REPORT TO PHYSICIANS

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THE UNIVERSITY OF TEXAS
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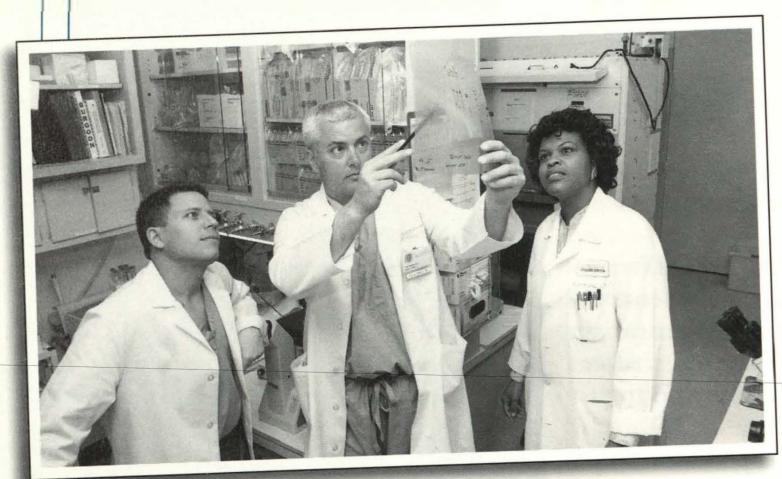
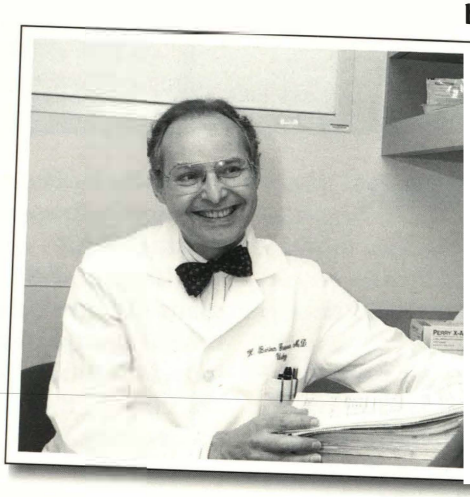
From Lab *to* Clinic:

Molecular Research Leads to Clinical Trials for Bladder Cancer

by Sunita Patterson





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Above left, *Urology fellow* **Paul Perrotte, M.D.**, *urologist* **Colin Dinney, M.D.**, *and research assistant* **Beryl Eve** (left to right) *examine a northern blot as part of their study of epidermal growth factor receptor expression.* Above right, *Urologist* **Barton Grossman, M.D.**, *discusses care with a patient in the Genitourinary/Urology Multidisciplinary Care Center.*

While urologists Barton Grossman, M.D., and Colin Dinney, M.D., are at work in the laboratory, they do not forget the patients they have seen and operated on that week.

"The ultimate goal of our basic research is to help patients with disease," said Dr. Grossman, professor and director of clinical research of the Department of Urology at The University of Texas M. D. Anderson Cancer Center. "We're trying to translate our data from the laboratory to the clinical arena." Dr. Dinney is an associate professor in the same department.

In bladder cancer study, years of genetic analysis and investigation of molecular biomarkers have yielded results now ripe for clinical trials. These and other physician-researchers are ready to exploit the increased understanding of bladder cancer at the molecular level to predict patient outcome, develop new therapeutic

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Bladder Cancer Clinical Trial Interventions Span Surgery, Chemotherapy, Radiotherapy, and Genetic Manipulation

Bladder cancer clinical trials currently in progress at The University of Texas M. D. Anderson Cancer Center include the following. Contact the M. D. Anderson Information Line or the M. D. Anderson clinical trials listing on the World Wide Web (see numbers and addresses below) for more information.

- A study of intravesical treatment of superficial bladder cancer in high- and low-risk patients characterized on the basis of tumor markers p53 and pRb. *Physician: Colin Dinney, M.D.*

  In this trial, Associate Professor Colin Dinney, M.D., and Barton Grossman, M.D., both of the Department of Urology, are investigating the effectiveness of the new drug AD 32 against bladder cancer. After undergoing surgery to remove bladder tumors, patients will have their bladders infused through the urinary tract with AD 32. After 90 minutes, AD 32 will be drained. Patients with a low level of protein p53 and pRb expression will receive an infusion of bacillus Calmette-Guérin (BCG) into the bladder once a week for six weeks. Patients with a high level of protein expression will also receive a BCG infusion once a week for six weeks. Both three and six months after the first infusion, they will receive one BCG infusion a week for three weeks. This three-week course will be repeated every six months for two years.

- Randomized chemoprevention trial with 4-HPR (fenretinide) in superficial bladder cancer (95-236). *Physician: Barton Grossman, M.D.*

  In this trial, Dr. Grossman is investigating the effectiveness of the antitumor drug 4-HPR (fenretinide) against superficial bladder cancer's repetitive recurrence. His aim is to stablize the urothelium. Patients will take either four 4-HPR capsules a day or four placebo capsules a day for one year.

- A phase I trial of intravesical adenoviral p53 treatment in locally advanced bladder cancer (DM96-172). *Physician: Lance C. Pagliaro, M.D.*

  Assistant Professor of Medicine Lance C. Pagliaro, M.D., of the Department of Genitourinary Medical Oncology is studying gene therapy for bladder cancer. Adenoviruses carrying the *p53* gene will be mixed with a salt water solution and then infused into the bladder through the urinary tract. The solution will be drained after 20 minutes. Patients will receive two, four, or eight treatments per month.

- Phase II evaluation of bladder preservation in T0, TA, TIS, and T1 bladder cancer after chemotherapy (URL96-005). *Physician: Colin Dinney, M.D.*

  In this trial, Department of Urology

From Lab *to* Clinic

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

strategies, and monitor results of therapy.

In recent work, Drs. Grossman and Dinney found that expression of tumor suppressor proteins p53 and Rb, which are known to have an important role in cell proliferation and to be altered in many cancers, correlated with rates of tumor progression and patient survival in bladder cancer. After two years, no patients in whom both proteins were expressed normally had disease that metastasized or even invaded muscle; however, patients in whom both proteins were expressed abnormally had a high rate of progression (46%), and patients in whom just one of the proteins was expressed abnormally had an intermediate rate of progression (23%). William Benedict, M.D., of the Department of Molecular Hematology and Therapy collaborated with them on this work.

Using these findings, Dr. Dinney plans to begin enrolling patients with recurrent superficial bladder cancer in a clinical trial this summer. After resection of their tumors and treatment with valrubicin (AD 32), patients with normal p53 and Rb expression will be observed with cystoscopy only, whereas those with abnormal expression of one or both proteins will undergo additional therapy with bacillus Calmette-Guérin. The goals of the trial are to determine whether progression rates at 12 and 24 months are indeed low in patients with normal p53 and Rb and to study the safety and efficacy of valrubicin in combating recurrence and progression.

"These proteins are helping us to individualize therapy based on the biologic status of the neoplasm rather than putting all patients with superficial bladder cancer in the same basket," Dr. Grossman said. Many of these patients will have recurrences, but in only a few will disease become invasive or life-threatening.

Molecular intervention is another therapeutic strategy. Reports that altered expression of p53 was associated with poorer prognosis prompted researchers to test whether restoring p53 expression by inserting an adenoviral vector could induce disease regression in patients with locally advanced or metastatic bladder cancer. "This approach has had encouraging results so far in clinical trials at M. D. Anderson in lung and head and neck cancer," said study chairman Lance Pagliaro, M.D., of the Department of Genitourinary Medical Oncology.

The preliminary trial in bladder cancer should determine whether intravesical administration of the adenoviral vector is safe and effec-

Associate Professor Colin Dinney, M.D., will treat patients who have superficial bladder cancer that is invasive or metastatic that has demonstrated a dramatic response to chemotherapy., They will receive injections of a culture of live BCG once a week for six weeks after excision of their tumors. Three months later, the injections will be given once a week for three weeks. This three-week course will be repeated after another three-month pause and then every six months for three years. Patients who have no evidence of disease after chemotherapy will undergo a physical exam and tests every three months for three years. These patients will not receive BCG unless disease recurs.

- A phase II prospective trial of accelerated concomitant boost radiotherapy in transitional cell carcinoma of the bladder (ID95-212). *Physician: Alan Pollack, M.D., Ph.D.*

  Associate Professor of Radiation Oncology Alan Pollack, M.D., Ph.D., of the Department of Radiation Oncology is studying the effectiveness of radiation therapy alone for locally advanced transitional cell carcinoma of the bladder. Patients will undergo radiation therapy once a day every weekday for three weeks. They will then undergo radiation therapy twice a day every weekday for two and one-half weeks.

- A phase II trial of taxol, methotrexate, and cisplatin as neoadjuvant therapy for advanced bladder cancer (ID95-198). *Physician: Randall E. Millikan, M.D., Ph.D.*

  Assistant Professor of Medicine Randall E. Millikan, M.D., Ph.D., of the Department of Genitourinary Medical Oncology is investigating the combination of paclitaxel (taxol), methotrexate, and cisplatin against bladder cancers that are not cured by excision of the bladder alone. The drugs will be given by long-line infusion over five hours. The infusion will be given 10 times (days 1 and 8 in five 21-day cycles).

- Phase II surgical consolidation for subdiaphragmatic retroperitoneal and pelvic lymph node metastases following response to chemotherapy in patients with transitional cell carcinoma of the bladder and node-only disease (ID96-193). *Physician: Louis L. Pisters, M.D.*

  Assistant Professor of Urology Louis L. Pisters, M.D., of the Department of Urology is studying the effects of excision of the bladder and retroperitoneal and pelvic lymph nodes in patients who have received chemotherapy for transitional cell carcinoma.

  Patients with subdiaphragmatic nodal metastasis from transitional cell carcinoma with or without the bladder present are study candidates.

FOR MORE INFORMATION *about these clinical trials, physicians or patients should call the M. D. Anderson Information Line. Those in the United States, call (800) 392-1611; those in Houston or outside the United States, call (713) 792-6161. Visit the M. D. Anderson Cancer Center clinical trials Web site at http://www.clinicaltrials.org.*

tive. "If the *p53* gene is incorporated and expressed by the bladder tumor cells, there may be a benefit to patients," Dr. Pagliaro said. Patient recruitment was expected to begin this month.

Another strategy employs chemoprevention to combat frequently recurring superficial bladder cancer by returning the urothelium to a stable state. Dr. Grossman will try to halt the pattern of recurrence by using 4-HPR (fenretinide), an agent that has shown antitumor activity in in vitro and animal studies. After resection, patients whose papillary bladder tumors have been diagnosed for the first time or patients who have had a recurrence more than a year after initial treatment will be randomized to receive either 4-HPR or a placebo for 12 months.

In the 4-HPR study, physicians also will examine a host of biomarkers to determine whether they can serve as intermediate endpoints, indicating treatment effect earlier than the standard endpoint of tumor recurrence or progression. Alteration of biomarkers may precede clinical evidence of disease by months or years. Conversely, normalization of biomarkers may indicate regression or eradication of disease.

"We are seeing that biomarkers do provide clinically relevant information," Dr. Grossman said. "The question is, how do we incorporate them into our practice?"

One answer is a biomarker laboratory project Dr. Dinney hopes to bring into the clinic within the next year. With Robert Radinsky, Ph.D., of the Department of Cell Biology, Dr. Dinney has been studying the effects of inactivating the epidermal growth factor receptor (EGFR), whose levels are elevated in 50% of bladder cancers. EGFR overexpression is associated with increased tumor size and grade and decreased patient survival rates.

Dr. Dinney has used several strategies to inactivate the EGFR in bladder cancer cell lines and a nude mouse model. For example, C225 anti-EGFR antibody produced remarkable regression of tumors. In addition to a grossly measurable effect, he found changes in biomarkers of apoptosis, angiogenesis, proliferation, and invasion. With Randall Millikan, M.D., of the Department of Genitourinary Medical Oncology, Dr. Dinney is designing a clinical trial that combines anti-EGFR therapy with chemotherapy. "An important aspect of the trial will be evaluating clinically some of the cellular proliferation, invasion, and metastasis biomarkers from our preclinical studies," Dinney said. •

FOR MORE INFORMATION, *contact Dr. Grossman or Dr. Dinney at (713) 792-3250, or call the M. D. Anderson Information Line at (800) 392-1611 or (713) 792-6161.*

What Happens to Me Now, Doctor?

Practice Guidelines and Collaborative Paths Point the Way

by Sunni Hosemann

People diagnosed with cancer want answers. They want reassurance. They want their physician to answer the question, *"What happens to me now, doctor?"*

For these patients as well as the health care professionals who serve them, answering the question of what happens next in a cancer diagnostic workup and treatment plan has been made more clear-cut by the creation of clinical guidelines and collaborative care paths, disease management tools essential in the age of managed care and limited resources. Each has specific uses, and each offers information that can reassure patients about what will happen next.

At The University of Texas M. D. Anderson Cancer Center, practice guidelines are created as clinical algorithms for specific disease processes. Each represents a broad overview of the disease process and the approaches to multidisciplinary medical care that encompass addressing the entire clinical spectrum: for example, diagnosis, initial evaluation, staging, further diagnostic workup, initial treatment, response assessment, adjuvant treatment, surveillance, and salvage (with rehabilitation and follow-up) or palliation.

Crafted by multidisciplinary teams of physicians, nurses, and others, each practice guideline sets out an evidence-based multidisciplinary medical model of care that incorporates up-to-date best practices and reports from the medical literature. The guidelines aggregate what is currently known and present it in a usable format.

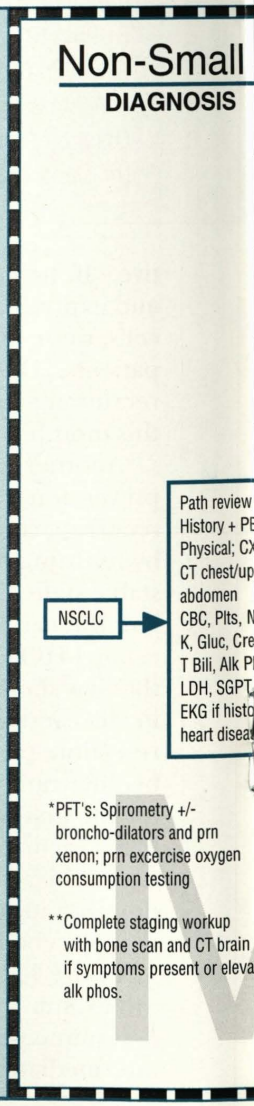
Collaborative care paths, more specific plans that define treatment and expected outcomes, are developed for on-the-scene clinical practice. These critical paths or care maps outline the expected or optimal sequence and timing of interventions for a specific procedure or course of treatment, and for a specific disease. For ovarian cancer, for example, there is a path for patients on carboplatin outpatient chemotherapy and another for patients on taxol-carboplatin chemotherapy. Paths at M. D. Anderson incorporate a comprehensive package for managing patient care: a timeline of expected outcomes, nursing documentation guidelines, standard (but flexible) sets of physician orders, consent forms, and patient education materials. Outcomes and variances from paths are tracked, and as new data accumulate, the path may change to ensure the best care. In this way, the path remains dynamic.

Mapping paths and guidelines in health care has been stimulated by the growth of managed care and efforts to use resources more efficiently, and their use at M. D. Anderson has decreased cost and variability of treatment, according to Mitchell Morris, M.D., vice president for information services and health care systems, who oversees guideline and path development. In fact, in an early cost comparison of patient care (30 patients enrolled on a path and 73 others treated before discussions of paths began), total costs fell 20%, and laboratory test costs dropped 74%. No patients on the path reported in a patient satisfaction survey that they believed they had been discharged too soon, and about 85% agreed or strongly agreed that the physicians were caring. Dr. Morris argues that the value of the paths goes beyond cost cutting, though length of stay and costs have seen significant reductions.

"It's about quality," he said. The goal is not to shorten length of patient stay, according to Dr. Morris, but to determine what the *appropriate* length of stay is—in essence, to determine how to provide the highest quality of care for every patient. Paths, then, become a foundation on which to

The director of the Thoracic Multidisciplinary Care Center, a thoracic surgeon, and a radiotherapist worked as the core team preparing this guideline for non–small cell lung cancer.

Abbreviations:
PE, physical examination; **CXR**, chest X-ray; **CT**, computed tomography; **CBC**, complete blood count, **Plts**, platelets; **Na**, sodium; **K**, potassium; **Gluc**, glucose; **Creat**, creatinine; **T Bili**, bilirubin; **Alk Phos**, alkaline phosphatase; **LDH**, lactate dehydrogenase; **SGPT**, serum glutamate pyruvate transaminase; **Ca**, calcium; **EKG**, electrocardiogram; **PFT's**, pulmonary function tests; **prn**, *pro re nata* (as needed); **MRI**, magnetic resonance imaging; **Wt**, weight; **chemo**, chemotherapy; **XRT**, X-ray therapy; **post-op**, postoperative; **met**, metastasis.



build care, a way to eliminate unnecessary or ineffective procedures, and to determine and document where variations from optimal care occur. By tracking the outcomes and variances from the path, physicians and nurses can revise plans and raise treatment quality.

"You don't know where you are until you look at the data," said Loretta Murphy, R.N., M.B.A., O.C.N, associate administrator in the Practice Outcomes Program, a part of Dr. Morris's guidelines and paths development team. "These are tools that will enable us to truly practice evidence-based medicine," she said.

"The fact that we're tracking outcomes is also important to patients," she added. "They want to see that they're in the best situation."

Dr. Morris is enthusiastic about specific features of M. D. Anderson's paths:

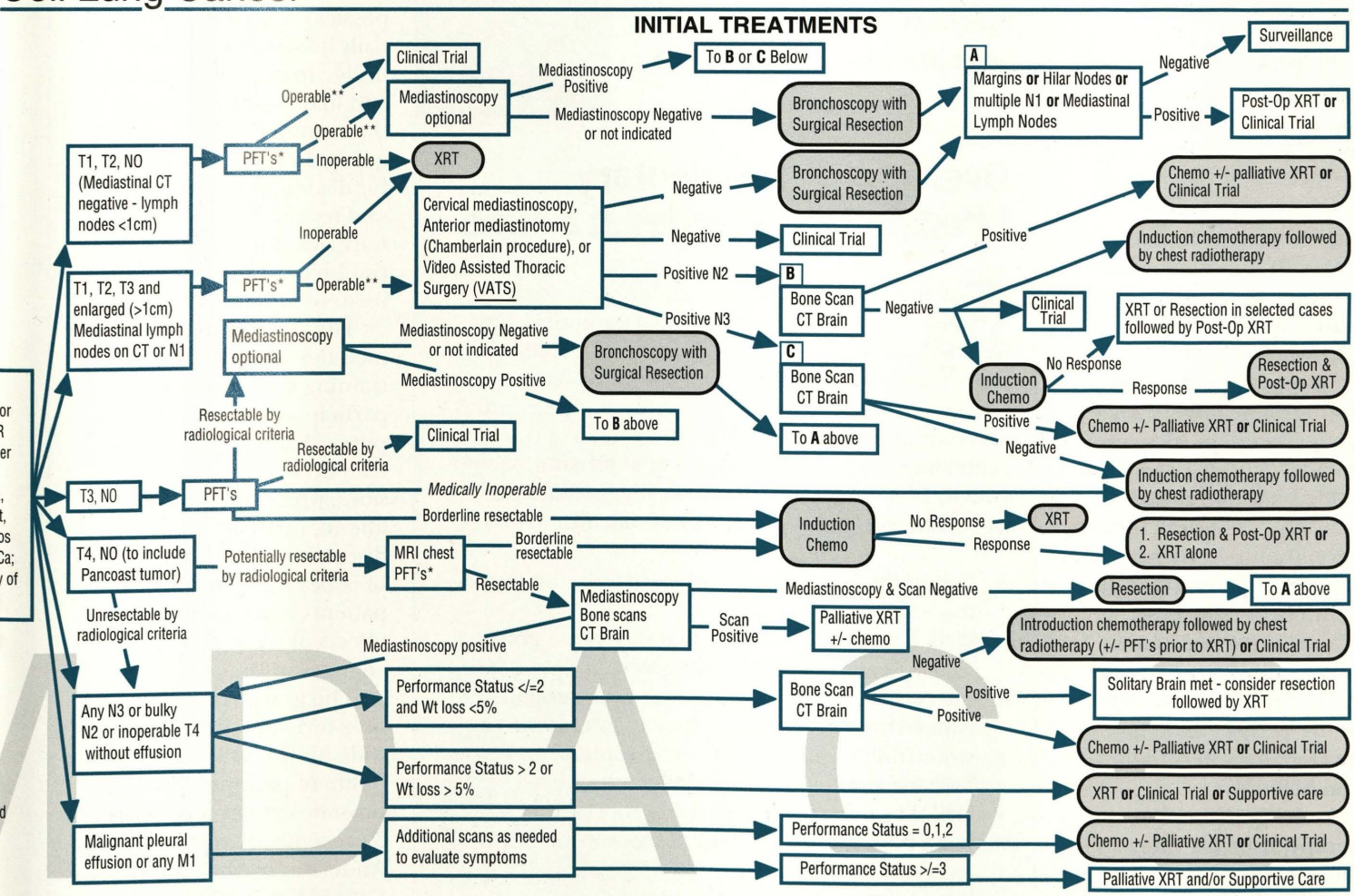
- They are physician driven, both in development and application. Advanced practice nurses are teammates. Dr. Morris and his group designed the process this way because, he said, "We [physicians and nurses] are the ones who should be defining care—not actuaries or insurance companies."

A team develops a guideline or care path, and then it is reviewed by all physicians who treat that type of cancer. After approval, the finished product is placed in a standard format for distribution and use.

- The paths are patient focused. At M. D. Anderson, more than 500 patients are currently on paths each month, and patient satisfaction is a major tracking point.
- The paths are enhanced with information for patients. Patient education materials are embedded in the paths and accessible through the same computer application program as the paths. The materials can be downloaded in some clinics; others obtain them from the Office of Patient Education. The education office has worked closely with the Practice Outcomes Program to develop materials that parallel the paths and present what Director of Patient Education Louise Villejo calls "a story" of their care. This story is a road map for the patient. "Most cancer patients are thirsty for knowledge," Murphy said. "It's often the only sense of control they have over this complex and potentially devastating disease."

Seventeen cancer guidelines are complete and available on the institution's Cancer Manager Program at http://www.cancermanager.org on the World Wide Web. Others will be added as they are completed. ●

Cell Lung Cancer



Prostate Cancer
Patients To Test Exercise Theory in Quality-of-Life Study

by Alison Ruffin

Can exercising "the easy way" by making a few lifestyle changes—climbing stairs rather than taking the elevator and using a push lawn mower instead of a riding mower—improve the life of patients with prostate cancer?

This is the question investigators at The University of Texas M. D. Anderson Cancer Center will examine in a $685,000 study funded by the American Cancer Society.

Proposed by M. D. Anderson researchers in response to a request by the American Cancer Society, the three-year project will evaluate what impact physical activity has on the quality of life of men with prostate cancer who were treated with androgen-ablation therapy.

"We want to determine whether a healthy lifestyle change, namely, increased physical activity, can lead to better symptom management and an overall feeling of well-being in these patients, in hopes that they will incorporate these changes on a permanent basis," said Ellen R. Gritz, Ph.D., principal investigator for the project and chair of the Department of Behavioral Science.

Androgen-ablation therapy, used for men whose prostate cancer has spread following unsuccessful initial treatment, seeks to control prostate cancer cell growth by eliminating the male sex hormones on which the cells depend. It may result in fatigue, muscle weakness, weight gain or change in weight distribution, and a decline in bone mass. Exercise is known to improve physical fitness and to help reduce some of these symptoms and, in addition, reduce levels of stress and depression, which many cancer patients experience.

"We are targeting several aspects of quality of life, including feelings of mental and physical well-being in these patients. This physical activity program may assist in rehabilitating these men, who often live many years with prostate cancer," said Bernard Levin, M.D., M. D. Anderson's vice president for cancer prevention.

The study's approach to exercise is to make physical activity a lifestyle habit rather than a practice restricted to a structured exercise regimen. Dr. Gritz believes a lifestyle-based program may be more appealing to older patients and to those who suffer from a chronic illness.

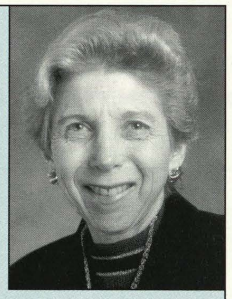
"Incorporating moderate physical activity into their daily lives may serve as a bridge to improved mood and may be more appealing than standard psychological group therapy, used by many for dealing with depression," said researcher Cindy Carmack, Ph.D., clinical psychologist in the Department of Behavioral Science.

The six-month program includes behavioral skills training that teaches participants to incorporate physical activity into their daily lives. The group sessions, which spouses may attend, incorporate discussion of a number of issues prostate cancer patients face, including effects of treatment and changes in sexuality.

The grant was one of only two awarded nationwide on the topic of quality of life of patients with prostate cancer and one of 39 recently given to M. D. Anderson by the American Cancer Society. ●

"We want to determine whether increased physical activity can lead to better symptom management and an overall feeling of well-being."

– Ellen R. Gritz, Ph.D.



Overcoming a Sedentary Lifestyle Two Minutes at a Time

For those who decline to undertake a structured exercise program, incorporating a few daily physical activities in their schedule is a way of overcoming a sedentary lifestyle. The increased activity can include integrating several two-minute walks throughout the course of the day. **A minimum of 30 minutes per day of physical activity of at least moderate intensity provides the opportunity to become more physically fit.**

- **Get off the bus** a block early and walk the rest of the way.
- **Walk a block or two** for lunch instead of going to the restaurant across the street.
- **Take a walk** during a television commercial.
- **Park farther away** from rather than closer to a store (don't look for the closest spot).
- **Take the stairs** instead of the elevator.
- **Make several trips** to bring in groceries.
- **Use a push mower** instead of a power or riding mower.
- **Use a rake** instead of a leaf blower.

TO PATIENTS.

New Survey

Put your stethoscope to the heart of *OncoLog* and tell us what you hear.

OncoLog's heart beats for you, and we want to know if you hear it. Respond to the questions below. Then fold, seal, and mail the card back to us. Or you can fax it to (713) 794-1370. No postage to pay; no cover sheet required. Your assessment is critical to ensuring *OncoLog* continues to meet your cancer information needs. *Now what do you hear?*

Question *(Answer in boxes on right first.)*	Yes	No
1 How is ONCOLOG valuable to you? *Check all boxes that apply:* ❑ Educational ❑ A partner in improving care ❑ A partner in interpreting basic science ❑ Useful in day-to-day practice ❑ Useful in interaction with patients ❑ Useful in planning treatment ❑ Other _____		
2 Has something you learned in ONCOLOG helped keep you up-to-date?	❑	❑
3 Has information you gained from ONCOLOG influenced your cancer care approach? *Check all boxes that apply:* ❑ Screening ❑ Diagnostic workup ❑ Treatment planning ❑ Other _____	❑	❑
4 Have you photocopied and distributed the patient education sheet for your patients?	❑	❑
5 By reading ONCOLOG, have you learned something about M. D. Anderson, about its services, or about its faculty?	❑	❑
6 Do you save issues of ONCOLOG for as long as a year?	❑	❑
7 Do you access ONCOLOG on the Internet? *For each statement, check the box that indicates your preference:* • On the Internet, you prefer for presentations to be ❑ longer ❑ shorter. • On the Internet, you prefer graphics to be ❑ expanded ❑ limited. • For the ONCOLOG, you prefer a version that comes to you by ❑ mail ❑ Internet.	❑	❑
8 Comments: _____ _____ _____ _____		

Thank You.

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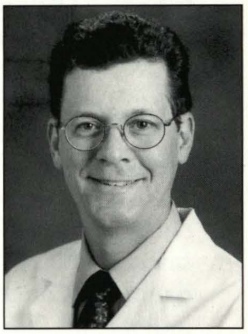
DiaLog

The New Math of Today's Health Care

Mitchell Morris, M.D.
Vice President for Information and Health Care Systems



The effects of the managed care movement and the controversy over financing health care stimulate a half dozen news stories across the country every day along with editorial page speculation about health care's future. The question is basic: how is less more? How can fewer caregivers, fewer tests, less medicine, and less time in the hospital add up to more—higher quality care?

This is the core of the debate for both physicians and patients. How do both ensure that quality of care remains high yet cost is reasonable? Unfortunately, what too often is left out of the equation by which we calculate today's care is what has been added and the nature of what has been subtracted.

What has been added is health care's collaborative multidisciplinary response to demands for more efficient care. That response, not represented in the DRG, FTE, and LOS litany, has been the crafting of practice guidelines and critical paths meant to guide decision making across the continuum of care, from diagnosis through rehabilitation or palliation.

But before implementation, these "additions" did not look like pluses. Some physicians understandably feared violation of the patient-physician relationship. Others feared loss of autonomy. Still others were wary of changing time-tested practices because of some reengineer's dream of cookie-cutter physicians or some insurer's desire for a fatter profit margin.

What determines their value is how they are created. The way to make viable care paths is not to use evidence from claims, but experience from physicians, nurses, and others involved intimately with care; not to rely on bottom-line thinking, but to aim for top-of-the-line caring; not to demand patients' outcomes conform to an artificial standard, but to use quality outcomes to identify appropriate measures. As I wrote elsewhere: "Medicine is more complex than cooking eggs; patients are not always ready to go home when the timer goes off."

What was subtracted was unnecessary—not necessary—practice variability, excessive—not essential—laboratory tests, and overextended—not requisite—hospital stays.

What's the sum? With implementation, the paths with their preprinted orders, multidisciplinary collaborative care orientation, supporting patient education materials, and quality outcomes component have reduced cost without reducing the quality of care. Nobody argues that that is less.

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