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4 **Hormone Replacement**
New data spark new questions

6 **In Brief**
Promising new genetic tests for cancer care

7 **House Call**
How journaling helps patients cope
Dear Journal

8 **DiaLog**
Communicating about complementary therapies

REPORT TO PHYSICIANS

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OncoLog

Endocrine Center Unites Specialists

by Manny Gonzales

*Thyroid cancer treatments may include surgery (**Dr. Gary Clayman** and colleagues), radioactive iodine, thyroid hormone suppression therapy, and other modalities.*

Thyroid cancer is one of the fastest growing cancer diagnoses in the United States, particularly among women. The good news, however, is that many cancers of the endocrine system, such as thyroid cancer, are usually slow-growing, and most patients with these diseases traditionally survive long-term. But any interference with the endocrine system's delicately balanced regulation of hormones and the vital roles these hormones play in the body may result in chronic illness requiring long-term treatment and follow-up care.

Before undergoing surgery or another form of treatment, patients who have endocrine tumors may require carefully coordinated endocrine evaluation and medical management to address hormone problems—and the collaboration of a range of specialists.

At The University of Texas M. D. Anderson Cancer Center, collaboration across multiple fields to treat endocrine tumors and cancer-related endocrine dysfunction is not new. Three such

(Continued on **next page***)*

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Endocrine Center Unites Specialists

(Continued from **page 1***)*

doctors, along with their colleagues, have been working together to treat these diseases for years—Steven I. Sherman, M.D., professor in the Department of Endocrine Neoplasia and Hormonal Disorders; Gary L. Clayman, M.D., professor in the Department of Head and Neck Surgery; and Nancy D. Perrier, M.D., associate professor in the Section of Endocrine Tumor Surgery in the Department of Surgical Oncology. Because these doctors had been working together in "virtual" space only, there was a growing need for a common physical space where endocrinologists, surgeons, medical oncologists, radiation oncologists, and nuclear medicine specialists could address the individual problems of their patients and collaborate on research and clinical trial activity. Thus, the Endocrine Center opened its doors in September 2006, with Dr. Sherman as its medical director and Drs. Clayman and Perrier as its associate medical directors, making clear the important role that each of their departments plays in the laboratory and clinical programs active in the new center.

"The Endocrine Center in fact is a manifestation of what M. D. Anderson doctors have been doing for more than a decade," said Dr. Sherman. "But one of the reasons behind the creation of the center was the increasing demand for services, which is being largely driven by a growth in clinical population, along with new research opportunities for innovative approaches to diagnosis and treatment of these patients."

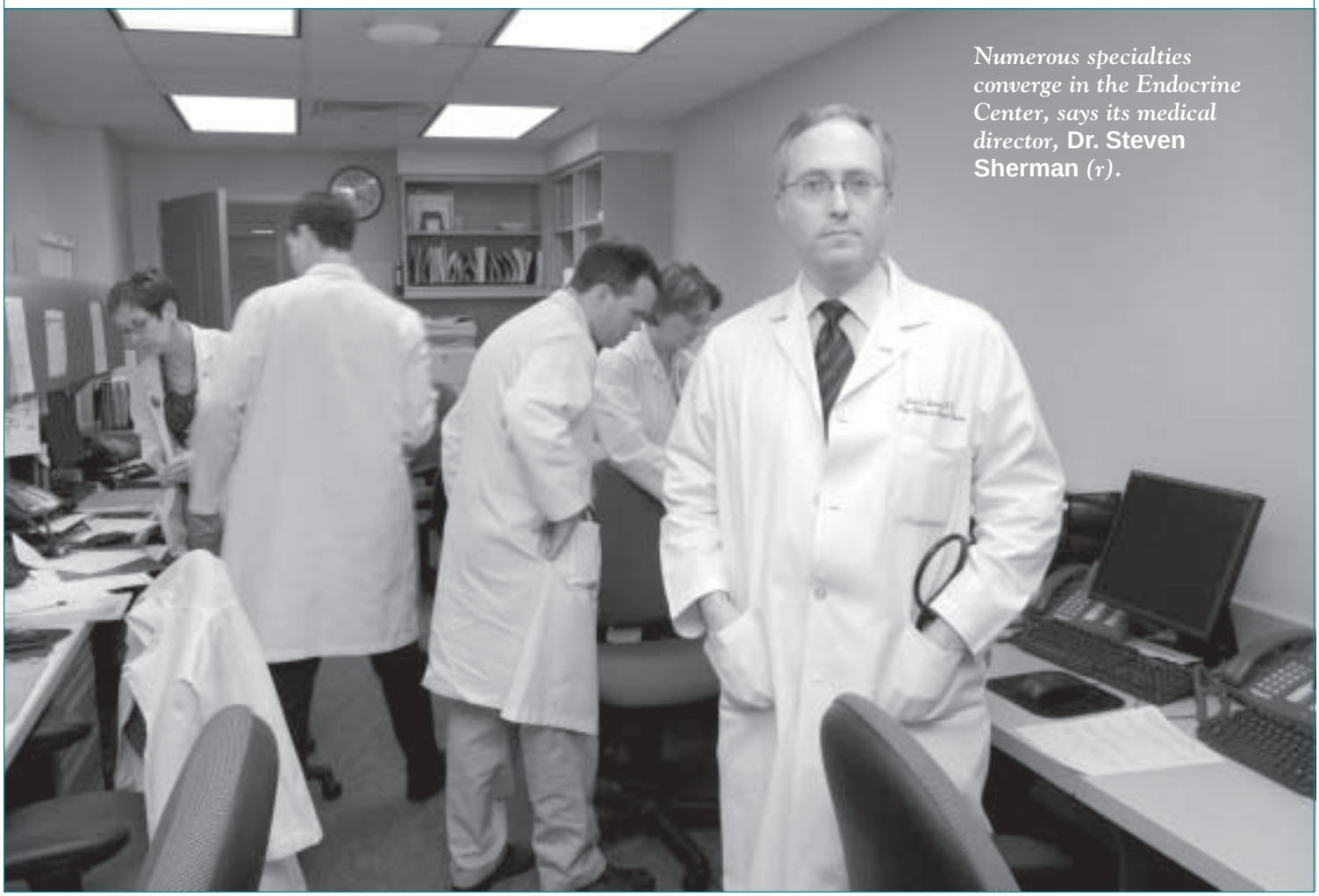
Possible reasons underlying increased incidence

Although some studies have suggested that the rise in thyroid cancer incidence is due to radiation fallout from nuclear testing, others have attributed the increase to advances in diagnostic imaging that have enabled better detection.

Whatever the cause, 35,000 Americans will be diagnosed with the disease this year, up from 31,000 last year. Historically, most patients with the disease live long enough to die of something else. For those who appear cured, there remains a long-term risk of recurrence. "We have patients here who have thyroid cancer grow back 30 or 40 years after they were treated," said Dr. Sherman. "Thus, the nature of our program is one in which we have an increasing number of patients coming in, and many of them survive long-term. The clinical program has grown by virtue of that fact alone."

Managing endocrine dysfunctions due to cancer and other causes

The primary focus of the new center is on treating thyroid cancer and other



Numerous specialties converge in the Endocrine Center, says its medical director, **Dr. Steven Sherman** *(r).*

endocrine tumors, but it also focuses on other types of endocrine dysfunction, which can be caused by or aggravated by cancers elsewhere in the body or treatment-related side effects. Anticipating such side effects and managing them as early as possible are essential in optimizing patient outcomes. "Half of what we do is consultation for M. D. Anderson patients being treated for other cancers," said Dr. Sherman. As an example, he points to the fact that 25%–35% of M. D. Anderson's inpatients have diabetes; therefore, the department has three endocrinologists who focus on treating diabetes in collaboration with specialists from elsewhere in the institution.

Collaborating against disease in the lab and clinic

The opening of the Endocrine Center was also driven by the need to accommodate the increasing amount of research and clinical trial activity generated by the collaborating departments. The Endocrine Center is currently home to one of the largest clinical trial programs in the country for patients with endocrine tumors, particularly thyroid cancer. This disease is of special concern because there has been no decline in its mortality rate since the introduction of radioactive iodine treatment in the 1940s. "For other forms of cancer, mortality rates are generally going down," said Dr. Sherman. "But that's not the case with thyroid cancer. In fact, in men, the mortality rate has actually increased."

> **"What we're proposing for the future is to develop clinical and research programs that will tie together patient care, patient history, tumors, pathology, and clinical data."**
>
> **– Dr. Sherman**

The active clinical trial program at M. D. Anderson opens up a completely different and heretofore unavailable set of options to patients with thyroid as well as other endocrine cancers. "We have seen the rapid expansion of clinical trial activity for thyroid cancer at M. D. Anderson, and that reflects a national trend, which to a large degree, we've been leading," said Dr. Sherman.

In the past few years, much of the research activity in the field has shifted toward developing targeted therapies because many endocrine diseases, including some endocrine tumors, are caused by inherited genetic mutations. The concept of targeting therapies to a molecular abnormality is under study in many cancers, but in fact, according to Dr. Sherman, some of the targeted therapies developed recently may have even greater potential for effectiveness against some forms of thyroid cancer. What is already known about the genetics of thyroid cancer should help accelerate the process of connecting the genetic abnormalities of the tumors to the therapy, said Dr. Sherman.

The largest ever multicenter clinical trial in thyroid cancer, a phase II trial to determine the efficacy of motesanib diphosphate, a promising oral multikinase inhibitor, is currently underway. Another phase II trial is currently underway with decitabine, a DNA methylation inhibitor recently pioneered for use in leukemia at M. D. Anderson. The goal of the decitabine study is to determine whether the drug can induce radio-iodine responsiveness in thyroid cancers that were previously unresponsive to radioactive iodine treatment.

Genetic counseling extends reach

The creation of the Endocrine Center also affords the unique opportunity to integrate genetic counseling and screening into the treatment of patients with endocrine disorders. To that end, the Endocrine Center genetics counselor, Thereasa A. Rich, M.S., meets with patients in the clinic along with the clinicians. She discusses the risk factors regarding family history and the available options for genetic testing and screening.

One of **Dr. Nancy Perrier's** *clinical interests is asymptomatic hyperparathyroidism.*

For instance, the fact that a patient with thyroid cancer has a family history of kidney stones could suggest the cancer is part of an inherited condition, multiple endocrine neoplasia type 2. The genetics counselor works to uncover such previously undiagnosed syndromes that might not ordinarily be found—information that could prove valuable for other family members.

Additional clinic space and an expansion of the screening program for patients at high risk for inherited endocrine syndromes are being planned. "What we're proposing for the future is to develop clinical and research programs that will tie together patient care, patient history, tumors, pathology, and clinical data," said Dr. Sherman, "because endocrine tumors really represent a great opportunity to develop individualized, personalized medicine." ●

FOR MORE INFORMATION, *call the Endocrine Center at (713) 563-7600 or visit its website at http://www.mdanderson.org/care_centers/endocrine/.*

Prescribing Hormone Replacement: What Now?

by Dianne C. Witter

Can hormone replacement therapy cause breast cancer? New findings have raised new questions about prescribing HRT for post-menopausal women.

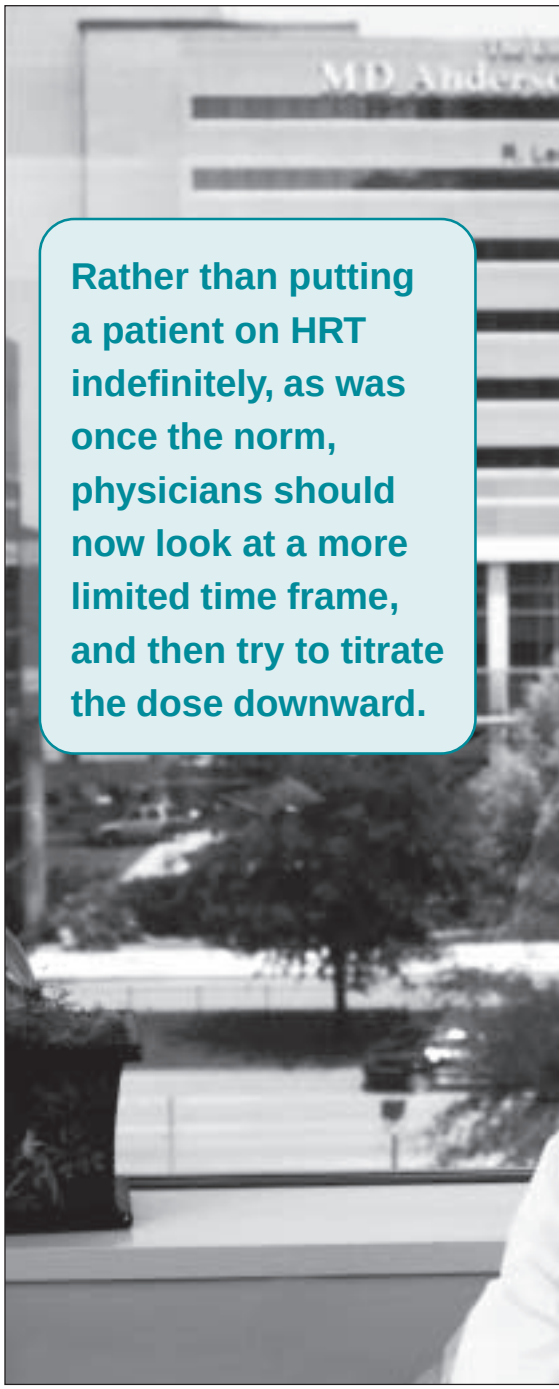
Rena Sellin, M.D., sums the issue up neatly, in five short words: "Nothing is good for everybody."

With this statement, Dr. Sellin, a professor in the Department of Endocrine Neoplasia and Hormonal Disorders at M. D. Anderson, encapsulates the ever-changing lessons—and the subsequent questions—generated during several decades of research into the issue of hormone replacement therapy (HRT) for post-menopausal women. Are there cardiovascular benefits? Does it cause breast cancer? Can it improve cognitive function? How long should women take it—or should it be prescribed at all?

A recent study by M. D. Anderson spurred the ongoing debate into high gear, generating hundreds of articles in both lay and medical media and leaving both doctors and patients wondering—again—about the best course of action. The study highlighted a sharp decline in breast cancer incidence in 2003, suggesting the decline may be due to the fact that millions of older women stopped using HRT in 2002. Prescriptions for HRT nosedived that year, after an ongoing study by the Women's Health Initiative found that the combination of estrogen and progestin significantly increased a woman's risk of developing invasive breast cancer.

What happened next makes for even more compelling statistics: between 2002 and 2003, there was a 7% overall decline in breast cancer incidence—in marked contrast to the steady *increase* in incidence over the previous 20 years. More to the point, the steepest decline was seen in the diagnosis of estrogen-receptor-positive breast cancer, which is dependent on hormones for growth, in women ages 50–69 years.

"To my knowledge, this represents the largest single drop in breast cancer incidence within a single year," said Peter Ravdin, M.D., Ph.D., a professor in the Department of Biostatistics at M. D. Anderson and an investigator on the M. D. Anderson study. "Something went right in 2003, and it appears to be the decrease in the use of hormone therapy; but the analysis was based on population statistics. From these data, we can only indirectly infer that is the case.



Rather than putting a patient on HRT indefinitely, as was once the norm, physicians should now look at a more limited time frame, and then try to titrate the dose downward.

"However, if the drop in incidence *is* due to the drop in HRT, it means that stopping the use of hormones had a dramatic effect on tumor growth over a short period of time—making the difference between whether a tumor was detected on a mammogram in one year's time."

A tricky intersection

This is one of the points at which drawing definitive conclusions becomes

Dr. Rena Sellin

tricky, however. As Dr. Sellin points out, "It's too soon to conclude that the incidence of breast cancer has been permanently affected—breast cancer develops over a long period of time. It's possible that stopping the use of HRT slowed the growth of tumors (and therefore the number that could be detected in a year's time) but didn't change the number of breast cancers that will ultimately be diagnosed."

Donald Berry, Ph.D., senior investigator on the M. D. Anderson study and professor and head of the Division of Quantitative Sciences, agrees that it's important to be cautious when making inferences. "Here, we are primarily talking about existing cancers that are fueled by hormones and that slow or stop their growth when a source of fuel is cut," he said. "These cancers are then more likely to make it under mammography's radar.

"Epidemiology can never prove causation," Dr. Berry noted. However, he and his colleagues looked at other factors that could be responsible for the decreased number of breast cancers diagnosed, such as decreased use of screening mammography or changes in the use of medications like anti-inflammatory agents, selective estrogen receptor modulators, or statins. "Of these factors, only the potential impact of hormone replacement therapy was strong enough to explain the effect."

Dr. Sellin notes that the current findings are part of a pendulum swing away from HRT that started about 5 years ago. For a number of years, women were automatically prescribed HRT during and after menopause, because studies had suggested it conferred a cardiovascular benefit as well. But in 2002, when the Women's Health Initiative study found a substantial increase in breast cancer incidence in women taking HRT—and no decrease in heart disease—the pendulum began swinging back the other way. Many women decided to forego HRT and soldier through the side effects of menopause without it.

But other factors likely also influenced the statistics, and most researchers agree that the final answers are not in yet. Some feel the drop in incidence was too fast to fully explain causation for a disease that develops as slowly as breast cancer. In addition, said Dr. Sellin, "Incidence is dependent in part on detection practices. If fewer women are getting mammograms, fewer cancers will be detected.

"An important note from the Women's Health Initiative that many overlooked was the fact that estrogen alone did *not* raise the incidence of breast cancer in the study—it was the combination of estrogen and progestin," she said. "So we need to ask how many women stopped taking which kinds of estrogen before the incidence dipped."

Finding middle ground

The real question, of course, is whether or not doctors should change the way they prescribe hormones for post-menopausal women based on this information—and what kind of counsel to give patients who are concerned about media reports they've heard.

In all likelihood, the answer is not to be found at either extreme, said Dr. Sellin. The answer, as it usually is in medicine, is that physicians should weigh the risks and benefits in each patient's situation, taking into account the woman's risk of breast cancer, the severity of her menopausal symptoms, and other factors. While the statistics are certainly of concern, Dr. Sellin notes that on an individual level, the risk of developing breast cancer is still quite small.

Current medical recommendations for HRT include prescribing a relatively low dose for a relatively short duration. "Hormone therapy should be now used specifically to address the symptoms of menopause rather than for any potential cardiovascular or cognitive benefits," said Dr. Sellin.

Rather than putting a patient on HRT indefinitely, as was once the norm, physicians should now look at a more limited time frame, and then try to titrate the dose downward. How long is again dependent on the individual, but many physicians are finding that 6–12 months works well. "But some women will need to be on it for much longer," Dr. Sellin cautioned.

Perhaps most important, physicians should develop a game plan in conjunction with their patients and explain the reasons for the recommendations. "There's no point in writing a prescription that a patient's going to carry around in her pocket for weeks, trying to decide whether or not to fill it," said Dr. Sellin. "Ask about any doubts or concerns she has during her appointment, so you can be the one to address them rather than the media." ●

Gene Expression May Soon Guide Breast Cancer Treatment

A multinational group of researchers has developed and validated a new genomic microarray test that may replace current tests as the best way to determine whether a patient with newly diagnosed breast cancer would be likely to benefit from specific therapies.

"This is one important step toward diagnosing and planning treatment based on a genomic test of an individual tumor," said W. Fraser Symmans, M.D., an associate professor in the Department of Pathology and the senior author of an article about the team's findings, which was published in the March issue of *Lancet Oncology*.

The article reports the latest development in the team's efforts to find a single test that would quickly and efficiently determine the characteristics and vulnerabilities of a patient's cancer.

In their experiments, the expression of mRNA by two specific genes, *ESR1* and *ERBB2*, correlated significantly with the status of the corresponding receptors: estrogen receptor and human epidermal growth factor receptor-2 (HER-2), respectively. The gene expression tests were 90% accurate for both receptors, which makes them comparable to, if not better than, the results obtained with immunohistochemistry assays and fluorescence in situ hybridization, the tests currently used to determine receptor status.

Of breast cancers, approximately 70% are estrogen-receptor-positive and can be treated with estrogen-suppressing drugs. Another 15%–25% of breast cancers are HER-2-positive and are sensitive to antibody-based drugs, such as trastuzumab, that bind to HER-2 receptors and block them from coupling with growth factors that fuel tumor growth.

"We have moved a step closer to developing an integrated genomic test that could accomplish several important diagnostic needs at once," said Lajos Pusztai, M.D., Ph.D., an associate professor in the Department of Breast Medical Oncology. Dr. Pusztai leads the research team with Dr. Symmans. "By combining these latest results with others, a genomic test could be designed to estimate the risk of cancer relapse after surgery, determine the estrogen-receptor and HER-2 receptor status, and gauge the sensitivity of the tumor to hormone therapy and chemotherapy."

The efforts to refine the use of genomic microarray testing will continue with a prospective clinical trial at M. D. Anderson, in which these tests will be used to recommend treatment for patients with newly diagnosed stage I to III breast cancer.

Two-Gene Test Differentiates Similar Gastrointestinal Tumors

With near-perfect accuracy, a powerful two-gene test can distinguish between a pair of nearly identical gastrointestinal cancers that require radically different courses of treatment.

"This simple and accurate test has the potential to be relatively quickly implemented in the clinic to help doctors determine appropriate treatment," said Wei Zhang, Ph.D., a professor in the Department of Pathology and the senior author of the article describing the study, published in the February issue of the *Proceedings of the National Academy of Sciences*.

One of the cancers, gastrointestinal stromal tumor (GIST), was once thought to be best grouped with spindle cell and other soft-tissue sarcomas, including leiomyosarcoma (LMS), because both originate in the smooth muscle cells of the gastrointestinal tract; but GIST has emerged as a distinct entity. In fact, GIST and LMS respond so differently to certain chemotherapies that the appropriate diagnosis can be a life-and-death decision, according to the researchers. Specifically, GIST tends to be very responsive to the tyrosine kinase inhibitors imatinib mesylate and sunitinib but resists cytotoxic therapy, while LMS responds to cytotoxic therapy but resists tyrosine kinase inhibitors.

Before the two-gene classifier, the best way to differentiate GIST from LMS was only about 87% accurate and could cause false-negative diagnoses, requiring intensive and time-consuming additional analyses.

"This new classifier may have been so successful because it used as simple an approach as possible to keep statistical pitfalls from lowering its accuracy," Dr. Zhang said. "We expect that the use of simple marker pairs, like the one used in this test, will be clinically useful in many situations."

Genomic approaches to diagnosing cancer, selecting treatment, and determining a cancer patient's prospects of responding to care are beginning to work their way into the clinic, the researchers noted. These approaches can rely on dozens of genes as biomarkers. However, top-scoring pair analysis, the analytical technique employed to identify this classifier's gene pair, allows the use of fewer genes to distinguish between similar cancers or between groups of patients who have one type of cancer but respond differently to treatment based on genetic indicators. For example, paired gene analysis may be used to determine which patients will benefit from different types of chemotherapy and which patients are at higher risk of relapse, the authors noted. As an analytical strategy, the method will have wider applications in the development of individualized treatments and diagnoses of other types of cancer, the researchers said.

Dr. Zhang and his colleagues developed the two-gene classifier by searching microarray data from 68 well-characterized tumor samples to find a straightforward gene expression pattern that could distinguish GIST from LMS with a high degree of accuracy. Instead of attempting to identify multiple genes that would distinguish GIST from LMS or trying to determine a level of expression that would characterize the two cancers, the researchers analyzed every possible pair of genes for their relative levels of expression. The technique used yielded a single classification rule: if *OBSCN* expression is greater than *C9orf65* expression, diagnose GIST; if not, diagnose LMS.

HOUSE•CALL

Writing for Wellness: Keeping a Journal

Especially when facing a serious illness like cancer, anyone can find it difficult to express personal feelings to others and sort through complicated emotions. If you find yourself in that position, one safe and private way to do both is to write in a journal. Keeping a journal allows you to come to terms with your situation at your own pace and in your own way, potentially helping you regain a sense of control in your life.

"Our culture seldom allows us to voice our real feelings," said Sandi Stromberg, who facilitates journaling sessions at M. D. Anderson's Place … *of wellness*. "So I encourage patients and caregivers to process what they are experiencing—to write down their anger and sadness, their frustrations and fears. I also suggest they write down three gratitudes at the end of the day, even if it's something as small as a good cup of coffee or less traffic on the road."

Research has shown that writing about stressful experiences, such as illness, may boost patients' health and psychological well-being. When people confront and work through an experience, they understand it more clearly. This can improve coping and sleep quality, reduce stress, and enhance social interactions, all of which result in a better quality of life.

How do I start journaling?

Follow the steps below to help you get started.

1 **Make a plan.** Choose a time of day that is most convenient for you. Then make a goal to write twice a week, for 15 minutes each time. Once that becomes a routine, try adding a day.

2 **Find a spot.** Choose a place to write that is comfortable and relaxing, where you can be alone and focus on your thoughts.

3 **Start writing.** Write down whatever comes to mind. Let your mind wander and your words flow. Don't edit yourself.

Once you are comfortable journaling, do not limit yourself to certain days or times. Journal whenever you have time or when you feel it can help you the most. Some people find it helpful to journal while waiting for appointments, as it helps to calm nerves and pass the time.

If you find yourself staring at the blank page without knowing how to start, write "I don't know what to write" over and over. Eventually, other words will come. Another way to begin the writing process is to try writing stories about your past. For example, you can journal about your first car or your experiences on your first day of school. You might record the unexpected humor of daily life or simply insights and observations. Don't feel pressured to tell the whole story—you can always expand on the bits and pieces you choose at a later time.

Journaling Tips

- Don't be hard on yourself if you miss a day.
- Always date your entries.
- If you prefer journaling on a computer, print the pages and keep them in a notebook. (This makes it easier to look back at later.)
- Write what you want to write. Remember, the journal is for you.
- Allow yourself to buy a nice journal. ***Your words are worth it!***

"I give patients and caregivers suggestions for topics during our sessions to remind them they were fully functional people with productive lives before cancer," Ms. Stromberg said. "It's so easy for them to tell about who they are in terms of their illness when the truth is that they are and have been so much more. Journaling helps them remember that."

If writing does not come naturally to you, try making lists of things that come easily to mind, such as:

- your best qualities,
- what you need and want from your doctor,
- things that make you happy,
- ten people who've had the greatest impact on your life, or
- your favorite books.

For more information, talk to your physician, or:

- *call askMDAnderson at (877) MDA-6789*
- *visit www.mdanderson.org.*

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S. Stromberg and L. Classen

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DiaLog

What Your Patients Aren't Telling You

Moshe Frenkel, M.D.
Associate Professor
Medical Director, Integrative Medicine Program

There's something important your patients may not be telling you, and what you don't know could hurt them—or affect their treatment. Many studies have confirmed that the majority of people undergoing conventional cancer therapy also use some form of complementary and integrative medicine. A survey at M. D. Anderson in 2000 revealed that 83% of patients used some form of complementary treatment—and most did not report it to health care professionals.

As physicians, we should invite dialog on this subject with our patients, for a number of reasons:

- To serve as a reliable source of information regarding potential benefits and drawbacks of different types of therapies;
- To reduce potential negative interactions between conventional and complementary treatments;
- To monitor whether complementary medicine affects clinical trial outcomes;
- Because the evidence suggests that complementary therapies provide psychological, social, and spiritual support and empower patients and their families.

While scientific and evidence-based thinking is fundamental to contemporary medical practice, failure to recognize that patients often do not reason in this way interferes with the physician's ability to address the unspoken needs of the patient. The physician who is receptive to inquiries and aware of subtle, non-verbal messages can create an environment of safety in which patients can openly discuss potential complementary medicine choices.

For patients with cancer, the psychological, social, and spiritual dimensions of care are crucial areas to address. Patients frequently see complementary therapies as a way to try to take control over their health and increase their quality of life. If physicians are not responsive to patients' needs in this area, patients will obtain information from a variety of sources, such as advice from friends and relatives, popular magazines, daily newspapers, the internet, advertisements, and other unreliable information provided at health food stores. Often this information is not accurate, and occasionally, it may even be dangerous.

Being open to patients' perspectives and sensitive to their need for autonomy and empowerment may require us to shift perspectives a bit. Today's informed patients truly value physicians who appreciate them as empowered participants in making their own health care choices. An open approach that implements some of these principles leads to a healthier and more productive journey for both the patient being treated and the physician overseeing that care.

Physicians can find more information at www.mdanderson.org/departments/CIMER.

OncoLog, M. D. Anderson Cancer Center's report to physicians, is a monthly newsletter sent to more than 30,000 physicians throughout the nation and the world. Published by the Department of Scientific Publications, *OncoLog* reports on innovative developments in research and treatment at M. D. Anderson. Current and previous issues are available online in English and Spanish at www2.mdanderson.org/depts/oncolog. For editorial information, call (713) 792-3305 or email scientificpublications@mdanderson.org. To refer a patient or request information, call (800) 392-1611 or (713) 792-6161, or visit www.mdanderson.org.

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