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OncoLog

Fertility After Cancer

by Stephanie Deming

Advances offer new hope for patients facing fertility-damaging treatment, but doctors need to inform patients early about their options.

Dr. Schover *created a "Banking on Fatherhood" CD-ROM to help doctors discuss fertility-sparing surgery options with male patients.*

Free of cancer but infertile. For cancer survivors who find themselves in this situation, happiness about conquering cancer is tempered by sadness about treatment-induced infertility. And for infertile survivors who feel that they weren't given adequate information about infertility before cancer treatment began, sadness can become anger.

In two recent surveys of oncologists and patients at major centers, Dr. Leslie Schover, professor in the Department of Behavioral Science at The University of Texas M. D. Anderson Cancer Center, found that oncologists sometimes do a poor job of informing patients about the possibility that certain treatments might cause infertility. "Maybe they mention it quickly during informed consent and it goes right over the patient's head, because they have so much information coming in," Dr. Schover said. Later, once patients have recovered from cancer treatment and realize that they might have been able to preserve their fertility if only someone had informed them in time about their options, they can feel devastated.

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Fertility After Cancer

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"Given that oncologists' primary focus is treating and hopefully curing the cancer, it's not surprising that infertility is not discussed as often as it should be," said Dr. Schover. Another factor could be that many oncologists may not be aware of recent advances that have made fertility preservation more practical, especially for men. But ideally, she said, every patient who may be facing infertility as a result of treatment should be informed about his or her options. Toward this end, Dr. Schover and colleagues at M. D. Anderson Cancer Center are working to heighten awareness about cancer-related infertility among oncology healthcare professionals and cancer patients and their families.

"Given that oncologists' primary focus is treating and hopefully curing the cancer, it's not surprising that infertility is not discussed as often as it should be."

– Dr. Leslie Schover

"Banking on Fatherhood"

Of all the interventions available to preserve cancer patients' fertility, one of the most straightforward is sperm banking in advance of radiation therapy or chemotherapy. Unfortunately, many men who might benefit from this option don't learn about it until it's too late.

Sperm banking is "kind of like insurance," said Dr. Schover. Many men who lose sperm function as a result of cancer treatment eventually become fertile again, but for those who don't, sperm banking preserves the chance to father a child through in vitro fertilization (IVF). With older methods, IVF success rates were relatively low because some sperm die during freezing, and the sperm that survive after thawing may have reduced motility. However, with the advent of intracytoplasmic sperm injection (ICSI), IVF success rates have greatly improved. With ICSI, a single sperm is injected into an egg. Thus, motility isn't an issue, and few sperm are needed. With ICSI, said Dr. Schover, "the woman still has to go through IVF, which is no small thing." But the higher success rates have made sperm banking much more attractive.

One of Dr. Schover's major projects is an interactive, educational CD-ROM, "Banking on Fatherhood," designed to raise awareness about sperm banking among both patients and healthcare providers. This project, funded by a small business grant from the National Cancer Institute, is a collaboration with Paul Martinetti, M.D., of AXIS Healthcare Communications, LLC. The section for healthcare professionals includes a medical update about cancer-related male infertility and sperm banking; information on major world religions and their views on masturbation for semen collection and the use of IVF to create children; and videos demonstrating good and bad communication with patients about sperm banking. The section for cancer patients and their families includes information about infertility and sperm banking, other options for fathering children, including adoption and donor insemination, and religious issues, along with videos of cancer patients describing their personal experiences with sperm banking and a decision aid to help patients clarify their feelings. "Banking on Fatherhood" also includes sections for female partners of men with cancer and parents of teenage boys with cancer, plus a national directory of sperm banks that will store samples for cancer patients.

Options for Women

For women facing the possibility of cancer-related infertility, many options are available, but none are as practical or successful as sperm banking. Overall, a greater proportion of women than men become infertile after cancer therapy. According to Dr. Schover, "It's really sad, but it's hard to know what to say to a young woman interested in preserving her fertility. To counsel her, we have to be really honest. We tell her how much it's going to cost and what evidence there is that any of these things really work."

In women, the closest parallels to sperm banking are embryo freezing, a standard infertility procedure, and egg freezing, which is considered experimental. However, whereas sperm banking is rapid and relatively straightforward, embryo freezing and egg freezing are time-consuming, complicated, and expensive, and must usually be funded out-of-pocket. According to the advocacy organization Fertile Hope, the chances of pregnancy with embryo freezing are approximately 10% to 25% per embryo stored. With egg freezing, rates of pregnancy are only about one-quarter to one-third what they are with embryo freezing. And there are concerns about the health of children created with frozen eggs: the spindle that keeps the chromosomes in the right alignment is sometimes damaged during freezing, raising concerns that embryos created from these frozen eggs could have genetic damage.

Embryo or egg freezing may be a reasonable option for women who can postpone cancer treatment the 3 or 4 weeks typically required for hormonal stimulation of the ovaries and egg retrieval, but many women—for example, women with acute leukemia—cannot afford to wait that long. And for breast cancer patients, the estrogen sensitivity of breast cancer cells raises concerns that high estrogen levels resulting from ovarian-stimulating hormones could promote the growth of the cancer. These women may be able to undergo ovarian stimulation with tamoxifen or letrozole, added to block estrogen from entering breast cancer cells. Another experimental option is to remove part of an ovary and freeze the tissue in the hope of transplanting it back to the woman in the future, so that it could grow new blood vessels and produce eggs.

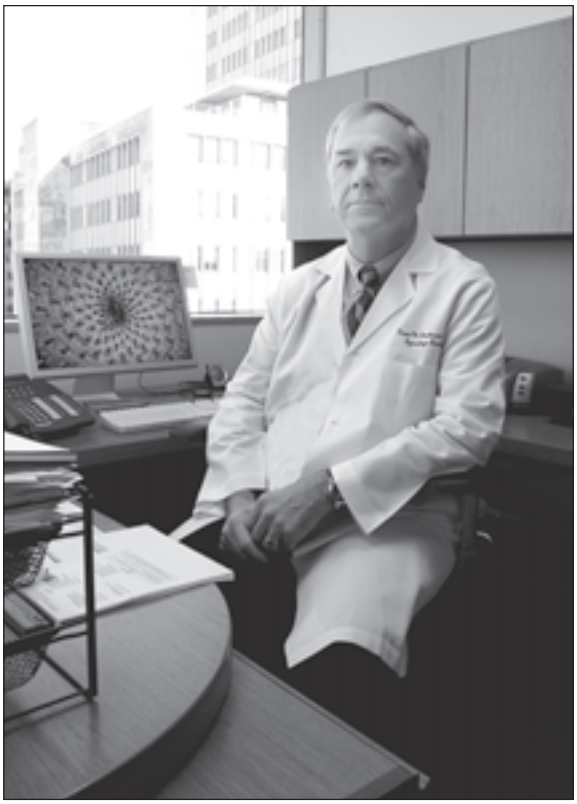
There are also more personal issues. If a woman is considering embryo freezing but does not have a male partner when her cancer is diagnosed, would she be willing to use donor sperm? If she eventually enters into a relationship with a male partner and wants to become pregnant, will he mind using embryos created with someone else's sperm?

Because embryo and egg freezing require the expertise of specialists in reproductive endocrinology and infertility (commonly referred to as REI), M. D. Anderson has a relationship with the REI experts at Baylor College of Medicine, another institution in the Texas Medical Center, so that patients who want to pursue assisted reproductive technologies before cancer treatment can be referred there.

In addition to assisted reproductive technologies, modified cancer treatments may be an option for a small group of women with cancer. These modified treatments include fertility-sparing surgery for women with gynecologic malignancies and chemoprotection of the ovaries for women undergoing chemotherapy.

One of the leading experts in fertility-sparing surgery for women with gynecologic cancers is David Gershenson, M.D., chair of the Department of Gynecologic Oncology at M. D. Anderson. "For anybody for whom future fertility might be a consideration, you always want to be very clear about discussing the options for preserving fertility," said Dr. Gershenson.

For women with certain types of ovarian cancer, ovarian cystectomy (removal of just part of an ovary) might be an option; if not, surgeons might be able to spare an ovary, the uterus, or both. (Depending on which reproductive organs remain, a woman might require assisted reproductive technology to have a child.) For some women with early-stage cervical cancer, conization (removal of just a cone of tissue) or radical trachelectomy (removal of the cervix without hysterectomy) might be appropriate.



Dr. Gershenson *says doctors must clearly discuss options for preserving fertility before treatment.*

If a woman with cervical cancer requires radiation therapy, the ovaries can sometimes be moved out of the radiation field ahead of time in an effort to protect them. Finally, for some women with early-stage endometrial cancer, treatment with hormonal therapy rather than surgery might be possible. Of course, throughout the processes of counseling patients, balancing the risks and potential benefits of fertility-sparing treatment, and ultimately making decisions, the primary concern is curing the cancer.

Dr. Gershenson noted that the success of fertility-sparing surgery at M. D. Anderson is based on two essential elements. "One is that the operating surgeon is very familiar with the biologic behavior of what they think they're dealing with. The second key is to have frozen section exam availability and a good gynecologic pathologist. It's a combination of the knowledge base and skills of the operating surgeon and the pathologist."

Because the gynecologist often isn't sure until surgery what he or she will find and what type of operation will be needed, counseling patients before surgery is complex. According to Dr. Gershenson, in addition to explaining the indications for surgery and any alternatives to surgery (eg, chemoradiation or chemotherapy), the gynecologist lays out all the potential intraoperative scenarios, including the possibility that the uterus and both ovaries will have to be removed, leaving the patient sterile. "It's important to explain how I'll make those decisions during surgery, so that they have as clear a picture as they can of what is going to happen," he said.

A new approach under investigation is based on the theory that chemically shutting down the ovaries—in effect, inducing a temporary menopause—may protect ovarian follicles from the damaging effects of chemotherapy. Naoto Ueno, M.D., Ph.D., associate professor in the Department of Blood and Marrow Transplantation, is conducting a phase II trial to determine whether this tactic will preserve the ovarian function of women undergoing hematopoietic stem cell transplantation. In the trial, women receive the gonadotropin-releasing hormone (GnRH) analogue leuprolide (Lupron) before and during high-dose chemotherapy. M. D. Anderson is also collaborating with a hospital in Tokyo to conduct a phase III trial to see whether another GnRH analogue, goserelin (Zoladex), protects ovarian function in young women receiving chemotherapy for breast cancer.

Multidisciplinary Conferences

To raise awareness in the medical community about issues related to infertility after cancer, Dr. Schover organized a conference, "Parenthood after Cancer," held at M. D. Anderson in the spring of 2004. Funded in part

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Fertility After Cancer

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For women with certain types of ovarian cancer, removal of just part of an ovary might be an option; if not, surgeons might be able to spare an ovary, the uterus, or both.

by the National Cancer Institute and attended by medical professionals from 13 countries, the conference included sessions on causes and prevention of cancer-related infertility, cryopreserving gametes and embryos, psychosocial, ethical, and legal issues, and more. (The proceedings were published in an issue of the *Journal of the National Cancer Institute Monographs* in 2005.) This first conference was such a success that it led to a follow-up, invitation-only consensus conference in the spring of 2005 at which attendees reached consensus about research priorities and recommendations for clinical practice.

The Future

Asked about the future of research on cancer-related infertility, Dr. Schover said, "I think there's a lot more attention now being given to this area. Just in the last year, the American Society of Reproductive Medicine published guidelines on fertility in cancer, and the American Society of Clinical Oncology is going to be publishing guidelines for oncologists soon."

Experts in cancer and fertility agree that the most important thing is to ensure that patients facing fertility-damaging cancer treatment are told about their options ahead of time. As Dr. Gershenson put it, "There are options for selected patients, and we need to make sure that we get that message out." ●

For more information, *contact Dr. Gershenson at (713) 745-2565, Dr. Schover at (713) 745-2681, or Dr. Ueno at (713) 792-8754.*

Improving the Odds in *Lu*

New advances, long in coming, are improving the odds

by Dianne Witter

It's been decades since the last substantial advances were made in the treatment of lung cancer; progress against this tenacious and lethal disease has been incremental, at best. That is, until now. In the last few years, several advances have significantly improved treatment success rates. As a result, more people than ever before can expect to survive lung cancer today.

For instance, last June, a study in the *New England Journal of Medicine* documented a substantial benefit from adding chemotherapy to the treatment regimen after surgery in certain lung cancer patients. The study reported a 15% improvement in the 5-year survival rate in people who were given chemotherapy after surgery for early-stage non-small cell lung cancer (NSCLC). (About 80% of lung cancers are the non-small cell type.)

"These results were amazing," said Katherine Pisters, M.D., a professor in the Department of Thoracic/Head and Neck Medical Oncology at The University of Texas M. D. Anderson Cancer Center and author of an editorial accompanying publication of the study. In the study, cisplatin and vinorelbine were administered to patients with early-stage disease and good performance status whose tumors had been completely removed surgically. Five years later, 69% of them were still alive, compared with 54% who underwent surgical resection only.

Previous studies had shown conflicting results, and there was no consensus among physicians about the best treatment. "This trial was the first to treat all patients with a 'third generation' chemotherapy agent (vinorelbine) and focus on a narrow subgroup of patients with operable tumors," said Dr. Pisters. "The findings of this study were supported by two similar randomized trials that also found improved survival. These results have defined a new standard of care for patients with operable lung cancer."

Combined Treatments in Advanced Disease

There is also good news in the treatment of more advanced lung cancer. The concept of combining two molecularly targeted therapies or combining one such therapy with chemotherapy in people with more advanced NSCLC has also been shown

Dr. Roy Herbst *(l), pictured with advanced practice nurse* **Mercedes Guerra**, *is researching the use of molecularly targeted therapies in combination.*

ng Cancer

of survival for people with lung cancer.

> **These successes...speak to the need for more studies combining different biologic agents in lung cancer..."** – Dr. Roy Herbst

to extend survival in some studies. Roy Herbst, M.D., Ph.D., a professor in the Department of Thoracic/Head and Neck Medical Oncology, has led a number of studies in this area.

Dr. Herbst is currently looking at the synergistic effects of pairing erlotinib (Tarceva) and bevacuzimab (Avastin) in the treatment of patients with advanced NSCLC. "Tarceva is an anti-epidermal growth factor receptor (EGFR) inhibitor; it's a small molecule that works inside the cell to inhibit tumor cell growth and block synthesis of angiogenic proteins," he explained. "Avastin is a monoclonal antibody that works on the outside of the cancer cell to inhibit angiogenesis, starving the tumor of the blood supply it needs to grow. Each drug has been shown to improve survival in its own right—Avastin in combination with chemotherapy in the frontline setting, and Tarceva in the second-line setting. That's why giving them as a combined treatment makes so much sense." After encouraging results in phase I and II studies, Dr. Herbst and colleagues are now doing a multi-institution phase III study. Dr. Herbst adds that, if active, these agents could ultimately be used as adjuvant therapy with even better results.

The two drugs are literally combined in the new agent ZD6474, which is also being studied at M. D. Anderson. "It's a pill that has both the anti-EGFR activity of Tarceva and the anti-cancer activity of Avastin all rolled into one," Dr. Herbst said. Based on initial positive results in clinical studies, a large, randomized trial is planned.

In describing his work, Dr. Herbst talks fast and thinks even faster, revealing the urgency he feels about the magnitude of the work to be done.

Dr. Komaki *(r), with* **Dr. Eugene Huang**, *resident, says that recent advances have made radiation a more effective treatment against lung cancer.*

Despite his scientific neutrality, his words carry an undercurrent of enthusiasm, even optimism about the possibilities—not a trait you find in every weary warrior on this battlefield. "Lung cancer is unlikely to respond well to just one agent, because it's a very heterogeneous disease, with many different targets and different mutations," Dr. Herbst said. "The success with Avastin and Tarceva in combination is promising but, more importantly, it speaks to the need for more studies combining different biologic agents in lung cancer to attack different targets at the same time." Tyrosine kinase inhibitors that target multiple pathways with one pill are another likely avenue of investigation, he added.

"This is just the tip of the iceberg," he said. "With all the new molecular therapies approved or in the pipeline, as well as more advanced methods of measuring disease status, we can learn how to better pinpoint which patients are most likely to benefit from which combinations of drugs." In fact, Dr. Herbst notes that a major focus of his group's current agenda will be to personalize therapy for lung cancer patients based on pretreatment molecular characteristics.

The Role of Radiation Therapy

In the past, radiation therapy, used in combination with surgery and/or chemotherapy, has shown definite benefits in lung cancer treatment—but it also had significant drawbacks. The synergistic effects of the combined treatments in some cases caused more serious toxicity, limiting the extent to which radiation could be used.

However, recent technological advances have made radiation a more effective contender. "Better immobilization techniques, along with an evolution in the precision of computed tomography and positron emission tomography have improved our ability to localize the radiation treatment field to the tumor itself and avoid the healthy tissue surrounding it," said Ritsuko Komaki, M.D., a professor in the Department of Radiation Oncology,

As a result, recent studies have shown improved survival from adding radiation therapy to surgery and chemotherapy in some patient groups, said Dr. Komaki. "A large study by the Radiation Therapy Oncology Group recently found that the addition of radiation in post-surgical stage 3 (microscopic positive mediastinal nodal) disease resulted in a 1-year survival rate of 60% and pushed the 5-year survival rate to 30%."

Dr. Komaki is even more optimistic about the prospect of using radiation with molecularly targeted therapies,

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Improving the Odds in Lung Cancer

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"These results have defined a new standard of care for patients with operable lung cancer."

– Dr. Katherine Pisters

particularly EGFR inhibitors. "Preclinical studies have shown EGFRs to be a great sensitizer to radiation—the medication suppresses the tumor's growth and then the radiation kills it. We think we can eventually add molecularly targeted treatments without causing additional toxicity."

Proton therapy also holds a lot of promise in lung cancer treatment, offering the potential for delivering very high doses of radiation to tumors while avoiding damage to the surrounding organs.

Today, lung cancer still holds the dubious distinction of being one of the nation's top killers. But there is tangible progress against lung cancer, progress that can be seen not just in charts and percentages but in survival. For anyone doing battle with this daunting opponent, "survival" is a word with a very sweet ring. ●

With reporting by Dawn Chalaire.

FOR MORE INFORMATION, *contact Dr. Herbst and Dr. Pisters at (713) 792-6363, or contact Dr. Komaki at (713) 563-2300.*

IN BRIEF

Weight Could Predict Prostate Cancer Progression

A man's weight at the time he is diagnosed with prostate cancer, as well as his history of weight gain, appear to play significant roles in how aggressive his cancer may become, say researchers at M. D. Anderson Cancer Center.

While a link between weight and the initial development of prostate cancer already has been made, this report, published in the October 1, 2005 issue of *Clinical Cancer Research*, is the first to associate a man's body mass at different ages and his weight gain as an adult with the risk of progression after prostatectomy.

"These findings support the view that the development of aggressive forms of prostate cancer may be influenced by environmental effects that occur early in life," said the study's lead researcher Sara Strom, Ph.D., an associate professor in the Department of Epidemiology.

Given further validation of the results, Dr. Strom suggests that a man's history of body weight should be a factor oncologists consider when designing a treatment plan for patients newly diagnosed with prostate cancer.

The data also suggest that interventions such as diet and exercise could be a way to reduce the risk of prostate cancer progression, Dr. Strom said.

Dr. Strom says that it is currently unclear how excess weight contributes to prostate cancer progression, although leading theories suggest it could be linked to changes in a number of different hormones (such as androgen and growth factors) and/or lifestyle behaviors (such as poor diet and inadequate physical activity). Understanding the mechanisms by which weight gain contributes to prostate cancer progression may lead to the development of rationally designed preventive strategies, she said.

Enzyme Complex Can Promote or Prevent Cancer Development

In a case of basic science detective work, researchers at M. D. Anderson Cancer Center have solved the puzzle of the "inconsistent biomarker" and, in the process, may have discovered an agent that can suppress cancer development.

In the October 14, 2005 issue of *Science*, researchers report that the biomarker in question—an enzyme known as EZH2—leads a duplicitous life. In its "native" state, the enzyme acts as a suppressor for cancer cell growth that works to inhibit cancer development. But when it is phosphorylated, it turns vicious and acts to promote oncogenesis.

The researchers found the two forms of EZH2 after they identified the "switch" that leads to its phosphorylation—the well-known culprit Akt, an enzyme that has already been associated with cancer development.

The findings explain not only why high levels of EZH2 (when bound to its partner proteins, such as EED) have been shown to identify people who have an aggressive, metastatic form of breast or prostate cancer, but also why elevated levels of EED appear to offer protective effects against virulent lymphoma.

"This has become a big riddle to cancer researchers who want to be able to use EZH2 as a marker upon which to base aggressive treatment," said the study's lead author, Mien-Chie Hung, Ph.D., chair of the Department of Molecular and Cellular Oncology. "We now know there are two different forms of EZH2. The phosphorylated one enhances oncogenesis, whereas the nonphosphorylated EZH2 works to inhibit cell growth."

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HOUSE•CALL

Understanding the Basics of Melanoma

You've probably heard of melanoma—a dark-pigmented and usually malignant tumor that commonly occurs in the skin—but you may wonder, What is it exactly? What does it look like? What causes it? What can I do to prevent it?

To start with, the incidence of melanoma is rising faster than any other type of cancer. It can occur at any age and is the most common cancer among young adults. Although the majority of melanoma cases involve the skin, there are rare types of melanomas that occur on other places, such as the lining of the inside of the eye, mouth, or rectum.

What is melanoma of the skin?

Melanoma is the most serious of the common skin cancers. The cancerous cells arise from melanocytes (cells that make melanin), which give skin its color. Everyone has these pigment cells, but they can sometimes change, either spontaneously or when damaged by sun exposure. With time, this damage can result in cancer.

What causes melanoma?

Most melanomas are caused by sun damage. The greatest risk for developing melanoma probably comes from sunburns. People with fair skin or those who tend to burn easily are more at risk for sun damage as well as for melanoma. Other factors may also increase the risk, such as a genetic tendency.

What are the symptoms of melanoma?

Any pigmented lesion that undergoes a change in size, shape, or color should be biopsied. The ABCDEs of early diagnosis provide an easy way to become familiar with the early signs of malignant melanoma.

ABCDEs of Early Melanoma Detection

Asymmetry
Look for lesions that look different when one side is compared with the other. If you draw a line down the center of the lesion, do the two sides look different?

Border
Look at the edges of the lesion. Are the borders jagged?

Color
Look for changes in the color of the lesion. Is it getting darker, is part of it changing color, or does it contain several different colors?

Diameter
Look at the size of the lesion. Is it more than 6 mm in diameter (the size of a pencil eraser)?

Elevation
Look for signs of the lesion becoming raised. Is it growing in height?

What is the main treatment for melanoma?

Melanoma is often curable, if detected and treated early. The main treatment for early-stage melanoma is surgery. A thin melanoma is usually treated with a wide local excision of the skin. In this procedure, an area surrounding the melanoma site is removed. Melanomas 1 mm or more in thickness are considered somewhat more serious than thin melanomas and may spread to nearby lymph nodes. A wide local excision is often done together with a lymph node biopsy to check for possible spread. If the melanoma has spread to the lymph nodes, patients may be offered treatment with interferon-alpha, a cytokine that stimulates the body's immune system. If the melanoma spreads beyond the lymph nodes, treatment is performed with chemotherapy, immune-stimulating cytokines, or a combination of both. Clinical research is currently being conducted to evaluate other methods to treat melanoma, including vaccines and small molecules that target specific growth pathways in the tumor.

How can I prevent future melanomas?

Prior sun exposure, a natural tendency to develop melanomas, or both, can sometimes cause people who have had melanoma before to develop a separate, new melanoma. You cannot necessarily prevent this. However, with regular skin self-exams, you may be able to identify suspicious moles in a very early stage. Any suspicious moles should be evaluated by a physician. Individuals should also limit their sun exposure and avoid sunburn. It is recommended that you limit your sun exposure during the peak periods of ultraviolet light exposure (10:00 a.m. –3:00 p.m.). When outdoors, wear a sunscreen rated at least SPF 30, a broad-brimmed hat, and a long-sleeved shirt.

How can I learn more about melanoma?

- Visit M. D. Anderson at www.mdanderson.org/diseases/melanoma and www.mdanderson.org/departments/melanomamed.
- Visit the American Melanoma Foundation at www.melanomafoundation.org.
- Visit the Melanoma Patients' Information Page at www.mpip.org.
- Call the Anderson Network at (800) 345-6324 to speak with another melanoma patient. ●

For more information, contact your physician or contact the M. D. Anderson Information Line:

(800) 392-1611, Option 3, *within the United States, or*

(713) 792-3245 *in Houston and outside the United States.*

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Online Information for Referring Physicians

Nearly half of new patients are referred to M. D. Anderson Cancer Center by a community physician. Now, a secure online portal at https://my.mdanderson.org gives those physicians ready access to information about their patient's care throughout treatment. *my*MDAnderson for Physicians also streamlines the referral process and offers a direct line of communication with M. D. Anderson physicians and care providers.

Created in response to community physician feedback, *my*MDAnderson for Physicians has a number of features, including the following:

- Online "smart" referral process
- Immediate access to view patients' appointment schedules
- Online access to patient reports and transcribed documents
- Secure messaging with M. D. Anderson staff
- Ability to maintain correct contact information
- Links to physician-oriented publications such as the online *Guide for Referring Physicians*, *CancerPro*, and *OncoLog*.
- Access to M. D. Anderson clinical trials information
- Access to the Office of Physician Relations and the support services it offers community and referring physicians
- Link to M. D. Anderson's Research Medical Library
- Updates regarding Continuing Medical Education events and programs

"Our plan is to not only support today's needs but to meet and exceed the needs and expectations of the community physician in the future," said Lyle Green, associate vice president of Physician Relations.

*my*MDAnderson for Physicians is available to community physicians—those who have referred patients to M. D. Anderson in the past and those who expect to do so in the future. To learn more and to sign up, please visit the *my*MDAnderson for Physicians Web site at https://my.mdanderson.org.

For additional information about *my*MDAnderson or to inquire about in-office or phone-based demonstrations, please contact the Office of Physician Relations by e-mail at physicianrelations@mdanderson.org or by phone at (713) 792-2202 or (800) 252-0502. ●

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