



# COMMUNITY ONCOLOGY

— CLINICAL ISSUES IN COMMUNITY PRACTICE —

## ORIGINAL RESEARCH

Promising therapies, prohibitive costs:  
a qualitative assessment of the effects of the  
**Medicare Part D doughnut hole** on access  
to costly cancer medications

Leslie Jackson Conwell et al

**Molecular tumor classification** using a  
92-gene assay in the differential diagnosis of  
squamous cell lung cancer

Robert S. McGee et al

*Pictured above: lung cancer cell in final stage of division*

## COMMENTARY

The **evolving role of molecular diagnosis**  
of cancer types and subtypes: stay tuned

F. Anthony Greco

## CASE REPORTS

**Breast-conservation surgery and adjuvant  
multicatheter balloon brachytherapy** after  
augmentation mammoplasty

Anthony E. Dragun et al

Association of spontaneous **bilateral femoral  
stress fractures** with zoledronic acid use in  
a patient with metastatic breast cancer—  
a cautionary tale

Chandravathi Loke et al

## PRACTICAL BIostatISTICS

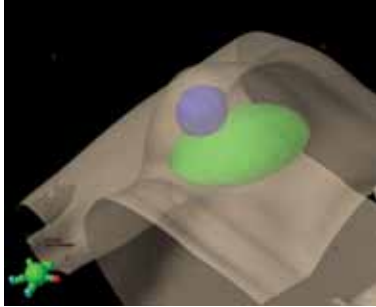
On **replicating studies**, phase II and phase III  
trials, and other vagaries of clinical research

David L. Streiner and Geoffrey R. Norman

## WASHINGTON UPDATE

NIH leads effort to **lower radiation doses in  
CT scans**

Monica Hogan



Three-dimensional reconstruction showing the virtual radioactive source positions within a balloon catheter (blue) overlying a breast augmentation implant (green) in a breast cancer patient who opted for breast-conservation surgery plus accelerated partial breast irradiation (see page 134)

### Washington Update

#### 143 NIH leads effort to lower radiation doses in CT scans

Monica Hogan, *The Gray Sheet*

The National Institute of Biomedical Imaging and Bioengineering, an imaging group within the National Institutes of Health, steps up its response to concerns over radiation exposure with a concerted effort to reduce the effective radiation dose from a routine CT exam by 80%–90%, challenging other federal agencies, industry, professional societies, and clinicians to find ways to reduce the routine CT radiation dose from the current average effective dose of about 7 mSv to less than 1 mSv.

With commentaries by Zaina P. Qureshi, PhD, MPH, Charles L. Bennett, MD, PhD, MPP, and Oliver Sartor, MD, and by Jondavid Pollock, MD, PhD.

### LETTER FROM THE EDITOR

#### 109 **Costly drugs and unfilled scripts: the socioeconomic impact is as devastating as the clinical**

Lee S. Schwartzberg, MD, FACP, *The West Clinic, Memphis, TN*

With the rising costs of cancer drugs, an increasing number of cancer patients cannot afford to fill their prescriptions. This trend toward unfilled prescriptions is an important aspect of cancer care delivery, given its negative impact on overall outcomes, costs, and quality of life for the patient.

### ORIGINAL RESEARCH

#### 111 **Promising therapies, prohibitive costs: a qualitative assessment of the effects of the Medicare Part D doughnut hole on access to costly cancer medications**

Leslie Jackson Conwell, PhD, Dominick Esposito, PhD, Margaret Colby, MPP, Daniel Ball, DrPH, Eric S. Meadows, PhD, and Martin Marciniak, PhD, *Mathematica Policy Research, Inc., Washington, DC; Mathematica Policy Research, Inc., Princeton, NJ; and Eli Lilly and Company, Indianapolis, IN*

Researchers interviewed oncology social workers and nurse practitioners in an effort to understand how the Medicare Part D doughnut hole affects beneficiaries' financial access to oral anticancer targeted therapies. The findings highlight the financial obstacles associated with the Part D coverage gap, which may not be fully addressed by recently passed healthcare reform legislation.

#### 123 **Molecular tumor classification using a 92-gene assay in the differential diagnosis of squamous cell lung cancer**

Robert S. McGee, MD, PhD, Nicole C. Kesty, PhD, Mark G. Erlander, PhD, and Catherine A. Schnabel, PhD, *Randolph Hospital, Asheboro, NC, and bioTheranostics, Inc., San Diego, CA*

In a retrospective study to characterize the clinical utility of molecular profiling in diagnosing and treating squamous cell lung cancer using a 92-gene molecular profiling assay, a physician survey of clinical strategy before and after the assay presented preliminary evidence that molecular profiling provides additional information on tumor site and subtype in conjunction with clinical evaluation.

#### 132 **The evolving role of molecular diagnosis of cancer types and subtypes: stay tuned**

F. Anthony Greco, MD, *Sarah Cannon Cancer Center, Sarah Cannon Research Institute, and Tennessee Oncology, PLLC, Nashville, TN*

Accurate molecular diagnosis of cancer type or subtype in selected groups has important therapeutic implications, and more definitive data from studies comparing molecular assay diagnoses and standard pathologic diagnoses and/or outcomes in patients with cancer of an unknown primary site are eagerly awaited.

Contents continued on page 106

# contents 2

## COMMUNITY ONCOLOGY

### Correspondence

Inquiries should be addressed to *Community Oncology*, 60B Columbia Road, Morristown, NJ 07960; tel: 973-290-8200; fax: 631-424-8905.

Editorial correspondence, including submissions for publication or Letters to the Editor, should be addressed to the Editor-in-Chief, Lee S. Schwartzberg, MD, FACP, e-mail: editor@communityoncology.net.

Guidelines for authors are at [www.communityoncology.net/guide.html](http://www.communityoncology.net/guide.html). For further information, contact the Editorial Office, 240-221-2461, or e-mail the Managing Editor, Renée Matthews, [renee.matthews@elsevier.com](mailto:renee.matthews@elsevier.com).

### Advertising

For information on advertising rates, reprints, and supplements, contact Devin Gregorie, tel: 516-381-8613, e-mail: [d.gregorie@elsevier.com](mailto:d.gregorie@elsevier.com).

### Copyright

Copyright © 2011 by Elsevier Inc. All rights reserved. No part of this publication may be reproduced or transmitted in any form or by any means, electronic or mechanical, including photocopy, recording, or any information storage and retrieval system, without written permission from the Publisher.

### Subscriptions

Annual subscription rates (12 issues): *Domestic*: US \$363; *International*: US \$394. *Single copy*: US \$42. For further information regarding subscriptions, contact [subs@elsevier.com](mailto:subs@elsevier.com).

*Community Oncology* (ISSN 1548-5315) is published monthly by Elsevier Oncology, 60B Columbia Road, Morristown, NJ 07960.

### Disclaimer

Discussions, views, opinions, and recommendations as to medical procedures, products, choice of drugs, and drug dosages are the responsibility of the authors or advertisers. No responsibility is assumed by the Publisher, Editor, or Editorial Board for any injury and/or damage to persons or property as a matter of product liability, negligence, or otherwise or from any use or operation of any methods, products, instructions, or ideas contained in the material herein. Because of rapid advances in the medical sciences, independent verification of diagnoses and drug dosages should be made. Advertiser and advertising agency recognize, accept, and assume liability for all content (including text, representations, illustrations, opinions, and facts) of advertisements printed and also assume responsibility for any claims made against the Publisher arising from or related to such advertisements.

In the event that legal action or a claim is made against the Publisher arising from or related to such advertisements, advertiser and advertising agency agree to fully defend, indemnify, and hold harmless the Publisher and to pay any judgment, expenses, and legal fees incurred by the Publisher as a result of said legal action or claim. The Publisher reserves the right to reject any advertising that he feels is not in keeping with the publication's standards.

The Publisher is not liable for delays in delivery and/or non-delivery in the event of Act of God, action by any government or quasi-governmental entity, fire, flood, insurrection, riot, explosion, embargo, strikes (whether legal or illegal), labor or material shortage, transportation interruption of any kind, work slowdown, or any condition beyond the control of the Publisher that affects production or delivery in any manner.

This journal is printed on paper meeting the requirements of ANSI/NISO Z39.48-1992 (Permanence of Paper) effective with Volume 1, Issue 1, 2004.



### CASE REPORTS

## 134 Breast-conservation surgery and adjuvant multicatheter balloon brachytherapy after augmentation mammoplasty

Anthony E. Dragun, MD, Keith T. Sowards, MS, and C. Matthew Brown, MD, *Department of Radiation Oncology, University of Louisville School of Medicine, Louisville, KY, and Louisville General Surgery PLCC, Louisville, KY*

The authors report a case in which an early-stage breast cancer patient who underwent augmentation mammoplasty opted for accelerated partial breast irradiation but wanted to avoid whole-breast radiation because of the risk to her implant. She underwent breast-conservation surgery and adjuvant multicatheter balloon brachytherapy. The results showed a low toxicity profile and an excellent cosmetic outcome with no capsular contracture.

## 137 Association of spontaneous bilateral femoral stress fractures with zoledronic acid use in a patient with metastatic breast cancer—a cautionary tale

Chandravathi Loke, MD, Wilson C. Mertens, MD, Michael J. Yunes, MD, Rebecca A. Levy, MD, and Grace Makari-Judson, MD, *Divisions of Hematology and Oncology and of Radiation Oncology, Department of Internal Medicine, Baystate Regional Cancer Program, Springfield, MA; Department of Pathology, Baystate Medical Center, Springfield, MA; and Tufts University School of Medicine, Boston, MA*

The researchers present the first case of spontaneous bilateral femoral fragility fractures—demonstrating characteristic radiologic findings and absence of malignancy on pathologic evaluation—in a patient with breast cancer who has been on long-term treatment with zoledronic acid (Zometa) for the treatment of osseous metastases. Although other factors may have contributed to the fractures, including prior radiation and osteoporosis, the patient's presentation mimicked progressive metastatic osseous disease with new scintigraphic changes in the area of symptoms. Unlike many previous cases, the patient did not present with a complete fracture, but rather with persistent pain despite seemingly appropriate therapy.

### PRACTICAL BIOSTATISTICS

## 141 On replicating studies, phase II and phase III trials, and other vagaries of clinical research

David L. Streiner, PhD, CPsych, and Geoffrey R. Norman, PhD, *Department of Psychiatry, University of Toronto, Toronto, Ontario, Canada, and Department of Clinical Epidemiology and Biostatistics, McMaster University, Hamilton, Ontario, Canada*

Our columnists use the recent promising findings in a phase II trial of iniparib plus gemcitabine (Gemzar) and carboplatin in metastatic triple-negative breast cancer and the failure in a subsequent phase III trial to meet one of the primary endpoints as a stepping stone in a discussion of the differences between phase II and phase III trials and the problems inherent in study replication.

Community Oncology is indexed by EMBASE and the Cumulative Index to Nursing and Allied Health Literature (CINAHL)

# Costly drugs and unfilled scripts: the socioeconomic impact is as devastating as the clinical

Lee S. Schwartzberg, MD, FACP, Editor-in-Chief | The West Clinic, Memphis, TN

**T**he rising costs of cancer care cannot be sustained. Although all components of the delivery system bear part of the cost burden, it is the patient who ultimately suffers most. Consider oral oncolytic therapy as an example. Oral agents are becoming ever more important in the medical oncology landscape, with current estimates suggesting that they will comprise at least 25% of the total usage of chemotherapy by 2020. But new oral oncolytics are expensive—sometimes costing more than \$2,000 monthly—and because the overwhelming majority of cancer patients cannot afford drugs priced at these levels, numerous benefit structures have been created to contain out-of-pocket expenses.

For commercial payers, deductibles are arranged into tiers. Patients may have to spend \$20–\$200 per prescription to receive their oral drugs from a specialty pharmacy. Occasionally, the out-of-pocket expenses in underinsured benefit plans can reach \$500 a month. At that level, it is no surprise that we start noticing that prescriptions go unfilled. This trend toward unfilled prescriptions is an important aspect of care delivery, given its negative impact on overall outcomes, costs, and quality of life for the patient, and it is worthy of closer scrutiny informed by sound research findings.

Medicare patients are covered for oral drugs under the Medicare Modernization Act's Part D, a benefit program that covers higher-priced brand-name drugs—but only up to \$2,510. At that point, patients fall into the “doughnut hole,” a period during which they have to pay out-of-pocket for their drugs until they reach a maximum of \$5,726, after which Part D will come into effect again to cover 50% of the prescription costs under catastrophic coverage.

Thankfully, effective this year, the doughnut hole out-of-pocket amount has been halved with the implementation of the Affordable Care Act (ACA), which will eventually close the hole completely by 2020, assuming that the law is not re-

pealed, re-funded, or declared unconstitutional. This change is welcome news to Medicare beneficiaries in the medium to long term, but a significant number of patients and practice professionals are grappling with the stark realities of unaffordable oral drugs right now.

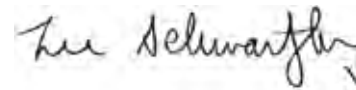
In this issue of *Community Oncology*, Conwell et al address the impact of Part D from the perspective of oncology social workers and nurse practitioners who are helping patients navigate the complexities of Part D coverage (page 111). Not surprisingly, these professionals spend a good deal of (uncompensated) time educating patients about Part D and helping them weather the financial and emotional burdens of the doughnut hole. Often they are a sounding board for patients and their family members who have to make the difficult choice between filling a prescription or paying the rent. Applications for patient assistance programs, such as Medicaid, and other governmental insurance programs are complicated, lengthy, and nuanced, meaning that practice professionals must almost always be on hand to assist patients with their submissions.

Even with assistance, the stress on the patient, family, and practice professionals is very real. As more individuals—including those with preexisting conditions such as cancer—gain some form of insurance under ACA, underinsurance in general, and for oral oncolytics in particular, will likely explode. At least the closing of the Part D doughnut hole is written into law. It's entirely possible that cost-sharing for beneficiaries under commercial plans will grow, jeopardizing delivery and adherence to life-saving medications. Oncology practices that are already feeling the strain of uncompensated services, such as financial counseling, must redouble their efforts to leverage other community resources to help them. Ultimately, all stakeholders, including and perhaps especially, the manufacturers of these highly priced agents, need to work together to find a broad-based solution to improving patient access to fairly priced oral oncolytics, which in turn will

achieve best outcomes. The socioeconomic impact of filling or not filling an oral oncolytic prescription is as important as the clinical aspects of the disease and must be taken seriously.

At our 6th Annual Community Oncology Conference last month in Las Vegas, we had an outstanding line-up of experts to speak about the scientific, social, clinical, legislative, and business and administrative dimensions of medical oncology. Their presentations were followed by lively panel discussions with the broadly based, highly engaged attendees. Next month, we will be featuring

in these pages some of the remarkable content and ideas generated by the group, some of which will be fleshed out with invited commentary. In the meantime, let the content in this issue be the stepping stone to new thoughts and perspectives on how we can best serve our patients in these changing and challenging times.



Lee S. Schwartzberg, MD, FACP  
Editor-in-Chief

## Call for articles

*Community Oncology* focuses on clinical oncology research within community practice and the translation of research outcomes as they apply to real-world oncology practice.

*Community Oncology* is a peer-reviewed journal that invites submissions of articles in the categories of reviews, original research, and perspective and commentary. *Community Oncology* welcomes studies that address the emerging research on evidence-based care and quality-of-life issues, as well as practical applications of advances in personalized medicine that guide clinicians as they assess the risks and benefits of cancer treatments for individual patients.

*Community Oncology* is an open-access journal that publishes online and monthly in print, with a circulation of over 26,000 physicians, physician assistants, nurses, nurse practitioners, pharmacists, and administrators.

For further information, see the Guide for Authors: [www.communityoncology.net/guide.html](http://www.communityoncology.net/guide.html).

# Promising therapies, prohibitive costs: a qualitative assessment of the effects of the Medicare Part D doughnut hole on access to costly cancer medications

Leslie Jackson Conwell, PhD,<sup>1</sup> Dominick Esposito, PhD,<sup>2</sup> Margaret Colby, MPP,<sup>1</sup> Daniel Ball, DrPH,<sup>3</sup> Eric S. Meadows, PhD,<sup>3</sup> and Martin Marciniak, PhD<sup>3</sup>

<sup>1</sup>Mathematica Policy Research, Inc., Washington, DC; <sup>2</sup>Mathematica Policy Research, Inc., Princeton, NJ; and

<sup>3</sup>Eli Lilly and Company, Indianapolis, IN

To understand how the Medicare Part D doughnut hole affects beneficiaries' financial access to oral anticancer targeted therapies, we conducted semistructured telephone discussions with oncology social workers and nurse practitioners. Respondents reported that targeted therapies' high costs pose considerable financial barriers. Some beneficiaries cease therapy upon reaching the doughnut hole, but others obtain financial assistance from copayment foundations or manufacturers' patient assistance programs. Higher-income beneficiaries may draw upon savings or incur debt. This study highlights the financial barriers associated with the Part D coverage gap that may not be fully addressed by recently passed healthcare reform legislation.

A major advance in oncologic therapeutics over the past decade has been the development of oral targeted cancer therapies that interfere with specific molecules that promote tumor growth.<sup>1,2</sup> Examples include imatinib (Gleevec) for leukemia and gastrointestinal stromal tumors and erlotinib (Tarceva) for non-small cell lung cancer and pancreatic cancer. Clinical trials continue to clarify the role of targeted therapies in cancer treatment; they are often prescribed after other treatments have failed.<sup>3,4</sup> Depending on the medication, patient side effects can range from skin or gastrointestinal toxicity to cardiac toxicity or interstitial lung disease.<sup>5</sup> Additionally, some of these medications are costly, exceeding \$100,000 annually.<sup>6,7</sup>

Each year, most new cancer cases occur among persons aged 65 years and older, making the Centers for Medicare & Medicaid Services the largest payer of oncology care in the United States.<sup>8</sup> Under Part B, Medicare pays 80% of the cost of infused chemotherapy agents or their oral equivalents, with beneficiaries—or their supplemental or secondary insurance—responsible for the remaining costs. Before the implementation of the Part D prescription drug benefit, Medicare coverage of oral anticancer medications was extremely limited. Although Part D drug plans now typically cover oral

targeted therapies,<sup>9</sup> beneficiaries with high annual medication costs face a substantial barrier in the doughnut hole—the coverage gap present in more than 70% of Part D plans in 2008. Those plans that do provide coverage during the gap typically only cover generic drugs, excluding many of the newer targeted therapies that are still branded.<sup>10–14</sup> Under the 2008 standard benefit design, beneficiaries were responsible for all medication costs between the spending thresholds of \$2,510 and \$5,726, after which cost sharing fell to 5% within a catastrophic coverage phase.

Taken together, the high costs of targeted therapies and the Part D doughnut hole may limit beneficiaries' access to anticancer medications, resulting in decisions to cease treatment, as has occurred among patients taking costly medications for other diseases.<sup>13</sup> Although some studies have examined the potential impact of the coverage gap on targeted therapy users' costs, few have considered the impact on access and continued use and on the strategies beneficiaries use to cope with high costs.<sup>15,16</sup>

Manuscript received October 19, 2010; accepted February 4, 2011.

Correspondence to: Dominick Esposito, PhD, Mathematica Policy Research, Inc., 600 Alexander Park, Princeton, NJ 08540; telephone: 609-275-2358; fax: 609-799-0005; e-mail: desposito@mathematica-mpr.com.

Commun Oncol 2011;8:111–117 © 2011 Elsevier Inc. All rights reserved.

This study describes the perspectives of oncology social workers and nurse practitioners regarding the effects of the doughnut hole on beneficiaries' access to oral targeted therapies and beneficiaries' strategies for handling out-of-pocket costs.

Oncology social workers and nurse practitioners are in a unique position to understand the challenges facing patients prescribed targeted therapies. In addition to helping patients through the psychosocial challenges associated with cancer, oncology social workers and nurse practitioners assist patients in finding financial assistance for prescription drugs. These professionals are especially useful to patients with low incomes or limited education, who often lack the skills, knowledge, or time to find assistance on their own.

## Methods

The institutional review board at Public/Private Ventures (Philadelphia, PA) approved our research design. The study took place in September and October 2008.

We conducted telephone interviews with oncology social workers and nurse practitioners across the United States. We required that respondents routinely worked with Medicare beneficiaries who use targeted therapies. Because targeted therapies are not typically a first-line treatment option and their use is limited, we recruited respondents who worked in large cancer facilities—those treating 650 or more new cancer patients per year.<sup>17</sup> We aimed for a mixture of cancer treatment facilities, such as those at community hospitals, teaching hospitals, National Cancer Institute (NCI)-designated cancer centers, and private physician practices. We also chose more states without state-sponsored pharmaceutical assistance programs (SPAPs) than states with such programs because patients in those states without SPAPs were more likely to have few options for obtaining financial assistance.<sup>18,19</sup> We recruit-

ed respondents using a combination of cold calling, letters, and e-mails, relying on both our own and respondents' contacts. Respondents received a \$100 honorarium.

The lead author (LJC) conducted or attended all discussions using a semistructured protocol with open-ended questions. Discussion topics included respondents' perceptions of Medicare beneficiaries' concerns related to targeted therapies and costs, beneficiaries' familiarity with the Part D doughnut hole, cost-reducing strategies utilized by beneficiaries, and beneficiaries' cost-related adherence to treatment. We asked clarifying follow-up questions and probed the respondents on particular cost-reducing strategies. Each 60- to 90-minute discussion was audiotaped. We continued to recruit respondents until no new themes emerged.

We entered notes from each discussion into ATLAS.ti, a software package to store, code, and analyze qualitative data. The lead author reviewed notes, assigned codes, identified thematic patterns across social workers and nurse practitioners and across locations, and summarized findings. A second author (DE) reviewed the findings and notes to ensure the data supported the findings. To protect respondent confidentiality, only three authors (LJC, DE, MC) had access to the audiotapes, transcripts, and respondent contact information. We have respected respondent confidentiality in this manuscript by identifying them only by letter (A, B, C, etc).

## Results

We interviewed 13 respondents from 11 facilities, including 11 social workers and 2 nurse practitioners. Respondents were from the East Coast, Midwest, and West. Six respondents worked at comprehensive cancer centers at community hospitals, three at NCI-designated centers, three worked at teaching hospitals,

and one worked at a private physician practice.

As summarized below, respondents initially discussed patient concerns about the costs of targeted therapies and awareness of the Part D doughnut hole before focusing on the significant financial and emotional burdens experienced by Medicare beneficiaries as they managed the costs of targeted cancer therapies.

### *Patient concerns about targeted therapies*

Respondents emphasized the pressures patients are under by the time targeted therapies are prescribed.<sup>20</sup> Because targeted therapies are often prescribed when other treatments have failed, patients are worried about their health and stressed by oncology-related medical bills for radiation, chemotherapy, imaging, and hospital stays. The additional expense of targeted therapies pushes many patients into a crisis situation.

Once targeted therapies are prescribed, patients' immediate concern is cost, followed closely by concerns about the drug's potential side effects and efficacy. Patients' cost concerns have resulted in respondents increasingly spending their time helping patients find financial assistance, leaving less time to address patients' psychosocial or medical needs:

*If there is an issue where a patient is going to have a financial burden or have difficulties getting a medicine they need, I am the referral for those patients to help them get help.... [A]t least half of my time is consumed with trying to connect people to financial help, whether it's helping them get medications, referrals to Medicaid, what to do about expensive medical bills in general. [Respondent A]*

### *Awareness of the doughnut hole*

Respondents reported having to educate Medicare beneficiaries about Part D because many beneficiaries are

often unaware of the doughnut hole, an observation consistent with other research.<sup>21,22</sup> One nurse practitioner estimated that half of her patients are unfamiliar with the coverage gap. In addition, beneficiaries expect Part D to provide financial assistance with relatively low cost sharing, similar to Medicare Part A and Part B, as one respondent explained:

*Many think that once they get on Medicare that it's going to take care of everything. They don't realize that there is a doughnut hole. Patients aren't aware of the doughnut hole before they reach it.* [Respondent B]

Awareness of the doughnut hole does not lessen beneficiaries' frustration, especially if they are already struggling financially:

*About 60% to 70% of my patients with targeted therapies have experienced the doughnut hole....They're very frustrated by it. They can't afford to pay for their meds...so they wonder, "How am I supposed to come up with \$2,500 until my insurance kicks in again?"* [Respondent C]

Another frustration among beneficiaries, according to respondents, is that beneficiaries cannot tell where their drug spending stands in relation to the doughnut hole until they reach it. Additionally, the high cost of some targeted therapies quickly propels patients through the doughnut hole (Figure 1). One respondent described beneficiaries' amazement that filling one 30-day supply of a targeted therapy places them in the doughnut hole and filling a second 30-day supply qualifies them for catastrophic coverage. Previously encountering the doughnut hole with other prescriptions does little to prepare beneficiaries for what will happen with targeted therapies:

*Some patients are very diligent and think they have it all figured out. They've taken heart meds or blood pressure pills, and it never cross-*

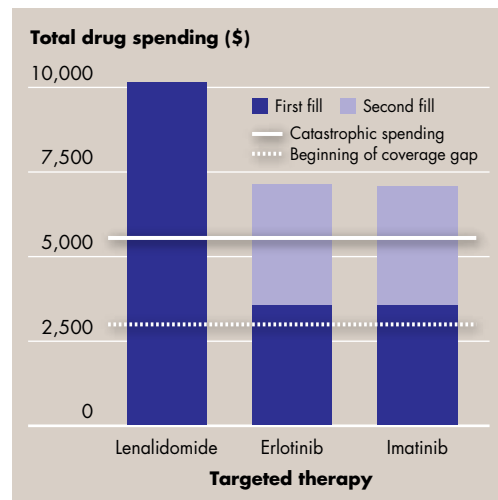
*es their mind that a single drug can propel them into the doughnut hole, even if they're very educated and savvy. Then there are some patients who are taking many meds and have hit the doughnut hole before. They're kind of glad that these drugs at least mean they go through the doughnut hole pretty fast, but they don't realize that they still have to pay 5%.* [Respondent D]

Not surprisingly, respondents identified low-income beneficiaries who are not eligible for Medicaid or the Part D low-income subsidy (LIS) program as having the greatest difficulty paying for targeted therapies. However, respondents were quick to note that beneficiaries with higher incomes struggle with targeted therapy copayments, although respondents did not encounter this population as often. Respondents reported these beneficiaries will draw upon their savings to cover their cost sharing but are reluctant to do so because they fear impoverishing a surviving spouse or having little to leave behind for their children. Others question why Medicare will not cover these expenses:

*They think their savings are their savings. There's definitely a group of individuals who have saved money for retirement and truly believe their retirement savings isn't something they should be dipping into for medical care; they view their savings as the money that they are supposed to live on. Medical care is differentiated.* [Respondent E]

Overall, respondents primarily focused on the financial struggles of patients who are not wealthy and have limited, if any, savings. From our discussions, three primary strategies emerged regarding how Medicare beneficiaries manage targeted therapy costs:

1. Obtaining financial assistance from a copayment foundation or a patient assistance program (PAP);
2. Paying out-of-pocket costs by



**FIGURE 1** Number of 30-day fills to reach catastrophic spending for selected targeted therapies under 2008 Medicare Part D benefit. Source: Authors' analysis of Medscape pricing data (<http://search.medscape.com/drug-reference-search>). Pricing data as of October 2008.

withdrawing money from savings or retirement accounts, assuming debt, or lowering living expenses; and

3. Declining targeted therapy treatments or stopping treatments when copayments become too high, typically upon encountering the doughnut hole.

*Obtaining financial assistance*

Low-income beneficiaries who do not qualify for Medicaid or LIS may be eligible for assistance from copayment foundations or from pharmaceutical manufacturers' PAPs.<sup>23-26</sup> These entities may provide full financial assistance or free medication for the remainder of the calendar year to eligible Part D enrollees who reach the doughnut hole. Eligibility is typically based on income and assets, diagnoses, and in some cases the specific medications prescribed. A SPAP is an additional option for beneficiaries residing in states that offer one. Oncology social workers and nurse practitioners are crucial to helping beneficiaries access these resources.

Respondents expressed frustration—both their own and beneficiaries'—with copayment foundations and PAPs because the application process is time-consuming, with no

**TABLE 1**

**Challenges in obtaining assistance from copayment foundations and manufacturers' patient assistance programs (PAPs)**

Key theme	Selected respondent quotations
Frustrations in working with copayment foundations and PAPs	<p>[W]e go to the copay foundations, which has been a complete nightmare. I'm thankful they're there, but I can't describe how frustrating they've been.... They have X amount of funds for copay assistance for different cancers. They open their phone lines for the first couple of days of the month, and you have to wait on hold until you access a representative to determine if the cancer group is within the network so you can even apply. Then they'll walk you through the application process to determine if you're in the network and are eligible. And after all that, then you find out the patient isn't eligible. [Respondent E]</p> <p>It's not an easy process. It takes at least a couple of hours per patient to find them resources. You're meeting with the patient, then you're following up with the patient and with the copay foundation. Then if there is no money left at the copay foundations, they send you back to the drug companies. At that point, the pharmaceutical company typically will assist. [Respondent D]</p>
Other financial pressures	<p>That's something else people worry about. [Patients say]: I can get help with [erlotinib] during the gap, but how will I pay out of pocket for my other five drugs during the gap? [Respondent A]</p>
Decisions about initiating treatment while awaiting assistance	<p>Some copay foundations are very generous and will pay \$4,000. But you never know who's going to get covered because it varies by drug and diagnosis.... There are built-in delays waiting for paperwork and limits on how much foundations can pay.... Patients are left wondering how they will keep affording these drugs. [Respondent D]</p> <p>Some people put their copays on their credit cards because they don't have the money but they're afraid to not start the drug. Then when they get enrolled in a drug program, the payments are not retroactive, so they eat \$1,000. [Respondent B]</p>

guarantee of approval (Table 1). Beneficiaries' success in obtaining assistance from copayment foundations or PAPs may reflect the experience of their social workers and medical staff. NCI-designated cancer center respondents specialize in a single tumor type, allowing them, as one respondent said, to have the process of obtaining assistance "down to a science." Other respondents deal with multiple kinds of cancer and must become familiar with the eligibility criteria of numerous organizations, sometimes relying on information from copayment foundation and PAP clearinghouses and approaching multiple entities for assistance (Table 1).

Our respondents worked in relatively large facilities and regularly en-

countered beneficiaries taking targeted therapies, giving their beneficiaries a comparative advantage over those treated in smaller facilities. A representative from an oncology social workers' association mentioned that social workers in smaller facilities or rural locations do not encounter such beneficiaries as frequently and, because of that, either are unaware of or lack the resources to access potential funding sources.

Obtaining financial assistance for targeted therapies does not completely ease beneficiaries' financial constraints. Assistance received from PAPs and copayment foundations does not count toward beneficiaries' doughnut-hole spending and does not help patients reach the catastrophic phase

more quickly.<sup>27</sup> Respondents emphasized that foundations do not typically cover the costs of beneficiaries' other medications, a factor that may figure into beneficiaries' decisions to begin treatment.

Foundations offer hope to beneficiaries, but respondents reported high stress for beneficiaries as they wait to see whether these hopes will be realized. Some beneficiaries have no choice but to wait for a copayment foundation or PAP's decision before beginning treatment. Others, concerned about delaying or skipping treatment, will initiate targeted therapies before a decision is made.

*Paying for medications out of pocket*

Beneficiaries who are not eligible for foundation or PAP assistance do not have many other options. Especially vulnerable, according to respondents, are beneficiaries who would have been considered the working poor when they held jobs. Often these beneficiaries have fixed incomes and insufficient savings to pay for targeted therapies over an extended period:

*They have some type of savings but not a lot. What may be a lot to some may be wiped out with one month's medications. [Respondent F]*

The high price of targeted therapies forces many patients to make tradeoffs between daily living expenses and medical expenses. Patients are reluctant to ask their families for assistance because many family members are not in a position to provide such help (Table 2). Although some patients move in with family members to save on housing costs, most patients view housing as a non-negotiable expense. Several respondents noted that patients do not typically forego rent or mortgage payments to pay for targeted therapies (Table 2).

Patients may leave utility bills unpaid due to overall cancer-related treatment costs, recognizing that local charities may provide assistance if

TABLE 2

## Patient efforts to manage out-of-pocket costs of targeted therapies

Key theme	Selected respondent quotations
Reluctance to accept assistance from family	Often times, the family can't assist with the costs either. They're in the same jam. Their children have children that they're caring for and can't help out—they have the same financial concerns. [Respondent C]
Tradeoffs between living expenses and drug costs	More often I see patients [who] will skip their meds before they skip paying their mortgage or other bills. Their homes and livelihoods are very important to them. They know their medications are important, but they are also thinking about their families—what are they going to be able to leave to their daughter or son? [Respondent C]

TABLE 3

## Decisions regarding declining or discontinuing treatment

Key theme	Selected respondent quotations
Weighing the costs and benefits of treatment	The targeted therapies can have bad side effects, like rashes or just making them feel very sick. They have the history of going through treatments and are kind of tired. They're reluctant to try another therapy. If there's a low percentage of it working, they want to know if the side effects are worth [having to pay the high cost of the drugs]. [Respondent G]
Being unable to afford treatment	A lot of these patients don't have tradeoffs to make. They try to see if there's someone else in the family who can pay or else they don't take the drugs. Those are their two alternatives.... The majority of patients who decide not to take the drugs do so because the copays for the drugs are more than people's monthly income. [Respondent H]
Discontinuing treatment upon reaching the doughnut hole	Some think they can make it through [the doughnut hole]. But then it's too much, so some patients will stop before they make it through the doughnut [hole], or a few prescriptions before. [Respondent C]

service is cut off. Patients may accrue credit card or other debt, occasionally leading to bankruptcy. Respondents also noted that many patients struggle to buy groceries.

*Declining or discontinuing treatment*

Despite the financial burden of targeted therapies, respondents perceived that many beneficiaries will at least initiate treatment, after first weighing the costs and benefits (Table 3). In particular, beneficiaries focus on whether the potential medication's side effects are worth the price of the targeted therapy.

Ultimately, the decision to start or continue targeted therapies comes down to money for many beneficiaries (Table 3). Some patients never speak about their financial struggles to so-

cial workers, due either to pride or the stigma attached to such problems:

*Some patients won't tell you anything. You'll start to wonder why they're not coming in for treatment, and most of the time it's because they can't afford to. [Respondent C]*

Beneficiaries may initiate but then discontinue therapy if the financial burden becomes too great. For some, this occurs upon reaching the doughnut hole if no assistance is available from a copayment foundation or PAP (Table 3).

Although adherence often is not discussed with patients, some social workers speculated that patients who obtain financial assistance may stop treatment or skip doses due to side effects but rarely due to costs. Some

patients, however, may continue to struggle financially and look for additional expenses to cut, such as not taking medications for other health problems if they are unlikely to experience long-term benefits:

*Given the poor lung cancer prognosis, patients will often stop other medications, especially those that are preventing problems over the long term like cholesterol drugs. We know they're going to die within a year, so what's the point of preventing a stroke in 3 years? [Respondent H]*

**Discussion**

Medications to treat cancer have emerged as a substantial driver of pharmacy spending; targeted therapies represent a fast-growing segment of these costs, with their utilization likely to increase considerably in the next decade as new treatments are developed.<sup>28</sup> Within the Medicare program, utilization of biologics—including targeted therapies—has tripled from 2006 to 2008, from 1.1% to 3.1% of beneficiaries, numbers that seem small except that these drugs are among the costliest covered by Medicare.<sup>29</sup> If the cost of oral targeted therapies remains at its current level, many beneficiaries using these drugs are likely to seek assistance from foundations or PAPs that are funded, in part, by donations from pharmaceutical manufacturers and others. The funding from these private entities can be subject to the whims of the business cycle, introducing uncertainty as to whether assistance will be available for Medicare beneficiaries.

A very real concern for policymakers is that users of targeted therapies increasingly will enroll in the LIS program because their medication costs drain their existing finances. Some respondents noted that they helped low-income beneficiaries apply for Medicaid. If an increasing number of Medicare beneficiaries enroll in the LIS program or Medicaid, it will only

shift the high costs of targeted therapies to an already overtaxed Medicare program. Indeed, a recent Government Accountability Office (GAO) report shows that LIS beneficiaries disproportionately utilize specialty medications compared with non-LIS beneficiaries.<sup>30</sup>

Based on information from workers on the front lines of cancer care, this study places a human face on the struggles of beneficiaries and adds a unique perspective to the growing literature on the association of the Part D coverage gap with the drug utilization and out-of-pocket costs of Medicare beneficiaries. Cancer-related treatment costs are a sizable portion of beneficiaries' income.<sup>31</sup> When prescribed a targeted therapy, beneficiaries question whether they can afford their copayments, even before their spending reaches the doughnut hole, of which many are unaware. Depending on their cancer diagnosis and medication, some low-income beneficiaries may qualify for assistance through a copayment foundation or a PAP but may delay or suspend treatment until they secure this assistance. Other beneficiaries do not obtain funding and may forego or stop treatment upon encountering the doughnut hole.

This study emphasizes the role of copayment foundations and PAPs in overcoming patients' financial barriers and complements other studies that have described the complexities of navigating these programs. Clearinghouses with information on copayment foundations and PAPs exist; ensuring that social workers in smaller facilities or more rural areas know about them may help these professionals secure assistance for their patients. But eligibility criteria and application processes do not appear to be centralized, and financially strapped facilities may have few resources to spare in navigating these programs, particularly if multiple organizations must be contact-

ed.<sup>24,32</sup> Patients who are sick and have low health literacy are unlikely to be able to access these programs on their own.<sup>24</sup> The Federal government could provide oversight of PAPs and copayment foundations, although doing so could lead these charitable organizations to cease offering assistance and could potentially divert attention from the real issue: the Part D doughnut hole.<sup>25</sup> Given the growth of targeted therapies and other high-cost biologics, many more beneficiaries are likely to find the doughnut hole an insurmountable barrier.

Our study has several limitations. First, we conducted discussions before the full impact of the recession had been felt, although several respondents nevertheless mentioned the difficult economic times. Over the past year, copayment foundations and PAPs reportedly have been overwhelmed by requests for assistance.<sup>33</sup>

Second, we interviewed a small number of social workers and nurse practitioners who work in large cancer facilities and regularly encounter patients taking targeted therapies. The data we received from respondents were remarkably consistent, despite the geographic diversity of the sample, allowing us to reach what is known in qualitative research as the saturation point. Nevertheless, because this sample is drawn from large institutions, it likely is not representative of where all cancer patients receive care.

To address this, we attempted to interview social workers at smaller facilities, but the ones we contacted were unfamiliar with targeted therapies. Yet despite our respondents' familiarity with copayment foundations and PAPs, they still described the frustrations of securing assistance for Medicare beneficiaries prescribed targeted therapies. In contrast, social workers in smaller facilities who have little familiarity with targeted therapies may not be aware such financial resources exist nor have the time to

seek them out; future research should be directed toward informing these professionals in smaller settings.

Third, this research relied on oncology professionals to identify the struggles and strategies of beneficiaries taking targeted therapies. Speaking directly to beneficiaries about their experiences potentially could provide additional detail. We originally planned to conduct focus groups with Medicare beneficiaries taking targeted therapies but aborted this effort because of difficulties in recruiting such sick patients to participate in focus groups. Our research could inform future studies that use representative surveys of beneficiaries and oncology professionals to measure the prevalence of such problems and behaviors—such research would be especially valuable in gaining insight into decisions made by those who have chosen not to seek financial assistance.

In theory, the doughnut hole encourages seniors to manage their use of drugs to avoid or limit exposure to the coverage gap. Other studies have discussed how patients who reach the doughnut hole cut back on essential medications.<sup>13,16</sup> Although Part D has helped to provide access to new anticancer medications, this study highlights the challenges posed by the doughnut hole for an extremely sick population for whom Part D-covered medications may be their last hope.

Medicare beneficiaries taking targeted therapies are unlikely to obtain immediate relief from changes to Part D in the recently enacted Patient Protection and Affordable Care Act. This law contains provisions to cut cost-sharing within the coverage gap in half starting in 2011 and gradually reduces cost-sharing to 25% by 2020, making it equivalent to cost-sharing before the coverage gap. This policy change reduces the financial burden of all beneficiaries who reach the coverage gap and eventually eliminates a controversial and highly debated

component of Medicare Part D, although the remaining cost-sharing is likely to continue to be a burden for some beneficiaries.<sup>34</sup>

## References

1. National Institutes of Health. Dictionary of Cancer Terms. <http://www.cancer.gov/dictionary/>. Accessed December 2, 2009.
2. Ciardiello F, Tortora G. EGFR antagonists in cancer treatment. *N Engl J Med* 2008;358:1160–1174.
3. Green MR. Targeting targeted therapy. *N Engl J Med* 2004;350:2191–2193.
4. Lynch TJ, Adjei AA, Bunn PA, et al. Summary statement: novel agents in the treatment of lung cancer: advances in epidermal growth factor receptor-targeted agents. *Clin Cancer Res* 2006;12:4365s–4371s.
5. Widakowich C, de Castro G Jr, de Azambuja E, Dinh P, Awada A. Side effects of approved molecular targeted therapies in solid cancers [review]. *Oncologist* 2007;12:1443–1455.
6. Tigue C, Fitzner K, Alkhatib M, Schmid E, Bennett C. The value of innovation: the economics of targeted drugs for cancer. *Target Oncol* 2007;2:113–119.
7. Lee TH, Emanuel EJ. Tier 4 drugs and the fraying of the social compact. *N Engl J Med* 2008;359:333–335.
8. Potetz L, DeWilde LF. Cancer and Medicare: A Chartbook. Washington, DC: American Cancer Society Cancer Action Network; 2009.
9. Bach PB. Limits on Medicare's ability to control rising spending on cancer drugs. *N Engl J Med* 2009;360:626–633.
10. Stemple C, Cammisa M, Evans S, Fenter TC, Gonzalez J, Lee H. Overview of current Medicare Part D offerings. *J Manag Care Pharm* 2008;14(6 suppl):S4–S7.
11. Hoadley J, Thompson J, Hargrave E, Merrell K, Cubanski J, Neuman T. Medicare Part D 2008 Data Spotlight: The Coverage Gap. Washington, DC: Kaiser Family Foundation; 2007.
12. Zhang Y, Donohue JM, Newhouse JP, Lave JR. Effects of the coverage gap on drug spending: a closer look at Medicare Part D. *Health Aff* 2009;28:w317–w325.
13. Schneeweiss S, Patrick AR, Pedan A, et al. The effect of Medicare Part D coverage on drug use and cost sharing among seniors without prior drug benefits. *Health Aff* 2009;28:w305–w316.
14. Cammisa CR, Evans S, Fenter TC, et al. Overview of current Medicare Part D offerings. *J Manag Care Pharm* 2008;14(6 suppl C):4.
15. Polinski JM, Mohr PE, Johnson L. Impact of Medicare Part D on access to and cost sharing for specialty biologic medications for beneficiaries with rheumatoid arthritis. *Arthritis Rheum* 2009;61:745–754.
16. Harrison C, Nguyen K. Cost-sharing for cancer patients in Medicare: seven case studies. Washington, DC: Avalere Health LLC; 2006.
17. Commission on Cancer. Cancer program accreditation: categories of approval. <http://www.facs.org/cancer/coc/categories.html>. Accessed September 23, 2008.
18. The Henry J. Kaiser Family Foundation. Benefits offered to qualified state pharmaceutical assistance programs. <http://statehealthfacts.org/comparetable.jsp?ind=642&cat=6>. Accessed January 20, 2010.
19. National Conference of State Legislatures. State pharmaceutical assistance programs. <http://www.ncsl.org/Default.aspx?TabId=14334#WI>. Accessed January 20, 2010.
20. Wagner L, Lacey MD. The hidden costs of cancer care: an overview with implications and referral resources for oncology nurses. *Clin J Oncol Nurs* 2004;8:279–287.
21. Hsu J, Fung V, Price M, et al. Medicare beneficiaries' knowledge of Part D prescription drug program benefits and responses to drug costs. *JAMA* 2008;299:1929–1936.
22. Cummings JR, Rice T, Hanoch Y. Who thinks that Part D is too complicated? Survey results on the Medicare prescription drug benefit. *Med Care Res Rev* 2009;66:97–115.
23. Choudhry NK, Lee JL, Agnew-Blais J, Corcoran C, Shrank WH. Patient assistance programs: information is not our enemy. *Health Aff* 2009;28:843–844.
24. Choudhry NK, Lee JL, Agnew-Blais J, Corcoran C, Shrank WH. Drug company-sponsored patient assistance programs: a viable safety net? *Health Aff* 2009;28:827–834.
25. Johnson K. Voluntary patient assistance programs: additional federal oversight unwarranted. *Health Aff* 2009;28:835–838.
26. Weinberg M. Reforming patient assistance programs: perfect world meets real world. *Health Aff* 2009;28:839–842.
27. Office of Inspector General. Publication of OIG Special Advisory Bulletin on Patient Assistance Programs for Medicare Part D Enrollees. In: Department of Health and Human Services, ed. Vol FR Doc. 05–23038. Tuesday, November 22 ed: Federal Register; 2005.
28. Medco Health Solutions I. News alert: cancer drugs emerging as top driver of specialty drug spending; 2009.
29. Centers for Medicare & Medicaid Services. 2010 Part D symposium. Baltimore, MD. 2010.
30. US Government Accountability Office. Medicare Part D: spending, beneficiary cost sharing, and cost-containment efforts for high-cost drugs eligible for a specialty tier. Washington, DC: Government Accountability Office; January 29, 2010.
31. Nonnemaker L, Sinclair SA. Medicare beneficiaries' out-of-pocket spending for health care services. Washington, DC: AARP Public Policy Institute; 2009.
32. Chauncey D, Mullins CD, Tran BV, McNally D, McEwan RN. Medication access through patient assistance programs. *Am J Health Syst Pharm* 2006;63:1254–1259.
33. Printz C. CancerScope: patient assistance programs struggle during tough economic times—programs cannot serve all those who need help. *Cancer* 2009;115:465–466.
34. Side-by-Side Comparison of Major Health Care Reform Proposals: Focus on Health Reform. Menlo Park, CA: The Henry J. Kaiser Family Foundation; 2010.

## ABOUT THE AUTHORS

**Affiliations:** Dr. Conwell and Ms. Colby are researchers at Mathematica Policy Research, Inc., Washington, DC. Dr. Esposito is a senior researcher at Mathematica Policy Research, Inc., Princeton, NJ. Dr. Ball is a research advisor and Dr. Meadows is a research scientist at Eli Lilly and Company, Indianapolis, IN. Dr. Marciniak, Vice President, Global Health Outcomes—US, GlaxoSmithKline, completed his contributions to this article while he was an employee of Eli Lilly and Company.

**Conflicts of interest:** This article was completed as part of a project funded by Eli Lilly and Company about the effects of the Medicare Part D benefit design on prescription drug utilization by beneficiaries with cancer, rheumatoid arthritis, and osteoporosis.

# Molecular tumor classification using a 92-gene assay in the differential diagnosis of squamous cell lung cancer

Robert S. McGee, MD, PhD,<sup>1</sup> Nicole C. Kesty, PhD,<sup>2</sup> Mark G. Erlander, PhD,<sup>2</sup> and Catherine A. Schnabel, PhD<sup>2</sup>

<sup>1</sup>Randolph Hospital, Asheboro, NC, and <sup>2</sup>bioTheragnostics, Inc., San Diego, CA

Recent progress in targeted cancer therapies for advanced non-small cell lung cancer (NSCLC) has expanded the selection of optimal treatment beyond platinum-based chemotherapy and identified differential response and safety profiles based on histology. Given that accurate pathologic classification is of increasing clinical interest, molecular diagnostics presents a standardized approach to determining the tissue of origin and the histologic subtype in conjunction with routine evaluation. The objective of this retrospective case study was to characterize the clinical utility of molecular profiling in diagnoses and treatment of squamous cell lung cancer by (1) comparing molecular results with pathologic correlates in lung classification and subclassification, (2) characterizing case features to better understand the clinical indications for molecular testing, and (3) evaluating the potential clinical impact based on how test results were utilized in rendering clinical diagnoses and treatment selections. Sixty-two cases predicted to be squamous cell lung cancer by a 92-gene molecular profiling assay (CancerTYPE ID) were evaluated. Specimen characteristics and abstracted pathology information revealed that the clinical indications for CancerTYPE ID were high-grade tumors with equivocal histopathology and/or immunohistochemistry and were utilized to potentially resolve a differential diagnosis (47%), to identify an unknown/uncertain primary tumor origin (32%), or to confirm a primary tissue origin (21%). A physician survey of clinical strategy pre and post assay showed that CancerTYPE ID guided, confirmed, or changed the primary tumor site for treatment purposes in 85% of the 20 evaluable cases and the tumor subtype in 60% of the tumors tested. Results of this case series present preliminary evidence that molecular profiling provides additional information on tumor site and subtype in conjunction with standard clinical evaluation.

**L**ung cancer is the leading cause of cancer-related mortality in both men and women and is associated with an estimated 160,000 deaths annually in the United States.<sup>1,2</sup> Approximately 85% of lung cancers are non-small cell type carcinomas (NSCLCs), which include adenocarcinoma (30%–40%), squamous cell carcinoma (25%–30%), and large cell carcinoma (10%–15%) histologies. Traditionally, classification of NSCLC into glandular and squamous subtypes had no therapeutic impact; however, recent clinical trials for NSCLC demonstrate that response to therapy may vary by histology.<sup>3–6</sup>

In a study comparing combination therapy of either pemetrexed (Alimta) or gemcitabine (Gemzar) with cisplatin in advanced-stage NSCLC, patients with nonsquamous cell carcinomas had significantly better survival with the pemetrexed combination, whereas the gemcitabine combination was more effective against squamous cell carcinomas.<sup>4,7</sup> Non-

squamous cell histology has also been associated with better outcomes in patients treated with the anti-VEGF (vascular endothelial growth factor) antibody bevacizumab (Avastin) in combination with carboplatin/paclitaxel.<sup>3,8</sup> Moreover, an increased risk of hemorrhagic or fatal bleeding events has been associated with bevacizumab and sorafenib (Nexavar), a multikinase inhibitor, in patients with squamous cell histology.<sup>3,9</sup> Therefore, precise histologic subclassification and detection of squamous cell components in lung neoplasms have distinct treatment implications.

## Histologic subclassification techniques

Lung carcinoma is routinely subclassified into its histologic variants based on morphology. How-

Manuscript received December 30, 2010; accepted February 16, 2011.

Correspondence to: Catherine A. Schnabel, PhD, bioTheragnostics, Inc., 9640 Towne Centre Drive, Suite 200, San Diego, CA 92121; telephone: 858-587-5884; fax: 858-587-5871; e-mail: cathy.schnabel@biotheragnostics.com.

Commun Oncol 2010;8:123–131 © 2011 Elsevier Inc. All rights reserved.

ever, varied histopathology and cellular heterogeneity are well-recognized features of these tumors, and reportedly less than 35% of lung carcinomas are of a single cell type.<sup>10-12</sup> Immunohistochemistry (IHC) has improved the precision of lung cancer classification with the use of particular markers, such as thyroid transcription factor-1 (TTF-1), p63, and cytokeratin (CK) 5/6.<sup>13-16</sup> In addition, the effectiveness of IHC is limited by technical inconsistencies in staining procedures, suboptimal sensitivities/specificities of individual markers, and nonstandardized interpretation.<sup>17-19</sup> Definitive diagnoses are further confounded in cases where diagnostic material is limited and in poorly differentiated tumors in particular.<sup>19-21</sup>

Although morphologic classification continues to be widely used, aided by IHC staining and other techniques, incorporation of molecular features can provide increased resolution and a standardized approach that complements current classification paradigms. CancerTYPE ID (bioTheranostics, Inc., San Diego, CA) is a reverse transcription-polymerase chain reaction (RT-PCR)-based molecular diagnostic test to determine the primary tissue of origin for 39 tumor types. It has a sensitivity of 87% and a specificity of > 99%.<sup>22</sup> Differential expression of 87 informative genes and 5 reference genes is the basis of this test. It is routinely performed on formalin-fixed, paraffin-embedded tissues, which requires approximately 300–500 tumor cells, and is a molecular extension to traditional IHC analysis.

The retrospective study reported here examined the clinical utility of the CancerTYPE ID test in facilitating a diagnosis of squamous cell lung cancer in tumor samples submitted for testing in 2009. The objectives were to conduct a preliminary evaluation of the clinical relevance of CancerTYPE ID test results in rendering diagnoses and

to estimate its added clinical value in patient management.

## Methods

### *CancerTYPE ID assay*

The 92-gene real-time RT-PCR assay (CancerTYPE ID) was developed as previously described.<sup>22</sup> Samples used in the CancerTYPE ID assay were formalin-fixed, paraffin-embedded tissue sections generated from tumor biopsies. Each tissue section was stained with hematoxylin and eosin for microscopic evaluation, and the areas with high tumor-cell density were marked by a pathologist. The tumor-enriched areas were isolated by manually scraping tissue off the slide or by employing laser microdissection to remove interfering tissue elements (normal cells, necrotic areas, fibrocytes, and lymphocyte infiltrations) to provide samples with a higher percentage of tumor cells. In this study, 53% of the specimens were harvested using laser microdissection.

The enriched tumor cells were lysed, with total RNA extracted and reverse transcribed to generate cDNA for the CancerTYPE ID assay, as previously described.<sup>22</sup> The RT-PCR assay was performed on an ABI 7900HT instrument using Taq Man technology (Applied Biosystems, Foster City, CA). The gene-expression profile for each patient sample was compared with the CancerTYPE ID tumor gene-expression database using a proprietary algorithm to predict the most likely primary tissue of tumor origin and histologic subtype.

Results are reported as ranked probabilities with single top predictions of primary tissue of origin and histologic subtype. The algorithm reports other possible cancer types in rank order based on probability, reflecting overlap in similar gene-expression profiles, and also calculates primary tissue types and histologic subtypes that can be “ruled out” with > 95% confidence. In these cases, 35%

of the CancerTYPE ID results were single predictions of squamous cell lung cancer. Consistent with the heterogeneity inherent in these tumors, 53% reported two possible predictions, and 11% contained ≥ three predictions. Second-rank results mainly included other squamous (such as skin) and lung (adenocarcinoma and neuroendocrine) predictions.

### *Study design*

This study was based on a retrospective review of all 64 cases reported as squamous cell lung cancer by CancerTYPE ID in 2009. The objectives were to characterize the indications for use of the CancerTYPE ID test in the differential diagnosis of squamous cell lung tumors and to survey the impact of molecular results in current practice and clinical decision-making. A total of 62 cases had complete pathology reports available (evaluable cohort, Table 1); two case reports were excluded: one due to incomplete information that could not be expanded and one due to a report that was not in English. Independent review board approval was granted with an exemption certification for the study.

### *Histopathologic evaluation*

All tumor samples were formalin-fixed, paraffin-embedded tissue sections. Descriptions of the tumor specimens, including biopsy site, suspected primary site(s), morphologic characteristics, tumor grading, and IHC analyses, were obtained from the sample requisition form and the pathology report submitted with each sample. During the collection of histologic grading data, tumor samples that were described as moderately to poorly differentiated were classified as poorly differentiated. If more than one description was listed (eg, squamous cell or transitional), the diagnosis was captured as not otherwise specified (NOS). When abstracting the interpretation of the prima-

ry site, if only one tissue was listed as the most likely primary tumor site, it was captured as the suspected primary for confirmation. When multiple potential primaries were listed, it was considered a “differential diagnosis.” Cases where the primary site was described as “unknown” or “other” (with specific tissues listed) were categorized as “unknown/uncertain.” When no primary tumor origin was listed, the specimen was classified as “unspecified.”

#### Clinician survey

For the clinician survey, molecular results were ranked by the strength of the CancerTYPE ID prediction. Using this approach, approximately one-third of the cases contained test results that predicted squamous cell lung cancer as single predictions; these were considered high confidence calls. The purpose of this component of the study was to conduct a preliminary inspection of potential clinical utility of CancerTYPE ID in a small series of cases wherein results were analytically compelling. Treating medical oncologists from these 22 cases were contacted to determine the diagnosis and treatment information using a standardized questionnaire. Specific questions in the questionnaire follow: (1) In regard to the primary tumor tissue type, would you say that the CancerTYPE ID guided/confirmed, changed, or did not affect your treatment decisions? (2) In regard to histology, would you say that the CancerTYPE ID guided/confirmed, changed, or did not affect your treatment decisions? (3) Which clinical diagnosis did you use to treat your patient? (4) What cancer treatment regimen did you use for this patient?

## Results

Patient demographics, specimen characteristics, and histologic characterizations for the 62 evaluable cases resulting in squamous cell lung tumor predictions by molecular test-

ing are given in Table 1. The mean age of the patients was 64 years. The lymph nodes (27%) and lungs (21%) represented approximately half of the biopsy sites. Clinical specimens included surgical, core-needle, and fine-needle aspirate biopsies. A majority of the cases in which grading was reported consisted of poorly differentiated epithelial tumors.

Antibody-based classification was performed predominantly through CK7, CK20, and TTF-1 IHC analysis in 68%, 69%, and 68% of the cases, respectively (Figure 1); p63 and CK5/6, markers suggesting squamous cell differentiation, were utilized in 21% and 15% of the cases, respectively. The number of IHC markers assayed ranged from 0 to 35, with a mean of 8.9 markers/sample and a median of 7.0 markers/sample.

An integrated schematic of the corresponding pathology data provided for the 62 evaluable squamous cell lung samples is shown in Figure 2. A lung origin was suspected or included in the differential diagnoses in less than 50% of cases ( $n = 29$ ); squamous cell morphology was noted in 47% of cases ( $n = 29$ ) and contained supportive IHC data in 21% of cases ( $n = 13$ ). Abstracted information from the pathology reports indicated that samples were submitted for molecular testing to resolve a differential diagnosis that included the lungs as a suspected site of tumor origin (47%), to confirm a suspected primary site that did not include the lungs (21%), or to identify an unknown/uncertain primary tumor origin or one that was not specified (32%).

Summary data for cases included in the clinician survey are shown in Table 2. Clinical sources for the table were extracted from pathology reports submitted with each case and from physician responses to the survey in regard to the particular cases. In 77% of these cases, CancerTYPE ID results were consistent with clinicopathologic correlates (squamous

**TABLE 1**

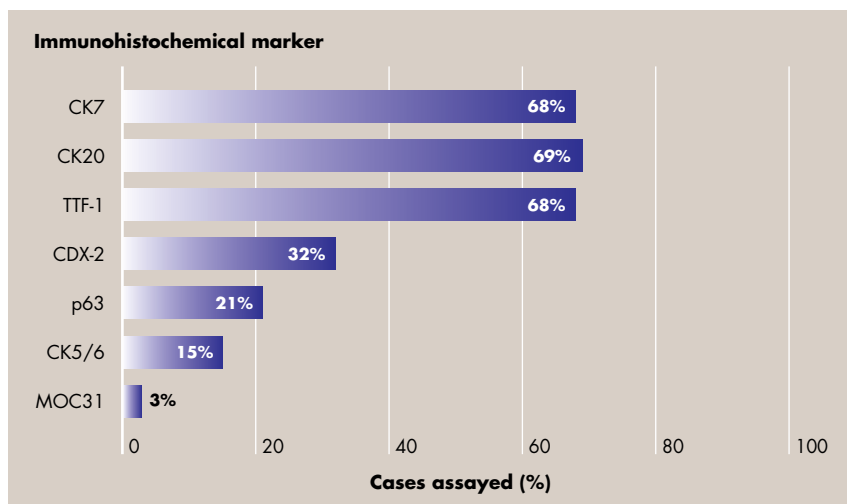
Demographics and specimen characteristics of 62 evaluable squamous cell lung tumor samples

Characteristic	Value <sup>a</sup>
Gender, male/female	60%/40%
Age, yr	64 ± 13 <sup>b</sup>
Biopsy type, n (%)	
Surgical	32 (52%)
Core needle	26 (42%)
Fine-needle aspirates/cell blocks	4 (7%)
Biopsy site, n (%)	
Lymph node	17 (27%)
Lungs	13 (21%)
Liver	9 (15%)
Head and neck	8 (13%)
Brain	3 (5%)
Other	12 (19%)
Histologic staging, n (%)	
Carcinoma	
Well	0 (0%)
Moderate	6 (10%)
Poor	19 (31%)
Undifferentiated	4 (7%)
NOS	19 (31%)
Adenocarcinoma	
Well	0 (0%)
Moderate	1 (2%)
Poor	6 (10%)
Undifferentiated	0 (0%)
NOS	5 (8%)
Neoplasm	
Undifferentiated	1 (2%)
NOS	1 (2%)
Histologic diagnosis, n (%)	
Squamous cell carcinoma	29 (47%)
Adenocarcinoma	13 (21%)
Carcinoma, NOS	9 (15%)
Other non-small cell carcinoma	7 (11%)
Carcinoma with neuroendocrine features	2 (3%)
Neoplasm	2 (3%)

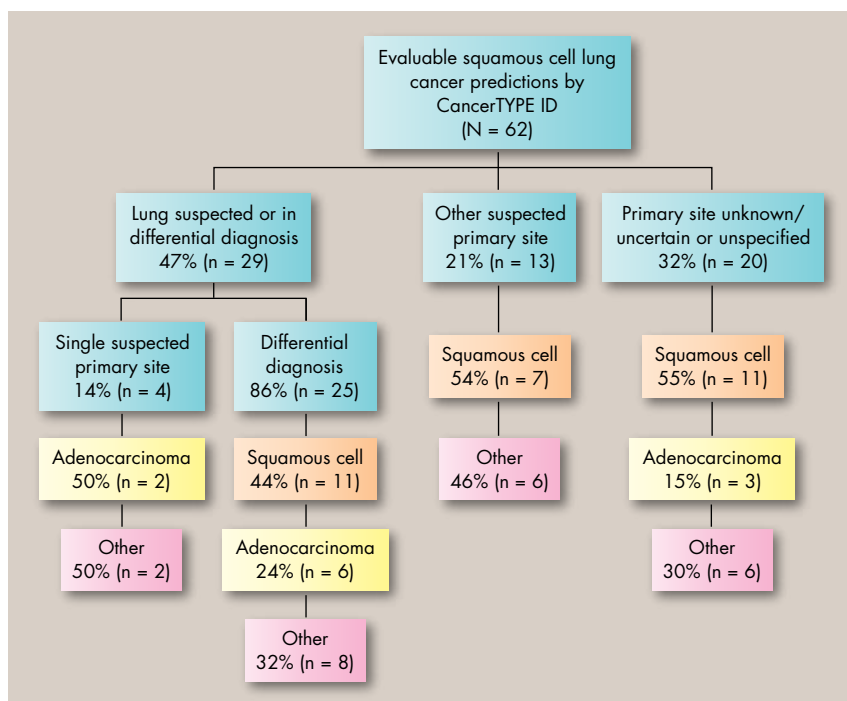
NOS = not otherwise specified

<sup>a</sup> Percentages may not sum to 100% due to rounding.

<sup>b</sup> Data are expressed as mean ± standard deviation.



**FIGURE 1** Distribution of immunohistochemical markers used to diagnose the evaluable squamous cell lung tumor samples prior to molecular profiling in the CancerTYPE ID assay.



**FIGURE 2** Suspected primary tumor site and histologic diagnosis prior to molecular profiling in the CancerTYPE ID assay.

cell morphology or lung origin in diagnosis). Notably, molecular classification provided additional information about the site of tumor origin in several diagnostic categories. In six cases, the pathologic diagnosis was reported as an unknown primary cancer, and molecular testing predicted a potential anatomic site of tumor origin. Molecular testing confirmed

clinical suspicion in nine cases where the lungs were proposed as a primary tumor site. Moreover, among these nine cases, six of them contained multiple differentials ranging from two to six possible sites of tumor origin, and molecular testing provided tumor sites that could be “ruled out” in addition to predicting the lungs as a possible primary tumor site. Regarding

histologic subtype, three of the cases were diagnosed as NSCLC, and molecular testing further subclassified the tumor as squamous cell cancer. In more than 50% of these cases, squamous cell morphology was noted; however, primary sites of tumor origin were not definitively diagnosed.

Treatment selection information is also summarized in Table 2. Therapeutic regimens for which molecular results were incorporated based on physician responses were predominantly broad-based chemotherapy doublets consistent with a diagnosis of squamous cell lung cancer. In two cases, the folate antimetabolite pemetrexed, which is contraindicated for squamous cell lung cancer, was applied.

Physician responses to a standardized questionnaire were used to assess whether the additional data provided by CancerTYPE ID (site of tumor origin and subtype) had any impact on clinical decision-making (Table 2, physician-reported responses). Prior to molecular profiling, the suspected primary tumor site included the lungs as a possibility in 41% of patients, was unknown/uncertain in 27% of patients, was not suspected to be the lungs in 23% of patients, and was not specified in 9% of patients. Based on clinicians’ responses, the clinical diagnosis after molecular testing was reported as the lungs for 15 tumors (68%), the head and neck for 2 tumors, the colorectum for 1 tumor, and unknown for 1 tumor. No data were available for the remainder of the cases (two physicians failed to respond to the post-ID questionnaire and one did not provide a final diagnosis). Two patients were surgically treated and two patients progressed too rapidly for any therapy and were referred to hospice.

Therefore, CancerTYPE ID results guided or confirmed the primary tumor site for treatment purposes in 50% of cases (10 of 20) and changed the clinical diagnosis of the

TABLE 2

Disposition of cases identified with high confidence as squamous cell lung tumors by the CancerTYPE ID assay

Information from pathology reports							Physician-reported responses			
No.	Gender	Age, yr	Biopsy site	Histology	Immunohistochemistry	Suspected primary site(s) prior to molecular testing	Clinical diagnosis after molecular testing	Diagnostic utility: primary site	Diagnostic utility: subtype	Treatment
1	M	59	Lung	Carcinoma, non-small cell	CK7+, CK20-, CDX2-, TTF-1-, PSA-, CK34BE12+, CK5/6+, CD56-	Lung, colorectal	Lung, squamous	Changed	Guided/confirmed	Carboplatin/ <i>nab</i> -paclitaxel
2	M	82	Lung	Poorly differentiated carcinoma, squamous transitional cell	CK7+, CK20-, TTF-1-, p63+, CK903+, thrombomodulin+	Pancreas	Pancreas, lung <sup>a</sup>	Changed	Changed	Gemcitabine/ carboplatin
3	M	75	Bone	Carcinoma, metastatic squamous cell	CK7-, CK20-, CDX2-, TTF-1-, PSA-, synaptophysin-, p63+, CK5/6+, CA19.9-, CEA-	Unknown	Lung, squamous	Changed	Guided/confirmed	Carboplatin/ paclitaxel
4	M	73	Axillary lymph node	Carcinoma, non-small cell squamous or transitional cell	CK7+, CK20-, TTF-1-, PSA-, thrombomodulin+, BCA225-, CEA-	Unknown	Unknown	Changed	Did not affect	Surgery
5	M	77	Tonsil	Undifferentiated neoplasm; favor squamous	CK7-, CK20-, CDX2-, S100-, HMB45-, PLAP-, CD138-, synaptophysin-, cKit-, CD34+, CD68+, CAM 5.2-, HMWK-, pancytokeratin-, inhibin-, chromogranin-, p63-, CK5/6-, calretinin-, TdT-, cCD3-, CD45-, vimentin+, MART-1-, CD20-, ALK1-, CD30-, CD43-, CD1a-, CD21-, CD31-, lysozyme-, myeloperoxidase-	Unknown	Lung, squamous	Changed	Did not affect	Docetaxel/ carboplatin
6	F	45	Cervical lymph node	Carcinoma, non-small cell	CK7+, CK20-, TTF-1-, ER-, CK-	Head and neck, lung	Lung, non-small cell	Changed	Guided/confirmed	Carboplatin/ docetaxel
7	F	75	Lung	Moderately differentiated carcinoma, squamous cell	TTF-1-, CK5/6+, CK8+	Anus, unknown	Lung, squamous	Changed	Changed	Docetaxel/ carboplatin/ radiation therapy
8	F	68	Liver	Carcinoma, metastatic squamous cell	p63+	Unknown	Lung, non-small cell	Guided/confirmed	Guided/confirmed	Paclitaxel/ carboplatin
9	M	75	Para-tracheal lymph node	Poorly differentiated carcinoma, non-small cell	CK7+, CK20+, CDX2-, TTF-1+, surfactant-	Lung	Lung	Guided/confirmed	Did not affect	Pemetrexed/ paclitaxel/ carboplatin

Table 2 continued on the following page

TABLE 2 continued

Disposition of cases identified with high confidence as squamous cell lung tumors by the CancerTYPE ID assay

Information from pathology reports							Physician-reported responses			
No.	Gender	Age, yr	Biopsy site	Histology	Immunohistochemistry	Suspected primary site(s) prior to molecular testing	Clinical diagnosis after molecular testing	Diagnostic utility: primary site	Diagnostic utility: subtype	Treatment
10	M	79	Axillary lymph node	Carcinoma, metastatic squamous cell	S100-, HMB45-, AE1/AE3+, HMWK+, CD3-, CD20-	Unknown	Lung, squamous	Guided/confirmed	Guided/confirmed	Carboplatin/paclitaxel
11	F	48	Soft tissue, buttock	Carcinoma, metastatic squamous, clear-cell type	CK7+, CK20+, TTF-1-, CD10-, AE1/AE3+, Ber-EP4+, CK5/6+	Lung, breast, urothelium, ovary, endometrium, pancreas	Lung	Guided/confirmed	Guided/confirmed	Progressed too quickly
12	M	71	Bone	Carcinoma, metastatic, neuroendocrine features	CK7+, CK20-, TTF-1-, PSA- synaptophysin+, AE1/AE3+, chromogranin-, PASP-	Pancreas, upper GI, lung, prostate	Lung	Guided/confirmed	Did not affect	Carboplatin/paclitaxel
13	F	59	Clivus	Undifferentiated carcinoma	S100-, synaptophysin+, cKit+, pancytokeratin+, NSE+, p53+, EMA+, LCA-, chromogranin-, EBV-	Sinonasal cavity	Head and neck, squamous cell	Guided/confirmed	Guided/confirmed	Etoposide/carboplatin
14	M	51	Lung	Poorly differentiated adenocarcinoma	CK7+, CK20-, TTF-1-, PSA-, CK5/6-	Lung, colon	Lung, squamous cell	Guided/confirmed	Changed	Surgery
15	M	46	Lung	Poorly differentiated adenocarcinoma	CK7+, CK20-, TTF-1-	Lung	Lung, non-small cell	Guided/confirmed	Changed	Docetaxel/GH302/capecitabine/sorafenib
16	F	59	Neck	Carcinoma, metastatic squamous cell	No data provided in pathology report	Not specified	Lung	Guided/confirmed	Did not affect	1. Cisplatin/pemetrexed 2. Irinotecan/capecitabine
17	M	69	Liver	Poorly differentiated carcinoma, metastatic squamous cell	CK7-, CK20-, CDX2-, TTF-1-, PSA-, CD10-, HMWK+, p63+, LMWK-	Kidney, anorectum, lung, head and neck	Lung, squamous cell	Guided/confirmed	Guided/confirmed	Platinum/docetaxel
18	M	48	Aryepiglottic fold	Moderately differentiated carcinoma, squamous cell	No data provided in pathology report	Head and neck	Head and neck	Did not affect	Did not affect	Not provided
19	M	38	Liver	Adenocarcinoma	CK7 equivocal, CK20-, CDX2-, TTF-1-, PSA-, AE1/AE3+, LCA-, HAS-, S100-	Colorectum	Colorectum	Did not affect	Did not affect	FOLFOX
20	M	78	Liver	Moderately differentiated carcinoma, squamous cell	No data provided in pathology report	Esophagus	Esophagus	Did not affect	Did not affect	Hospice
21	M	58	Peritoneum	Poorly differentiated carcinoma, squamous cell	S100-, HMB45-, synaptophysin-, CK5/6+, p63+, CD56-	Lung, esophagus, urinary bladder, skin	No data available	No data available	No data available	No data available

Table 2 continued on the following page.

TABLE 2 continued

Disposition of cases identified with high confidence as squamous cell lung tumors by the CancerTYPE ID assay

Information from pathology reports							Physician-reported responses			
No.	Gender	Age, yr	Biopsy site	Histology	Immunohistochemistry	Suspected primary site(s) prior to molecular testing	Clinical diagnosis after molecular testing	Diagnostic utility: primary site	Diagnostic utility: subtype	Treatment
22	F	66	Cervical lymph node	Poorly differentiated carcinoma, metastatic squamous cell	CK7+, CK20-, TTF-1-, pancytokeratin+, CEA+, mucicarmine-	Not specified	No data available	No data available	No data available	No data available

M = male; F = female; CEA = carcinoembryonic antigen; CK = cytokeratin; MART = melan A; PSA = prostate-specific antigen; TTF = thyroid transcription factor; GI = gastrointestinal; FOLFOX = folinic acid, fluorouracil, and oxaliplatin

<sup>a</sup>Pancreas and lung considered in treatment regimen decision

primary tumor site in an additional 35% of cases (7 of 20). In regard to the histologic subtype, CancerTYPE ID guided, confirmed, or changed the subtype in 60% of the tumors tested (12 of 20).

## Discussion

A preliminary evaluation of the clinical utility of the CancerTYPE ID test was examined through this retrospective study of cases predicted to be squamous cell lung carcinoma in a diagnostic setting. The specimen characteristics associated with these cases submitted for molecular testing in 2009 suggested the clinical indication for CancerTYPE ID included high-grade metastatic tumors where specimen availability may be limited (~ 50% core-needle and fine-needle aspiration biopsies; Table 1). Additionally, CancerTYPE ID was used to confirm or reduce possibilities in differential diagnoses (68%) or to classify cases of unknown origin (24%). In the evaluable cohort, 47% of cases included the lungs in the differential diagnosis, and for 32% of cases, the primary tumor site was unknown/uncertain or unspecified (Figure 2). Furthermore, squamous cell morphology was noted in 47% of the cases and contained supportive IHC data in 21%.

Therefore, CancerTYPE ID had the potential to provide diagnostic utility in both the determina-

tion of the tissue of origin and the classification of histologic subtype. CancerTYPE ID may represent an additional analytic approach to histopathologic evaluation to aid in strengthening diagnosis.

There is a growing need for standardized methods for classifying lung carcinomas, as treatment and side effects specific to different subtypes are becoming more widely recognized. It is estimated that approximately 20%–30% of NSCLC samples do not show sufficient morphologic differentiation to be amenable to classification by light microscopy and thus require further investigation by IHC or other diagnostic techniques.<sup>23</sup> However, despite advances in protocols, the effectiveness of IHC may be limited due to technical inconsistencies in immunostaining techniques and the lack of standardization in interpretation.<sup>17–19,24</sup> In addition, interpretation of the analysis is further challenged by samples that are poorly differentiated and/or lack cytologic and architectural features.<sup>19–21</sup> Currently, there is no molecular-based test used in routine practice to facilitate histopathologic diagnoses. Therefore, the need for adjunctive, standardized assays to aid in tumor typing and subclassification is evident, particularly in cases where standard morphologic evaluation and IHC do not lead to a definitive diagnosis.

CancerTYPE ID uses gene-ex-

pression profiling to determine the tissue of origin; to distinguish among the different subtypes of lung cancers with no prior morphologic or IHC identification required; and to reduce the diagnostic uncertainty associated with differential diagnoses, metastatic cancers, cancers of an unknown primary, and others not confirmable through other diagnostic or histopathologic means alone. It has demonstrated a sensitivity of 80%–90% in the identification of squamous cell lung carcinomas in small blinded test sets and internal validation studies.<sup>22,25</sup> Although these test sets provide an initial estimate of assay accuracy, further studies aimed at evaluating the performance characteristics of CancerTYPE ID with a diverse and large number of tumor samples are ongoing, and are required to establish its clinical validity.

In addition to CancerTYPE ID, which is an mRNA-based RT-PCR assay using the differential expression of 92 genes, another commercially available diagnostic assay based on microRNA expression subclassifies diagnosed NSCLC tumors.<sup>26,27</sup> These molecular tests have been optimized for formalin-fixed, paraffin-embedded clinical samples, have demonstrated a high degree of sensitivity and specificity, and can be readily integrated into current diagnostic workflows.

A key objective of this small study

was to investigate whether the availability of molecular profiling data in the context of standard clinical evaluation was associated with a change in the clinical diagnoses rendered and/or in treatment selection. Physician-reported feedback using a standardized questionnaire demonstrated that results from molecular testing guided, confirmed, or changed the primary tumor site for treatment purposes in 85% of the 20 evaluable cases and guided, confirmed, or changed the tumor subtype in 60% of the tumors tested. These preliminary results support the clinical utility of CancerTYPE ID as an additional diagnostic tool, which may have an impact on clinical decision-making in conjunction with standard clinicopathologic evaluation.

Until recently, treatment decisions for patients with lung cancer have been largely empirical. With this empirical approach, the outcomes of patients with NSCLC have only marginally improved during the past several decades. Of the estimated 222,520 patients expected to be diagnosed with lung cancer in 2010, 71% of these patients will die in the same year from this malignancy.<sup>28</sup>

Prognoses and treatment of metastatic cancer rely fundamentally on the identification of the site of tumor origin. This is particularly relevant in the case of squamous cell cancer, where each anatomic site has its own particular spread pattern and prognosis. For instance, in the United States, the 5-year patient survival rate is approximately 15% for NSCLC, whereas for all sites and stages in the head and neck region, the 5-year survival rate averages 59%.<sup>29,30</sup> Emerging clinical data have resulted in paradigmatic shifts in the treatment of squamous cell cancer, with an increasing number of novel strategies available, including both chemotherapy and targeted therapy-based approaches. These data further underscore the significance of both the identifica-

tion of the tumor site as the first step to understanding cellular context and tumor subclassification to guide optimal therapy. Molecular tools such as CancerTYPE ID have demonstrated potential in providing additional data to aid in diagnosis and in supporting decision-making in the era of increasingly sophisticated oncology treatment protocols.

Limitations of this study include the retrospective design, a small sample set, and the lack of direct clinical validation with confirmed diagnoses or long-term clinical follow-up. However, the design allowed examination in a more heterogeneous patient population than is representative of actual daily clinical practice.

## Conclusion

This study underscores the potential clinical utility of the CancerTYPE ID assay in the differential diagnosis of lung tumors. Incorporation of CancerTYPE ID into current diagnostic procedures may facilitate more accurate diagnoses leading to consequent patient benefit, such as the potential to use clinically appropriate site-directed therapy. Prospective clinical trials for further validation of the clinical utility of this test are ongoing.

*Acknowledgments:* The authors thank Loretta L. Nielsen, PhD, for writing support and Amy Marrs for administrative support.

## References

1. American Cancer Society. Cancer facts and figures 2008. Atlanta: American Cancer Society; 2008:1-72.
2. Jemal A, Siegel R, Ward E, et al. Cancer statistics, 2008. *CA Cancer J Clin* 2008;58:71-96.
3. Johnson DH, Fehrenbacher L, Novotny WF, et al. Randomized phase II trial comparing bevacizumab plus carboplatin and paclitaxel with carboplatin and paclitaxel alone in previously untreated locally advanced or metastatic non-small-cell lung cancer. *J Clin Oncol* 2004;22:2184-2191.
4. Scagliotti GV, Parikh P, von Pawel J, et al. Phase III study comparing cisplatin plus gemcitabine with cisplatin plus pemetrexed in chemotherapy-naïve patients with advanced-stage non-small-cell lung cancer. *J Clin Oncol*

2008;26:3543-3551.

5. Zinner RG, Novello S, Peng G, Herbst R, Obasaju C, Scagliotti G. Comparison of patient outcomes according to histology among pemetrexed-treated patients with stage IIIB/IV non-small-cell lung cancer in two phase II trials. *Clin Lung Cancer* 2010;11:126-131.

6. Tan EH, Rolski J, Grodzki T, et al. Global Lung Oncology Branch trial 3 (GLOB3): final results of a randomised multinational phase III study alternating oral and i.v. vinorelbine plus cisplatin versus docetaxel plus cisplatin as first-line treatment of advanced non-small-cell lung cancer. *Ann Oncol* 2009;20:1249-1256.

7. Scagliotti G, Hanna N, Fossella F, et al. The differential efficacy of pemetrexed according to NSCLC histology: a review of two phase III studies. *Oncologist* 2009;14:253-263.

8. Sandler A, Yi J, Dahlberg S, et al. Treatment outcomes by tumor histology in Eastern Cooperative Group Study E4599 of bevacizumab with paclitaxel/carboplatin for advanced non-small cell lung cancer. *J Thorac Oncol* 2010;5:1416-1423.

9. Scagliotti G, Novello S, von Pawel J, et al. Phase III study of carboplatin and paclitaxel alone or with sorafenib in advanced non-small-cell lung cancer. *J Clin Oncol* 2010;28:1835-1842.

10. Roggli VL, Vollmer RT, Greenberg SD, McGavran MH, Spjut HJ, Yesner R. Lung cancer heterogeneity: a blinded and randomized study of 100 consecutive cases. *Hum Pathol* 1985;16:569-579.

11. Durnill MS, Gatter KC. Cellular heterogeneity in lung cancer. *Histopathology* 1986;10:461-475.

12. Brambilla E, Travis WD, Colby TV, Corrin B, Shimosato Y. The new World Health Organization classification of lung tumours. *Eur Respir J* 2001;18:1059-1068.

13. Kargi A, Gurel D, Tuna B. The diagnostic value of TTF-1, CK 5/6, and p63 immunostaining in classification of lung carcinomas. *Appl Immunohistochem Mol Morphol* 2007;15:415-420.

14. Ring BZ, Seitz RS, Beck RA, et al. A novel five-antibody immunohistochemical test for subclassification of lung carcinoma. *Mod Pathol* 2009;22:1032-1043.

15. Wu M, Wang B, Gil J, et al. p63 and TTF-1 immunostaining: a useful marker panel for distinguishing small cell carcinoma of lung from poorly differentiated squamous cell carcinoma of lung. *Am J Clin Pathol* 2003;119:696-702.

16. Wu M, Szporn AH, Zhang D, et al. Cytology applications of p63 and TTF-1 immunostaining in differential diagnosis of lung cancers. *Diagn Cytopathol* 2005;33:223-227.

17. Tan D, Zander DS. Immunohistochemistry for assessment of pulmonary and pleural neoplasms: a review and update. *Int J Clin Exp Pathol* 2008;1:19-31.

18. Pelosi G, Sonzogni A, Viale G. The classification of lung carcinoma: time to change the morphology-based approach? *Int J Surg*

Pathol 2010;18:161-172.

19. Cataluña JJ, Perpiñá M, Greses JV, Calvo V, Padilla JD, Paris F. Cell type accuracy of bronchial biopsy specimens in primary lung cancer. *Chest* 1996;109:1199-1203.

20. Thomas JS, Lamb D, Ashcroft T, et al. How reliable is the diagnosis of lung cancer using small biopsy specimens? Report of a UKCCCR Lung Cancer Working Party. *Thorax* 1993;48:1135-1139.

21. Edwards SL, Roberts C, McKean ME, Cockburn JS, Jeffrey RR, Kerr KM. Preoperative histological classification of primary lung cancer: accuracy of diagnosis and use of the non-small cell category. *J Clin Pathol* 2000;53:537-540.

22. Ma XJ, Patel R, Wang X, et al. Molecular classification of human cancers using a 92-gene real-time quantitative polymerase chain reaction assay. *Arch Pathol Lab Med* 2006;130:465-473.

23. Rossi G, Papotti M, Barbareschi M,

Graziano P, Pelosi G. Morphology and a limited number of immunohistochemical markers may efficiently subtype non-small-cell lung cancer. *J Clin Oncol* 2009;27:e141-e142.

24. Stang A, Pohlabein H, Müller KM, Jahn I, Giersiepen K, Jöckel KH. Diagnostic agreement in the histopathological evaluation of lung cancer tissue in a population-based case-control study. *Lung Cancer* 2006;52:29-36.

25. CancerTYPE ID. 2011. bioTheragnostics, Inc., San Diego, CA. Data on file.

26. Bishop JA, Benjamin H, Cholakh H, Chajut A, Clark DP, Westra WH. Accurate classification of non-small cell lung carcinoma using a novel microRNA-based approach. *Clin Cancer Res* 2010;16:610-619.

27. Lebanony D, Benjamin H, Gilad S, et al. Diagnostic assay based on hsa-miR-205 expression distinguishes squamous from non-squamous non-small-cell lung carcinoma. *J Clin Oncol* 2009;27:2030-2037.

28. Jemal A, Siegel R, Xu J, Ward E.

Cancer statistics, 2010. *CA Cancer J Clin* 2010;60:277-300.

29. Minna JD. Neoplasms of the lung. In: *Harrison's Principles of Internal Medicine*, Kasper DL, Braunwald E, Hauser S, et al. New York: McGraw-Hill; 2005:506-515.

30. Marur S, Forastiere AA. Head and neck cancer: changing epidemiology, diagnosis, and treatment. *Mayo Clin Proc* 2008;83:489-501.

#### ABOUT THE AUTHORS

*Affiliations:* Dr. McGee is Laboratory Medical Director at Randolph Hospital, Asheboro, NC; Dr. Kesty is a Senior Medical Affairs Scientist, Dr. Erlander is the Chief Scientific Officer, and Dr. Schnabel is Director of Medical & Scientific Affairs at bioTheragnostics, Inc., San Diego, CA.

*Conflicts of interest:* Dr. McGee has received consultancy fees and speakers' honoraria from bioTheragnostics, Inc. Drs. Kesty, Erlander, and Schnabel are employees of bioTheragnostics, Inc. and hold stock options in the company.

# The evolving role of molecular diagnosis of cancer types and subtypes: stay tuned

F. Anthony Greco, MD

Sarah Cannon Cancer Center, Sarah Cannon Research Institute, and Tennessee Oncology, PLLC, Nashville, TN

**I**n the majority of cancer patients, clinical features, sites of involvement, and standard pathologic evaluation clearly indicate the type of cancer present. However, there are circumstances where the primary tumor site is uncertain or unknown and/or the histologic subtype is unclear. A large group of patients in this category (about 80,000 per year in the United States) have cancer of an unknown primary site (CUP),<sup>1</sup> and many others who have an unequivocal primary site identified do not have a definitive histologic subtype diagnosed by standard pathology, including immunohistochemistry (IHC). Non-small cell lung cancer (NSCLC) is one example where subtype recognition (squamous cell versus adenocarcinoma/large cell) now has important therapeutic implications, as discussed by McGee et al in this issue of *Community Oncology*.

## Molecular profiling in the differential diagnosis of NSCLC subtypes

Standard pathologic evaluation can usually reliably determine NSCLC subtypes. However, a minority of patients with NSCLC (about 10%), who represent a sizable number of those with a common cancer, are given equivocal or not-otherwise-specified (NOS) pathologic subtype diagnoses.<sup>2</sup> The more widespread use of appropriate IHC, particularly CK5/6 and p63 stains (which are usually positive in squamous cell lung cancer) and other panels of stains<sup>3</sup> in difficult cases, would further reduce this number of NOS diagnoses.

As described by McGee et al, molecular profiling with the commercially available CancerTYPE ID reverse transcriptase-polymerase chain reaction assay may complement standard pathology and provide a subtype NSCLC diagnosis in otherwise equivocal cases. In the setting of scant biopsy material, as occurs frequently with fine-needle aspiration specimens in NSCLC, the use of a molecular assay may have particular usefulness in the NOS category. Of the 62 patients reviewed by McGee et al from 2009, all with a molecular assay diagnosis

of “squamous cell lung cancer,” 29 were suspected initially to be from a lung primary, 20 were from uncertain/unknown primary sites, and 13 were from other suspected primary sites. The initial histologic diagnosis prior to the molecular assay was squamous cell carcinoma in 29 patients (47%). Furthermore, in 22 patients with a high confidence of squamous cell lung carcinoma diagnosed by molecular assay (Table 2 in McGee et al), 14 (64%) were initially considered to have squamous cell carcinoma or have squamous features by standard pathologic evaluation, thus supporting the accuracy of the molecular diagnoses.

The physicians surveyed used the molecular assay results to confirm or change diagnoses for treatment decisions in 12 of these 22 patients (55%). However, in all the tumors suspected to be lung tumors (Figure 2 of McGee et al), 18 of 29 patients were initially diagnosed as having adenocarcinoma (8 patients) or another subtype, including NOS (10 patients), and in all these patients the molecular assay diagnosis was “squamous cell lung cancer.” In several of these tumors IHC staining supported a possible squamous cell histology, including negative TTF-1 stains and, when performed, positive p63 and/or CK5/6 stains.

The retrospective study reported here is small, and patient selection bias is at play. The authors admit there is no direct clinical validation of the molecular assay diagnoses with confirmed NSCLC subtype diagnoses. The issue of the general degree of accuracy or validity of the molecular profile assay diagnoses is critical. If the assay is reasonably accurate (ie, correct  $\geq 70\%$ ), then molecular diagnosis will surely be useful or complementary to standard pathology in NSCLC subtype identification and in many other clinical settings, includ-

Manuscript received and accepted March 11, 2011.

Correspondence to: F. Anthony Greco, MD, Tennessee Oncology, PLLC, 250 25<sup>th</sup> Avenue North, Suite 110, Nashville, TN 37023; telephone: 615-320-5090; fax: 615-986-0029; e-mail: fgreco@tnonc.com.

Commun Oncol 2011;8:132-133 © 2011 Elsevier Inc. All rights reserved.

ing the determination of the primary tumor type in CUP patients.

### How accurate are molecular profile assays?

In patients with known primary cancers (localized or metastatic), various molecular profile assays are accurate in diagnosing the primary tumor in 76%–89% of reported studies.<sup>4–9</sup> In CUP, validation is more difficult because the primary tumor site remains elusive in most instances, but it would seem reasonable to assume that the accuracy of molecular assays would be similar to that seen in known primary tumors. Retrospective studies support the accuracy of molecular assays (66%–85%), but most of these data are indirect, being based on correlations of the molecular assay results with clinical pathologic features and response to treatment.<sup>4,5,10–13</sup> In one small series, direct validation was provided where latent primary cancers were ultimately discovered months to years later in CUP patients.<sup>14</sup> The commercially available CancerTYPE ID assay was utilized on the initial biopsies and was correct in 15 of 20 patients (75%). Additional unpublished data support the relatively high accuracy ( $\geq 75\%$ ) of molecular assays in CUP as a new diagnostic technology, and these data will soon be available for critical review.

Molecular assays may complement standard pathologic evaluation and help to determine the primary tumor type in CUP patients.<sup>15</sup> The usefulness of such tests in determining subtypes in various other groups of patients with known primary cancers, such as NSCLC, also appears to be promising. CUP patients with a molecular signature of colorec-

tal carcinoma treated with colorectal site-specific chemotherapy regimens seem to respond and survive similarly to known advanced colorectal cancer patients receiving the same regimens.<sup>10,16</sup> These preliminary data are encouraging.

Oncologists need to stay tuned to learn the clinical utility of molecular assays in various groups of patients, as this area of molecular diagnosis is now rapidly evolving. Prospective studies comparing molecular assay diagnoses with standard pathologic diagnoses and/or outcomes in CUP patients after receiving site-specific treatment based on these assays are ongoing. These more definitive data are eagerly awaited, because the accurate molecular diagnosis of cancer type or subtype in select groups of patients has important therapeutic implications.

#### References

1. Greco FA, Hainsworth JD. Cancer of unknown primary site. In: DeVita VT Jr, Hellman S, Rosenberg M, eds. *Cancer: Principles and Practice of Oncology*. 8th ed. Philadelphia, PA: Lippincott; 2008:2363–2387.
2. Scagliotti G, Hanna N, Fossella F, et al. The differential efficacy of pemetrexed according to NSCLC histology: a review of two phase III studies. *Oncologist* 2009;14:253–263.
3. Righi L, Graziano P, Formari A, et al. Immunohistochemical subtyping of nonsmall cell lung cancer not otherwise specified in fine-needle aspiration cytology: a retrospective study of 103 cases with surgical correlation. *Cancer* 2011;10:78–81.
4. Tothill RW, Kowalczyk A, Rischin D, et al. An expression-based site of origin diagnostic method designed for clinical application to cancer of unknown origin. *Cancer Res* 2005;65:4031–4038.
5. Talantov D, Baden J, Jatkoe T. A quantitative reverse transcriptase-polymerase chain reaction array to identify metastatic carcinoma tissue of origin. *J Mol Diag* 2006;8:320.
6. Rosenfeld N, Aharonov R, Meiril E, et al. MicroRNAs accurately identify cancer tissue origin. *Nature Biotech* 2008;26:462–469.
7. Monzon FA, Lyons-Weiler M, Buturovic LJ, et al. Multicenter validation of a 1,550-gene expression profile for identification of tumor tissue of origin. *J Clin Oncol* 2009;27:2503–2509.
8. Ma XJ, Patel R, Wang X, et al. Molecular classification of human cancers using a 92-gene real-time quantitative polymerase chain reaction array. *Arch Pathol Lab Med* 2006;130:465–472.
9. Pillai R, Deeter R, Rigl CT, et al. Validation of a microarray-based gene expression test for tumors with uncertain origins using formalin-fixed paraffin-embedded (FFPE) specimens. *J Clin Oncol* 2009;27(15S):e22015. <http://meeting.ascopubs.org/cgi/content/abstract/27/15S/e22015>. Accessed September 13, 2009.
10. Varadhachary G, Talantov D, Raber M, et al. Molecular profiling of carcinoma of unknown primary and correlation with clinical evaluation. *J Clin Oncol* 2008;26:4442–4450.
11. Bridgewater J, van Laar R, Floore A, et al. Gene expression profiling may improve diagnosis in patients with carcinoma of unknown primary. *Br J Cancer* 2008;98:1425–1430.
12. Horlings HM, van Laar R, Kerst J-M, et al. Gene expression profiling to identify the histogenetic origin of metastatic adenocarcinomas of unknown primary. *J Clin Oncol* 2008;26:4435–4439.
13. Monzon FA, Medeiros F, Lyons-Weiler M, Henner WD. Identification of tissue of origin in carcinoma of unknown primary with a microarray-based gene expression test. *Diagn Pathol* 2010;5:3–7.
14. Greco FA, Spigel DR, Yardley DA, et al. Molecular profiling in unknown primary cancer: tissue of origin prediction. *Oncologist* 2010;15:500–506.
15. Thompson, DS, Hainsworth JD, Lane CM, et al. Molecular tumor profiling (MTP) in cancer of unknown primary site (CUP): a complement to standard pathologic diagnosis. Supplement to *Journal of Clinical Oncology* 2011 ASCO Annual Meeting Proceedings. In press.
16. Greco FA, Hainsworth JD. In: DeVita VT Jr, Hellman S, Rosenberg M, eds. *Cancer: Principles and Practice of Oncology*. 9th ed. Philadelphia, PA: Lippincott; 2011. In press.

#### ABOUT THE AUTHOR

**Affiliations:** Dr. Greco is Director of the Sarah Cannon Cancer Center and is associated with the Sarah Cannon Research Institute and Tennessee Oncology, PLLC, Nashville, TN.

**Conflicts of interest:** Dr. Greco is on the speakers' bureau of bioTherapeutics.

# Breast-conservation surgery and adjuvant multicatheter balloon brachytherapy after augmentation mammoplasty

Anthony E. Dragun, MD,<sup>1</sup> Keith T. Sowards, MS,<sup>1</sup> and C. Matthew Brown, MD<sup>2</sup>

<sup>1</sup>Department of Radiation Oncology, University of Louisville School of Medicine, Louisville, KY, and

<sup>2</sup>Louisville General Surgery PLCC, Louisville, KY

A 51-year-old woman had a medical history significant for bilateral subpectoral breast augmentation approximately 8 years prior to a routine screening mammogram, which identified a new, suspicious group of microcalcifications in a central location in the right breast. Stereotactic core-needle biopsy confirmed the presence of ductal carcinoma in situ (DCIS), intermediate nuclear grade.

The patient was offered breast-conservation surgery (BCS) with standard whole-breast radiotherapy versus accelerated partial breast irradiation (APBI) but wished to avoid whole-breast radiation due to the risk to her implant. The patient opted for APBI and thus underwent a needle-localization partial mastectomy, with temporary placement of a balloon cavity evaluation device (CED). The exit incision for the CED was placed in the inframammary fold. The final surgical pathology specimen showed cribriform DCIS, completely excised with widely negative surgical margins and no invasive component. The patient's CED was exchanged for a MammoSite ML balloon brachytherapy catheter (Hologic Inc., Marlborough, MA). The patient then underwent three-dimensional CT-based brachytherapy treatment planning for APBI. The target tissue was defined as breast tissue surrounding the lumpectomy cavity within a 1-cm margin, with exclusion of 5 mm from the skin surface and the implant (Figure 1). The balloon volume was 34 cc, and minimum balloon-to-skin distance was 5.5 mm. Three of four brachytherapy catheters were used for fractionated high-dose-rate brachytherapy delivery with iridium-192.

The patient completed a total dose of 34 Gy and 10 treatment fractions of 3.4 Gy per fraction delivered twice daily over 5 treatment days, prescribed to cover a planned treatment volume per current Ra-

diation Therapy Oncology Group (RTOG) specifications. She was maintained on prophylactic antibiotics, and routine daily catheter wound care was performed throughout the course of treatment. On the final day of treatment, the catheter was deflated and explanted. The catheter wound site was closed with Steri-Strips.

Approximately 7–10 days post treatment, the patient experienced acute side effects of localized erythema and patchy moist desquamation of the inferior portion of the nipple-areolar complex (grade 2 radiation dermatitis, Common Terminology Criteria for Adverse Events, version 4.0<sup>1</sup>), which healed completely within 6 weeks of treatment completion. At follow-up appointments approximately 7 and 12 months post treatment, the patient had no residual toxicity, with an excellent cosmetic outcome judged by the Harvard Scale<sup>2</sup> (Figure 2). The primary surgical scar healed completely, as did the catheter entry site. The patient had no long-term skin toxicity and no significant evidence of radiation-induced pain, hyperpigmentation, telangiectasia, or fibrosis. There was no clinical evidence of capsular contracture.

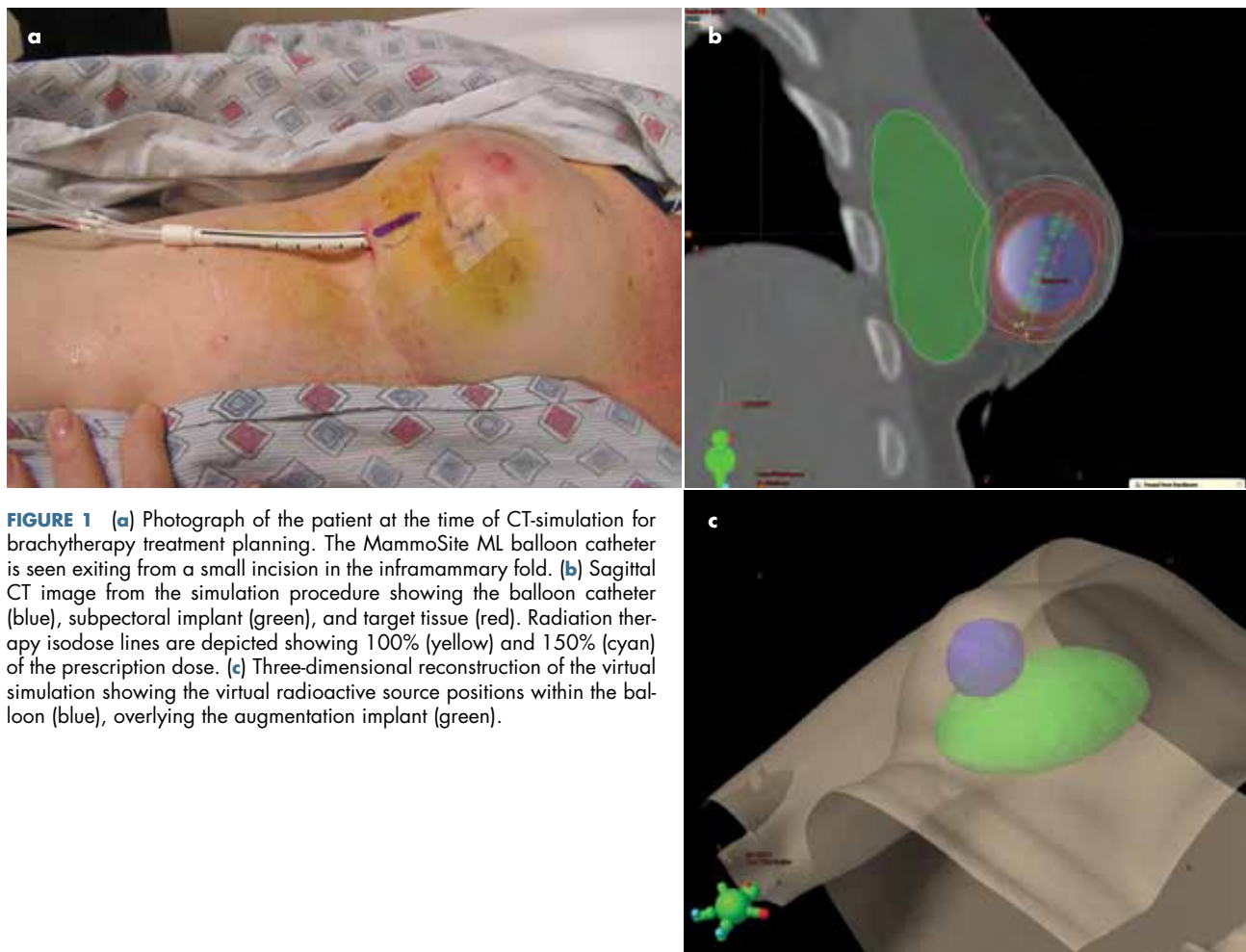
## Discussion

Although breast-conservation therapy (BCS and adjuvant radiotherapy) is preferred by the overwhelming majority of patients diagnosed with early-stage breast cancer and noninvasive disease in the

Manuscript received September 14, 2010; accepted March 4, 2011.

Correspondence to: Anthony E. Dragun, MD, Department of Radiation Oncology, University of Louisville, James Graham Brown Cancer Center, 529 South Jackson Street, Louisville, KY 40202; telephone: 502-561-2703; fax: 502-561-2709; e-mail: aedrag01@louisville.edu.

Commun Oncol 2011;8:134–136 © 2011 Elsevier Inc. All rights reserved.



**FIGURE 1** (a) Photograph of the patient at the time of CT-simulation for brachytherapy treatment planning. The MammaSite ML balloon catheter is seen exiting from a small incision in the inframammary fold. (b) Sagittal CT image from the simulation procedure showing the balloon catheter (blue), subpectoral implant (green), and target tissue (red). Radiation therapy isodose lines are depicted showing 100% (yellow) and 150% (cyan) of the prescription dose. (c) Three-dimensional reconstruction of the virtual simulation showing the virtual radioactive source positions within the balloon (blue), overlying the augmentation implant (green).

United States, this approach has been associated with mixed cosmetic outcomes in patients with a history of cosmetic augmentation.<sup>3-5</sup> The main risk is capsular contracture, which may occur after a traditional course of 6-week whole-breast radiation therapy.<sup>3</sup>

Handel et al analyzed 26 patients with previous cosmetic augmentation who underwent BCS and whole-breast radiation therapy; they showed that approximately 75% of patients had significant radiation-induced capsular contracture, which required further surgical intervention.<sup>3</sup> Significant capsular contracture was associated more often with patients who had augmentation for a longer period, those who had adjuvant chemotherapy, and those with subpectoral as opposed to subglandular implants. Additionally,

approximately half of the patients who had radiation-induced capsular contracture required revisionary surgery.

Conversely, Gray et al reported acceptable cosmetic outcomes and no significant risk of capsular contracture in approximately 17 patients undergoing BCS and whole-breast radiation therapy.<sup>4</sup> Likewise, Tuli et al reported satisfactory outcomes in six patients.<sup>5</sup>

APBI with balloon brachytherapy has been shown to be an effective alternative to whole-breast radiotherapy after BCS in select patients with pre-invasive disease and early-stage breast cancer.<sup>6</sup> The main advantage of brachytherapy is the convenience of treatment acceleration (from 6 weeks to 5 days), minimization of acute toxicity, and optimization of cosmetic results.<sup>7,8</sup> The largest national cooperative group

trial randomizing patients to whole-breast radiotherapy versus APBI following BCS is NSABP B39/RTOG 0413. This trial is currently open to only younger (< 50 years of age) and/or node-positive patients, but it specifically excludes those with breast augmentation. Although this trial is expected to reach final accrual in 2011, meaningful results on toxicity and disease endpoints are likely to take years.

Outside of a clinical trial, appropriate use of APBI is currently controversial; however, recent consensus guidelines put forth by the American Society for Radiation Oncology (ASTRO) have been favored by most radiation oncologists in the proper selection of patients.<sup>9</sup> These guidelines triage patients into “unsuitable,” “suitable,” and “cautionary” (the patient



**FIGURE 2** (a) Photograph of the patient's treated (right) breast at 12 months follow-up. (b) Comparison of the treated breast with the untreated breast at 12 months follow-up.

presented here), based on the state of the available evidence for the use of APBI in patients of various ages and disease factors. However, the ASTRO report largely steers clear of commenting on the use of APBI in appropriate patients who may have technical factors (cosmetic augmentation) or medical comorbidities (collagen vascular disease) that exclude them from participation in most APBI protocols.

## Conclusion

Management of early-stage breast cancer in patients with previous cosmetic augmentation remains a challenge. Although BCS is preferred by the majority of patients, adjuvant whole-breast radiation therapy may result in capsular contracture and subsequently a poor cosmetic outcome.<sup>3</sup> APBI using balloon brachytherapy has been used widely and successfully in select patients with preinvasive disease and early-stage breast cancer.<sup>6,7,10</sup> There is a growing collective experience with the newest generation of multicatheter brachytherapy applicators, which allow customization of radiation dosimetry for maximum target tissue coverage and normal tissue

sparing. These devices may offer a particularly advantageous alternative to whole-breast radiation therapy in select patients with previous cosmetic augmentation who undergo BCS. The results with our patient are encouraging, exhibiting a low toxicity profile and an excellent cosmetic outcome with no capsular contracture. Further studies of this approach are warranted in patients similar to our patient.

## References

1. Common Terminology Criteria for Adverse Events (CTCAE), version 4.0. Published May 28, 2009. [http://www.acrin.org/Portals/0/Administration/Regulatory/CTCAE\\_4.02\\_2009-09-15\\_QuickReference\\_5x7.pdf](http://www.acrin.org/Portals/0/Administration/Regulatory/CTCAE_4.02_2009-09-15_QuickReference_5x7.pdf). Accessed March 6, 2011.
2. Rose MA, Olivetto I, Cady B, et al. Conservative surgery and radiation therapy for early breast cancer: long-term cosmetic results. *Arch Surg* 1989;124:153-157.
3. Handel N, Lewinsky B, Jensen JA, Silverstein MJ. Breast conservation therapy after augmentation mammoplasty: is it appropriate? *Plast Reconstr Surg* 1996;98:1216-1224.
4. Gray RJ, Forstner-Barthell AW, Pockaj BA, Schild SE, Halyard MY. Breast-conserving therapy and sentinel lymph node biopsy are feasible in cancer patients with previous implant breast augmentation. *Am J Surg* 2004;188:122-125.
5. Tuli R, Flynn RA, Brill KL, Sabol JL, Usuki KY, Rosenberg AL. Diagnosis, treatment, and management of breast cancer in previously augmented women. *Breast J*

2006;12:343-348.

6. Keisch M, Vicini F, Beitsch P, et al. American Society of Breast Surgeons MammoSite Radiation Therapy System Registry Trial: ductal carcinoma-in-situ subset analysis—4-year data in 194 treated lesions. *Am J Surg* 2009;198:505-507.

7. Vicini F, Beitsch PD, Quiet CA, et al. Three-year analysis of treatment efficacy, cosmesis, and toxicity by the American Society of Breast Surgeons MammoSite Breast Brachytherapy Registry Trial in patients treated with accelerated partial breast irradiation (APBI). *Cancer* 2008;112:758-766.

8. Khan AJ, Vicini F, Beitsch P, et al. Local control, toxicity, and cosmesis in women younger than 50 enrolled onto the American Society of Breast Surgeons MammoSite Radiation Therapy System registry trial. *Ann Surg Oncol* 2009;16:1612-1618.

9. Smith BD, Arthur DW, Buchholz TA, et al. Accelerated partial breast irradiation consensus statement from the American Society for Radiation Oncology (ASTRO). *J Am Coll Surg* 2009;209:269-277.

10. Jenkins RW, Cannick L 3rd, Harper, JL. Use of MammoSite balloon brachytherapy for early-stage breast cancer. *Commun Oncol* 2011;8:37-40.

## ABOUT THE AUTHORS

**Affiliations:** Dr. Dragun is an assistant professor and Mr. Sowards is a medical physicist in the Department of Radiation Oncology, University of Louisville, Louisville, KY. Dr. Brown is a breast surgeon affiliated with Louisville General Surgery PLCC, Louisville, KY.

**Conflicts of interest:** The authors have nothing to disclose.

# Association of spontaneous bilateral femoral stress fractures with zoledronic acid use in a patient with metastatic breast cancer—a cautionary tale

Chandravathi Loke, MD,<sup>1</sup> Wilson C. Mertens, MD,<sup>1,4</sup> Michael J. Yunes, MD,<sup>2,4</sup> Rebecca A. Levy, MD,<sup>3</sup> and Grace Makari-Judson, MD<sup>1,4</sup>

Divisions of <sup>1</sup>Hematology and Oncology and <sup>2</sup>Radiation Oncology, Department of Internal Medicine, Baystate Regional Cancer Program, Springfield, MA; <sup>3</sup>Department of Pathology, Baystate Medical Center, Springfield, MA; and <sup>4</sup>Tufts University School of Medicine, Boston, MA

Osseous metastatic disease occurs frequently in patients with disseminated breast cancer and is the most common manifestation of distant disease. Patients frequently present with pain and are often palliated with radiation therapy. Patients with osseous metastases are often treated with bisphosphonate agents, such as zoledronic acid (Zometa) and pamidronate, based on the results of clinical trials that have demonstrated a reduced rate of adverse skeletal events with their use in patients with malignant bony involvement.<sup>1</sup> We report a case of a patient treated with bisphosphonates over a prolonged period who presented with signs and symptoms in keeping with progressive and symptomatic femoral osseous metastases but who, in fact, suffered from benign stress fractures.

## Case study

Our patient, a 57-year-old woman, was initially diagnosed in 1993 with a T1N0M0 invasive ductal carcinoma of the left breast that was estrogen- and progesterone-receptor positive; she underwent mastectomy with reconstruction and adjuvant chemotherapy with CMF (cyclophosphamide, methotrexate, and 5-fluorouracil). She did not receive any adjuvant hormonal treatment.

In 2001, she was diagnosed with metastatic bony disease based on imaged abnormalities involving the thoracic, lumbar, and cervical spine; the anterior ribs on the right; a small focus of activity in the right greater trochanter on technetium-99m-MDP (methylene diphosphate) nuclear scintig-

raphy; and an elevated alkaline phosphatase level of 323 units/L. She was started on tamoxifen and monthly pamidronate. Alkaline phosphatase levels normalized, and no other tumor markers were elevated at any time.

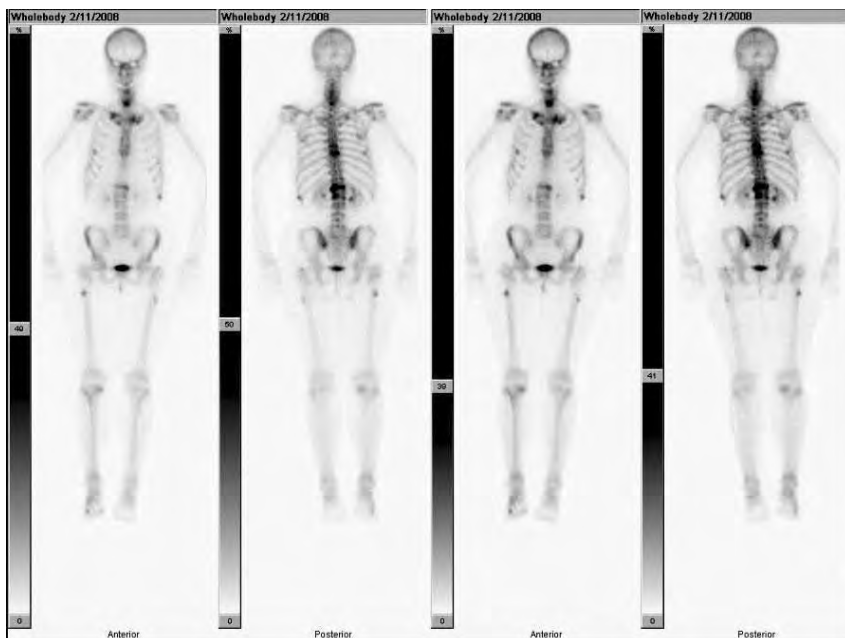
After a year, her follow-up bone scans revealed new foci of increased activity along the proximal right femur and at the lateral cortical margin of the left proximal femur. Tamoxifen was discontinued, and therapy with anastrozole was initiated; concurrently, when it became available, zoledronic acid was substituted for pamidronate. Over the next few years, the patient sustained compression fractures of the spine associated with falls as well as a rib fracture after shoveling snow. In 2006, she received radiation to the left hip for pain, with an area of increased activity at the left sacroiliac joint, which resulted in pain relief.

Aside from a brief period of every-other-month zoledronic acid, she had received monthly intravenous bisphosphonate therapy for nearly 6 years when she began to complain of bilateral hip pain in early 2008. Nuclear scintigraphy performed in February 2008 (Figure 1) revealed new increased activity in the lateral cortical areas of both proximal femurs compared with a previous bone scan obtained in April 2007. Assuming this was progressive disease, exemestane was initiated

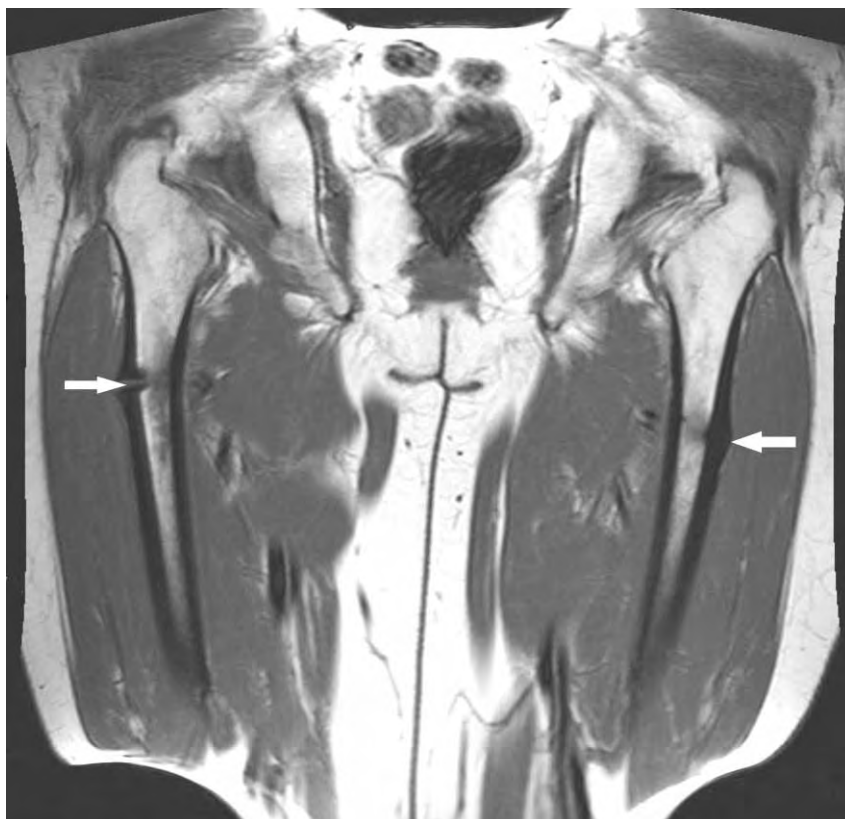
Manuscript received August 5, 2010; accepted March 4, 2011.

Correspondence to: Grace Makari-Judson, MD, Baystate Regional Cancer Program, D'Amour Center for Cancer Care, 3350 Main Street, Springfield, MA 01107; telephone: 413-794-9338; fax: 413-794-3613; e-mail: Grace.Makari-Judson@baystatehealth.org.

Commun Oncol 2011;8:137-140 © 2011 Elsevier Inc. All rights reserved.



**FIGURE 1** Nuclear scintigraphy revealed new increased activity in the lateral cortical areas of both proximal femurs compared with a previous bone scan obtained 10 months earlier.



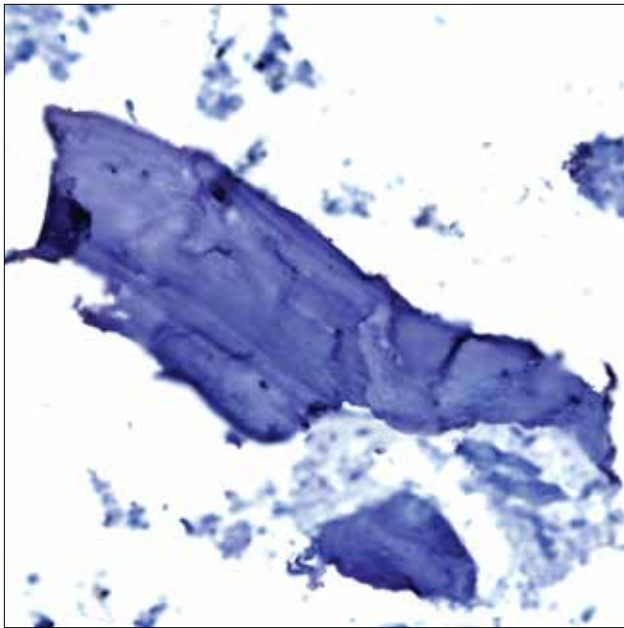
**FIGURE 2** MRI of the lower extremities revealed incomplete transverse fractures involving both the right and left proximal femurs with lateral cortical thickening, suggesting a bony reaction to injury (arrows). These fractures corresponded to the location of the new abnormalities discovered 8 months previously and were consistent with stress injury and not typical of metastatic involvement.

as a salvage hormonal therapy, as she had completed 5 years of treatment with anastrozole.

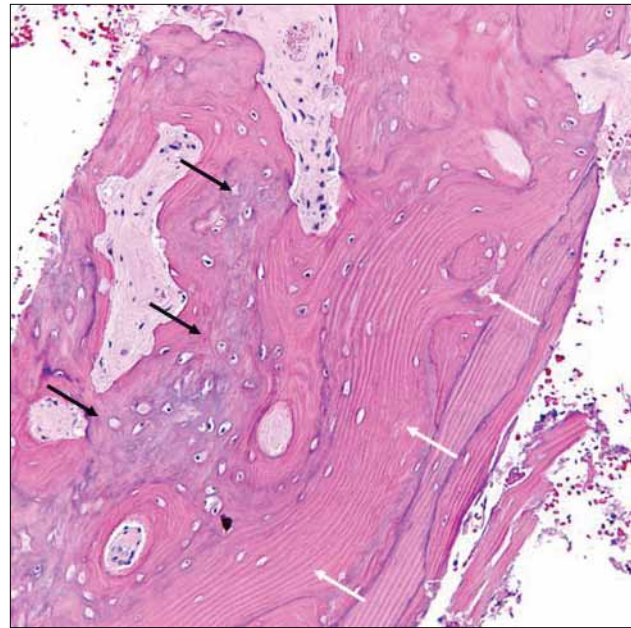
Despite titration of pain medications, she reported worsening pain in both hips and thighs, especially with activity such as walking. She was referred for radiation oncology and received radiation therapy (30 Gy over 10 fractions) to both proximal femurs in July 2008, but the patient had not experienced pain relief 5 weeks after completing treatment. MRI of the lumbar spine performed in September 2008 showed subacute compression of L1 vertebrae without stenosis and without evidence of metastatic disease, suggesting that the compression was the result of osteoporosis.

In October 2008, the patient required hospitalization for pain control. At that time, MRI of the lower extremities revealed an incomplete transverse fracture involving both the right and left proximal femurs with lateral cortical thickening, suggesting a bony reaction to injury (arrows, Figure 2). These fractures corresponded to the location of the new abnormalities discovered on the most recent bone scan and were consistent with stress injury and not typical of metastatic involvement. Surgical fixation with bilateral intramedullary rodding of both femurs resulted in prompt and significant relief of pain.

Pathology of both right and left femur bone reamings showed no evidence of metastasis by routine histology or immunohistochemistry for cytokeratin (Figure 3). The bone in the biopsy specimens consisted of fragments of lamellar bone with smooth layers of bone matrix and an area with a jagged, haphazard arrangement of osteocytes and bone matrix, suggesting some prior remodeling (Figure 4). Subsequent to the biopsy, zoledronic acid administration was changed to every 3 months in December 2008 and later to every 6 months with stable disease, no non-osseous sites of



**FIGURE 3** Pathology of both right and left femur bone reamings showed no evidence of metastasis by routine histology or immunohistochemistry for cytokeratin.



**FIGURE 4** The bone in the biopsy specimen consisted of fragments of lamellar bone (white arrows) with smooth layers of bone matrix and an area (black arrows) with a jagged, haphazard arrangement of osteocytes and bone matrix, suggesting some prior remodeling.

disease, and no further requirement for radiation therapy or surgery.

## Discussion

Fragility or insufficiency fractures are stress fractures that affect osteoporotic bone subjected to normal, low-energy, repetitive impact.<sup>2</sup> Typically seen in vertebrae, hip, distal radius, or proximal humerus following minimal or no trauma, these fractures are rarely seen in the proximal femur. Reports have described nontraumatic or low-impact stress fractures of the subtrochanteric and proximal femoral shaft in a small proportion of patients with long-term bisphosphonate use.<sup>2-10</sup> These cases have demonstrated uniquely characteristic findings: subtrochanteric unicortical fracture(s) without evidence of metastatic disease in an area of cortical thickening, particularly laterally. Localized pain antecedent to frank fracture is a frequent symptom.<sup>2-5</sup> Although a number of reports have described these findings in patients who were using oral bisphosphonates, intrave-

nous bisphosphonates have also been implicated.<sup>2-4,11</sup>

In a case-control study, Lenart and colleagues found bisphosphonate use associated with 15 of 41 subtrochanteric femoral shaft fractures, compared with 9 of 82 intertrochanteric fractures (odds ratio, 4.44;  $P = 0.002$ ).<sup>8</sup> The development of fragility fractures in patients treated with bisphosphonates remains relatively uncommon, however; one report from two Swedish hospital districts found 5 stress fractures among 3,087 patients treated with bisphosphonates, compared with 8 of 88,869 patients without such therapy.<sup>12</sup> Ing-Lorenzini and colleagues,<sup>4</sup> analyzing a case series, found an average duration of bisphosphonate use—in this case, predominantly alendronate for osteoporosis—of 4.5 years prior to fracture diagnosis; others describe similar findings.<sup>7</sup> Suppression of bone remodeling by bisphosphonates is postulated as a cause, preventing the repair of microdamage that may allow accumulation of microdamage to the

point of frank fracture.<sup>13,14</sup> Although a recent review of randomized trials employing bisphosphonates in osteoporosis patients demonstrated a low rate of subtrochanteric or diaphyseal fractures that was not statistically different from placebo,<sup>15</sup> bisphosphonate use in the metastatic osseous disease setting is much more dose-intensive and may yield a higher incidence of fractures in patients receiving long-term treatment.

Bisphosphonates are widely used in the care of cancer patients to reduce skeletal complications related to bone metastases, such as pain, pathologic fractures, hypercalcemia, spinal cord compression, and the need for palliative radiation therapy.<sup>1</sup> We believe this is the first reported case of spontaneous bilateral femoral fragility fractures—demonstrating characteristic radiologic findings and absence of malignancy on pathologic evaluation—in a patient with breast cancer who had been on long-term treatment with zoledronic acid for osseous metastases; other factors may have contributed

to the fractures, including prior radiation therapy and osteoporosis. Our patient's presentation mimicked progressive metastatic osseous disease, with new scintigraphic changes in the area of her symptoms. Unlike many previous cases, the patient did not present with a complete fracture but rather with persistent pain despite seemingly appropriate therapy.

Patients with known malignancy and painful skeletal lesions are often assumed to have cancer-associated bone discomfort and are treated as such based on clinical presentation and imaging studies—predominantly nuclear scintigraphy—particularly if metastatic disease has already been confirmed pathologically elsewhere. Clinicians must consider bisphosphonate-associated stress fractures as an alternative cause of new or progressive pain in patients with long-term bisphosphonate use. In patients on long-term bisphosphonate therapy who present with subtrochanteric or diaphyseal scintigraphic changes or frank femoral fracture, radiographs of the contralateral femur should also be obtained for the purpose of obtaining evidence of bilateral cortical thickening.<sup>7,8</sup> MRI imaging may be useful in determining the presence of metastatic disease. If a stress fracture is discovered, prophylactic fixation may be indicated to achieve pain relief and prevent a complete fracture.

Finally, as most patients report-

ed in the literature had prolonged bisphosphonate therapy, limiting the treatment duration or frequency is reasonable until more definitive data on the long-term safety of dose-intensive bisphosphonate therapy in cancer patients have accumulated.

#### References

1. Ali SM, Estava FJ, Hortobagyi G, et al. Safety and efficacy of bisphosphonates beyond 24 months in cancer patients. *J Clin Oncol* 2001;19:3434–3437.
2. Kwek EB, Goh SK, Koh JS, Png MA, Howe TS. An emerging pattern of subtrochanteric stress fractures: a long-term complication of alendronate therapy? *Injury* 2008;39:224–231.
3. Capeci CM, Tejwani NC. Bilateral low-energy simultaneous or sequential femoral fractures in patients on long-term alendronate therapy. *J Bone Joint Surg Am* 2009;91:2556–2561.
4. Ing-Lorenzini K, Desmeules J, Plachta O, Suva D, Dayer P, Peter R. Low-energy femoral fractures associated with the long-term use of bisphosphonates: a case series from a Swiss university hospital. *Drug Saf* 2009;32:775–785.
5. Schneider JP. Bisphosphonates and low-impact femoral fractures: current evidence on alendronate-fracture risk. *Geriatrics* 2009;64:18–23.
6. Goddard MS, Reid KR, Johnson JC, Khanuja HS. Atraumatic bilateral femur fracture in long-term bisphosphonate use. *Orthopedics* 2009;32:pil.
7. Lenart BA, Lorich DG, Lane JM. Atypical fractures of the femoral diaphysis in postmenopausal women taking alendronate. *N Engl J Med* 2008;358:1304–1305.
8. Lenart BA, Neviasser AS, Lyman S, et al. Association of low-energy femoral fractures with prolonged bisphosphonate use: a case control study. *Osteoporosis Int* 2009;20:1353–1362.
9. Goh SK, Yang KY, Koh JS, et al. Subtrochanteric insufficiency fractures in patients on alendronate therapy: a caution. *J Bone Joint Surg Br* 2007;89:349–353.
10. Neviasser AS, Lane JM, Lenart BA, Edobor-Osula F, Lorich DG. Low-energy femoral shaft fractures associated with alendronate use. *J Orthop Trauma* 2008;22:346–350.
11. Wernecke G, Namdari S, Dicarolo EF, Schneider R, Lane J. Case report of spontaneous, nonspinal fractures in a multiple myeloma patient on long-term pamidronate and zoledronic acid. *HSS J* 2008;4:123–127; erratum: *HSS J* 2009;5:204.
12. Schilcher J, Aspenberg P. Incidence of stress fractures of the femoral shaft in women treated with bisphosphonates. *Acta Orthop* 2009;80:413–415.
13. Visekruna M, Wilson D, McKiernan FE. Severely suppressed bone turnover and atypical skeletal fragility. *J Clin Endocrinol Metab* 2008;93:2948–2952.
14. Lee P, van der Wall H, Seibel MJ. Looking beyond low bone mineral density: multiple insufficiency fractures in a woman with postmenopausal osteoporosis on alendronate therapy. *J Endocrinol Invest* 2007;30:590–597.
15. Black DM, Kelly MP, Genant HK, et al. Bisphosphonates and fractures of the subtrochanteric or diaphyseal femur. *N Engl J Med* 2010;362:1761–1771.

#### ABOUT THE AUTHORS

**Affiliations:** Dr. Loke is a fellow in Hematology and Oncology, Baystate Regional Cancer Program, Springfield, MA. Dr. Mertens is Medical Director, Cancer Services, Baystate Regional Cancer Program, and Associate Professor of Medicine, Tufts University School of Medicine, Boston, MA. Dr. Yunes is a radiologist in the Division of Radiation Oncology, Baystate Regional Cancer Program, and Instructor of Radiation Oncology, Tufts University School of Medicine. Dr. Levy is a resident in the Department of Pathology, Baystate Medical Center, Springfield, MA. Dr. Makari-Judson is Medical Director, Comprehensive Breast Center, Division of Hematology and Oncology, Baystate Regional Cancer Program, and Associate Professor of Medicine, Tufts University School of Medicine.

**Conflicts of interest:** The authors have nothing to disclose.

# On replicating studies, phase II and phase III trials, and other vagaries of clinical research

David L. Streiner, PhD, CPsych,<sup>1</sup> and Geoffrey R. Norman, PhD<sup>2</sup>

<sup>1</sup>Department of Psychiatry, University of Toronto, Toronto, Ontario, Canada, and <sup>2</sup> Department of Clinical Epidemiology and Biostatistics, McMaster University, Hamilton, Ontario, Canada

In a recent issue of the *New England Journal of Medicine*, researchers reported promising results from a phase II trial of iniparib (a PARP [poly(ADP-ribose) polymerase] inhibitor) plus gemcitabine (Gemzar) and carboplatin for treating metastatic triple-negative breast cancer.<sup>1</sup> Needless to say, the oncology community, not to mention the drug company developing iniparib and its stockholders, was dismayed when that news was quickly followed by a press release from sanofi-aventis and its subsidiary, BiPar Sciences, Inc., announcing that a phase III trial of the drug had failed to meet one of the primary endpoints.<sup>2</sup>

Why the dramatic difference between these phase II and phase III studies? Was it because of the differences in general between phase II and phase III trials, the differences between these two studies in particular, fatal flaws in the design of one of the trials, or something else? The company noted in the press release that it would have to take a closer look at the data before commenting on the possible reasons for the discrepant results, and, not having access to an article reporting the negative findings, we can't be sure ourselves. (In response to an e-mail inquiry, a company spokesman said that the "final results will be presented at an upcoming medical meeting.") However, a lack of hard data has never stopped us from pontificating in the past, and we see no reason to change now.

## The difference between phase II and phase III trials

The first place to look is the difference between phase II and phase III trials, a topic we discussed in the very first article in this series.<sup>3</sup> Briefly, a phase IIB trial is an *efficacy* study, which asks whether the drug can work under ideal circumstances, whereas phase III trials tend to be *effectiveness* studies, look-

ing at whether the drug works in the real world.<sup>4</sup> So, even though both are randomized controlled trials,<sup>5</sup> they may use different criteria regarding who gets into the study, how the intervention is delivered, what gets measured, and so on.

For example, the original iniparib study was an open-label trial, meaning that the clinicians and the patients knew who was getting what, whereas we presume that the phase III trial was blinded and that neither party knew who was getting what. Could this have affected the outcome? There is some tantalizing evidence from the field of psychoneuroimmunology that a person's psychological state can affect the rate of progression of some diseases, including cancer.<sup>6</sup> Women in the iniparib group in the phase II trial would have known that they were getting a new, experimental drug for a disease for which there are no approved treatments, and that awareness might have had an effect on their emotions and possibly their outcomes.

Another major difference between the two studies was the criterion for success. In the phase II trial, women in the iniparib group survived longer than women who received gemcitabine and carboplatin alone (median, 12.3 vs 7.7 months, respectively); had more progression-free months (median, 5.9 vs 3.6 months); and had a higher rate of clinical benefit than those in the control arm (56% vs 34%). However, it appears from the press release that the phase III trial had somewhat different endpoints—combined overall and progression-free survival—

Manuscript received February 27, 2011; accepted February 28, 2011.

Correspondence to: David L. Streiner, PhD, CPsych, Professor, Department of Psychiatry, University of Toronto; Professor Emeritus, Department of Psychiatry and Behavioural Neurosciences, McMaster University, West 5<sup>th</sup> Campus, 100 West 5<sup>th</sup>, Box 585, Hamilton, Ontario, Canada, L8N 3K7; telephone: 905-522-1155 ext 36809; fax: 905-575-6085; e-mail: streiner@mcmaster.ca.

Commun Oncol 2011;8:141-142 © 2011 Elsevier Inc. All rights reserved.

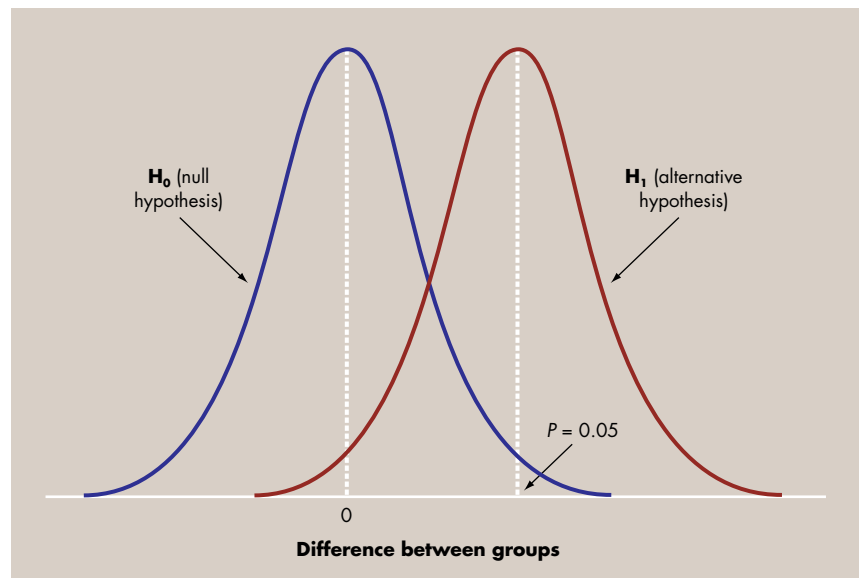
which were not different between the groups. Thus, to some degree, we're comparing apples (surrogate endpoints such as progression-free months and rate of clinical benefit) with oranges (the primary endpoint, which was survival). To be more accurate in the analogy, we're comparing pristine, peak-of-the-growing-season, right-off-the-tree apples with old, bottom-of-the-barrel oranges.

In general, the differences between phase II and phase III trials make it more likely that differences between groups will be found in the former. In a phase II trial, compliance is monitored more closely, follow-up is done more frequently and carefully, measurements are more specific, and, critically, the patients are selected to be more homogeneous—and hence less typical. On this last point, the less patient variability there is, the greater the likelihood of a significant result, because you've reduced the noise (which is in the denominator of the test).

Finally, in this case, there is a clear difference between the endpoints of the trials. For the phase II study, the endpoints are specific to the therapy; for the phase III trial, looking at combined survival, any death, regardless of cause, will be counted, which will add noise to the statistics.

### The trouble with study replication

In addition, there is some subtlety in the statistical game when it comes to replication. A  $P$  value of  $< 0.05$  seems to imply that, if we were to do the study again, there would be a 95% chance we would also find a significant result. Regrettably, this is not so. Let's say we do a study and find that the treatment arm does significantly better, with  $P = 0.05$ .<sup>7</sup> Now, we'll replicate the study exactly—the same design, the same inclusion and exclusion criteria, the same intervention, the same analyses, and so on. What is the probability that the study will



**FIGURE 1** The null and alternative hypotheses, after a study is significant at  $P = 0.05$ .

again show that the treatment is significantly better? Our first inclination would be to say 95%, but that would be wrong.

You have to think about our null ( $H_0$ ) and alternative ( $H_1$ ) hypotheses curves.<sup>7</sup> If the probability is exactly 0.05, and we have therefore rejected  $H_0$ , that literally means that we have rejected the possibility that the sample mean came from the null distribution and accepted the idea that it came from the  $H_1$  distribution, which is centered on the treatment effect that we found.

What is our best guess at the “true” treatment effect? The one we observed, of course. And that mean is sitting right on the  $H_0$  curve at the point corresponding to a tail probability of 0.05 (Figure 1). Half of the  $H_1$  distribution lies to the left of the critical point and half to the right. So if we reject  $H_0$  with a probability of exactly 0.05, the chance of replicating the study a second time is only 50%. Of course, as the  $P$  value from the study gets smaller (more significant), the chance that a second study will also find a significant result increases. But there is no direct correspondence between the  $P$  value and the chance of replication.

Now you know why the systematic reviews you read are so messy. Does it apply to these studies? It's difficult to tell without more data. But it *might* apply. Put your money in oil these days.

### References

1. O'Shaughnessy J, Osborne J, Pippen JE, et al. Iniparib plus chemotherapy in metastatic triple-negative breast cancer. *N Engl J Med* 2011;364:205–214.
2. Sanofi-aventis reports top-line results from phase III study with BSI-201 in metastatic triple-negative breast cancer. BiPar Sciences Web site. <http://www.biparsciences.com/000019.html?n=44>. Accessed March 11, 2011.
3. Streiner DL, Norman GR. Drug trial phases. *Commun Oncol* 2009;6:36–37, 39–40.
4. Streiner DL, Norman GR. Efficacy and effectiveness trials. *Commun Oncol* 2009;6:472–474.
5. Streiner DL, Norman GR. Randomized controlled trials. *Commun Oncol* 2009;6:83–85.
6. Cohen S, Herbert TB. Health psychology: psychological factors and physical disease from the perspective of human psychoneuroimmunology. *Health Psychol* 1996;47:113–142.
7. Norman GR, Streiner DL.  $P$  less than 0.05: statistical inference. *Commun Oncol* 2009;6:284–286.

### ABOUT THE AUTHORS

**Affiliations:** Dr. Streiner is Professor of Psychiatry, University of Toronto, Toronto, Ontario, Canada. Dr. Norman is Canada Research Chair in Cognitive Dimensions of Clinical Expertise; Assistant Dean, Programme for Educational Research and Development; and Professor of Clinical Epidemiology and Biostatistics, McMaster University, Hamilton, Ontario, Canada.

**Conflicts of interest:** The authors have nothing to disclose.

# NIH leads effort to lower radiation doses in CT scans

Monica Hogan, “*The Gray Sheet*”

An imaging group within the National Institutes of Health (NIH) has stepped up its response to public concerns over radiation exposure with a concerted effort to reduce the effective radiation dose from a routine CT exam by 80%–90%.

At a summit on radiation dose management in computed tomography last month, the National Institute of Biomedical Imaging and Bioengineering (NIBIB) challenged other Federal agencies, industry, professional societies, and clinicians to find ways to reduce the routine CT radiation dose to less than 1 millisievert (mSv).

Currently, the average effective dose from a CT exam is around 7 mSv.

James H. Thrall, MD, FACR, chairman of the radiology department at Massachusetts General Hospital in Boston and current president of the American College of Radiology, said that aside from reimbursement issues, concern over radiation risk is the top threat to the field of medical imaging. According to his estimates, radiation exposure from CT imaging contributes to roughly 2% of newly diagnosed cancers each year.

“If we can achieve an order-of-magnitude reduction of radiation exposure and therewith an order-of-magnitude reduction in the putative estimations of cancer inductions and cancer death, [then CT’s role in causing cancer] will be truly background noise,” Dr. Thrall argued.

Jeffrey E. Shuren, MD, JD, director of the US Food and Drug Administration’s (FDA’s) Center for Devices and Radiological Health, noted that

the NIBIB summit differed from previous meetings on radiation exposure in that the stated goal was to reduce radiation dose by an order of magni-

tude, rather than by “small, incremental amounts.”

“This goal will only be achieved through a revolutionary change in

## COMMENTARY

### Reconsidering regulatory requirements might be the answer

■ IN THE UNITED STATES, concerns over radiation overexposure have been prominent for years, and the recent National Institute of Biomedical Imaging and Bioengineering summit focused on those concerns. Despite the lack of clear consensus on the root cause and the limited potential for corrective action, the US Food and Drug Administration (FDA) has initiated investigations and provided guidance to prevent radiation overexposure.<sup>1</sup>

Lessons learned from recent developments in routine radiographic imaging may prove useful in mitigating the multiple short-term and unidentified long-term effects of CT scan radiation dosing nationally. Etta Pisano, MD, vice president and dean of the School of Medicine at the Medical University of South Carolina, is developing a new technology that will improve medical imaging while requiring only 1% of the radiation dosages associated with conventional radiology.<sup>2</sup> Similar advances are needed in the area of CT scanning. However, even if she is successful in the laboratory, the road to regulatory approval from the FDA is long and arduous.

The goal to achieve an order-of-magnitude reduction of radiation exposure with these scans—and subsequently to reduce cancer inductions and cancer deaths—is ambitious. A major concern is regulatory requirements. Based on these concerns, it is likely that our colleagues in Europe, Asia, and Canada will see this new technology (when developed) sooner than we will in the United States. To avoid trailing the rest of the world, we might need to reconsider the regulatory requirements for new CT scanners. If regulatory approval of promising technologic advances occurs, long-term pharmacovigilance with programs such as the Southern Network on Adverse Reactions will be essential in strengthening postmarketing surveillance efforts.

Zaina P. Qureshi, PhD, MPH  
Charles L. Bennett, MD, PhD, MPP  
Oliver Sartor, MD

South Carolina Center of Economic Excellence for Medication Safety and Efficacy and the Southern Network on Adverse Reactions (SONAR)  
South Carolina College of Pharmacy, University of South Carolina, Columbia, SC  
Hollings Cancer Center, Medical University of South Carolina, Charleston, SC  
Tulane Cancer Center, Tulane University, New Orleans, LA

#### References

1. Qureshi ZP, Sartor O, Bennett CL. Radiation overexposure following brain perfusion CT scans in California, Florida, and Alabama (2008–2009). *Commun Oncol* 2011;8:89–91.
2. Parham C, Zhong Z, Connor DM, Chapman LD, Pisano ED. Design and implementation of a compact low-dose diffraction enhanced medical imaging system. *Acad Radiol* 2009;16:911–917.

how we approach every aspect of CT imaging, requiring significant advances in imaging equipment, detection, and modeling technology,” Dr. Shuren said.

The FDA has been heavily involved in CT radiation issues over the past year. Last November, it recommended a number of steps CT equipment manufacturers should take to help prevent radiation overexposure (*Commun Oncol* 2011;8:89–91). The agency plans to issue draft guidance later this year on CT equipment safety and pediatric radiology equipment standards, according to Dr. Shuren.

The FDA is also working with the National Council on Radiation Protection Measurements to publish diagnostic reference levels for the most common medical imaging procedures and has partnered with the American Association of Physicists in Medicine to standardize CT nomenclature, improve imaging protocols, and provide guidance on how to use new dose-reduction technologies developed by industry.

However, he made clear that much more is needed. “We must also turn to the next steps...to drastically reduce radiation exposure while assuring that medical imaging studies are of adequate resolution for clinical use,” Dr. Shuren cautioned.

Manufacturers at the summit, including Toshiba, GE Healthcare Technologies, Philips, and Siemens, voiced willingness to meet their end of the challenge but also called for government support by way of speedier clearances of improved products and additional funding for technology research.

Some of the newest dose-reduction technologies are available overseas but are still going through the clearance process in the United States. “It’s taken a long time to get that technology cleared in the United States, and so many of the other countries nearby and

## COMMENTARY

### Focus on best clinical judgment, adequate training, and reassuring the public

■ **RADIATION EXPOSURE**, be it from medical imaging, radiation therapy, or even melting fuel rods, has been subject to public scrutiny of late. This journal’s alert, published last month,<sup>1</sup> clearly described the worrisome events associated with suboptimal training and the potential effects that may have on a patient undergoing a CT angiogram of the head. *The New York Times* recently published a series of events associated with a radiation therapy center wherein several patients received unintended doses of high-energy stereotactic radiotherapy, causing blindness and even death.<sup>2,3</sup> The cause of the problem was concluded to be poor quality-assurance training on the part of the medical physicist and radiation therapy technologists.

Following the recent summit, the National Institute of Biomedical Imaging and Bioengineering has convened a working group to evaluate the radiation-based technologies that are used daily in the care of patients. Issues such as dosimetry, patient shielding, and quality assurance will undoubtedly be points of focus. For the community oncologist, who relies heavily on cross-sectional anatomic imaging, there are a few salient points worthy of discussion:

First, how often and for what indications should patients undergo radiation-based imaging (mainly CT scans and fused PET imaging)? There are various sources, such as the National Comprehensive Cancer Network and the American Society of Clinical Oncology, offering guidance for clinicians, but in the end, best clinical judgment should be exercised.

Second, there is no substitute for adequate training. The problems with overdosing will continue to occur if human error persists; minimization of error will result from quality education.

Third, it is imperative for all of us to reassure the public that medical imaging and radiation therapy are safe and effective. We should not shy away from the opportunity to engage our patients and the public in general on what we all know is an issue worth controlling.

Jondavid Pollock, MD, PhD  
Schiffler Cancer Center, Wheeling, WV

#### References

1. Qureshi ZP, Sartor O, Bennett CL. Radiation overexposure following brain perfusion CT scans in California, Florida, and Alabama (2008–2009). *Commun Oncol* 2011;8:89–91.
2. Bogdanich W. The radiation boom—stereotactic radiosurgery overdoses harm patients. *The New York Times*. December 29, 2010.
3. Bogdanich W. Radiation offers new cures, and ways to do harm. *The New York Times*. January 24, 2010.

overseas in Europe and Asia are getting ahead of us,” said Richard Mather, PhD, senior manager of clinical programs, research division, for Toshiba Medical Research Institute USA.

Richard L. Morin, MD, professor of radiologic physics at the Mayo Clinic in Jacksonville, Florida, argued that calls to require randomized, controlled trials to validate new technologies is a decades-old challenge.

“By the time you answer the question with scientific proof that this particular algorithm is better than anything that you’ve had before, the community will already be buying and using a different algorithm,” he said.

A summit working group plans to draft a list of consensus recommendations for NIH research projects aimed at achieving the goal of a routine sub-millisievert radiation dose CT exam.