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ONCOLOGY ISSUES

This publication is a benefit of membership Association of Community Cancer Centers

September | October 2015

Building a Personalized Medicine Program

ACCC
Association of Community Cancer Centers

AstraZeneca

In EGFRm+ advanced NSCLC,

NEARLY 2 OUT OF 3

cases of progression with first-generation EGFR TKIs are related to the T790M mutation[1,2]

NEARLY **2 OUT OF 3**

CASES ARE RELATED TO T790M

T790M is an acquired mutation and has been identified as the most common mechanism of acquired resistance in nearly 2 out of 3 patients with advanced NSCLC.[1,2]

When patients with EGFRm+ status progress, prior to changing therapy, a biopsy is reasonable to identify mechanisms of acquired resistance, as stated in NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®).[3]

Find out how the T790M mutation could affect the future of NSCLC at: EGFRevolution.com.

AstraZeneca is conducting ongoing research to understand the science of the T790M mutation as a driver of resistance.

References: 1. Yu HA, et al. Analysis of tumor specimens at the time of acquired resistance to EGFR-TKI therapy in 155 patients with EGFR-mutant lung cancers. *Clin Cancer Res.* 2013;19:2240-2247. **2.** Arcila ME, et al. Rebiopsy of lung cancer patients with acquired resistance to EGFR inhibitors and enhanced detection of the T790M mutation using a locked nucleic acid-based assay. *Clin Cancer Res.* 2011;17:1169-1180. **3.** Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Non-Small Cell Lung Cancer V.7.2015. ©National Comprehensive Cancer Network, Inc. 2015. All rights reserved. Accessed June 12, 2015. To view the most recent and complete version of the guideline, go online to NCCN.org. NATIONAL COMPREHENSIVE CANCER NETWORK®, NCCN®, NCCN GUIDELINES®, and all other NCCN Content are trademarks owned by the National Comprehensive Cancer Network, Inc.

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ONCOLOGY ISSUES
The Journal of the
Association of Community Cancer Centers

Oncology Issues serves the multidisciplinary specialty of oncology care and cancer program management.

Archived editions of *Oncology Issues* are available to members at: mynetwork.accc-cancer.org.

FROM THE EDITOR

It's All in the Delivery

BY CHRISTIAN DOWNS, JD, MHA

Most of you reading this journal are deeply immersed in treating and serving cancer patients and their families on a daily basis. And yet, if you could step back and look at our country's cancer delivery infrastructure through the lens of a casual observer, you might have some interesting observations.

For example, in the last 15 years, with the advent of guidelines and pathways, the oncology community has been able to standardize care for most cancers.

Living in the U.S., we also enjoy the benefit of a very robust delivery network. Unlike some countries, we do not have patients with cancer waiting for care because of a lack of providers or treatment options.

Affordability—on the other hand—is an altogether different issue. Nearly every day we are reminded that this country is struggling with how to pay for cancer treatment. And this is not just a matter of being able to afford expensive anti-cancer drugs. Across the cancer care continuum—medical, radiation, surgical, imaging, pathology—costs are soaring.

Another area where the oncology community could improve is in coordination of patient care. Some of the best-run healthcare systems still over-treat patients, perform tests more than once, and require patients to make multiple trips to different locations.

One of the most positive aspects of working in the field of oncology is that we are constantly striving to improve—the quality of care we provide, the patient experience, our workplace processes, and our understanding of the disease. And ACCC is here to support your efforts.

In our cover article, Thomas D. Brown, MD, MBA, shares how Swedish Cancer Institute (SCI) made personalized, genomic medicine a cornerstone of its program. SCI looks to use this personalized approach to cancer care to "make treatment fundamentally better, improve outcomes and quality of life, and deliver extraordinary care to its patients."

Next, James Pellicane, MD, describes how molecular subtyping is changing our understanding of breast cancer. One key finding: breast cancer is not just a single disease, but rather a category of diseases made up of several different tumor types (molecular subtypes). Each subtype behaves differently, which means each subtype may need to be treated differently to achieve the best outcome. Dr. Pellicane shows the multiple advantages molecular subtyping may hold for breast cancer patients, cancer programs, and the healthcare community.

Our next feature article, "The Embedded Nurse Navigator Model," is a great example of how to improve care coordination and the patient experience. After conducting a baseline assessment of the physical and psychosocial needs of cancer survivors and providers in the community, the Helen F. Graham Cancer Center and Research Institute retooled its survivorship services. Today this survivorship program has a two-fold goal: to empower survivors to take responsibility for ongoing surveillance and preventive care and to foster a more collaborative approach between the oncology team and primary care providers.

Finally, Matthew Sturm and Katherine Liljedahl Ye focus on how small, rural programs and larger urban programs can work together to improve the quality of cancer care, the patient experience, and care coordination. Further, the authors suggest that these types of partnerships can help programs compete in today's value-focused oncology marketplace.

In our final feature article, Cary Presant, MD, FACP, offers his perspective on ASCO 2015, including the studies and findings that may change how you practice.

As you can see, the oncology community is already addressing some of the weaknesses we see in the delivery infrastructure. And while we must accept that our delivery infrastructure will always have its strengths and weaknesses, our job is to leverage the expertise of our clinicians with cutting-edge technology to improve care, while simultaneously identifying ways to most wisely spend our finite healthcare dollars. OI

Preparing for a New Frontier

BY STEVEN L. D'AMATO, BSPharm, BCOP

The current pillars of cancer treatment incorporate radiation, surgery, and chemotherapy, with the goal of targeting the tumor and inducing complete or partial responses. Immuno-oncology (I-O) is a rapidly developing area of science and treatment that focuses on harnessing the ability of the patient's own immune system to fight cancer. While great strides have been made in the fight against cancer, improved survival remains a challenge for some advanced malignancies. Yet, malignant melanoma, renal cancer, and prostate cancer are potentially immunogenic, which makes them good candidates for immunotherapeutic approaches. Currently, more than 900 I-O clinical trials are in various phases of development.

The history of immunotherapy dates all the way back to 1796 when Edward Jenner used cowpox to induce immunity to smallpox. The first cellular immunotherapy (sipuleucel-T) was approved for prostate cancer in 2010. Ipilimumab (anti-CTLA-4) was approved for advanced melanoma in 2011. This year saw the first programmed cell death protein 1 (PD-1) monoclonal antibody inhibitors (nivolumab and pembrolizumab) approved.

These two new PD-1 inhibitors are currently indicated for the treatment of advanced melanoma (nivolumab, pembrolizumab) and squamous non-small cell lung cancer (nivolumab). These agents also have activity in a variety of other disease states and are currently being evaluated in numerous clinical trials. In addition to the development of anti-PD-1 agents, therapies are being developed that target the PD-1 receptor and its ligands (PD-L1/2). I-O therapies have the potential to be used as monotherapy or as a part of combination regimens. Combinations of complementary I-O therapies with chemotherapy, radiotherapy, and targeted therapy have the potential to enhance anti-tumor effects. One can imagine the complexities of incorporating these new agents into the treatment of various diseases as more agents are developed and approved for use.

The anti-PD-1/PD-L1 agents are relatively well tolerated. However, there are many drug-related adverse events with potential immune-related causes, such as pneumonitis, vitiligo, colitis, hepatitis, hypophysitis, and thyroiditis. Because most tumor-associated antigens are also expressed in normal cells, the potential exists for toxicity against healthy tissues. Adverse events can be serious and potentially lethal, demanding vigilance throughout and after treatment. When combined with other forms of cancer treatment, I-O therapies can lead to numerous toxicities that must be identified early and managed appropriately. Another caveat with I-O is the monitoring of response with these new agents. Therapies that affect the immune system may not induce a measurable effect on tumor growth immediately. After initiating I-O therapy, immune activation and T-cell proliferation can start within days to weeks, but measurable antitumor effects may not be realized until weeks to months after initial treatment; the potential effects on survival may not be seen until several months after initial administration.

This new frontier of medicine requires specialized education so that we can understand the immune system, its relationship to different tumor types, how these new agents interact with the immune system, and how to identify and manage immune-related events. To meet this critical need, ACCC formed the Institute for Clinical Immuno-Oncology (ICLIO), which launched in June 2015. ICLIO translates the latest I-O scientific research and findings for the multidisciplinary cancer care team, making the information accessible and—most importantly—breaking it into digestible action items that can be easily implemented in the community setting. ICLIO has brought the new frontier of immuno-oncology to your door. The next step is up to you. Visit accc-iclio.org today for information about clinical optimization, coverage and reimbursement, management best practices, patient access and advocacy, and training and development. OI

Coming in Your 2015 *ONCOLOGY ISSUES*

- A Patient Tracking System Helps Transition Patients to a Multidisciplinary Nurse Care Model
- The Cancer Care Collaborative—Where Patients are An Active Member of the Cancer Care Team
- Developing & Implementing a Patient Advisory Council
- Building Bridges, Breaking Down Barriers: One Psycho-Oncology Program's Approach to Quality Patient Centered Care
- A Support Program for Providers that Prevents Burnout and Improves Care
- Cancer Education for Nurse Practitioners New to Cancer Care
- Everything You Need to know about Patient Navigation Core Competencies, Training, and Certification
- Closing the Loop with a Post-Biopsy Breast Clinic
- Improve Patient Engagement, Improve Your Cancer Program
- The Oncology Nursing Fellowship Program: A Pipeline for the Future

more online @ www.accc-cancer.org

TOOL

What Cancer Patients Need to Know About Oral Meds

Providers across all care settings—physician practices, hospital-based cancer programs, and freestanding cancer centers—can use this tool to educate patients about how patients and providers can work together to improve care. Dispensing physicians can also use this tool to educate patients about options to fill their prescription(s). accc-cancer.org/chemotherapy.

LISTEN

Proposed 2016 OPPS and PFS Rules

Nearly 200 ACCC members listened to the July 21 conference call and summary analyses of the proposed 2016 hospital outpatient prospective system (OPPS) and physician fee schedule (PFS) rules. If you missed this important call, listen today at mynetwork.accc-cancer.org.

VIDEO

ASCO Post Interview with ICLIO Advisory Committee Chair

Lee S. Schwartzberg, MD, FACP, of The West Clinic, talks about the Institute of Clinical Immuno-Oncology (ICLIO), a new initiative of the Association of Community Cancer Centers, which is designed to speed the adoption of immuno-therapeutics in the community setting. video.ascopost.com/conferences/2015-asco-annual-meeting/iclio-adopting-immunotherapy-in-the-community-setting.

TOOL

2015 Trends in Cancer Programs

Key findings on the biggest challenges facing today's cancer programs, including reimbursement issues, marketplace competition, patient-centered care, quality improvement initiatives, outreach and screening efforts, and more. The full report is available to members only at mynetwork.accc-cancer.org.

Oncology Issues is published bimonthly at the Association of Community Cancer Centers, 11600 Nebel St., Suite 201, Rockville, MD 20852. Editorial correspondence, changes of address, manuscripts, and letters to the editor should be addressed to: Managing Editor, Oncology Issues, 11600 Nebel St., Suite 201, Rockville, MD 20852-2557. Author's instructions available at www.accc-cancer.org.

Articles, editorials, letters to the editor, and other contributed materials represent the opinions of the authors and do not represent the opinions of the Association of Community Cancer Centers or the institution with which the author is affiliated unless the contrary is specified.

Basic rate: $55 per year for healthcare providers, plus $4.99 for shipping. ACCC membership dues pay for general, delegate, and chapter member subscriptions. Back issues available for $12.50 per copy, prepaid. Bulk rates available upon request.

Send correspondence, display advertising, insertion orders, printing materials to Mal Milburn, Oncology Issues, 11600 Nebel St., Suite 201, Rockville, MD 20852. Questions for general information may be directed to 301-984-5704.

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fast

IRS reports that about 7.5 million taxpayers paid a tax penalty in 2015 because they didn't have health insurance coverage.

Source. Bloomberg *BNA Health Care Daily Report*, July 21, 2015.

10 Reasons OCM Could Fail

1. It's vulnerable to being gamed
2. Oncologists can't control all costs
3. Lack of risk adjustment
4. No real-time tracking
5. Unrealistic expectations
6. Little incentive to reduce drug costs
7. Cherry picking (selecting less-sick patients to avoid higher costs)
8. Stinting (switching patients to less expensive, but inappropriate, treatment regimens or recommending against clinically beneficial services, in order to receive performance-based payments)
9. Meaningful Use attestation required
10. Oncologists' behavior

Source. Clark C. 10 reasons why CMS's cancer payment model could fail. *HealthLeaders Media*. http://healthleadersmedia.com/content.cfm?content_id=313899&page=1&topic=HEP.

facts

5 Tips for Your Patients' Caregivers

1. Caregivers must remember to put themselves first.
2. Caregivers need to learn to laugh at the insanity that comes with the job.
3. It's important to have a plan in place before bad things happen.
4. Working with an eldercare coach can significantly lower stress and save time and money.
5. Caregivers must accept that feeling guilty comes with the job, and not be surprised when it happens or believe their own negative self-talk.

Source. Carol Core. *50 Sanity Saving Tips for Caregivers: You Don't Have to Kill Yourself to Keep Them Alive.* www.carolcare.net.

1 in 4 Children with Leukemia Not Taking Maintenance Medication?

- About **25%** of children in remission from acute lymphocytic leukemia (ALL) are missing too many doses of an essential maintenance medication that minimizes their risk of relapse.
- Maintenance medication adherence was lower in African American and Asian children in remission from ALL than in non-Hispanic white children, with **46%** of African Americans and **28%** of Asians not taking enough medication to prevent relapse, compared with **14%** of non-Hispanic whites.
- Regardless of race, families reported that the most common reason for children not taking their medication was forgetfulness.

Source. Bhatia S, et al. Adherence to oral 6-mercaptopurine in African American and Asian children with acute lymphoblastic leukemia: a Children's Oncology Group study. *Blood.* 2014;124(15): 2345-2353.

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Defining the Indefinable

BY LEAH RALPH

On the heels of ASCO 2015 this summer, in which a common theme was the high—and rising—cost of cancer drugs, ASCO released its much anticipated value framework, a proposed methodology designed to assist physicians and patients in assessing the "value" of different cancer treatment options.

While the framework is not yet ready for the clinical setting, it represents an important step in the broader conversation about measuring "value" in cancer care. As a conceptual framework, it seems to have done its job: jumpstarted an important conversation in a thoughtful way. But as ASCO itself points out, it is critical to consider this tool in context. The methodology contains significant, and noted, limitations in data, practicality, and scope. Thus, payers and policymakers should be cautioned that this framework is not meant to serve as a basis for reimbursement or coverage determinations.

ASCO's approach uses randomized clinical trial data to compare new treatments with an established standard of care under two different scenarios: the advanced disease setting and the adjuvant, potentially curable, setting. A treatment receives a net health benefit (NHB) score (up to 130 points for advanced and 100 points for adjuvant) by combining a score for clinical benefit (80 points), toxicity (up to 20 points), and up to 30 bonus points for quality of life measures, including palliation of symptoms and treatment-free intervals in the advanced disease setting. The NHB score is intended to demonstrate the added benefit patients may receive from a new cancer drug compared with a prevailing standard of care.

Under the proposed framework, the clinical benefit score gives most weight to therapies that increase overall survival, followed by progression-free survival, and finally response rate. ASCO chose these clinical endpoints because they represent data most commonly collected and reported in clinical trials.

The combined clinical benefit, toxicity, and bonus points make up the NHB score, which is then displayed next to (and, notably, separately from) cost. Here ASCO uses drug acquisition cost, and concedes that while this is not the most complete or meaningful measure, particularly for the patient, it was the most straight forward to quantify. Any methodology to truly determine value should include total cost of care, including estimated costs for diagnostics, surgery, imaging, hospitalization, and provider charges. Ultimately ASCO envisions including another figure, the cost to the patient, which will have to be individualized based on the patient's specific health benefit design. ASCO also notes that in a clinical tool, the goal is that the patient will also be able to modify the importance of both clinical benefit and/or toxicity based on his or her personal values and goals.

As we know, defining value is not an easy task. There are, of course, limitations to this model, many of which ASCO points out. The first is that the NHB calculation is only valid within the context of the clinical trial, which does not allow for intertrial comparisons. Regimens cannot be compared that have not been compared head-to-head in clinical trials. Additionally, this model lacks the patient's perspective on value, excluding critical endpoints, such as quality of life and patient-reported outcomes in the calculation of NHB. The framework also needs to provide more clarity on how a clinical tool would incorporate a patient's unique characteristics, preferences, and treatment goals. We also know that the relative value of a given treatment will likely change over its lifetime; there needs to be more clarity on how this conceptual framework will become a practical, dynamic tool that will repopulate data and update NHB scores over time.

From the physician's perspective, many questions remain. How exactly will this tool be used in a clinical setting? When will this conversation happen at the point of care? Who will ultimately do the analysis, input the patient's cost-sharing data and preferences, and present the numbers to patients? Some physicians will use the tools themselves, while others will rely on nurses, administrators, or pharmacists to perform the analytics. While the proposed framework is "not meant to substitute for physician judgment or patient preference," it may leave the patient with more questions than answers—will physicians be prepared?

ACCC recently submitted comments on ASCO's value framework, and we look forward to continuing to engage with ASCO and others on the challenging issue of cost and quality in the cancer care delivery system. OI

Leah Ralph is ACCC manager of provider economics & public policy.

Chronic Care & Transitional Care

These May Not Be The Codes You Are Looking For...

BY CINDY PARMAN, CPC, CPC-H, RCC

Care management is an emerging concept that refers to a set of evidence-based, integrated clinical care activities that are tailored to the individual patient and ensure each patient has his or her own coordinated plan of care and services.[1] The care plan may include multiple medical conditions managed by different medical specialists and is designed to optimize the patient's health and quality of life by generating, planning, organizing, and administering medical care and services. The care plan may include prevention, treatment, and management of illnesses, and the preservation of the patient's mental and physical well-being.

There are procedure codes to report care management services, providing that all documentation requirements are met. It is important to note that while these are billable procedure codes, not all insurers reimburse for these services. Two types of care management services are included in the current code set:

1. Transitional care management services
2. Chronic care management services.

Transitional Care Management Services

Transitional Care Management (TCM) codes were created in 2013 and are used to report services provided to patients transitioning from the inpatient hospital setting to the community setting. The Centers for Medicare & Medicaid Services (CMS) adds that the services must be required by the beneficiary, which means there must be documentation of medical necessity.[2] TCM begins at the date of hospital discharge when the healthcare professional accepts the care of the patient post-discharge without a gap and continues for the next 29 days. These services include:

One (1) face-to-face visit performed within specified time frames. This initial face-to-face visit is part of the TCM service and not separately billed. Additional medically necessary patient visits provided on subsequent dates may be coded and reported separately as established patient visits (codes **99211-99215**).

TCM services can be charged for both new patients and established patients, providing that all criteria are met.

An interactive contact with the patient or caregiver within two business days of discharge. This contact may be direct (face-to-face), by telephone, or by electronic means. The healthcare professional who bills for TCM takes responsibility for the patient's total care. According to CMS, healthcare professionals who can furnish TCM services include physicians, certified nurse-midwives, clinical nurse specialists, nurse practitioners, and physician assistants.

The healthcare provider who performs TCM bills for the service directly; this is not considered to be an "incident-to" service that can be performed by a nonphysician practitioner and billed in the name of a physician. For Medicare purposes, if attempts to communicate with the patient have been unsuccessful within two business days of discharge, providers must continue their attempts to communicate until successful. A successful attempt requires a direct exchange of information and appropriate medical direction by clinical staff with the beneficiary and/or caregiver and not merely delivery of a voicemail or email without response from the patient or caregiver. If there is no successful interactive contact, TCM codes cannot be charged.

Medication reconciliation and management must occur no later than the date of the face-to-face visit. TCM medication reconciliation requires that the medications on discharge be reconciled with the medications that the patient was taking prior to hospital admission. The nurse can obtain the medication information, but the physician must review this data and order any changes, additions, or deletions to the medication list.[3]

Non-face-to-face services performed by the physician or other qualified healthcare professional and/or licensed clinical staff under his/her direction. The physician or qualified nonphysician healthcare professional may be required to:

- Obtain and review discharge information.
- Determine the need for follow-up of any pending diagnostic tests.
- Interact directly with other specialists who will assume or re-assume patient care for non-oncology medical conditions.
- Establish or re-establish referrals.
- Arrange for community resources.
- Assist with scheduling for all necessary visits to other medical professionals.
- Educate the patient, family, and/or caregivers on the transitional care plan.

Table 1. TCM Procedure Codes*

TCM CODE	COMMUNICATION	MEDICAL DECISION MAKING	FACE-TO-FACE VISIT
99495	Direct contact within 2 business days	Moderate complexity	Within 14 days
99496	Direct contact within 2 business days	High complexity	Within 7 days

* Medical decision making is defined by the evaluation and management services guidelines. Documentation must support that the patient has medical and/or psychosocial problems that require moderate or high complexity medical decision making. In addition, the claim for TCM services must include diagnosis codes for all medical conditions managed as part of this care.

Services provided by clinical staff include:

- Monitoring communications from community services or agencies used by the patient.
- Providing assessment and support for treatment regimen adherence and medication management.
- Reinforcing patient and caregiver education.
- Facilitating access to care and services needed to ensure transitional care plan compliance.

Key to charging for TCM is that the physician must be able to address any needed coordination of care performed by other medical disciplines and community service agencies. By reporting the TCM codes, the provider agrees to oversee the management and coordination of services for all medical conditions, psychosocial needs, and support for activities of daily living (ADLs) by providing first contact and continuous access. Only one individual may report these services and then only once per patient within 30 days of discharge. Remember that if an oncologist provides TCM services, it means that the physician and staff are responsible for continuous access for all patient medical conditions—not just the hematology/oncology concern. The physician who performs and bills TCM will manage all medical conditions and all patient medications. For example:[4]

On the day after discharge, the physician speaks with the wife, who is concerned that the patient remains confused. The physician reviews the medication regimen and instructs the wife to discontinue one of the psychoactive medications. The wife is counseled about avoidance of anticholnergic over-the-counter (OTC) medications.

The clinical staff nurse contacts the hospital to obtain the discharge summary to find out who attended the patient during the hospitalization, and which home-health agency received the referral. The physician calls the hospitalist and the consultants to clarify the indications for the medications.

The patient comes to the office 3 days later, at which time the physician has received and reviewed additional records, makes further adjustments to the medication regimen, including tapering anti-diabetic medications that are no longer necessary with resolution of the stressors. Care goals are reviewed (resuscitation status, glycemic control, and lipid goals in a patient with limited life expectancy). Additional diagnostic/monitoring tests are ordered. The nurse care-manager calls the wife several days later to follow up, and the patient is managed for 30 days with additional nurse calls to monitor progress in resolution of the delirium and blood glucose testing.

When all criteria are met, the date of the first face-to-face visit and the extent of documented medical decision making are used to select the TCM procedure code (see Table 1, above).

Because the TCM services will occur over a period of 30 days, medical record documentation must include all face-to-face and non-face-to-face services. Supporting information should include documentation

of the timing of the initial post-discharge communication with the patient or caregivers, date of the face-to-face visit, and the complexity of medical decision making.[5] The date of service for TCM is the last date of the 30-day service period, unless there is an individual insurance payer policy to the contrary. The place of service reported by the billing provider will correspond to the place of service where the required face-to-face visit occurred (e.g., physician's office, patient's home, etc.). Also, while the same provider can bill for both the hospital discharge and TCM, seeing the patient on the day of discharge does not meet the requirements for the follow-up face-to-face visit.

Chronic Care Management

While TCM codes are billed only once per patient per hospital discharge, other procedure codes describe Chronic Care Management (CCM) or Complex Chronic Care Management (CCCM). Similar to the TCM codes, the physician or other qualified healthcare professional oversees, manages, and coordinates care for all medical conditions. Approximately two-thirds of Medicare beneficiaries have two or more chronic conditions and one-third have four or more chronic conditions.[6]

Remember: the patient will be liable for any coinsurance and/or deductibles associated with chronic care management services. As a result, the patient must complete an informed consent for CCM services prior to initiating the service. The patient must specifically acknowledge in writing that:

- The provider has explained the nature of CCM, including how CCM may be accessed.
- Only one provider at a time may furnish CCM for the patient.
- The patient's health information will be shared with other providers for care coordination purposes.
- The patient may stop CCM services at any time by revoking consent (effective at the end of the current calendar month).
- The patient will be responsible for any coinsurance and deductible amounts associated with these services.

While CMS strongly recommends that a provider furnish an annual wellness visit (AWV) or an initial preventive physical exam (IPPE) for each patient receiving CCM, there are no prerequisite services required to bill for CCM at this time.

Chronic care management services are appropriate for patients with medical and/or psychosocial needs that require establishing, implementing, revising, or monitoring a care plan. These patients have two or more chronic continuous or episodic health conditions that are expected to last at least 12 months or until the death of the patient. In addition, these conditions place the patient at significant risk of death, acute exacerbation, decompensation, or functional decline.

CMS maintains a Chronic Conditions Warehouse (CCW) to provide researchers with beneficiary, claims, and assessment data that includes information on 22 specified chronic conditions.[7] This warehouse may not constitute an exclusive list of chronic medical conditions, and CMS has not provided a definition of which medical conditions are required for CCM reimbursement. In addition, while cancer is listed as a chronic medical condition, providers should ensure that they can manage all patient medical conditions prior to billing chronic care management services.

The CCM code can be reported when at least 20 minutes of clinical staff time (including face-to-face and non-face-to-face time) is spent in care management activities during a calendar month. Because this physician-directed service may result in staff time that occurs after hours, CMS states that this service requires general supervision rather than direct supervision. The code for this service is:

- **99490.** At least 20 minutes of clinical staff time directed by a physician or other qualified healthcare professional, per calendar month. Multiple chronic conditions, expected to last at least 12 months or until the death of the patient, places the patient at significant risk of death, acute exacerbation, decompensation, or functional decline, with a comprehensive care plan established, implemented, revised, or monitored.

(Note: Chronic care management services of less than 20 minutes duration in a calendar month are not reported separately. In addition, clinical staff time cannot be counted toward the monthly total when the physician or other qualified healthcare professional reports a professional service on the same day.)

The plan of care must be documented and shared with the patient and/or caregiver. This care plan is based on a physical, mental, cognitive, social, functional, and environmental assessment and includes all health problems. It generally includes:

- A problem list.
- Expected outcome and prognosis.
- Measurable treatment goals for all medical concerns.
- Symptom management.
- Planned interventions.
- Medication management.
- Community and/or social services.
- How the services of agencies and specialists that are not connected with the practice will be directed/coordinated.
- Identification of the individuals responsible for each intervention.
- Requirements for periodic review and any necessary revisions of the care plan.
- A list of current practitioners and suppliers that are regularly involved in providing medical care to the patient and address all health issues (not just chronic conditions).

CCM is reported only once each calendar month and only reported by the single physician or other qualified healthcare professional who assumes the care management role for the individual patient.[8] If there is a month where the 20-minute minimum time requirement is not met, chronic care management cannot be billed for that calendar month. Activities performed by clinical staff generally include:

- Education, communication, and engagement of the patient and family in the care plan.
- Communication with agencies and community services used by the patient.
- Collection of health outcomes data and registry documentation.

Table 2. Time-Based Codes for Complex Chronic Care Management*

CCCM CODE	DEFINITION
99487	Complex chronic care management services, for multiple chronic conditions expected to last at least 12 months, placing the patient at risk of death, acute exacerbation, decompensation, or functional decline. Requires the establishment of a comprehensive care plan, with moderate or high medical decision making, 60 minutes of clinical staff time directed by a physician or other qualified healthcare professional, per calendar month.
+99489	Each additional 30 minutes of clinical staff time directed by a physician or other qualified healthcare professional, per calendar month.

* Medical decision making is defined by the evaluation and management services guidelines.

- Assessment and support for treatment regimen adherence and medication management.
- Facilitating access to necessary care and services.
- Ongoing review of patient status.
- Maintenance of a comprehensive care plan.

In addition to these requirements, the practice or program that performs CCM must have the following capabilities:

- Provide 24/7 access to physicians or other qualified healthcare professionals or clinical staff, including providing patients and/or caregivers with a means to make contact with healthcare professionals to address urgent needs—regardless of the time of day or day of week.
- Provide continuity of care with a designated member of the care team with whom the patient is able to schedule successive routine appointments.
- Provide timely access and management for follow-up after an emergency department visit or facility discharge.
- Utilize an electronic health record (EHR) system so that care providers have timely access to clinical information:
  - The patient's demographics, problems, medications, and medication allergies, which must be included in structured clinical summary records using certified EHR technology.
  - The patient's care plan must be available electronically at all times to anyone within the practice or program providing the CCM service. Specifically, all clinical staff whose time is counted toward the monthly maximum must have electronic access to the care plan.
  - The care plan must be electronically shared outside the program or practice as appropriate.
- Use a standardized methodology to identify patients who require care management services.
- Have an internal care management process and/or function whereby a patient identified as meeting the requirements for these services starts receiving them in a timely manner.
- Use a form and format in the medical record that is standardized within the practice or program.
- Be able to engage and educate patients and caregivers, as well as coordinate care among all service professionals, as appropriate for each patient.
- Provide enhanced opportunities for the patient and any caregiver to communicate with the practitioner regarding the patient's care. This can be accomplished through telephone, secure messaging, secure Internet connection, or other asynchronous non-face-to-face consultation methods that comply with HIPAA (Health Insurance Portability and Accountability Act).

Effective January 1, 2015, CMS established a payment for procedure code **99490**, and noted that payment for CCM is only one part of a multifaceted initiative to improve Medicare beneficiaries' access to primary care.[9] By providing CCM reimbursement, payers are also establishing a bridge between fee-for-service and value-based reimbursement.

Complex Chronic Care Management

CCCM services are provided during a calendar month that includes all criteria for CCM services, as well as the establishment or substantial revision of a comprehensive care plan; medical, functional, and/or psychosocial problems requiring medical decision making of moderate or high complexity; and clinical staff care management services of at least 60 minutes. If the care plan is unchanged or requires only minimal changes, CCCM cannot be charged.

The program or practice will identify patients who require CCCM services through practice- or program-specific algorithms or other published algorithms that recognize multiple illnesses, multiple medication use, inability to perform activities of daily living, requirement for a caregiver, multiple emergency department visits, and/or multiple hospital admissions. Typical patients:

- Are treated with three or more prescription medications.
- Receive other types of therapeutic interventions (e.g., physical therapy, occupational therapy).
- Have two or more chronic continuous or episodic health conditions that are expected to last at least 12 months or until the death of the patient.
- Have chronic conditions that place the patient at a significant risk of death,

Table 3. Criteria for Assigning Time-Based CCCM Codes

TOTAL DURATION OF STAFF CARE	CCCM CODES
Less than 60 minutes	Not reported separately
60 minutes to 89 minutes	Code 99487
90 minutes to 119 minutes	Code 99487 + 99489 x 1
120 minutes or more	Code 99487 + 99489 x 2 + 99489 for each additional 30 minutes

acute exacerbation, decompensation, or functional decline.
- Require the coordination of a number of specialties and services.
- Are unable to perform ADLs.
- May have cognitive impairment, resulting in poor adherence to the treatment plan without substantial assistance.
- May have psychiatric and medical comorbidities.
- Have social support requirements or difficulty with access to care.

There are two time-based codes for these services (see Table 2, page 15). Table 3, above, can help providers assign these time-based codes.

While Medicare currently reimburses for chronic care management, CCCM services have a bundled status under the Medicare Physician Fee Schedule.

Other Considerations

Research studies continue to demonstrate that care management reduces the total cost of care for patients with chronic diseases and improves overall patient health. In a May 2015 Fact Sheet, CMS states:[10]

The Centers for Medicare & Medicaid Services (CMS) recognizes care management as one of the critical components of primary care that contributes to better health and care for individuals as well as reduced spending.

Last, there are a number of other services that are considered to be inclusive to care management; a comprehensive list is located in the CPT® Manual, and includes procedures such as:

- Care plan oversight
- Prolonged services without direct patient contact
- Anticoagulant management
- Medical team conferences
- Education and training
- Telephone services
- ESRD (end stage renal disease) services
- Online medical evaluations
- Preparation of special reports
- Data analysis
- Medication therapy management services.

These codes are ideal for a strong team approach, covering services many family physicians are providing on a regular basis and recognizing that primary care physicians take care of many time-consuming issues of care coordination for patients. By developing and implementing a CCM program, a provider will grow skill sets and internal processes critical to population health management, all the while receiving fee-for-service payment to support those activities. OI

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References

1. DOQ-IT University. Care Management Definition. Available online at: www.ddcmultimedia.com/doqit/Care_Management/CM_Overview/index.html. Last accessed July 28, 2015.

2. CMS. Transitional care management services. *Medicare Learning Network*. Available online at: www.cms.gov/Outreach-and-Education/Medicare-Learning-Network-MLN/MLNProducts/Downloads/Transitional-Care-Management-Services-Fact-Sheet-ICN908628.pdf. Last accessed July 28, 2015.

3. AAFP. Frequently Asked Questions: Transitional Care Management. Available online at: www.aafp.org/dam/AAFP/documents/practice_management/payment/TCMFAQ.pdf. Last accessed July 28, 2015.

4. AMA. CPT® Changes: An Insider's View 2013.

5. AMA. CPT® Assistant, July 2013, page 11.

6. Lochner KA, Cox CS. Prevalence of multiple chronic conditions among Medicare beneficiaries, United States, 2010. *Preventing Chronic Disease: Public Health Research, Practice, and Policy.* Available online at: www.cdc.gov/pcd/issues/2013/12_0137.htm. Last accessed July 28, 2015.

7. CMS. Chronic Conditions Data Warehouse. Available online at: www.ccwdata.org/web/guest/home. Last accessed July 28, 2015.

8. AMA. CPT® Changes: An Insider's View 2015.

9. AMA. CPT® Assistant, February 2015, page 3.

10. CMS. Transitional care management services. *Medicare Learning Network*. Available online at: www.cms.gov/Outreach-and-Education/Medicare-Learning-Network-MLN/MLNProducts/Downloads/ChronicCareManagement.pdf. Last accessed July 28, 2015.

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Join Teri U. Guidi, OMC Group's President and CEO on October 11-14, 2015 in Washington, DC at the 2015 **SHSMD CONNECTIONS meeting,** ***"the event of the year for healthcare marketing, public relations, communications, and strategic planning professionals"***

Ms. Guidi has been invited to speak on utilizing data from OMC Group's **National Hospital Oncology Benchmark Study (NHOBS)™** (www.NHOBS.com) to enable hospitals to find ways to grow their cancer programs through marketing, new initiatives or acquisition of physician practices and to project the future needs for staff and facility. Her presentation will offer key data points for expansion planning of outpatient infusion and radiation centers. The data is also vital in assessing the efficiency, productivity and quality of existing cancer programs.

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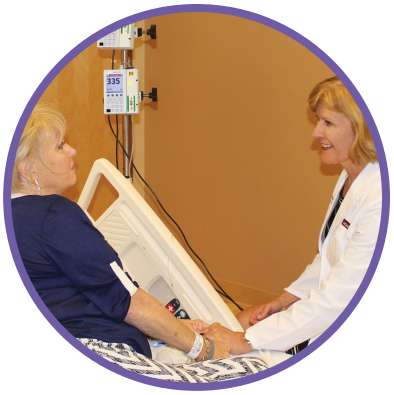
spotlight

Virginia G. Piper Cancer Center at HonorHealth

Scottsdale, AZ



The Virginia G. Piper Cancer Center is an outpatient cancer center located on the HonorHealth Scottsdale Shea Medical Center campus. It is part of HonorHealth, a non-profit health system serving the greater Phoenix area. The company encompasses five acute care hospitals, an extensive medical group, outpatient surgery centers, a cancer center, clinical research, medical education, two foundations, and community services.

"Our program provides patients with access to tertiary level services in a community setting" said Matt Schneider, associate vice president, Oncology Services.

A Full Menu of Service Offerings

For patients, this arrangement means easy access to inpatient and outpatient facilities, emergency services, and the full support of the HonorHealth network, with multiple disciplines for advanced care. The cancer center has medical and radiation oncology services and a bone marrow transplant center, as well as genetics, infusion, lymphedema, an image boutique/DME supplier, a library, a social worker, an oncology-certified dietitian, and patient navigators in one location.

On the first floor of the cancer center, patients and visitors are greeted and given directions as needed at the concierge desk. The boutique, Tina's Treasures, named after cancer survivor Tina Johnson, offers prostheses, wigs, and bra fittings for breast cancer patients. The cancer center also has an educational conference room, which is used by the hospital and community for oncology education. A chapel and large resource library for patients, staffed with a full-time librarian, are also located on the first floor.

The Radiation Oncology Department rounds out the first-floor services. Radiation oncologists extensively use HDR brachytherapy, and while many centers offer this treatment, the cancer center has an innovator in HDR programs, Robert Kuske, MD, as part of its team. Dr. Kuske developed the Kuske applicator, which is commonly used in this treatment. The cancer center offers HDR brachytherapy for various diagnoses, with GYN cancers and breast cancers comprising the highest volume. Other forms of radiation therapy include IMRT, IGRT, and radiosurgery.

The Outpatient Infusion Services Center is staffed by chemotherapy-certified oncology nurses along with two oncology nurse navigators who are responsible for following up with patients discharged from the inpatient oncology unit.

Surgical oncology services include access to one of the largest robotics programs in Arizona. HonorHealth network currently has seven da Vinci robots, including three on the Shea campus for multi-quadrant surgery. By the end of 2015, Schneider estimates the health system will have performed 10,000 robotic surgeries.

The cancer center has a dedicated social worker who works collaboratively with the Shea inpatient social workers in oncology to ensure that discharged inpatients receive proper follow-up care. Other supportive care services on-site include:

- Genetic counseling
- An oncology-certified dietitian
- Cooking and nutrition classes
- Body, mind, and spirit programs.

The Lymphedema Treatment Center at the cancer center is a Phase 1 treatment center and a National Lymphedema Network-sponsored facility.

The cancer service line at HonorHealth is composed of both outpatient imaging and treatment services, as well as multiple inpatient units. The Shea campus, where the outpatient cancer center is physically located and connected to the inpatient hospital, has three inpatient oncology units: a 14-bed dedicated Bone Marrow Transplant Unit, a 24-bed Hematology/Medical Oncology Inpatient Unit, and a 24-bed Oncology Medical/Surgical Unit.

The Breast Health and Research Center located at the HonorHealth Deer Valley Medical Center was the first in Arizona to offer 3D mammography. The main campus offers:

- Low-dose 3D mammography
- Interventional technologies
- Breast biopsy
- Breast MRI
- Breast ultrasound
- Bone densitometry
- Body composition analysis
- Spa-like setting.

In addition, two satellite locations offer 3D imaging. The HonorHealth Deer Valley Medical Center offers many oncology services, including extensive breast surgical and reconstructive services. The Deer Valley campus also features radiation oncology, medical oncology, and fellowship-trained breast and GYN oncology surgeons.

The HonorHealth Scottsdale Osborn Medical Center offers extensive surgical

oncology services including robotic surgery and on-site radiation and medical oncology services.

"Bridge between Care and Cure"

The Virginia G. Piper Cancer Center is joined by a pedestrian bridge to the Debi and Jerry Bisgrove Research Pavilion, which houses HonorHealth's Research Institute. Dubbed the "Bridge between Care and Cure," this walkway symbolizes the integration of advanced technology and science with state-of-the-art standard patient care. The core program at the research institute is early drug development in cancer. This is a joint program between HonorHealth and the Translational Genomics Research Institute (TGen).

"Our concept is to have the rigors and technology of an academic setting, but placed within the community where we can accelerate innovation to the patients," said Mark Slater, PhD, vice president of Research for the HonorHealth System and chief executive for the HonorHealth Research Institute.

Currently, 65 cancer clinical trials are open through the research institute; focused on targeted therapies and precision medicine. All of the physician investigators have joint appointments both in the HonorHealth network and with TGen. These physician scientists are paired with PhD bench-scientists in laboratories at TGen for the discovery work. The clinical care, clinical research, and clinical development part of the translation is done at HonorHealth, embodying the concept of linking the bench and the bedside.

Patients enrolled in clinical trials receive the full complement of services through the cancer center, as well as access to new technologies and all of the support services surrounding clinical trials. Free navigation services, offered to all patients, are performed by oncology-certified APRNs. The research institute has three navigators; one dedicated to pancreas and GI cancers, and two others that work across disciplines. The navigators assist patients in identifying appropriate clinical trials, answering any patient questions, and determining sites or options near their home, as well as trial options on-site. These navigators also help patients gather medical records needed for the intake process to determine eligibility for a trial and then ultimately go through the consenting process with patients.

Dr. Slater stresses the importance of the concept of "an institute without walls." The research institute began with a lead gift from the Virginia G. Piper Trust, establishing collaboration with TGen in November 2005. Since then, "through research, we've brought collaborations, technologies, talent, and connections with universities, companies, and other research institutes, both local and distant. This has brought patients from 48 states and two dozen countries to the cancer center for clinical trials and care," said Dr. Slater.

The cancer center was selected as one of the original Stand Up to Cancer (SU2C) Dream Team sites. It was also the only facility in the Southwest participating as a collaborator in the $18 million SU2C pancreatic cancer Dream Team grant.

Dr. Slater cites advanced molecular medicine, state-of-the-art full genome sequencing, access to immunotherapies, such as PD-L1, and imaging capabilities, as highlights of the program.

Additionally, RADAR (Rapid Detection and Assessment of Response), a rapid cancer detection program developed through a collaboration between local physicians, HonorHealth's Research Institute, and the Virginia G. Piper Cancer Center, uses textural analysis of images to show the biology of tumors and whether they are responding to therapies.

Robust Transplant Program

The peripheral stem cell transplant program, as a whole, transplants nearly 200 patients a year, putting it in the top 5 percent of the country as far as quantity of transplants. The program's success is due to the Cancer Transplant Institute at the Virginia G. Piper Cancer Center, located on the campus of HonorHealth Scottsdale Shea Medical Center. With five transplant physicians on staff, the institute keeps open appointments for same-day or next-day consults.

The institute is accredited by FACT (Foundation for the Accreditation of Cellular Therapy) for both autologous and allogeneic adult transplants.

The transplant institute strives to give cancer patients the most personalized care possible, and assigns a transplant coordinator the first day. That coordinator serves as the patient's point of contact and will walk patients through each step of the transplant process. "Our patient experience scores are very high and many of the comments we hear from patients are 'I really felt like I was being taken care of by family,' " said Selma Kendrick, RN, MS, OCN, BMTCN, director, peripheral stem cell transplant program. OI

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- Navigation
- Nutrition and dietary counseling
- Survivorship care
- Body, mind, and spirit
- Resource library

Percentage of patients accrued to clinical trials annually: 6%

Number of new analytic cases seen in 2014: 4,114

tools

Approved Drugs

• Seattle Genetics, Inc. (www.seattlegenetics.com) announced that the Food and Drug Administration (FDA) has approved **Adcetris® (brentuximab vedotin)** for the treatment of patients with classical Hodgkin lymphoma at high risk of relapse or progression as post-autologous hematopoietic stem cell transplantation consolidation. Adcetris is an antibody-drug conjugate directed to CD30, which is expressed in classical HL and systemic anaplastic large cell lymphoma (ALCL), as well as other lymphoma subtypes. This is the third indication for the drug, which was granted accelerated FDA approval in August 2011 for two other indications: treatment of Hodgkin lymphoma patients who fail autologous transplant or who fail at least two prior multi-agent chemotherapy regimens and are not autologous transplant candidates, and treatment of systemic ALCL patients who fail at least one prior multi-agent chemotherapy regimen.

• FDA has approved AstraZeneca's (www.astrazeneca.com) drug **Iressa® (gefitinib)** for the treatment of patients with metastatic non-small cell lung cancer (NSCLC) whose tumors have epidermal growth factor receptor (EGFR) exon 19 deletions or exon 21 (L858R) substitution mutations as detected by an FDA-approved test. This approval of gefitinib is being approved concurrently with a labeling expansion of the *theracreen*® EGFR RGQ PCR Kit, a companion diagnostic test for patient selection.

• **Odomzo® capsules (sonidegib)**, Novartis Pharmaceuticals Corporation, (www.us.novartis.com), has received FDA approval for the treatment of patients with locally advanced basal cell carcinoma (BCC) that has recurred following surgery or radiation therapy, or those who are not candidates for surgery or radiation therapy.

CMS Expands Medicare Anti-Cancer Treatment Compendia List

On Aug. 12, 2015, the Centers for Medicare & Medicaid Services (CMS) issued a decision adding Wolters Kluwer *Lexi-Drugs*® to the list of compendia in Chapter 15, section 50.4.5 of the Medicare Benefit Policy Manual, for use in the determination of a "medically-accepted indication" of drugs and biologicals used off-label in an anticancer chemotherapeutic regimen, unless the Secretary has determined that the use is not medically appropriate or the use is identified as not indicated in one or more such compendia.

Drugs in the News

• ZIOPHARM Oncology, Inc. (www.ziopharm.com) announced that the FDA has granted orphan drug designation for **Ad-RTS-hIL-12 + veledimex** in the treatment of patients with malignant glioma. Ad-RTS-hIL-12 is a novel gene therapy candidate for the controlled expression of IL-12, a critical protein for stimulating an anti-cancer T cell immune response.

• The FDA has granted orphan drug designation to Novogen Limited (**www.novogen.com**) for its chemotherapy candidate drug, **Anisina (ATM-3507)**. The drug is for neuroblastoma.

• ASLAN Pharmaceuticals (www.aslanpharma.com) announced that the FDA has granted orphan drug designation to its pan-HER inhibitor **Varlitinib (ASLAN001)** for cholangiocarcinoma, a rare and very aggressive form of bile duct cancer.

• Cleave Biosciences (www.cleavebio.com) announced that its lead drug candidate, **CB-5083**, has been granted orphan drug designation by the FDA for the treatment of multiple myeloma. CB-5083 is an oral inhibitor of p97, a critical enzyme that controls various aspects of protein homeostasis. Cleave is currently evaluating CB-5083 in two Phase I studies, including one in patients with multiple myeloma, and one in patients with solid tumor malignancies.

• The FDA has granted NanoSmart Pharmaceutical (www.nanosmartpharma.com) orphan drug designation for a second drug product that uses NanoSmart's proprietary drug delivery platform. The drug product is a formulation of **dactinomycin** for the treatment of Ewing's sarcoma.

• The FDA has granted PNP Therapeutics (www.pnptherapeutics.com) orphan drug status for **Gedeptin™** (adenoviral vector expressing *E. coli* purine nucleoside phosphorylase gene) for the intratumoral treatment of anatomically accessible oral and pharyngeal cancers, including cancers of the lip, tongue, gum, floor of mouth, salivary gland, and other oral cavities.

• Valor Biotherapeutics, LLC, (www.valorbio.com) announced that the FDA has approved an investigational new drug (IND) for **IGN002**. The approved IND is a key step in allowing Valor to begin a Phase I clinical study of IGN002 in patients with non-Hodgkin lymphoma (NHL).

• **ImMucin** (Vaxil Bio, www.vaxilbio.com) has been granted FDA orphan drug designation for the treatment of multiple myeloma (MM). ImMucin is an immunotherapeutic treatment that educates the MM patient's immune system to attack MM cancer cells via a specific domain, termed signal peptide, of the tumor marker MUC1.

• Takeda Pharmaceutical Company Limited (www.takeda.com) has submitted a new drug application (NDA) to the FDA for **ixazomib**, an investigational oral proteasome inhibitor for the treatment of patients with relapsed and/or refractory multiple myeloma.

• KaloBios Pharmaceuticals, Inc. (www.kalobios.com) announced that the FDA has cleared the company's IND application for **KB003**, an anti-GM-CSF monoclonal antibody (mAb), in patients with chronic myelomonocytic leukemia (CMML). The acceptance of this IND allows KaloBios to initiate an open-label Phase I study designed to evaluate the safety, pharmacokinetics, and clinical activity of KB003 in previously treated CMML patients.

• Amgen (www.amgen.com) has submitted a supplemental new drug application (sNDA) to the FDA for **Kyprolis® (carfilzomib) for Injection** to seek an expanded indication for the treatment of patients with a form of blood cancer, relapsed multiple myeloma, who have received at least one prior therapy. Kyprolis currently has accelerated approval in the U.S. for the treatment of patients with relapsed multiple myeloma as a monotherapy.

• The FDA has granted breatkthrough designation to **Lenvima™ (lenvatinib)** (Eisai Inc., www.eisai.com/US), a multiple receptor tyrosine kinase inhibitor, for the investigational use in patients with advanced or metastatic renal cell carcinoma (RCC) who were previously treated with a vascular endothelial growth factor (VEGF)-targeted therapy.

• Delcath Systems, Inc. (www.delcath.com) announced that the FDA has granted orphan drug designation for **melphalan** for the treatment of cholangiocarcinoma (a tumor in the bile duct that arises within the liver).

• BioDelivery Sciences International, Inc. (www.bdsi.com) announced that the FDA has approved an sNDA for a new formulation of **Onsolis® (fentanyl buccal soluble film)** for the management of breakthrough pain in patients with cancer who are opioid tolerant.

• The FDA has granted fast track designation to **Toca 511** and **Toca FC** (Tocagen Inc., www.tocagen.com) for the treatment of recurrent high grade glioma, which includes glioblastoma and anaplastic astrocytoma.

Devices in the News

• Medrobotics Corporation (www.medrobotics.com) has received FDA market clearance to sell its **Flex® Robotic System** in the U.S.

• Elekta's (www.elekta.com) **Leksell Gamma Knife® Icon™ radiosurgery** system has received 510(k) clearance from the FDA.

Genetic Tests and Assays in the News

• Roche (www.roche.com) has submitted its **cobas® EGFR Mutation Test v2** for premarket approval to the FDA as a companion diagnostic test for **AZD9291**, an AstraZeneca investigational therapy for NSCLC patients with an acquired resistant mutation.

• The **Ventana ALK (D5F3) CDx Assay** (Ventana Medical Systems, Inc., www.ventana.roche.com) has received FDA approval as a companion diagnostic to aid in the identification of patients for Pfizer's FDA-approved targeted therapy, Xalkori® (crizotinib). OI

Online Course on Male Oncofertility

This free online video course for the oncology community explores male fertility preservation. The course includes interviews with a testicular cancer survivor, as well as experts in the oncology, reproductive medicine, and cryogenics fields. The objective is to help oncology providers feel comfortable in having the fertility risk conversation with their pediatric, adolescent, and young adult cancer patients to maximize the opportunity for fertility preservation. Learn more at www.oncofertu.org.

Favorable Medicare Final Coverage Decision for the Polaris® Test

On Aug. 13, 2015, Myriad Genetics, Inc. (www.myriad.com) announced that Noridian, the Medicare Administrative Contractor (MAC) for Myriad, has issued a final local coverage determination (LCD) for **Prolaris®**, a prognostic test for assessing the aggressiveness of prostate cancer. This decision follows a final LCD decision from Palmetto GBA on Jan. 15, 2015. The final LCD is posted to the Medicare Coverage Database on the Centers for Medicare & Medicaid Services website with an effective date of Oct. 15, 2015, and provides Medicare coverage for prostate cancer patients defined as low and very low risk by the National Comprehensive Cancer Network (NCCN).

Building a Personalized Medicine Program

BY THOMAS D. BROWN, MD, MBA

As a non-university research program based in Seattle, Wash., the Swedish Cancer Institute (SCI) has a long history of providing the nurturing care of a community-based hospital while giving patients access to the latest cancer therapies. In 2013 we took on the question of how to integrate personalized, genomic medicine into our program.

Getting Started

Personalized medicine has a dual meaning at SCI. First, it means using genetic and molecular information from patients or their tumors to pinpoint the genetic alterations that cause cancerous cells—and then using targeted therapies, when applicable, to disarm them. Second, it means providing holistic, supportive care for each patient's unique psychological, social, and spiritual needs (see Figure 1, page 24).

Our challenge was to decide to what extent to adopt personalized approaches at a time when many key questions—from which genes to sequence to how to secure reimbursement from third-party payers—remain. A nine-month strategic planning process led to the conclusion that personalized medicine was essential to SCI's vision. Our planning team included more than 100 providers and staff. Some made thoughtful arguments that we should proceed slowly until personalized medicine was more established, while others advocated for making a substantial commitment to personalized medicine now.

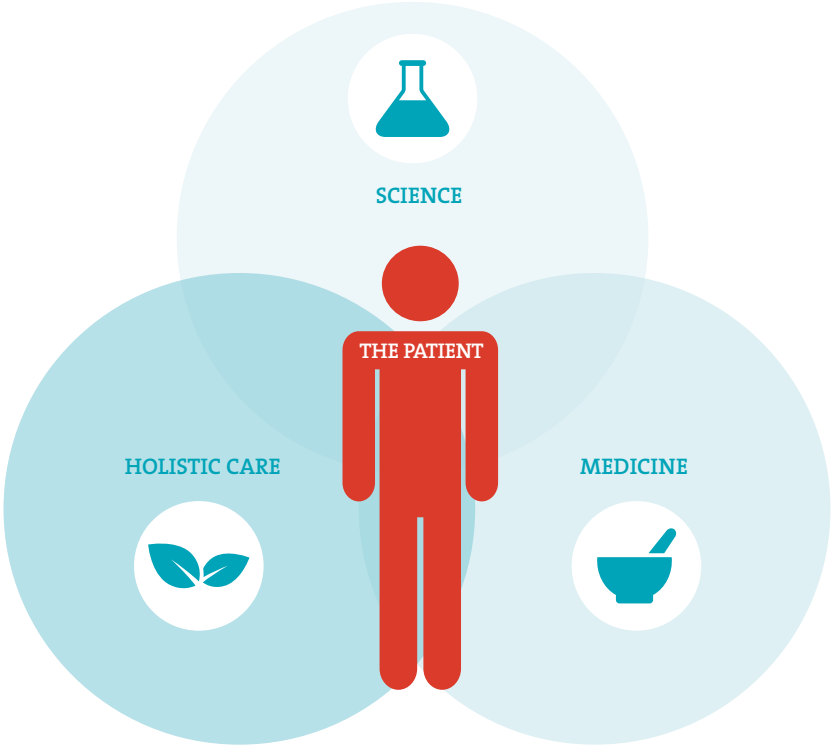
Our final decision was driven by a core belief that perfection should not be the enemy of progress. SCI feels a responsibility not only to improve our patients' access to advanced care, but also to contribute to research that makes care fundamentally better across the U.S. and abroad. With that in mind, our team decided to create a Personalized Medicine Program and make it a cornerstone of SCI.

Developing a Gene Alteration Panel

One key clinical challenge was deciding how to conduct genomic sequencing to pinpoint the alterations and/or mutations that help a particular tumor grow. While several commercial gene alteration panels are available—including a number of labs that conduct sequencing and analysis—we elected to create our own panel in partnership with our exclusive anatomic pathology partner, CellNetix Pathology and Laboratories. Our goal was to develop a next generation sequencing (NGS) panel that is targeted and highly actionable, and one that would enable our team to select the most promising therapies for an individual patient.

In collaboration with our pathology partner, we recruited Anna Berry, MD, then head of molecular pathology at the University of California-San Francisco Medical Center, to our team. With input from SCI clinicians, she and Danbin Xu, MD, PhD, developed an initial, 68-gene panel that sequences the genes most relevant to known cancer treatments. The pathology partnership

Figure 1. SCI Care Model



enables us to quickly expand the panel when new alterations and treatments are discovered. We are currently working on the panel's next iteration, which will include more than 160 gene alterations, a hematologic gene fusion panel, and a gene copy number. In the future, we anticipate including RNA sequencing, proteomics, etc.

The partnership also lets our physicians work hand-in-hand with pathologists to optimize specimen collection, evaluate test results, confirm diagnoses, and identify the most promising treatments and clinical trials for each patient; collaboration that would be much more difficult if we outsourced the testing to a larger commercial lab.

To make the panel results easy for providers to understand and use, we created a new, electronic report. The report:

- Details findings on each available gene
- Explains which alterations are present in a patient's tumor
- Indicates which drugs might be effective against those alterations
- Includes hyperlinks to literature that provides context for the findings
- Provides links to clinical trials that might be viable options for the patient. (As of July 2014, SCI was participating in 76 clinical trials of new cancer therapies, including 50 personalized therapy trials.)

Creating a Research Protocol

As SCI prepared to start offering the panel to patients in 2014, we realized that the line between personalized treatment and research remains blurry. Treatments aimed at particular gene alterations often involve investigational agents or off-label usage of medications. For that reason, we ask all patients in our Personalized Medicine Program to consider enrolling in an IRB-approved registration protocol. This research protocol allows for the collection, organization, and analysis of molecular phenotypic data in the context of the patient's medical history, laboratory, anatomic pathology, and radiology data. To reach the most diverse population possible, we translate the consent form into multiple languages commonly spoken in our region, including Spanish, Chinese (Cantonese and Mandarin), Korean, Russian, and Vietnamese.

SCI has taken the approach of offering the NGS panel to patients when they arrive at SCI for care. We do not reserve its use for those patients who have failed first- or second-line therapies, which is currently a common practice. Our goal is to identify unexpected alterations that may impact treatment decisions from the start and avoid selecting therapies which may have little benefit to the patient.

We do not reserve [the NGS panel] for those patients who have failed first- or second-line therapies...a common practice. Our goal is to identify unexpected alterations that may impact treatment decisions from the start and avoid selecting therapies which may have little benefit to the patient.

Data Mining to Improve Personalized Medicine

Patients who enroll in the protocol give SCI permission to collect key information, including:

- Type of cancer
- Molecular testing results
- Laboratory, pathology, and imaging studies
- A detailed personal medical history.

Over time, our team will gather details about how the patient's tumor was treated at SCI and whether that treatment was effective.

The database, which SCI is building in partnership with Syapse, enables the use of large-scale genomic and clinical data to support the whole patient over the arc of his or her treatment experience, including prevention, diagnosis, and well-being (survivorship). This precision medicine data platform (www.syapse.com) integrates with SCI's enterprise electronic health record (EHR) and allows the treatment team to mine patient data and research results to identify which treatments work best for tumors with particular gene alterations.

The database will ultimately include profiles of thousands of individual tumors, making it one of the largest databases of its kind. We will review each study participant's data every year and inform physicians and/or participants when we learn of commercially-available therapies or clinical trials that could benefit them.

Approximately 5,000 newly-diagnosed patients enter the SCI network each year and we hope to enroll 9,000 patients in the study by the end of 2017. The ultimate goal is to routinely publish results from this database, and help physicians and researchers across the globe find better ways to diagnose, treat, and stop cancer.

Making Cancer Treatment More Cost-Effective

SCI launched its Personalized Medicine Program and started offering the panel to a subset of patients in April 2014, based on medical necessity. One of the main challenges we have faced relates to reimbursement for the panel.

Next generation sequencing is progressing so quickly that it is difficult for third-party payers to keep up with the latest advances. This leaves the reimbursement criteria in flux and makes it hard to know when payers will reimburse for the panel, or how much they will pay. Fortunately, there are signs that the payment landscape will stabilize in the relatively near future.

For example, the Centers for Medicare & Medicaid Services (CMS) is working with Palmetto Health to define a unique code for each company's molecular tests, including the one offered by CellNetix. This will give third-party payers a specific description of our assay and make the reimbursement decision process more straightforward.

New challenges will surely arise, and we believe we can overcome them by being flexible and finding innovative solutions.

For instance, SCI will partner with the Hutchinson Institute for Cancer Outcomes Research (HICOR) to evaluate the health outcome impacts and cost effectiveness of NGS and our Personalized Medicine Program; that is, to evaluate the value proposition of this program. This evaluation reflects the idea that genomic medicine will enable our clinicians to know which therapies work best for particular tumors and particular patients. Helping physicians and patients avoid therapies that are costly but ineffective illustrates how genomic testing, while expensive, can ultimately help control costs.

Expanding our Social Work Team

SCI's strategic planning process underscored our core value that psychosocial services and supportive care are integral to cancer care and personalized medicine. This reflects the reality that cancer is more than a medical crisis—it's a personal crisis that affects all aspects of a patient's life.

SCI started one of the nation's first supportive care services programs in 2003 with a range of services to include:

- Outpatient palliative care and symptom management
- Genetic counseling
- Survivorship services
- Psychological counseling

- Naturopathic care
- Social services
- Nutritional counseling
- Touch therapies
- Art therapy
- Music therapy.

Some of these supportive care services are also available to patients' families and caregivers. For instance, family members can receive counseling to help them cope with a loved one's diagnosis and to help them support the patient throughout treatment and beyond.

SCI's social work team, led by Sandra Johnson, MSW, LICSW, is the linchpin of our supportive care program. Our social workers assess patients, direct them toward the services they need, and deliver everything from emotional support to financial counseling (see box on right). Unfortunately, our patients' needs for social work services have traditionally exceeded our team's capacity. Our team's budget, and therefore its size, has been limited by the fact that social work is not reimbursed by payers and does not generate direct revenue.

As SCI designed its Personalized Medicine Program, we set the goal of making a social worker available to every patient. We expanded our social work budget and now plan to add 10 social workers to our team—which currently includes 11 full-time social workers—over the next two years. This staffing increase will enable us to embed a social worker in each of our clinics, ensuring patients easy access to social work services, whether it's for a quick check-in or a weekly counseling session.

Future Challenges

Within three years, SCI anticipates that our Personalized Medicine Program will begin accruing approximately 5,000 patients a year. Taking a personalized, genomic approach to these patients will necessitate a shift in the way we think about their tumors and their treatment. Instead of approaching patients based on which organ their cancer originated in, physicians will base their approach on the individual genetic and molecular characteristics of the patients and their cancers.

SCI has learned first-hand that this transistion can be difficult for physicians, who are often not familiar with the detailed molecular pathways that drive oncogenesis, or with thinking about cancer in terms of its molecular mechanisms. To overcome this challenge, we are actively involving molecular pathologists, genetic counselors, and pharmacists to collaborate with our physicians in understanding the molecular changes at hand, and the agents meant to target these changes. For instance, we have created a "molecular tumor board;" a multidisciplinary group of expert clinicians that review patients' NGS results and help physicians decide on the best course of action. The recommendations are then relayed to the primary cancer provider for discussion with the patient.

Taking on this and other challenges will help SCI chart a path toward personalized treatment and find solutions that help all cancer centers make treatment fundamentally better, improve outcomes and quality of life, and deliver extraordinary care. OI

Thomas D. Brown, MD, MBA, is executive director of the Swedish Cancer Institute, Seattle, Wash.

References

1. Ramsey S, Blough D, Kirchhoff A, Kreizenbeck K, et al. Washington State cancer patients found to be at greater risk for bankruptcy than people without a cancer diagnosis. *Health Affairs*. 2013;32(6): 1143-1152.

Helping Patients Overcome Financial Challenges

Financial stress is one of cancer care's most common—yet least discussed—challenges. Those diagnosed with cancer are more than twice as likely to experience bankruptcy as compared to those who do not suffer from the disease.[1] SCI's supportive care program offers financial counseling to our patients to help them absorb and manage cancer's financial demands.

In our experience, the top three sources of patients' financial stress are lack of insurance, lack of financial resources, and loss of work hours or employment. When patients' distress screens indicate that they are under financial stress, one of our social workers meets with them to discuss their financial challenges and any other stresses they may face.

Our social workers, who often work together with a staff financial advocate, help patients find insurance and develop strategies for overcoming financial problems. Sometimes this means finding ways to help them afford transportation costs related to their treatment. It could mean connecting patients with financial assistance from the Swedish Medical Center Foundation so they can afford co-pays for pharmaceuticals. Or it may mean helping them enroll in programs that deliver income while the patient is out of work.

This helps SCI minimize the financial cost of uncompensated care. More importantly, it helps reduce patients' financial stress so they can focus on treatment and getting better.

In EGFRm+ advanced NSCLC,

NEARLY 2 OUT OF 3 CASES OF PROGRESSION WITH FIRST-GENERATION EGFR TKIs ARE RELATED TO THE T790M MUTATION[1,2]

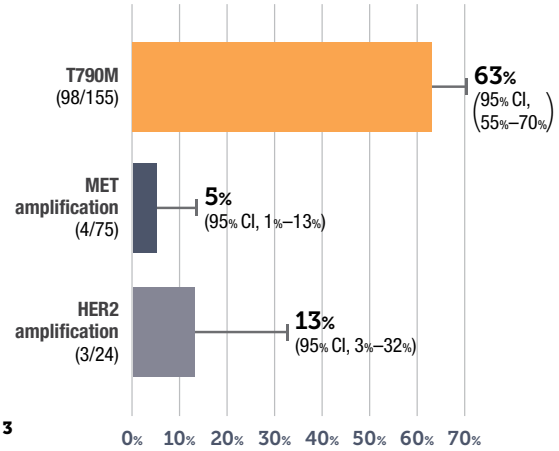
Lung cancer is the leading cause of cancer-related deaths both in the US and worldwide.[3,4]
For NSCLC EGFRm+ patients, the recommended first-line treatment is EGFR tyrosine kinase inhibitors (TKIs).[5]

The majority of tumors will acquire EGFR TKI–resistance mutations

Despite initial high response rates with first-generation EGFR TKIs, many tumors will develop new mutations and become resistant.[6,7] A major barrier to disease control is resistance to treatment. Resistance to first-generation therapy will develop in most patients with EGFRm+ advanced NSCLC on a currently approved EGFR TKI.[7]

After disease progression, clinical guidelines recommend subsequent treatments including either continuing with an EGFR TKI therapy or beginning platinum-based chemotherapy.[5]

T790M Is the Most Common Mechanism of Acquired Resistance to First-Generation EGFR TKI Therapy[1]



Study of 155 patients with radiographic progression following a response or durable stable disease with first-generation EGFR TKI therapy.

Other rare mechanisms of acquired resistance may include BRAF, FGFR, and PIK3CA mutations, and transformation to small-cell histology.[10,11]

Nearly 2 out of 3 cases of progression with first-generation EGFR TKIs are related to the T790M mutation

In patients with NSCLC who are EGFRm+, T790M is an acquired mutation and has been identified as the most common mechanism of acquired resistance in nearly 2 out of 3 patients.[1,2] Development of T790M mutation may confer resistance through several potential mechanisms, which may include[8,9]:

- Steric hindrance, which reduces receptor binding of reversible EGFR TKIs
- Increased binding affinity of EGFR for ATP, resulting in reduced TKI potency

NEARLY 2 OUT OF 3

CASES ARE RELATED TO T790M

Discovering the cause of resistance

Patients should be monitored for radiologic or clinical progression. Tumors can also be assessed for molecular progression to uncover additional acquired mutations.[1,12-16] When patients with EGFRm+ status progress, prior to changing therapy, a biopsy is reasonable to identify mechanisms of acquired resistance, as stated in NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®).[5]

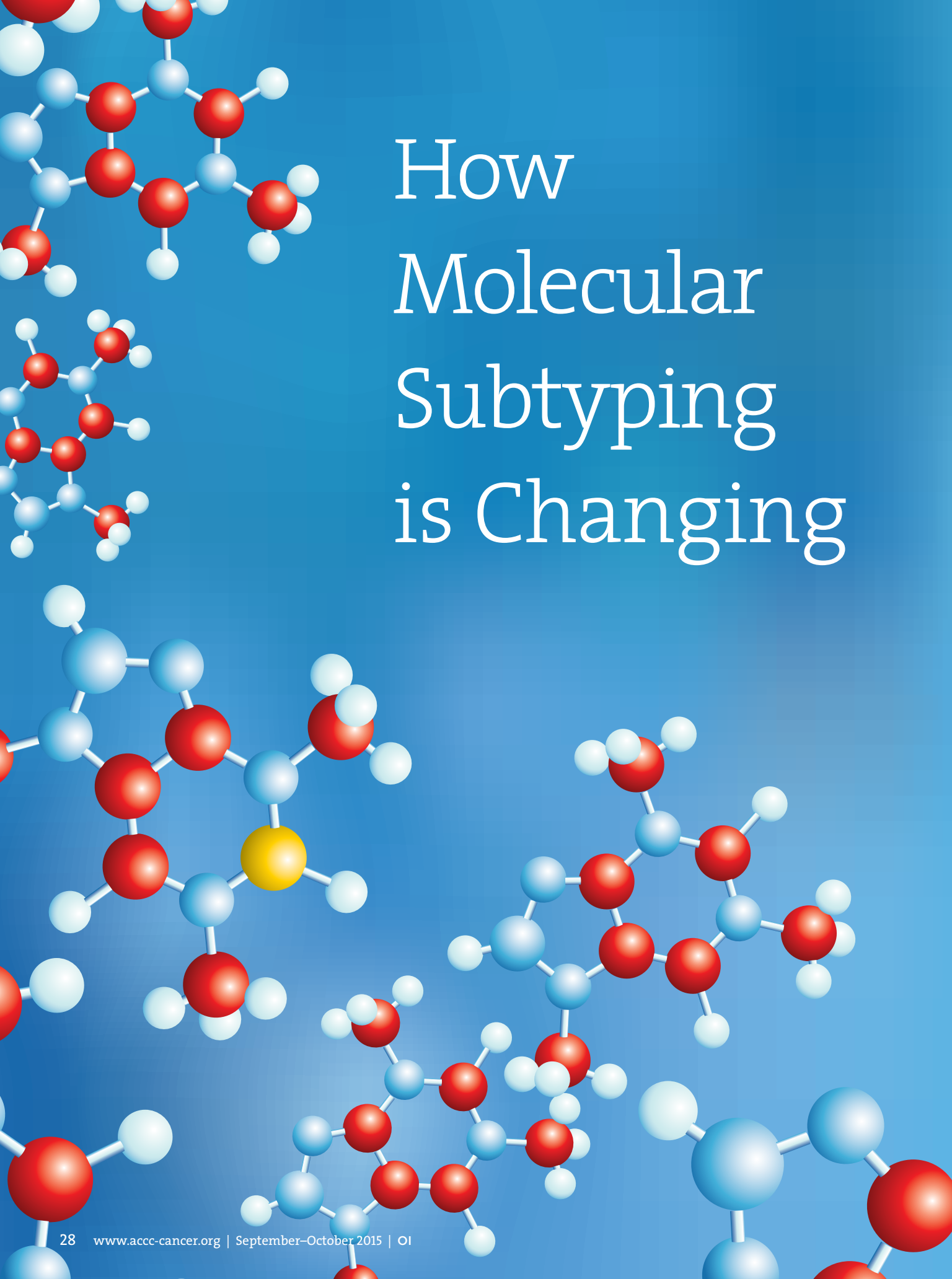
AstraZeneca is a leader in lung cancer research

AstraZeneca is conducting ongoing research to understand the science of the T790M mutation as a driver of resistance.

Find out more at **EGFRevolution.com**.

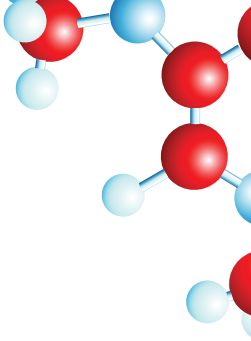
AstraZeneca

References: 1. Yu HA, Arcila ME, Rekhtman N, et al. Analysis of tumor specimens at the time of acquired resistance to EGFR-TKI therapy in 155 patients with EGFR-mutant lung cancers. *Clin Cancer Res.* 2013;19:2240-2247. **2.** Arcila ME, Oxnard GR, Nafa K, et al. Rebiopsy of lung cancer patients with acquired resistance to EGFR inhibitors and enhanced detection of the T790M mutation using a locked nucleic acid-based assay. *Clin Cancer Res.* 2011;17:1169-1180. **3.** American Cancer Society. *Cancer Facts & Figures 2015.* http://www.cancer.org/acs/groups/content/@editorial/documents/document/acspc-044552.pdf. Accessed March 17, 2015. **4.** GLOBOCAN 2012. http://globocan.iarc.fr. Accessed February 9, 2015. **5.** Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Non-Small Cell Lung Cancer V.7.2015. ©National Comprehensive Cancer Network, Inc. 2015. All rights reserved. Accessed June 12, 2015. To view the most recent and complete version of the guideline, go online to NCCN.org. NATIONAL COMPREHENSIVE CANCER NETWORK®, NCCN®, NCCN GUIDELINES®, and all other NCCN Content are trademarks owned by the National Comprehensive Cancer Network, Inc. **6.** Mok TS, Wu YL, Thongprasert S, et al. Gefitinib or carboplatin-paclitaxel in pulmonary adenocarcinoma. *N Engl J Med.* 2009;361:947-957. **7.** Sequist LV, Yang JCH, Yamamoto N, et al. Phase III study of afatinib or cisplatin plus pemetrexed in patients with metastatic lung adenocarcinoma with EGFR mutations. *J Clin Oncol.* 2013;31:3327-3334. **8.** Kobayashi S, Boggon TJ, Dayaram T, et al. EGFR mutation and resistance of non–small-cell lung cancer to gefitinib. *N Engl J Med.* 2005;352:786-792. **9.** Yun CH, Mengwasser KE, Toms AV, et al. The T790M mutation in EGFR kinase causes drug resistance by increasing the affinity for ATP. *Proc Natl Acad Sci U S A.* 2008;105:2070-2075. **10.** Cheng L, Alexander RE, MacLennan GT, et al. Molecular pathology of lung cancer: key to personalized medicine. *Mod Pathol.* 2012;25:347-369. **11.** Ware KE, Marshall ME, Heasley LY, et al. Rapidly acquired resistance to EGFR tyrosine kinase inhibitors in NSCLC cell lines through de-repression of FGFR2 and FGFR3 expression. *PLoS One.* 2010;5:e14117. doi:10.1371/journal.pone.0014117.**12.** Johnson KR, Ringland C, Stokes BJ, et al. Response rate or time to progression as predictors of survival in trials of metastatic colorectal cancer or non-small-cell lung cancer: a meta-analysis. *Lancet.* 2006;7:741-746. **13.** Lussier YA, Khodarev NN, Regan K, et al. Oligo- and polymetastatic progression in lung metastasis(es) patients is associated with specific microRNAs. *PLoS One.* 2012;7:e50141. doi:10.1371/journal.pone.0050141. **14.** Jackman DM, Miller VA, Cioffredi, et al. Impact of epidermal growth factor receptor and KRAS mutations on clinical outcomes in previously untreated non–small cell lung cancer patients: results of an online tumor registry of clinical trials. *Clin Cancer Res.* 2009;15:5267-5273. **15.** Noronha V, Joshi A, Gokarn A, et al. The importance of brain metastasis in EGFR mutation positive NSCLC patients. *Chemother Res Pract.* doi:10.1155/2014/856156. **16.** Eisenhauer EA, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). *Eur J Cancer.* 2009;45:228-247.



How Molecular Subtyping is Changing

BY JAMES V. PELLICANE, MD, FACS



Our Understanding of Breast Cancer

Our understanding of breast cancer continues to evolve with the release of every new study. One finding researchers have already confirmed: breast cancer is not just a *single* disease. Rather, breast cancer is a *category of diseases* made up of several different tumor types called molecular subtypes. Each subtype behaves differently, which in turn means each subtype may need to be treated differently to achieve the best outcome.

As the understanding of molecular subtypes evolves, it is becoming clear that the appearance of the cell based on traditional pathologic parameters, that is, IHC and FISH testing of estrogen receptor (ER), progesterone receptor (PR), and HER2 neu (HER2), may not always indicate the dominant pathway. While this finding is not news in itself, there are providers and cancer programs that have not yet integrated the results of the latest large studies of functional molecular subtyping. In other words, these providers and programs may be relying on diagnostic and treatment approaches that do not reflect the most recent findings. This is particularly true today of neoadjuvant treatment (i.e., preoperative), and will possibly encompass all breast cancer treatment in the coming years. Moreover, molecular subtyping is a component of precision medicine that is now becoming part of the national healthcare discussion.[1]

This article describes molecular subtyping and shows how it is changing both the understanding of breast cancer and how to treat it. The article summarizes the most important new studies and details the impact of this new information for community cancer centers.

Molecular subtyping is a component of precision medicine that is now becoming part of the national healthcare discussion.[1]

Molecular Subtyping 101

Molecular subtyping of breast tumors means grouping tumors according to their gene expression patterns. Subtyping can contribute to better outcomes, because different subtypes appear to have different prognoses and different responses to the various treatment alternatives, based on the functional pathway of the specific subtype.

Subtypes can be assessed using either clinical or molecular methods. Genomic tests for molecular subtyping include BluePrint

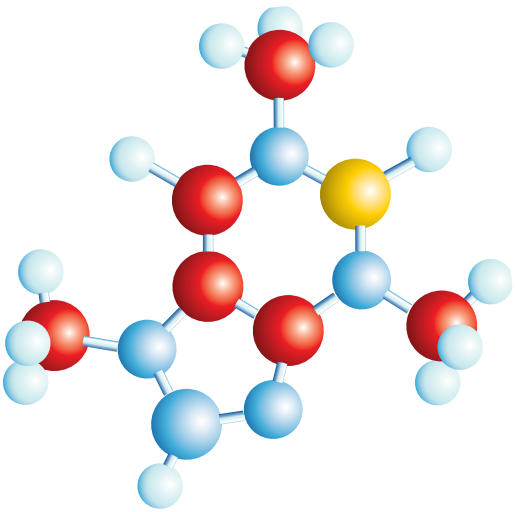
(Agendia, Inc.) and the PAM50 gene signature via Prosigna (Nanostring, Inc.). Prior to the availability of these molecular subtyping tests, different types of breast cancer have been distinguished by assessing the presence of the ER, PR, and HER2 biomarkers through standard assays, and by measuring the proliferation of the nuclear protein known as Ki-67, which is associated with cellular proliferation.

These standard assays examine the cell surface characteristics of the breast tumor to classify the tumor as a particular subtype. The two tests are known as IHC (immunohistochemistry) and FISH (fluorescence *in situ* hybridization). These tests are the current gold standard when assessing the presence of the above-mentioned biomarkers. But there has been some controversy over how to measure the biomarkers and how accurate those measurements are. Also, these measurements may not correlate with the dominant pathway that influences cell growth and cell survival.

IHC and FISH are considered complementary tests that pursue a similar goal: determining the presence or absence of the ER and PR receptors and if a tumor has extra copies of the HER2 gene. This latter gene makes proteins that act as receptors for certain signals that direct cell activity. In a healthy breast, the signals govern cell growth, division, and repair.

Extra copies of the HER2 gene are a red flag and may lead to uncontrolled cell growth. If a test result shows the tumor to have extra copies of HER2, the tumor is classified as "HER2-positive." If the test result is normal, the tumor is classified as "HER2-negative."

IHC and FISH tests are performed on a tumor sample from a core biopsy. Commonly, the IHC test will be used to determine ER and PR status. But sometimes the IHC test for HER2 assessment can be equivocal, which then prompts the pathologist to order the FISH test.



Inaccurate IHC-FISH results can have a profound effect on treatment recommendations and patient outcomes.

IHC-FISH testing is problematic for several reasons, including intrinsic problems with how the tests are conducted:

- The standards that establish criteria to determine whether a tumor is HER2-positive or negative continue to evolve
- If results are not clear-cut, individual pathologists may differ in their interpretations
- Sometimes, one part of a tumor can show up as HER2-positive, while another part tests as HER2-negative.

Inaccurate IHC-FISH results can have a profound effect on treatment recommendations and patient outcomes. For instance, if a tumor is incorrectly classified as HER2-negative, the patient may not be prescribed a drug, such as trastuzumab, which could help shrink the tumor before surgery.

Fortunately, the emergence of molecular subtyping means that a more accurate and reliable analysis of a tumor's subtype is now available. The 80-gene BluePrint subtyping assay, for example, is used in tandem with a test called MammaPrint, a 70-gene genomic assay that definitively stratifies patients as low-risk or high-risk for cancer recurrence. One of the advantages of this assay over other commercially-available tests is that it applies across all age groups, and is not restricted by estrogen or HER2 receptor status.

Some providers use a 21-gene test called Oncotype DX (Genomic Health, Inc.) to determine risk of recurrence. But the 21-gene test has a shortcoming: it does not always provide an absolute breakdown between low-risk and high-risk that the 70-gene test does. With the 21-gene test, more than one-third of patients receive an "intermediate" result that provides no clear indication about whether the cancer is likely to recur. Moreover, this test does not have any accompanying ability to provide molecular subtyping, nor is the test backed by the rigorous oversight reflected in an FDA clearance.

Both the 70-gene MammaPrint and the PAM50-based assays have achieved 510(k) clearance from the FDA. Both have also been acknowledged in the 2015 National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology as "clinically validated for prediction of [breast cancer] prognosis." (Note: Oncotype DX is also included in the 2015 NCCN Clinical Practice Guidelines in Oncology.)

Major Molecular Subtypes

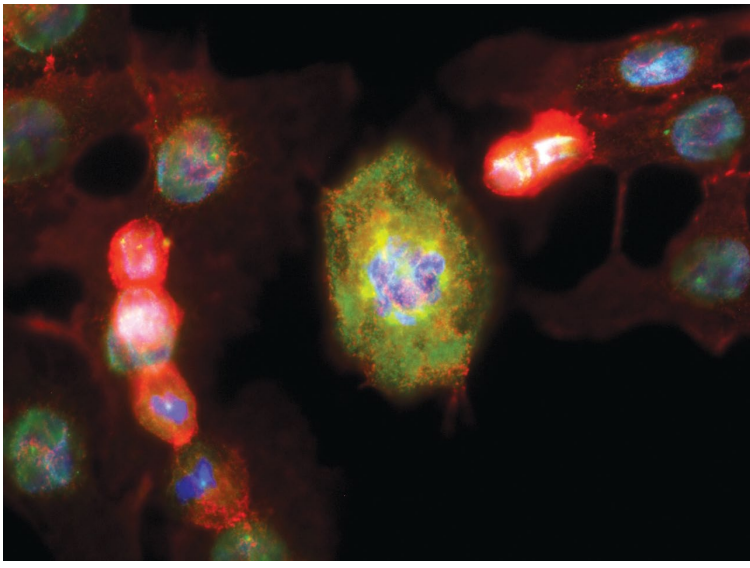
Again, there are two genomic tests for molecular subtyping: the BluePrint/MammaPrint combination and the PAM50 assay. Both BluePrint/MammaPrint and PAM50 identify four major subtypes:

Luminal A. Luminal breast cancers involve overexpression of the luminal epithelial cells that line the breast ducts and glands. When Luminal A breast cancers are identified by the BluePrint functional subtyping assay, it means these cancers are driven by the estrogen pathway and tend to be the least worrisome. These cancers grow slowly and, in most cases, can be successfully treated with limited surgery, radiation, and endocrine therapy—without chemotherapy. The cure rate is greater than 90 percent. Most breast tumors detected by screening mammograms are the Luminal A subtype.

Luminal B. Tumors of this subtype can be identified using one of the molecular subtyping technologies, for example, by a MammaPrint high-risk result in combination with a BluePrint Luminal result. While also driven by the estrogen pathway, these cancers are more concerning than Luminal A cancers because they tend to grow more aggressively. Chemotherapy is usually prescribed.

HER2. This subtype has extra copies of the HER2 receptor and, more importantly, is driven by the HER2 pathway. Although HER2-positive cancers are considered aggressive with the potential to recur, recent progress in treatment has increased the odds of a cure. In particular, targeted therapies, such as trastuzumab and pertuzamab, have been shown to be effective. The fact that targeted therapies can cure many HER2-positive cancers is an important reason to use genomic assays to more accurately identify the pathway driving them.

Basal. Basal tumors get their name because they involve overexpression of genes associated with basal-myoepithelial cells, which generally occupy a thin layer beneath the luminal cells. As these cancers are not driven by the estrogen or HER2 pathways, they typically do not have estrogen and progesterone receptors and do not feature an over expression of HER2. These cancers are aggressive, fast-growing tumors that have a substantial danger of spreading. Often these tumors are noted to be "triple negative." Although most triple negative breast cancers are of the basal subtype, not all basal subtype cancers are triple negative. In fact, about 20 percent of basal subtype patients are estrogen-receptor positive. By including them in the basal subtype group, they are added to a group that tends to respond better to chemotherapy. These tumors may not respond as well to endocrine therapy or drugs such as trastuzumab and pertuzamab, which are often prescribed for HER2-positive tumors.



Molecular Pathways in Human Breast Cancer Cells
Source: NCI Center for Cancer Research

The Latest Research

Recent studies support the accuracy and reliability of risk-recurrence and molecular subtyping assays.

NBRST. Among the important studies is the ongoing Neoadjuvant Breast Registry Symphony Trial (NBRST, pronounced "N-breast"), of which this author is a co-author.

Enrollment in this large, multi-site, prospective observational study is now closed, and some results have already been published.

For example, a study of 426 NBRST enrollees, published in the October 2014 issue of the *Annals of Surgical Oncology,* showed that 22 percent of patients who had been subtyped using IHC-FISH were reclassified and placed into more appropriate subtypes by the 70- and 80-gene assays. Commenting on the results, lead author and surgical oncologist Pat Whitworth, MD, noted that the study could especially affect the treatment of patients identified as "triple positive" in IHC-FISH. Roughly half of those patients do not exhibit HER2-type responses, the study found, so these patients might do better with a different treatment than would normally be given to an HER2-positive patient.

The study also concluded that neoadjuvant chemotherapy given to patients with Luminal A breast cancer (the most common subtype) will usually provide little if any benefit.[2] This finding confirms an earlier published study led by Stefan Gluck, MD.[3]

In a separate study of more than 300 patients, a similar percentage of patients (up to 25 percent) were more accurately classified by the 70- and 80-gene tests. This study was led by

medical oncologist Massimo Cristofanilli, MD, from Thomas Jefferson University. In this research, the genomic tests were compared to IHC alone.[4]

Finally, a prospective, outcome-based study confirmed the accuracy of the 70-gene test in stratifying breast cancer patients as either low- or high-risk for recurrence. In particular, the study showed that patients who received a low-risk score could safely choose to avoid chemotherapy and expect an excellent outcome, as measured at the five-year point.[5]

RASTER. This peer-reviewed study, called Microarray Prognostics in Breast Cancer (or RASTER), involved 427 breast cancer patients. Of the 219 patients who received a low-risk score, 85 percent decided not to receive chemotherapy. After five years, 95 percent of those patients were disease-free. The remaining 208 patients were determined by the 70-gene test to be at high-risk for recurrence. Of those patients, 81 percent received chemotherapy and 91 percent were disease-free after five years. The research, which was conducted in the Netherlands, was published in 2013 in *The International Journal of Cancer.*

Financial Implications of Molecular Subtyping

The primary benefits of molecular subtyping are obviously clinical, in terms of matching patients to the most appropriate treatment. Further, molecular subtyping may eventually enable patients to avoid side effects from treatments that will not really help them. But patients can also benefit financially from appropriate treatment-matching, as can the overall healthcare community.

Take, for example, patients whose IHC-FISH test results show they have an HER2 tumor. This is the type of breast cancer for which trastuzumab is usually prescribed. But molecular subtypes frequently identify these patients as Luminal subtype, suggesting that the ER pathway is driving the cell and that trastuzumab therapy may produce little or no benefit. If the NBRST findings are supported by further outcome studies, the savings from avoiding the cost of trastuzumab treatment could be substantial. Note: until further research is conducted, all of these patients should be treated with anti-HER2 therapy. In other words, it is a protocol that should remain in place until there is adequate outcome data based on molecular subtyping to change the existing protocol.

The potential financial benefits from improving how clinicians match patients to therapy can be extrapolated by looking at the number of women affected by breast cancer. In 2014 new cases of breast cancer totaled 232,670. Looking at this data another way, roughly 12.3 percent of women will be diagnosed with breast cancer during their lifetime, based on data analyzed from 2009 to 2011.[6]

Taking into account the cost of chemotherapy and other drugs used to treat breast cancer, one can estimate potential treatment costs. Today, the average brand-name drug used to treat cancer of any type is about $10,000/month (up from $3,000 in 2005).

> Molecular subtyping may eventually enable patients to avoid side effects from treatments that will not really help them.

Some cancer drugs cost three times that amount, or $30,000/month.[7] The cost of trastuzumab is not quite so steep, but a complete course, given over a year, can cost about $70,000 or nearly $6,000/month (as of 2012). Annual sales of the drug in 2011 were $5.5 billion.[8,9,10]

It is not uncommon for health insurers to require patients to pay 25 percent of their drug-related expenses.[11] Extrapolating from these data, a patient's out-of-pocket expenses responsibility could be estimated to be between $2,500 to $7,500/month for chemotherapy and about $1,500/month for trastuzumab.

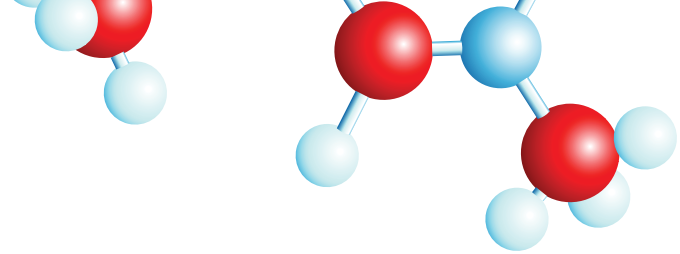
With more than 200,000 new breast cancer patients each year, you can see how the healthcare community as a whole could benefit financially if a large numbers of patients were able to avoid chemotherapy, while also avoiding potential side effects and the cost of treating those side effects.

A New Paradigm of Breast Cancer

Molecular subtyping offers a better way of individualizing breast cancer treatment. But the implications are bigger than that. By presenting a more nuanced view of breast cancer than clinical subtyping, molecular subtyping also suggests that our previous paradigm of breast cancer needs to be updated.

Before breast cancer subtyping (of any type) came along, patients would normally undergo surgery as their first treatment and then be referred to specialists for post-surgical radiation, or chemotherapy, or both.[12] Clinical subtyping via IHC/FISH made cancer specialists think differently about the whole treatment model, at least for some patients. First, clinicians understood that treatment needed to be matched to subtypes, since not all subtypes benefited from the same drugs. Second, clinicians understood that patients with certain subtypes benefited from treatment before surgery.

These findings also apply to molecular subtyping; however, the research community does not yet have longer-term outcomes from molecular subtyping studies. The benefit has so far been seen neoadjuvantly in patients who have a pathological complete response (pCR), meaning they have no measurable cancer after treatment that is informed by molecular subtyping. Pre-surgical treatment for HER2-positive patients with trastuzumab can sometimes destroy all traces of the disease so that only limited



surgery is needed to prevent recurrence.[13] Pre-surgical elimination of detectable cancer also makes breast reconstruction after surgery easier.[13] Today, clinicians frequently view this pCR outcome as a surrogate for a favorable long-term outcome.

Now that studies such as the NBRST Trial are consistently showing molecular subtyping to be more accurate than IHC-FISH, it is probably time to again revise our understanding of breast cancer. A paradigm based on IHC-FISH defines subtypes of breast cancer based on whether certain receptors are overly represented on a tumor cell's surface, indicating overexpression of an associated gene. Molecular subtyping demonstrates that this way of looking at cancer may be inadequate. To understand how a tumor is actually behaving, one has to examine the molecular profile and identify the genes driving that behavior.

Understanding which genes are driving a tumor's behavior, in turn, may eventually change the treatment paradigm. It could potentially provide more accurate information than IHC-FISH about which treatments will be effective in the long-term and which treatments will not. With pre-surgical treatment having assumed a greater role in cancer treatment, this difference is even more important than it would have been in the days when surgery always preceded drug therapies.

This evidence suggests the eventual arrival of a new treatment paradigm in which tumors are classified by molecular subtype/chemosensitivity so that patients and their physicians can make better-informed decisions about whether pre-surgical chemotherapy will be helpful. According to NBRST data, about 20 percent of HER-positive breast cancers are reclassified as basal subtype, placing them into a more chemosensitive group compared to a clinical luminal subtype. This data has clinical utility today—because it does not involve withholding therapy, but instead identifies more aggressive subtypes that will benefit from more aggressive treatments.

Patient & Programmatic Benefits

Incorporating molecular subtyping into daily practice creates multiple advantages for breast cancer patients, cancer programs, and the overall healthcare community, including:

- In the future, certain patients may benefit from receiving neoadjuvant treatment that is based on greater knowledge of their cancer and is more targeted for their tumor's molecular subtype. Patients may also be able to avoid treatments that are shown to be less effective for their subtype as we continue to accumulate more data, specifically outcomes data relating to specific therapies.
- Cancer programs can both update and expand the services they offer patients. Analyses of tumors' molecular subtypes are as readily available to community cancer centers as they are in the academic setting.
- The healthcare community benefits if molecular subtyping generates refined treatments that are more effective in combating breast cancer. In the future, molecular subtyping may help reduce the number of expensive treatments that are shown to be ineffective for certain tumor subtypes, potentially resulting in substantial cost savings.
- Genomic tests are accessible by any cancer program, no matter its size (large or small) or location (rural or urban). Just as important, payers are now educating themselves about these tests and starting to support the technology.
- Because molecular tests are performed on breast biopsy tissue, these tests do require an extra procedure. Insurance coverage for genomic tests is a developing situation, but it is headed in the right direction, with widespread coverage for both the 21-gene and 70-gene assays.

It is hard to make predictions about what lies farther down the road with regards to breast cancer research and treatment, but certain trends seem clear. Because genomic testing for breast cancer is a relatively new and immensely promising field, it is rich in ongoing research. Future research will help providers to better individualize the treatments prescribed for breast cancer patients. As these improvements are made, outcomes will improve, too, and the medical and insurance communities will more fully embrace the progress. But that does not mean cancer programs should wait to use this technology. Molecular subtyping is sufficiently advanced to be helping patients right now. For example, clinicians should consider using molecular subtyping for any newly diagnosed patient with Stage I or Stage II invasive breast carcinoma that is lymph-node-negative or lymph-node-positive.

What Might the Future Hold?

New research will lead to further division of the four-subtype scheme used today. For instance, there are indications that the HER2-positive subtype may actually consist of two or three separate types of breast cancer, each with a different response to chemotherapy. The same may be true of Luminal B cancers.

Treatment for the HER-positive, basal subtype is an evolving situation.

Some HER2-positive and Luminal cancers do not respond to pre-surgical chemotherapy. What clinicians do not know for certain is if that's because those patients would have a poor outcome anyway or because anti-HER2 therapy is unnecessary.

Current research should yield stronger outcome data about molecular subtyping. Once we have that data, clinicians may be able to take full advantage of the latest research findings, including some of the data coming out of the NBRST study.

It is a new day for breast cancer analysis and treatment. Genomic tools are making a difference in many breast cancer patients' lives. While there is so much more to learn and apply,

TWO PATIENT CASE STUDIES

Here are some examples of how molecular subtyping has affected actual patients.

At age 39, Kara S. of Nashville discovered a lump in one of her breasts. IHC-FISH testing showed her tumor to be "triple-positive," positive for overproduction of HER2, ER, and PR receptors. But molecular subtyping revealed that the IHC-FISH subtyping was wrong. She received neoadjuvant treatment based in part on the genomic analysis, and the treatment was successful, meaning there was no invasive carcinoma detectable in her breast or axilla (underarm) before surgery.

Susan B. was 52 when her cancer was discovered. After her tumor was analyzed with IHC-FISH, test results gave no clear indication of the tumor subtype. Molecular subtyping showed that Susan had a basal tumor with a high risk of recurrence, which helped Susan and her physician to make a well-informed treatment decision. She was given pre-operative chemotherapy and, similar to Kara S., had a complete pathologic response (no apparent remaining cancer) to the treatment.

This kind of pathologic complete response to pre-operative therapy is believed to predict a highly favorable outcome for the patient.

that is no different from the state of knowledge with any form of cancer. Thanks to molecular diagnostics, outcomes and many patients' disease-related life experiences are already much improved. Because of all the ongoing research into genomic testing, those outcomes and experiences will only get better in the years to come. OI

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References

1. Kolata G. A path for precision medicine. The New York Times. Available online at: www.nytimes.com/2015/02/03/health/a-path-for-precision-medicine.html?_r=0. Last accessed July 21, 2015.

2. Whitworth P, Stork-Sloots L, de Snoo FA, Richards P, et al. Chemosensitivity predicted by BluePrint 80-gene functional subtype and MammaPrint in the Prospective Neoadjuvant Breast Registry Symphony Trial (NBRST). *Ann Surg Oncol.* 2014;21(10): 3261-3267.

3. Glück S, de Snoo F, Peeters J, Stork-Sloots L, et al. Molecular subtyping of early-stage breast cancer identifies a group of patients who do not benefit from neoadjuvant chemotherapy. *Breast Cancer Res Treat.* 2013;139(3):759-767.

4. Cristofanilli M, Yao K, Turk M, Kaul K, et al. MammaPrint and BluePrint in early breast cancer: Clinical implications of prognostic stratification and molecular subtyping. Scientific Poster presented at: 2013 San Antonio Breast Cancer Symposium; Dec. 10–14, 2013; San Antonio, Texas. Available online at: www.abstracts2view.com/sabcs13/view.php?nu=SABCS13L_742&terms. Last accessed July 21, 2015.

5. Drukker CA, Bueno-de-Mesquita JM, Retel VP, van Harten WH, et al. A prospective evaluation of a breast cancer prognosis signature in the observational RASTER study. *Int J Cancer.* 2013;133:929-936.

6. National Cancer Institute. SEER Stat Fact Sheets: Breast Cancer. Available online at: http://seer.cancer.gov/statfacts/html/breast.html. Last accessed July 21, 2015.

7. Rabin RC. Chemo costs in U.S. driven higher by shift to hospital outpatient facilities. Available online at: www.webmd.com/health-insurance/20140506/chemo-costs-in-us-driven-higher-by-shift-to-hospital-outpatient-facilities. Last accessed July 21, 2015.

8. Nordqvist C. One year on Herceptin for breast cancer ideal. Available online at: www.medicalnewstoday.com/articles/250912.php. Last accessed July 21, 2015.

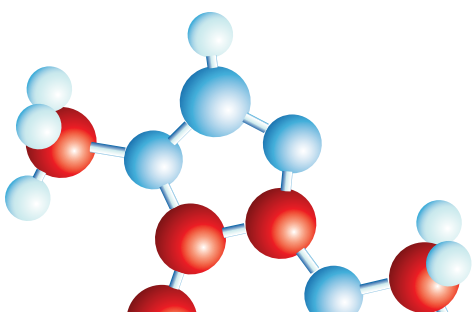
9. Pollack A. Studies back length of Herceptin cancer treatment. The New York Times. Available online at: www.nytimes.com/2012/10/02/business/current-length-of-herceptin-treatment-is-supported-by-studies.html?_r=1&. Last accessed July 21, 2015.

10. Pivot X, Romieu G, Debled M, Pierga JY, et al. 6 months versus 12 months of adjuvant trastuzumab for patients with HER2-positive early breast cancer (PHARE): a randomized phase 3 trial. *Lancet Oncol.* 2013; 14(8):741-748.

11. American Cancer Society. Managing the costs of your cancer treatment. Available online at: www.cancer.org/treatment/findingandpayingfortreatment/managinginsuranceissues/the-cost-of-cancer-treatment. Last accessed July 21, 2015.

12. Citrin D. The new paradigm of treating early breast cancer. Available online at: www.cancercenter.com/discussions/blog/the-new-paradigm-of-treating-early-breast-cancer/. Last accessed July 21, 2015.

13. OncLive. Abandoning Old Paradigms: Embracing Molecular Targeting in Breast Cancer Treatments. Available online at: www.onclive.com/publications/obtn/2012/april-2012/abandoning-old-paradigms-embracing-molecular-targeting-in-breast-cancer-treatments/1. Last accessed July 21, 2015.



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The Embedded Nurse Navigator Model

BY DARCY BURBAGE, RN, MSN, AOCN, CBCN,
AND SCOTT SIEGEL, PHD

A novel approach to providing survivorship care in a community cancer center

In Brief

There are more than 14 million cancer survivors in the United States, a number that is expected to grow exponentially due to an aging population and improved methods for early detection and treatment.[1] In an effort to provide survivorship care to these patients, many cancer programs have implemented a survivorship clinic model, typically led by a nurse practitioner with physician oversight. This approach to survivorship care is not without its limitations, however. This article describes another approach—the embedded nurse navigator model—developed at the Helen F. Graham Cancer Center and Research Institute at Christiana Care in Newark, Del.

Cancer survivors often experience physical and psychosocial long-term and late effects after treatment ends.[2] Long-term effects include fatigue, peripheral neuropathy, pain, and cognitive changes that may manifest during treatment and continue well beyond the end of treatment.[3] Late effects of therapy, such as cardiac dysfunction, pulmonary fibrosis, lymphedema, and secondary malignancies, can occur as late as 20 years post-treatment.[3] As newer chemotherapeutic agents are integrated into treatment, unanticipated side effects may emerge.

In addition to physical challenges, studies have shown an increased risk of psychosocial distress in cancer survivors who:[4,5]

- Are younger
- Have inadequate socioeconomic resources
- Have limited access to care
- Have communication barriers
- Exhibit underlying co-morbid illness
- Have a history of psychiatric disorders.

Psychosocial adjustments to life after cancer can include difficulty concentrating, anxiety, insomnia related to these issues, depression, and post traumatic stress disorder.[4,5] In 2006 Vachon and colleagues reported that even though approximately one-third of individuals with cancer experience some psychosocial distress, only about 10 percent of these individuals receive therapy to address their distress.[4] In a survey of more than 3,000 cancer survivors, 98 percent of respondents indicated that they experienced continued concerns as a result of cancer treatment.[5] Of these same respondents, 75 percent indicated a fear of recurrence, followed by depression and/or sadness (65 percent), while 53 percent reported low energy, sleep disturbance, and difficulty concentrating.[5] In 2013 Ness and colleagues identified these top five concerns of cancer survivors:[2]

- Fear of recurrence
- Fatigue
- Living with uncertainty
- Managing stress
- Sleep disturbance.

Table 1. Survivorship Care Models & Features

FEATURES	MODEL			
	EMBEDDED	CONSULTATIVE	MULTI-DISCIPLINARY CLINIC	INTEGRATED CARE
Individualized and personalized care and resources	✓	✓	✓	✓
On-site consultation at time of scheduled appointments to avoid travel to multiple locations at different times	✓			
Point of contact for questions or concerns post-treatment	✓			✓
Impromptu referrals	✓			
Comprehensive physical examination performed by a mid-level provider of the survivor's primary oncology team		✓	✓	✓
Multiple providers are available and provide follow-up care at the same visit; usually based on diagnosis			✓	

Cancer survivors also identified social isolation, intimacy issues, spiritual concerns, alterations in body image, and sexuality as causes of distress.[2,6]

The American Society of Clinical Oncology (ASCO) describes the stages of survivorship as acute, extended, and permanent.[7] The acute phase describes the time frame from diagnosis through initial treatment. The extended time frame is the period immediately after treatment is completed. The permanent phase is a longer time frame—usually measured in years.[7]

Survivorship Care Models & Features

As there is no "one size fits all" model of delivering survivorship care, the oncology community has developed multiple models for survivorship programs. These models include a consultative model, a multidisciplinary clinic model, and an integrated care model (see Table 1, above). Adult follow-up programs traditionally focus on a medical model. In this model, cancer survivors are usually seen by a mid-level provider from their primary oncology team who performs a physical examination and assesses patients for long-term and late effects of treatment. The provider makes referrals for additional services to programs within the facility or to resources in the community.[8]

A consultative model employs a one-time comprehensive visit for cancer survivors at the end of treatment, which reviews the therapy received and recommendations for health promotion and surveillance.[8,9] Additional consultations with ancillary support services, such as rehabilitation and psychosocial counseling, can be recommended and the ongoing care continues to be provided by the cancer survivor's oncology team.[8,9]

In a multidisciplinary clinic model, multiple providers are available during the cancer survivor's scheduled appointment time. This model was the first developed, and is still used today, in pediatric survivorship programs.[8] Because this model is usually costly and resource intensive, it may not be feasible for adult survivorship programs.

In an integrated care model, cancer survivors remain under the care of their primary oncology team; however, care is usually delivered by a mid-level provider from the cancer care team. Care may then be transitioned to the cancer survivors' primary care providers at a specific interval.[8] To ensure a successful transition, primary care providers must be given the necessary information

to provide ongoing surveillance for long-term and late effects of cancer treatment.

With each of these models, however, cancer survivors will need an additional post-treatment appointment to review long-term and late effects of treatment, health promotion, and surveillance recommendations.

Developing a New Model of Survivorship Care

After publication of the 2006 Institute of Medicine (IOM) report highlighting the unmet needs of cancer survivors,[10] the Helen F. Graham Cancer Center and Research Institute conducted a baseline assessment of the physical and psychosocial needs of cancer survivors and providers in the community.[11] This assessment revealed several key points.

First, cancer survivors wanted more individualized education, versus a class or seminar format, on the potential physical and psychosocial long-term and late effects of the treatment that they received.

Second, cancer survivors indicated that it was difficult to know which healthcare providers they should contact in times of need; therefore, many did not seek assistance. This finding highlighted the importance of screening cancer survivors for distress. Our team could not assume that cancer survivors would tell us the issues that they face. Instead, our team believed that we needed a structured and standardized distress assessment.

Cancer survivors also expressed feeling disconnected from their treatment team after active treatment was completed.

Finally, cancer survivors expressed a desire to have follow-up appointments scheduled conveniently in the same location, thus avoiding travel to multiple facilities at different times.[11]

From our cancer survivors, our team has learned that survivorship is not a linear process, but a journey. Healthcare providers who deliver care to cancer survivors should provide consistent, continuous education and evaluation to address the ongoing challenges these individuals face over time. Based on these findings, our team revised our survivorship services.

The "Embedded Model"

Based on our baseline assessment results, our team piloted a program in the Radiation Oncology Department where the nurses met with cancer survivors during their final week of treatment to discuss the challenges of life post treatment. In addition, nurses provided cancer survivors with written educational materials and information on available support services.

Next, to build our survivor-centered approach to care and with support from the NCI Community Cancer Centers Program (NCCCP), the Helen F. Graham Cancer Center and Research Institute hired a full-time survivorship nurse navigator dedicated to meeting the needs of our cancer survivors. The survivorship nurse navigator position is located within the Radiation Oncology Department since radiation therapy tends to be the end point for the most common types of cancers that we treat (i.e., breast and prostate). Initially, the survivorship nurse navigator met with breast cancer survivors during their last week of treatment; however, feedback from cancer survivors and staff indicated that it would be more beneficial for survivors to meet with the survivorship nurse navigator earlier in their radiation treatment to establish a relationship and provide timely intervention.

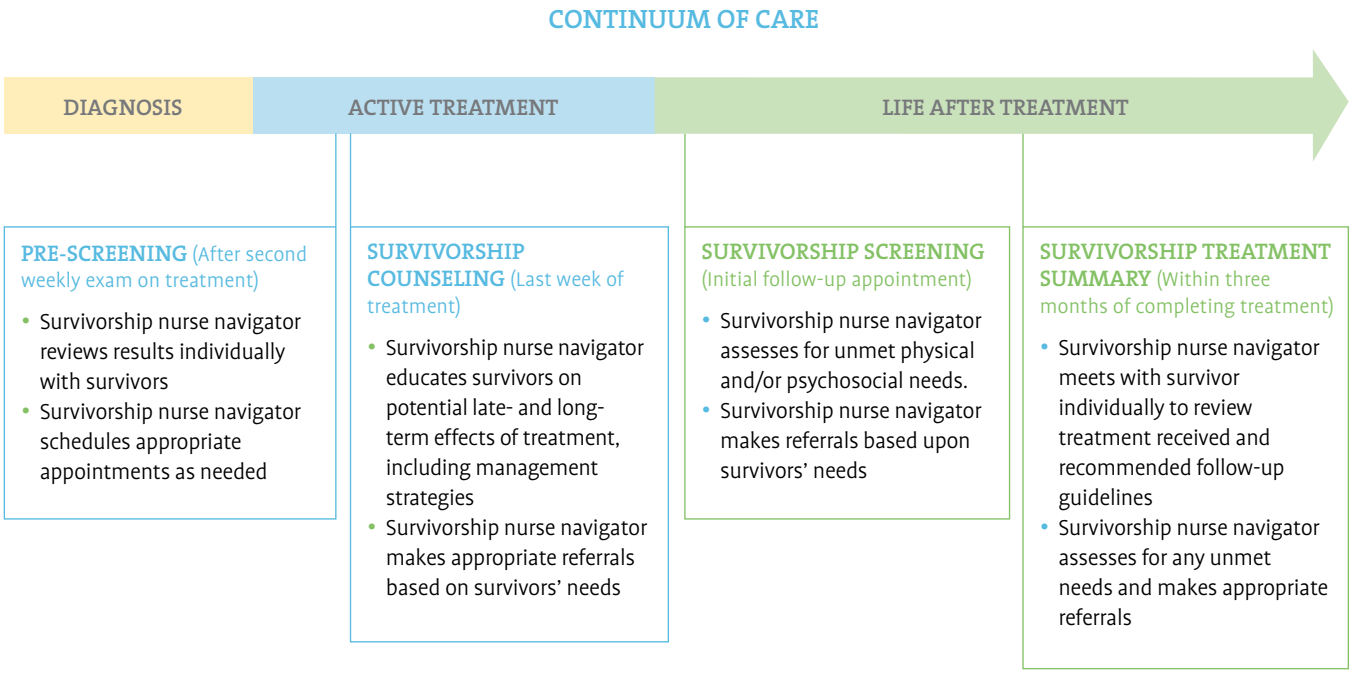
From our cancer survivors, our team has learned that survivorship is not a linear process, but a journey. Healthcare providers who deliver care to cancer survivors should provide consistent, continuous education and evaluation to address the ongoing challenges these individuals face over time.

In an effort to establish a consistent way to triage those who may need additional support, cancer survivors complete a psychosocial distress screening tool two weeks after beginning radiation therapy (see Figure 1, page 40). This process aligns with the 2012 Commission on Cancer (CoC) standard 3.2, which mandates that cancer programs screen their survivors for psychosocial distress. Cancer survivors who screen positive for psychosocial distress or request more information regarding programs and services are seen by the survivorship nurse navigator at the time of their established daily radiation treatment. Interestingly, it has been our experience that screening for psychological distress also predicts which cancer survivors will tend to struggle with physical late and long-term effects of treatment. In other words, if patients test positive for distress, they are more likely to struggle with long-term effects of treatment.

Currently, the survivorship nurse navigator meets individually with breast and prostate cancer survivors as they near the end of treatment, counsels them on the potential long-term physical and psychosocial effects that may occur, and suggests management strategies. During this meeting, cancer survivors receive written information about support services and programs available within the Helen F. Graham Cancer Center and Research Institute, as well as resources within the community.

Because the survivorship nurse navigator is embedded in the Radiation Oncology Department, she is often asked to meet with

Figure 1. Timeline of Survivorship Treatment



cancer survivors who are receiving treatment for other cancers, such as lymphoma, lung, head and neck, and colorectal cancer. Although these cancer survivors may continue with other treatment once they complete radiation therapy, they benefit from the early intervention and support that the survivorship nurse navigator provides. It also allows the navigator to introduce the concept of survivorship and review the survivorship program services that are available to these patients.

Unless contacted earlier by the patient, the survivorship nurse navigator meets with cancer survivors at their established first follow-up appointment with the radiation oncologist. Having the navigator meeting during the same visit provides the convenient scheduling patients cited in our baseline assessment. During this visit, cancer survivors complete a quality of life (QOL) questionnaire that assesses how they are coping with the most common physical and psychosocial side effects of cancer treatment, including fatigue, cognitive changes, body image concerns, anxiety, and fear of recurrence. Based on their individual responses to the follow-up QOL survey, cancer survivors may be referred to additional support services and programs, such as:

- A support group
- Individual counseling with a health psychologist
- A mind/body/spirit program (i.e., yoga and/or meditation)
- Social work
- Cancer rehabilitation
- Consultation with a dietitian.

At this appointment, cancer survivors are offered the opportunity to receive a treatment summary and survivorship care plan. If the patient opts to have these tools created, the survivorship nurse navigator will prepare both documents and present them to the patient at a face-to-face follow-up visit. The survivorship care plan provides a synopsis of the treatment that patients received as a result of their cancer diagnosis along with evidence-based follow-up recommendations.

For those cancer survivors interested in receiving a survivorship care plan, the survivorship nurse navigator obtains written consent from cancer survivors for release of medical information to access their medical records. When the survivorship care plan is completed, the survivorship nurse navigator contacts patients to schedule an appointment to review their survivorship care plan. The survivorship nurse navigator uses this individual appointment as an opportunity to:

1. Review evidence-based follow-up guidelines
2. Assess physical and psychological concerns
3. Educate cancer survivors on the importance of continued surveillance and health promotion.

Cancer survivors receive a copy of their survivorship care plan and are encouraged to share this information with their primary care provider and other specialists involved in their care. A copy of the survivorship care plan is also scanned into the patient's

electronic health record (EHR) for review by other members of his or her healthcare team.

Although the Commission on Cancer sets the survivorship care plan as a standard and several cancer advocacy groups recommend that cancer survivors receive a summary of the treatment that they received, we have found that more than half of patients decline the summary when it is offered.[12] Some cancer survivors ask, "Why do I need this when my doctor has this information?" Others state, "I don't want to be reminded of what I went through." In some instances, cancer survivors have become very emotional upon reviewing the information provided in the summary. Some of our cancer survivors have not returned messages left to schedule an appointment to review their treatment summary; others have received a survivorship care plan, but do not remember having received one. Although we offer treatment summaries and care plans to all of our cancer survivors, it has been our experience that patients can—and often do—decline to receive this information.

Closing Thoughts

The goal of our survivorship program is to help cancer survivors transition to life after treatment. Since implementing the survivorship nurse navigator role in October 2010, this team member has met individually with more than 1,400 cancer survivors. Patient satisfaction survey results are overwhelmingly positive regarding the role of the survivorship nurse navigator and the information that is provided. Physician and ancillary staff satisfaction survey results reveal that the survivorship nurse navigator role has benefitted their patients. In fact, staff had even requested that a survivorship nurse navigator assist survivors who had completed treatment prior to the program implementation.

The transition from active treatment to survivorship care is now being recognized as a distinct phase of the cancer care continuum.[10] Although payers do not currently reimburse for survivorship services, other cancer programs have addressed this funding issue by obtaining grant support. To optimize the IOM's triple aim approach to healthcare,[13] the goal of our survivorship program is two-fold:

- To empower survivors to take responsibility for ongoing surveillance and preventive care.
- To foster a more collaborative approach between the survivors' oncology team and their primary care providers as patients transition their care back to their primary care provider. This includes providing these clinicians with the information and education needed to recognize and manage long-term side effects. OI

Darcy Burbage, RN, MSN, AOCN, CBCN, has 30 years of oncology nursing experience in a variety of roles, including bedside nursing, clinical trials, community outreach, radiation oncology, private practice, performance improvement, and as the cancer care coordinator in the Christiana Care Breast Center. She implemented the role of the survivorship nurse navigator at the Helen F. Graham Cancer Center and Research Institute where she works with individuals who have completed cancer treatment using evidence-based management strategies. Scott Siegel, PhD, is a licensed psychologist and the director of Psychosocial Oncology & Survivorship at the Helen F. Graham Cancer Center & Research Institute within the Christiana Care Health System in Newark, Del.

References

1. American Cancer Society. Cancer Treatment and Survivorship Facts and Figures: 2014-2015. Available online at: www.cancer.org. Last accessed June 8, 2015.

2. Ness S, Kokal J, Fee-Schroeder K, et al. Concerns across the survivorship trajectory: results from a survey of cancer survivors. *Oncol Nurs Forum*. 2-13; 40: 35-42.

3. Stricker C, Jacobs L. Physical late effects in adult cancer survivors. *Oncol Nurse Edition*. 2008; 22: 33-42.

4. Vachon M. Psychosocial distress and coping after cancer treatment. *Am J Nurs*. 2006; 106: 26-31.

5. LIVESTRONG Foundation. "I Learned to Live With It" Is Not Good Enough: Challenges Reported by Post-Treatment Cancer Survivors in the LIVESTRONG Surveys. A LIVESTRONG Report 2010. Available online at: www.livestrong.org/what-we-do/our-approach/reports-findings/survivor-survey-report/. Last accessed June 8, 2015.

6. Pelusi J. Sexuality and body image. *Am J Nurs*. 2006; 106: 32-38.

7. Cancer.net. About Cancer Survivorship. Available online at: www.cancer.net/survivorship/about-cancer-survivorship. Last accessed June 8, 2015.

8. McCabe M, Jacobs L. Clinical update: Survivorship care models and programs. *Semin Oncol Nurs*. 2012; 28(3): 1-8.

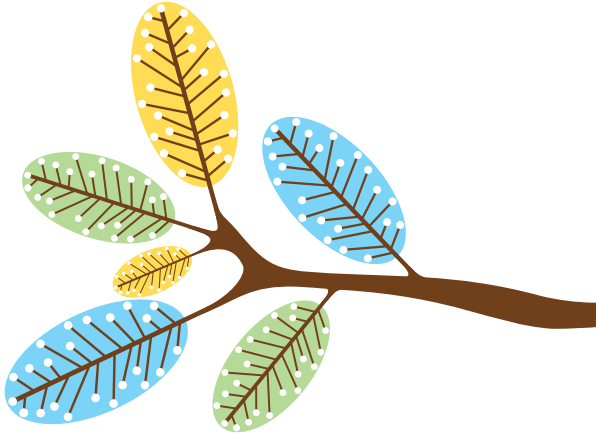
9. Landier W. Survivorship care: Essential components and models of delivery. *Oncol Nurse Edition*. 2009; 23: 1-10.

10. Hewitt M, Greenfield S, Stovall E. *From Cancer Patient to Cancer Survivor: Lost in Transition*. Washington, D.C.; National Academies Press; 2006.

11. Siegel S. Lessons learned in managing cancer survivorship in the community. Available online at: http://meetinglibrary.asco.org/sites/meetinglibrary.asco.org/files/Educational%20Book/PDF%20Files/2010/zds00110000e39.pdf. Last accessed June 8, 2015.

12. American College of Surgeons Commission on Cancer. Cancer Program Standards 2012, Version 1.1: Ensuring Survivor-Centered Care Manual. Available online at: www.facs.org/cancer/coc/programstandards2012.html. Last accessed June 8, 2015.

13. Grunfield E, Earle C. The interface between primary and oncology specialty care: Treatment through survivorship. *J Natl Cancer Inst Monogr*. 2010; 40: 25-30.



BY MATTHEW R. STURM, MBA, AND
KATHERINE LILJEDAHL YE, MD, MBA

Collaboration

The Key to Creating Value-Based Cancer Care in Rural Communities

The oncology landscape is becoming increasingly complicated for healthcare providers. Offering a comprehensive cancer care delivery system requires sophisticated operational and technical expertise, not to mention significant capital investments, all of which may be out of reach for smaller programs. For larger oncology programs, sustaining and growing patient volumes to support large investments presents a meaningful challenge given the competition for patients. Regardless of size, all programs are also dealing with a shift in the payment environment toward risk-based contracts, which require additional managerial competencies and a large covered population.

Collaborative partnerships that marry the convenience of community cancer care with the expertise and resources available through larger healthcare systems can create a successful strategy in the value-focused oncology marketplace. This article presents a framework for collaboration between small community oncology programs—often located in rural settings—and large cancer centers—often located in urban settings.

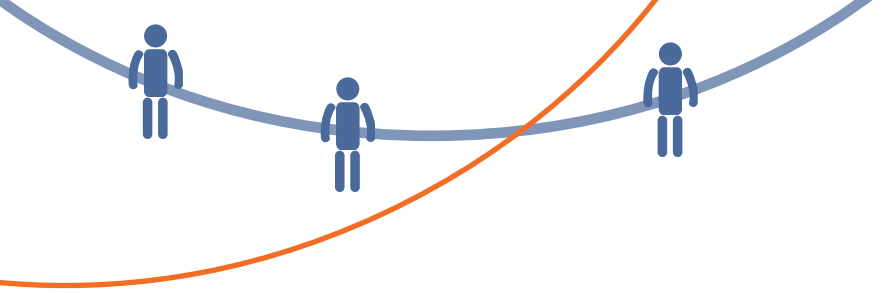
Examining Program Challenges

The economics of the current oncology market expose and magnify the disparities between the resources and capabilities of large and small oncology programs, a distinction commonly observed along the urban-rural geographic divide.

Rural or remote communities typically face issues associated with providing access to specialized oncology care to a fairly limited volume of patients. Local demand is often too low to fund or justify specialized services or technologies. There may also be an insufficient supply of oncology experts relative to the needs of the local patient population. A recent American Society of Clinical Oncology (ASCO) report indicated that only 3 percent of oncology providers are located in rural communities and over 70 percent of counties surveyed had no medical oncologists.[1] Additionally, some patients may choose to travel outside of their community to receive cancer treatment at well-known regional cancer programs.

Rural or remote communities typically face issues associated with providing access to specialized oncology care to a fairly limited volume of patients.

On the other side of the equation, urban oncology programs that have developed comprehensive service offerings face continual challenges maintaining patient volumes that support their investments. At the same time, most are wrestling with how to transition to a value-based care model and reduce costs. Achieving these goals often requires realizing greater economies of scale. In response, successful cancer centers are striving to create larger



and more integrated programs across multiple sites of service, often through the development of partnerships that do not require additional capital investments.

Exploring the Benefits of a Rural–Urban Partnership Strategy

The rural–urban partnership construct offers a number of concrete benefits to participants and communities. Complex specialty care is made more easily available to rural residents through established connections to tertiary centers, while routine services are kept in the local community, supported by the expertise and resources of a larger system. As a result, the network is able to offer patients superior convenience at lower costs. Patients who seek care in both settings derive value from seamless care coordination.

Rural cancer programs can offer distinct benefits to larger programs, as well. Aligning with rural programs enables urban cancer programs to serve a larger geographic area. The expanded footprint allows the larger program to increase volumes of more complex services and offer more comprehensive coverage for ACOs (accountable care organizations) or managed care networks. Further, by building care integration tools and adapting system-wide clinical pathways, closer relationships with area clinicians may develop. These relationships are critical for keeping patients in the regional program and improving accruals to clinical research efforts. The expanded footprint may also provide access to populations with different demographic profiles compared to the urban community, which is of significant value for research efforts.

Defining Goals & Objectives

Working together, rural and urban cancer programs have the opportunity to advance regional care and clinical outcomes in a more cost-effective, patient-centered manner. Once participating organizations determine that a partnership can further their strategic objectives, the first step is to define specific goals and objectives for the partnership. Potential goals for a small rural cancer program may include:

- Increasing access to clinical research
- Improving the availability of oncologists in the community
- Improving care coordination for patients, including those who might otherwise leave the community to receive cancer treatment
- Obtaining greater management expertise for the program
- Expanding the clinical services offered in the community
- Developing capabilities to participate in population health programs
- Improving the program's financial performance.

Potential goals for larger, urban cancer programs may include:

- Increasing the geographic reach of the program
- Accessing a more culturally diverse patient population for research studies
- Increasing volumes of complex cancer cases.

Achieving widespread support among administrators and clinicians for partnership goals is critical, since the individuals in these roles shape the scope and structure of the collaboration. Hospital administrators and clinicians may be wary of collaboration, though, viewing it as a competitive threat to their businesses. Thus, identifying these concerns, as well as potential strategies to mitigate them, is essential for a successful planning process.

Assessing a Strategic Partner

Well-matched partners are generally interested in long-term commitments and exhibit a willingness to adapt their current processes and care models to new, shared standards. Ensuring an appropriate "fit" between two cancer programs is often a long process, potentially taking a year or more to complete, depending upon the degree of integration. When you consider the time and effort required to successfully launch a collaboration, the stakes are high for finding the right partner.

Potential partner organizations should be assessed on a number of criteria to determine if they will be a match with the organization's culture and needs. Key assessment criteria could include:

- Experience in developing successful collaborations
- Cultural similarities
- Willingness to develop a collaborative model to deliver appropriate care in the most appropriate setting
- Interest in a long-term commitment
- Support for partnership by the medical staff
- Quality of operational performance
- Strength of financial performance and ability to support the program
- Community perception of the prospective partner.

The selection and relative prioritization of criteria should be tailored to the goals of the specific entities. For example, at many academic centers, such as Seattle Cancer Care Alliance (SCCA) and Fox Chase Cancer Center, the mission focuses on supporting oncology research and expanding access to clinical trials, whereas other organizations, such as MD Anderson Cancer Center and Rutgers Cancer Institute of New Jersey, articulate a broader vision for collaborating programs.

Exploring Alignment Models

Once a strategic partner is identified, a variety of structures can be used to develop a partnership between an urban and rural

cancer program. Potential alignment models and their implications are shown in Figure 1, pages 46 and 47, which is organized along a spectrum of limited-to-tight integration.

Contractual Relationships

Historically, the partnership model of choice between cancer programs has been the contractual relationship, characterized by local ownership and a moderately low degree of affiliation. In this structure, partners contract with one another for specific services, potentially including day-to-day program management. This model offers the flexibility to build or eliminate affiliation components over time pursuant to the needs and experiences of both partners.

For initial partnerships between urban and rural cancer programs, this remains the preferred model. The structure promotes coordination of patients and select services and/or resources within the network, while allowing each entity to retain a significant degree of local control. However, more tightly aligned models will become increasingly common as organizations are incentivized to develop deeper financial integration under the value-based paradigm.

Joint Ventures

An emerging alignment model for such programmatic collaborations is a service line joint venture (JV). This arrangement facilitates the alignment of services between two organizations that are not part of the same healthcare system. Under this model, partners collaborate to grow their service lines together through the formation of a new entity. The JV entity assumes contracting responsibility for both partners, and assets are often pooled through the new entity. Once operational, the net income from the program is shared based on the value of assets and business initially contributed to the JV.

A similar structure, the joint operating agreement (JOA), can function as a "virtual JV" and achieve results that are comparable to the JV without forming a separate legal entity.

As a result, the JOA may be easier to implement (especially for governmental entities) and may have tax advantages for nonprofit organizations. JV and JOA models present solid options for organizations that want to cooperate financially, operationally, and clinically in developing clinical programs. More specifically, these models enable two organizations to collaborate in restructuring services to improve clinical offerings and reduce operating costs, thereby improving value. These models also create a venue for stronger future integration between the parties, if desired.

Other Options

At the far right end of the spectrum, tightly integrated models, such as management agreements and long-term leases, can be used to outsource all services of the rural program (or specific facets of it, such as radiation oncology or PET/CT) to the urban partner. Typically, these models are not as attractive for oncology collaborations, as they afford the rural partner less participation in governing and operational decisions, as well as less economic upside and/or downside potential.

> Once a strategic partner is identified, a variety of structures can be used to develop a partnership between an urban and rural cancer program.

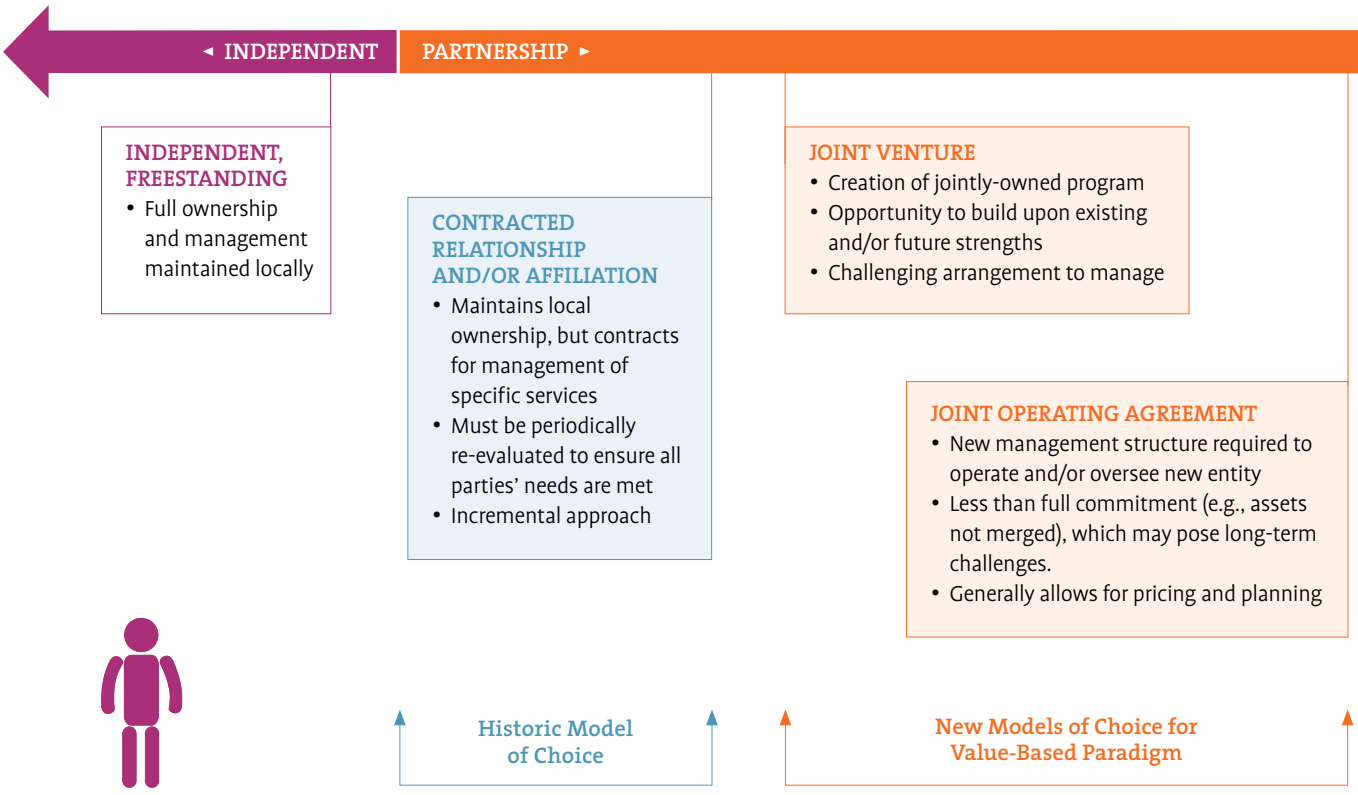
Yet, for smaller programs with limited oncology infrastructures or limited capital to invest in program development, these models may be an acceptable option. These arrangements can benefit rural communities through the preservation or even enhancement of locally-delivered services that could not otherwise be sustained. Urban cancer programs find the degree of control offered by these models highly attractive, as they can produce a seamless, highly coordinated network of services across sites. There may also be a financial return for the larger program, depending upon the profitability of the rural program and degree of subsidization by the local community.

Getting From Here to There

While each oncology arrangement has unique characteristics, there are typically four phases to the development of any strategic partnership:

- ***Phase I. Partnership Planning.*** During the planning phase (2 to 3 months), organizations establish their partnership goals and objectives, identify the preferred partnership structure, and assemble a core planning team.
- ***Phase II. Partner Exploration & Transaction Development.*** This phase, generally lasting between 3 to 12 months, is defined by identifying and evaluating potential partners, selecting a preferred partner, negotiating key terms, and executing a Letter of Intent.
- ***Phase III. Due Diligence & Partnership Planning.*** Once the prospective partners have expressed the intent to move forward, they enter a new phase that involves conducting due diligence, negotiating definitive agreements, and securing approvals from their respective institutional leadership. Phase III usually takes between 3 to 6 months to complete.
- ***Phase IV. Implementation.*** Once partnership arrangements have been made, the entities must assemble the necessary

Figure 1. Potential Alignment Models



resources (e.g., personnel, technology) and establish the structure for implementation.

The time frames noted above are a general frame of reference. More complicated structures with shared governance and financial performance will require more time to develop than simpler contractual models.

Realizing Your Goals

The formation of an urban-rural cancer program partnership is an effective strategy to help entities realize their strategic and clinical goals. There is strength in numbers, and a partnership enhances the ability of both partners to effectively compete in a value-based marketplace by delivering more cost-effective and comprehensive cancer care to a larger patient population than either party could independently. The benefits of collaboration between cancer programs are many, but so are the consequences of poorly designed partnerships. To maximize the benefits and minimize the risks, organizations banding together need to carefully evaluate their goals and ensure that potential partners and arrangement structures closely align with the program's service line strategy.

Successful affiliation partners routinely follow five guidelines when initiating partnership planning. When one or more of these rules are broken, discussions are far more likely to collapse. These five guidelines are:

1. Ensure that the partnership planning process is supported by all key members of the leadership team and medical staff.
2. Commit appropriate resources and personnel to the planning process.
3. Establish and adhere to a firm timetable for discussions.
4. Communicate deal breakers and must-haves early in the planning process and well before any negotiations commence.
5. Establish procedural ground rules up front regarding items such as communication with third parties, decision-making processes, and changes in committee membership.

A Case Study

Seattle Cancer Care Alliance (SCCA) is a world-class cancer treatment network owned by three prominent Seattle healthcare organizations: the Fred Hutchinson Cancer Research Center, UW Medicine, and Seattle Children's Hospital. SCCA's tripartite mission is to provide state-of-the-art care, support cancer clinical research and education, and enhance the standard of cancer care throughout the region. The alliance strives to accomplish the latter goal through a broad network of community cancer program affiliates in the Northwest region and beyond. Through these

HOSPITAL-WITHIN-A-HOSPITAL

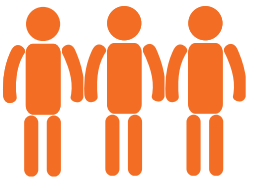
- Program owned and operated by one hospital within another hospital
- Contractual arrangement critical to defining partnership
- Degree of integration or collaboration potentially limited

LEASE

- Local ownership maintained, but program operated by partner
- Typically a long-term arrangement (e.g., 10+ years)
- Questions about lease termination and capital investment as lease term nears

MANAGEMENT AGREEMENT

- Varying approaches
- Typically involves formation of a management company that operates the services
- May include joint ownership of the management company
- Proceeds split in proportion to ownership or based on utilization of specific services



partnerships, SCCA provides four key services to affiliates:

1. ***Research & Access to Clinical Trials.*** Physicians at UW Medicine and Fred Hutchinson Cancer Research Center open community-ready clinical trials to affiliate physicians as collaborative investigators who, in turn, enroll local patients in these protocols.
2. ***Education.*** SCCA organizes educational programs for affiliated physicians, nurses, and other medical staff. Programs are often co-developed with the affiliate's cancer committee and tailored to the interests and needs of local physicians.
3. ***Physician Relations.*** Affiliate physicians are in close communication with SCCA providers and receive streamlined referrals, remote access to specialty tumor boards, and assistance with quality reporting and improvement initiatives.
4. ***Marketing & Brand Presence.*** SCCA supports affiliates in the development and launch of advertising campaigns and co-branding.

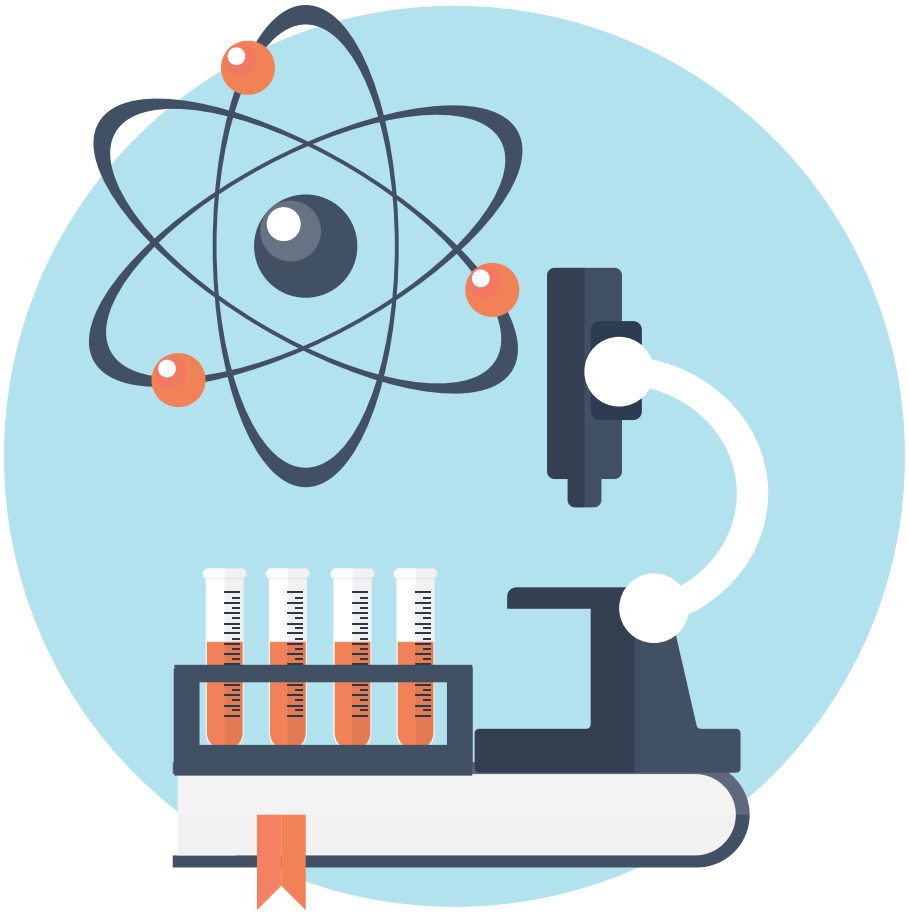
SCCA's affiliate strategy benefits community residents by expanding local access to novel therapies and trials and ensuring better care coordination for patients referred for services at its main campus.

In addition to furthering its research mission, the affiliate network forms the groundwork for delivering high-value cancer care at a regional level. SCCA seeks to create shared standards of practice throughout the network, using a common educational framework based on evidence-based, high-value clinical pathways. The organization's data analytics capabilities are being employed to advance oncology population and business-related intelligence. Through these measures, SCCA and its network member affiliates are striving to deliver reliable, affordable care and positioning themselves to be competitive in new contracting and payment models. OI

Matthew R. Sturm, MBA, is senior manager, and Katherine Liljedahl Ye, MD, MBA, is manager, at ECG Management Consultants, Inc. For more information, visit: www.ecgmc.com.

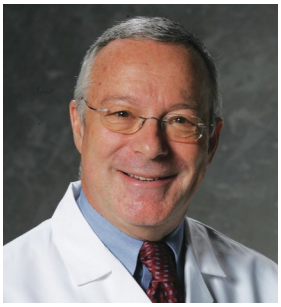
References

1. ASCO. The State of Cancer Care in America, 2014: A Report by the American Society of Clinical Oncology," *J Oncol Pract.* March 2014. Available online at: http://jop.ascopubs.org/content/early/2014/03/10/JOP.2014.001386. Last accessed June 4, 2015.



Highlights of ASCO 2015

BY CARY A. PRESANT, MD, FACP, FASCO



Thoughts from a community oncologist

ASCO 2015 WAS HELD IN CHICAGO, ILLINOIS FROM MAY 29 through June 2. Once again, more than 37,000 of our closest friends and colleagues from all over the world attended to hear the latest advances from clinical trials and preclinical translational information as well. It was an exciting meeting for several reasons.

First, major changes are coming in the payment strategy for medical oncology services. These include supplemental payments for compliance with industry developed guidelines:

- Jennifer Malin, MD, presented on behalf of Anthem Blue Cross
- Barbara McAneny, MD, presented on the medical oncology home (the COME HOME program)
- Ron Kline, MD, presented on the newly developed Oncology Care Model (OCM) from the Center for Medicare and Medicaid Innovation.

These presentations were in addition to discussions on bundled payments and participation in IPA, HMO, and ACO activities, which were part of the pre-ASCO meeting on the Economics of Oncology Care. This was a comprehensive introduction to a topic that will affect all practices and programs in the next few years. The information will be necessary to help make decisions in the practice setting. Further information, which will be published in the *Journal of Clinical Oncology, Journal of Oncology Practice*, and *ASCO Post,* will help to inform providers and state oncology societies.

Another hot topic at ASCO 2015—immunotherapy for cancer patients, including approved uses of nivolumab and pembrolizumab, as well as other investigational drugs. There was discussion of these drugs alone or in combination with ipilimumab, and the results are discussed in the abstracts that follow. Obviously, providers will need to understand how to use these active medications, alone or in combination, and how to create an environment where patients and payers can afford these very expensive pharmaceuticals.

Immunotherapy was also a strong presence at the Association of Community Cancer Centers (ACCC) ASCO 2015 booth with the launch of the Institute for Clinical Immuno-oncology (ICLIO), a unique initiative that will accelerate the adoption of immunotherapy in the community. Learn more at accc-iclio.org.

[In the keynote lecture, Dr. Porter] anticipated that bundled payments for conditions would be necessary and integrated multi-site care delivery systems focused around individual diseases, such as breast cancer or lung cancer, would be needed.

Keynote Lecture

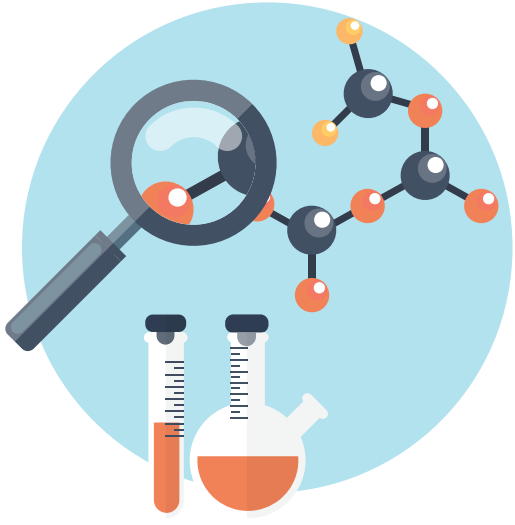
The ASCO 2015 keynote lecture was delivered by Michael E. Porter, MD, PhD, an economist at Harvard Business School. He discussed value-based healthcare delivery, and emphasized that to really deliver value, oncology must reorganize the delivery systems to go beyond individual practices. He stressed developing integrated practice units, organized around trying to meet the needs of individual patients and involving multiple disciplines, as well as developing facilities for measuring outcomes and costs for every patient. Porter anticipated that bundled payments for conditions would be necessary and integrated multi-site care delivery systems focused around individual diseases, such as breast cancer or lung cancer, would be needed.

Karnofsky Lecture

Suzanne Topalian, MD, of Johns Hopkins University, presented a discussion of immune checkpoint modulators in oncology. She pointed out that after the cloning of CTLA-4 in 1987, in 2011 ipilimumab was approved. Furthermore, after the cloning of PD-L1 in 1992, in 2014 anti-PD-L1 therapy was approved by the FDA. She went on to say that measurement of PD-L1 may be important in determining responsiveness of tumors to anti-PD-L1 therapy, but measurement of PD-L1 is very difficult and has substantial pathologist-to-pathologist and assay-to-assay variability, and further difficulty due to variable expression over time in a tumor. (These points were later underscored by discussions from Roy Herbst, MD, PhD, of Yale). Nonetheless, Dr. Topalian emphasized that the activity of anti-PD-L1 therapy was very broad, showing activity in melanoma, lung cancer, kidney cancer, bladder cancer, ovarian cancer, head and neck cancer, Hodgkin's disease, gastric cancer, hepatoma, breast cancer, and mesothelioma. Some of these activities will be discussed later in this article. Her lecture underscored the importance of immunotherapy to the entire ASCO 2015 experience.

Breast Cancer

Abstract LBA500 (R. Margolese et al.) looked at patients with DCIS (ductal carcinoma *in situ*). Postmenopausal patients in study B35 received either tamoxifen or anastrozole. The breast cancer free interval was increased by 4% in anastrozole-treated patients, and was equal in patients under 60 or over 60 years of age. Overall survival (OS) was equal. However, there were fewer uterine cancers and fewer thromboembolic events on anastrozole, while osteoporosis was 40% more common on anastrozole. The practice changing recommendation: anastrozole as the treatment of choice for these patients, dependent on the preferred side effect profile.



Abstract LBA502 (N. Turner et al.) identified that palbociclib added to fulvestrant showed a progression free survival (PFS) of 19.2 months, compared to fulvestrant alone at 3.8 months in patients who were progressing after aromatase inhibitor or other hormonal therapy (hazard ration [HR] 0.42, P<0.001).

Abstract 503 (J. Gralow et al.) presented findings from the S0307 study where patients were randomized between zoledronate, clodronate, and ibandronate. The frequency of ONJ (osteonecrosis of the jaw) was 1.3% on zoledronate, 0.3% on clodronate, and 0.7% on ibandronate. There was no change among the three arms in disease-free survival (DFS) or OS. Since bisphosphonates increase DFS in postmenopausal patients, the authors concluded that the preferred treatment would be clodronate, if it is available. Furthermore, bisphosphonates also appear to reduce breast cancer mortality in other studies summarized by the EBCTCG.

Abstract 504 (M. Gnant et al.) looked at patients receiving adjuvant therapy for postmenopausal breast cancer. Patients were randomized to placebo versus denosumab. There was no difference in bone pain, no cases of ONJ observed, and no occurrence of atypical fractures. The denosumab schedule was every six months of therapy. The frequency of fractures was reduced by denosumab (HR 0.5, P=0.0001). Importantly, reduced fracture rates were seen at 3 years (4% on denosumab, 10% on placebo), and also at 6 years (6% on denosumab, 19% on placebo). Results were equally good in patients who had baseline osteopenia versus patients who had baseline normal bone density. At 36 months, bone density had decreased by 2.75% in placebo-treated patients, whereas it has increased by 7% in denosumab-treated patients. Therefore, use of denosumab should be strongly advised for postmenopausal patients receiving adjuvant hormonal therapy.

Abstract 508 (A. Chan et al.) presented findings from the ExteNET study. In HER2 patients who had completed chemotherapy plus trastuzumab as an adjuvant treatment, patients randomized to neratinib had an invasive-disease-free interval of 93.9% following 12 months of neratinib compared to only 91.6% after placebo (HR 0.67, P=0.0009). In patients with estrogen receptor negative disease, results were equal, whereas in patients who were estrogen receptor positive the invasive-disease-free interval was longer with neratinib (HR 0.51, P=0.001). When approved by the FDA, this will become a treatment of choice following adjuvant therapy in HER2-positive patients.

Abstract 519 (P. Shah et al.) looked at the results of Onco*type* DX testing in patients with BRCA mutations. The test showed high risk of recurrence in 28% of patients, compared to only 7% in sporadic patients. There was a low assay result in 16% of mutation patients, compared to 57% in sporadic patients. Therefore, Onco*type* DX testing should be expected to show higher

risks in patients with BRCA mutations, supporting the use of chemotherapy in appropriate patients.

Abstract 1009 (S. Mougalian et al.) discussed that patients randomized to ACT versus TC showed a 5-year OS which was equal. The authors pointed out that the trend between 2004 and 2010 showed a decrease in CMF use from 18% down to 6%, a decrease in AC from 25% down to 3%, an increase in TC from 0% to 48%, and a slight decrease in ACT from 26% to 22%.

Abstract 1010 (H. Kaplan et al.) looked at evidence of results in stage II and III patients treated with adjuvant chemotherapy between 1990 and 2007. The 5-year disease-specific survival (DSS) had increased. In patients ages 65 to 69, survival had increased from 86% to 95%, but in patients over age 70 there was no increase, with OS remaining similar at 85% in 1990 compared to 86% in 2007. It was pointed out that because such patients received 20% less chemotherapy and 10% less hormonal therapy, patients over the age of 70 should be carefully evaluated to make certain that they are treated maximally with adjuvant therapy.

Abstract 1017 (V. Kaklamani et al.) showed in triple-negative breast cancer (TNBC) that the combination of carboplatin plus eribulin demonstrated a 43% pathologic complete response from neoadjuvant treatment. This combination will be studied more and will possibly be used in such patients at various stages.

Abstract 9518 (H. Rugo et al.) looked at the use of the DigniCap Scalp Cooling System. After six cycles of TC, alopecia had occurred in 100% of patients without the cap, versus 37% of patients with the cap. Based on these findings, I expect the cap to be more widely available in the United States very soon.

Non-Small Cell Lung Cancer

Abstract 8002 (J. Soria et al.) showed that afatinib was more effective than erlotinib in OS in patients who had developed platinum-resistant squamous cell carcinoma.

Abstract 8023 (M. Kris et al.) studied the use of the IBM Watson computer to make patient treatment recommendations, versus the recommended therapy by lung cancer experts at Memorial Sloan Kettering Cancer Center. In patients with localized disease, there was agreement between Watson and physician only 66% of the time. In patients with metastatic disease, agreement was higher at 85%. The authors pointed out that Watson failed to consider patient preferences, co-morbidities, or elderly age in making recommendations. These differences can be resolved somewhat by inputting those variables into the Watson computer, but this needs to be done in future development.

Abstract LBA109 (L. Paz-Ares et al.) summarized the CheckMate 057 study. In patients with non-small cell carcinoma of the lung who had failed prior platinum doublet therapy, OS with nivolumab was 12.2 months compared to only 9.4 months with docetaxel (HR 0.73, P=0.002). The conclusion: while the drug is approved for advanced squamous non-small cell lung cancer (NSCLC), the FDA should also approve this drug for non-squamous NSCLC.

Survivorship

Abstract 6509 (A. Bansal et al.) reported on bankruptcy rates. Bankruptcy in cancer patients was increased 2.5 fold compared to non-cancer patients. The overall incidence of bankruptcy was 2%. Astonishingly, the occurrence of bankruptcy subsequently increased the mortality rate in cancer patients, with a hazard ratio of 1.79. Obviously, financial considerations and needs must be taken into account when treating cancer patients.

Abstract 9542 (T. Wildes et al.) looked at geriatric assessments and correlation with fall risk. In geriatric cancer patients, use of anti-depressants increased the risk of falls 2.9 fold. Therefore, extreme caution should be used in prescription of anti-depressants, with patients and caregivers being aware of fall risk when considering anti-depressant use in elderly patients.

Abstract 9546 (M. Delgado-Guay et al.) looked at the most common wishes in patients who were being followed in a palliative care oncology unit at MD Anderson Cancer Center. Patients identified their top five wishes as being at peace with God, having an ability to pray, having family present, being free of pain, and not being a burden to the family. It is important to consider these findings when evaluating elderly patients.

Abstract 9614 (S. Jamshed et al.) looked at the use of influenza vaccine in patients receiving chemotherapy. Seroconversion (the development of detectable antibodies in the blood that are directed against an infectious agent) in patients under age 65 using high-dose vaccine administered at the same time as chemotherapy was 80%, compared to only 40% to 58% with standard dose vaccine. Based on this finding, all cancer patients should be immunized with high-dose influenza vaccines during the next influenza season.

Abstract 9625 (A. Menendez et al.) looked at use of complementary and alternative (CAM) medications and diets. Before cancer diagnosis, patient use was 11%; after diagnosis, patient use had increased to 58%. However, of those who used CAM medications, only 23% told their physician. The conclusion:

Astonishingly, the occurrence of bankruptcy subsequently increased the mortality rate in cancer patients with a hazard ratio of 1.79. Obviously, financial considerations and needs must be taken into account when treating cancer patients.

better history should be taken when evaluating patients in oncology practices to determine concordant use of CAM medications, diet, and other practices.

Melanoma

Abstract 3003 (A. Ribas et al.) studied an experimental anti-PD-L1 drug MED14736 plus dabrafenib and trametinib in patients with metastatic melanoma. There was a 100% disease control rate, and 69% partial response rate, indicating the ability to combine targeted agents with immunotherapy.

Abstract 9004 (F. Hodi et al.) looked at the study CheckMate 069. Patients with stage III and IV melanoma randomized to nivolumab plus ipilimumab had a response rate of 60%, compared to only 11% of patients with ipilimumab alone. PFS had not been reached on the combination compared to 3.3 months on ipilimumab, which was significant. Toxic deaths were seen in about 4% of patients on the combination, but in no patients on the single drug.

Abstract 9006 (J. Larkin et al.) presented the results of the coBRIM study. Patients with stage IV melanoma who received the combination of vemurafenib with cobimetinib had a PFS of 12.5 months, compared to vemurafenib alone of only 7.3% months (HR 0.5). Mutation did not affect the results of these outcomes.

Abstract 9009 (H. Kluger et al.) studied pembrolizumab 10 mg/kg in patients with untreated brain metastases. Remarkably, 50% of patients showed a measurable decrease in metastases. Therefore, immunotherapy may have a role in patients with brain metastases in melanoma, and perhaps in other diseases as well.

Abstract 9019 (D. Johnson et al.) presented research on ipilimumab in patients who had autoimmune disease. Sixty-seven percent of those patients showed a flare of the autoimmune disease, but these were all managed by corticosteroids, and none of the patients had to stop the ipilimumab.

Abstract LBA1 (J. Wolchok et al.) compared the combination of nivolumab plus ipilimumab with nivolumab alone and with ipilimumab alone. PFS favored the combination (HR 0.57, P=0.001). In the 75% of the patients who were negative for expression of PD-L1 (less than 5% staining, a cut off which has been variable in different studies), the combination was superior to nivolumab alone and superior to ipilimumab alone, with a response rate of 72% in the combination versus 57% in the best single arm. However, response rates were equal in nivolumab versus the combination if the PD-L1 assay was over 5% (both of these groups were still superior in response rate to ipilimumab alone). Importantly, 36% of patients on the combination discontinued treatment, but two-thirds of the patients who discontinued treatments had improved response after the combination had been discontinued. This indicates continuing activity of the drugs even after the patient stops taking the drugs. The authors suggested that when an immediate response is needed, the combination would be better. However, the single agent use of nivolumab would be better when low toxicity was preferred.

This drug combination is very costly, and financial considerations need to be taken into account. In a plenary session titled "Perspectives on Value," Leonard Saltz, MD, of Memorial Sloan Kettering Cancer Center said that the cost of the combination was $295,000 for an 11.5 month course. Furthermore, if one were to use pembrolizumab at a dose of 10 mg/kg, Dr. Saltz said the cost would be $1,000,900 per year of treatment for one patient. Therefore, Dr. Saltz recommended that providers consider value when approving or using these drugs.

Abstract LBA9002 (U. Leiter et al.) looked at the use of sentinel lymph node biopsy with or without completion of regional lymph node dissection. In patients who had lymph node dissection, there was a decrease in regional lymph node recurrence, but surprisingly, no change in PFS or OS compared to patients who had positive sentinel lymph nodes but no completion regional lymph node dissection. Accordingly, consideration of delayed lymph node dissection at time of regional recurrence remains a strong option for certain patients.

Prostate Cancer

Abstract 5001 (N. James et al.) looked at the results of the STAMPEDE trial. In patients with metastatic or node-positive prostate cancer or patients with a PSA relapse who had not

received any hormonal therapy, the use of docetaxel was superior to the use of zoledronic acid with an overall survival of 77 months on docetaxel versus 67 months on zoledronic acid (HR 0.62). This finding suggests earlier use of chemotherapy in patients who have relapsing cancer.

Abstract 5003 (E. Small et al.) looked at the histology of patients who have a repeat biopsy following use of enzalutamide or abiraterone. Remarkably, 13% of such patients had converted to small cell prostate cancer and 26% had evolved into an intermediate atypical aggressive form of cancer. The OS of both groups was short, indicating that the use of these agents can be associated with a less favorable outcome of patients once they had relapsed and again indicating possible need for early and aggressive chemotherapy in such patients.

Abstract 5010 (P. Corn et al.) found that carboplatin was useful in castrate-resistant prostate cancer.

Abstract 5018 (G. Lu-Yao et al.) showed that the use of statin in prostate cancer patients was associated with a decreased prostate-specific mortality rate (HR 0.60). Furthermore, overall mortality was also reduced (HR 0.75). Use of metformin was not associated with any improved survival.

Abstract 5037 (C. Sweeney et al.) showed that cabozantinib plus abiraterone showed a 58% PSA response rate in castrate-resistant prostate patients.

Abstract 5066 (M. Gross et al.) found an 80% partial response rate in the combination of everolimus plus bevacizumab plus docetaxel.

Pediatric Oncology

Abstract 10073 (S. Mostoufi-Moab et al.) showed that adults who had survived pediatric tumors and who had received a transplant showed an increase in adipose tissue, a decrease in muscle mass, and an increase in osteopenia, as well as a high frequency of hormonal deficiencies. Therefore, primary care physicians and medical oncologists should consider younger adults (perhaps 30 years old) more like a patient with age-associated morbidities (perhaps like a 50 year old). This should improve the comprehensive evaluation of these patients and lead to improvement in health outcomes as these complications would be effectively treated.

Prevention

Abstract 1500 (D. Wickerham et al.) summarized the long-term results of the STAR P2 protocol. After 5 years of treatment with tamoxifen or raloxifene, the HR for survival in tamoxifen-treated patients (with a median follow up of 9.7 years) was 1.19 (P=0.01), versus raloxifene. Raloxifene was only 81% as active but did show a marked decrease in side effects of uterine cancer, with no osteoporosis. Therefore, the use of raloxifene as a cancer preventive (appropriate only in postmenopausal patients) can be strongly considered when avoidance of side effects is desired.

Abstract 1502 (R. Chlebowski et al.) looked at the effect of estrogen (Premarin) in preventing breast cancer. The use of Premarin reduced breast cancer (HR 0.79), but this effect was only seen in African-American patients (HR 0.40). African-

Americans were defined as over 80% African ancestry by patient self-reporting. Notably, there was no change in breast cancer incidence in white women who had been given Premarin.

Abstract 1505 (G. Oxnard et al.) looked at patients with lung cancer who had EGFR mutation at diagnosis involving a T790M mutation (the INHERIT EGFR study). Sixty-eight percent of such patients had germline mutations rather than somatic mutations in the tumor alone. Nearly all of these patients had a positive family history of cancers. Therefore, in patients with a T790M mutation, germline testing should be performed, and carriers should be screened with CT chest examination to detect cancer at the earliest stage.

Leukemia Lymphoma

Abstract LBA7005 (A. Chanan-Khan et al.) reported the results of the HELIOS study. In patients with CLL/SLL who were treated with ibrutinib plus bendamustine and rituximab for six months, continuation of ibrutinib showed an increased progression-free survival compared to continuing a placebo (HR 0.20, P <0.0001). Overall survival showed an HR of 0.62, P=0.06, but there was crossover to ibrutinib later in many patients. Although this would suggest that the combination would be the treatment of choice, the treatment with ibrutinib alone may be just as active.

Abstract LBA7006 (R. Mesa et al.) looked at the use of pacritinib in the PERSIST-1 trial. In patients with myelofibrosis with no prior therapy, randomization to pacritinib showed a 19.1% response in reduction of spleen size versus only 4.7% in patients randomized to hydroxyurea (P=0.0003). Reduction in symptoms was 35% versus 10% on hydroxyurea and transfusion independence was 26% versus 0% on hydroxyurea.

Abstract LBA8502 (L. Sehn et al.) reported data on patients with indolent non-Hodgkin lymphoma. Patients treated with bendamustine plus obinutuzumab showed a PFS advantage of 29 months versus only 14 months on bendamustine alone (HR 0.52, P=0.0001).

Mesothelioma

Abstract 7500 (G. Zalcman et al.) reported the results of the MAPS study. In patients with mesothelioma, the use of cisplatin plus pemetrexed plus bevacizumab showed a PFS of 9.59 months versus only 7.48 months on cisplatin plus pemetrexed alone (HR 0.61), and an OS of 18.9 months versus 16.1 months (HR 0.76, P=0.01). In a serious disease like mesothelioma, these data represent a significant improvement and bevacizumab use should be considered.

Small Cell Lung Cancer

Abstract 7502 (P. Ott et al.) looked at use of a PD-L1 inhibitor pembrolizumab in the KEYNOTE-028 study. The response rate was 35%.

Abstract 7503 (S Antonia. et al.) studied the combination of nivolumab plus ipilimumab in the CheckMate 032 study. The combination produced a response rate of 32%.

Pancreatic Neuroendocrine Tumors

Abstract 4005 (M. Kulke et al.) compared everolimus plus octreotide with the combination plus bevacizumab. The triplet treatment showed a PFS of 16.7 months compared to 14.0 months on the doublet (HR 0.8, P=0.12). The overall response rate on the triplet was 31% versus only 12% on the doublet, and time-to-treatment failure was equal.

Non-Melanoma Skin Cancer

Abstract 9000 (A. Martin et al.) presented findings from the ONTRAC prevention study where patients who had experienced significant numbers of non-melanoma skin cancers were randomized to nicotinamide or placebo. There was a 25% reduction in non-melanoma skin cancers observed, an important observation for cancer prevention in patients plagued with recurrent skin cancers.

Value Therapy in Oncology

As reported on page 52, in a plenary session, "Perspectives on Value," Dr. Saltz emphasized that providers should consider the cost of therapy when evaluating the relative value of improved outcomes.

Abstract 6504 (D. Schrag et al.) compared the cost of the equally effective treatments of FOLFIRI plus cetuximab with FOLFIRI plus bevacizumab in protocol 80405 of SWOG and CALGB. The cetuximab arm cost $105,000 and the bevacizumab arm cost $66,000. The conclusion: bevacizumab should be the preferred treatment based on value.

Abstract 6507 (A. Lipitz Snyderman et al.) evaluated the Choosing Wisely program. Compliance with the program's recommendation of no PET or bone scan in low-risk prostate cancer was only 41%. Compliance with no imaging in low-risk breast cancer was only 27%. Compliance with the guideline of no IMRT in breast cancer patients following lumpectomy was only 27%. In the prostate and lumpectomy categories, any use of those procedures in prior patients was associated with a marked increased use of the modality in subsequent patients, suggesting that this was not dependent upon individual patient characteristics but rather a common practice of using those modalities in all patients. Takeaway message: careful consideration of the Choosing Wisely recommendations should be important to physicians.

Colorectal Cancer

Abstract 3502 (P. Gibbs et al.) reported that the use of SIRT in patients with colorectal cancer metastases showed an improvement in PFS in patients with liver metastases (HR 0.60, P=0.02) compared with no SIRT, but with no change in OS. Use of the combination of radioembolization plus chemotherapy (SIRFLOX study) showed no change in overall PFS in patients with other than liver metastases. Therefore, use of the radioembolization was appropriate only in patients who had liver metastases.

Abstract 3503 (K. Ng et al.) looked at the results of SWOG study 80405. Patients who had the highest levels of vitamin D showed an improved OS (HR 0.65) and an improved PFS (HR 7.9). Since vitamin D levels can be modified, this may represent an area for individualized treatment of patients to maintain higher levels of vitamin D.

Abstract 3510 (F. Loupakis et al.) reported the results of the TRIBE study. Patients with metastatic disease who used FOLFOXIRI plus bevacizumab showed a median overall survival of 29.8 months versus only 25.8 months on FOLFIRI plus bevacizumab (HR 0.8, P=0.03).

Abstract LBA100 (D. Le et al.) looked at the use of pembrolizumab in patients with proficient versus deficient mismatch repair (MMR). In colorectal cancer patients with deficient MMR (which is 15% of all colorectal cancer specimens), the response rate was 62%. In patients who were proficient in MMR, response rate was 0%. Surprisingly, in patients who had Lynch-associated tumors other than colorectal cancer who were also MMR deficient, the response rate was 71%.

Bladder Cancer

Abstract 4504 (D. Quinn et al.) looked at the use of eribulin in urothelial cancers. The response rate was 35%; OS was 9.5 months. This drug has activity that can be utilized in patients with this disease.

Ovarian Cancer

Abstract 5509 (M. Disis et al.) studied the use of adalimumab, an anti-PD-L1 drug. The response rate was 10.7%, but the disease control rate was 55%, indicating activity in this disease.

Abstract 5510 (A. Varga et al.) looked at the use of pembrolizumab in ovarian cancer patients with PD-L1 positive disease. The response rate was 11.5%.

Abstract 6512 (M. Simon et al.) evaluated compliance with the Choosing Wisely campaign. Compliance with end-of-life recommendations was only 73%, compliance with breast staging recommendations was only 77%, and compliance with breast surveillance recommendations was only 59%.

Head and Neck Cancer

Abstract 6009 (H. Mehanna et al.) looked at the use of PET scans in determining who should have a neck dissection for primary disease management. Patients were randomized to have a neck dissection immediately; or to PET-guided therapy. Patients on the PET-guided arm had a PET scan, and if the PET scan was negative patients were simply observed, versus if the PET scan was positive, a neck dissection was performed. OS was equal among the arms randomized to PET scan-guided therapy versus patients who had a planned neck dissection alone. Only 19% of patients who had a PET scan performed had a neck dissection, versus 100% of patients, of course, on the neck dissection arm. Cost savings were approximately 1,400 euros (or about $1,568) per patient.

Abstract LBA6008 (T. Seiwert et al.) reported on findings on use of pembrolizumab 200 mg every three weeks in patients with metastatic head and neck cancer. The response rate was 25%, with 56% showing at least some reduction in tumor size.

Hepatoma

Abstract LBA101 (A. El-Khoueiry et al.) showed that nivolumab produced a 23% response in patients with advanced hepatocellular carcinoma.

Sarcomas

Abstract LBA10502 (P. Schöffski et al.) looked at patients with adipocytic sarcoma and leiomyosarcoma. Patients randomized to eribulin showed an OS of 13.5 months, compared to only 11.5 months with the use of dacarbazine [DTIC] (HR 0.77, P=0.02).

Abstract 10503 (G. Demetri et al.) looked at second-line therapy of liposarcoma and leiomyosarcoma. Patients randomized to trabectedin (available in over 80 countries) showed an equal survival compared to patients treated with DTIC. PFS was 4.2 months on trabectedin and only 1.5 months on DTIC (HR 0.55, P=0.0001).

Abstract 10504 (O. Mir et al.) looked at the use of regorafenib. Patients randomized to regorafenib showed a PFS of 3.7 months, compared to only 1.9 months on placebo.

Abstract 10506 (J. Blay et al.) reported the results of the PAZOGIST trial. In patients who were resistant to sunitinib and imatinib, patients randomized to pazopanib showed a PFS at 4 months of 45% versus only 18% on best supportive care (HR 0.59, P=0.03).

General Health Services

Abstract 6512 (M. Simon et al.) evaluated compliance with the Choosing Wisely campaign. Compliance with end-of-life recommendations was only 73%, compliance with breast staging recommendations was only 77%, and compliance with breast surveillance recommendations was only 59%. Although these findings indicate room for improvement, the authors had not looked at these compliance rates in relationship to co-morbidities and symptoms, which have caused changes in breast staging and changes in breast surveillance numbers. Regardless, evaluating patients near the end of life is important to comply with the Choosing Wisely campaign.

Brain Metastases

Abstract LBA4 (P. Brown et al.) reported the results of the Alliance protocol N0574. In patients with one to three brain metastases, all less than 3.0 cm, the addition of whole brain radiation therapy to stereotactic radiosurgery resulted in a cognitive decline of 91.7%, compared to only 63.5% on stereotactic radiosurgery alone. The difference observed at three months was persistent at six months. OS was statistically equal on each arm, but the quality of life measures were reduced on the patients who had whole brain radiation therapy. Deficiencies in cognitive function were evident in decreased recall, decreased communication, and decreased memory. There was a higher resection rate in patients who had stereotactic radiosurgery.

Conclusions

As you can see, diverse and interesting research results were presented at ASCO 2015. These studies will all be published, and I urge readers to pay close attention to the details as final results are reported in peer-reviewed published papers. Nevertheless, consideration of many of these findings is appropriate as we evaluate each of our patients. OI

Cary A. Presant, MD, FACP, FASCO, is a staff oncologist at City of Hope, Duarte, Calif. He is also professor of Clinical Medicine, University of Southern California KECK School of Medicine; past president, Association of Community Cancer Centers; past president, American Cancer Society California Division; chairman of the Board, Medical Oncology Association of Southern California; and chief medical officer, DiaTech Oncology, Nashville, Tenn.

FREE! ACCC Oncology Reimbursement Meetings

- **Boston, Mass. | November 17, 2015**
- **Birmingham, Ala. | December 10, 2015**

Attend the meeting that's most convenient to you for a 360° look at oncology reimbursement issues, tools to strengthen your program, and information to help you weather market changes. Any member of the cancer care team who deals with oncology business and reimbursement will benefit from these meetings. Gain a full-spectrum perspective in just one day of sessions:

- ✔ Hear the latest trends in oncology coding and billing, navigate new regulations in 2015, and gain strategies to overcome reimbursement obstacles
- ✔ Learn how recent shifts from volume-based payment to reimbursement based on quality will impact providers
- ✔ Gain practical how-to's for increasing efficiency through the proper management of financial data
- ✔ Hear strategies for the practical application of radiation oncology CPT codes in physician office and hospital settings.

Best of all, these essential meetings are free to ACCC members! Non-members are invited to join us at the low registration rate of $69. Learn more and register at accc-cancer.org/ReimbursementMeeting.

TRENDS IN CANCER PROGRAMS

Resources & Tools for the Multidisciplinary Team

This is Year 6 of the annual survey, a joint project between ACCC and Lilly Oncology. Key findings on reimbursement issues, marketplace challenges, patient-centered care, quality improvement initiatives, outreach and screening efforts, and more. The biggest challenges facing today's cancer program, according to the 2015 survey respondents:

• Lack of reimbursement for supportive care services	65%
• Budget restrictions	61%
• Lack of physical space	49%
• Marketplace competition	49%
• Cost of drugs	45%
• Increased number of patients unable to afford treatment	44%

The full 2015 Trends in Cancer Programs report is available to members only at mynetwork.accc-cancer.org.

ACCC Welcomes its Newest Members

Central Care Cancer Center
Salina, Kansas
Delegate Rep: Wendy Leith
Website: www.cccancer.com

St. Rita's Regional Cancer Center
Cincinnati, Ohio
Delegate Rep: Julie Rowland, MBA, RT(R)(T)
Website: www.mercy.com

Chester County Hospital-Abramson Cancer Center
West Chester, Pa.
Delegate Rep: Judith Suska, MHA, FACHE, CMPE
Website: www.chestercountyhospital.org

Hospital of the University of Pennsylvania
Philadelphia, Pa.
Delegate Rep: Richard Funnell, MHA, FACHE, CMPE
Website: www.pennmedicine.org/hospital-university-pennsylvania

Penn Presbyterian Medical Center
Philadelphia, Pa.
Delegate Rep: Neil Ravitz, MBA
Website: www.pennmedicine.org/penn-presbyterian-medical-center

Pennsylvania Hospital-Abramson Cancer Center
Philadelphia, Pa.
Delegate Rep: Susan Ley, MLT/ASCP, HEW
Website: www.pennmedicine.org/pahosp

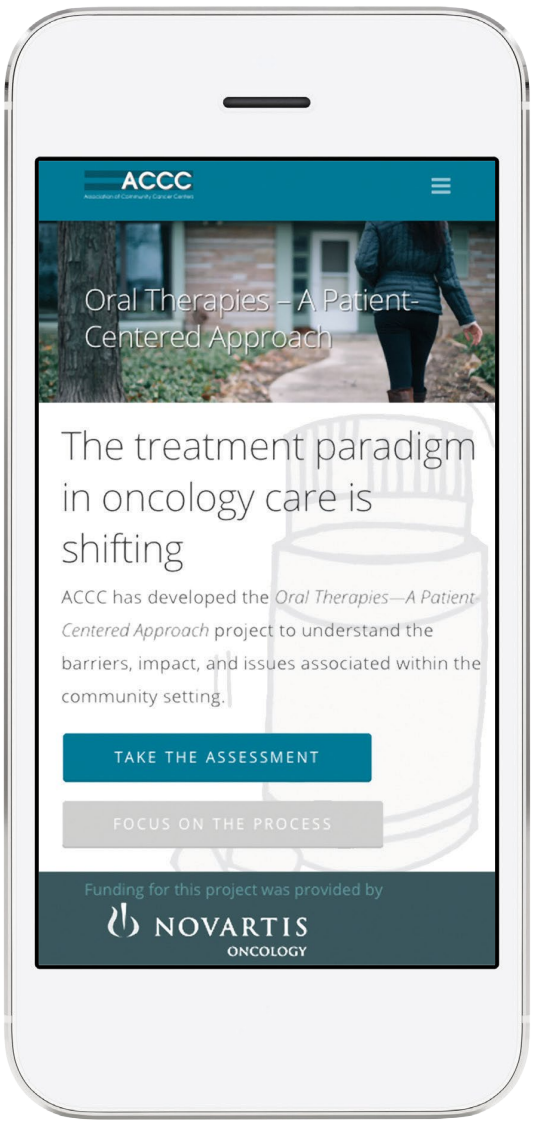
Oral Therapies Present New Challenges for Cancer Care Providers

ACCC Presents a New Way to Help You Meet Those Challenges

New Mobile Oral Therapies Assessment Tool

Access ACCC's free, easy-to-use Oral Therapies Assessment Tool from any mobile device to help you evaluate a patient's potential success rate for oral therapies, and to identify areas where additional education and support may be needed.

http://accc-oralchemo.org/home1/accc



ORAL CHEMOTHERAPY
New! Patient Adherence Assessment Tool

NOVARTIS

Funding for this project was provided by Novartis Oncology.

careers

ASSISTANT PROFESSOR, HEMATOLOGY/ONCOLOGY
Shreveport, Louisiana

LSU Health Sciences Center at Shreveport in the Section of Hematology-Oncology, Feist-Weiller Cancer Center is seeking full-time physicians at the Assistant Professor level.

Practice includes all facets of the Department of Medicine and the Feist-Weiller Cancer Center; serve as an attending faculty on the clinical services staffed by the Section of Feist-Weiller Cancer Center. In addition, physicians are expected to participate in overall faculty activities, including medical student, house staff and fellow teaching responsibilities. Physicians are also expected to conduct research and publish findings in journals and make presentations at medical conferences; MD or equivalent.

Applicants must qualify for a Louisiana license. BE/BC necessary. Opportunities available now. Positions will remain open until filled.

LSU is an Equal Opportunity / Affirmative Action employer.

LSUHealthShreveport
Feist-Weiller Cancer Center

Please send C.V. and three letters of reference to Glen Mills, MD, Professor of Medicine, Chief, Section of Hematology and Oncology, Director, Feist-Weiller Cancer Center at *gmills@lsuhsc.edu*.

ADMINISTRATOR
Galesburg, Illinois

Western Illinois Cancer Treatment Center, a freestanding radiation treatment center, serving West-Central Illinois since 1987, seeks an experienced administrator. The ideal candidate will have a minimum of a Bachelor's Degree and 3-5 years of experience in radiation oncology. Excellent verbal and written skills required. A Master's Degree and experience with EHR, coding/billing, and physician relations and marketing is highly desired.

The Administrator reports to Physician Partners and works with the medical director to effectively manage and coordinate patient care. Other duties and responsibilities include strategic planning, budget and finance, regulatory compliance, and knowledge and application of accounting principles through processing of Accounts Payable and Receivables. Day to day operations include human resource management, facility and equipment maintenance, marketing and public relations, community and physician relations, development and application of policies and procedures, preparation of reports and documents, credentialing, contract negotiations, purchasing and procurement, physician billing, supervision of staff, and 24/7 responsibility for the center.

Submit letter of application and resume or CV to Matthew Carpenter, MD, at Matthew.Carpenter@unitypoint.org.

CANCER DATA REGISTRAR
Cortlandt Manor, New York

At New York-Presbyterian/Hudson Valley Hospital, the cancer data registrar is responsible for ensuring the accuracy and completeness of the registry data, including case finding, follow-up, coding, and abstracting, as well as the maintenance of the Cancer Registry information system. The registrar also coordinates and/or participates in cancer service line activities.

Requirements include:

- A minimum of an associate's degree; successful completion of a cancer registry program and certification (CTR) by NCRA.
- 3 years of recent cancer registry.
- A strong commitment to customer service and excellent interpersonal skills.
- Broad knowledge of community health concepts, services, and resources.
- Ability to respond to data requests by analyzing and presenting data in an understandable format.
- Ability to display and present relevant data.
- Ability to work collaboratively with healthcare staff at all levels as part of an interdisciplinary team.

Apply online at www.hvhc.org.

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Paying It Forward

BY DANIEL KINGSLEY

Many times in life different obstacles are thrown in our way. For me, my biggest obstacle hit on Aug. 7, 2008, when I was diagnosed with acute lymphoblastic leukemia (ALL) at the age of 12. The attending physician kept telling me, "Well, this could be one of two things: cancer or just a viral infection. We won't know until we test your bone marrow." Of course I was hoping for it to simply be something viral; however, it turned out to be cancer. I remember continually asking myself, "Why me? Why do I have to battle this?"

Back when I was 12, I didn't know that I would decide to become a pediatric oncologist. And if I hadn't fought cancer, I'm not sure I would have chosen this path. Through my career, I want to be able to encourage other patients and their family members going through a similar ordeal by telling them that there is hope. I am living proof of it, and I believe my experience has given me unique insight into what others are battling. While I would never presume to know exactly what each individual with cancer is facing, I know firsthand the range of emotions they may be feeling in their search for answers.

My Treatment Experience

When being treated for ALL, I received traditional chemotherapy. The worst of the treatments were cytarabine (Ara-C) injections, rounds of steroid shots, and high-dose methotrexate—with the last being the most difficult to endure. High-dose methotrexate is given by liter intravenously; it requires an inpatient stay lasting at least one week. Sometimes, after the high-dose regimen, my body could barely handle low doses of methotrexate during the maintenance phase. During the weeks that I would receive high-dose treatment, I would be confined to a bed for most of the week; most times I was barely strong enough to walk to the bathroom. Truthfully, I think the only reason I could fight through it was because I slept the majority of the week. Treatments like this made it difficult to continue doing the things I loved, like playing sports and being with friends.

Maintaining a normal life was next to impossible until I completed chemotherapy. The biggest issue with maintaining a normal life was having enough stamina to do everyday activities. Everything became a chore. However, I did the best I could. I played sports to the best of my ability and marched in my school's band. I went to school when possible, but most of my classwork was done from home. Baseball was the toughest activity to engage in due to the mediport placed beneath the skin in my chest, and because the steroid treatments had weakened my knees so much that I was never able to play the role of catcher again. Thankfully, I avoided the mediport issue by specially modifying my shirts to place a HeartGuard chest protector over the top. I never had to endure a ball to the protector.

One of the best days of my life was when I received my last dose of chemotherapy on Dec. 1, 2011. December 12 is my birthday, and ending chemo was the best birthday present I've ever received. I was elated that I could start what would become a normal life; although, I would still have to make the trip to Rainbow Babies and Children's Hospital in Cleveland, Ohio, to ensure that I had not relapsed. Two weeks later I was able to travel to Disney World in Florida with my school's music program, and that spring I was strong enough to play baseball for my high school. It wasn't much longer before I started planning where I wanted to go to college and eventually medical school.

Life after Cancer

I knew that to be considered as a candidate for either an MD or MD/PhD program I would need research experience. Therefore, I turned to a member of my oncology team, Alex Huang, MD, PhD, the director of the Pediatric Hematology/Oncology Fellowship Training Program at Rainbow Babies & Children's Hospital. I contacted Dr. Huang in November 2014 to see if he had any lab positions available to summer students, and if he would be willing to invite me to work there. He was very pleased that I was interested in working with him and his team, and so we began looking into possible grants or scholarships to fund my research. Dr. Huang contacted the St. Baldrick's Foundation (www.stbaldricks.org) and together we completed the necessary paperwork to apply for a grant. We anxiously waited to hear back, and about two months after submitting, I received an email from Dr. Huang saying, "We did it! We got the grant!" I was excited to begin working in his lab on possible immunotherapy treatments.

(*continued on page 62*)

ACCC: MEETING YOUR NEEDS

Gear up for a full menu of meetings with need-to-know information for the entire cancer care team. Don't miss out on unparalleled opportunities to advance your learning in critical areas, and earn CE credits. Be sure to share this information with your colleagues who can benefit from these events.

ACCC
Association of Community Cancer Centers

FINANCIAL ADVOCACY NETWORK CASE-BASED WORKSHOPS

Bridging the Gap between Patient Needs and Financial Resources

These FREE one-day collaborative workshops help sharpen the skills and knowledge base of financial advocates. Experience real-world case studies, group-based discussion, and interactive exercises led by financial advocacy experts.

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Tuesday, November 10, 2015
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Transform Care Today!

As an initiative of ACCC, the Institute for Clinical Immuno-Oncology (ICLIO) National Conference will bring together expert faculty to empower multi-disciplinary team members to address the dynamic and unique intricacies of the treatment and delivery of immuno-oncology.

October 2, 2015
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Philadelphia, Pennsylvania

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Any member of the cancer care team who deals with oncology business and reimbursement will benefit from these FREE one-day meetings. Gain a full-spectrum perspective with sessions on payment reform; the latest trends in coding and billing; proper management of financial data; and the practical application of radiation oncology CPT codes.

Tuesday, November 17, 2015
Boston, Massachusetts

Thursday, December 10, 2015
Birmingham, Alabama

ACCC 42nd ANNUAL MEETING
CANCERSCAPE
Policy, Value & Quality

Gain the latest insight on the evolving healthcare policy landscape, alternative payment models, quality measures and reporting, how big data can improve care, and much more! Get involved in Capitol Hill Day and advocate for quality cancer care directly to legislators.

March 2–4, 2016
Hyatt Regency Washington on Capitol Hill
Washington, D.C.

For details on all ACCC meetings go to accc-cancer.org/meetings

(*continued from page 60*)

My Research Efforts

Laboratory research is tough work—not tough as in physical backbreaking labor—but my brain received a huge workout every day from absorbing and learning so much information. I have truly enjoyed my fellowship this summer and hopefully some of the studies that my partner, Dr. Hasan Hashem, and I have been working on will lead to a breakthrough.

Specifically, we have been working on a treatment for Ewing sarcoma (the second most common bone cancer after osteosarcoma) using natural killer (NK) cells. We hope to perfect this treatment because NK cells are not major histocompatibility complex (MHC) restricted; meaning, these cells do not cause graft versus host disease. Therefore, any patient can receive NK cells from another person; screening for a perfect match like in the case of bone marrow transplants is not needed. The osteosarcoma cells that we are studying are to produce a new cell line and immortalize it. We want to create a cell line that will grow quickly and be readily accessible to use in future experiments.

Paying It Forward

I would not have had this incredible experience if it were not for the St. Baldrick's Foundation, a nonprofit dedicated to raising money for childhood cancer research. St. Baldrick's is truly a great group of people who care about kids and are extremely passionate about their cause. Each year they raise and donate millions of dollars to pediatric cancer research and fund fellows, like myself.

Finally, I would not have embarked on this path without the support of the doctors on my oncology team at Rainbow Babies and Children's Hospital (www.uhhospitals.org/rainbow). These cancer care providers inspired me to become a pediatric oncologist. In the end, cancer changed my life forever, redirecting me down a path and career that I might not have chosen. I don't think that—even if I could—I would have had it any other way. OI

Daniel Kingsley with Dr. Agne Petrosiute, his primary oncologist and a St. Baldrick's Fellow, and Dr. Alex Huang, who Daniel worked with as a St. Baldrick's Summer Fellow.

Daniel Kingsley is a St. Baldrick's Foundation Summer Fellow and cancer survivor. Read more about his remarkable story at www.stbaldricks.org/blog/post/undergrad-goes-from-childhood-cancer-survivor-to-summer-fellow.

This is not the first time ACCC has covered some of the great work being done by St. Baldrick's. In the September-October 2013 *Oncology Issues*, Kathleen Ruddy, chief executive officer of the St. Baldrick's Foundation, contributed a column entitled "Shaving the Way to Conquer Child Cancers." St. Baldrick's head-shaving events began as a challenge between businessmen and have grown from one event in 2000 to over 1,300 events in 2013, raising critical funds for childhood cancer research. Events take place in pubs, restaurants, schools, churches, parks, malls, military bases, firehouses, and any other place you can imagine. ACCC members can access Ruddy's column online at mynetwork.accc-cancer.org.

FINANCIAL ADVOCACY NETWORK

Resources & Tools for the Multidisciplinary Team

Comprehensive resources to reduce the cost burden of cancer care–for your patients & your staff

ACCC's newly-revamped and expanded Financial Advocacy Network provides a robust portfolio of tools and resources for your financial advocates–easily accessible online, in print, or at free regional meetings. Looking to expand your program? We've got you covered.

Explore this one-stop destination:

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Justifying the Financial Advocate Position

Maximizing Reimbursement

ONLINE INTERACTIVE FORUM

What should I know about ICD-10?

How do I make a case for hiring a financial advocate?

How can I improve processes to leverage copay programs?

Are there strategies to help maximize reimbursement?

TOOLS

Programmatic Tools:

- Job descriptions
- Flowcharts
- Resources to help with denials and appeals
- Staffing models
- Financial tracking and reporting tools

NEW! PATIENT ASSISTANCE APP

ACCC just launched a powerful new app for busy financial advocates who want easy-access to payment assistance and reimbursement programs from their mobile device.

In just a few clicks, you can search by Foundations and Co-pay Assistance Programs, Drug Name (brand or generic), and Manufacturer name.

Access at accc-FAN-App.org

ACCC
Association of Community Cancer Centers

This program is a benefit of membership.
Association of Community Cancer Centers

IRESSA® (gefitinib) tablets for oral use

Brief Summary of Prescribing Information.
For complete prescribing information consult official package insert

INDICATIONS AND USAGE

IRESSA is indicated for the first-line treatment of patients with metastatic non-small cell lung cancer (NSCLC) whose tumors have epidermal growth factor receptor (EGFR) exon 19 deletions or exon 21 (L858R) substitution mutations as detected by an FDA-approved test *[see Clinical Studies (14) in the full Prescribing Information]*.

Limitation of Use: Safety and efficacy of IRESSA have not been established in patients with metastatic NSCLC whose tumors have EGFR mutations other than exon 19 deletions or exon 21 (L858R) substitution mutations *[see Clinical Studies (14) in the full Prescribing Information]*.

DOSAGE AND ADMINISTRATION

Patient Selection

Select patients for the first-line treatment of metastatic NSCLC with IRESSA based on the presence of EGFR exon 19 deletion or exon 21 (L858R) substitution mutations in their tumor *[see Indications and Usage (1)* and *Clinical Studies (14) in the full Prescribing Information]*. Information on FDA-approved tests for the detection of EGFR mutations in NSCLC is available at: http://www.fda.gov/CompanionDiagnostics.

Recommended Dose

The recommended dose of IRESSA is 250 mg orally once daily with or without food until disease progression or unacceptable toxicity.

Do not take a missed dose within 12 hours of the next dose.

Administration to Patients Who Have Difficulty Swallowing Solids

Immerse IRESSA tablets in 4 to 8 ounces of water by dropping the tablet in water, and stir for approximately 15 minutes. Immediately drink the liquid or administer through a naso-gastric tube. Rinse the container with 4 to 8 ounces of water and immediately drink or administer through the naso-gastric tube.

Dose Modification

Dose Modifications for Adverse Drug Reactions

Withhold IRESSA (for up to 14 days) for any of the following:

- Acute onset or worsening of pulmonary symptoms (dyspnea, cough, fever) *[see Warnings and Precautions (5.1) in the full Prescribing Information]*
- NCI CTCAE Grade 2 or higher in ALT and/or AST elevations [*see Warnings and Precautions (5.2) in the full Prescribing Information*]
- NCI CTCAE Grade 3 or higher diarrhea *[see Warnings and Precautions (5.4) in the full Prescribing Information]*
- Signs and symptoms of severe or worsening ocular disorders including keratitis *[see Warnings and Precautions (5.5) in the full Prescribing Information]*
- NCI CTCAE Grade 3 or higher skin reactions *[see Warnings and Precautions (5.6) in the full Prescribing Information]*

Resume treatment with IRESSA when the adverse reaction fully resolves or improves to NCI CTCAE Grade 1.

Permanently discontinue IRESSA for:

- Confirmed interstitial lung disease (ILD) *[see Warnings and Precautions (5.1) in the full Prescribing Information]*
- Severe hepatic impairment *[see Warnings and Precautions (5.2) in the full Prescribing Information]*
- Gastrointestinal perforation *[see Warnings and Precautions (5.3) in the full Prescribing Information]*
- Persistent ulcerative keratitis *[see Warnings and Precautions (5.5) in the full Prescribing Information]*

Dose Modifications for Drug Interactions

Strong CYP3A4 Inducers

Increase IRESSA to 500 mg daily in the absence of severe adverse drug reaction, and resume IRESSA at 250 mg seven days after discontinuation of the strong CYP3A4 inducer *[see Drug Interactions (7)* and *Clinical Pharmacology (12.3) in the full Prescribing Information]*.

CONTRAINDICATIONS

None.

WARNINGS AND PRECAUTIONS

Interstitial Lung Disease (ILD)

ILD or ILD-like adverse drug reactions (e.g., lung infiltration, pneumonitis, acute respiratory distress syndrome, or pulmonary fibrosis) occurred in 1.3% of the 2462 patients who received IRESSA across clinical trials; of these, 0.7% were Grade 3 or higher and 3 cases were fatal.

Withhold IRESSA and promptly investigate for ILD in any patient who presents with worsening of respiratory symptoms such as dyspnea, cough and fever. Permanently discontinue IRESSA if ILD is confirmed [*see Dosage and Administration (2.4) and Adverse Reactions (6.1) in the full Prescribing Information*].

Hepatotoxicity

In patients who received IRESSA across clinical trials, 11.4% of patients had increased alanine aminotransferase (ALT), 7.9% of patients had increased aspartate aminotransferase (AST), and 2.7% of patients had increased bilirubin. Grade 3 or higher liver test abnormalities occurred in 5.1% (ALT), 3.0% (AST), and 0.7% (bilirubin) of patients. The incidence of fatal hepatotoxicity was 0.04%.

Obtain periodic liver function testing. Withhold IRESSA in patients with worsening liver function and discontinue in patients with severe hepatic impairment *[see Dosage and Administration (2.4)*, *Adverse Reactions (6.1)*, and *Use in Specific Populations (8.7) in the full Prescribing Information]*.

Gastrointestinal Perforation

Gastrointestinal perforation occurred in three (0.1%) of the 2462 IRESSA-treated patients across clinical trials [*see Adverse Reactions (6.1) in the full Prescribing Information*]. Permanently discontinue IRESSA in patients who develop gastrointestinal perforation [*see Dosage and Administration (2.4) in the full Prescribing Information*].

Severe or Persistent Diarrhea

Grade 3 or 4 diarrhea occurred in 3% of 2462 IRESSA-treated patients across clinical trials. Withhold IRESSA for severe or persistent (up to 14 days) diarrhea *[see Dosage and Administration (2.4)* and *Adverse Reactions (6.1) in the full Prescribing Information]*.

Ocular Disorders including Keratitis

Ocular disorders [keratitis (0.1%), corneal erosion and aberrant eyelash growth (0.2%), conjunctivitis, blephritis and dry eye (6.7%)] occurred in the 2462 IRESSA-treated patients across clinical trials. The incidence of Grade 3 ocular disorders was 0.1% [*see Adverse Reactions (6.1) in the full Prescribing Information*]. Interrupt or discontinue IRESSA for severe, or worsening ocular disorders [*see Dosage and Administration (2.4) in the full Prescribing Information*].

Bullous and Exfoliative Skin Disorders

Bullous conditions including toxic epidermal necrolysis, Stevens Johnson syndrome and erythema multiforme have been reported from treatment with IRESSA. Erythema multiforme and dermatitis bullous have been reported in two patients (0.08%) across NSCLC trials (Study 2, Study 3 and Study 4). IRESSA treatment should be interrupted or discontinued if the patient develops severe bullous, blistering or exfoliating conditions.

Embryo-fetal Toxicity

Based on its mechanism of action and data from animal reproduction studies IRESSA can cause fetal harm when administered to a pregnant woman. In animal reproductive studies, oral administration of gefitinib from organogenesis through weaning resulted in fetotoxicity and neonatal death at doses below the recommended human dose. Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment with IRESSA and for at least two weeks following completion of therapy [*see Use in Specific Populations (8.1, 8.3) in the full Prescribing Information*].

ADVERSE REACTIONS

The following adverse drug reactions are discussed in more detail in other sections of the labeling:

- Interstitial Lung Disease *[see Warnings and Precautions (5.1) in the full Prescribing Information]*
- Hepatotoxicity *[see Warnings and Precautions (5.2) in the full Prescribing Information]*
- Gastrointestinal Perforation *[see Warnings and Precautions (5.3) in the full Prescribing Information]*
- Severe or Persistent Diarrhea *[see Warnings and Precautions (5.4) in the full Prescribing Information]*
- Ocular Disorders including Keratitis *[see Warnings and Precautions (5.5) in the full Prescribing Information]*
- Bullous and Exfoliative Skin Disorders *[see Warning and Precautions (5.6) in the full Prescribing Information]*

Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The safety of IRESSA is based on the data from 2462 patients with NSCLC who received IRESSA 250 mg daily monotherapy in three randomized clinical studies (Study 2, Study 3 and Study 4). Patients with a history of interstitial lung disease, drug-induced interstitial disease, radiation pneumonitis that required steroid treatment or any evidence of clinically active interstitial lung disease were excluded from these studies.

Controlled Studies:

Study 2 was a randomized, multicenter, open-label trial in which 1217 patients were randomized to receive first-line treatment for metastatic NSCLC; 607 patients received IRESSA 250 mg daily and 589 patients received carboplatin/paclitaxel. The median duration of treatment with IRESSA was 5.9 months. The study population characteristics were: median age 57 years, age less than 65 years (73%), female (79%), Asian (100%), NSCLC adenocarcinoma histology (100%), never smoker (94%), light ex-smoker (6%), ECOG PS 0 or 1 (90%).

Study 3 was a randomized, multicenter, double-blind, placebo-controlled trial in which 1692 patients were randomized to receive second- or third-line treatment for metastatic NSCLC; of which 1126 patients received IRESSA 250 mg daily and 562 patients received placebo. The median duration of treatment with IRESSA was 2.9 months. The study population characteristics were: median age 62 years, age less than 65 years (60%), female (33%), Caucasian (75%), Asian (21%), NSCLC adenocarcinoma histology (48%), never smoker (22%), ECOG PS 0 or 1 (65%), PS 2 (29%), PS 3 (5%) and two or more prior therapies (51%).

Study 4 was a randomized, multicenter, open-label trial in which 1466 patients were randomized to receive second-line treatment for metastatic NSCLC; 729 patients received IRESSA 250 mg daily and 715 patients received docetaxel. The median duration of treatment with IRESSA was 2.4 months. The study population characteristics were: median age 61 years, age less than 65 years (61%), female (36%), Caucasian (79%), Asian (21%), NSCLC adenocarcinoma histology (54%), never smoker (20%), ECOG PS 0 or 1 (88%) and two or more prior therapies (16%).

The pooled safety database from the three randomized trials was used to evaluate for serious and uncommon adverse drug reactions. Common adverse reactions were evaluated in Study 3. The most frequent adverse reactions in Study 3 (incidence of >20% and greater than placebo) reported in IRESSA-treated patients were skin reactions (47%) and diarrhea (29%). The most frequent fatal adverse reactions in IRESSA-treated patients were respiratory failure (0.9%), pneumonia (0.8%), and pulmonary embolism (0.5%).

Approximately 5% of IRESSA-treated patients and 2.3% of placebo-treated patients discontinued treatment due to an adverse event. The most frequent adverse reactions that led to discontinuation in patients treated with IRESSA were nausea (0.5%), vomiting (0.5%) and diarrhea (0.4%).

Table 1 – Selected Adverse Drug Reactions Occurring with an Incidence Rate ≥5% and an Increase of >2% of IRESSA-treated Patients in Study 3

	Percentage (%) of patients			
	IRESSA (N=1126)		Placebo (N=562)	
Adverse Reaction	**All Grades**	**Grade 3 and 4**	**All Grades**	**Grade 3 and 4**
Skin and subcutaneous tissue disorders				
Skin reactions[1]	47%	2%	17%	0.4%
Nail disorders[2]	5%	0.1%	0.7%	0%
Gastrointestinal disorders				
Diarrhea[3]	29%	3%	10%	1%
Vomiting	14%	1.2%	10%	0.4%
Stomatitis[4]	7%	0.3%	4%	0.2%
Metabolism and nutrition disorders				
Decreased appetite	17%	2.3%	14%	2.0%

Table 1 – Selected Adverse Drug Reactions Occurring with an Incidence Rate ≥5% and an Increase of >2% of IRESSA-treated Patients in Study 3 (cont'd.)

	Percentage (%) of patients			
	IRESSA (N=1126)		Placebo (N=562)	
Adverse Reaction	**All Grades**	**Grade 3 and 4**	**All Grades**	**Grade 3 and 4**
Eye disorders				
Conjunctivitis/blepharitis/dry eye[5]	6%	0%	3.2%	0%

[1] Includes Acne, Acne pustular, Dermatitis, Dermatitis acneiform, Dermatitis exfoliative, Drug eruption, Dry skin, Erythema, Exfoliative rash, Folliculitis, Pruritus, Pruritus generalized, Rash, Rash erythematous, Rash generalized, Rash macular, Rash maculo-papular, Rash papular, Rash pruritic, Rash pustular, Rash vesicular, Skin exfoliation, Skin toxicity, Xeroderma
[2] Includes Ingrowing nail, Nail bed infection, Nail disorder, Nail infection, Onychoclasis, Onycholysis, Paronychia
[3] Includes Diarrhea, Feces soft, Frequent bowel movements
[4] Includes Aphthous stomatitis, Cheilitis, Glossodynia, Mouth ulceration, Mucosal inflammation, Oral mucosal blistering, Stomatitis, Tongue disorder, Tongue ulceration
[5] Includes Blepharitis, Conjunctival hyperemia, Conjunctivitis, Dry eye, Eye irritation, Eye pruritus, Eye swelling, Eyelid irritation, Eyelid edema, Eyelids pruritus

Table 2 – Treatment Emergent Laboratory Abnormalities Occurring More Frequently in IRESSA-Treated Patients in Study 3

	IRESSA		Placebo	
Adverse Reaction	**All Grades %**	**Grade 3 and 4 %**	**All Grades %**	**Grade 3 and 4 %**
Alanine aminotransferase increased[1]	38%[2]	2.4%	23%[2]	1.4%[4]
Aspartate aminotransferase increased[1]	40%[3]	2.0%	25%[3]	1.3%[5]
Proteinuria	35%	4.7%	31%	3.3%

[1] Patients were allowed to enter the clinical study with lab values of ALT or AST CTCAE grade 1 or 2
[2] 14% gefitinib patients and 10% placebo patients were CTC grade 1 or 2 ALT at baseline
[3] 15% gefitinib patients and 12% placebo patients were CTC grade 1 or 2 AST at baseline
[4] 0.2% of placebo patients were CTC grade 3 at baseline
[5] 0.4% of placebo patients were CTC grade 3 at baseline

The following adverse reactions have been reported with IRESSA across NSCLC trials (Study 2, Study 3 and Study 4) and are not listed elsewhere in Section 6: nausea (18%), asthenia (17%), pyrexia (9%), alopecia (4.7%), hemorrhage (including epistaxis and hematuria) (4.3%), dry mouth (2%), dehydration (1.8%), allergic reactions including angioedema and urticaria (1.1%), elevations in blood creatinine (1.5%), and pancreatitis (0.1%).

Postmarketing Experience
The following adverse reactions have been identified during post-approval use of IRESSA. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Renal and urinary disorders: cystitis, hemorrhagic cystitis

Skin and subcutaneous tissue disorders: cutaneous vasculitis

DRUG INTERACTIONS

Drugs Affecting Gefitinib Exposure

CYP3A4 Inducer
Drugs that are strong inducers of CYP3A4 increase the metabolism of gefitinib and decrease gefitinib plasma concentrations. Increase IRESSA to 500 mg daily in patients receiving a strong CYP3A4 inducer (e.g., rifampicin, phenytoin, or tricyclic antidepressant) and resume IRESSA at 250 mg 7 days after discontinuation of the strong inducer [*see Dosage and Administration (2.4)* and *Clinical Pharmacology (12.3) in the full Prescribing Information*].

CYP3A4 Inhibitor
Drugs that are strong inhibitors of CYP3A4 (e.g., ketoconazole and itraconazole) decrease gefitinib metabolism and increase gefitinib plasma concentrations. Monitor adverse reactions when administering strong CYP3A4 inhibitors with IRESSA.

Drugs Affecting Gastric pH
Drugs that elevate gastric pH (e.g., proton pump inhibitors, histamine H_2-receptor antagonists, and antacids) may reduce plasma concentrations of gefitinib. Avoid concomitant use of IRESSA with proton pump inhibitors, if possible. If treatment with a proton-pump inhibitor is required, take IRESSA 12 hours after the last dose or 12 hours before the next dose of the proton-pump inhibitor. Take IRESSA 6 hours after or 6 hours before an H_2-receptor antagonist or an antacid [*see Clinical Pharmacology (12.3) in the full Prescribing Information*].

Hemorrhage in Patients taking Warfarin
International Normalized Ratio (INR) elevations and/or hemorrhage have been reported in some patients taking warfarin while on IRESSA therapy. Patients taking warfarin should be monitored regularly for changes in prothrombin time or INR.

USE IN SPECIFIC POPULATIONS

Pregnancy

Risk Summary

Based on its mechanism of action and animal data, IRESSA can cause fetal harm when administered to a pregnant woman. In animal reproductive studies, oral administration of gefitinib from organogenesis through weaning resulted in fetotoxicity and neonatal death at doses below the recommended human dose (*see Animal Data*). Advise pregnant women of the potential hazard to a fetus or potential risk for loss of the pregnancy.

The background risk of major birth defects and miscarriage for the indicated population is unknown; however, the background risk in the U.S. general population of major birth defects is 2-4% and miscarriage is 15-20% of clinically recognized pregnancies.

Data

Animal Data
A single dose study in rats showed that gefitinib crosses the placenta after an oral dose of 5 mg/kg (30 mg/m^2, about 0.2 times the recommended human dose on a mg/m^2 basis). When pregnant rats were treated with 5 mg/kg from the beginning of organogenesis to the end of weaning there was a reduction in the number of offspring born alive. This effect was more severe at 20 mg/kg (approximate the human clinical dose on a mg/m^2 basis) and was accompanied by high neonatal mortality soon after parturition. In rabbits, a dose of 20 mg/kg/day (240 mg/m^2, about twice the recommended dose in humans on a mg/m^2 basis) caused reduced fetal weight.

Lactation

Risk Summary

It is not known whether IRESSA is excreted in human milk. Animal studies indicate the gefitinib and its metabolites are present in rat milk at a concentration higher than those in maternal plasma. Because of the potential for serious adverse reactions in nursing infants from IRESSA, advise women to discontinue breast-feeding during treatment with IRESSA.

Data

Animal Data
Levels of gefitinib and its metabolites were 11-to-19-fold higher in milk than in blood, after oral exposure of lactating rats to a dose of 5 mg/kg.

Females and Males of Reproductive Potential

Contraception

Based on its mechanism of action and animal data, IRESSA can cause fetal harm when administered to a pregnant woman [*see Use in Specific Populations (8.1) in the full Prescribing Information*]. Advise females of reproductive potential to use effective contraception during treatment with IRESSA and for at least two weeks following completion of therapy.

Infertility

IRESSA may result in reduced fertility in females of reproductive potential [*see Nonclinical Toxicology (13.1) in the full Prescribing Information*].

Pediatric Use
The safety and effectiveness of IRESSA in pediatric patients have not been established.

Geriatric Use
Of the 823 patients enrolled in two randomized, active-controlled clinical trials 374 patients (45%) were 65 years and older, and 93 patients (11%) were 75 years and older. No overall differences in safety were observed between patients 65 years and older and those younger than 65 years. There is insufficient information to assess for differences in efficacy between older and younger patients.

Renal Impairment
Less than four percent (<4%) of gefitinib and its metabolites are excreted via the kidney. No clinical studies were conducted with IRESSA in patients with severe renal impairment.

Hepatic Impairment
The systemic exposure of gefitinib was compared in patients with mild, moderate, or severe hepatic impairment due to cirrhosis (according to Child-Pugh classification) and healthy subjects with normal hepatic function (N=10/group). The mean systemic exposure ($AUC_{0-\infty}$) was increased by 40% in patients with mild impairment, 263% in patients with moderate impairment, and 166% in patients with severe hepatic impairment. Monitor adverse reactions when IRESSA is administered to patients with moderate and severe hepatic impairment.

In a study comparing 13 patients with liver metastases and moderate hepatic impairment (addition of CTC grade of baseline AST/SGOT, ALP, and bilirubin equals 3 to 5) to 14 patients with liver metastases and normal hepatic function, the systemic exposure of gefitinib was similar [*see Warnings and Precautions (5.2) in the full Prescribing Information*].

OVERDOSAGE
Twenty three patients were treated weekly with doses from 1500 mg to 3500 mg, and IRESSA exposure did not increase with increasing dose. Adverse events were mostly mild to moderate in severity, and were consistent with the known safety profile of IRESSA. In the event of suspected overdose, interrupt IRESSA, institute supportive care, and observe until clinical stabilization. There are no specific measures/treatments that should be taken following IRESSA overdosing.

PATIENT COUNSELING INFORMATION
Advise the patient to read the FDA-approved patient labelling (Patient Information).

Interstitial Lung Disease: Advise patients to immediately contact their healthcare provider for new onset or worsening of pulmonary symptoms such as dyspnea, cough and fever [*see Warnings and Precautions (5.1) in the full Prescribing Information*].

Hepatotoxicity: Inform patients that they will need to undergo lab tests to monitor for liver function. Advise patients to contact their healthcare provider to report any new symptoms indicating hepatic toxicity [*see Warnings and Precautions (5.2) in the full Prescribing Information*].

Gastrointestinal Perforation: Advise patients that IRESSA can increase the risk of gastrointestinal perforation and to seek immediate medical attention for severe abdominal pain [*see Warnings and Precautions (5.3) in the full Prescribing Information*].

Severe or Persistent Diarrhea: Advise patients to contact their healthcare provider for severe or persistent diarrhea [*see Warnings and Precautions (5.4) in the full Prescribing Information*].

Ocular Disorders including Keratitis: Advise patients promptly to contact their healthcare provider if they develop eye symptoms, lacrimation, light sensitivity, blurred vision, eye pain, red eye or changes in vision *[see Warnings and Precautions (5.5) in the full Prescribing Information].*

Bullous and Exfoliative Skin Disorders: Advise patients that IRESSA can increase the risk of bullous and exfoliative skin disorders and to seek immediately medical attention for severe skin reactions [*see Warnings and Precautions (5.6) in the full Prescribing Information*].

Embryo-fetal Toxicity: Advise pregnant women of the potential risk to a fetus or potential risk for loss of the pregnancy [*see Warnings and Precautions (5.7) and Use in Specific Populations (8.1) in the full Prescribing Information*]. Advise females of reproductive potential to use effective contraception during treatment with IRESSA and for at least two weeks following completion of therapy [*see Use in Specific Populations (8.3) in the full Prescribing Information*].

Lactation: Advise women to discontinue breast-feeding during treatment with IRESSA [*see Use in Specific Populations (8.2) in the full Prescribing Information].*

Manufactured for:
AstraZeneca Pharmaceuticals LP Wilmington, DE 19850
By: AstraZeneca UK Limited Macclesfield, Cheshire, England Product of Belgium

3148105 7/15 Issued: 07/15

NOW APPROVED!

For the treatment of metastatic NSCLC

A TKI for first-line use in EGFR mutation–positive patients

IRESSA®
gefitinib

Indication

IRESSA is indicated for the first-line treatment of patients with metastatic non-small cell lung cancer (NSCLC) whose tumors have epidermal growth factor receptor (EGFR) exon 19 deletions or exon 21 (L858R) substitution mutations as detected by an FDA-approved test.

Limitation of Use: Safety and efficacy of IRESSA have not been established in patients with metastatic NSCLC whose tumors have EGFR mutations other than exon 19 deletions or exon 21 (L858R) substitution mutations.

Important Safety Information

- There are no contraindications for IRESSA
- Interstitial Lung Disease (ILD): ILD occurred in patients taking IRESSA. Withhold IRESSA for worsening of respiratory symptoms. Discontinue IRESSA if ILD is confirmed
- Hepatotoxicity: Obtain periodic liver function testing. Withhold IRESSA for Grade 2 or higher for alanine aminotransferase (ALT) and/or aspartate aminotransferase (AST) elevations. Discontinue for severe hepatic impairment
- Gastrointestinal Perforation: Discontinue IRESSA for gastrointestinal perforation
- Diarrhea: Withhold IRESSA for Grade 3 or higher diarrhea
- Ocular Disorders Including Keratitis: Withhold IRESSA for signs and symptoms of severe or worsening ocular disorders including keratitis. Discontinue for persistent ulcerative keratitis
- Bullous and Exfoliative Skin Disorders: Withhold IRESSA for Grade 3 or higher skin reactions or exfoliative conditions
- Embryo-fetal Toxicity: Can cause fetal harm. Advise of potential risk to a fetus and use of effective contraception
- Advise women to discontinue breast-feeding during treatment with IRESSA
- The most commonly reported adverse drug reactions, reported in more than 20% of the patients and greater than placebo, were skin reactions and diarrhea

Please see Brief Summary of complete Prescribing Information on adjacent pages.

Learn more about IRESSA at www.iressa-usa.com.

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