H&O What are some recent advances in personalized medicine?

LS In recent years, the field of oncology has been maturing toward a more in-depth understanding of cancers, well beyond the anatomical description of the original site of diagnosis. Before the era of personalized medicine, cancer diagnosis, prognosis, and treatment decisions were based on histopathologic parameters, including the tissue of origin and the stage and grade of the tumor. We are now complementing that knowledge with molecular information, particularly with the use of predictive biomarkers that allow us to select patients who are most likely to benefit from certain treatments. As this genomic era continues to evolve, it will likely lead to more effective treatments, fewer side effects, and opportunities for patients to have proactive and participatory roles in their own care.

H&O How has the knowledge of tumor heterogeneity played a role in modern research?

LS The existence of tumor heterogeneity has been known and recognized for many years. In a 2012 *New England Journal of Medicine* article, Swanton and associates carried out the first ever genome-wide analysis of the genetic variation between different regions of the same tumor. Using kidney cancer samples, they found that approximately two-thirds of gene faults were not found in other biopsies from the same tumor. This has triggered a lot of interest among researchers around the world to deeply focus on tumor heterogeneity as a serious issue in cancer.

H&O What are some developments in this technology?

LS The field of cancer genomics is growing rapidly thanks to revolutionary advances in DNA sequencing technologies. The improved timeliness, accuracy, and costs associated with genome sequencing have driven discovery not only in cancer genomics but also in clinical translation. The ability to perform whole-genome or whole-exome sequencing at the point-of-care is a tangible possibility. What is much more prohibitive in terms of technology is being able to understand all of the data. Having the expertise to help analyze the true message from the cancer itself versus extraneous information is going to be germane to make this reasonably useful in the clinic.

We can utilize other technologies when examining surgical specimens that are removed from patients. It is important to look at different regions in the tumor in order to tackle tumor heterogeneity. Multiregional biopsy is an option, although it is not likely to be routinely performed. It is unusual to do biopsies in multiple parts of the body because of the risk and invasiveness of such procedures. We are looking at using finer needles to see if this will be less invasive and still yield the amount of nucleic acids that are useful to perform the analysis.
A lot of groups are looking at circulating technology, like circulating tumor cells and circulating DNA, which are noninvasive strategies. Their isolation and analysis hold great promise for the early detection of invasive cancer and the management of advanced disease.

Imaging is another strategy that we may learn how to use in order to visualize heterogeneity. However, imaging is challenging. There must be some sort of granular resolution in order to see at the cellular level, and we are not quite there yet. Perhaps with radionuclide imaging, we will one day be able to look at heterogeneity without inserting a needle or drawing anything out of a patient.

**H&O What role should clinical trials play?**

**LS** In a recent article published in the *Journal of Clinical Oncology*, we highlighted the processes, challenges, and issues involved in the translation of cancer genomics to the clinic. How do we design trials looking ahead? We have laid out some framework in terms of what is feasible. Of course, each cancer and each patient might be different based on their complexity.

I think we will be focusing more and more on very select subgroups of patients with a common molecular aberration that we can target while looking for big differences in their cancer treatment. In order to have a true clinical impact, molecular profiling must be able to identify actionable genetic aberrations in a substantial proportion of patients, and novel agents targeting these aberrations must be available and accessible through clinical trials. Breaking down even a single tumor type into multiple subsets may be beneficial, as a certain kind of subset may actually transcend across histology, so that you can have patients with similar mutations or aberrations in lung cancer, colon cancer, breast cancer, etc. Perhaps one way to analyze it is to really break the histopathologic barrier and examine mutations that are similar in one basket. However, a *KRAS* mutation in colon cancer likely behaves differently from a *KRAS* mutation in lung or pancreatic cancer, so even if you are going to do a basket trial, that kind of context-dependence is still important. The histology and the molecular data are going to be important and complementary, and both will have to be factored in together in the design of future trials.

**H&O What are some ongoing efforts?**

**LS** Many groups across the globe are now doing what we call molecular profiling. This includes using an archived tumor specimen to perform genome-sequencing or genotyping to identify mutations to select drugs, or actively biopsying patients to profile them to see if they have any mutations that are potentially drivers and important in tumor growth and metastasis.

In addition, there are many programs—including ours—that have studies aimed at sequential sequencing and sampling of either tumor cells by biopsy or circulating technology to look at tumor DNA or tumor cells in the circulation to see how these molecular changes evolve over time, and then trying to correlate with clinical data to make sense of it. Multiple teams and studies are needed in order to add to the database and general knowledge before we can truly understand how to tackle this complex problem.

**H&O What are the biggest remaining challenges?**

**LS** The biggest challenge is how to deal with the enormous amount of data that we will be facing. Obviously, as a drug developer, another challenge is having this information but lacking effective drugs to offer, making the former somewhat pointless. We know from our experience that if you have a molecular profiling program without a drug development program coupled to it, then you have basically only done profiling. Nothing useful has been achieved with that information. We have to be able to identify new drugs and drugs that have activity that can be used to target these mutations to test if they are beneficial to our patients in properly-designed clinical trials.

Another challenge is how to return this information to oncologists and patients as well. In order for a busy oncologist seeing hundreds of patients each year to take the time to understand this kind of molecular information to the extent that they can go back and return the results to the patient, a lot needs to be done to make the data more understandable and simple. I think that is a whole science in and of itself.

**H&O What do you think the future holds?**

**LS** Ideally, for all patients who walk through the door, we would immediately know everything about their cancer. We would find the right treatment for them because we have already done properly-designed clinical trials to help us understand whether matching works. There would be no waste of time by trying treatments that we know are not going to be beneficial. That would truly be precision and personalized medicine. I think that we are not quite there yet, but we are making progress very rapidly, and we all have to work together to make this more cohesive. There is an overwhelming amount of information, and everybody is trying to put the pieces together. With everyone contributing to the science, we are moving in the right direction.

**Suggested Readings**


