In addition, patients focus first on what is needed to save their life and may not worry about what life after cancer will be like. The navigator can start discussions on what the person’s life goals are and help to communicate to the rest of the health care team any that might change treatment options.

“If the person wants to start a family in the future, then there should be a fertility consult prior to treatment,” Shockney said. “How will the surgery affect a waitress being able to carry heavy plates around? The navigator helps to prevent or limit adverse effects, preserve quality of life, and preserve life goals.”

Recently the Commission on Cancer, an organization that accredits cancer centers throughout the U.S., has said that all cancer centers must have a navigator system in place by 2015. However, individual centers decide what system to use to achieve that goal.

**Medical Navigators**

Individuals who knew about the community’s dynamics were the original navigators and remain important in many programs. They focus primarily on screening and early diagnosis. However, as the complexity of cancer care evolved, oncology nurses began to take a role either throughout the process or after diagnosis.

“What I am seeing throughout the country is that some areas use lay navigators, some use nurses, and many use both at different points along the cancer care continuum,” De Groot said. “Each organization looks at its goals, resources, and community needs in determining the best navigation model(s) for the patient, community, and organization.”

**Navigators Are Unique**

What ties navigators together, regardless of credentials or background, is that they know the medical system. They speak the language of health care and know the back doors and shortcuts needed to get things done.

“A couple of things make navigators unique from other roles in the health care system,” Freund said. “One is being able to spend a lot of time with patients without constraints of limited time and the distractions that physicians and other nurses have.”

The other is to bridge the world of medicine and that inhabited by the patient. Navigators have feet in both, not only having time for the patient but also knowing the intricacies of the health care system and, perhaps even more important, how to bypass problems.

Navigators lower health care costs, too. Studies have shown that navigators get patients through treatment faster, with fewer delays that can increase treatment costs and chances of cancer recurrence. They save hospitals money by decreasing missed appointments, an expensive proposition when hospitals still must pay for physician and staff time.

Although much early research was related to breast cancer, newer studies have shown similar results when navigation expanded to other types of malignancies.

“Over time and into the present, navigation has changed how people are getting their cancer care,” McMullen said. “We guide and educate patients throughout their cancer diagnosis and help them tease out what is most important to them to get the care they want.”

**Setting the Bar Higher for Ovarian Cancer Survival**

By Susan Jenks

Blanket large-scale clinical trials of therapies that yield minor differences in toxic effects and show little activity on ovarian cancer survival are not only misguided but also a waste of time, according to Robert F. Ozols, MD, PhD, senior vice president of medical science at Fox Chase Cancer Center in Philadelphia.

“We need to be smarter about what we do in the future, set the bar higher,” Ozols said, citing a 5-year survival rate in ovarian cancer that has inched up from 37% to just 46% in more than three decades. “There’s a huge difference between a clinical success and a commercial one.”

Ozols, now retired, was the keynote speaker at an American Association for Cancer Research conference, “Advances in Ovarian Cancer Research: From Concept to Clinic,” in Miami, September 18–21. He called for more basic research into the new molecular paradigm of these distinct malignancies, collectively known as ovarian cancer, and for smaller, more efficient studies to identify their genetic vulnerabilities. Even though women may be living longer with their disease, “we’ve seen nothing make a difference in ovarian cancer death rates,” he said. “There’s no new entity out there. And, with targeted therapy, we are way behind other cancers, such as breast cancers and even melanoma, where such treatments have brought dramatic improvements (in care). We simply cannot accept this and must do better.”

In the United States, the American Cancer Society estimates that some 22,240 women will receive a new diagnosis of ovarian cancer in 2013 and that 14,230 will die of their disease. Ovarian cancer carries the highest death rate of any cancer.
of the female reproductive system, with almost all these cancers still eluding early detection. Some 75% of women present with advanced disease; an equal percentage, who initially respond to therapy, have a recurrence.

In part, these grim statistics underscore the complexity of these cancers, which share an anatomic location and perhaps little more, Ozols and others said.

The most common form of the disease, high-grade serous ovarian cancer, metastasizes rapidly and is now thought to arise largely from the distal fringes of the fallopian tubes, not the ovary. Ovarian clear-cell and endometrioid cancers, which together account for about 20% of these cancers, have strong links to endometriosis, whereas mucinous ovarian cancers often spread from other tumor sites, notably the gastrointestinal tract.

Untangling Differences

“Until recently, we were not able to untangle why such different outcomes occur” in different women with this disease, said David Bowtell, PhD, head of Cancer Genomics and Genetics at the Peter MacCallum Cancer Center in Melbourne, Australia. “The concept now held is that ovarian cancer is a series of different diseases with different biology.”

For example, mutation of p53, known as the guardian of the cell, occurs in 30%–80% of women with mixed ovarian cell types, he said, but that percentage jumps to 97% when researchers look only at women with high-grade serous carcinomas. Similarly, genetic risks to women carrying BRCA1 and BRCA2 mutations, which are present in 5%–10% of ovarian cancers, rise to 18% in histotype-specific cohorts, Bowtell said.

“What we’re realizing is these tumors are molecularly very different,” said Ronny Drapkin, MD, PhD, assistant professor of pathology at Harvard Medical School and a principal investigator in medical oncology at Dana–Farber Cancer Institute. Agreeing with Ozols, he added, “We can’t keep doing clinical trials without knowing whether what’s being targeted is common to only one subtype, with other patients simply muddying the waters” of study results.

Ultimately, anatomy may not matter as much as shared molecular characteristics across tumor types, such as researchers see with clear-cell cancers in both ovarian and kidney cancers, Drapkin said. “These walls are breaking down.”

Ozols, however, seemed less certain that this will happen anytime soon.

“Cross-tumor analyses raise huge regulatory issues,” he told meeting participants, because the US Food and Drug Administration lacks a mechanism for approving drugs that cross tumor types. “We will need a seascape of changes.”

But in a follow-up phone interview, he fully supported the idea. “I would much rather we spent our resources on this than ask small questions in clinical trials, many of which we’ve already answered,” he said. “I’m not suggesting it’s not important to know whether you should give a drug once a week or more, but for patients the question is, ‘Will it improve my survival?’”

Ozols described his keynote address as realistic, not negative. Present obstacles to improved care, he said, include lack of an early screening test; little room for further surgical advances; limited future potential with classic chemotherapy; and disappointing biomarkers, such as CA125, which “tells you disease may be present, but you still need surgery to know for sure.”

Promising Strategies

The highest immediate priority, he said, should go to PARP [poly(ADP–ribose) polymerase] inhibitors, which block tumors’ ability to repair DNA, making them vulnerable to cancer drugs or apoptosis. One dominant question is whether PARP inhibitors should be selectively studied only in women with BRCA mutations, or more broadly studied in all women with high-grade serous tumors, he said.

Ozols believes vaccine studies where investigators manipulate the immune system to enhance antitumor responses hold promise, as do studies that target dormant tumor stem cells to head off incipient disease. More emphasis should be placed on preventive strategies such as this, he said, and on identifying new biomarkers to assess drug activity and success.

Whether removal of the fallopian tubes also will emerge as a preventive strategy in the general population remains unknown. In Canada, public policy mandates that women who have their uterus removed, even if no cancer is present, also have their fallopian tubes taken out. But determining whether doing so lowers their risk for ovarian cancers will take years, Drapkin said.

In 2011, his group at Dana–Farber reported that they immortalized fallopian tube cells, supporting a stepwise progression from the fimbriae inside these reproductive tubes to high-grade serous tumors in an estimated 60%–70% of cases. The results of that study appeared online in April and in print in May (Proc. Natl. Acad. Sci. USA 2011;108:7547–52).

Where the rest of these tumors originate is not clear, despite one participant’s suggestion that displaced fallopian tube epithelium may play a role.

“We don’t have great answers yet,” Drapkin conceded. “These tumors overgrow everything so rapidly, there’s nothing left to examine. Or it may be explained by inadequate sampling.”

As investigators tackle these and other issues, they generate many data in a push toward understanding which genomic
events are “drivers” in ovarian cancers’ development and which are merely “passengers” owing to the genomic instability inherent to many cancers.

“We need to focus on functional genomics,” Drapkin said. “We have more data today than we have drugs or druggable targets.”

Possible new targets highlighted at the meeting include the following:

- University of Michigan Medical School investigators are studying genetically engineered mice to look at the molecular characteristics of some endometrioid carcinomas. Although these tumors generally carry a more favorable outcome, some patients who develop them don’t do well and may cross over to high-grade lesions that carry a poor prognosis similar to that seen in serous carcinomas, according to Kathleen Cho, MD, Peter A. Ward Professor of Pathology and professor of internal medicine. Ultimately, this group may be the most amenable to targeted therapy, she said, with the mouse model a valuable tool for preclinical legwork, so “when we put together a trial, it has the best chance of success.” One gene of interest: ARID1A, which encodes proteins that work with other proteins to remodel chromatin. “It’s quite specific for clear-cell and endometrioid cancers,” Cho said, and may have therapeutic potential.
- At the University of California, Los Angeles, researchers tested a 10-gene signature in four datasets that predict poor outcomes in patients with ovarian cancer. All the genes are probably regulated by the same mechanism and originate in the same cell type, such as carcinoma-associated fibroblasts or macrophages, which are enriched during cancer progression, said Sandra Orsulic, PhD, associate professor in the department of obstetrics and gynecology at UCLA’s David Geffen School of Medicine. She also directs women’s cancer biology at the Women’s Center at Cedars–Sinai Medical Center. One gene that emerged is COL11A1, which she said appears to be an outstanding marker of tumor progression, especially in recurrent tumors. The gene predicts poor outcomes not only in ovarian cancer but also in several others, including breast and colon cancer.
- Gordon Mills, MD, PhD, chair of the department of systems biology at the University of Texas M. D. Anderson Cancer Center in Houston, called for better collaboration between industry and academia to explore genomic differences at the protein level, using the publicly available Cancer Genome Atlas. “There are a million different proteins in each cell we work on,” he said, “with the hope of learning more [about function] than at the DNA-to-RNA level.” Of more than 1,000 mutations analyzed in ovarian cancer, Mills said, some 20% had “tail aberrations,” whose importance is not yet known. The M. D. Anderson investigators also are looking at RNA editing in tumors, through which cancers hijack a cell’s genetic instructions to create a structurally and functionally different protein. “This is a whole new language of genes,” Mills said, raising the prospect of someday targeting RNA abnormalities for cancer therapy.

Debates Emerge Over Active Surveillance in Testicular Cancer

By Charlie Schmidt

With cure rates approaching 100%, stage I testicular cancer is a success story in oncology. But disagreements have broken out over how to manage patients at the highest risk of relapse, meaning those whose tumors extend beyond the testes into surrounding tissues and lymph nodes. Relapsed cancers are also highly curable. Yet experts debate whether high-risk patients should be monitored with active surveillance or adjuvant treatments to minimize likelihood of recurrence. At stake is the potential for overtreatment and the possibility that too many patients are harmed in the effort to protect a few.

Two articles in the October 1 Journal of Clinical Oncology presented both sides of the debate. One group of experts argued that guidelines should universally recommend active surveillance after orchietomy or surgery to remove the cancer. Craig Nichols, MD, a medical oncologist at Virginia Mason Medical Center in Seattle, and lead author of the article in support of this approach, said clinicians should deviate from active surveillance only at high-volume treatment centers “ schooled in the nuances of the disease.” The paper’s 22 authors include Lawrence Einhorn, MD, an oncologist and professor at the University of Indiana School of Medicine who pioneered curative chemotherapy regimens for testicular cancer.

The opposing editorial rejected this broad-sweeping approach. George Bosl, MD, a coauthor and chair of clinical oncology at Memorial Sloan–Kettering Cancer Center (MSKCC) in New York, emphasized that patients with testicular cancer, most of them diagnosed at a young age, face “decades of survival” and that active surveillance doesn’t fully consider the treatment consequences of relapse. In his view, adjuvant treatments—comprising up to two cycles of cisplatin-based chemotherapy or surgery to remove the surrounding lymph nodes—cuts the risk of relapse by up to 90% and limits...