Genomic Medicine: New Frontiers and New Challenges

Maria D. Pasic,1,2 Sara Samaan,3,4 and George M. Yousef1,3,4*

BACKGROUND: The practice of personalized medicine has made large strides since the introduction of high-throughput technologies and the vast improvements in computational biotechnology. The personalized-medicine approach to cancer management holds promise for earlier disease detection, accurate prediction of prognosis, and better treatment options; however, the early experience with personalized medicine has revealed important concerns that need to be addressed before research findings can be translated to the bedside.

CONTENT: We discuss several emerging “practical” or “focused” applications of personalized medicine. Molecular testing can have an important positive impact on health and disease management in a number of ways, and the list of specific applications is evolving. This list includes improvements in risk assessment, disease prevention, identification of new disease-related mutations, accurate disease classification based on molecular signatures, selection of patients for enrollment in clinical trials, and development of new targeted therapies, especially for metastatic tumors that are refractory to treatment. Several challenges remain to be addressed before genomics information can be applied successfully in the routine clinical management of cancers. Further improvements and investigations are needed in data interpretation, extraction of actionable items, cost-effectiveness, how to account for patient heterogeneity and ethnic variation, and how to handle the risk of “incidental findings” in genetic testing.

SUMMARY: It is now clear that personalized medicine will not immediately provide a permanent solution for patient management and that further refinement in the applications of personalized medicine will be needed to address and focus on specific issues.

The concept of personalized medicine, which is to use the individual’s genetic makeup to predict disease risk, accurately plot the course of the disease, and tailor the management plan according to the patient’s unique needs, was proposed several years ago (1, 2). Revolutionary improvements in the analytical tools required for personalized medicine have accompanied the introduction of high-throughput technologies. These advances, which enable simultaneous analyses of thousands of molecules, have increased the momentum of this field. These technologies have developed in parallel with unprecedented improvements in computational biotechnology that allow the analysis and interpretation of the huge data sets obtained in such experiments. Finally, the introduction of targeted therapy has increased the demand for molecular characterization of diseases to identify new candidate markers for prognosis and prediction (3–5) and to facilitate the development of new targeted therapies (6–8).

Such molecular analyses are predicted to be important for managing cancer patients by offering improvements in early cancer detection, accurate prediction of prognosis, and better treatment options with minimal side effects (1, 9, 10). Information gained by these methods will also help in evolving our understanding of disease pathogenesis by switching the focus to a search for altered “biological processes” from a focus on the discovery of individual disease biomarkers (4). The change to processes rather than markers will be useful for investigating complex diseases, such as cancer, diabetes, and hypertension, which often involve large numbers of genes, pathways, and environmental factors (4, 5). Thus, we are stepping into a new era of “genomic” medicine. It is not surprising that 10% of the labels for drugs cleared by the U.S. Food and Drug Administration already contain pharmacogenomic information (11), and this number will only increase as genomic testing becomes increasingly used in routine care (12).

After a period of initial enthusiasm for personalized medicine, it became apparent that several impor-
tant concerns needed to be addressed before these discoveries can be translated to the bedside (13). It is now clear that personalized medicine is not going to immediately provide a permanent solution for all patient-management issues and that we need to refine its applications for specific and focused issues. In this review, we discuss some of the emerging “practical” or “focused” applications of personalized medicine. In addition, we use cancer as an example for highlighting the challenges to be faced as we step into the era of personalized medicine.

Evolution of New Applications in Patient Management

Table 1 presents an evolving list of specific applications in which molecular testing can play an important role in improving health and disease-management plans.

<table>
<thead>
<tr>
<th>Table 1. The potential applications of genomic medicine.</th>
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</thead>
<tbody>
<tr>
<td>1. Examination of variation among healthy individuals</td>
</tr>
<tr>
<td>2. Understanding disease risk, susceptibility, and etiology</td>
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<tr>
<td>3. Disease prevention</td>
</tr>
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<td>4. Early diagnosis at the preclinical stage (to help modify disease course, e.g., diet and exercise in diabetes)</td>
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<td>5. Identification of new disease-related mutations</td>
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<td>6. Accurate diagnosis of challenging cases with inconclusive results for clinical parameters</td>
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<td>7. Accurate disease classification based on molecular signature</td>
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<td>8. Health management (prognosis and predictive markers)</td>
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<td>9. Identification of personal drug-related profile</td>
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<td>10. Selection of patients for clinical trials</td>
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<td>11. Monitoring disease status (e.g., recurrence)</td>
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<td>12. Monitoring tumor evolution in response to treatment</td>
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<tr>
<td>13. Developing new targeted therapies, especially for metastatic tumors refractory to treatment</td>
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The USE OF GENOME SEQUENCING AND INTEGRATED MOLECULAR ANALYSIS FOR ASSESSING DISEASE RISK

Next-generation sequencing has several promising applications in personalized medicine. Predicting risk through molecular analysis, usually via next-generation sequencing, can have an important impact on disease outcomes. Genome sequencing also can make important contributions to reproductive health. Such improvements include prescreening of mothers for mutations related to metabolic and other mendelian disorders (14). A recent study showed the ability of an integrated analysis to identify genetic variants associated with the risks of mendelian diseases, development of a recognized drug response, and pathogenicity (14). This study also highlights the importance of using the expanding number of disease-specific mutation and pharmacogenomics databases as valuable sources for identifying disease risk.

Moreover, an interesting study has demonstrated the potential power of exome sequencing to render a “molecular-based diagnosis.” A novel mutation was identified in a patient with Crohn disease after all standard diagnostic modalities had failed to reach the correct etiologic diagnosis (15). This and similar reports have shown the feasibility of using comprehensive genomic analyses for identifying causes of known diseases. These studies have underscored the need to address many of the issues related to implementing genomic testing directly into the clinic, as we detail below.

A pressing question to be addressed is how to estimate the accuracy of sequencing technologies for predicting disease risk. Kohane et al. recently provided an excellent review on this topic (16). Roberts et al. analyzed the capability of personal genome sequencing for predicting the risk of 24 different diseases (17). On the negative side, these investigators found that most monozygotic twins had negative results in sequencing tests for 23 of the 24 diseases. On the positive side, however, about 95% of the tested individuals were alerted to clinically important predispositions for at least 1 disease. A related major challenge is the ability to reliably distinguish pathogenic mutations, benign variants, and variants of uncertain importance. Moreover, analyses of diseases with a complex, multifactorial etiology, such as hypertrophic cardiomyopathy, which has a vast genetic variability and a high frequency of novel mutations, have revealed unforeseen difficulties in translating complex science into the clinical arena.

Other major concerns in this regard are the ability to translate this information into meaningful health improvements and the costs of these expensive screening tools. Table 2 lists several strategies for improving the cost-effectiveness of genomic screening. One stra-
nergy is to restrict the use of molecular screening tests for identifying disease susceptibility to individuals in “clinically appropriate” categories, e.g., populations at risk (18). Furthermore, assessing risks for such chronic diseases as diabetes, hypertension, and cancer is economically efficient, because it will substantially reduce the burdens of treatment and follow-up for extended periods of time. It is also advantageous to focus on identifying the diseases with known interventions that can modify or alleviate disease progression (18). Another practical approach is to look for molecular changes that are directly related to short-term benefits for managing patient outcomes. Several genomic studies have tried to identify patients with the greatest likelihood of receiving short-term benefits from whole-genome sequencing tests, specifically in the areas of diagnosis and management (19–21).

INTEGRATED GENOMICS DATABASES
Several genomewide association studies have applied analyses of single-nucleotide polymorphisms (SNPs)5 to assess for the presence of genetic variants in different individuals and their potential associations with disease risk. The first successful study, published in 2005, investigated age-related macular degeneration (22). Since then, thousands of genomewide association studies of humans have investigated >200 diseases and traits, and almost 4000 SNP associations have been identified (23). On the oncology frontier, several international projects have been developed to catalog multilevel somatic alterations in cancer through analyses of exome sequences, DNA copy numbers, promoter methylation, and mRNA and microRNA (miRNA) production. These projects include the Cancer Genome Atlas (http://cancergenome.nih.gov/) (24), the Cancer Genome Project (25, 26), and the International Cancer Genome Consortium (25). Furthermore, to allow broad analyses of genomic variation in several disease conditions, the NIH has launched various initiatives, including providing support for genome analyses of participants in the Framingham Heart Study, collecting samples from infants in the National Children’s Study, and conducting genetic analyses of 20 different types of tumors (2). Other investigative initiatives include cataloging the variation among healthy individuals, such as the 1000 Genomes project (http://www.1000genomes.org/).

Also evolving are new databases that incorporate multilevel molecular information for assessing disease risk and responses to different drugs. The accumulating evidence suggests that integrating multiple levels of molecular data holds great promise for refining our understanding of disease pathogenesis and patient management (14, 27, 28). Appropriate data collection and database integration will be necessary to efficiently assess the potential clinical and biological importance of rare genetic variants (1, 29).

Moreover, now becoming available are several national and international public databases that integrate different levels of molecular high-throughput analyses to draw meaningful “actionable” conclusions that can help in managing patients. Examples of such databases are i2b2 (Informatics for Integrating Biology & the Bedside; https://www.i2b2.org) (30) and locus-specific mutation databases, such as the Human Gene Mutation Database, or HGMD (http://www.hgmd.cf.ac.uk/ac/index.php) (31). Several databases also catalog somatic mutations occurring in different cancers (32). The promising preliminary analyses of such data have shown that many of these mutations are present in many types of cancer and that they are targetable via drug therapy (29).

Integrated analyses are best interpreted in the clinical contexts of a specific patient, such as medical history, family history, physical/clinical assessments, immunological factors for risk prediction, and so forth (33). Also important is to recognize that molecular changes are the product of both genomic alterations and the environment (food, exercise, and so forth) and that some mutations and SNPs are reflections of environmental changes. Therefore, molecular data obtained via high-throughput technologies must be interpreted in the context of clinical variables and environmental conditions to provide a better assessment of a patient’s risk of disease.

MONITORING THE PERSONAL GENOME
A new, promising approach is “integrative personal omics profiling” (iPOP) (34). iPOP combines genomic, transcriptomic, proteomic, metabolomic, and autoantibody profiles from the same individual to follow their genomic/transcriptomic composition over long periods—during times of health and disease. A recent study demonstrated that longitudinal iPOP can evaluate healthy and disease states by connecting the genomic information with additional dynamic “omics” activities (34). Chen et al. repeatedly collected data from a single individual over time. The data analysis revealed heteroallelic changes in both the healthy and disease states, as well as changes in RNA-editing mechanisms, that would have been masked otherwise. The results indicated that differential allele-specific expression is extensive in humans, with especially distinct differences between healthy and disease states (34). This approach allowed the inte-

5 Nonstandard abbreviations: SNP, single-nucleotide polymorphism; miRNA, microRNA; iPOP, integrative personal omics profiling.
igration of multiple profiles associated with different physiological states across multiple time points, thereby providing detailed information that, owing to interindividual variability, would not have been apparent in group studies (34). Furthermore, a large database can be created with complete profiles from more individuals with different types of diseases. Such a database may be valuable in the diagnosis, monitoring, and treatment of diseases (34).

DISEASE DIAGNOSIS AND BIOLOGICAL CLASSIFICATIONS

Molecular signatures can be the basis for discovering new diagnostic markers for many diseases. There is a wealth of literature on the use of differential gene expression and protein production for identifying new biomarkers for early disease detection and assessment of prognosis (35, 36).

As mentioned above, exome sequencing has identified a novel mutation that permitted a molecular-based diagnosis for a patient with Crohn disease. On another interesting frontier, genomic analyses hold promise for establishing new biological subclassifications of many diseases, including cancer, which could change how cancer is managed. Molecular signatures are now used to classify tumors according to their “biological behavior,” rather than by their tissue, organ of origin, or morphology (37). Examples of molecular signatures are documented in the literature. DNA microarray data have permitted the subcategorization of lymphomas and glioblastomas (38), and alternative-splicing data obtained with microarrays have aided in defining breast cancer subtypes and improving treatment options (39). A recent study has documented that data on the differential production of miRNAs are capable of accurately classifying the different subtypes of kidney cancer (40). Another study has highlighted the ability of unique molecular profiles to accurately predict prostate cancer prognosis, especially in patients with low or average Gleason scores (41), and miRNA production signatures have accurately predicted the risk of biochemical failure in prostate cancer at the time of surgery (42). In addition, a growing body of evidence supports the potential utility of genotype changes for predicting clinical outcome and response to treatment (43).

An important step toward the translation of these applications to the clinic is the advent of commercially available systems for screening large numbers of mutations simultaneously. These systems include MassARRAY (Sequenom; http://www.sequenom.com), which can be used with presdesigned, optimized panels (such as the OncoCarta™ panel) or custom-designed arrays. Another system, the IonAmpliSeq™ Cancer Panel (Invitrogen/Life Technologies), can simultaneously analyze 739 COSMIC (Catalogue of Somatic Mutations in Cancer) mutations at 604 loci. Similar platforms include the MiSeq Personal Sequencer and HiSeq platforms (Illumina) and semiconductor sequencing (Ion Torrent Systems/Life Technologies).

TARGETED THERAPY AND DRUG TRIALS

Molecular information can also be used for improving treatment, either through development of targeted therapy or rediscovery of previously failed drugs for use in subgroups of patients likely to benefit from them (2). The numbers remain small, however, both for known “actionable” genetic abnormalities and for the targeted agents that are to be tested within the next few years (1).

Molecular markers can also be used to predict treatment efficacy so that patients not expected to respond to therapy will avoid unnecessary treatments. Furthermore, molecular markers can serve as prognostic markers of disease aggressiveness, information that could be reflected in treatment plans. An interesting example is the concern regarding “overtreatment” of prostate cancer patients who have less aggressive forms of the cancer and would better be candidates for “active surveillance.” Such patients are awaiting the development of accurate molecular markers that can better guide their treatment choices (44). Well-designed prospective clinical trials are needed to measure patient outcomes for various genomic applications, the advantages of which are not yet evident compared with current standards of care (1, 12).

Molecular signatures are also expected to revolutionize the eligibility criteria for clinical trials. Currently, inclusion criteria for clinical trials are organ based. The availability of molecular data allows the possibility of switching to pathway-based selection criteria for clinical trial enrollment, rather than organ-based criteria (37). Inclusion criteria for such trials should allow patients with different tumor types to enroll in a study as long as they have the biological targets and mutations relevant to the therapy being evaluated. A recent study has shown that integrative high-throughput sequencing of patients with cancers in advanced stages can generate a comprehensive mutational landscape that would facilitate biomarker-driven clinical trials in oncology (28).

Several web-based applications have recently been established to identify and catalog mutations that have therapeutic implications and can affect patient enrollment in clinical trials. One such endeavor is My Cancer Genome (http://www.mycancergenome.com) (45).

Another interesting area to explore is to apply genomic approaches to pharmacogenomics. Genomic analysis can play an important role in predicting treatment efficacy for individual patients (46). To appreciate the importance of pharmacogenomics, consider that $>2 \times 10^6$ adverse drug reactions occur annually in
the US alone. The approximately 1000 deaths that result make adverse drug reactions the fourth leading cause of death (47). Moreover, the estimated annual cost of drug-related morbidity and mortality in the US is >$76 billion. Added to this is the waste of medications administered to the patients who do not respond. On average, a given medication will have a therapeutic effect in only 25% to 60% of patients (48–50).

Treatments guided by pharmacogenomic evaluations will also overcome an important limitation of current treatment strategies, which base drug efficacy on the average response in clinical trials, not the responses of the individual patients. The reality is that responses to treatment vary greatly among individuals; thus, the optimal approach is to determine targeted therapies individually, in accordance with the unique genetic composition of each patient (46).

**The Role of Proteomics in Genomic Medicine**

Currently, most techniques for personalized medicine are based on genomics; however, proteomic techniques—including measurement of individual circulating or tissue-based proteins, identification of disease-specific posttranslational modifications, and generation of prognostic/predictive protein signatures for fluids or tissues—are increasingly being used to assist in diagnosis, prognosis, therapy selection, and predicting therapeutic responses to drugs (25, 51–53). Historical proteomic tests, such as measuring estrogen and progesterone receptor proteins in breast tumor tissues to predict a patient’s response to tamoxifen, are still widely used. Recently, mass spectrometry has been used to identify pancreatic cancer proteomes. These efforts have led to the identification of new candidate biomarkers, including at least 1 marker, CUZD1 (CUB and zona pellucida–like domain-containing 1), that has a sensitivity and a specificity superior to the currently used cancer antigen marker CA19–9 (54). Others have used these techniques to identify markers of taxane sensitivity in breast cancer patients receiving adjuvant paclitaxel and radiation therapy (55) and to identify new prognostic biomarkers (56).

We anticipate that we will soon be able to quantify thousands of proteins and assess the function or disease of many organs simply by using a drop of blood (57).

**New Challenges for Genomic Medicine**

We are witnessing a revolutionary era with a large number of omics, including genomics (chromosomes, SNPs), epigenetics (methylation, miRNA), transcriptomics (mRNA, splice variants), proteomics, cytokines, metabolomics, antibody-omics, and microbiomics. Another interesting emerging field is “metagenomics,” the study of host–microbe genomic interactions, the goal of which is to gain a better understanding of diseases with complex etiology, such as inflammatory diseases, in which microbial elements play a role in pathogenesis (58). On the one hand, metagenomics analyses may facilitate a much better understanding of pathogenesis at the pathway level of analysis (59). On the other hand, however, extracting meaningful information from these multilevel analyses is becoming more difficult. There is a need to focus on developing interpretation pipelines for omics investigations that identify “actionable” or “druggable” items that can directly improve patient outcomes and that can connect all the steps between the identification of a potential therapeutic target in the laboratory setting and the approval of a therapy for clinical use (i.e., moving candidate compounds into commercial development) (60). An interesting strategy that also shows promise is the classification of molecular changes into those that represent the “primary etiology” and those that are “contributing modifiers,” because, ultimately, not all that glitters is gold.

By the time a cancer is diagnosed, billions of cells containing gene abnormalities have already been produced, and many secondary genetic mutations are being acquired. Some of these secondary mutations may be drivers (mutations selected for during tumorigenesis), and some may be passengers (incidental or effector mutations). Mutations in both classes arise via such processes as mutational exposures, genome instability, and large numbers of cell divisions (61). Driver genes are ideal candidates for actionable targets.

The goal of delivering genetic testing to patients faces several challenges, including determining which genetic markers have the most clinical importance, limiting the off-target effects of gene-based therapies, conducting clinical trials to identify genetic variants that correlate with drug response, and regulating genetic testing to protect patients while still encouraging innovation (2). Table 3 is a partial list of some of the potential challenges to be addressed. Some of these challenges have recently been addressed in detail (25).

<table>
<thead>
<tr>
<th>Table 3. Potential challenges of the era of genomic medicine.</th>
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<tr>
<td>1. Data interpretation and extraction of actionable items</td>
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<tr>
<td>2. Guidelines for implementing new molecular testing</td>
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<tr>
<td>3. Cost-effectiveness of molecular testing</td>
</tr>
<tr>
<td>4. Patient heterogeneity and ethnic variation</td>
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<td>5. Test optimization and standardization</td>
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<td>6. The risk of incidental findings and false-positive results</td>
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<td>7. Need for training and teamwork efforts</td>
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<td>8. Between-platform variation in results</td>
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DEVELOPING AND IMPLEMENTING NEW MOLECULAR TESTS

A challenge that should be considered is the setting of rules for implementing new molecular testing in the clinical laboratory. Currently, the trigger for molecular testing can come from the treating physician in response to information obtained from a recent journal article or at a meeting. The trigger can also be a new program initiative at the institution. A substantial proportion of new molecular testing is driven by the patient in response to the electronic media. A well-structured committee should be in place to evaluate new testing on the basis of cost-effectiveness and the higher levels of confidence that evidence-based medicine requires (62, 63).

Among the technical challenges that should be considered when developing a new test is the variation between different platforms that measure the same molecular changes. A recent study of 7 diseases demonstrated an agreement of \( \leq 50\% \) between the 2 platforms evaluated (64).

Cost-effectiveness remains an important concern in implementing new molecular tests. In this regard, molecular testing of markers predictive for targeted therapy in metastatic cancer represents an ideal model for application, because patients with metastatic cancer undergo costly drug therapies that have serious adverse reactions (65). Although a genomics-based predictive test can be expensive, it may eventually lead to substantial financial savings by excluding a large proportion of patients predicted to be nonresponders. In addition, it would substantially reduce the costs of treating side effects and treatment complications.

It must also be recognized that developing a new test is a complicated multistep process that continues after the discovery phase. Validation, especially independent validation, is one of the necessary steps to be completed; others steps include standardization, test interpretation, the technical range, quality control, and so on (66, 67).

Another important consideration is that “test accuracy” improves with time; consequently, reevaluating test performance might be necessary. An example of this consideration is hormone receptor testing in breast cancer, in which improvements in sensitivity and specificity for the antibody used and additional evidence on hormone treatment efficacy prompted a change in the cutoff for positivity.

THE NEED FOR TRAINING AND TEAMWORK EFFORTS

In the era of personalized genomics, it is important to emphasize the concept of collaboration rather than competition. Making the huge costs of such projects economically feasible requires different centers worldwide to work together. International legislation will be necessary to make the results of all studies publicly available and easily accessible.

Another important step to be addressed before personalized genomics can move into clinical applications is the consolidation of multidisciplinary teams of clinicians, laboratory scientists, and bioinformaticians who can extract meaningful information from the millions of data points regarding molecular changes.

Accompanying the evolution of applications in genomic medicine is the need to provide caregivers information about these new applications. Understanding the benefits and challenges of molecular testing is a key issue that will have to be addressed. Genetic tests are not perfect because most gene mutations do not predict outcomes perfectly. Thus, clinicians will need to understand the specificity and sensitivity of new diagnostic measures (2, 12). It will also be necessary to educate clinicians about whether or when to order certain diagnostic tests. For instance, it would be inappropriate to order a test when the clinician is unsure about how to use the results [e.g., for rare sequence variants in \( BRCA1 \) (breast cancer 1, early onset) and \( BRCA2 \) (breast cancer 2, early onset) genes in a breast cancer patient (12)]. In addition, the feedback between clinical practice and data interpretation is also an important factor to consider. The information that clinicians can give to biochemists and bioinformaticians is potentially crucial.

Equally important is the need to train the new generation of clinicians and laboratory scientists to understand the different dimensions of these evolving applications. Training programs, such as the TRIG (Training Residents in Genomics) curriculum (http://www.pathologytraining.org), have already been established. Studies have suggested that the “genetic literacy” of the general public is inadequate to prepare citizens for this unprecedented access to genomic information. Given that the current generation of high school students will come of age in an era when personal genetic information is becoming increasingly used in healthcare, ensuring that students understand the genetic concepts necessary to make informed medical decisions is of vital importance (68).

THE RISK OF THE INCIDENTALOME IN GENETIC TESTING

As the number of combined tests increases, the false-discovery rate will become very high, perhaps reaching 60% if 10 000 SNPs are analyzed simultaneously. This increased false-positive rate represents a phenomenon known as the “incidentalome,” a concatenation of a

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6 Human genes: \( BRCA1 \), breast cancer 1, early onset; \( BRCA2 \), breast cancer 2, early onset.
huge number of complex positive findings that are poorly understood (16).

Kohane et al. highlighted the fact that substantially increasing the number of tested molecules will produce substantial increases in the number of false-positive results, especially in a population with a low disease prevalence (16). That will create several problems, including unnecessary and costly follow-up studies for falsely identified diseases. Such studies will add to the already burdened healthcare system.

The lack of accuracy and precision for screening tests will put physicians into the challenging situation of either ignoring the results of incidental findings (with the subsequent risk of liability) or expending more resources to perform confirmatory “gold standard” testing. Several steps have been suggested to reduce the impact of the incidentalome. They include assessing the overall disease prevalence and using information system technologies to understand the “real” risks associated with positive results in screening tests and to help physicians make cost-effective decisions. We obviously have a long way to go before we truly understand the relationship between the millions of SNPs and disease risk. Interestingly, even SNPs that have a documented effect on the population with disease might not confer a risk for the same effect in an asymptomatic general population (69).

**PATIENT HETEROGENEITY AND ETHNIC VARIATION**

Ethnic variation should be considered when interpreting genomic data and should be carefully addressed when translating results of high-throughput genetic analyses to the clinic. Another important challenge is the heterogeneity that exists among patients with the same cancer type. Recent studies have shown that only a small number of gene mutations (also called “mountains”) are present in the majority of a large population of patients with a particular cancer, whereas most other
genes (known as “hills”) are mutated less frequently. Studies of cancer genome landscapes have found that gene “mountains” in a large proportion of tumors and gene “hills” in <5% of tumors (70); however, most mutations in cancers that are likely to be driver mutations do not occur in mountains. Ultimately, the hills drive tumor progression (70). The landscape of individual patients has also been shown to overlap very little with the overall landscape of consensus mutations. This fact accounts for the great heterogeneity in biomarker expression observed among cancer patients (70). Adding to the complexity of the problem is the fact that not all driver mutations that occur with tumor progression are essential for tumor maintenance; consequently, they may not be good therapeutic targets (61). The ability to identify driver mutations and to distinguish them from the many incidental mutations will help in capturing the full genetic heterogeneity in cancer, a feat that will require a very large sample size (61).

Another interesting obstacle is the presence of intratumoral heterogeneity. A recent elegant study has shown that analyzing a single sample obtained from a single region of a tumor can underestimate intratumoral heterogeneity (i.e., the tumor’s genomic landscape). Such heterogeneity may present a big challenge for biomarker-identification approaches. It can also affect therapeutic choices (71).

ETHICAL AND LEGAL CONSIDERATIONS

Several ethical considerations should be carefully addressed. They include the accessibility of test results, especially for other family members who might be at risk for the same disease, prospective employers, and legal authorities (72). Another interesting point is the reporting of incidental findings. Should the patients be informed of only results that are directly related to the disease of concern, or should all results, including incidental findings, be reported? There are also concerns about reporting the potential risk of developing a disease for which no prophylactic measures exist and whether such reporting would lead to anxiety in the patient. The issue of securing these large amounts of data is also a concern (73). Patenting issues (Who owns the genes?) is another ongoing debate in the scientific community. Finally, direct-to-consumer genetic testing should be evaluated cautiously in terms of its reliability and the impact of these tests on the public. In addition, providing these tests to the public must be regulated (72).

Concluding Remarks

Despite the many existing challenges, there is light at the end of the tunnel. The cost of high-throughput analyses has dramatically declined. For instance, $1000 full-genome sequencing will become a reality in the very near future. Additionally, targeted approaches that focus on specific “actionable” molecules will bring down the costs of molecular testing to a very reasonable level (28). Furthermore, the costs of whole-genome sequencing will be small when they are amortized over an individual’s expected lifetime, because the baseline genomic information can be consulted at any stage of life. Finally, as the cost of biomarker discovery decreases, the rate of discovery will accelerate (12).

We are indeed moving into a new revolutionary era of personalized medicine. The recognition of the merits and limitations of genomic medicine can guide us to more-realistic expectations and foster new directions for research (74). At present, we can generate data much faster than we can interpret them. Fig. 1 is a proposed outline of the multistep process required to achieve “real-life” applications of high-throughput genomic data. The contribution of genomic analysis is no longer controversial (69), and genomic data, combined with transcriptomic, proteomic, and metabonomic data, are expected to provide a much deeper understanding of the healthy and disease states (10).

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