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Network Enlists Practicing Oncologists to Develop Plans

Tony Hagen

Years ago, it might have been enough for an oncologist to go onto a golf course with other physicians from the community and, during a round of 18 holes, cement a deal to refer patients and gain referrals. These days, the talk is all about value and outcomes, and every physician is on the hook to measure up against those 2 variables. Physicians are carefully evaluating potential partnership and referral deals to ensure that whatever they do is perceived as aligned with delivering better, more efficient care, according to Kathleen Lokay, president and CEO of Via Oncology, a pathways developer.

These days, an oncology specialist's partners in care delivery "want to make sure you're not only someone who will take care of patients but that you're thoughtful about resources," Lokay said during a presentation on treatment pathways at the 2017 Patient-Centered Oncology Care Conference (PCOC), held in November in Philadelphia, Pennsylvania.

Via is a Pittsburgh, Pennsylvania, company that says it has created a network of 1500 providers in 27 states that shares a system of oncology treatment pathways that can help to standardize care along lines of evidence-based medicine and reduce what has been labeled in the profession as unwarranted variation—tests and procedures that add little or nothing to the treatment outcome.

The pathways are developed through an extensive system of physician committees that meet frequently throughout the year to review pathway choices, make sure they are up to date with the latest clinical findings, and develop new pathways. The theory is that being able to demonstrate pathway compliance will improve synergies with payers, smooth out the payment and treatment authorization process, and preserve a level of physician autonomy in treatment selection. "Practices are certainly getting a lot of pressure from the commercial payers to deliver something in the way of value," Lokay said.

In her presentation at PCOC, Lokay discussed progress in the evolution of pathways and some of the lingering issues. Pathways clearly are the wave of the future in oncology care, and after a

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period of slow adoption and acceptance, they have gathered a great deal of momentum in just the past few years. Development of national standards, systems of accreditation, and incorporation of real-world data in pathways formulation remain objectives that have yet to be realized, she said.

Via has a system of 36 physician committees that meet to develop pathways. This gives many providers an opportunity for buy-in, and it improves the chances that physicians will adhere to pathways, which is critical for success of these programs, Lokay said. At Via, a top-down approach to development of pathways in which nationally recognized experts are the authors of these guidelines was rejected in favor of a model in which the physicians who are users of the pathways are contributors to it. There were pros and cons to that selection.

"We don't necessarily have the best name in a certain disease on our pathway, but we have someone who's an expert and who also uses those pathways. We like that because it builds in accountability. It makes those physicians who are contributing to those pathways think about what they're doing," Lokay said.

Although it is difficult to coordinate these meetings and have people participate from different time zones, there is not a week in the year aside from the Christmas holiday that these committees are not holding sessions, Lokay said. When there is a particularly important development in oncology—something groundbreaking— they'll schedule another meeting to ensure that the findings are considered for possible incorporation into the treatment methodology.

Role of ASCO

The development of clinical pathways has been of great concern to the American Society of Clinical Oncology (ASCO). In the past several years, ASCO has issued consensus reports on the high levels of confusion and administrative burden that the proliferation of pathways has caused. ASCO has stated that physicians have had to contend with as many as 8 different pathways for a single disease category owing to the diversity of payers and payer policies for approval.[1] The organization has sought to bring clarity and logic to the process by developing a set of guidelines for the formulation of pathways, while acknowledging the savings and reduction in unwarranted variation that pathways can contribute to the oncologic treatment process (**TABLE**).[1]

There are limitations to coming up with an ideal set of pathways. There remains the problem of insufficient interoperability among electronic devices. Ideally, pathways would interface with the patient's electronic health record (EHR) and pull data from it to provide physicians with a more seamless data analysis and treatment selection process. Lokay said that the plethora of EHRs currently in use makes that an elusive goal. "When we think about pathways, we think about digital decision support. The first input has to be content. You have to have some way of turning that content into decision support. The software has to be able to interface with other systems, and you have to have the ability to collect data as you go along."

A second challenge is matching real-world practice to the clinical data sets used in the development of pathways. Lokay said there is a place in pathways for data collected from actual clinical practice and from the type of

Table. ASCO Recommendations for Clinical Pathways in Cancer Care[1]

- A collaborative, national approach is necessary to remove the unsustainable administrative burdens associated with the unmanaged proliferation of oncology pathways.
- The process of developing pathways should be consistent and transparent to all stakeholders.
- The full spectrum of cancer care should be addressed, from diagnostic evaluation through medical, surgical, and radiation treatments, and include imaging, laboratory testing, survivorship, and end-of-life care.
- Plans should promote the best possible evidence-based care in a manner that is updated continuously to reflect the rapid development of new scientific knowledge, as well as insights gained from clinical experience and patient outcomes.
- Pathways should recognize patient variability and autonomy, and stakeholders must recognize that 100% concordance with oncology pathways is unreasonable, undesirable, and potentially unsafe.
- Care plans should be implemented in ways that promote administrative efficiencies for both oncology providers and payers.
- Education, research, and access to clinical trials should be a pathways objective.
- Robust criteria must be developed to support certification of oncology pathway programs. Pathway programs should qualify based on these criteria, and payers should accept all oncology pathway programs that achieve certification through such a process.
- Those who develop and use pathways, along with private and governmental funding agencies, should support research to understand the impact of pathways on care and outcomes.

patients whom physicians normally see—not just the relatively healthy ones who participate in clinical trials. "What we really need to do is make sure that real-world evidence has the same kind of veracity that published trial data do. I can see a world of the future where those data become one of the inputs that committees look at and incorporate, but we're just not there yet."

Real-world data could also play a huge role in the understanding of toxicities. Such information could tell physicians whether additional pathways need to be constructed to account for patients with sensitivities to medicines that warrant extra options for care, Lokay said. "I think real-world evidence is something we will incorporate over time," she added.

There is uniformity in thinking among physicians when they are first approached about the subject of implementing pathways, Lokay said. "Before they say anything else, every one of them says, 'We want to make sure we're giving quality and measuring that and proving that.'" This has a lot to do with the direction oncology payment and delivery models are taking.

CMS is increasingly nudging practices toward models of integrated care in which payment is based on achievement rather than the standard fee for service. "There is absolutely a secondary goal here that is economic," Lokay said. One challenge is keeping up with the fastpaced world of medical oncology because that is where change is happening most rapidly.

Surgical and radiation oncology do not see as many groundbreaking developments. Still, it's important to bring representatives of these disciplines to the discussion table because they, too, have a role in developing pathways, although getting physicians and other specialists to agree is sometimes an issue. Nevertheless, integrated, multidisciplinary care is the future of oncology care, and pathways need to go there too, Lokay said.

Pathways Gain Acceptance

Via has been at work for more than a decade on the complex problem of developing pathways, but until recently, these efforts were ahead of their time, Lokay said. The impetus in terms of a willingness to follow through was not there. Now payers are pushing hard for pathways because they recognize the savings that can accrue. And whereas it was difficult to formulate pathways in the beginning, it has become more so because of new lines of care and the need to look more closely at the evidence. "We've learned that the pathways have to be much more nimble—what makes a second-line treatment for 1 patient is not going to be second-line [treatment] for another patient. It gets more and more complex with the permutations you have," Lokay said.

Along the way, Via has realized that it can't make pathways as restrictive as it was doing before. For example, some patients want to take only oral drugs. "We found that we were being too strict with everyone. We tried to be really super, super narrow. We had to make sure that common patient preferences were accommodated," Lokay said. Another example of how pathway options had to be relaxed is found in fourth-line treatment of breast cancer. There are too many permutations in this disease stage for there to be 1 overriding pathway, she added.

The other big eye-opener was learning to understand that even innovations that lead to positive results may not be embraced by the physician community, especially if added work and complexity are involved. "Don't even think for a moment that there's an oncologist who gets up in the morning and says, 'I want another piece of software, and I want it to tell me what to do, and then I want my readership to see if I actually did it.' We're up against those 3 things every day," Lokay said.

Many of Lokay's points are embodied in a set of guiding principles for pathway development formulated by ASCO and released in March 2016.[1] That includes an ASCO point that 100% conformance with pathways should not be a goal because there are often legitimate reasons for variance. Indeed, in the statistics Via has reported for its own pathways, physician adherence rates differ widely among the major cancers, and this is because it is more difficult to achieve conformance in some cancers than in others, Lokay said.

Another issue is the potential for adoption of a single pathway program across private and public payer systems. There are advantages and disadvantages to the establishment of widely accepted standards for pathways in oncology. Prior authorization requirements potentially could be waived for pathways conformance, and payment processes would move faster. However, in a paper released in March 2017, ASCO raised the concern that standardization could stifle innovation.[2] Also, regulation would likely be involved in any broad-based system, leading to slow and cumbersome bureaucratic processes, ASCO wrote. ■

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Precision Medicine in HER2+ Breast Cancer Treatment Is Essential

DANIELLE BUCCO

Precision medicine is vital in delivering optimal and individualized care for patients with HER2-positive breast cancer.

Specifically, this type of approach was investigated in the NSABP B-47 trial, which aimed to determine the value of trastuzumab (Herceptin) plus standard adjuvant chemotherapy in patients with low levels of HER2 protein. This trial's findings showed no significant efficacy, demonstrating the importance of targeting treatments for patients based on their genetic mutations, explained Mothaffar Fahed Rimawi, MD, in an interview during the 2017 San Antonio Breast Cancer Symposium (SABCS).

In the NSABP B-47 study, which was presented at the meeting, results showed that the 5-year invasive disease-free survival rate was 89.6% among the 1640 patients who received trastuzumab and 89.2% among the 1630 patients who did not (95% CI, 0.77-1.26; *P* = .9). Investigators said the findings were no different whether patients were subdivided by HER2 immunohistochemistry level, extent of lymph node involvement, or hormone receptor status.

Rimawi, associate professor, Baylor College of Medicine, medical director and director of clinical research at Baylor's Lester and Sue Smith Breast Center and the Smith Clinic/Ben Taub Hospital, and co-leader of the breast program at Baylor's Dan L. Duncan Cancer Center, discussed the significance of precision medicine in HER2-positive breast cancer, as well as the possible role of immunotherapy for this specific population.

CURE: What is the importance of precision medicine in HER2-positive breast cancer?

Rimawi: [At SABCS] I discussed the research that is shedding light on HER2-positive breast cancer, including mechanisms of resistance, sensitivity, and the efforts to tailor treatments to the individual patient.

I moderated 2 sessions where a panel of experts received challenging cases from the audience and provided treatment recommendations based on the latest available evidence. These contributions show the strength of this [medical] meeting, where science and clinical medicine come together to push forward patient care by utilizing the best possible care models and the best science.

From your perspective, what was the most exciting advancement in the field of breast cancer in 2017?

It is hard to pinpoint 1 thing. In my opinion, the most impressive thing about breast cancer is the incremental improvement in patient outcomes that have been ongoing year after year. Although a small increment does not sound exciting, when you add those up with different treatment modalities for years, we are seeing the mortality from breast cancer going down and women are living longer, healthier lives.

You see 3 different levels of improvements or achievements. One involves very robust meta-analyses where clinical trials from all over the world pool their data together. When that happens, there are 10,000 women treated with similar treatments and followed for 10 to 20 years. Powerful data have shown us that giving patients the treatments that we know work, such as chemotherapy for higher-risk patients and endocrine therapy for estrogen receptor (ER)-positive patients, are continuing to make a difference in the lives of women. We know that giving the chemotherapy on a more dose-dense schedule has robustly demonstrated to improve outcomes for these patients. The power of collective knowledge is one area of achievement.

The other area is the strength that we are seeing in precision medicine. Multiple trials have reported showing that we need to target the right treatment to the right person. The NSABP B-47 trial that was reported at SABCS sought to determine whether anti-HER2 therapy with trastuzumab would be beneficial to women who have lower levels of HER2 expression.

This trial would be considered negative under clinical standards but, the question was, "If they have some level of HER2 expression, would they benefit from anti-HER2 treatment?" This trial showed conclusively that it is not the case. You need to target anti-HER2 treatment to those who are HER2-positive and extending a treatment that works well for 1 group of patients to other patients may not work. That is a win for precision medicine and for the idea that it is important to tailor treatment to the patients.

The third area that is exciting is we are still seeing a robust flow of data from new agents that are in development. We are seeing many trials focusing on the immune system and how to best stimulate it or reprogram it to fight cancer with a lot of promise. There are many other agents for other pathways that are being explored.

We need to understand the biology of the tumor and the patient, and then focus the treatment that way. Hopefully, those achievements will continue year after year.

Moving forward, what role will immunotherapy have in the treatment of patients with HER2-positive breast cancer?

The idea of using, or reprogramming, the immune system or stimulating it to fight cancer has been a dream that many people were following. The introduction of checkpoint inhibitors in many cancers over the last few years has been making a difference for the treatment of patients with cancer.

In breast cancer, there has been a robust interest in the immune system and immuno-oncology agents. Due to the clinical unmet need in triple-negative breast cancer, there is a focus of immunotherapy there because, biologically, those tumors have a higher mutational load and are more immunogenic. There is also interest in other subsets of breast cancer like ER-positive breast cancer.

There is going to be a role for immunotherapy for HER2-positive breast cancer. There are many agents that are being studied in several settings and in combination with other agents. We will see that there is a subset of patients with breast cancer who benefit from immunotherapy. Who those patients are with HER2-positive disease is something that remains to be determined based on our understanding of the biology and the impact the treatment is making. I am optimistic that the future of immune-oncology is bright. ■

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Potentially Transformative Treatments Emerge in Pancreatic Cancer

Caroline Seymour

Antistromal agents, vitamin D analogs, high-dose intravenous (IV) vitamin C, and immunotherapy agents are just a few therapeutic strategies currently being investigated in pancreatic cancer, explains Allyson Ocean, MD.

Targeting the tumor stroma led to encouraging data in a randomized phase II trial of patients with untreated metastatic pancreatic ductal adenocarcinoma who received nab-paclitaxel (Abraxane) and gemcitabine with or without PEGPH20 (pegvorhyaluronidase alfa).

The triplet was associated with significantly better progression-free survival (PFS) than nab-paclitaxel/gemcitabine alone (6.0 vs 5.3 months; HR, 0.73; 95% CI, 0.53-1.00; *P* = .048). When investigators stratified patients by hyaluronic acid (HA) expression, PFS in HA-high expressers was also improved with the triplet regimen versus the doublet (9.2 vs 5.2 months; HR, 0.51; 95% CI, 0.26-1.00; *P* = .048).

Ocean spoke to the development of these novel therapeutic regimens in the pancreatic cancer paradigm in a presentation at the 2018 *OncLive*® State of the Science Summit™ on Gastrointestinal Cancers.

In an interview during the meeting, Ocean, a medical oncologist and attending physician in gastrointestinal oncology at Weill Cornell Medicine/NewYork-Presbyterian Hospital, medical oncologist, The Jay Monahan Center for Gastrointestinal Health, associate professor of medicine, Weill Medical College of Cornell University, gave a glimpse of these emerging treatment strategies in pancreatic cancer.

OncLive: Please provide background of your lecture on the evolution of pancreatic cancer treatment.

Ocean: Regarding therapies, I gave background on what exists today in terms of standard of care, metastatic disease, first-line therapy, second-line therapy, sequencing regimens, and the data that led to their approvals as standard regimens.

I also spoke about what's on the horizon with regard to newer therapies in terms of categories. One of the categories targets the stroma, and a main reason why patients with pancreatic cancer progress, is because the therapies cannot penetrate these fibroblast-enriched stromata that are devoid of immune cells.

I spoke about some emerging antistromal agents, including PEGPH20 and vitamin D analogs, and also touched

on immunotherapy agents that are being tested now. I spoke about my own research at Weill Cornell Medicine involving high-dose IV vitamin C in *KRAS*-mutated cancers. I finished with some precision medicine topics in targeted therapies such as BRCA-mutated cancers and other targeted pathways that we can approach with newer therapies.

How will these therapies affect the patient population?

If there is a drug that is successful at targeting the stroma, it's going to affect all patients with pancreatic cancer. This is related to the ongoing phase III PEGPH20 clinical trial looking at PEGPH20 in combination with gemcitabine and nab-paclitaxel. That is showing more promise in tumors that are HA–positive. This population of patients, approximately 25% of the overall patient population, did better in the phase II studies with that combination.

What are some of these emerging targeted agents?

The first one I spoke about is in the vitamin D analog category. We know from the research of Ronald M. Evans, PhD, at the Salk Institute for Biological Studies, that the vitamin D receptor is very important in the stroma. The activation of the vitamin D receptor relates to the pancreatic stellate cell, which is responsible for the immune cross-talk and signaling that happens within pancreatic cancer in the stroma. Research has shown that inhibiting the vitamin D receptor with vitamin D analogs can turn the stellate cell into a less active cell. This can ultimately bring more immune cells into the stroma and allow for better penetration with chemotherapy.

In relation to the *BRCA*-mutated cancers, there are ongoing investigations using PARP inhibitors. These medicines are already approved for *BRCA*-mutated breast and ovarian cancers. Because the pathway is similar in pancreatic cancer, we hope to get positive data using PARP inhibitors in pancreatic cancer and also in combination with chemotherapy. Right now, they're approved as single agents in those other diseases. They're not approved in combination with chemotherapy, so that's a promising ongoing area of research for *BRCA*-mutated cancers.

I also highlighted our research on high-dose IV vitamin C in *KRAS*-mutated cells. The use of high-dose IV vitamin C is being studied in both colon cancer and pancreatic cancer. The way that vitamin C targets the *KRAS*-mutated cell is through the Warburg effect, in which cells travel through a pathway where their energy metabolism is affected when they receive high-dose vitamin C. In a sense, it is a metabolic killing of the cell, forcing the cells into oxidative phosphorylation rather than [taking] the glycolytic pathway. The use of high-dose IV vitamin C in KRAS-mutated cancers is currently being studied in a pilot trial at Weill Cornell Medicine.

Stem cell inhibitors are also on trial. Napabucasin (BBI-608) is a stem cell inhibitor that's being used in combination with gemcitabine and nab-paclitaxel in multiple cancers, including pancreatic cancer.

How are inherited versus noninherited genes factored into a physician's treatment approach?

When we find a family that carries an inherited predisposition to developing pancreatic cancer, sometimes we can use that to help the patient. If a patient carries the BRCA mutation, we might treat them with a platinum-based therapy because we know those cancers tend to respond better to platinum-based therapies, and we can use ongoing research about PARP inhibitors for these cancers.

What is important to keep in mind regarding the progression of treatment in pancreatic cancer?

When you don't treat pancreatic cancer on a daily basis, it's easy to assume that the research is slow and lacking in effective therapies. However, we are making strides, and oncologists need to know that there are many ongoing clinical trials for patients. The number-one discussion you should have with your patients should be the potential of enrolling in clinical trials. Helping them find a clinical trial close to the institution where they are being treated is also important, so they can potentially receive a therapy that may improve the standard of care in pancreatic cancer.

Lastly, patients and oncologists should have hope in pancreatic cancer. We showed a series of videos of long-term pancreatic cancer survivors, specifically more than 3 years with metastatic disease, and of patients who have been cured of their disease. We want patients who are starting their journey to know that there are long-term survivors. Eventually, we plan to study these patients to find out what patterns exist in their tumor types and in their genetic makeup that enabled them to be cured of their disease for many years. ■

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Understanding the Implications of Mutational Status in Intrahepatic Cholangiocarcinoma

Angelica Welch

There continues to be a dramatic increase in both incidence and mortality rate of cholangiocarcinoma worldwide, according to Jesper B. Andersen, MSc, PhD.

In a study recently published in *Hepatology* from the Andersen Group at Biotech Research and Innovation Center, it was shown that using a single-gene dissection approach in patients with intrahepatic cholangiocarcinoma can characterize divergent cancer programs and drug vulnerabilities. Through this, therapeutic sensitives for this patient population can be identified, aiding in the process of targeted genotyping.

This study evaluates the genomic, epigenetic, and pharmacologic landscapes of intrahepatic cholangiocarcinoma, which is both molecularly heterogeneous and resistant to chemotherapy.

"There is a clinical need to highlight these patients," said Andersen in an interview with *OncLive*. "This is not only a question of highlighting our study. This disease is a rare malignancy that has progressed since the 1980s. Whereas the therapeutic options have improved for many other diseases, the clinical opportunities for most patients diagnosed with cholangiocarcinoma are limited—this is a dismal disease."

The appropriate stratification of patients with intrahepatic cholangiocarcinoma comes with implications for the development of precision medicine in this disease, Andersen adds. This could be groundbreaking, as there are no approved therapies for this patient population, and only 10% to 30% of patients are eligible for curative surgery.

During an interview with *OncLive*, Andersen, who is an associate professor and leader of the Andersen Group at Biotech Research and Innovation Centre, Department of Health and Medical Sciences at the University of Copenhagen, discussed the findings of this study and the implications it could have on the future treatment of patients with cholangiocarcinoma.

OncLive: Can you please provide an overview of this study?

Andersen: The study is focused on tumors that arise in the bile duct epithelium within the liver, meaning they are anatomically classified as intrahepatic cholangiocarcinomas. That was a deliberate strict inclusion of patients into this study to introduce minimal genomic heterogeneity, because cholangiocarcinoma is a tumor type that exists both in the liver and right outside the liver (extrahepatic). We used a total cohort size of 496 intrahepatic tumors, and analyzed these by whole-exome sequencing, targeted-exome sequencing, transcriptomics, structural variances, and DNA methylation.

We have defined a novel strategy that stratified the patient based on the recurrent genetic alterations that occur and give rise to unique or distinct regulatory networks between groups. We did that by stratifying the patient based on 3 driver-gene groupings—*IDH1/2, KRAS*, and *TP53*—that led to the discovery of a fourth group that we termed "undetermined." This means we did not know the cause of the underlying driver of this disease subgroup. As such, the undetermined group is wild-type for the 3 driver genes. Those could be distinctly classified based on distinct mutational signatures, structural alterations and DNA-methylation profiles.

This classification scheme led to a stratification of unique pathway enrichment for each of these 4 patient groups who were associated with pharmacogenomic and -epigenetic signatures, clinical significance, and specific therapeutic response when we tested patient-matched cell lines in a large-scale drug screening of 525 different drugs that are late-stage or FDA approved.

The undetermined group became quite interesting in the sense that we didn't know what was causing that group. There, we found an enrichment of *FGFR2* gene fusions and amplification in the chromosomal focal region of the gene (*METTL13*). This gene is a putative novel methyltransferase with very little information in the literature (metyltransferase-like 13). We are continuing to identify the role of METTL13 in general and its oncogenic potential in patients with intrahepatic cholangiocarcinoma.

In conclusion, our study has led to elucidating 4 different patient groups —*IDH1/2, KRAS, TP53*, and undetermined—based on different genomic and epigenetic signatures, resulting in unique pathways enrichment and specific drug sensitivity with putative therapeutic application to treat these patient subgroups. The *IDH*group indicated a specific enrichment and potential for drugs that would target metabolic modifiers. The *KRAS* group indicated a role for microtubule modulators and potential for immune therapy, *TP53* indicated potential for topoisomerase inhibitors, and the undetermined group was only highlighted by inhibitors of the mTOR pathway.

What are the next steps moving forward?

Theoretically, there are 2 potential next steps. In this study, we matched based on the genetic substitutions (the different mutational profiles) of these patients the best-fitting cell lines for the drug screening in our library.

The next step would be either in vivo modeling or directly test in the clinic these drug families for efficacy in the 4 enriched patient subsets. The problem with in vivo testing is that there currently are no animal models specifically for each of the 4 different groups. Of course, one interesting approach could be to generate patient-derived xenografts (PDXs) of each of these 4 groups. This challenging in a rare malignancy.

Alternate, this approach could be tested in the clinic since the drugs are approved for other indications. This means that we would do genotyping of all the patients coming into the clinic, then associate them with one of the 4 groups, and then give the drugs that are already approved for clinical use. That is the advantage of precision medicine. At the end of the day, we are using a drug library not of investigative drugs, but FDA-approved drugs or drugs in late stages of clinical trials. These drugs are already tested and safe to use in the clinic, but they are not approved for cholangiocarcinoma (approach is termed drug repositioning).

Are there any roadblocks that you foresee moving forward?

The main roadblock would be that this is a rare disease. It is challenging to acquire enough fresh tissue from patients to generate PDXs that would match the 4 different groups. Going straight to a clinical trial outlining these 4 different groups, and getting approval for testing the drug families in each of their assigned patient group would require a longer enrollment, and would likely need the involvement of multiple institutions.

What are the main takeaways from this study for oncologists?

The main message is that we need to subgroup the patients to see the benefit of drug treatment. There are possibilities to uniquely treat these patients rather than treating them as one group. There is a need for precision medicine for these patients. Do not treat cholangiocarcinoma patients as one. ■

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