas may fall outside the NHGRI’s scope: e.g. cancer genomics and the microbiome. In other areas, NHGRI will be heavily involved but in partnership with other funding bodies, e.g. rare and common diseases as well as computational genomics where NHGRI will partner with others. NHGRI has identified key areas that will guide the planning process:

- Basic genomics and genomic technologies
- Genomic data science
- Genomics in medicine and health
- Society, education, and engagement

Genomics of Aging in a Genetically Homogeneous Population

According to UNESCO’s Preservation of Parsi Zoroastrian Project, 31% of the Parsi population in India lives to be >60 years of age, compared to 7% nationally. A better understanding of the genetic causes of longevity could have a major impact on the Indian Government’s healthcare budget and drug companies’ marketing efforts. Affymetrix signed an agreement with Avesthagen Ltd. (Bangalore, India), whereby Affymetrix’ microarray technology will be used for the AVESTAGENOME Project™, which will explore the genetic basis of longevity and create a genetic, genealogic and medical database of the Parsi-Zoroastrian population. The use of Affymetrix technology will enable researchers to correlate genes with longevity, as well as neurodegenerative conditions, breast cancer, diabetes, and other complex diseases that affect the Parsi community. The Parsi community was selected because of its longevity and its relatively genetically homogeneous population. This project takes a systems biology approach that includes not only genotyping but also expression profiling and transcriptomics. The genotyping phase of the project, which began in 2007, consisted of 10,000 samples in the first year. By the middle of 2008, the team had performed expression profiling and transcript mapping experiments across a subset of the samples. The project was completed by 2013. Genetic information for The AVESTAGENOME Project™ is being collected following informed consent. Data confidentiality is being maintained as in accordance with the Indian Council of Medical Research guidelines.

Comparison of DNA polymorphisms with data from other populations has uncovered a unique signature for the Parsi population, and WGS from these samples is ongoing to discover all the polymorphisms in this unique population that potentially bridges the eastern and western populations. Peripheral blood mononuclear cells from the participants are to be transformed for potential therapeutic applications. Importantly, the integration of data sets from genome, transcriptome, proteome, and metabolome from the same sample would enable a comprehensive picture of both health and disease event(s) at the molecular level (Guzder et al. 2010).

Translational Science and Personalized Medicine

Translational science deals with transfer of technologies from preclinical research into clinical application. Table 28.1 shows translational methods that are relevant to personalized medicine. Biomarkers play an important role as described earlier.
Translation of Genomic Research Into Genetic Testing for Healthcare

Advances in genomics have led to mounting expectations about their impact on health care and disease prevention. There is a need for a comprehensive research agenda to move human genome discoveries into health practice in a way that maximizes health benefits and minimizes harm to individuals and populations. A continuum of multidisciplinary translation research that builds on previous characterization efforts in genomics and other areas in health care and prevention includes four phases of translation research that revolve around the development of evidence-based guidelines:

- Phase 1 translation (T1) research seeks to move a basic genome-based discovery into a candidate health application (e.g., genetic test/intervention).
- Phase 2 translation (T2) research assesses the value of a genomic application for health practice leading to the development of evidence-based guidelines.
- Phase 3 translation (T3) research attempts to move evidence-based guidelines into health practice, through delivery, dissemination, and diffusion research.
- Phase 4 translation (T4) research seeks to evaluate the “real world” health outcomes of a genomic application in practice.

Because the development of evidence-based guidelines is a moving target, the types of translation research can overlap and provide feedback loops to allow integration of new knowledge. Although it is difficult to quantify genomics research is T1, no more than 3% of published research focuses on T2 and beyond. Evidence-based guidelines and T3 and T4 research are scarce. With continued advances in genomic applications, however, the full continuum of translation research needs adequate support to realize the promise of genomics for human health.

Long-Term Behavioral Effects of Personal Genetic Testing

In 2008, Scripps Translational Science Institute (STSI), Navigenics (now acquired by Life Technologies/Thermo Fisher Scientific), Affymetrix, and Microsoft embarked on a decades-long study to determine the long-term behavioral effects of personal genetic testing. Genetic scans will be offered to up to 10,000 individuals.

Table 28.1 Methods of translational science that are relevant to personalized medicine

| Biomarkers                          |
|------------------------------------|
| Biomarker discovery and development, e.g. imaging or body fluids |
| Biomarker scoring systems to grade their predictive potency |
| Translational toxicology using biomarkers |

| Preclinical to clinical studies    |
|-----------------------------------|
| Animal models that are representative of human disease |
| Cautious transfer of results of preclinical studies to predict clinical effects |
| Careful early human exploratory clinical trial design prior to phase I/II trials |
| Following a consistent set of biomarkers from preclinical studies to phase III trials |
| Image analysis software should be the same for preclinical and clinical studies |

| Bioinformatics                      |
|------------------------------------|
| Human genetics                     |
| Systems biology approaches         |

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Scripps Health system employees, family members, and friends in the study, the first of its kind, said STSI. Eventually, researchers hope to determine whether participating in personal genomic testing spurs individuals to make beneficial lifestyle changes such as improving their diet and exercise regimes. The team plans to track participants’ lifestyle changes using self-reported health questionnaires. Participants will complete the questionnaires at baseline and again 3 and 6 months after receiving the personal genetic test, which is designed to assess individuals’ genetic propensity for more than 20 health conditions, including diabetes, heart disease, and some cancers. Those enrolled will also be asked to participate in surveys periodically over the next 20 years. The results will be compiled in a database hosted by the Scripps Genomic Medicine program. To maintain participants’ genetic privacy, researchers will de-identify both saliva samples and health assessment questionnaires, encrypt the data, and store it in a secure database. In addition, researchers plan to use genetic variations identified in the study to improve their understanding of the genetics underlying diseases and the application of this genetic information for preventing, diagnosing, and treating diseases. Affymetrix will perform the genome scans, while Navigenics (now acquired by Life Technologies) will interpret the results and offer guidance on steps individuals can take to try to decrease health risks based on their personal genetic information.

**Personalized Predictive Medicine**

There has been an increasing emphasis on preventive medicine during the past decade and now it is gaining popularity for improving future healthcare. Predictive medicine involves prediction of risk of disease in an individual and its personalized management. It is sometimes referred to as preemptive approach as it involves treatment before the disease develops. By the time most diseases are diagnosed, some damage is already done and is irreparable in some cases. Chances to cure diseases such as cancer may improve with this approach. Advances in molecular diagnostics, proteomics, and metabolomics are facilitating development of tests for predictive medicine. The concept of predictive medicine is extended further to predict response of the disease to a therapeutic. A significant reduction in disease-related mortality as well as a reduction in costs can be expected if prevention and screening are focused on individuals at risk. In the pharmaceutical industry, predictive modeling of disease can be used to test efficacy of drugs before developing them.

**Connected Health and Personalized Medicine**

The term ‘connected health (CH)’ has been increasingly used in recent years to describe this new technology enabled model of healthcare delivery. The following definition proposed: ‘Connected Health encompasses terms such as wireless, digital, electronic, mobile, and tele-health and refers to a conceptual model for health management where devices, services or interventions are designed around the patient’s needs, and health related data is shared, in such a way that the patient can receive care in the most proactive and efficient manner possible’ (Caulfield and Donnelly 2013).

Over the past decade, connected health (CH) has shown great value in the management of chronic disease (CD), but has limited application in preventing these diseases that remain a huge burden to the society. Technological advances have made determination of genetic predisposition to disease possible and have gained wide use in medicine of developing personalized medicine. There is growing interest in the application of these genetic tests in predicting risk for complex genetic diseases as direct-to-consumer tests are increasingly becoming available and affordable. CH has shown great potential in collecting phenotypic data, which can be integrated with genomic data to deliver a more precise and personalized preventive care for patients. The goal of a CH program that uses genetic data would be to monitor individuals’
risk factors and predict the onset of CD, which would be coupled with advice to prevent the onset of disease. However, the challenge is that many CDs are due to complex interaction between genes and modifiable environmental risk factors that are still under-studied (Agboola et al. 2013).

**Challenges and Opportunities for Personalized Medicine**

**Limitations of Personalized Medicine**

Limitations of personalized medicine are shown in Table 28.2.

**Comparative-Effectiveness Research and Personalized Medicine**

The American Reinvestment and Recovery Act of 2009 gave comparative-effectiveness research (CER) a large boost in funding over the following 2 years. Despite a consensus that better information about the relative effectiveness of different medical interventions is needed to improve the quality and value of care, some view CER with skepticism. However, by supporting comparative studies it might counteract the criticism that there is a paucity of studies comparing personalized with conventional care and may help in promoting further acceptance of personalized medicine. Although CER’s methods are not entirely new, the federal initiative will support research that is both more comprehensive — encompassing many more treatments and conditions, as well as more complete outcome measures — and more relevant to real-world clinical decisions than traditional clinical research (Garber and Tunis 2009). For example, large observational databases and pooled trial results can be used to learn more about the subgroups of patients who benefit from therapy. CER is not a panacea, but it is a key to individualized care and innovation, not a threat. An initiative to advance our knowledge about the effectiveness of clinical strategies can hasten the day when personalized medicine transforms health care.

**Impact of Molecular Diagnostics on Personalized Medicine**

Molecular diagnosis played an important role in the initial clinical applications of personalized medicine. According to the Association for Molecular Pathology, over the past several years, there have seen significant technological advances in molecular diagnostics that have helped transform our ability to detect, monitor, and treat cancer and other complex diseases. In 2020, the following innovative technologies will continue to evolve, improve, and be adopted by more clinical laboratories around the world to advance patient care in future:

- Use of large-scale genomic analysis to drive therapy decisions, including determination of

| Table 28.2 Limitations of personalized medicine |
|-----------------------------------------------|
| Factors other than genes also affect response to drugs |
| Not all the treatments can be personalized |
| Limited support from politicians or governments |
| Lack of knowledge of personalized medicine among physicians |
| Ethical, legal and social problems need to be addressed |
| Approval of new biomarkers from regulatory agencies is difficult |
| Shortage of bioinformatic manpower needed for management of huge amounts of data |
| Technologies required for implementation of personalized medicine still need refinement |
| Routine genetic testing revealing clinically non-relevant information - Incidentalome |

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microsatellite instability and tumor mutational burden for immunotherapies.
• Use of exome and WGS for genetic diagnosis of multigenic disorders.
• Use of plasma analysis for detection of ctDNA.
• Use of CRISPR technology for molecular diagnostic and therapeutic applications.
• Use of NGS and phylogenetic analysis to characterize the organisms important for infectious diseases and the normal human microbiome.
• Use of clinical sequencing interpretation tools to categorize disease-causing pathogenic variants and normal human genetic variability.

Initiative for Delivery for Precision Medicine

An exclusive focus on laboratory-based genotype-phenotype-therapy links ignores the real-world challenges of delivering expensive technology, assessing preferences and trade-offs, and undertaking shared decision making. The National Academy of Sciences has acknowledged this dichotomy between research and clinical application and called for greater integration of research data, clinical data, and ongoing clinical care (National Research Council US Committee on a Framework for Developing a New Taxonomy of Disease 2011). The gaps in the biology-focused efforts argue for expanding the Precision Medicine Initiative’s priorities to include delivery-focused applications of personalized healthcare as shown in Table 28.3.

The growth of available personal and medical data and advances in informatics could enable clinicians to practice “precision delivery” — to use electronic health data and analytics, in conjunction with principles of epidemiology, health services research, and biostatistics, to better predict risk, diagnose problems, and translate scientific advances into personalized care.

| Table 28.3 Delivery of personalized healthcare |
|-----------------------------------------------|
| Feature | Challenges | Potential Applications |
| Analysis, integration, and use of real-time clinical data | Training additional informatics professionals Developing scalable analytics methods Enabling interoperability of EMRs | Real-time prediction of clinical deterioration in the ICU using EMRs, vital signs, and laboratory data Managing discharge planning using claims and hospitalizations |
| Expanding sources of data | Expanding the evidence base regarding use of unstructured data to directly support health interventions Identifying conditions that can be reliably detected and tracked using data on social media Validating and training predictive algorithms, possibly using payer claims databases or real-time electronic registries Developing techniques for extracting valid and reliable signals from vast amounts of personal data on social media | Tracking infectious disease outbreaks (e.g., COVID-19) using Twitter and Facebook Using publicly available government data to predict food shortage and target home-delivered meals |
| Patient ownership of data | Relieving fears about data privacy Relaxing regulatory barriers to sharing of protected health information Developing technology for sharing data electronically in patient-friendly formats Amending HIPAA regulations to enable reading by machine of patient-accessible data | Enable patients to share genomic, medical, and demographic data in clinical trials Personalized health dashboard integrating data from EMRs, wearable devices, social media, and other sources |

Modified from: Parikh et al. (2017)

ICU intensive care unit, EMRs electronic medical records, HIPAA Health Insurance Portability and Accountability Act
IGNITE Network – Implementing Personalized Medicine in Clinical Care

A study has synthesized data on challenges identified by six diverse projects that are part of a National Human Genome Research Institute (NHGRI)-funded network focused on “Implementing GeNomics In pracTicE (IGNITE)” network (Sperber et al. 2017). Three challenges were identified by all six projects, and strategies to address these challenges varied across the projects. One common challenge was to increase the relative priority of integrating genomics within the EHR system. Four projects used data warehousing techniques to accomplish the integration. The second common challenge was to strengthen clinicians’ knowledge and beliefs about genomic medicine. To overcome this challenge, all projects developed educational materials and conducted meetings and outreach focused on genomic education for clinicians. The third challenge was engaging patients in the genomic medicine projects. Strategies to overcome this challenge included use of mass media to spread the word, actively involving patients in implementation (e.g., a patient advisory board), and preparing patients to be active participants in their healthcare decisions. Findings suggest that strategies to facilitate integration of genomic data within existing EHRs and educate stakeholders about the value of genomic services are important for effective implementation. Future work could build on these findings to evaluate which strategies are optimal under what conditions. This information will be useful for guiding translation of discoveries to clinical care, which, in turn, can provide data to guide continual improvement of genomic innovations and their applications.

These findings complement work of other NHGRI-funded consortia that also are working to further implementation of personalized medicine into clinical care. The CSER (Clinical Sequencing and Exploratory Research) consortium (https://www.genome.gov/27546194/clinical-sequencing-exploratory-research/(2017).) is focused on studying implications of clinical sequencing for clinical care. eMERGE (Electronic Medical Records and Genomics) is a consortium that is focused on developing ways to best use EHRs for linking biorepository and phenotypic data within EHRs. This synthesis of IGNITE projects provides the necessary evidence to understand how precision medicine can be incorporated innovatively into practice settings and thus allow for the ongoing development of evidence about what works under which conditions in real-world settings-evidence that is not possible to obtain prior to implementation.

Prospects and Limitations of Genetic Testing

Genotyping will be for twenty-first century medicine what the X-rays were for twentieth century clinical practice. Currently there are some reservations about the value of genetic testing in prediction of disease as there are multiple factors involved. It is currently being debated if it is worthwhile to continue with the expensive genomewide studies or to decode the entire genomes of individual patients. Although genomewide association studies have worked better and faster than expected, they have not explained as much of the genetic component of many diseases and conditions as was anticipated, and the trend is more towards the study of rare variants. Thus, schizophrenia would be caused by combinations of 1000 rare genetic variants, not of 10 common genetic variants. One should be concerned about diseases for which testing shows that an individual’s risk is three times as great as average, but not for trivial increases in risk. The undiscovered share of genetic risk for common diseases probably lies not with rare variants, but in unexpected biological mechanisms. Also, the same genetic variant carries risks that differ depending on whether it is inherited from the mother or the father.

Rare mutations of several genes are responsible for a substantial portion of complex human disease. Evolutionary forces generate vast genetic heterogeneity in human illness by introducing many new variants in each generation. Many of them may stem from factors other than a true association with disease risk. Current sequencing technologies offer the possibility of finding rare disease-causing mutations and the genes that harbor them.
Genetic testing will eventually improve predictions about what diseases we are predisposed to, the timing of their onset, their extent and eventual severity as well as which treatments or medications are likely to be efficacious or deadly. Genotyping, however, does not necessarily correlate with response to medications and other factors such as environmental need to be taken into consideration in personalizing treatment. Finally, all diseases do not require personalized treatment.

Pharmacogenomics and pharmacogenetics are providing the basis for the development of molecular diagnostics to improve drug selection, identify optimal dosing, maximize drug efficacy or minimize the risk of toxicity. Rapid advances in basic research have identified many opportunities for the development of personalized treatments for individuals and/or subsets of patients defined by genetic and/or genomic tests. However, the integration of these tests into routine clinical practice remains a major multidisciplinary challenge. Although physicians and patients are optimistic about the health benefits that genetic testing might provide, neither group is well informed, and there are likely too few experts available to meet growing demands for genetic testing. Attempts to integrate genomic medicine into clinical practice are still in the early stages, and as a result, many questions surround the current state of this translation. There is a need for a large-scale effort to educate both health professionals and the public about genomic medicine, and to develop and evaluate new ways to deliver genetic services.

Genomics-based molecular profiling and related technologies may impact on the delivery of healthcare even before genomics-based drugs hit the market. Identification of genetic factors affecting the prognosis of disease is likely to be of most clinical relevance. Relationships of known genes, such as BRCA1 and BRCA2, with risk factors will be clarified; permitting evidence based preventive action in people at high genetic risk and better quantification of risk in family members. Greatest progress will be made in understanding the genetic contribution to the intermediate phenotypes linking genes and disease, and thus the biology of the disorder, as in atherosclerotic disease. The greatest impact of personalized medicine will be in the treatment of cancer, cardiovascular diseases, infections, and neurological disorders.

The emerging fields of metabolomics (metabolite profiling to identify genotype-phenotype associations) and phenomics might offer solutions for anticipating and decreasing risk of adverse drug reactions in each individual patient, but tests based on these approaches are not expected to become generally available to the practicing clinician for at least the next 5 years.

**Personalized Medicine and Public Health**

Personalized medicine has never claimed to be a solution to the problems of inequalities in healthcare or health problems associated with poverty, natural disasters, wars and famine. Yet critics of personalized medicine focus on socioeconomic issues to point out that personalized medicine fails to address these. In the US, there is widespread dissatisfaction with unequal distribution of resources such as healthcare within a deeply divided society. A publication recognizes the possible gains in clinical care from implementation of personalized medicine at individual level but considers it a mistake and a distraction from the goal of producing a healthier population in general (Bayer and Galea 2015). US, with free enterprise and generous support of medical research, has pioneered the development of personalized medicine. Personalized medicine is being adopted even in communist countries such as China and Russia where the traditional focus was on public health with equality of care for the masses.

Beyond the conventional practice of medicine in any country, the scope of personalized approach is applicable to international public health issues. One example is evolution of response to AIDS epidemic. The first breakthrough was identification of the causative agent and understanding of the molecular mechanisms followed by development of medications that were tested during years of clinical trials. In practical use, the treatment was guided by molecular diagnostics and quantification of viral load. Discoveries in new biotechnologies, particularly those applicable to omics, were incorporated to modify and refine the management of AIDS. Heterogeneity in the response of individu-
las to disease as well as treatment today requires requires that the future of public health must address not only the adaptation of systems and services, but also incorporate patient-reported outcomes and novel approaches to patient activation (Geng et al. 2019). These novel directions would seek to make the response more personalized and include those who cannot afford access to new technologies ensuring that they also benefit from these advances, even if this occurs later on. Successful implementation of personalized public health into practice will require inclusion of all types of patient populations.

Pharmacotyping

Pharmacotyping is individualized drug selection and dosage profiling by the physician based on clinical evaluation of the patient’s genotyping and haplotyping data for genes involved in the pharmacokinetics and pharmacodynamics of drugs in the body. Pharmacotyping could be another dimension of pharmacogenetics/pharmacogenomics and its application in routine clinical practice in the post-genomic era could better depict drug selection and dosage. This means a transition from a drug-selection process mainly based on the physician’s own experience, into a more, highly integrated, information-based and computer-aided pharmacotherapy-based decision, thus making drug delivery digitized, more efficient and safer. Advances in in silico modeling for predicting ADME (absorption, distribution, metabolism, excretion) could be incorporated into this system.

Examples of pharmacotyping include organoids, 3D cultures of neoplastic cells derived from primary tumor specimens for direct testing the survival of these organoid cultures when exposed to clinically relevant chemotherapeutic agents (Burkhart et al. 2018).

Medicine in the Year 2025

In the future, clinicians will increasingly embed newer technologies such as remote monitoring, telehealth, and analytics deep into their practices to better engage patients, provide more targeted diagnoses and treatments. Personalized medicine fits with these trends. Medicine is evolving rapidly in the postgenomic era and some of the general advances anticipated by the year 2025 are:

- Pathomechanism of most of the currently known major diseases will be understood at the molecular level.
- Genomic, proteomics, metabolic data from various research and commercial sources will be integrated in clinical medicine.
- Most of the ethical and policy issues about genetic testing will be resolved and it will be a routine for some population groups.
- Pharmacogenetics will be applied to identify those at risk of adverse drug events from certain drugs.
- Improvements in targeted drug discovery and increase in pharmacogenomics-based clinical trials.
- Preventive medicine will be well recognized with acceptance of presymptomatic diagnosis and pre-emptive treatments.
- Automation, robotics, and informatics will be partially integrated into clinical medicine.

Pharmacogenomics is already used in clinical trials and will become the standard. Companies that do not use pharmacogenomic testing in drug development will lose out to the ones that do so. Although some of the pharmacogenomics-new drugs being discovered now have not completed the development, use of some of the older drugs is being individualized and several components of personalized medicine are being put into place now. Molecular and diagnostic tests have a shorter time to approval than drugs and some are already in the market. Low throughput genotyping for some disease biomarkers is already in use. Integration of diagnostics and therapeutics is also taking place and it is anticipated that personalized medicine will develop parallel with the introduction of pharmacogenomic-based medicines.

Genotyping will be for twenty-first century medicine what the x-rays were for twentieth century clinical practice. Genetic testing will eventually improve predictions about what diseases we are predisposed to, the timing of their onset, their extent and eventual severity as well as which
treatments or medications are likely to be efficacious or deadly. Genotyping, however, does not necessarily correlate with response to medications and other factors such as environmental need to be taken into consideration in personalizing treatment. Finally, all diseases do not require personalized treatment.

Concluding Remarks About the Future of Personalized Medicine

In the year 1998, when the first edition of this report was published, there was little interest in personalized medicine. Currently, there is a tremendous interest in this topic, often referred to as precision medicine, and many experts have suddenly appeared. Some of them have backgrounds in pharmacogenetics and pharmacogenomics but had not made any efforts to connect these disciplines to personalized medicine.

Some skeptics of the results of HGP, HapMap and genome-wide association studies say that a decade after completion of the HGP the expected personalization of medicine had not occurred. In fact, sequencing of the human genome has brought about considerable advances in technologies relevant to development of personalized medicine. Some of these are stated briefly as:

- Sequencing is becoming cheap enough only recently to look for rare variants, and that many common variants do have roles in diseases.
- Numerous sites on the genome, most of them near genes, have been implicated in common diseases. Although many more remain to be discovered, work can proceed to develop diagnostics and look for therapeutic possibilities of some diseases.
- The only way to find rare genetic variations is to sequence a person’s whole genome. That approach is now becoming feasible because the cost of sequencing is coming down to <$1000 genome is now feasible.
- HGP has provided a common scaffold of sequencing where every gene and control element can now be mapped to its correct site on the genome, enabling all the working parts of the system to be related to one another. This is accelerating further progress.
- The genome sequence has facilitated the development of many powerful new techniques for exploring its meaning, e.g. chip sequencing, which gives researchers access to chromatin, the complex protein machinery that both packages the DNA of the genome and controls access to it.
- Data from the HapMap has enabled population geneticists to reconstruct human population history since the dispersal from Africa some 50,000 years ago. They can pinpoint which genes bear the fingerprints of recent natural selection, which in turn reveals the special challenges to which the populations on different continents have had to adapt.
- The completion of the HGP provides a road map for thorough interrogation of gene functions. In addition to identifying novel transcription factor targets, current studies may shift our attention to genome-wide characterization of histone modifications and DNA methylation. The importance of this type of study is further echoed by the Human Epigenome Project. This requires genome-wide technologies with high-throughput capability.
- Genomewide association studies, despite critics, have yielded important new biologic insights into some common diseases or polygenic traits that facilitate efforts to develop new and improved treatments and preventive measures on basis of these. The rapid progress being made through meta-analyses suggests that many more common variants conferring a risk of disease will be identified in the next several years, leading to increasing stability of individual risk estimates. Once risk estimates are more stable, the usefulness of genetic screening will need to be considered for each disease, and recommendations about potential interventions will need to be made for persons whose predicted risk exceeds some threshold. Appropriate guidelines are urgently needed to help physicians advise patients who are considering this form of genetic testing as to how to interpret, and when to act on, the results as they become more stable.
Personalized approaches are available and are expected to be used where they are deemed appropriate. In conclusion, the progress in personalized medicine and related technologies justifies a more optimistic view. There will be significant activity relevant to personalized medicine in the clinical as well as biopharmaceutical sectors in the US by the year 2025. The interest in personalized medicine is worldwide although the implementation may be delayed due to socioeconomic factors in some developing Asian countries. Japan, with an advanced healthcare system and a prominent position of research activity in genomic medicine, has good prospects for introduction of personalized medicine. China, which is making considerable advances in new biotechnologies and applying them in genomics and sequencing, has the facilities for developing personalized medicine. The US will be the first country to adopt personalized medicine on a large scale.

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