Genetic profiling vies with IHC in retune of CUP testing

Anne Paxton

March 2015—Tesla beats Camry. Online catalogs replace paper. Keurig edges out Chemex. Mobile trounces landline. When paradigms shift, the theory goes, we can only cling to the technology in the outbox for just so long.

But that's a theory that may not apply to diagnostic testing for cancer of unknown primary (CUP). Microarray-based gene expression profiling (GEP) has recently gained a foothold in the quest to identify origins and therapeutic targets for metastatic cancer, but traditional immunohistochemistry is not about to be sidelined. In research and in the field, oncologists and pathologists are still weighing whether GEP has advantages over IHC in diagnosing CUP, or if IHC should continue to retain its central role with GEP serving as an adjunct.

Relative cost, precision, timeliness, and efficiency are among the competing concerns. And they reveal as much about pathologists' changing role in diagnosis, and relationships between pathology and oncology, as they do about scientific advances in diagnosing and treating cancer.

Between three percent and five percent of metastatic cancers are CUPs, generally poorly differentiated tumors that present a diagnostic challenge and often a dismal prognosis for the patient.

"Tumors of unknown primary are a thorn in your daily diagnostic practice. It's a frustrating clinical problem that we all, pathologists and oncologists, face on a fairly routine basis," says Lynette Sholl, MD, assistant professor of pathology at Harvard Medical School and a pathologist at Brigham and Women's Hospital in Boston. "You're kind of treating a black box, and the usual regimens just don't apply, whether you're approaching it from a diagnostic or a therapeutic standpoint."

Immunostains have been the primary diagnostic tool for CUPs for decades. Gene expression profiling came on the scene about five or six years ago, with manufacturers offering to diagnose CUP at a cost of $3,000 and up. The commercial landscape now includes the ResponseDX Tissue of Origin Test (developed by Pathwork which declared bankruptcy in 2013 and was acquired by Response Genetics), Cancer of Origin Test made by Rosetta Genomics, and CancerTypeID made by bioTheranostics.

Dr. Handorf

GEP has had a somewhat hard time catching on, says Charles R. Handorf, MD, PhD, vice chair of the National Comprehensive Cancer Network unknown primary panel and a professor of pathology at the University of Tennessee College of Medicine. Standard-setting organizations like NCCN and the National Cancer Institute have not begun to call for use of GEP in diagnosing CUP. But the dramatic growth of new targeted therapies, some of them for previously hopeless cancers, is intensifying interest in GEP as a tool for finding the targets. "As we get more targeted therapies," Dr. Handorf notes, "it moves us to do a better job of learning the biological behavior and sensitivity of a particular cancer, and not just simply writing it off because it's poorly differentiated or in an advanced clinical stage."

Dr. Handorf, who was first author on a 2013 study comparing GEP and IHC for the identification of the primary site

in metastatic tumors (*Am J Surg Pathol.* 2013;37[7]:1067–1075), believes that early on, the commercial companies making expression assays mistakenly took a combative view of the pathology world. “Instead of trying to work with pathologists on the best use of the assays, they came out, guns blazing, claiming that pathologists do IHC only because they make money doing it.”

“So all these moving parts are going on at the same time. We wanted to see if there was a meeting ground on the interface between IHC and GEP, where maybe one leaves off and the other picks up. That was the focus of our study.”

The multicenter study was prospective. He and colleagues took known primary cancers, presented them to study participants as unknown, then asked pathologists to proceed through their normal rounds of immunostains. “Across the board, with both difficult and easy cases, metastases of all kinds, the pathologists got the right tissue of origin just on the H&E evaluation about 70 percent of the time. They would then get it up to 80 percent after a round of immunostains; further rounds of IHC didn’t improve on that. GEP was able to assign the correct origin about 90 percent of the time.”

One major conclusion from the study was that “after one round of stains you are much less likely to get a definitive answer, so stop and consider using GEP to get an answer,” Dr. Handorf says. That would avoid spending several thousand dollars on a GEP in many cases.

Perhaps more important, he emphasizes: It’s a mistake to consider finding what organ a cancer arises from as the central goal. “We pathologists are trained that way, because there are different treatment protocols directed against the organ if it’s ovarian, breast, or stomach cancer. But we have to realize when we have targeted therapy, it’s therapy against some druggable target, a mutation in the gene sequence of the tumor. So where the tumor comes from is not going to be nearly as important as the mutation that you know the drugs work against.”

In five percent to 10 percent of CUP cases, after all the best efforts, “we still won’t know the primary organ.” But even in some of those cases, “if you can find that druggable target in the genes, you could cure the cancer—it can happen.” This is in contrast to 10 years ago, he adds, when the treatment options were few and the patient would likely survive only a few months.

It’s important for pathologists and the diagnostics industry to work together on CUPs, Dr. Handorf stresses. “The biggest mistake as these tests were being developed—and that’s not pathologists’ fault—is the companies were working at odds with pathologists. It was industry’s miscalculation of how the world really works.”

Cancer of unknown primary could be seen as the epitome of personalized medicine, says Gauri R. Varadhachary, MD, professor of GI medical oncology at the University of Texas MD Anderson Cancer Center. “There is no one designated recipe for first-line/second-line treatment with an unknown primary. Given that the patients’ cancers are very different from each other, there is no primary tumor, and they’re all stage IV presentations,” each case is unique, she says.

Dr. Varadhachary

The lack of a systematic, tiered approach to conducting IHC is a chronic issue in pathology, in her view. “The stains today do tend to be a little all over the place,” says Dr. Varadhachary, who has been studying CUP for the past 15

years. “The pathologists are very removed from the clinician who is seeing the patient, and they get a small piece of tissue without any history or additional data. So some do too many stains, some don’t do enough, some don’t do the right ones. There isn’t any clarity on how it should be uniform, but it would benefit all of us to really understand how we can use the least number of stains to get the most out of it.”

Exhausting the tissue is only one of the dangers. “The more complicated the diagnosis, the more undifferentiated the tumor, the more stains we seem to do. But we really don’t learn more from that.”

Wayne J. Lennington, MD, coauthor of another study finding that molecular profiling complements IHC for CUP (*J Natl Cancer Inst.* 2013;105 [11]:782–790), agrees. “That’s one of the things that was really apparent from our study, because we saw material from a large geographic area, many different practices. People are all over the board with what they order and what they don’t. If you don’t have a refined, almost standardized approach to how you deal with these things, you’re going to miss some tumors that you could identify,” Dr. Lennington says.

Bigger and more academically oriented practices tend to be more uniform. “Certainly some practices don’t see many tumors that fall into this category, and smaller practices may not have the kind of immuno capability that larger ones do, so they tend to be more rudimentary in their ordering practices, which makes it tougher to identify less well differentiated tumors,” he says.

When Dr. Lennington was in training, “we would order 50 immunostains on a case, just to have it or to see how it worked. You can’t do that anymore. You have to think about what you’re going to order, to try to tailor it so that you have tissue you can still use and you don’t end up having the patient re-biopsied just to get tissue for molecular profiling.”

Dr. Lennington, who practices with Associated Pathologists (PathGroup) in Nashville, says one of the goals of his study “was to show pathologists this [molecular profiling] is a tool you can use, but it’s certainly not the be-all and end-all. We’ve had some cases where molecular profiling was really, really helpful, and we’ve probably had an equal number of cases where it was virtually no help—in particular for sarcomatoid carcinoma or carcinomas with metaplastic changes. I generally try to stay away from GEP on those kinds of carcinomas because the tumor profiles tend to segregate them into sarcomas, and morphologically that’s clearly not what they are.”

In Dr. Varadhachary’s own practice, she says, “I look at the IHC, I look at the patient’s overall presentation including risk factors and imaging, and if there is significant room for doubt about the working diagnosis, and I believe the patient is going to have several options of therapies, I integrate tissue-of-origin testing in that patient. It’s not cheap and it’s not for each patient who walks through the door.”

Her previous research focused primarily on abdominal CUP cancer presentations. “If you take all the patients who present with CUP to my clinic, which is based in the Department of Gastrointestinal Medical Oncology, more than half of them have a cancer process involving either liver and/or the lining of the bowels.” Based on IHC—and in some patients, molecular assays—patients diagnosed with an intestinal profile now have many more therapy opportunities than 10 years ago, she says. “We use colon-cancer–like drugs and they tend to have a more favorable outcome.”

The premise of gene expression profiling is that metastatic tumors have molecular patterns that match their primary origin. “That’s not proven, but it is extrapolated from other cancers,” Dr. Varadhachary says. “If you look at nodes from breast cancer patients, their genetic signature will resemble the primary. So because metastatic cancers do tend to retain some part of the primary signature, one can probably apply the same to CUP.”

“There’s sometimes a discordancy that we see as CUP clinicians that makes CUP diagnosis both intriguing and confusing,” she says. “For example, you might have a patient, chronic smoker, with a chest mass that looks like lung cancer on imaging, but then you do IHC and that is non-specific and negative for lung cancer stains, and a genetic molecular profiling test suggests an intestinal cancer. That’s where the discordancy comes in. The clinical presentation fits lung cancer, endoscopy and colonoscopy do not reveal a primary, and additional tools tell you it’s something else. Which one do you believe? We are sometimes at such a crossroads with these presentations.”

Fifteen or 20 years ago, it didn't matter that much, because there were limited options, and everyone got the same treatment, Dr. Varadhachary adds. "But today we have more and more subclassifications of cancer and the therapies can become more specific."
She believes there has to be greater integration between oncologists and pathologists. "I had never heard of going straight to GEP in practice, but for several of the patients who come to see me, the oncologist has already ordered the gene profiling test." Pathologists may need to adapt to this changed environment. "If pathologists believe they are doing too many IHCs to get some level of confidence in placing the lineage of the cancer, they can stop early, do additional tests like mutational profiling or tissue-of-origin profiling, then come back to perform additional IHCs later."

The clinical utility of GEP in increasing life expectancy of patients, in her view, remains to be seen. "Also, there tends to be some hype in believing that next-generation sequencing is clearly the wave of the future. That is absolutely a wave we want to ride, but the question remains exactly what impact it's going to have in the quality and duration of life of our patients. On that point we are still in the trial design phase and will have to wait for the outcome phase to have some answers. How the therapies are going to be different is what we're teasing out right now."

It may be that the putative primary site isn't critical to treatment. "The unknown primary situation may be unique in a way, but not unique enough that you need to make the distinction," Dr. Varadhachary says. Her own current research on CUP, still in the planning stages, will be less treatment based and more translational biology based. "We want to leapfrog into looking at circulating DNA in the blood to see if that gives us better information than the tumor tissue to determine the tissue origin and the mutational profile, and to inform therapies." This "liquid biopsy platform" for unknown primary would be much easier for patients and allow more real-time testing, but it's in its infancy, she adds.

Too frequently, pathologists adopt the stance that "here's a tumor of unknown primary, let's start with a large panel of IHC markers," says Fan Lin, MD, PhD, director of anatomic pathology at Geisinger Medical Center, Danville, Pa.

Dr. Lin

Lack of standardization and uniformity is one of the obstacles to the appropriate use of IHC, and his recent paper is an effort to further discussion of IHC standardization and the concept of best practices of diagnostic IHC (Lin F, et al. Arch Pathol Lab Med. 2014;138[12]:1583–1610). "But I don't think there is an easy answer for this question; it doesn't happen overnight. We are making progress," he says.

Dr. Lin praises the CAP's standards for validation of IHC antibodies, requiring 10 positive and 10 negative tissues for testing to validate a new antibody before applying it to patient care (20 positive and 20 negative tissues for predictive markers). "This kind of initiative has never happened before. In the past, many IHC labs did things based on their own experience." However, he points out, validating can be challenging for small laboratories that may have trouble getting 10 or 20 positive tissues for controls to optimize their antibodies. "Standardization of diagnostic IHC panel for a certain differential diagnosis will be the next challenge," he says.

Dr. Lin believes the triple test—correlating clinical findings, imaging, and histomorphology—is still fundamental and essential, and it's imperative for pathology to use it. But "how to have the smallest IHC panel, containing the most

organ-specific antibodies, to tackle a differential diagnosis based on the so-called triple test is a key question," he says.

At Geisinger, "We're probably lucky. We have a very good working relationship with oncology because of the weekly tumor conferences covering pretty much every organ, and this has been going on for many years." Nevertheless, he finds that oncology often pushes for something new that might not be fully validated, especially molecular testing. "Most medical oncologists are very up to date. They usually go to the ASCO meetings and may even bring back new markers, but many are research use only."

In his view, molecular testing is not ready for prime time in identifying CUPs because of its lack of diagnostic specificity for challenging cases, longer turnaround time when compared with IHC, and lack of cost-effectiveness.

Could genetic profiling ever replace IHC? "Unlikely," Dr. Lin says. "IHC will still be retained as primary screening for challenging cases of CUP. Molecular technology will continually bring more and more of these organ-specific markers, and we can apply these markers to tissues of unknown origin. But I don't think molecular testing alone is going to solve the problem."

In the mid 1990s, he recalls, "The first time we posted a cDNA microarray, people became excited and panicked, especially people in training. They said, 'There will be no surgical pathology jobs because molecular technology is taking over.' But now we're 20 years later and it didn't happen."

So IHC in his view will continue to be worked up in determining primary sites of undifferentiated tumors, especially for undifferentiated carcinomas. "New molecular technology such as RNAscope [Advanced Cell Diagnostics] will improve the diagnostic sensitivity of certain organ-specific markers, if validated clinically." Ideally, he would like to see further research to discover more organ-specific markers like TTF1, GATA3, SATB2, OCT4, PAX8, and SOX10 or markers against specific genetic alterations like BRAF, IDH1, INI1, TFE3, E-cadherin, mismatch repair proteins (MLH1, PMS2, MSH2, and MSH6), and ALK. But, he points out, "Even if we have a cancer of unknown primary, the important question is what is the cancer signal pathway and what are the treatment options for this patient." More time and resources should be spent, therefore, on discovering new signal pathways instead of focusing on how to work up undifferentiated tumors.

Next-generation sequencing is routine at Brigham and Women's Hospital and Dana Farber Cancer Institute because an institutional initiative makes NGS a priority in tumor management. "We perform a 300-gene NGS panel of essentially any tumor type for any cancer patient who walks in the door," Dr. Sholl says. "It's a pretty unbiased approach to try to understand how sequencing can help with clinical management of tumors."

Dr. Sholl

NGS, however, is not proving to be a magic bullet in CUP. The long turnaround time for hybrid capture NGS limits its incorporation into routine clinical practice, Dr. Sholl says. "If they're waiting on you to make a diagnosis to initiate therapy, hybrid capture NGS is probably not the way you want to go."

Nevertheless, her practice has found that in a small subset of CUPs, NGS can reclassify tumors. In one case, for example, the pathologists were able to reclassify a tumor as a gastrointestinal stromal sarcoma, even though it was outside the norm of expected morphologies, because they were able to find an activating KIT mutation. "But if you have a poorly differentiated tumor that simply cannot be characterized using conventional IHC or morphologic criteria, it's relatively rare that this NGS approach allows you to characterize it further."

For diagnosing CUP, the genomic profiling doesn't stand on its own. "I think there has to be a complete package," Dr. Sholl says. Managing the data from all these genomic studies is very difficult, and using them to comprehensively classify something can be difficult as well. "It depends on the context, so the meaning of a BRAF mutation, for instance, is very different if you're looking at a melanoma versus a colon cancer."

The entire medical infrastructure is built around a system of traditional morphologic classification, Dr. Sholl points out. "I think that will slowly change. For instance, in hematopathology, we've seen a lot of reclassification based on translocations that are present within a morphologically similar spectrum of acute myeloid leukemia, and that's helping guide very specific, precise therapies in these subgroups with AML. And something similar is beginning to happen in the solid tumor space."

The gene expression profiling approach can be powerful, Dr. Sholl says. "It's unbiased, and if you're operating in the realm of zero data because nobody put any information on your specimen requisition sheet, unbiased analysis can be helpful."

On the other hand, having the opportunity to use professional judgment through choosing different immunostains is valuable for pathologists, she says. "If you have an a priori differential in your mind that may or may not be correct, you could definitely go down the wrong route, so there's a lot of wiggle room in the type of judgment used in terms of IHC." The lack of uniform proficiency testing in immunohistochemistry labs means that in her practice, when a consult case comes in, "oftentimes we will request material to repeat the immunostains, if they show unexpected results, because we simply don't know if we can trust the quality of the stains coming out of the referring laboratory."

"IHC is an incredibly powerful tool. It's fast, pretty easy, and if you have a well-controlled laboratory, very reliable and reproducible," Dr. Sholl emphasizes. The cost of a gene expression profile or NGS is also far more than IHC. "But if I think I need to run 30 immunostains, then the cost differential begins to converge. In difficult cases, the cost and the turnaround time can be similar."
There is certainly a role for GEP somewhere in the average diagnostic workup of CUP, she says. "But in most cases, if you have some clinical context and you have the IHC lab, you can generate a diagnosis that's going to be sufficient for the oncologist to make a treatment decision."

With both GEP and NGS, there is still a subset of cases that simply do not have a specific profile, she says. "That's just a biologic fact. The tumor has gotten so undifferentiated, or you might say it's acquired enough of a stem-cell–like phenotype, that it no longer has enough differentiation markers for us to figure out where it came from."

She has been involved in projects in which oncology groups are driving sequencing initiatives. "But in many cases, ultimately what they'll come back to in terms of a gold standard for verifying, say, the functionality for a particular mutation in a gene is they want to know what's the IHC output. They want to see what's happening on the protein level."

Many outside the pathology laboratory may think that NGS or comprehensive genome testing is going to solve all our woes, she says. "But we're realizing that's not going to be the case. For example, if you're seeing a mutation and don't know what it means but you can correlate it back to the over-expression of that protein, that's pretty good evidence you're dealing with something potentially important in that tumor."

"We're beginning to recognize there are potentially targetable alterations in CUPs even when we can't assign them to a particular origin," Dr. Sholl notes. "So the question will be: Are CUPs going to be equally responsive to targeted therapies if you do in fact find a target? Are all these alterations that seem targetable just markers of genomic instability or markers of a lot of high mutational burden in these tumors, or do they mean something is driving that tumor that you can shut down by targeting those particular alterations?" She says there was very little shift in survival in lung cancer, for example, until there were targeted therapies that were effective in patients with EGFR mutations; then the shifts in the survival curve were dramatic.

"GEP is only as good as the material that goes into the tube," Dr. Sholl says, noting that looking at the whole

package is what's most important. "None of the information that you derive from any of these tests can be taken in a vacuum. The role for pathology is A: to give you sort of a general categorization, and B—and I think this can't be overestimated—quality control and synthesizing all the data. Ultimately, integrated pathology is the way we're going to deliver the best diagnoses to the oncologists, and it's going to permit them to provide the best care therapeutically to the patients."

At Rhode Island Hospital in Providence where Murray Resnick, MD, PhD, is director of anatomical pathology and GI pathology, oncologists have ordered 10 or 15 GEPs from Pathwork or bioTheranostics in cases of CUP. But he's been unimpressed with the genetic profiles' utility. "None of them really helped in the workup, other than one or two that just pretty much confirmed what we were saying based on the immunohistochemistry and the pathology."

Dr. Resnick

"There are certain organ systems like colon, kidney, and liver where IHC is very helpful, and others such as pancreas, gastric, or bladder cancer where IHC can only go so far. But if you look at the GEP results, the companies are having troubles with the same cancers that IHC has trouble with; both have relatively low sensitivity."

A big problem with CUP is that it's hardly ever known for sure, even retrospectively, what the primary was, Dr. Resnick points out. Clinically, the origin of only five to 10 percent of CUPs will be discovered in the patient's lifetime, "and autopsies, while they might be helpful, are not being performed as frequently anymore. So there is no definitive answer in the majority of those cases."

Dr. Resnick, a professor of pathology and laboratory medicine at Brown University School of Medicine, still advocates a good comprehensive IHC panel. "I haven't been convinced that GEP has reached the point where it can replace IHC." Furthermore, he says, "novel antibodies continue to be developed, increasing the sensitivity and specificity of IHC."

"Going forward, I doubt IHC will be the ultimate answer. The problem with GEP, though, is that the profiles are based on a set number of tumors from each of the wide variety of cancers out there, and you really need a huge number of cancers to create these expression panels, plus a lot of the panels were based on well-differentiated tumors, whereas a lot of CUPs are poorly differentiated and probably not the same animal. CUPs are unknown for a reason: They're behaving differently biologically or don't look like their organ-specific counterpart."

Similarly, the two good studies in which GEP was compared back to back with IHC involved known primaries that were given to pathologists as CUPs, Dr. Resnick points out (Handorf CR, et al. Am J Surg Pathol. 2013;37[7]:1067–1075; Weiss LM, et al. J Mol Diagn. 2013;15[2]:263–269). Even so, in those studies, the results for IHC were as good as or even better than GEP for certain tumors.

He agrees with the conclusions of those studies to a certain degree. "When dealing with a poorly differentiated tumor, if the IHC is inconclusive, it may be worth giving GEP a shot because the accuracy in these studies was better for the poorly differentiated tumors using GEP than IHC. However, once nine or more IHC stains have been run, more stains will probably not be very helpful."

He says its important for pathologists to know when to stop ordering stains and conserve tissue, "and if it's still an enigma and really matters to the oncologist, then maybe it's worth doing the GEP." But he also believes in

community hospitals, where IHC support is not as strong as in academic institutions, oncologists may be pressured or influenced by the companies to send the case out for GEP. “I’m absolutely sure there are more sendouts in non-academic practices than academic practices,” Dr. Resnick says.

At this point, guidelines from the National Cancer Institute state that GEP is not part of the standard workup for CUPs but it might be considered, Dr. Resnick notes. “The latest recommendation from NCCN, which includes pathologists involved in GEP analysis on the committee, state clearly that GEP for tissue of origin is ‘not recommended’ for standard management at this time.”

He doesn’t consider the relatively high cost of GEP the major factor. “If you look at the total amount of money spent on the workup on these patients, between CT scans, MRIs, biopsies, and treatment after that, what’s $3,000 when you’re talking about tens of thousands? Not to mention the tens or hundreds of thousands of dollars in targeted therapy or chemotherapy, so $3,000 in the grand scheme of a workup on an oncology patient is not a lot of money.”

Dr. Resnick doesn’t know how the companies that created GEP algorithms plan to improve them or how they see their field moving forward. “The problem with genetic profiling is these are relatively rare tumors, and the study published by Hainsworth, et al., is probably as large a study as you can perform. The bottom line in that study was that the overall survival for those included was 12 to 12.5 months, and if you look at other published studies, they show around nine, some 12, and some are 13 months (Hainsworth JD, et al. J Clin Oncol. 2013;31[2]:217–223). So they really don’t show a huge improvement by using GEP, and maybe that’s why some of the hype from these tests has kind of diminished.”

Dr. Lennington has found that pathologists and oncologists are working more closely together than ever. “I talk to my oncologists multiple times a day about multiple cases. We’re sort of the information gatekeepers with regard to their prognostic markers.”

Still, he thinks molecular testing does present a certain risk to the profession of pathology. “The truth is if pathologists don’t get on board and get active in the process, oncologists are going to find somebody to help track down the results, make sure things get sent where they need to, collate molecular results, and so on. They’ll hire a study coordinator to do that or contract with another molecular company, and at that point the pathologist just becomes a tissue manager.”

Pathologists are good at categorizing tumors and identifying tissue of origin. “We’re a lot better at that than we were even five or six years ago, and that will help decide what molecular profiles are studied or evaluated,” Dr. Lennington says. Going straight to whole genome testing is problematic. “We could do that, but then you’re sorting through a lot of information that’s not actionable to find 50 or 60 genes that are actionable. At some point that could be the standard, but I don’t think we’re there yet.”

GEP is not cheap and you have to have a high certainty from the test to have something actionable, he adds. “Our general rule is if there was an 80 percent or less certainty with a GEP study, then it probably wasn’t worth paying attention to. It needs to be above 80 percent before it’s helpful information.”

In reviewing pathology cases for CUP, his group has noticed that about 10 or 15 percent appear more obvious in retrospect but fell through the cracks when they were reviewed initially. “One of the sites that frequently came up was urothelial carcinoma. For whatever reason, people tended not to consider that primary with distant metastases, and didn’t approach the case with the markers specific for urothelial carcinoma. The same is true with mesothelial neoplasms in the pleural and peritoneal space.”

It’s a lesson in keeping an open mind with regard to what a tumor could be, Dr. Lennington says. “It’s easy to decide you think you know what it is and order your immunostains accordingly. But if you’re not careful, you can be running down the wrong track.”

He hopes there will be continued progress in developing more specific immunostains. “We’ve got some immunostains that are more readily applicable to different tumors like PAX8, and we’re on the cusp of making

breakthroughs with regard to therapeutic options for patients," if cost doesn't stymie the efforts. But he doesn't think the mystery of CUPs is about to be solved. "Molecular profiling helps; the new immunostains help. But I don't know that we'll ever get to zero on tumors of unknown primary," Dr. Lennington says.

Diagnostic tools for CUP are in a transitional phase, Dr. Varadhachary says. "We are trying to understand the role of cellular context which is informed by IHC and GEP. But does that matter? Could we disregard that and move straight to molecular and genomic tools that suggest actionable and driver mutations? That's the burning question today, and we haven't answered it. There are trials looking at this question in known cancers, and those can be extrapolated to cancers of unknown primary to a certain extent. I'm hopeful we will have some answers in the next five years. We have these various tools available to us, and we need to learn how to use them in an optimal way so that we are most effective in making a difference in our patients' lives."
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