The next generation of cancer management

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As readers of Cancer Biology and Medicine well know, there has been a seismic shift in human molecular biology over the past few years, as momentous in its own way as the discovery of the double-helical structure of DNA by Watson and Crick 60 years ago, the elucidation of the genetic code shortly thereafter, the advent of recombinant DNA and gene cloning in the 1970s, and the introduction of the polymerase chain reaction in the mid-1980s. For the first time in history, we now have ready access to the entire complement of human genes and intergenic regions—all 6.6 billion nucleotides of the human genome—of any individual, for either research or medical purposes. No longer limited in our technology of examining one individual gene or sub-segment of a gene at a time by the traditional methods of PCR and Sanger sequencing, we can now produce, with astonishing accuracy and precision, the complete genome sequence within a few days and at reasonable cost. Nor are we restricted to any particular cell type or body site: we can obtain the germline genomic sequence from nucleated cells in the peripheral blood or saliva, from free fetal DNA circulating in the mother’s bloodstream, or—with singular relevance to this special issue—the somatic genome sequence from cancer cells, revealing both their acquired “driver” and secondary mutations that produce the malignant phenotype and serve as potential targets for “precision” or “personalized” therapies.

The technology that has enabled all of these applications—which only a few years ago would have been in the realm of science fiction—is, of course, massively parallel or “next-generation” DNA sequencing. As described in the following articles in this special issue, this technology produces highly repetitive (i.e. massively parallel) sequences of all genomic regions in a non-targeted (“shotgun”) fashion, at speeds and throughput many orders of magnitude beyond that of traditional sequencing approaches. The limitations thus become not those of sequencing speed or length, but of our ability to analyze and interpret the huge mass of data (about 5 terabytes in its rawest form) produced. For that we have to rely on modern computer power and the filtering and annotation processes of bioinformatics. But those tools, powerful as they are, can only take us so far, and the ultimate decisions over pathogenicity of detected sequence variants, and which ones to report to the ordering physician, must be left in the hands of expert molecular diagnosticians. Therein lies the great challenge of this new frontier, its thorny ethical dilemmas, and also its intellectual and scientific rewards.

In retrospect, we were in fact quite naïve to believe (or at least to hope, in the sense of wishful thinking) that the single genes we were able to probe and sequence in the initial decades of molecular medicine would provide the full answer to tumor biology, behavior and response to therapy. With the limited technology available to us, we naturally went after the “low-hanging fruit”: HER2/neu amplification in breast cancer, KRAS mutations in colon cancer, and BCR-ABL gene fusion in chronic myelogenous leukemia. This is not meant to disparage those groundbreaking discoveries, but it does help to explain the subsequent frustration when it was found that therapies targeted to these deranged genes (and their protein products) did not produce lasting cures for the respective malignancies (though imatinib in CML certainly comes close). Malignancy is a highly complex phenotype, dependent upon acquired mutations in multiple genes (some...
accruing over many years), inherited variants in tumor suppressor and immune function genes, environmental and epigenetic factors. No individual gene or mutation test could possibly encompass this range of mechanistic phenomena. Indeed, even access to the sequence of all the genes will not be sufficient, since it will not address epigenetic, proteomic and metabolomic factors (all of which are discussed in this issue)—but it does bring us a long way. By observing mutations in multiple oncogenes and signal-transduction genes within tumors, we can begin to target them in parallel, analogous to the strategy of highly-active anti-retroviral therapy that has been so remarkably effective in treating HIV infection.

Despite all this wonder and promise, sometimes genome-level sequencing can be a case of "too much of a good thing". For every causative or "druggable" mutation detected, the test yields thousands of variants of uncertain significance (VUS) that don't match the so-called "reference" human genome (actually 10-30,000 variants from whole-exome sequencing, and 2-3 million variants from whole-genome sequencing). While most of these can be filtered out by the computer software, one is usually still left with tens or hundreds (depending on the nature of the assay) of variants that require manual interpretation. Even with the more targeted method of next-generation sequencing (NGS) that is typically applied to tumor genomes, this remains a problem, simply because the assay employs sequencing rather than allele-specific probe hybridization. Of the 300-500 genes that are currently targeted in many NGS cancer tests, only a handful are truly "actionable" in the sense of having an approved drug available to target them. Yet there are many other drugs still in the research and clinical trial pipelines; if a patient's tumor exhibits a targetable mutation for one of those, should the physician demand access to it on a "compassionate use" basis? What if the patient's tumor shows a variant in a codon just adjacent to the one known to be targetable—should that be worth a try with the drug, on the chance that it might have some effect (keeping in mind that most of these new biologics are both expensive and toxic)? And how should we handle the inherited cancer mutations (e.g. BRCA1 and BRCA2) that may be picked up in the course of tumor DNA sequencing, let alone other potentially actionable but unrelated "incidental findings" (e.g. hereditary cardiac arrhythmias) one may stumble upon? Should they even be disclosed, especially if the patient is a child?

These are the promises and challenges we are just starting to come to terms with, now that NGS has released the genomic genie from the bottle. The articles in this issue all address these questions thoughtfully and pragmatically, but it will be up to each practitioner to weigh the risks and benefits for the individual patient. Genomic sequencing truly lies at the juxtaposition of the science and the art of medicine.

Conflict of interest statement

No potential conflicts of interest are disclosed.

References
