The promise of personalized medicine has been around for many years, and growth in the field is rapidly gaining momentum. The concept is to use information from an individual’s genomic, transcriptomic, and proteomic profiles to tailor a custom management plan for his or her disease based on an assessment of the disease’s risks and aggressiveness (1). A recent revolution in personalized medicine has arisen after the introduction of “molecular profiling” approaches. These approaches, including high-throughput sequencing, microarray analysis, array comparative genomic hybridization, and mass spectrometry, provide an enormous amount of information by allowing screening of an individual’s entire genome in a single experiment (2). The recent evidence has shown that the integration of molecular changes from multiple levels of analysis, including the genomic, the epigenetic, microRNA, mRNA, and the proteomic, can provide a much better understanding of the pathways that are affected in cancer. This evidence has led to a change in focus from the discovery of individual biomarkers to a search for “biological processes” that are altered in individual patients (3).

After the initial period of optimism for an imminent revolution in medical practice whereby the molecular “fingerprint” for each cancer patient would replace the clinico-pathologic parameters, it has now become clear that the transition from the research bench to bedside is more challenging than was previously expected. One important challenge is the ability to analyze and extract meaningful information from this overwhelming amount of data. Different strategies have been suggested to translate molecular-profiling data into the clinic. One approach is to use high-throughput multiparametric analysis as a clinical test directly. This approach is more attractive and more likely to be useful, because such multiparametric tests can achieve better sensitivity and specificity. Obstacles include the very high cost of such testing and the long times needed to perform it. An intermediate strategy is a “targeted approach” that would use a selected number of molecular-profiling tests that are more likely to be informative. This potential of this strategy is shown in the elegant work of Chinnaiyan and his colleagues from the Michigan Center for Translational Pathology at the University of Michigan (4).

The Michigan group recently published a feasibility study for using a comprehensive sequencing strategy to obtain multimolecular-level data that are then integrated to answer the question of the eligibility of metastatic-cancer patients with refractory or end-stage disease to enter certain clinical trials (4). The investigators used a multidimensional approach including whole-genome sequencing, whole-exome sequencing of tumor and normal DNA, and transcriptome sequencing (i.e., the complete set of genomic transcripts, including coding RNA, noncoding RNA, and microRNA molecules). The combination of these data was used to identify clinically relevant, potentially informative mutations for helping the assignment of specific patients to their potentially most useful clinical trials.

A multidisciplinary sequencing tumor board of experts in oncology, pathology, molecular cancer biology, and bioinformatics analyzed the data obtained for chromosomal aberrations, mutations, and gene expression alterations and matched this information with the potentially available clinical trials. To verify that their strategy could work before testing on actual patients, the Michigan group performed the sequencing experiment with xenografts established from patients with metastatic prostate cancer. They then moved on to test this new approach with 2 actual cancer patients, one with metastatic colorectal cancer and the other with malignant melanoma.

This Michigan study has several unique features that could pave the road to more-practical applications of genomics for personalized medicine. The first is the...
integration of multiple levels of molecular analysis. This approach has a great advantage over previous studies that focused on only a single dimension of the picture (e.g., gene expression or mutations) (5). A second advantage is the study’s goal of having results available within the clinically relevant time frame of about 4 weeks. Added to this approach is the benefit of designing an experiment that can be performed at a reasonable cost, i.e., comparable to the cost of currently available commercial tests (approximately $5000). Finally, this study focused on a single question, i.e., the enrollment of patients in clinical trials.

This study also highlights another unique aspect of personalized medicine that had previously been underestimated. Most profiling approaches have been aimed at subclassifying patients into smaller subgroups. It is now obvious that such approaches are not fully satisfactory, because cancer is a very heterogeneous disease and because we need to zoom into the individual patient’s genome to apply personalized-medicine regimens successfully, i.e., to focus on the “individual patient-specific” genomic landscape.

The Michigan study may also give a great boost to revitalize clinical trials for targeted therapies, which are usually hampered by their costs and the overall limited rates of success. Focusing on a very specific and small subgroup of patients will greatly enhance the success rate and reduce the costs of administering treatments to those who are unlikely to respond. Such an approach will require modification of the approach for setting inclusion criteria, as is discussed below.

The report of this study and similar publications teach us a number of important lessons. The results of the study emphasize a recently emerging trend of basing treatment of tumors on the way they behave, rather than on where they are (i.e., the biological behavior rather than the anatomic location). For instance, mutations in the HRAS (v-Ha-ras Harvey rat sarcoma viral oncogene homolog) gene and structural rearrangements affecting the CDKN2C (cyclin-dependent kinase inhibitor 2C (p18, inhibits CDK4)] gene were identified in the melanoma patient of the aforementioned study. RAS signaling leads to downstream activation of the MAPK/MEK (mitogen-activated protein kinase (also known as MEK)] and PI3K/mTOR (phosphatidylinositol 3 kinase/mammalian target of rapamycin) pathways. Thus, although HRAS mutations have not been described before in melanoma, the sequencing tumor board suggested that a combination treatment of PI3K and MEK inhibitors would be of benefit for this particular patient. The inclusion criteria for clinical trials should be opened to allow patients with similar tumor types in other organs to enroll in the study as long as they have the biological targets and mutations. A number of additional mutations and arrangements were also identified in the colorectal cancer patient. These changes included NRAS [neuroblastoma RAS viral (v-ras) oncogene homolog] and CDK8 (cyclin-dependent kinase 8) aberrations that were labeled as “informative” because they could be matched in the future to clinical trials with MEK, PI3K, or CDK inhibitors. Current trials do not include NRAS because of the low frequency of aberrations in this gene in colon cancer. KRAS (v-Ki-ras2 Kirsten rat sarcoma viral oncogene homolog) and BRAF (v-raf murine sarcoma viral oncogene homolog B1) gene aberrations, on the other hand, are used as predictive markers for epidermal growth factor receptor therapy. A number of genetic aberrations were labeled as “biologically interesting” because they suggested possible mechanisms for tumor progression in this particular patient. The study also identified a number of mutations and aberrations that could serve as potential new drug targets in the future.

Although the results are promising, the Michigan study highlights several existing challenges that need to be addressed, including certification of the technique, ethics approval, and the patient’s informed consent. Cost remains a substantial challenge for scaling up the experiment; however, the cost is expected to decrease after the technique becomes approved for clinical practice.

The study also highlights the need for national and international collaborative efforts, not only for clinical trials but also to facilitate the different aspects of personalized medicine in cancer. In the future, it will be interesting to see the consolidation of the sequencing tumor board into an electronic algorithm that can assign the patient to the available clinical trials.

The results show that an important question remains to be answered: How are the more informative molecules to be identified within this “ocean” of new information? One interesting approach would be to go “backwards” by focusing the analysis on those molecular changes that are informative for the currently existing or potentially available targeted therapies, i.e., focusing on the clinically actionable targets.

Finally, it is now clear that molecular-profiling techniques will not be able to provide a global solution for all problems at once. Instead, we now have started to take the more practical approach of addressing one

\(^1\) Human genes: HRAS, v-Ha-ras Harvey rat sarcoma viral oncogene homolog; CDKN2C, cyclin-dependent kinase inhibitor 2C (p18, inhibits CDK4); NRAS, neuroblastoma RAS viral (v-ras) oncogene homolog; CDK8, cyclin-dependent kinase 8; KRAS, v-Ki-ras2 Kirsten rat sarcoma viral oncogene homolog; BRAF, v-raf murine sarcoma viral oncogene homolog B1.

\(^2\) Nonstandard abbreviations: MAPK/MEK, mitogen-activated protein kinase (pathway) (also known as MEK); PI3K/mTOR, phosphatidylinositol 3 kinase/mammalian target of rapamycin (pathway).
specific question at a time. In addition to aiding in en-
rolling patients in clinical trials, molecular signatures
can help in prediction of cancer risk, accurate assess-
ment of prognosis, prediction of treatment efficiency,
and early detection of relapse and metastasis. The over-
all impact on patient management is expected to be
substantial, because it will permit closer follow-up and
intensive therapy only for those patients with aggres-
sive disease, while avoiding unnecessary treatment for
patients who exhibit a more benign disease course.

Another breakthrough in the field of clinical on-
cology that will be made possible through molecular
profiling is the introduction of a new era of “molecular
subclassification” of cancer. Several emerging exam-
pies are showing the ability of molecular signatures to
classify tumors of the same organ according to their
behavior, rather than by morphology and thereby are
slowly bringing this revolutionary concept into reality.

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References

1. Diamandis M, White NM, Yousef GM. Personalized
medicine: marking a new epoch in cancer patient
management. Mol Cancer Res 2010;8:1175–87.
2. Arsanious A, Bjarnason GA, Yousef GM. From
bench to bedside: current and future applications
of molecular profiling in renal cell carcinoma. Mol
Cancer 2009;8:20.
3. Karagiannis GS, Pavlou MP, Diamandis EP. Cancer
secretomics reveal pathophysiological pathways in
cancer molecular oncology. Mol Oncol 2010;4:
496–510.
4. Roychowdhury S, Iyer MK, Robinson DR, Loni-
gro RJ, Wu YM, Cao X, et al. Personalized on-
cology through integrative high-throughput seq-
quencing: a pilot study. Sci Transl Med 2011;3:
111ra121.
5. Beadling C, Heinrich MC, Warrick A, Forbes EM,
Nelson D, Justusson E, et al. Multiplex mutation
screening by mass spectrometry evaluation of 820
cases from a personalized cancer medicine registry.