NGS to detect oncogenes—sizing panels, reporting results

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June 2014—Scientific wonders always abound at the Advances in Genome Biology and Technology conference, and this year's meeting in February was no exception. Attendees had their first opportunity at a scientific meeting to learn about the newly announced Illumina HiSeq X Ten, a combination of 10 HiSeq X systems, which, Illumina says, can sequence 16 whole human genomes per three-day run at a read depth of 30× and a cost of $1,000 per genome. At the other end of the scale, attendees saw the unveiling of Oxford Nanopore's MinION, a sequencer the size of a pack of chewing gum.

But what if you don't need to sequence 18,000 whole human genomes this year, or don't have $10 million to acquire the HiSeq X Ten? And perhaps you want to do clinical next-generation sequencing now, which the MinION is not quite ready for.

A scan of the scientific program turned up several talks on using NGS platforms for their most prominent clinical application to date—analyzing genes of cancer patients for variants that are relevant to causation of cancer and, in some cases, can point to targeted therapies. (See page 38 for microbiological applications.) Interviews with these presenters, and others who have experience in this area, provide a convincing case for the value of NGS in this setting. Two fundamental questions are still being hashed out, however.

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NGS for determining the vaginal microbiome in clinical samples

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First, what size oncogene panel is optimal? Laboratories are evaluating various homebrew and commercial panels consisting of 23 to 409 genes. Some sequence every exon of a cancer gene or whole genes; others sequence only so-called hotspots, regions where pathogenic variants cluster and where well-known, frequently theranostic mutations are located. These are typically single nucleotide variants or small deletions.

Speaking for a big panel, Doron Lipson, PhD, of Foundation Medicine Inc. (FMI), noted that its 236-gene FoundationOne test "uncovered a high frequency of [genomic] alterations which can inform targeted treatment decisions" in non-small cell lung cancer. Finding these alterations "can result in immediate benefit for patients with metastatic disease," Dr. Lipson, who is senior director of computational biology methods in the Foundation Medicine reference laboratory, told attendees.

Jeffrey Ross, MD, FMI's medical director, says that more than 80 percent of NSCLC patients tested with

FoundationOne have an alteration. They get a new targeted therapy or are referred to a clinical trial for which the variant qualifies them. “Of the first 1,000 lung cancer patients [tested with FoundationOne], more than 800 had alterations that we thought were actionable,” says Dr. Ross, Merrill professor and chair of pathology and laboratory medicine at Albany (NY) Medical College.

Marc Ladanyi, MD, collaborated with Foundation Medicine in this work. “The data certainly support the notion that this kind of [NGS] assay that is more comprehensive than what most centers have previously used is worth doing, at least in cases where a standardized assay doesn’t come up with anything,” Dr. Ladanyi, the William Ruane chair in molecular oncology at Memorial Sloan Kettering Cancer Center, tells CAP TODAY.

A year ago he and MSKCC colleagues developed their own in-house assay, called MSK-IMPACT, that’s similar to FoundationOne. “It includes all coding exons of 341 cancer genes and picks up selected rearrangements and copy number changes in those genes. Our assay is similar to FoundationOne’s updated gene list. We are moving in the same direction,” says Dr. Ladanyi, who is also chief of the molecular diagnostics service at MSKCC.

Dr. Singh

Clinical investigators in the molecular diagnostics laboratory at MD Anderson Cancer Center have looked in the past few years at both smaller and larger panels. They presented some of their data at last year’s meeting of the Association for Molecular Pathology. “When we started doing it, there was nothing,” says Rajesh R. Singh, PhD, assistant professor in the Department of Hematopathology, Division of Pathology and Laboratory Medicine. “People were aware that the technology was powerful and was generating discovery markers like never before. We asked, ‘Why not bring it to the clinic?’”

“It is not easy to do all of these markers with single-gene assays, especially in solid tumors,” Dr. Singh adds, saying there has been a shift in the mentality of the doctors ordering tests. Most tumors now have more than three genes ordered, making broader panel testing practically necessary. While larger panels are attractive, “they have to be prudently applied,” Dr. Singh cautions.

Work by Eric E. Schadt, PhD, Crystal professor and chair of the Department of Genetics and Genomic Sciences, Icahn School of Medicine at Mount Sinai, also spans the size range of gene panels. His department runs the clinical genetics laboratory at Mount Sinai. “We are in the process of getting approval both for BRCA1/2 sequencing to characterize germline variation that may put an individual at high risk for breast and ovarian cancer, as well as a panel of roughly 300 genes that are important for characterizing tumor samples at the molecular level,” Dr. Schadt tells CAP TODAY. The laboratory is carrying out extensive testing of the Illumina, Ion Proton, and Pacific Bioscience (PacBio) systems on these types of panels. He has found that the PacBio instrument has “strong advantages” for detecting certain types of important genetic changes. “Our two PacBio instruments run in a CLIA-certified genomics laboratory, so they are geared for use in the clinical arena,” says Dr. Schadt, who is also director of the Icahn Institute for Genomics and Multiscale Biology at Mount Sinai.

Dr. Schadt’s remarks bring up the second fundamental question: Which commercial platform is best?

CAP TODAY spoke to advocates for all three major instruments—Illumina's HiSeq, Life Technologies' Ion Proton, and PacBio's RSII. Just as Dr. Schadt sees advantages to the PacBio RSII, each proponent gave cogent reasons for his preference—Dr. Ross for the Illumina HiSeq and Dr. Singh for the Ion Proton.

Before we discuss panels and platforms in more detail, let's talk about a presentation at the Advances in Genome Biology and Technology conference that addressed a topic at the heart of pathology, one that's every bit as important as getting a good result: getting that result to the ordering clinician in a simple, automated electronic format with a clear interpretation, along with the underlying evidence. Oncologist Mia Levy, MD, PhD, Ingram assistant professor of cancer research at Vanderbilt-Ingram Cancer Center, and pathologist Carl Morrison, MD, DVM, executive director of the Center for Personalized Medicine at Roswell Park Cancer Institute, described a collaboration that achieved that goal with oncogene data obtained by NGS.

Dr. Morrison

At the base of the project was My Cancer Genome, a genomic knowledge database that originated at Vanderbilt-Ingram Cancer Center. In her part of the session, Dr. Levy described My Cancer Genome as a knowledge resource that provides clinical interpretation of variants, classifying their clinical effect and reporting actionable results. It was developed with the assistance of 59 contributors at 22 institutions in 10 countries. It's an open resource and receives more than 4,700 visits per week from physicians, patients, caregivers, and researchers. It went online in 2010; it has detailed information on 19 cancers, 42 genes, and 398 disease gene variants.

Dr. Levy listed four types of information that can be derived from My Cancer Genome: diagnostic, prognostic, and sensitivity or resistance to targeted therapies. She showed a graph of strength of effect versus strength of evidence for the 42 genes; only four were in the quadrant with strong effect and strong evidence. "For the most part we focus on genes in the upper right quadrant," Dr. Levy tells CAP TODAY. In addition to clinically relevant variants, My Cancer Genome includes translational content—investigational targeted therapy available only in clinical trials.

"At Vanderbilt we developed a linking method for reports," says Dr. Levy, who is also director of cancer clinical informatics, assistant professor of biomedical informatics, and assistant professor of medicine in the Division of Hematology and Oncology at the cancer center. The method has been in use since 2010. It incorporates genomic results into the electronic medical record and links them to My Cancer Genome. It works only within the Vanderbilt system. For the collaboration, Vanderbilt-Ingram Cancer Center made an agreement with Roswell Park Cancer Institute to allow it to use My Cancer Genome in its workflow. Roswell Park created proprietary software, which is being used for reporting and links with My Cancer Genome. "Dr. Morrison and Roswell Park were the first to pilot how to do that [outside the Vanderbilt system]," Dr. Levy says.

A second new feature about the Roswell Park reporting program is that it was designed to report data

from next-generation sequencing. For genomic analysis, Vanderbilt-Ingram uses not NGS but SNaPshot panels, which are based on primer-extension technology, not sequencing, and which are targeted to hotspots. Dr. Morrison and his colleagues at Roswell Park transformed My Cancer Genome content for use in an NGS interpretive profile.

Dr. Morrison called the software they wrote "an enabling process" for NGS. "No one is thinking about how we enable the process for ordering physicians," he tells CAP TODAY. "Until we do, we will not move into the clinical arena. That's what we've done at Roswell Park. We made My Cancer Genome able to be used in the clinical arena on a day-to-day treatment basis." The software he and his colleagues wrote makes it possible for NGS results and information from My Cancer Genome to go into the EMR and flow through to doctors for clinical decisionmaking. Links to My Cancer Genome are directly embedded in the patient report in the EMR.

Content in the genomics report is based on physician feedback. It includes a summary of all genes tested, test method, whether a genetic alteration was detected, name and type of alteration, and whether that alteration is clinically actionable in the patient's disease or in any other disease. "We report all variants detected, whether they are actionable or not," says Dr. Morrison, who is also director of the cancer institute's Pathology Resource Network, director of molecular pathology, and associate professor of pathology.

"All conventional pathology tools available today will not support this type of reporting," Dr. Morrison told the conference attendees. In an interview he added: "Look at typical pathology tools like CoPath or Tamtron, which have been around for 10 to 15 years and are used to report typical surgical pathology data. They will not manage NGS data at all. You have to come up with your own tools." Of a reporting tool for NGS developed by Agilent, he says, "The best thing about the Agilent tool is that it's free."

NGS results must be associated with a knowledge database, he says. "The data we produce in the lab is so extensive that no oncologist or pathologist can walk around informally and know all the associations in the knowledge database." One way to deliver information from the database to clinicians is to condense it and put it into the report. Dr. Morrison's group took another tack. "We said, Let's use API [application program interface] hyperlinks and distribute them directly into the EMR test report." One advantage of this approach is that as the database is updated, test reports automatically change, so the reports are always up to date.

"There is a whole army of people working on knowledge databases and developing tools to aid processing of NGS results," Dr. Morrison says. "What people aren't doing—and this is what I was trying to get at through our talk—is approaching the front end of the process. Our system goes all the way from order entry to associating the final report with a knowledge database that can enable physicians."

Now that Dr. Morrison and his Roswell Park Cancer Institute colleagues have demonstrated proof-of-concept for an NGS decision support tool, Dr. Levy says, "We have licensed My Cancer Genome content to GenomOncology so that other people can make something similar to what Roswell Park has done using GenomOncology's tools." GenomOncology made the first move. "It was the right collaboration," she says.

In his talk on the FoundationOne test—which Foundation Medicine prefers to call a "bait set"—Dr. Doron Lipson said its bait set captures whole exons of 236 known clinically and biologically relevant cancer genes along with introns of 19 commonly rearranged genes. It contains the four main

oncogenes associated with lung cancer—*KRAS, EGFR, EML4-ALK* fusions, and *BRAF*—as well as hotspots in other genes, among them *ERBB2, AKT1,* and *PIK3CA.* For the clinical evaluation, data were collated from an analysis of 893 consecutive formalin-fixed, paraffin-embedded non-small cell lung cancer specimens received in FMI's laboratory. Median depth of sequencing was greater than 800×. Illumina HiSeq instruments were used for sequencing. Turnaround time was 14 days from sample receipt to report. Since almost all of the samples were from patients with refractory or metastatic cancer, this turnaround time was adequate. "We are gradually lowering the turnaround time," Dr. Jeffrey Ross says.

Genomic profiling was successful in 95 percent of specimens, yielding 1,313 unique genomic alterations in 181 genes, Dr. Lipson reported. Fusions in *ALK, RET, ROS1,* and *FGFR3* made up 10 percent of alterations. Using standard methods for comparison, positive predictive value was greater than 99 percent for substitutions, indels, copy number alterations, and gene fusions. Sensitivity was 98 percent or 99 percent for all alterations except copy number alterations, for which sensitivity was 95 percent. Successful profiling required more than 20 percent tumor content. "We have four pathologists to review the samples," Dr. Ross says. "We can enrich or microdissect to take away benign tissue, but we only need to do this in five percent of cases."

Followup of two patients, one with a complex ALK rearrangement and one with a novel *RET* fusion, demonstrated sensitivity to crizotinib and cabozantinib, respectively (Peled N, et al. *J Thorac Oncol.* 2012;7:e14–16; Lipson D, et al. *Nat Med.* 2012;18:382–384; Drilon A, et al. *Cancer Discov.* 2013;3:630–635).

Dr. Ross explains that FoundationOne is intended to be a comprehensive genomic profile for all solid tumors except sarcomas and some pediatric solid tumors. These exceptions, along with leukemias and lymphomas, are profiled with FoundationOne Heme, the company's second commercial test, which includes RNA sequencing to detect a broader range of gene fusions that appear in higher frequencies in these malignancies. Both bait sets are reviewed and updated regularly as the science evolves, Dr. Ross says.

For profiling purposes, Foundation Medicine uses Illumina's HiSeq 2500 system. "We feel that the 2500 is the best technology platform for us," Dr. Ross says. "When we link our computational approach and lab processes with the 2500, we are able to do all types of alterations at the same time." He said they would not be able to produce similar results with an Ion Torrent platform. While Dr. Ross acknowledges that Ion Torrent systems require less input DNA—20 ng, compared with the advertised specification of 150 to 250 ng for Illumina—he notes that Foundation Medicine is processing results now with 20 ng of DNA. The FoundationOne validation study was published last year (Frampton GM, et al. *Nat Biotechnol.* 2013;31:1023–1031).

In a similar fashion, Dr. Morrison and his group at Roswell Park have evaluated the Illumina and Ion Torrent platforms but have found that optimal results are attained by doing parallel sequencing on both platforms. This has resulted in 95 percent sensitivity at a low variant allelic frequency of 2.9 percent, which Dr. Morrison says is critical for evaluating tumor heterogeneity and planning for patient therapy. The Roswell Park team uses a patented IT solution to merge not only the VCF files from both platforms but also the associated BAM files to reach one final result. "Not only does this provide optimal sensitivity at very low variant allelic frequencies, it also provides dual technology confirmation that almost entirely excludes false-positives," Dr. Morrison says.

“I am not sure how much the clinical community understands that NGS, both Illumina and Ion Torrent, while they have excellent sensitivity compared to our traditional technology of Sanger sequencing, have relatively frequent false-positives that seriously impact positive predictive value unless a second technology confirmation is performed. Additionally, most practicing physicians do not realize that the Ion Torrent and Illumina technologies are more different from each other than, for example, Sanger sequencing is to the latter.” He thinks Roswell Park’s approach provides an advantage given that false-positives are generally random events across both platforms, as would be expected, and that both platforms have excellent sensitivity for true positives. “With new technologies like NGS we cannot afford to be wrong from the outset,” he says.

Dr. Rajesh Singh and his colleagues at MD Anderson have validated and implemented the 46- , 50- , and 409-gene panels from Life Technologies on the Ion Torrent PGM and Proton sequencers. “Validation is one of the challenges on the clinical side,” Dr. Singh says. “We looked at the 46-gene AmpliSeq panel from Life Technologies and found it suited us very well.” (Singh RR, et al. *J Mol Diagn.* 2013;15:607–622.) It’s compatible with DNA from paraffin blocks, from which the majority of tumors give a low quantity and quality of DNA, he notes, and it requires only 10 ng of DNA. “It has many genes that are already established as markers for tumors. The 46-gene panel was our primary test for solid tumors since April 2012, subsequently replaced by the 50-gene panel implemented in September 2013, which includes all of the 46 genes with four additional genes,” he says. They have sequenced and reported more than 6,000 samples using the 46- and 50-gene panels. Average turnaround time is four days from sample receipt.

In addition to the Ion Torrent PGM, the molecular diagnostics laboratory also uses Illumina sequencers. They validated the Illumina TruSeq 48-gene panel, which was further customized by adding six genes for acute myeloid leukemia on an Illumina MiSeq instrument (Luthra R, et al. *Haematologica.* 2014;99:465–473), and implemented it in October 2012. Turnaround time for this platform-panel combination is five days from sample receipt.

In a poster at the AMP meeting, Dr. Singh and colleagues reported their validation of the Life Technologies 409-gene panel on the Ion Proton. “For first-line testing, smaller mutation hotspot-based panels are the best,” Dr. Singh advised in an interview. “However, you may also want to have a 409-gene panel for those samples that do not show any actionable/targetable mutations by hotspot-panel testing and may need a more comprehensive screening of genomic aberrations.” In a pilot trial, they are currently evaluating its clinical utility.

In addition to detecting the substitution mutations and insertion/deletions, the NGS assays can provide valuable information regarding gene copy number alterations, which he says can be obtained reliably by either Illumina or Life Technologies target capture and sequencing platforms.

Dr. Shadt

In addition to preparing a 300-gene panel for clinical use, Dr. Eric Schadt at Mount Sinai has

used PacBio sequencers in several medical discovery investigations. In one, he was part of a group that showed that the oncogene *FLT3* was a key driver of AML and that the lack of efficacy observed in clinical trials for *FLT3* inhibitors was a consequence of mutations in *FLT3* that were selected for as a result of the treatment (Smith CC, et al. *Nature.* 2012;485:260–263). In that case, Dr. Schadt says, the PacBio's ability to identify phasing mutations (which of the mutations are co-occuring on the same chromosome or along the same stretch of a given gene) was a key advantage. "In other papers we have demonstrated PacBio's ability to detect structural variations," Dr. Schadt adds (Bashir A, et al. *Nat Biotechnol.* 2012;30:701–707; Rasko DA, et al. *N Engl J Med.* 2011; 365:709–717).

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NGS for determining the vaginal microbiome in clinical samples

While next-generation sequencing is often used to detect oncogenes in cancer and genetic variants in inherited disorders, it can also provide clinically valuable microbiological information. Ulf Gyllensten, MD, professor of immunology, genetics, and pathology at Uppsala University in Sweden, and his colleagues have used both the Ion Proton (Life Technologies) and the Pacific Bioscience (PacBio) RSII instruments to study the vaginal microbiome in Swedish and South African women, with focus on human papillomavirus genotypes.
"Our results ended up being something other than we thought they would be," Dr. Gyllensten tells CAP TODAY. They found not only HPV but also many co-infections.

"Both of these instruments enable high-throughput screening of vaginal biofilm," Dr. Gyllensten said at the Advances in Genome Biology and Technology conference. In particular, he emphasized the utility of the PacBio RSII, which has not been used much in this setting. "The PacBio generated single reads of entire viral genomes, providing rapid and unambiguous pathogen identification," Dr. Gyllensten said. "The rapid turnaround time makes this methodology suitable for high-throughput pathogen screening in clinical samples."

Dr. Gyllensten and his colleagues do NGS through the National Genomics Infrastructure, a Swedish facility established as a joint activity of Uppsala and Stockholm universities. Initially, they performed whole genome sequencing of samples from hospitalized patients with unknown multiresistant bacteria, where results are needed rapidly to treat the patient and prevent nosocomial spread. With Ion Proton sequencing, medically actionable results can be provided by day four, Dr. Gyllensten says. For instance, they identified an organism that was not resistant to methicillin but had the *mecA* gene missing. Also, they found plasmids carrying beta-lactamase genes.

"We are doing sequencing and submitting these results to clinicians," Dr. Gyllensten says. In Sweden, "If I set up a test and validate it, I can use it," he explains. "I don't need CLIA-type certification."

When they introduced the PacBio platform into this clinical setting, it provided even more rapid, three-day delivery of genome sequences, Dr. Gyllensten says. "Its simplified bioinformatics allow complete bacterial sequence assembly in one contig with a complete genome."

Next they used NGS to analyze vaginal biofilms. Screening for HPV by real-time PCR was introduced in Sweden for some segments of the population in 2011, but the assay delineates only a limited number of HPV genotypes. To get a more detailed picture of the vaginal biofilm, the Swedish investigators used NGS to analyze the vaginal flora of Swedish women and HIV-positive South African women on

antiretroviral therapy. “We need information about co-infections,” Dr. Gyllensten said. This is particularly true for HIV-positive women because infection with HIV increases the risk of acquiring secondary viral and bacterial infections, and methods are needed to determine the spectrum of co-infections for proper treatment. Sequencing of the entire vaginal microbiome met this need.

After identifying known viruses and bacteria by comparison to reference databases, remaining unmapped reads revealed many novel HPV genotypes in these patient samples, as well as plasmids. About twice as many HPV types were identified by NGS as by rtPCR, including two novel types (Ameur A, et al. *Sci Rep.* 2014;4:4398). “The pattern of co-infections varied dramatically, with each woman having a unique spectrum of viral, bacterial, and parasitic co-infections,” Dr. Gyllensten said.

Looking specifically at the performance of the PacBio instrument, Dr. Gyllensten noted that it provides complete full-length HPV genomes in a single read, which aids in genome assembly and annotation. In addition, it allows visualization of the evolution of recombination between viral genotypes. Its main drawback is that its throughput is much smaller than that of Ion Proton and Illumina sequencers.

In general, NGS is “quite an effective tool” for screening the vaginal flora, Dr. Gyllensten says.
He is thinking now of using NGS to identify organisms in blood infections, particularly sepsis. It would provide a more rapid turnaround time than even current molecular methods. “That would be really satisfying,” he says.
—*William Check, PhD*[/box]

Dr. Schadt disputes the belief of some that PacBio machines don’t have sufficient throughput for clinical work. A targeted panel with a few hundred genes, where mainly exons are being sequenced, covers about a megabase of sequence. “We are getting between 500 megabases to one gigabase of sequence data per PacBio SMRT Cell,” Dr. Schadt says, “so enough to cover that megabase of DNA about 1,000 times, enough to reliably detect somatic variants.” With his laboratory’s workflow, Dr. Schadt estimates that with an appropriate bar-coding strategy, he could run as many as 80 samples a day per machine for a panel in the range of 10 genes, or 16 patient samples a day for a panel with a few hundred genes. “The PacBio SMRT technology does not achieve the throughput at this point that an Illumina HiSeq 2500 does,” Dr. Schadt acknowledges, “but that mainly limits its utility in sequencing large genomes, such as whole genome sequencing in humans.”

At Memorial Sloan Kettering, Dr. Marc Ladanyi has introduced the panel called MSK-IMPACT, for Integrated Mutational Profiling of Actionable Cancer Targets. It is based on hybrid capture followed by sequencing on Illumina HiSeq 2500s. “We launched IMPACT in the clinical laboratory as a research assay in January,” Dr. Ladanyi says. “Recently we received conditional approval from the New York State Department of Health to run it as a clinical assay.” He says it is now in “soft launch” mode.

Evaluating accurately the yield of these large panels is difficult, Dr. Ladanyi says. “How hard do you look before you go to an NGS panel? Do you send all cases of colorectal cancer or lung cancer that you would otherwise study? Or only a subset that is negative for all the common mutations?”

Also important to point out, he adds, is that some cancers, such as lung, require multiple different assays on the same small tissue sample. Doing separate assays for mutations, copy number alterations, and gene fusions can take a lot of time and use a lot of tissue. In this context, “it becomes attractive to run a single NGS-based assay that can pick up all those changes at once,” he says.

**Dr.
Ladanyi**

Dr. Ladanyi raises two other issues. First, which genes have clear therapeutic implications, either FDA approved or in process? “Obviously that number is very small, maybe 10 to 20 genes that are immediately and widely actionable. When you have a panel with hundreds of genes, the majority are of exploratory use,” he says.

Second, large panels are efficient from a laboratory workflow perspective. “We can have one assay that includes every gene you might possibly want to know about in virtually any solid tumor, so you don’t have to have multiple different separate assays for every histology of cancer,” Dr. Ladanyi says. “Of course it is a very complex assay,” he adds. “But it does allow you to route any cancer into one common workflow.”

Vanderbilt continues to use several small tumor-specific SNaPshot panels—lung, melanoma, breast, colorectal cancer, hematology, and brain. Panels range from three to 11 or 12 genes, Dr. Mia Levy says, with many variants. “We do track the percent of patients with and without mutations,” she adds. In a recent followup of 200 melanoma patients, 64 percent had mutations detected and went on to gene-directed therapy.
Vanderbilt-Ingram’s panels are limited in size for two reasons. “That is what the [SNaPshot] technology allows us,” Dr. Levy says. And “we do bill for these tests. We want to make sure we are billing for clinically actionable results.”

She draws a distinction between two types of institutions. “Do you have a business model that requires you to be financially self-sustaining from day one? Or do you have a large pool of money where testing is done on a research basis and not billed to insurance? Because those large panels are not reimbursable.

“Over the next 12 to 18 months we will see how this will shake out,” she predicts. “When you have to pay on the order of $5,000 for 200-gene panels for each patient, you can’t [be financially self-sustaining]. What people [in that situation] are banking on is that eventually reimbursement will come, and they are trying to ride the wave until that comes. But it is a gamble.”

Dr. Morrison’s approach to oncogene testing at Roswell Park is similar to Dr. Levy’s. “The size of our [NGS] panel is determined by the knowledge database. Our panel today is 23 genes. That is what the databases support. It is like the old lawyer’s axiom: Don’t ask a question if you don’t know the answer.” In pathology parlance: “Don’t test for something if you don’t know what to do with it,” Dr. Morrison translates. “That goes not just for genes, but for specific variants within a gene.”

A somewhat different question, he says, is what payers are going to reimburse for. “Our decision here is to choose variants that are therapeutic because we believe that is what payers will reimburse for.”

Dr. Ladanyi offers these thoughts about reimbursement. “Right now reimbursement is not for the panel;

it’s for the individual genes that are useful in a given patient. So the size of the panel doesn’t matter to the payer as long as it provides information on the few genes that are critical in that patient.

“I think next year there will be a change in CPT codes, so there could be a CPT code specific for panel testing. My understanding is that CPT codes will cover smaller panels first.

“All this is evolving and hard to predict,” he says.

What he sees happening in the future is a reduced version of these panels becoming more accessible to labs, so instead of 300 or 400 genes it might be 100 genes. “And it may be possible to run in easier ways. That might meet the vast majority of a laboratory’s needs,” he says, “and if that doesn’t work, it might be an indication to send out to a reference lab.”
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