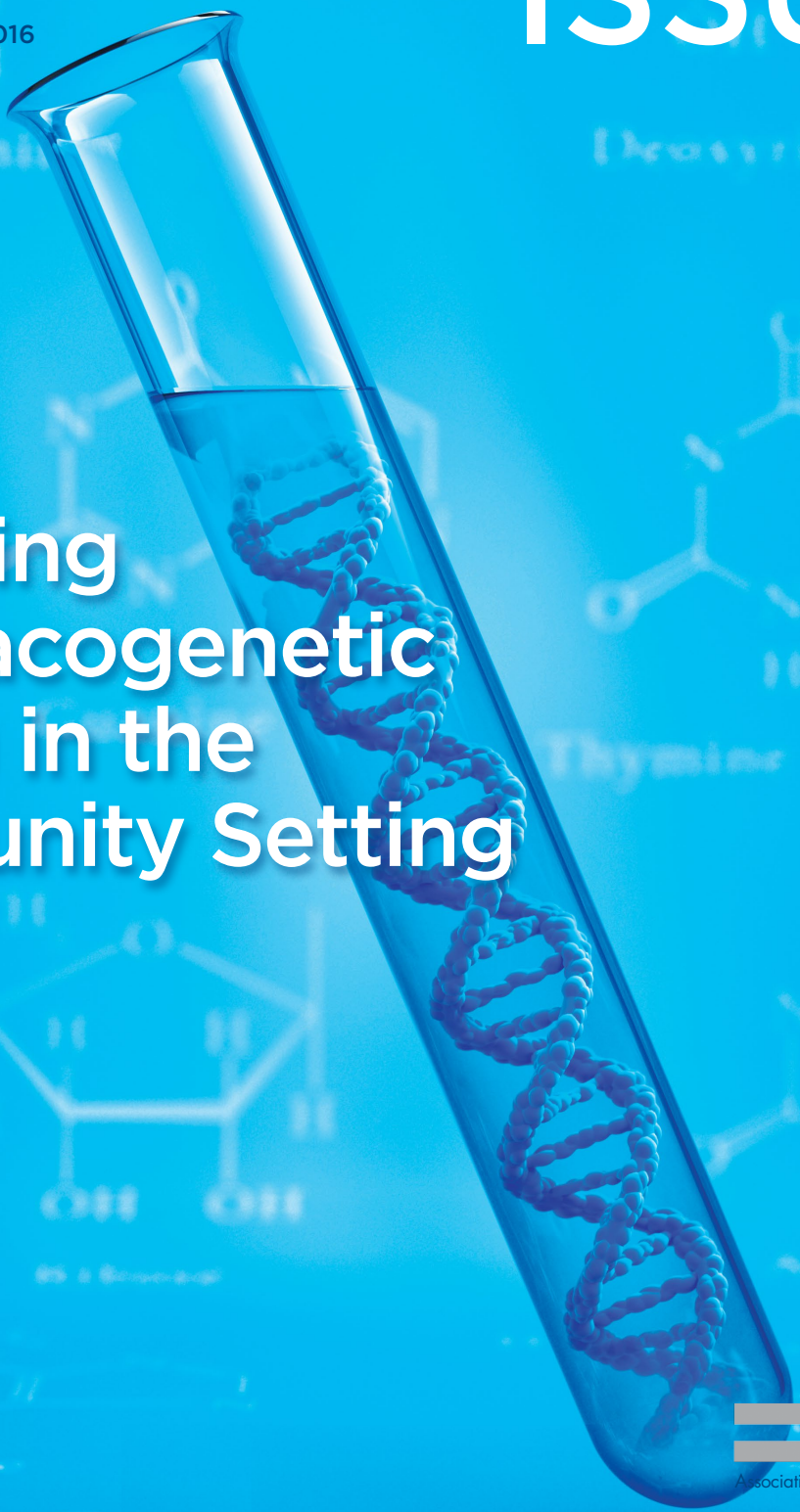
ONCOLOGY ISSUES

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

September | October 2016



Delivering Pharmacogenetic Testing in the Community Setting

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Association of Community Cancer Centers

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contents

Oncology Issues
September | October 2016
Vol. 31 | No. 5

DEPARTMENTS

ACCC
Association of Community Cancer Centers

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

Think Globally, Act Locally

BY CHRISTIAN DOWNS, JD, MHA

"Think Globally, Act Locally" is a great bumper sticker more likely found on the back of a Prius than a cancer clinic courtesy shuttle. Its origins, in the 1970s, was a grassroots rallying cry for the environmental movement. But take a moment and apply the phrase to your cancer program operations.

"Think Globally." What universal challenges do all cancer patients and providers face? What services should be provided to all patients—regardless of their ability to pay? How will these services be reimbursed?

"Act Locally." What is my cancer program doing that sets it apart from its competitors? Are there unique needs specific to my patients and my providers? Has my institution made a commitment to meeting those needs?

This edition of *Oncology Issues* offers some great examples of programs and providers that "Think Globally, Act Locally."

In our cover article, Mark Wagner, who completed his PGY2 oncology pharmacy practice residency at St. Luke's Mountain States Tumor Institute (MSTI), shares his experience as part of a multidisciplinary team that piloted a service delivery model to implement pharmacogenetic testing. To succeed, the team had to come together to "Act Locally" on data collection, physician acceptance to ordering tests, insurance coverage, test turn-around times, and test results. This article challenges us to "Think Globally" about how to integrate this testing to advance delivery of precision medicine.

In their feature article, Paul Baron and Josh Mondschein "Think Globally" about the experience of women with breast cancer and how combining breast cancer surgery with plastic and reconstructive surgery can improve the patient experience. The article also describes how they "Act Locally" bringing oncoplastic surgery to the women in their community.

Even big global thinkers like Duke Cancer Institute demonstrate the value and importance of acting locally. In her article, Nadine Barrett and colleagues detail Duke's initiative to address local health disparities by leveraging community health assessments. The authors encourage other programs to "Act Locally" to reduce disparities by sharing tips for meeting organizational expectations, engaging in community outreach and screening activities, and increasing participation in clinical research.

In "Training Community Nurses & Administrators to Implement Cancer Clinical Trials," nurse researchers from the Hospital of the University of Pennsylvania, City of Hope, and the Mount Sinai Hospital came together to "Think Globally" and develop a two-day curriculum to meet that goal. Courses began in 2013 and continued through the Spring of 2016. Attendees left prepared to "Act Locally" and put what they learned to work; each participant identified a list of three goals to be implemented when returning to their care setting.

Next, in one of the best examples of "Think Globally, Act Locally," Cary Presant shares his annual wrap-up of ASCO 2016, identifying overarching themes—including genomics, immunotherapy, precision medicine, new payment methodologies, cost of care, and practice management issues—and giving context to research findings to help community physicians "Act Locally" to implement these new treatments and technologies.

Lastly, don't forget, one of the most important actions you can take is to attend the ACCC National Oncology Conference, Oct. 19-21, St. Louis. Come together to "Think Globally" about cancer care; network and learn from your peers; and then return home to "Act Locally" by putting the strategies you learned to work at your cancer program! OI

Putting the Future of Cancer in Focus: The Moonshot Summit

BY JENNIE R. CREWS, MD, MMM, FACP

The Cancer Moonshot is all of us who are trying to understand and defeat cancer.

—Vice President Biden at the Cancer Moonshot Summit
Washington, D.C., 2016

The quote above encapsulates the overarching theme of collaboration that was present at the Cancer Moonshot Summit held in Washington, D.C., in June 2016. I had the privilege to attend the summit as a representative of ACCC.

The Moonshot Summit brought together a diverse group of stakeholders, including cancer patients, advocacy groups, researchers, providers, and members of industry, including technology, IT, and drug development. This group was tasked with developing action items to address a number of challenges in cancer care:

- Access to clinical trials
- Ethnic, socioeconomic, and geographic disparities
- Data sharing and interoperability of medical records
- Use of precision medicine
- Regulatory issues impeding research
- Value and cost of care
- Cancer prevention and control
- Survivorship needs.

Summit responses to these action items will be presented to the Cancer Moonshot Taskforce and incorporated into the overall Moonshot initiative.

As we addressed these issues in working groups, it was clear that the expectation of the Cancer Moonshot is for the cancer community to take ownership for solutions to these issues and to collaborate in new ways. The role of the federal government will be to facilitate and support—but not necessarily regulate—the path to success.

The Summit provided a venue for networking and conversation that promoted such collaboration among cancer care stakeholders. Already, an impressive number of initiatives from federal agencies, private companies, and public-private partnerships have formed to further the goal of the Cancer Moonshot: "to make a decade of advances in cancer prevention, diagnosis, treatment, and care in five years."

To date, much of the Cancer Moonshot focus has been on research and academic medicine. However, to reach many of its goals, the Cancer Moonshot team needs to engage with community oncology, where the majority of cancer care is delivered. This is where ACCC members come in. ACCC is well suited to be a partner in this endeavor. We are a collaborative organization with diverse, multidisciplinary representation from the cancer community. Our members continue to develop innovative solutions to the same challenges in cancer care that were addressed during the Cancer Moonshot Summit. Many of these innovations will be highlighted at the ACCC National Oncology Conference, Oct. 19-21, 2016, including access to clinical trials, enhancing survivorship, early detection in the underserved, and managing population health.

In addition, ACCC Director of Health Policy Leah Ralph and I are working closely with the Cancer Moonshot Taskforce to explore ways that ACCC can be the voice of community oncology for the Cancer Moonshot initiative, including a virtual focus group with ACCC members held August 17, 2016, and a special session during the ACCC National Oncology Conference in St. Louis.

I am excited about the momentum and possibilities that the Cancer Moonshot creates for ACCC and for all of us who are trying to understand and defeat cancer. OI

Coming in Your 2016-2017 *ONCOLOGY ISSUES*

- The Evolution of Clinical Pathways & Their Role to Identify Quality and Cost Effective Care
- High Intensity Focused Ultrasound (HIFU) Treatment for Prostate Cancer
- Building Supportive Care Programs through Philanthropy
- Forming Partnerships to Bring Clinical Trials to the Community
- Developing a Nurse Practitioner Productivity Measurement Tool
- Lessons from the Trenches on Strategic Planning for Oncology
- Tele-Health Technology Connects Patients with Nutrition Services
- The Study of High-Cost Oncology Patients to Improve Care & Curb Costs
- Enhancing Survivorship through Improved Provider Communication, Care Coordination & Professional Education
- Early Detection of Cancer for the Medically Underserved
- Establishing Personal Pain Goals in Oncology Patients to Improve Care & Decrease Costs
- HPV Vaccination: Engaging Community Partners for Success
- Building a Palliative Care Program from the Inside Out

more online @ accc-cancer.org

Network and learn firsthand from these 2016 ACCC Innovator Award winners at the ACCC National Oncology Conference, Oct. 19-21, St. Louis, accc-cancer.org/oncologyconference.

VIDEO

HPV Vaccination: Engaging Community Partners for Success

Changing the conversation helped Outer Banks Hospital Cancer Services implement an evidence-based outreach strategy on the importance of HPV vaccination: http://bit.ly/OBH-ACCC.

VIDEO

Tele-Health Technology Connects Patients with Nutrition Services

Pennington Cancer Center incorporated tele-health into its nutrition services—streamlining scheduling, reducing travel time, and improving patient access: http://bit.ly/PCC-ACCC.

VIDEO

Personal Pain Goals to Improve Patient Care & Decrease Costs

Frauenshuh Cancer Center advanced patient understanding of opioid use and educated clinicians on cost and comparative effectiveness, decreasing out-of-pocket costs and enhancing the patient and provider experience. http://bit.ly/FCC-ACCC.

VIDEO

Palliative Care—It's About Living

University of Maryland Upper Chesapeake Health, Kaufman Cancer Center developed a three-step process that uses existing resources to create a proactive approach to delivering outpatient palliative care. http://bit.ly/KCC-ACCC.

VIDEO

Early Detection of Cancer for the Medically Underserved

Mary Bird Perkins Cancer Center's mobile medical clinics provide free screenings; culturally appropriate practices eliminate barriers to care; and strategic partnerships maximize patient transitions throughout the care continuum. http://bit.ly/MBP-ACCC.

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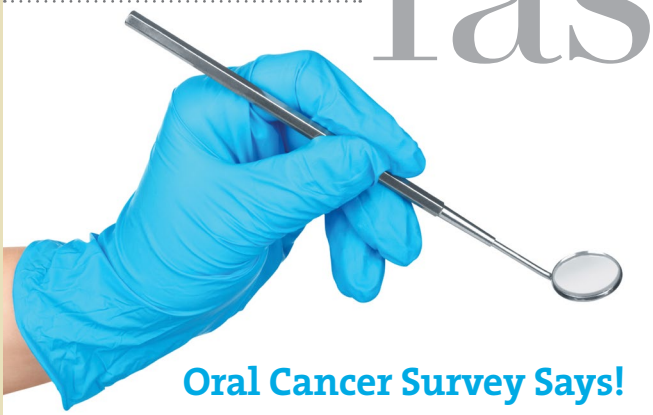
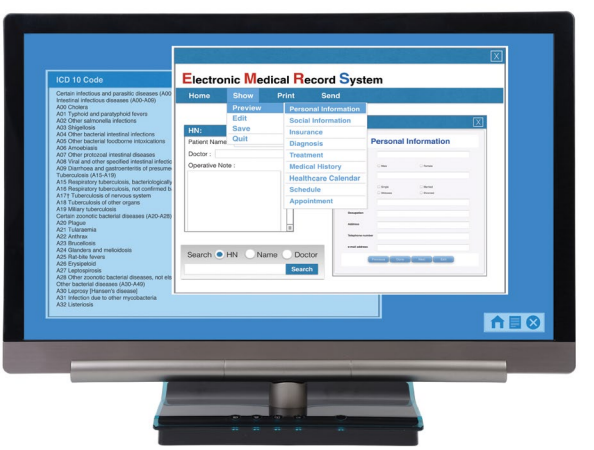


Oral Cancer Survey Says!

- More than **86%** of respondents want their dental professional to help them learn ways to reduce their risk of developing oral cancer.
- **83%** want to be screened for oral cancer during routine check-ups; only **37%** actually are.
- **65%** were unaware that HPV is a risk factor for oral cancer.
- Only **23%** recall talking to their dental professional about oral cancer risks at their last dental check-up.

Source. Consumer Survey Conducted by Vigilant Biosciences (vigilantbiosciences.com) in collaboration with Head and Neck Cancer Alliance (headandneck.org) and Support for People with Oral and Head and Neck Cancer (spohnc.org).



Improvement Needed!

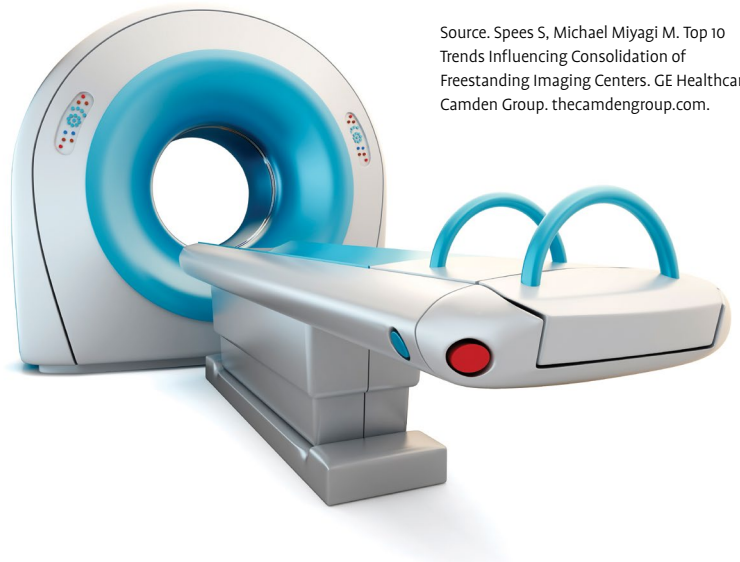
Less than half of doctors are sharing health records with other providers, leaving many without the information needed to properly care for patients.

Source. Council of Accountable Physician Practices. Better Together: Patient Expectations and the Accountability Gap Consumer Healthcare Survey Results. accountablecaredoctors.org/wp-content/uploads/2016/06/SHP-CAPP-2016-Consumer_Physician-Survey-FINAL.pdf.

facts

Top 10 Trends Influencing Consolidation of Freestanding Imaging Centers

1. Access & population health
2. Capitation & cost
3. Consumerism & transparency
4. Reimbursement differential
5. Purchasing power
6. Survival of the fittest
7. Shifting physician demographics
8. Advancing technology
9. Management & clinical benefits
10. Concentrating referrals



Source. Spees S, Michael Miyagi M. Top 10 Trends Influencing Consolidation of Freestanding Imaging Centers. GE Healthcare Camden Group. thecamdengroup.com.

By the Numbers

Likelihood of Drug Approval from Phase I

Hematology: **26%**
Oncology: **5%**

Probability of Phase II Success

Hematology: **57%**
Oncology: **25%**

Probability of Phase III Success

Hematology: **75%**
Oncology: **40%**

Source. Biotechnology Innovation Organization. Clinical Development Success Rates 2006-2015.

Top 5 Concerns for Hospital & Health System Executives

1. Engaging physicians in minimizing clinical variation
2. Redesigning health system services for population health
3. Meeting rising consumer expectations for service
4. Patient engagement strategies
5. Controlling avoidable utilization

Source. The Advisory Board Company. Annual Health Care CEO Survey. advisoryboardcompany.com.

Bringing the Moonshot Down to Earth

What the taskforce means for ACCC members

BY LEAH RALPH

On January 12, 2016, President Obama used his State of the Union address to announce that Vice President Biden would be leading a national moonshot to end cancer as we know it. By the end of January, a Presidential Memorandum was in place establishing the Federal Cancer Moonshot Taskforce, which was charged with doubling the rate of progress in cancer research and treatment, making a decade worth of advances in five years. The Vice President has said "we're not trying to make incremental change here—we're trying to get to a quantum leap on the path to a cure."

By early February, the Administration had made what they were calling an initial down payment on the Moonshot Initiative: $1 billion through FY2017 for cancer-related research activities at the National Institutes of Health and the Food and Drug Administration.

The Moonshot framed their work by laying out several areas where there seems to be consensus—and opportunity for advances—in the cancer community:[1]

1. ***We're at an inflection point, and the science is ready.*** We need to break through barriers—whether it be research, funding, or information sharing—to speed progress and increase access.
2. ***We have the potential to take advantage of big data and supercomputing with greater data sharing.*** Allow researchers, scientists, and physicians access to the wealth of information that cancer centers keep, including genetic history, medical records, and tissue banks. Ensure this information is interoperable and accessible to speed up research advances and improve patient care.
3. ***We need to increase access to game-changing treatments.*** Only five percent of cancer patients participate in a clinical trial. Expand access to these trials and empower patients by providing them with their data.

Since January, we've seen a number of partnerships and commitments emerge—and the Moonshot seems to be harnessing private sector commitments and increased federal funding to develop innovative solutions to breaking down barriers to both data and patient access.

I know what you're thinking: this all sounds very Washington D.C. The goals are admirable, but how do we get there? As Dr. Jennie Crews said in her "President's Message," the Vice President has been clear that this is not only something everyone can be a part of, but the onus is "on all of us" to help carry this work forward. The Moonshot website (whitehouse.gov/cancermoonshot) provides specific, tangible opportunities to be part of this initiative, including sharing your personal story with cancer or collaborating with others on novel ways to fund and advance cancer research; strengthening the drug development process; developing a robust and secure IT infrastructure for sharing research results and clinical health information; or formulating novel strategies for engaging the public in prevention and awareness efforts.

ACCC members also attended many of the Cancer Moonshot summits that took place across the country in late June, discussing a variety of issues, including the challenges of getting medical advances to the community setting. Since those meetings, Dr. Crews and I have worked closely with the Moonshot staff to facilitate conversations with our members to ensure their recommendations to the Vice President—that will be made by the end of the year—truly reflect how cancer care is delivered in the community setting. During a virtual focus group with the Moonshot staff in late August, ACCC members were asked about access to clinical trials in the community setting; gaps in addressing survivorship; challenges in capturing patient treatment goals; the use of clinical navigators; and community cancer program participation in big data efforts and precision medicine.

In October, the Vice President's staff will join us at the ACCC National Oncology Conference in St. Louis to share what they've learned from groups like ours and to get your feedback on draft recommendations around community oncology. Be sure to join us for this special session to learn more about what the Cancer Moonshot means for your cancer program, and what you—as the cancer care professionals on the frontlines—can share with this important initiative. OI

Leah Ralph is ACCC director of Health Policy.

References

1. Office of the Vice President. The Cancer Moonshot Task Force: Removing Bureaucratic Hurdles and Supporting Scientific Advances. Available online at: medium.com/cancer-moonshot. Last accessed Aug. 23, 2106.

Why insight$_2$oncology®?

i$_2$o® can reveal insightful data about your cancer service line.

How many patient and cancer directed services were provided?

513 cancer patients received

836 cancer-directed services

What are your top sites in volume?

Top 3 sites treated = 1/2 of total cancer patient volumes

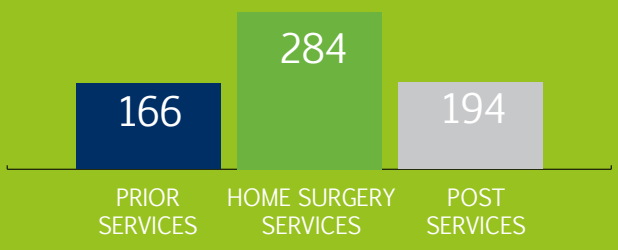
1. **Breast**
   24% of total cancer patient volume | 5% increase from prior year
2. **Lung**
   14% of total cancer patient volume | 10% increase from prior year
3. **Prostate**
   12% of total cancer patient volume | 29% increase from prior year

How many patients came to your facility for treatment that were diagnosed elsewhere?

IN-MIGRATION

207 patients or **40%** of total cancer patient volume

Have you thought about your downstream revenue?



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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.

There's marking time...

and there's making memories

Efficacy was demonstrated in the IFUM* study

- IRESSA achieved a 50% objective response rate (ORR) (95% confidence interval [CI]: 41, 59) by blinded independent central review (BICR) and a 70% ORR (95% CI: 61, 78) by investigator assessment

Efficacy was confirmed by the IPASS† study

- 3.5-month improvement in progression-free survival (median) vs chemotherapy—10.9 months with IRESSA vs 7.4 months with carboplatin/paclitaxel (HR=0.54; 95% CI: 0.38, 0.79) by BICR

Safety was established in the ISEL‡ study

- The most frequent adverse reactions (incidence of >20% and greater than placebo) reported in IRESSA-treated patients were skin reactions (47%) and diarrhea (29%)
- ≤5.1% of IRESSA-treated patients experienced severe adverse reactions
- 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%)

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) or ILD-like reactions (eg, lung infiltration, pneumonitis, acute respiratory distress syndrome, or pulmonary fibrosis) occurred in 1.3% of 2462 IRESSA patients; of these, 0.7% were Grade ≥3 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
- In patients who received IRESSA, 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 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
- Gastrointestinal perforation occurred in three (0.1%) of 2462 IRESSA patients. Permanently discontinue IRESSA in patients who develop gastrointestinal perforation
- Grade ≥3 diarrhea occurred in 3% of 2462 IRESSA patients. Withhold IRESSA for severe or persistent (up to 14 days) diarrhea
- Ocular disorders [keratitis (0.1%), corneal erosion and aberrant eyelash growth (0.2%), conjunctivitis, blepharitis and dry eye (6.7%)] occurred in 2462 IRESSA patients. The incidence of Grade 3 ocular disorders was 0.1%. Interrupt or discontinue IRESSA for severe or worsening ocular 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. IRESSA treatment should be interrupted or discontinued if patients develop severe bullous, blistering or exfoliating conditions
- 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
- Advise women to discontinue breast-feeding during treatment with IRESSA
- The most commonly reported adverse drug reactions reported in more than 20% of patients and greater than placebo, were skin reactions (47%) and diarrhea (29%)

Please see brief summary of complete Prescribing Information on adjacent pages.

*IRESSA efficacy was evaluated in a multicenter, single-arm, open-label study as a first-line treatment of 106 Caucasian patients with EGFR mutation–positive metastatic NSCLC. IFUM=IRESSA Follow-Up Measure.

†IPASS included an exploratory analysis of a subset of a randomized, multicenter, open-label trial conducted in patients with metastatic adenocarcinoma histology NSCLC receiving first-line treatment. Patients received IRESSA 250 mg orally once daily (n=88) or up to 6 cycles of carboplatin/paclitaxel (n=98). IPASS=IRESSA Pan-Asia Study.

‡Common adverse reactions were evaluated in ISEL, a randomized, multicenter, double-blind, placebo-controlled study of 1692 metastatic NSCLC patients. Patients received IRESSA 250 mg daily (n=1126) or placebo (n=562). ISEL=IRESSA Survival Evaluation in Lung Cancer. A pooled safety database from 3 randomized trials was used to evaluate for serious and uncommon adverse drug reactions.

IRESSA®
gefitinib

AstraZeneca

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].*

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Vanishing Reimbursement:
Bundling & Packaging

BY CINDY PARMAN, CPC, CPC-H, RCC

Medical and surgical procedures, services, and supplies performed on patients are defined by CPT® and HCPCS Level II codes. Once the service has been completed and documented, medical coding staff review the patient's medical record and translate the services rendered into procedure, supply, and drug codes. Some procedure codes are very specific and define a single service, while others define comprehensive services that may consist of many separate steps or processes.

In addition, CPT and HCPCS Level II code descriptors provided in coding manuals typically do not list all of the components included in a procedure. There are often services inherent in a procedure or group of procedures that may not be part of the official code definition. For example, drug administration services include local anesthesia, starting the IV or accessing a port or catheter, flush at the conclusion of treatment, and standard supplies. In another example, radiation treatment management includes completing documentation, writing prescriptions, application of topical medication, nutrition, skin care, and inpatient hospital care during the course of therapy.

In an effort to prevent improper payment, the Centers for Medicare & Medicaid Services (CMS) and other payers have implemented edits and bundled payment policies for certain services. Non-governmental payers may refer to unbundled billing as fragmented charging, which means the use of more than one procedure code to bill for a procedure or service that may be adequately described by a lesser number of codes. In this scenario, inappropriately fragmented procedures are considered to be part of the reimbursement for the major procedure or service performed.

The reimbursement concept of bundling is not new; the Office of Inspector General (OIG) published a report titled "Fragmented Physician Claims" in September 1992, when CMS was still known as HCFA (the Health Care Finance Administration).[1] This report primarily addressed fragmented surgical billing, and states:

The most important coding issue discussed in this report is what is called "fragmentation." Even the simplest surgical procedure involves many steps, from the preparation of the skin, to the incision, to the control of bleeding and eventual suture of the incision. All of these steps are integral to the procedure itself; other, less obvious, links exist between the major procedure being performed and other minor procedures which, when performed alone, can be coded separately.

Although many healthcare providers use the terms interchangeably, there are very important billing and payment differences between "packaged" services and "bundled" services. Knowing the difference in these terms may help to avoid incorrect coding practices and prevent potential revenue loss for the healthcare organization.

Bundling

The term "bundling" refers to the application of coding rules to ensure that the procedure codes submitted on the claim accurately reflect the services provided. The bundling concept applies to all practice settings, including hospitals, freestanding cancer centers, and oncology practices. CMS utilizes the National Correct Coding Initiative (NCCI), which provides an overall set of guidelines that define how multiple procedure codes will be reimbursed if submitted for the same patient on the same date of service.[2] NCCI includes three types of edits:

1. NCCI Procedure-to-Procedure (PTP) Edits
2. Medically Unlikely Edits (MUE)
3. Add-on Code Edits.

The National Correct Coding Policy Manual for 2016 accompanies the PTP edits and states:

Procedures should be reported with the most comprehensive CPT code that describes the services performed. Physicians must not unbundle the services described by a HCPCS/CPT code.

In this Manual many policies are described utilizing the term "physician." Unless indicated differently, this usage term does not restrict the policies to physicians only but applies to all practitioners, hospitals, providers, or suppliers eligible to bill the relevant HCPCS/CPT codes pursuant to applicable portions of the Social Security Act (SSA) of 1965, the Code of Federal Regulations (CFR), and Medicare rules.

NCCI PTP edits are utilized by Medicare claims processing contractors to adjudicate provider claims for physician services, outpatient hospital services, and outpatient therapy services.

Since the NCCI is a CMS program, its policies and edits represent CMS national policy.

Other insurance payers may employ the same NCCI edits or develop separate payer-specific bundling guidelines. For example, BlueCross BlueShield of Tennessee

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states that it applies bundling rules based on guidelines from the NCCI, American Medical Association (AMA), CMS, American Academy of Orthopaedic Surgeons (AAOS), American College of Obstetricians and Gynecologists (ACOG), and its own in-house clinical experts.[3] Cigna uses software called ClaimsXten™ that edits submitted claims for adherence to its medical coverage polices[4] and Humana includes an online search function to view its bundling edits.[5] A provider who has a signed participation agreement or contract with an insurer has generally agreed to accept its payer-specific bundling edits, which may be different from those applied by Medicare.

Unbundling is defined as the billing of multiple procedure codes for a group of procedures that are covered by a single comprehensive code. There are two types of unbundling: 1) unintentional, resulting from a misunderstanding of coding and 2) intentional, when an entity manipulates code assignment in order to inappropriately maximize payment. Following are examples of unbundling:

- Coding component parts of a procedure with separate procedure codes (e.g., billing the supervision, handling, and loading service in addition to remote afterloading brachytherapy treatments; or billing hydration codes for infusions provided solely to maintain line patency, in the absence of medically necessary fluid replacement).
- Reporting separate codes for related services when the code for the primary procedure includes all related services (e.g., separately reporting replacement fluid administration with a therapeutic phlebotomy).
- Down-coding a service in order to use an additional code when a single higher level, more comprehensive code is appropriate (e.g., coding multiple units of the complex treatment device code instead of a single unit of the IMRT device code).
- Separately billing the components of a procedure when one procedure code exists to accurately describe the service performed (e.g., billing image-guided localization in addition to stereotactic radiosurgery or stereotactic body radiation therapy; or billing "keep open" fluid administration between units of blood transfusion).
- Coding a unilateral service twice instead of reporting a single bilateral code (e.g., billing two simulation charges for treatment to the right and left breast, when the complex simulation includes simulating three or more separate treatment areas).

CMS has repeatedly stated that bundled services should *not* be billed to Medicare; the physician, practice, or facility should apply all bundling edits prior to issuing a claim. However, under certain circumstances, it may be appropriate to bypass the bundling edits to indicate that a procedure or service was distinct or independent from other services performed on the same day. It is important to remember that just because an edit *can* be bypassed does not mean that it *should* always be bypassed. It is essential to review each coding situation to ensure compliance.

Modifier 59 (distinct service) or HCPCS **modifiers XE** (separate encounter), **XS** (separate structure), **XP** (separate provider), or **XU** (unusual, non-overlapping service) indicate that the ordinarily bundled code represents a service performed at a different anatomic site or at a different patient encounter on the same date.

In addition to publishing a list of current bundling edits, the CMS National Correct Coding Policy Manual provides specific examples of correct and incorrect coding. For example:

The column one/column two code edit with column one CPT code 38221 (bone marrow biopsy) and column two CPT code 38220 (bone marrow, aspiration only) includes two distinct procedures when performed at separate anatomic sites or separate patient encounters. In these circumstances, it would be acceptable to use modifier 59. However, if both 38221 and 38220 are performed through the same skin incision at the same patient encounter, which is the usual practice, modifier 59 should NOT be used. Although CMS does not allow separate payment for CPT code 38220 with CPT code 38221 when bone marrow aspiration and biopsy are performed through the same skin incision at a single patient encounter, CMS does allow separate payment for HCPCS level II code G0364 (bone marrow aspiration performed with bone marrow biopsy through same incision on the same date of service) with CPT code 38221 under these circumstances.

Packaging

On Aug. 1, 2000, CMS implemented the Outpatient Prospective Payment System (OPPS) to pay for designated hospital outpatient services. In most cases, the unit of payment under the OPPS is the Ambulatory Payment Classification (APC), and CMS assigns individual procedure codes to APCs based on similar costs and clinical characteristics. Packaging is a critical feature of the OPPS; APCs generally include payment for the primary procedure plus dependent, ancillary, supportive, and adjunctive items and services.[6]

Packaging is a reimbursement term—not a coding concept—which relates only to outpatient hospital services. Packaging refers to the practice of making a single payment that includes payment for a significant procedure, as well as the "minor, ancillary services" generally associated with the procedure. Even though CMS may not provide separate payment, the codes for packaged services *should still be reported on the claim* unless contraindicated by authoritative coding guidance or superseded by bundling edits. It is especially important that hospitals continue to charge for packaged services so that CMS can collect accurate cost data for individual procedures. Also, not all payers follow Medicare payment policies, and some may provide payment in situations where CMS does not.

Examples of services that are typically packaged include:

- Supplies
- Ancillary services
- Anesthesia
- Operating and recovery room use
- Clinical diagnostic laboratory tests
- Procedures described by add-on codes
- Implantable medical devices (such as pacemakers)
- Inexpensive drugs under a per-day drug threshold packaging amount
- Drugs, biologicals, and radiopharmaceuticals that function as supplies (including diagnostic radiopharmaceuticals, contrast agents, stress agents, implantable biologicals, and skin substitutes)
- Guidance services
- Image processing services
- Intraoperative services
- Imaging supervision and interpretation services
- Observation services.

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For example, imaging guidance codes (with limited exceptions) are unconditionally packaged—that is, separate payment will *never* be made by Medicare contractors for any imaging guidance service. Instead, payment for the image guidance is included in the payment for the associated procedure. This means that Medicare reimbursement for radiation treatment delivery in the hospital (codes **77402-77412**) includes payment for all image guidance and motion tracking performed (code **77387**). The hospital continues to charge separately for image guidance and Medicare tracks this cost, but there is no separate payment for image guidance codes. In another example, the procedure code for a concurrent infusion (**96368**) is billed separately by the hospital, but is packaged by Medicare into other infusion services performed during the same encounter. The use of modifiers does not impact payment for packaged services. Applying any modifier, including **modifier 59** (distinct service), will not provide separate reimbursement for a packaged service.

Effective Jan. 1, 2014, Medicare packaged clinical laboratory charges into any other payable outpatient service performed on the same day for hospital billing. The following are exceptions to this packaging decision, but these exceptions would typically not apply to oncology patients:[7]

1. Non-patient referred specimen
2. A hospital collects a specimen and furnishes only the outpatient labs on a given date of service (a "specimen only" service)
3. A hospital conducts outpatient lab tests that are clinically unrelated to other hospital outpatient services furnished the same day. "Unrelated" means the laboratory test is ordered by a different practitioner than the practitioner who ordered the other hospital outpatient services, for a different diagnosis.

In other words, the hospital will only be paid separately for laboratory tests when it functions as an independent reference laboratory. Should this ever be the case, the hospital uses a special bill type for these non-patients to report that the patient is not present at the hospital.

Effective Jan. 1, 2015, CMS established comprehensive APCs (C-APCs) to provide all-inclusive payments for certain procedures. This policy packages payment for all items and services performed as part of the primary service into a single payment amount and includes stereotactic radiosurgery and intraoperative radiation treatment.

Going Forward

Review the Medicare bundling edits and National Correct Coding Initiative Policy Manual, in addition to non-governmental payer contracts and participation agreements. Also, when negotiating any type of payer agreement, make sure to obtain as much information about bundling edits as possible. Remember, once the contract is signed, the healthcare organization has generally agreed to the payer's bundling guidelines.

Services should never be unbundled, fragmented, or inappropriately unpackaged and billed to any insurer. Medicare considers this practice to be an abusive one that can easily cross the line to perceived fraudulent behavior. In addition, based on the bundling mechanism employed, the healthcare provider could actually lose reimbursement dollars. Remember, it is not only Medicare that can institute an audit—all commercial payers have a Special Investigations Unit or Department that monitors billing for unusual or aberrant behavior.

Bundling is allowable because in many instances it's the accurate means for coding an encounter. If there's one comprehensive major procedure code existing that encompasses two or more services that took place during the same encounter, it's only proper to use the more significant inclusive code. If the provider wants to track bundled services included in a single reimbursement, a "no-charge" code can be used for tracking purposes. And remember, the patient cannot be billed for unbundled or packaged services, even by non-participating Medicare providers. The National Correct Coding Policy Manual states:

CPT codes representing services denied based on NCCI PTP edits may not be billed to Medicare beneficiaries. Since these denials are based on incorrect coding rather than medical necessity, the provider cannot utilize an "Advanced Beneficiary Notice" (ABN) form to seek payment from a Medicare beneficiary. Furthermore, since the denials are based on incorrect coding rather than a legislated Medicare benefit exclusion, the provider cannot seek payment from the beneficiary with or without a "Notice of Exclusions from Medicare Benefits" (NEMB) form. OI

Cindy Parman, CPC, CPC-H, RCC, is a principal at Coding Strategies, Inc., in Powder Springs, Ga.

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The $0 Co-pay Programs are offered through the Eisai Assistance Program, which is designed to help facilitate access and reimbursement support for health care providers and patients. Additional benefits include reimbursement information, insurance verification, alternate coverage advising, and financial assistance programs. Eisai cannot guarantee coverage or eligibility for any benefits or programs.

To learn more about the $0 Co-Pay Programs and the Eisai Assistance Program

THE EISAI ASSISTANCE PROGRAM

- Call 1-866-61-EISAI (1-866-613-4724), 8 AM to 8 PM ET, Monday through Friday
- Visit www.EisaiReimbursement.com

***Maximum benefit:** The HALAVEN and LENVIMA $0 Co-Pay Programs each provide eligible patients up to $18,000 and $40,000 per year, respectively, to assist with the out-of-pocket costs for prescriptions. Depending on the insurance plan, your patient could have additional financial responsibility for any amounts over Eisai's maximum liability. Other terms and conditions apply.

tools

Approved Drugs

• Merck Sharp & Dohme Corp.'s (merck.com) **Keytruda® injection (pembrolizumab)** has been granted accelerated approval by the Food and Drug Administration (FDA) for the treatment of patients with recurrent or metastatic head and neck squamous cell carcinoma with disease progression on or after platinum containing chemotherapy.

Drugs in the News

• The FDA has granted fast track designation to Advaxis, Inc.'s (advaxis.com) lead immunotherapy candidate, **AXAL (axalimogene filolisbac)** for adjuvant therapy for high-risk locally advanced cervical cancer patients.

• Array BioPharma (arraybiopharma.com) has submitted a new drug application (NDA) to the FDA for **binimetinib** for patients with advanced *NRAS*-mutant melanoma.

• The FDA has cleared Bexion Pharmaceuticals, LLC's (bexionpharma.com) application to initiate a Phase I clinical trial with **BXQ-350**. This open-label trial will include adult patients with advanced solid tumors (including glioma, a type of brain cancer). The trial is designed to determine the maximum tolerated dose of BXQ-350 and to characterize its safety and pharmacokinetics.

• Calithera Biosciences, Inc. (calithera.com) announced that the FDA has accepted the company's investigational new drug (IND) application for **CB-1158** for the treatment of solid tumors. CB-1158 is an orally available small molecule inhibitor of the enzyme arginase.

• The FDA has granted breakthrough therapy designation to the immunotherapy drug **Darzalex® (daratumumab)** (Janssen Biotech, Inc., janssen.com) in combination with lenalidomide (an immunomodulatory agent) and dexamethasone, or bortezomib (a proteasome inhibitor [PI]) and dexamethasone, for the treatment of patients with multiple myeloma who have received at least one prior therapy. Janssen has also submitted a supplemental biologics license application (sBLA) for Darzalex to expand the current indication.

• The FDA has granted a fourth breakthrough therapy designation for Janssen Biotech's (janssen.com) **Imbruvica® (ibrutinib)** as monotherapy for the treatment of patients with chronic graft-versus-host-disease after failure of one or more lines of systemic therapy.

• Loxo Oncology, Inc. (loxooncology.com) announced that the FDA has granted breakthrough therapy designation to **LOXO-101**, a selective inhibitor of tropomyosin receptor kinase (TRK), for the treatment of unresectable or metastatic solid tumors with NTRK-fusion proteins in adult and pediatric patients who require systemic therapy and who have either progressed following prior treatment or who have no acceptable alternative treatments.

• The FDA has granted fast track designation to Merrimack Pharmaceuticals, Inc.'s (Merrimack.com) **MM-121 (seribantumab)** for development in patients with heregulin-positive, locally advanced or metastatic non-small cell lung cancer (NSCLC) whose disease has progressed following immunotherapy.

• Oncoceutics (oncoceutics.com) announced that it has been awarded an orphan grant from the FDA to evaluate its lead molecule, **ONC201**, a selective antagonist of DRD2 that belongs to the superfamily of G protein-coupled receptors, in a multiple myeloma clinical trial.

• The FDA has granted breakthrough therapy designation to Bristol-Myers Squibb Company's (bms.com) **Opdivo® (nivolumab)** for the potential indication of unresectable locally advanced or metastatic urothelial carcinoma that has progressed on or after a platinum-containing regimen.

• MEI Pharma, Inc. (meipharma.com) announced that the FDA has granted breakthrough therapy designation for the investigational drug **Pracinostat** in combination with azacitidine for the treatment of patients with newly diagnosed acute myeloid leukemia (AML) who are ≥75 years of age or unfit for intensive chemotherapy. In addition, agreement has been reached with the FDA on the company's proposed Phase III study design.

(continued on page 20)

With over

1.6M

new cancer cases expected this year,[1]

foundational treatments

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*The foregoing contains a forward-looking statement concerning the Company's projection of product launches by 2018. This forward-looking statement is made pursuant to the safe harbor provisions of the Private Securities Litigation Reform Act of 1995. Because this forward-looking statement inherently involves risks and uncertainties, actual future results may differ materially from those expressed or implied by such statement. The Company undertakes no obligation to update this forward-looking statement.

Reference: 1. American Cancer Society. *Cancer Facts & Figures 2016*. Atlanta, Georgia; American Cancer Society; 2016.

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(continued from page 18)

Approved Devices

• Ethicon (ethicon.com) announced that **HARMONIC® HD 1000i** has received 510(k) clearance from the FDA. The HARMONIC HD 1000i is a next generation ultrasonic surgical device designed to address unique challenges in complex open and laparoscopic procedures.

• The FDA has approved Concordia International Corp.'s (concordiarx.com) premarket approval application for its new **Photofrin® 630 PDT Laser.** Photodynamic therapy (PDT) with Photofrin is Concordia's light-based cancer treatment that combines a photosensitizing drug called Photofrin® (porfimer sodium) with a specific type of light administered by a laser to attack cancer cells.

• Accuray Incorporated (accuray.com) announced today it has received 510(k) clearance from the FDA for its **Radixact™ Treatment Delivery Platform**. Accuray also received 510(k) clearance for its new treatment planning and data management systems, Accuray **Precision™ Treatment Planning System** and **iDMS™ Data Management System**. The system features a more powerful linear accelerator, MVCT imaging, and helical treatment delivery, so clinicians can apply highly conformal and homogenous dose distributions to any target volume, while precisely sparing normal healthy tissue during each treatment fraction.

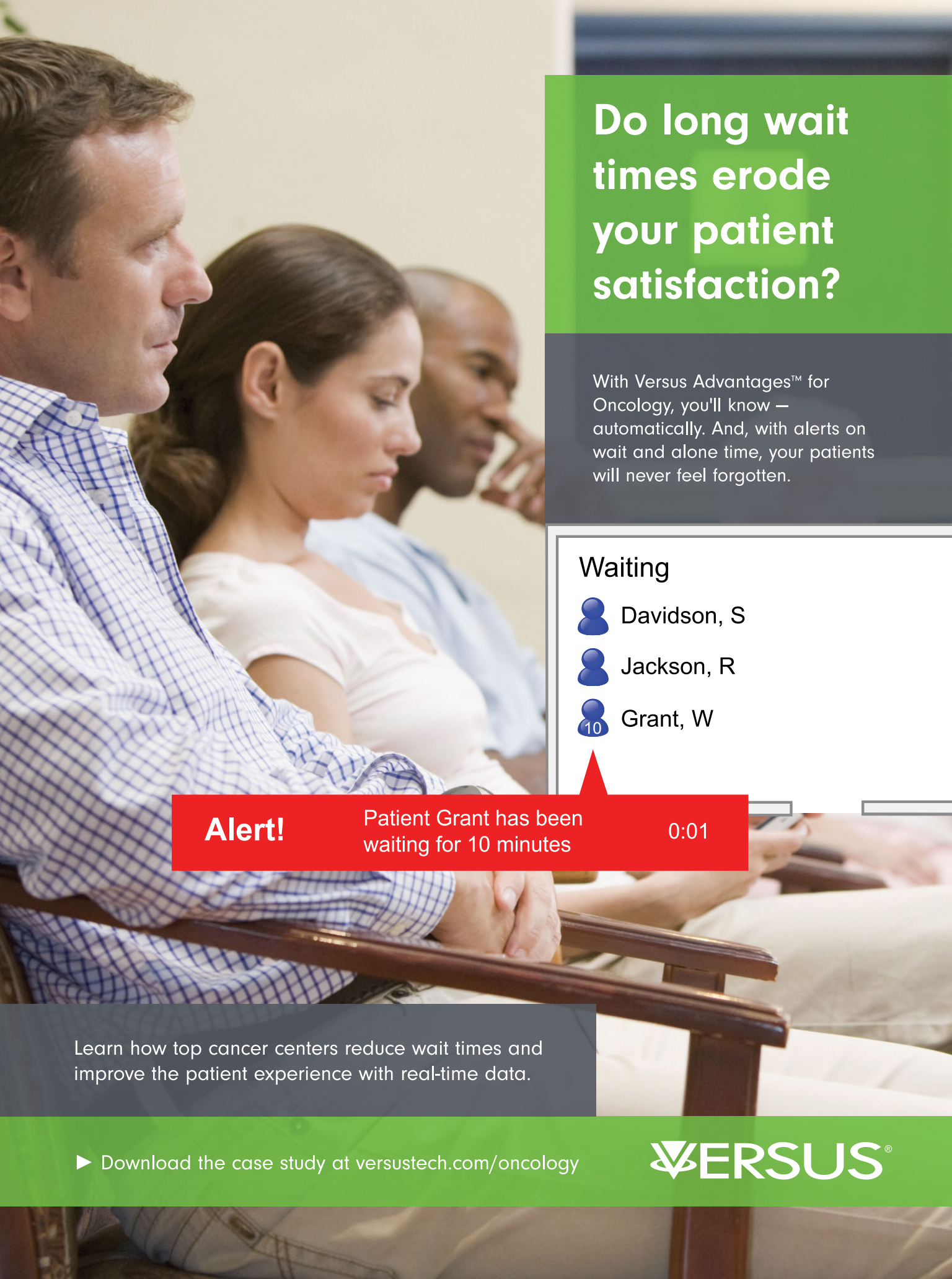
Genetic Tests & Assays in the News

• Roche (roche.com) announced that it has received FDA approval for performing the cobas® HPV Test from cervical specimens collected in **BD SurePath™ Preservative Fluid** using the **BD SurePath™ vial**.

• Asuragen, Inc. (asuragen.com) announced that it received premarket clearance from the FDA for the **QuantideX® qPCR BCR-ABL IS Kit** for the monitoring of molecular response in chronic myeloid leukemia (CML) patients. It is the first FDA-cleared diagnostic kit for use in CML management. OI

FDA Allows Enrollment of Patients to Metastatic NSCLC Phase I/II Trial

BeyondSpring Pharmaceuticals (beyondspringpharma.com) announced that on June 20, 2016, the FDA notified Dr. Lyudmila Bazhenova at the UC San Diego Moores Cancer Center that the Phase I/II study of Opdivo® (nivolumab) in combination with NPI-2358 (plinabulin) for patients with metastatic NSCLC may proceed with enrolling patients.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Waiting
Davidson, S
Jackson, R
10
Grant, W
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spotlight

Oncology San Antonio
San Antonio, Texas

Oncology San Antonio is a network of community-based cancer care practices treating patients from San Antonio, Texas, and outlying areas. With five practice locations (Medical Center and Live Oak led by Zulfi Jaffar, MD; Downtown and Stone Oak led by Jayasree Rao, MD; and Mission Trail led by Syed Raza, MD) spread throughout the San Antonio region, patients do not have to travel more than 10-15 miles to access one of the practices. According to medical oncologist Zulfi Jaffar, MD, this careful geographic dispersal of the Oncology San Antonio offices allows the group to have a large footprint in the community, while also being convenient for the patient population.

"A lot of times you'll see practices or offices that are set up to be convenient to the physician who works in the office. In our situation, we intentionally wanted to make sure that our clinics were located where patients needed them," said Dr. Jaffar.

Patient-Centered Care

In addition to reducing the travel burden for many patients, Oncology San Antonio also put a great deal of thought into the cancer patient experience. For example, during the construction of the Medical Center in 2004, stakeholders stressed patient comfort as an important factor in building design.

"When we moved into this building we had a lot of construction done to make it aesthetically pleasing, including oversized waiting areas with bright colors and lights, free Wi-Fi, complimentary snacks and drinks; features that could help ease the conditions and environment of our patient's treatment," said Dr. Jaffar.

The staff of Oncology San Antonio strives to provide a personal touch to patient care. All employees, including front desk receptionists, medical assistants, and nurses, are handpicked by the physicians.

"We strongly believe that if a person has cancer, they should be treated by a team that is most empathic with their condition. We do not want our patients to just feel like a number," said Dr. Jaffar. He continued, "each and every member of our staff make sure we take care of patients as if they were a member of our own family. We want to make sure our patients don't have to remember 10 things when they leave. We want to make it as easy an experience for them as possible."

State-of-the-Art Services

The Medical Center office, one of the locations where Dr. Jaffar practices, is one of the larger locations and includes Oncology San Antonio's business office. In addition to providing medical oncology services, the Breast Institute, a collaboration between Oncology San Antonio and the Aurora Breast Center, is also based in the same building. Comprehensive breast care is provided by a dedicated nurse practitioner, Dr. Jaffar as the medical oncologist, and radiation oncologist Jui-Lien "Lillian" Chou, MD. The Breast Institute offers the only dedicated breast MRI in San Antonio.

Oncology San Antonio also performs a high number of screenings for breast cancer, as well as genetic testing. The Medical Center practice location has had the highest number of patients undergo genetic testing in all of south Texas for some time. Test results are interpreted by providers who are qualified to review and counsel patients.

Medical oncology services are offered at all five practice locations and include infusion, chemotherapy, antibody therapy, immunotherapy, and iron transfusion. Radiation oncology services are offered at three of the five practice locations.

Staffing across all locations includes five medical oncologists, two radiation oncologists, seven nurse practitioners, and more than 100 support staff. Physicians participate in multidisciplinary tumor boards for breast cancer, head and neck cancer, and geriatric oncology.

Infusion services are provided at all locations—spacious areas with about 10 chairs plus additional seating for family members. A separate area for patients who have requested a bit more privacy includes semi-private bays as well as one completely private room.

Pharmacy technicians also work on-site, and Oncology San Antonio is currently working on plans to add an in-house pharmacy at the Live Oak office to dispense drugs with a full-time pharmacist joining the team. The in-house dispensing pharmacy should go live in early 2017.

As for cancer research and clinical trials, Oncology San Antonio has fostered a relationship with nearby MD Anderson Cancer Center. "At the community level, where we are, we believe our resources are best directed to helping the patients directly rather than spending those resources in building up a research program when we

(continued on page 24)

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(continued from page 22)
have access to one of the best research programs in the world," said Dr. Jaffar.

Oncology San Antonio maintains close relationships with MD Anderson physicians, so when treating a patient who can better benefit from a research protocol, it can refer the patient to MD Anderson for any investigational drugs. Dr. Jaffar estimates the practice sends about 10 percent of the patient population to MD Anderson for clinical trials. All of the required follow-up care after the trial, including any blood work or additional treatment, is performed by the care team at Oncology San Antonio.

Connecting with the Community

According to Dr. Jaffar, a large portion of Oncology San Antonio's patient population is elderly. Many of these patients are on Medicare and do not have secondary insurance, making drug costs a significant barrier to accessing treatment. "The cost of drugs is enormous. Take, for example, colon cancer, where the cost of one year of treatment is between $100,000 to $200,000 a year. Twenty percent of the total care cost is almost impossible for most people to afford," said Dr. Jaffar.

To help cancer patients with costs associated with treatment, Oncology San Antonio offers financial assistance support. Patient service representatives work on-site at each location to help patients receive the financial assistance they need. The representatives are in direct contact with many different community and national organizations, as well as pharmaceutical companies, to help patients pay for the treatments they require.

Financial assistance through the representatives also gives patients help with other basic needs, such as transportation to and from appointments (via the American Cancer Society Road to Recovery program) and utility bills. "Our patient service reps are extremely active and they have certain programs in the community that help with the elderly; and it's not just limited to their drugs, it's their entire lifestyle. Patients are very appreciative of those programs," said Dr. Jaffar. OI

Select Support Services

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- Genetic testing
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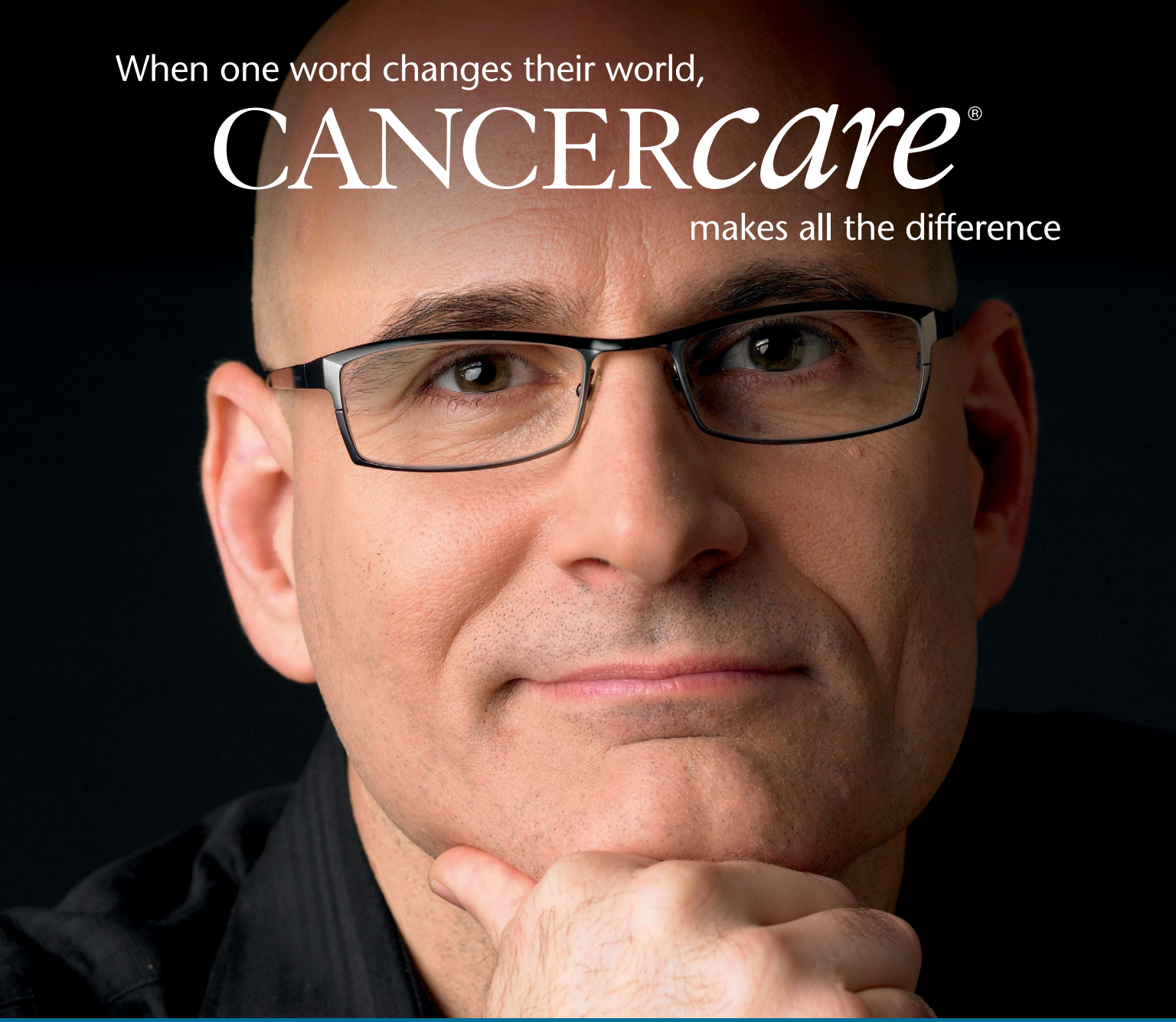

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TAGRISSO®(osimertinib): BREAK THROUGH THE T790M RESISTANCE BARRIER

in patients with metastatic EGFR T790M mutation-positive NSCLC, as detected by an FDA-approved test, at progression on or after EGFR TKI therapy

A targeted therapy researched in two clinical trials

- Effective in two separate global, Phase II, single-arm, open-label clinical trials in patients with metastatic EGFR T790M mutation-positive NSCLC who had progressed on or after EGFR TKI therapy[1]
  - A 59% objective response rate (95% CI: 54–64) in patients who progressed with previous EGFR TKI therapy
- In a separate dose-finding part of AURA, 63 patients with centrally confirmed EGFR T790M-positive NSCLC who progressed on prior systemic therapy, including an EGFR TKI, were administered TAGRISSO 80 mg[1]:
  - 51% (32/63) of patients in the 80-mg cohort had a confirmed response by BICR
  - The median DoR was 12.4 months
- Grade 3/4 adverse events occurred at <3.5%[1]
- <6% of patients in a pooled analysis (N=411) had either dose reductions or discontinuations due to adverse events[1]
- Interstitial Lung Disease (ILD)/Pneumonitis occurred in 3.3% and was fatal in 0.5% of 813 TAGRISSO patients. Withhold TAGRISSO and promptly investigate for ILD in any patient presenting with worsening of respiratory symptoms indicative of ILD (e.g., dyspnea, cough and fever). Permanently discontinue TAGRISSO if ILD is confirmed[1]
- The most common adverse events in a pooled analysis of TAGRISSO patients (N=411) were diarrhea (42%), rash (41%), dry skin (31%) and nail toxicity (25%)[1]

IMPORTANT SAFETY INFORMATION

- There are no contraindications for TAGRISSO
- Interstitial Lung Disease (ILD)/Pneumonitis occurred in 3.3% and was fatal in 0.5% of 813 TAGRISSO patients. Withhold TAGRISSO and promptly investigate for ILD in any patient presenting with worsening of respiratory symptoms indicative of ILD (e.g., dyspnea, cough and fever). Permanently discontinue TAGRISSO if ILD is confirmed
- QTc interval prolongation occurred in TAGRISSO patients. Of the 411 patients in two Phase II studies, 0.2% were found to have a QTc greater than 500 msec, and 2.7% had an increase from baseline QTc greater than 60 msec. Conduct periodic monitoring with ECGs and electrolytes in patients with congenital long QTc syndrome, congestive heart failure, electrolyte abnormalities, or those who are taking medications known to prolong the QTc interval. Permanently discontinue TAGRISSO in patients who develop QTc interval prolongation with signs/symptoms of life threatening arrhythmia

Visit **TAGRISSOhcp.com** for more information

IMPORTANT SAFETY INFORMATION (cont.)

- Cardiomyopathy occurred in 1.4% and was fatal in 0.2% of 813 TAGRISSO patients. Left Ventricular Ejection Fraction (LVEF) decline >10% and a drop to <50% occurred in 2.4% of (9/375) TAGRISSO patients. Assess LVEF before initiation and then at 3 month intervals of TAGRISSO treatment. Withhold TAGRISSO if ejection fraction decreases by 10% from pretreatment values and is less than 50%. For symptomatic congestive heart failure or persistent asymptomatic LV dysfunction that does not resolve within 4 weeks, permanently discontinue TAGRISSO
- Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during TAGRISSO treatment and for 6 weeks after the final dose. Advise males with female partners of reproductive potential to use effective contraception for 4 months after the final dose
- The most common adverse reactions (>20%) observed in TAGRISSO patients were diarrhea (42%), rash (41%), dry skin (31%) and nail toxicity (25%)

INDICATION

TAGRISSO is indicated for the treatment of patients with metastatic epidermal growth factor receptor (EGFR) T790M mutation-positive non-small cell lung cancer (NSCLC), as detected by an FDA-approved test, who have progressed on or after EGFR tyrosine kinase inhibitor therapy.

This indication is approved under accelerated approval based on tumor response rate and duration of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trials.

Please see Brief Summary of complete Prescribing Information.

Reference: 1. TAGRISSO [package insert]. Wilmington, DE: AstraZeneca Pharmaceuticals LP; 2015.

AstraZeneca

TAGRISSO®
osimertinib

TAGRISSO™ (osimertinib) tablet, for oral use

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

INDICATIONS AND USAGE

TAGRISSO is indicated for the treatment of patients with metastatic epidermal growth factor receptor (EGFR) T790M mutation-positive non-small cell lung cancer (NSCLC), as detected by an FDA-approved test, who have progressed on or after EGFR tyrosine kinase inhibitor (TKI) therapy.

This indication is approved under accelerated approval based on tumor response rate and duration of response *[see Clinical Studies (14) in the full Prescribing Information]*. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trials.

DOSAGE AND ADMINISTRATION

Patient Selection

Confirm the presence of a T790M EGFR mutation in tumor specimens prior to initiation of treatment with TAGRISSO *[see Indications and Usage (1) and Clinical Studies (14) in the full Prescribing Information]*. Information on FDA-approved tests for the detection of T790M mutations is available at http://www.fda.gov/companiondiagnostics.

Recommended Dosage Regimen

The recommended dose of TAGRISSO is 80 mg tablet once a day until disease progression or unacceptable toxicity. TAGRISSO can be taken with or without food.

If a dose of TAGRISSO is missed, do not make up the missed dose and take the next dose as scheduled.

Administration to Patients Who Have Difficulty Swallowing Solids

Disperse tablet in 4 tablespoons (approximately 50 mL) of non-carbonated water only. Stir until tablet is completely dispersed and swallow or administer through naso-gastric tube immediately. Do not crush, heat, or ultrasonicate during preparation. Rinse the container with 4 to 8 ounces of water and immediately drink or administer through the naso-gastric tube *[see Clinical Pharmacology (12.3) in the full Prescribing Information]*.

Dose Modification for Adverse Reactions

Table 1 Recommended Dose Modifications for TAGRISSO

Target Organ	Adverse Reaction[a]	Dose Modification
Pulmonary	Interstitial lung disease (ILD)/Pneumonitis	Permanently discontinue TAGRISSO.
Cardiac	QTc[†] interval greater than 500 msec on at least 2 separate ECGs[b]	Withhold TAGRISSO until QTc interval is less than 481 msec or recovery to baseline if baseline QTc is greater than or equal to 481 msec, then resume at 40 mg dose.
	QTc interval prolongation with signs/ symptoms of life threatening arrhythmia	Permanently discontinue TAGRISSO.
	Asymptomatic, absolute decrease in LVEF[c] of 10% from baseline and below 50%	Withhold TAGRISSO for up to 4 weeks. • If improved to baseline LVEF, resume. • If not improved to baseline, permanently discontinue.
	Symptomatic congestive heart failure	Permanently discontinue TAGRISSO.
Other	Grade 3 or higher adverse reaction	Withhold TAGRISSO for up to 3 weeks.
	If improvement to Grade 0-2 within 3 weeks	Resume at 80 mg or 40 mg daily.
	If no improvement within 3 weeks	Permanently discontinue TAGRISSO.

[a] Adverse reactions graded by the National Cancer Institute Common Terminology Criteria for Adverse Events version 4.0 (NCI CTCAE v4.0).
[b] ECGs = Electrocardiograms
[c] LVEF = Left Ventricular Ejection Fraction
[†] QTc = QT interval corrected for heart rate

CONTRAINDICATIONS

None.

WARNINGS AND PRECAUTIONS

Interstitial Lung Disease/Pneumonitis

Across clinical trials, interstitial lung disease (ILD)/pneumonitis occurred in 3.3% (n=27) of TAGRISSO treated patients (n=813); 0.5% (n=4) were fatal.

Withhold TAGRISSO and promptly investigate for ILD in any patient who presents with worsening of respiratory symptoms which may be indicative of ILD (e.g., dyspnea, cough and fever). Permanently discontinue TAGRISSO if ILD is confirmed *[see Dosage and Administration (2.4) and Adverse Reactions (6) in the full Prescribing Information]*.

QTc Interval Prolongation

The heart rate-corrected QT (QTc) interval prolongation occurs in patients treated with TAGRISSO. Of the 411 patients in Study 1 and Study 2, one patient (0.2%) was found to have a QTc greater than 500 msec, and 11 patients (2.7%) had an increase from baseline QTc greater than 60 msec *[see Clinical Pharmacology (12.2) in the full Prescribing Information]*.

In Study 1 and 2, patients with baseline QTc of 470 msec or greater were excluded. Conduct periodic monitoring with ECGs and electrolytes in patients with congenital long QTc syndrome, congestive heart failure, electrolyte abnormalities, or those who are taking medications known to prolong the QTc interval. Permanently discontinue TAGRISSO in patients who develop QTc interval prolongation with signs/symptoms of life threatening arrhythmia *[see Dosage and Administration (2.4) in the full Prescribing Information]*.

Cardiomyopathy

Across clinical trials, cardiomyopathy (defined as cardiac failure, pulmonary edema, ejection fraction decreased or stress cardiomyopathy) occurred in 1.4% (n=11) of TAGRISSO treated patients (n=813); 0.2% (n=2) were fatal.

In Study 1 and Study 2, Left Ventricular Ejection Fraction (LVEF) decline >10% and a drop to <50% occurred in 2.4% (9/375) of patients who had baseline and at least one follow up LVEF assessment. Assess LVEF by echocardiogram or multigated acquisition (MUGA) scan before initiation of TAGRISSO and then at 3 month intervals while on treatment. Withhold treatment with TAGRISSO if ejection fraction decreases by 10% from pretreatment values and is less than 50%. For symptomatic congestive heart failure or persistent, asymptomatic LV dysfunction that does not resolve within 4 weeks, permanently discontinue TAGRISSO *[see Dosage and Administration (2.4) in the full Prescribing Information]*.

Embryo-Fetal Toxicity

Based on data from animal studies and its mechanism of action, TAGRISSO can cause fetal harm when administered to a pregnant woman. In animal reproduction studies, osimertinib caused post-implantation fetal loss when administered during early development at a dose exposure 1.5 times the exposure at the recommended human dose. When males were treated prior to mating with untreated females, there was an increase in preimplantation embryonic loss at plasma exposures of approximately 0.5-times those observed in patients at the 80 mg dose level.

Advise pregnant women of the potential risk to a fetus.

Advise females of reproductive potential to use effective contraception during treatment with TAGRISSO and for 6 weeks after the final dose. Advise males with female partners of reproductive potential to use effective contraception for 4 months after the final dose *[see Use in Specific Populations (8.1), (8.3) and Clinical Pharmacology (12.3) in the full Prescribing Information]*.

ADVERSE REACTIONS

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

Interstitial Lung Disease/Pneumonitis *[see Warnings and Precautions (5.1) in the full Prescribing Information]*

QTc Interval Prolongation *[see Warnings and Precautions (5.2) 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 data described below reflect exposure to TAGRISSO (80 mg daily) in 411 patients with EGFR T790M mutation-positive non-small cell lung cancer who received prior EGFR TKI therapy, in two single arm studies, Study 1 and Study 2. Patients with a past medical history of ILD or radiation pneumonitis that required steroid treatment, serious arrhythmia or baseline QTc interval greater than 470 ms were excluded from Study 1 and Study 2. Baseline patient and disease characteristics were: median age 63 years, 13% of patients were ≥75 years old, female (68%), White (36%), Asian (60%), metastatic (96%), sites of brain metastases (39%), World Health Organization (WHO) performance status of 0 (37%) or 1 (63%), 1 prior line of therapy [EGFR-TKI treatment only, second line, chemotherapy-naïve (31%)], 2 or more prior lines of therapy (69%). Of the 411 patients, 333 patients were exposed to TAGRISSO for at least 6 months; 97 patients were exposed for at least 9 months; however no patient was exposed to TAGRISSO for 12 months.

In Studies 1 and 2, the most common (>20%) adverse reactions (all grades) observed in TAGRISSO-treated patients were diarrhea (42%), rash (41%), dry skin (31%), and nail toxicity (25%). Dose reductions occurred in 4.4% of patients treated with TAGRISSO. The most frequent adverse reactions that led to dose reductions or interruptions were: electrocardiogram QTc prolonged (2.2%) and neutropenia (1.9%). Serious adverse reactions reported in 2% or more patients were pneumonia and pulmonary embolus. There were 4 patients (1%) treated with TAGRISSO who developed fatal adverse reactions of ILD/pneumonitis. Other fatal adverse reactions occurring in more than 1 patient included pneumonia (4 patients) and CVA/cerebral hemorrhage (2 patients). Discontinuation of therapy due to adverse reactions occurred in 5.6% of patients treated with TAGRISSO. The most frequent adverse reactions that led to discontinuation were ILD/pneumonitis and cerebrovascular accidents/infarctions.

Tables 2 and 3 summarize the common adverse reactions and laboratory abnormalities observed in TAGRISSO-treated patients.

Table 2 Adverse Reactions (>10% for all NCI CTCAE* Grades or >2% for Grades 3-4) in Study 1 and Study 2

Adverse Reaction	TAGRISSO N=411	
	All Grades	Grade 3-4[f]
	%	%
Gastrointestinal disorders		
Diarrhea	42	1.0
Nausea	17	0.5
Decreased appetite	16	0.7
Constipation	15	0.2
Stomatitis	12	0
Skin disorders		
Rash[a]	41	0.5
Dry skin[b]	31	0
Nail toxicity[c]	25	0
Pruritus	14	0
Eye Disorders[d]	18	0.2
Respiratory		
Cough	14	0.2
General		
Fatigue	14	0.5
Musculoskeletal		
Back pain	13	0.7
Central Nervous System		
Headache	10	0.2
Infections		
Pneumonia	4	2.2
Vascular events		
Venous thromboembolism[e]	7	2.4

* NCI CTCAE v4.0.

[a] Includes cases reported within the clustered terms for rash adverse events: Rash, rash generalized, rash erythematous, rash macular, rash maculo-papular, rash papular, rash pustular, erythema, folliculitis, acne, dermatitis and acneform dermatitis.
[b] Includes dry skin, eczema, skin fissures, xerosis.
[c] Includes nail disorders, nail bed disorders, nail bed inflammation, nail bed tenderness, nail discoloration, nail disorder, nail dystrophy, nail infection, nail ridging, onychoclasis, onycholysis, onychomadesis, paronychia.
[d] Includes dry eye, vision blurred, keratitis, cataract, eye irritation, blepharitis, eye pain, lacrimation increased, vitreous floaters. Other ocular toxicities occurred in <1% of patients.
[e] Includes deep vein thrombosis, jugular venous thrombosis, and pulmonary embolism.
[f] No grade 4 events have been reported.

Additional clinically significant adverse reactions occurring in 2% or more of patients treated with TAGRISSO included cerebrovascular accident (2.7%).

Table 3 Common Laboratory Abnormalities (≥20% for all NCI CTCAE Grades) in Study 1 and Study 2

Laboratory Abnormality	TAGRISSO N=411	
	Change from Baseline All Grades (%)	Change from Baseline to Grade 3 or Grade 4 (%)[a]
Clinical Chemistry		
Hyponatremia	26	3.4
Hypermagnesemia	20	0.7
Hematologic		
Lymphopenia	63	3.3
Thrombocytopenia	54	1.2[a]
Anemia	44	0.2
Neutropenia	33	3.4

[a] The only grade 4 laboratory abnormality was 1 patient with grade 4 thrombocytopenia.

DRUG INTERACTIONS

Drug interaction studies with inhibitors, inducers or substrates of CYP enzymes and transporters have not been conducted with TAGRISSO.

Effect of Other Drugs on Osimertinib

Strong CYP3A Inhibitors

Avoid concomitant administration of TAGRISSO with strong CYP3A inhibitors, including macrolide antibiotics (e.g., telithromycin), antifungals (e.g., itraconazole), antivirals (e.g., ritonavir), nefazodone, as concomitant use of strong CYP3A inhibitors may increase osimertinib plasma concentrations. If no other alternative exists, monitor patients more closely for adverse reactions of TAGRISSO *[see Dosage and Administrations (2.4) and Clinical Pharmacology (12.3) in the full Prescribing Information]*.

Strong CYP3A Inducers

Avoid concomitant administration of TAGRISSO with strong CYP3A inducers (e.g., phenytoin, rifampicin, carbamazepine, St. John's Wort) as strong CYP3A inducers may decrease osimertinib plasma concentrations *[see Clinical Pharmacology (12.3) in the full Prescribing Information]*.

Effect of Osimertinib on Other Drugs

Avoid concomitant administration of TAGRISSO with drugs that are sensitive substrates of CYP3A, breast cancer resistance protein (BCRP), or CYP1A2 with narrow therapeutic indices, including but not limited to fentanyl, cyclosporine, quinidine, ergot alkaloids, phenytoin, carbamazepine, as osimertinib may increase or decrease plasma concentrations of these drugs *[see Clinical Pharmacology (12.3) in the full Prescribing Information]*.

USE IN SPECIFIC POPULATIONS

Pregnancy

Risk Summary

Based on data from animal studies and its mechanism of action, TAGRISSO can cause fetal harm when administered to a pregnant woman. There are no available data on TAGRISSO use in pregnant women. Administration of osimertinib to pregnant rats was associated with embryolethality and reduced fetal growth at plasma exposures 1.5 times the exposure at the recommended human dose *[see Data]*. Advise pregnant women of the potential risk to a fetus.

In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically-recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

Data

Animal Data

When administered to pregnant rats prior to embryonic implantation through the end of organogenesis (gestation days 2-20) at a dose of 20 mg/kg/day, which produced plasma exposures of approximately 1.5 times the clinical exposure, osimertinib caused post-implantation loss and early embryonic death. When administered to pregnant rats from implantation through the closure of the hard palate (gestation days 6 to 16) at doses of 1 mg/kg/day and above (0.1-times the AUC observed in patients at the recommended dose of 80 mg), an equivocal increase in the rate of fetal malformations and variations was observed in treated litters relative to those of concurrent controls. When administered to pregnant dams at doses of 30 mg/kg/day during organogenesis through lactation Day 6, osimertinib caused an increase in total litter loss and postnatal death. At a dose of 20 mg/kg/day, osimertinib administration during the same period resulted in increased postnatal death as well as a slight reduction in mean pup weight at birth that increased in magnitude between lactation days 4 and 6.

Lactation

Risk Summary

There are no data on the presence of osimertinib in human milk, the effects of osimertinib on the breastfed infant or on milk production. Administration to rats during gestation and early lactation was associated with adverse effects, including reduced growth rates and neonatal death *[see Use in Specific Populations (8.1) in the full Prescribing Information]*. Because of the potential for serious adverse reactions in breastfed infants from osimertinib, advise a lactating woman not to breastfeed during treatment with TAGRISSO and for 2 weeks after the final dose.

Females and Males of Reproductive Potential

Contraception

Females

Advise females of reproductive potential to use effective contraception during treatment with TAGRISSO and for 6 weeks after the final dose *[see Use in Specific Populations (8.1) in the full Prescribing Information]*.

Males

Advise male patients with female partners of reproductive potential to use effective contraception during and for 4 months following the final dose of TAGRISSO *[see Nonclinical Toxicology (13.1) in the full Prescribing Information]*.

Infertility

Based on animal studies, TAGRISSO may impair fertility in females and males of reproductive potential. It is not known if the effects on fertility are reversible *[see Nonclinical Toxicology (13.1) in the full Prescribing Information]*.

Pediatric Use

The safety and effectiveness of TAGRISSO in pediatric patients have not been established.

Geriatric Use

One hundred eighty-seven (45%) of the 411 patients in clinical trials of TAGRISSO were 65 years of age and older, and 54 patients (13%) were 75 years of age and older. No overall differences in effectiveness were observed based on age. Exploratory analysis suggest a higher incidence of Grade 3 and 4 adverse reactions (32% versus 25%) and more frequent dose modifications for adverse reactions (23% versus 17%) in patients 65 years or older as compared to those younger than 65 years.

Renal Impairment

No dedicated clinical studies have been conducted to evaluate the effect of renal impairment on the pharmacokinetics of osimertinib. Based on population pharmacokinetic analysis, no dose adjustment is recommended in patients with mild [creatinine clearance (CLcr) 60-89 mL/min] or moderate (CLcr 30-59 mL/min) renal impairment. There is no recommended dose of TAGRISSO for patients with severe renal impairment (CLcr <30 mL/min) or end-stage-renal disease *[see Clinical Pharmacology (12.3) in the full Prescribing Information]*.

Hepatic Impairment

No dedicated clinical studies have been conducted to evaluate the effect of hepatic impairment on the pharmacokinetics of osimertinib. Based on population pharmacokinetic (PK) analysis, no dose adjustment is recommended in patients with mild hepatic impairment [total bilirubin <upper limit of normal (ULN) and AST between 1 to 1.5 times ULN or total bilirubin between 1.0 to 1.5 times ULN and any AST]. There is no recommended dose for TAGRISSO for patients with moderate or severe hepatic impairment *[see Clinical Pharmacology (12.3) in the full Prescribing Information]*.

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Patient Information).

Interstitial Lung Disease/Pneumonitis

Inform patients of the risks of severe or fatal ILD, including pneumonitis. Advise patients to contact their healthcare provider immediately to report new or worsening respiratory symptoms *[see Warnings and Precautions (5.1) in the full Prescribing Information]*.

QTc Interval Prolongation

Inform patients of symptoms that may be indicative of significant QTc prolongation including dizziness, lightheadedness, and syncope. Advise patients to report these symptoms and to inform their physician about the use of any heart or blood pressure medications *[see Warnings and Precautions (5.2) in the full Prescribing Information]*.

Cardiomyopathy

- TAGRISSO can cause cardiomyopathy. Advise patients to immediately report any signs or symptoms of heart failure to their healthcare provider *[see Warnings and Precautions (5.3) in the full Prescribing Information]*.

Embryo-Fetal Toxicity

- TAGRISSO can cause fetal harm if taken during pregnancy. Advise pregnant women of the potential risk to a fetus.
- Advise females to inform their healthcare provider if they become pregnant or if pregnancy is suspected, while taking TAGRISSO *[see Warnings and Precautions (5.3) and Use in Specific Populations (8.1) in the full Prescribing Information]*.

Females and Males of Reproductive Potential

- Advise females of reproductive potential to use effective contraception during treatment with TAGRISSO and for 6 weeks after the final dose *[see Use in Specific Populations (8.3) in the full Prescribing Information]*.
- Advise males to use effective contraception during treatment and for 4 months after the final dose of TAGRISSO *[see Use in Specific Populations (8.3) in the full Prescribing Information]*.

Lactation

Advise women not to breastfeed during treatment with TAGRISSO and for 2 weeks after the final dose *[see Use in Specific Populations (8.2) in the full Prescribing Information]*.

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BY MARK WAGNER, PHARMD; JENNIFER EICHMEYER, MS, CGC;
PAUL G. MONTGOMERY, MD; JESSICA MONITZ, PHARMD;
JESSIE MODLIN, PHARMD; NATALIE PERRY, BA

Delivering Pharmacogenetic Testing in the Community Setting

The ability to individualize medication therapy for cancer patients has significantly advanced in recent years and continues to expand into new areas of practice. One of these areas is pharmacogenetic testing, which evaluates inherited genetic differences in drug metabolic pathways that can affect individual responses to drugs both in terms of therapeutic effect as well as adverse effects.[1] While more than 130 FDA-approved medications have references to pharmacogenetic testing in their package insert, until recently there has been little guidance on how to apply this information in the clinic setting.[2] The Clinical Pharmacogenetic Implementation Consortium (CPIC, cpicpgx.org) was established to provide clinical practice guidelines for meaningful prescribing decisions of specific drug/gene pairs. Since the development of the CPIC guidelines, there are currently specific dosing recommendations for 35 medications.[3] However, the majority of pharmacogenetic testing continues to be done in the academic setting—even with CPIC's supporting data, few community cancer programs are performing this form of personalized medicine.

In November 2014, St. Luke's Mountain States Tumor Institute (MSTI), Boise, Idaho, initiated a pilot program to determine the feasibility of a pharmacogenetic testing program in a community cancer program. Led by a multidisciplinary team of pharmacists, genetic counselors, and physicians, MSTI selected pharmacogenetic drug/gene pairs based on:

- Frequency of medication use
- CPIC recommendations for dosing changes
- Inclusion of genes in FDA medication labeling

For community cancer programs looking to implement or grow the use of pharmacogenetic testing, here are processes and lessons learned from MSTI's pilot pharmacogenetic testing program.

- Test cost
- Significant potential for toxicity in patients with particular genotypes.

This multidisciplinary team developed a service delivery model to facilitate the process of pharmacogenetic testing; data collection included physician acceptance to ordering tests, insurance coverage, test turn-around times, and test results.

Since the inception of the pilot program, approximately 50 percent of patients eligible to receive pharmacogenetic testing have had the test ordered, and this percentage continues to increase, with the average nearing 90 percent from February through April 2016. The current rate of DPYD (dihydropyrimidine dehydrogenase) pharmacogenetic testing insurance approval is approximately 66 percent, which has stayed fairly consistent since the beginning of the pilot. The majority of third-party payers are routinely covering DPYD and TPMT

St. Luke's Mountain States Tumor Institute, Boise, Idaho

(thiopurine s-methyltransferase) pharmacogenetic tests; however, several major payers still deny coverage. At MSTI, coverage remains a significant barrier for roughly one third of the patient population. On average, test results are received in 13.3 days for DPYD and 9 days for TPMT. Results are reported through April 2016; to date, one patient has been found to carry a variant associated with decreased DPYD activity.

For community cancer programs looking to implement or grow the use of pharmacogenetic testing, here are processes and lessons learned from MSTI's pilot pharmacogenetic testing program.

Why Test?

For cancer patients receiving chemotherapy, the development of severe toxicity as a result of genetic variations may lead to the interruption or discontinuation of potentially effective therapy, hospitalization, or fatal outcomes. One class of chemotherapy drugs, the fluoropyrimidines, are the standard of care in the treatment of colorectal cancer patients and are often associated with side effects such as diarrhea, mucositis, hand-foot syndrome, and myelosuppression. The unexpected toxicities experienced from the specific drugs in this class, 5-fluorouracil (5-FU) and capecitabine, are primarily associated with a deficiency of DPYD. This enzyme is responsible for breaking down approximately 85 percent of 5-FU to an inactive form that is eliminated from the body. However, pharmacogenetic variants of this enzyme in 3 to 5 percent of patients treated with fluoropyrimidines may lead to severe, potentially life-threatening toxicity. Published results from Adam M. Lee and colleagues, the largest study to date, demonstrate statistically significant associations between DPYD variants and the increased incidence of grade 3 or greater 5-FU adverse events.[4]

While some providers may wait to order DPYD testing until after a patient has experienced toxicity, treatment interruptions, discontinuation, or even hospitalization all significantly impact a patient's prognosis and quality of life (QOL). In addition to toxicity, a recent study from the Netherlands published in the *Journal of Clinical Oncology* demonstrated cost savings from performing upfront genotyping in patients receiving fluoropy-

Table 1. Pharmacogenetic Test Information

	DPYD [6]	TPMT [13,14]
MEDICATIONS	Fluorouracil, Capecitabine	Mercaptopurine, Thioguanine
HETEROZYGOUS VARIANT PREVALENCE	3% to 5%	3% to 14%
PHENOTYPE OF HETEROZYGOUS VARIANT	30% to 70% decreased enzyme activity	N/A
CPIC DOSING RECOMMENDATION	50% initial dose reduction	Mercaptopurine: start at 30% to 70% of the initial recommended dose
HOMOZYGOUS VARIANT PREVALENCE	0.2%	0.03 to 0.6%
PHENOTYPE OF HOMOZYGOUS VARIANT	100% decreased enzyme activity	N/A
CPIC DOSING RECOMMENDATION	Contraindicated	Start at 10% of the initial recommended dose
CPT CODE	81400	81401
COST OF TEST	approximately $210	approximately $507

rimidines.[5] The authors conclude by stating, "[prospective screening]…should therefore become standard of care in treatment with fluoropyrimidines."[5]

Multiple barriers hinder the adoption of pharmacogenetic tests into routine clinical practice, especially in the community setting, for example:

- The lack of knowledge and awareness by both patients and providers.
- The lack of a working process for performing tests in a preemptive fashion, disseminating test results, and incorporating test results into patients' medical records.
- The lack of insurance coverage.

CPIC is one of several organizations advocating for the advancement of pharmacogenetic testing.[6] CPIC's goal: to enable the translation of genetic laboratory tests into actionable prescribing decisions. CPIC conducts rigorous reviews of scientific literature when writing specific dosing recommendation guidelines. The peer-reviewed guidelines are published in the *Journal of Clinical Pharmacology and Therapeutics* with immediate online availability at PharmGKB (pharmgkb.org). The work of the consortium ultimately provides clinicians with updated pharmacogenetic testing information without the overwhelming burden of trying to gain the knowledge independently.

Utilizing CPIC recommendations, several large medical centers and academic institutions have developed their own processes for the routine ordering of pharmacogenetic tests.[7] James Hoffman, PharmD, at St. Jude's Children's Research Hospital has been a major proponent of implementing pharmacogenetic testing as a standard of care.[8,9,10] He and his colleagues have detailed their successful preemptive implementation in several publications. Their philosophy is that pharmacogenetic test results should be a part of the electronic health record (EHR) prior to drug prescribing.

Mills and Haga published an article in 2013 calling for a partnership between genetic counselors and pharmacists in the delivery of pharmacogenetic testing.[11] The authors highlight the important roles each profession contributes. Genetic counselors are well suited to provide patient education and post-test counseling, interpret pharmacogenetic variants for providers, and stay up to date on genome testing technologies. With an extensive knowledge of pharmaceuticals, pharmacists are able to make therapeutic recommendations to providers and conduct drug monitoring based on test results and other clinical factors. While this collaborative approach may seem ideal in theory, community cancer programs often lack the resources to develop infrastructure for a sustainable model.

In 2014 the American Society of Health-System Pharmacists (ASHP) released a statement on the pharmacist's role in clinical pharmacogenomics.[12] The society advocates for the profession of pharmacy to establish a leadership role in improving medication-related outcomes in the area of pharmacogenomics. ASHP asserts that this role should be shared with other hospital and health-system leaders, such as physicians, laboratory professionals, and genetic counselors. In addition, ASHP has endorsed the published CPIC guidelines in its efforts to promote safe, effective, and cost-efficient medication practices.

Genetic counselors are well suited to provide patient education and post-test counseling, interpret pharmacogenetic variants for providers, and stay up to date on genome testing technologies.

Below is a discussion of the model developed by MSTI, including its continued efforts to overcome barriers surrounding pharmacogenetic testing.

Pilot Program Methodology

St. Luke's MSTI gathered extensive background material to determine best practices for implementing a successful pharmacogenetic testing program. These preparatory activities included contacting academic institutions currently performing these services, selecting which agents and corresponding tests would be most practical for our institution, and setting up the overall process. Secondary objectives included determining to what extent insurance companies were covering pharmacogenetic testing, measuring test turn-around times from date of lab draw to receipt of test results, and application of the results.

Step 1. Selected Specific Pharmacogenetic Tests

MSTI determined the most advantageous tests for its patient population by analyzing a variety of factors, including:

- Specific dosing recommendations made by the CPIC guidelines
- The number of patients receiving the medications that would necessitate a test
- Significance of a mutation
- Incidence of genetic mutations for the test
- Cost and availability of the test from contract labs.

As discussed previously, the applicable tests identified were dihydropyrimidine dehydrogenase (DPYD), indicated for

(continued on page 35)

Figure 1. Electronic Dosing Recommendation Sheet Utilized to Disseminate Test Results to Providers

St Luke's Mountain States Tumor Institute

NAME:

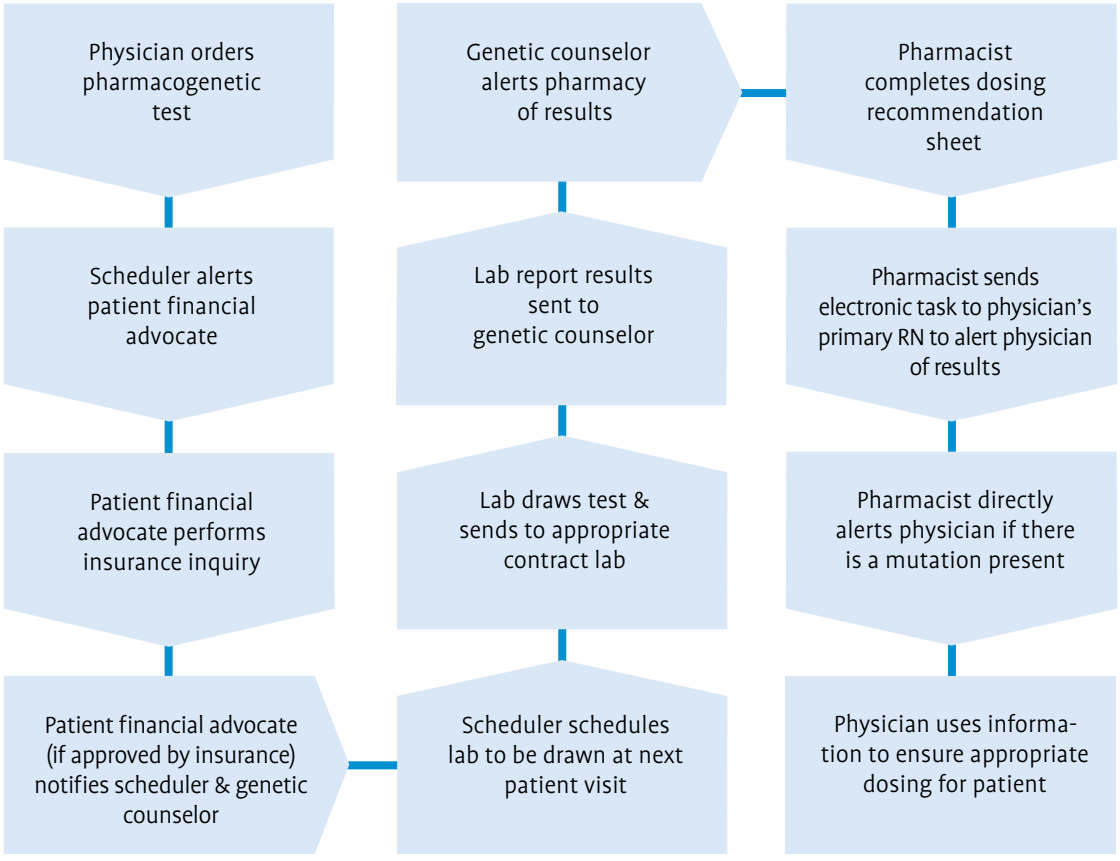
MEDICAL RECORD NUMBER:

DATE OF BIRTH:

DATE:

TEST	DRUG	RESULT	RECOMMENDATION
☐ DYPD	☐ Fluorouracil (5-FU)	☐ Homozygous Wild Type (No mutation detected)	☐ No dose adjustment
		☐ Heterozygous (One copy of the IVS14+1 G>A mutation)	☐ Start at 50% of the initial recommended dose; titrate dose based on toxicity
		☐ Homozygous Variant (Two copies of the IVS14+1 G>A mutation)	☐ CONTRAINDICATED; select alternative therapy
	☐ Capecitabine	☐ Homozygous Wild Type (No mutation detected)	☐ No dose adjustment
		☐ Heterozygous (One copy of the IVS14+1 G>A mutation)	☐ Start at 50% of the initial recommended dose; titrate dose based on toxicity
		☐ Homozygous Variant (Two copies of the IVS14+1 G>A mutation)	☐ CONTRAINDICATED; select alternative therapy
☐ TPMT	☐ Mercaptopurine (6-MP)	☐ Homozygous Wild Type (TPMT*1/TPMT*1)	☐ No dose adjustment
		☐ Heterozygous (TPMT*1/TPMT*2)	☐ Start at 30% to 70% of the initial recommended dose, allow 2 to 4 weeks to reach steady state, adjust dose based on degree of myelosuppression and disease specific guidelines
		☐ Homozygous Variant (TPMT*2/TPMT*2)	☐ Malignancy: start at 10% of the initial recommended dose and change frequency from daily to 3 days/week, allow 2 to 4 weeks to reach steady state after each dose adjustment ☐ Non-malignant condition: Consider alternative non-thiopurine immunosuppressant therapy
	☐ Thioguanine	☐ Homozygous Wild Type (TPMT*1/TPMT*1)	☐ No dose adjustment
		☐ Heterozygous (TPMT*1/TPMT*2)	☐ Start at 50% to 70% of the initial recommended dose, allow 2 to 4 weeks to reach steady state after each dose adjustment, adjust dose based on degree of myelosuppression and disease specific guidelines
		☐ Homozygous Variant (TPMT*2/TPMT*2)	☐ Start at 10% of the initial recommended dose and change frequency from daily to 3 days/week, allow 4 to 6 weeks to reach steady state after each dose adjustment, adjust dose based on degree of myelosuppression and disease-specific guidelines

Figure 2. St. Luke's Mountain States Tumor Institute's Process for Performing Pharmacogenetic Testing



(continued from page 33)

patients receiving 5-FU or capecitabine, which was comprised primarily of patients with gastrointestinal malignancies, and thiopurine methyltransferase (TPMT), indicated for patients receiving 6-mercaptopurine or thioguanine, which was comprised primarily of patients with acute lymphocytic leukemia. Genetic testing of DPYD or TPMT genes identify variants that decrease a patient's ability to metabolize the corresponding chemotherapy agents, resulting in potential increased toxicity. From analysis of the current literature, CPIC developed specific dosing guidelines that correspond with certain genetic variants to achieve appropriate therapeutic levels of each medication or to discontinue therapy. The specific testing information is summarized in Table 1, page 32.

Step 2. Determined Which Patients Should Be Tested

MSTI performed preemptive screening on all new patients, as well as current patients who were undergoing a chemotherapy regimen change. Physicians were alerted via e-mail, phone, and/or in the electronic health record.

Step 3. Established Processes & Educate Staff

In brief, here is how the process works. MSTI Pharmacy notifies the physician's primary registered nurse (RN) when patients are eligible for testing and then orders the recommended pharmacogenetic test. Once ordered, schedulers alert patient financial advocates to submit insurance prior authorization using CPT 81400 for DPYD and CPT 81401 for TPMT. If prior authorization is approved, patient financial advocates notify schedulers to add the pharmacogenetic test on the patient's next scheduled lab draw. Patient financial advocates also notify genetic counselors who track patients potentially receiving testing. Once pharmacogenetic tests are drawn and processed, they are sent out to the contracted lab: DPYD to Quest Diagnostics and TPMT to Prometheus Laboratories, Inc.

Test results are faxed directly to genetic counselors and emailed to pharmacists and scanned into the electronic health record. When results are received, pharmacists complete an electronic eScribe document in the medical record that includes:

- The test performed
- Corresponding medication(s)

Table 2. Number of Pharmacogenetic Tests Ordered on Eligible Patients
(Results from November 4, 2014 to April 1, 2016)

DRUG	# OF TESTS ORDERED	ELIGIBLE PATIENTS	PERCENT ORDERED
Fluorouracil	73	148	49.3%
Capecitabine	63	125	50.4%
Mercaptopurine	5	5	100%
Thioguanine	0	0	N/A
Total	141	278	50.7%

Table 3. Number of Pharmacogenetic Tests Ordered on Eligible Patients
(Results from February 1, 2016 to April 1, 2016)

DRUG	# OF TESTS ORDERED	ELIGIBLE PATIENTS	PERCENT ORDERED
Fluorouracil	14	17	82.4%
Capecitabine	13	14	92.9%
Mercaptopurine	1	1	100%
Thioguanine	0	0	N/A
Total	28	32	87.5%

- Test results
- Subsequent dosing recommendation from the CPIC guidelines (Figure 1, page 34).

An electronic message is sent to the physician's primary RN requesting that he or she print out the electronic document and deliver it to the physician. If the results show a variant, pharmacists call the physician directly to discuss the best therapy for the patient.

Once the pharmacogenetic testing process was established, MSTI provided education and training to all personnel that would be involved in this new process. A pharmacist provided training to schedulers, patient financial advocates, nursing, lab technicians, pharmacists, genetic counselors, and physicians through one-on-one and group meetings with oncologists, leadership, and staff. The training included MSTI's pharmacogenetic testing process—from ordering to result dissemination—which is summarized in Figure 2, page 35.

Pilot Program Results

From November 4, 2014, through April 1, 2016, 278 patients were eligible to receive pharmacogenetic testing at St. Luke's MSTI. Over the entire study period, the number of pharmacogenetic tests ordered compared to the number of patients who met eligibility for ordering was 50.7 percent (Table 2, above). However, over the last two months of the pilot program, the percentage of patients for whom testing was ordered essentially tripled, from 27 percent in the first seven months to 87.5 percent (Table 3, above).

Pharmacogenetic testing was approved by the majority of insurance companies covering our patient population. Approximately 66 percent of patients received insurance coverage for DPYD testing; 80 percent for TPMT testing. For almost all patients, Medicare has not required prior authorization for DPYD and TPMT pharmacogenetic testing. Insurance coverage without a prior authorization results in the best scenario—with minimal delay in time from when the test was ordered to when it is scheduled

(continued on page 38)

Table 4. DPYD & TPMT Pharmacogenetic Testing Insurance Coverage

INSURANCE COMPANY	DPYD	APPROVED	DENIED	TPMT	APPROVED	DENIED
AARP MEDICARE CMPLT HMO	7	7	0	-	-	-
AETNA	1	1	0	-	-	-
BLUE CROSS	22	8 (6 out-of-state)	14 (3 out-of-state)	-	-	-
BRIGHT PATH MOUNTAIN CO-OP	3	1	2	-	-	-
CIGNA	4	1	3	1	1	0
COUNTY	1	0	1	-	-	-
ODS PLUS NETWORK	1	0	1	-	-	-
HEALTH PARTNERS	1	1	0	-	-	-
IDAHO STATE CORRECTIONAL FACILITY	1	1	0	-	-	-
IPN	1	0	1	-	-	-
IPN STARMARK	1	1	0	-	-	-
KACI SMITH	1	1	0	-	-	-
MEDICAID	6	5	1	1	0	1
MEDICARE	36	35	1	1	1	0
MEDICARE ADVANTAGE	1	0	1	-	-	-
MODA	1	1	0	-	-	-
MODA MEDICARE ADVANTAGE	1	0	1	-	-	-
MOLINA	1	1	0	-	-	-
MOUNTAIN HEALTH CO-OP	1	1	0	-	-	-
PACIFIC SOURCE	5	3	2		-	-
REGENCE	9	4	3 (2 pending)	-	-	-
REGENCE MEDICARE ADVANTAGE	2	1	1	-	-	-
SELECT HEALTH	4	2	2	1	1	0
SELECT HEALTH MEDICARE ADVANTAGE	2	1	1	-	-	-
SELF-PAY	5	3 paid	2 opted out	-	-	-
SNAKE RIVER CORRECTIONAL FACILITY	1	1	0	-	-	-
TRICARE	5	1	4	-	-	-
TRUE BLUE	6	1	5	-	-	-
UNITED HEALTHCARE	6	6	0	-	-	-

TOTAL	APPROVED	DENIED	SELF-PAY
DYPD	85	44 (2 pending)	5 (3 paid, 2 opted out)
TMPT	4	1	0

Table 5. Pharmacogenetic Test Results

TEST	HOMOZYGOUS WILD TYPE	HETEROZYGOUS VARIANT	HOMOZYGOUS VARIANT
DPYD	77 (8 pending)	1	0
TPMT	5	0	0

(continued from page 36)
and drawn. The majority of commercial payers approved DPYD testing with little or no delay in time from ordering to approval. Table 4, page 37, summarizes insurance coverage by company.

St. Luke's MSTI measured the length of time from test drawn to results received from the contract lab. Turn-around time averaged 13.3 days and 9 days for DPYD and TPMT, respectively. Of the test results received (Table 5, above), one patient tested positive for a DPYD heterozygous variant; all other patients were negative for known variants. The patient with the DPYD variant was appropriately dose reduced, resulting in no significant side effects.

A Patient Case Study

Interestingly, a patient not previously tested for DPYD was transferred from an outside facility with severe capecitabine toxicity. After the patient's first cycle of treatment, the patient experienced severe myelosuppression, ultimately resulting in sepsis, hospital admission, and stays at two separate rehabilitation facilities prior to discharge. The patient then transferred care to St. Luke's MSTI.

Due to participation with this pilot program, the oncologist had greater awareness and knowledge of the impact of DPYD status on patient care, prompting the physician to order DPYD pharmacogenetic testing to determine if continued fluoropyrimidine therapy would be a viable treatment option.

The patient was found to have a heterozygous variant in the DPYD gene, indicating that the patient should have had a 50 percent dose reduction on initial treatment. If this patient had been tested prior to receiving treatment, extensive side effects, large healthcare costs, and months of hospital admissions could have been avoided. As the testing was ordered after treatment, this test result is not included in our prospective data.

Lessons Learned

The ability to perform DPYD and TPMT pharmacogenetic testing has brought St. Luke's MSTI a step forward in offering personalized medicine. The majority of St. Luke's MSTI clinics are utilizing the aforementioned pharmacogenetic testing process effectively. Expanding to outlying sites with less direct oversight created some additional challenges, but implementation was successfully achieved at all but one site. The process provides a self-sustaining program that can be applied to a variety of pharmacogenetic tests in different practice settings.

This study found 1 of 85 patients with a DPYD variant, which is similar to population prevalence. Other patients were likely missed primarily due to lack of access to pharmacogenetic testing as a result of insurance denial. However, it should be noted that current CPIC guidelines include only specific variants in DPYD, which account for approximately 50 percent of variants believed to cause decreased ability to metabolize capecitabine and fluorouracil. This implies that 50 percent of variants that increase the risk for adverse events may be missed without full sequencing of the DPYD gene. This hypothesis could explain at least one patient in our study population with no detected DPYD variants that experienced severe toxicity after receiving a first dose of fluorouracil.

At the start of this project, pharmacogenetic testing was done infrequently by a minority of physicians. Physicians questioned the clinical significance of performing this testing, which prompted MSTI to track physician ordering in an effort to measure compliance with recommendations. Through continued physician education, process improvement, and consistent patient identification, testing was readily adopted as a routine part of patient care with 88 percent of eligible patients having the DPYD test ordered. In addition, the expansion of supporting literature during this time has strengthened the evidence behind this testing.

The biggest challenge to pharmacogenetic testing in a community cancer program is the necessity for insurance coverage, which may not always be relevant in an academic setting. The majority of insurance companies are currently approving coverage; however, a few still claim that DPYD pharmacogenetic testing is experimental. Pharmacogenetic tests are considered a standard of care by several organizations and recommended in the FDA labeling of more than 130 medications. By increasing the number of requests for coverage of pharmacogenetics tests, payers may review and amend policies to follow national standards in the future. However,

the long duration of this approval and review process should be expedited as technology and knowledge are rapidly changing while patient care continues to be critically impacted.

Another barrier to this process is the delay in obtaining results once the tests are ordered. The hospital system does not perform either of these pharmacogenetic tests on site, thus requiring the use of contracted labs, which batch DPYD testing two days per week. If more tests were ordered on a regular basis, the contract lab would be able to offer the analysis more frequently. However, unlike academic centers that have on-site facilities and can report results in 24 to 48 hours, this time-frame is simply not possible for community cancer programs using a contracted lab. Further delays occur due to lack of a standardized way of ordering pharmacogenetic testing before the chemotherapy regimen is chosen and insurance coverage is verified. If the start of treatment is not delayed for results, the patient may not be prescribed the appropriate dose of chemotherapy based on their genotype.

Next Steps

Future plans are to continue to collect data and provide justification to insurance companies for coverage of these pharmacogenetic tests without a delay in therapy. Through the appeal process, one insurance company has already reversed its decision to deny insurance coverage for the DPYD pharmacogenetic testing. This change increases confidence that through continued conversations with payers, this pharmacogenetic testing program will impact coverage. In addition to collecting data, St. Luke's MSTI has initiated a subsequent project to determine if there are any differences in healthcare costs and/or additional services required for patients who receive chemotherapy in a community cancer program prior to knowing their DPYD mutation status.

While St Luke's MSTI has overcome multiple obstacles to allow patients to access pharmacogenetic testing that, until now, was only available at select academic institutions, there are still barriers to address to make this program an ideal model. The plan is to expand pharmacogenetic testing in the oncology setting, make the process more self-sufficient, and encourage pharmacogenetic testing in other disciplines throughout the St. Luke's Health System. The hope is that St. Luke's MSTI pharmacogenetic program will serve as an example to other community cancer centers of the feasibility of developing their own pharmacogenetic testing programs and help pave the way for greater application of personalized medicine. OI

Mark Wagner, PharmD, completed his PGY2 oncology pharmacy practice residency at St. Luke's MSTI in 2016 and is practicing as a clinical oncology pharmacist at the Cowell Family Cancer Center. Jessie Modlin, PharmD, is research pharmacist; Jennifer Eichmeyer, MS, CGC, is lead genetic counselor; and Jessica Monitz, PharmD, completed her PGY1 pharmacy practice residency at St. Luke's Medical Center. Paul Montgomery, MD, is the medical director of MSTI Research and one of three principal investigators of the newly formed Pacific Cancer Research Consortium that includes Providence Portland Medical Center, Swedish Cancer Institute; and Mountain States Tumor Institute. Natalie Perry is research project coordinator at MSTI.

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BY PAUL BARON, MD, FACS, AND
JOSH MONDSCHEIN, MD, MSCI

Beyond Breast Conservation

Oncoplastic surgery in the community setting

Today's cancer programs must be many things at once to their patients. They strive to be technologically up-to-date so their patients know they are receiving the safest, most precise procedures possible. While being sensitive to patients' personal needs, they must also draw on the most advanced thinking about diseases because our understanding of cancer is constantly evolving.

These factors are especially relevant to breast cancer patients, because the disease threatens not only a patient's future health but also body image, sense of well-being, and quality of life (QOL). Thus, for many patients, the challenge of treating breast cancer extends far beyond eradicating the disease and preventing a recurrence.

Central to our message: Cancer programs that do not currently have specialists who offer oncoplastic surgery to their breast cancer patients should consider learning more about these procedures and setting up a program to offer these services. To do so, cancer programs should also consider adopting new technologies to assist in the process.

> Oncoplastic surgery is now becoming a better-known option at a time when there is increased focus on patient-centered care and shared decision-making.

What Oncoplastic Surgery Offers

Oncoplastic surgery combines breast cancer surgery with plastic and reconstructive surgery techniques to make the cosmetic results of lumpectomy as pleasing and natural as possible. This surgery also encompasses nipple-sparing mastectomies with reconstruction, although this article focuses largely on surgeries involving lumpectomy.

Rather than a specific group of techniques, oncoplastic surgery is, in part, a mindset about breast conservation (see "Getting It Right," page 43) that emphasizes not just cancer control but also cosmetic outcomes.

Oncoplastic surgery aims to achieve state-of-the-art cancer control while leaving patients with aesthetically pleasing cosmetic results that often hide the fact that they have had cancer surgery. Put another way, the advances that have made oncoplastic surgery possible mean that for many patients, it's no longer necessary to sacrifice a satisfying cosmetic outcome to get optimal cancer control.

Offering oncoplastic surgery demonstrates a commitment to delivery of cutting-edge, high-quality care. It is the only approach to breast conservation that combines cancer control, optimal cosmetic outcomes, and patient satisfaction.

Oncoplastic surgery builds on the benefits of conventional breast conservation treatment in which a lumpectomy is usually followed by radiation therapy and, when indicated, chemotherapy.

This article discusses the main considerations for a cancer program in offering oncoplastic surgery. We also examine the challenges that oncoplastic surgery presents for the radiation oncologist. These challenges arise because the tissue rearrangement occurring with oncoplastic surgery requires new approaches to locating, defining, and precisely irradiating the correct area of the breast.

Patient Benefits

The efficacy of breast conservation treatment has now been demonstrated by multiple published long-term studies with at least 20-year follow-up results. The data show that this treatment matches mastectomy's overall survival rates[2,3] and in some scenarios has advantages over mastectomy.[4] But while breast conservation treatment has been shown to be equivalent to mastectomy in regards to cancer control, the cosmetic results for patients often fall short of the ideal, i.e., preservation of the appearance of a woman's breast as it looked prior to treatment. Lumpectomy surgery can often leave a patient with an indentation or divot in her breast. This occurs because cancerous tissue has been removed and the tissue deep in the breast has not been replaced or the area has been partially closed, without addressing gaps that might remain. Radiation therapy may then add to the cosmetic damage.[5] Research shows that roughly 30 percent of lumpectomies result in a deformity.[6]

Oncoplastic surgery is now becoming a better-known option at a time when there is increased focus on patient-centered care and shared decision-making. Today patients have greater access to information and education regarding breast cancer treatment options, along with quality of life considerations. Patients want their cancer cured, but they also want optimal cosmetic results following surgery. Oncoplastic surgery is the treatment option most in tune with a woman's desire to clear the breast cancer hurdle intact and enjoy a vital post-disease life.

Programmatic Benefits

In addition to the patient benefits cited above, by adding oncoplastic surgery services, community cancer programs can demonstrate that they are:

- ***Keeping up with the trend toward better cosmetic outcomes.*** The trend is toward greater incorporation of oncoplastic surgery. The last five years or so have seen consistent growth in the approach. Oncoplastic surgery is clearly on the path to becoming a mainstream breast cancer treatment alternative.[7]
- ***Responding to patient demands & interests.*** Breast cancer patients may be well aware of the cutting-edge treatment options that are available today. Today's patients are often well informed through peer-to-peer networking, online discussion forums, and by high quality, forward-looking articles and other materials shared via online groups and through their own research efforts. Because oncoplastic surgery meshes with the hopes and desires of so many women, it is a popular topic among patients participating in online discussion forums. So community cancer programs should not be surprised when patients ask about oncoplastic surgery options.
- ***Creating marketing & branding differentiators that are patient-centered.*** Offering oncoplastic surgery demonstrates a commitment to delivery of cutting-edge, high-quality care. It is the only approach to breast conservation that combines cancer control, optimal cosmetic outcomes, and patient satisfaction. Cancer programs that provide oncoplastic surgery are responding to breast cancer patients' full range of concerns, thus offering patient-centered care.
- ***Aligning with payer focus on value-based coordinated care.*** Consistent with the goals of the Affordable Care Act (ACA), the Centers for Medicare & Medicaid Services (CMS) continues to develop payment models that reward "value and care coordination" as opposed to "volume and care duplication." Oncoplastic surgery is aligned with this incentive structure, providing optimal clinical and cosmetic value through well-coordinated care, while minimizing the chance of multiple surgeries that have related clinical risks and increased costs.
- ***Providing an alternative option for patients inclined to undergo mastectomy.*** There is a large cohort of breast cancer patients who are inclined to choose mastectomy today even though breast conservation treatment is an option for them. This cohort encompasses women whose post-surgical radiation therapy will possibly compromise their cosmetic outcome. Also included are women who hope to minimize the chance of local cancer recurrence. (Breast conservation treatment does present a slightly greater risk of local recurrence even though overall survival rates are comparable to mastectomy.)[5] In addition, this group includes breast conservation treatment candidates who want to avoid post-surgical radiation or chemotherapy.

Oncoplastic surgery can provide a better cosmetic outcome for many of the women in all of these subgroups. That's because skin-sparing (and sometimes nipple/areola-sparing) techniques can be employed without raising clinical risk.

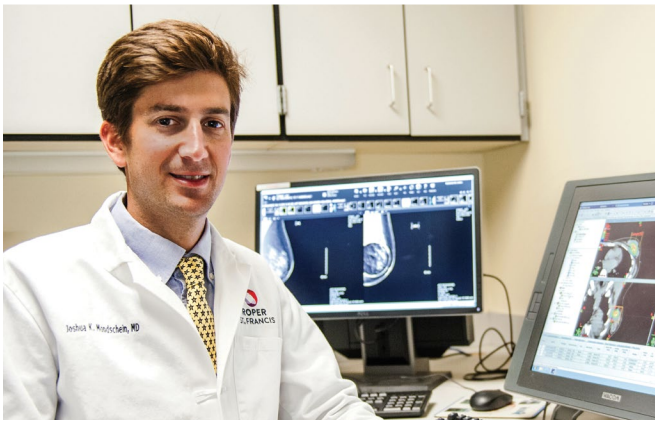
Some women may be considering mastectomy because they do not believe that the cosmetic outcomes of breast conservation treatment offer a good enough alternative. However, it's important to note that the cosmetic results of oncoplastic surgery improve upon standard breast conservation treatment. Indeed, a recent article in *The Breast Journal* reports that reconstruction of lumpectomy defects is often driven by women's concern about aesthetics and quality of life. The article further points out the need for training surgeons to expand the availability of oncoplastic surgery.[8]

Despite the logic that supports cancer programs offering oncoplastic surgery, the approach is not yet widely practiced by breast surgeons in the U.S. In part this is because oncoplastic surgery is not usually included as part of general surgeons' training or residency, although it is sometimes taught as part of a breast surgery fellowship. However, community cancer programs can take steps to develop a program offering oncoplastic surgery even if their breast surgeons are not currently proficient in the approach. Two possible pathways to offering oncoplastic surgery are:

1. A breast surgeon on the cancer program's staff can work in tandem with a plastic surgeon in the community or region, with the breast surgeon responsible for excising the tumor and the plastic surgeon performing the lumpectomy reconstruction.
2. A breast surgeon can receive training in oncoplastic surgery so that he or she can both excise the cancer and perform the lumpectomy reconstruction. It is important that the surgeon's instruction include hands-on training and not just lectures. Although there is no professional certification in oncoplastic surgery per se, it is taught in a number of forums across the country—from lectures to courses offered at some national conferences. For more on oncoplastic surgery training, see the box on page 44.

Getting It Right: Ideal Dimensions of a Community-Based Oncoplastic Surgery Program

Oncoplastic surgery came into existence because of the growing importance of treating the "whole patient" and understanding patients' needs beyond the solely clinical. Patients who request oncoplastic surgery are likely to be women who want a holistic approach to care such that their opinions, desires, and emotions are respected in planning and executing their treatment. These patients also want to feel good about themselves in their post-treatment life, and they need their physicians to share that priority.



Paul Baron, MD, FACS (top), and Josh Mondschein, MD, MSCI.

Thus, an oncoplastic surgery program should be designed to reflect this "whole patient" approach, which may be somewhat different than the design of an exclusively clinical program. The holistic mindset of an oncoplastic surgery program applies comprehensively to all phases of the treatment process, including how the program is organized.

Ideally, the various specialties involved in the patient's treatment—surgical oncology, radiology, plastic and reconstructive surgery, radiation oncology, and medical oncology—will function in a tightly integrated manner within the confines of the cancer program itself. But even if the oncoplastic surgery program pulls together various specialists affiliated with other entities in different locations or practice settings, it is important that each patient's case is comprehensively reviewed and discussed by all the specialists involved. This coordination can be accomplished via the tumor board or by detailed discussions between the breast surgeon and the other physicians involved in the care of the patient.

More on Oncoplastic Surgery Training

In our opinion, lectures alone are insufficient in training for oncoplastic surgery because the confidence it takes for surgeons to competently perform procedures that are new to them comes from practicing them first. Currently, only a few of the courses available in this country include cadaver labs, where that practice takes place. While cadaver tissue is not as pliable as living tissue, the cadaver labs do provide valuable hands-on experience.

Courses offered by the American Society of Breast Surgeons (breastsurgeons.org), the School of Oncoplastic Surgery (2016sos.com), and the American College of Surgeons (facs.org) are among those that incorporate cadaver labs. The American Society of Breast Surgeons and American College of Surgeons courses are offered at the organizations' annual meetings. The School of Oncoplastic Surgery was founded by Gail Lebovic, MD, one of the pioneers of oncoplastic surgery.

Courses are also available internationally, especially in Europe, where oncoplastic surgery is practiced more widely than in the U.S. and where development of oncoplastic surgery began. For example, the Royal College of Surgeons of England (rcseng.ac.uk) presents a course titled "Specialty Skills in Breast Surgery: Principles in Breast (Level 2)" that teaches oncoplastic and other reconstructive skills. The course includes a cadaver component. The Breast Surgeons of Australia and New Zealand organization (rcseng.ac.uk) offers level 1 and 2 courses in oncoplastic surgery, with the level 2 course including a cadaver workshop.

At the School of Oncoplastic Surgery's sculpture lab, surgeon participants learn about the aesthetics of the breast while working with real-life clay models.

This type of coordination is important in part because the cosmetic aspects of oncoplastic surgery are based on the patient's own wishes. However, before the patient can make her choices, she needs to understand all her options and their implications. The best way to facilitate this shared-decision making process is to have all the specialists work together as a team and communicating to the patient in a mutually agreed-upon manner. This team approach is also good for the cancer program itself as it aligns with the reimbursement trend towards value-based, coordinated care.

During the preoperative evaluation, the patient should be asked about her cosmetic goals for surgery—i.e., what shape and size she would like her breasts to be when treatment is complete—and the implications of those choices should be discussed in full.

Preoperative Evaluation & Surgical Planning

Although most of the clinical details of an oncoplastic surgery program are beyond the scope of this article, here are a few important points on preoperative evaluation and surgical planning for oncoplastic surgery.

During the preoperative evaluation, the patient should be asked about her cosmetic goals for surgery—i.e., what shape and size she would like her breasts to be when treatment is complete—and the implications of those choices should be discussed in full. For instance, the patient's goals may require bilateral surgery to achieve the intended outcome. If the specifics of the tumor permit, the breast cancer surgery can be performed in tandem with a breast reduction, augmentation, or lift—if that is the patient's wish.

Surgical planning encompasses the choices that are made after a surgical path (breast conservation treatment or mastectomy) is chosen and the other steps in the preoperative evaluation are completed: the examination of prior records, a comprehensive medical history, the physical exam, imaging, and so on. Every part of the plan needs to combine clinical and cosmetic considerations.

At this point of the process, it may be determined that a lift, reduction, or augmentation is recommended to achieve breast symmetry, even if this step was not initially on the patient's wish list.[9] Patients with severe ptosis of the breast—that is, sagging, normally as a consequence of aging—may benefit from a lift, or mastopexy, as part of their breast cancer treatment. Women with macromastia (abnormally large breasts) may wish to include a breast reduction in their treatment plan once they better understand the details of how this would be accomplished. Lifts and reductions can be done either at the same time as a lumpectomy or as a second surgery after there is pathologic confirmation that the lumpectomy achieved clear margins. If a mastopexy is done as a second-stage procedure, the initial lumpectomy incision will be planned in such a way that it is included in the subsequent mastopexy incision.

Many times, the patient will just want the cancer removed and not want to go through the additional time and effort needed to improve breast symmetry or size. Usually these are older

patients. However, before a patient makes this decision, it's important for the breast surgeon to make sure that she fully understands the options available.

Incision placement is an important aspect of surgical planning. Oncoplastic surgeons seek to avoid leaving an unsightly scar. Even when a mastopexy is not involved, it helps, when feasible, to "hide" the incision in a location where it will not be visible—for example, along the inframammary fold. This can be done even when the tumor is located in a more central area of the breast.

Oncoplastic surgeons also aim to avoid a deformity caused by retraction, asymmetry, or a divot in the breast. Put another way, the surgical plan must include steps that ensure the breast will not look significantly different from the contralateral one. Normally, breast tissue that is adjacent to the surgical cavity will be advanced and sutured to partly fill the space, with the surgeon making adjustments as needed during the procedure to prevent any subsequent retraction.

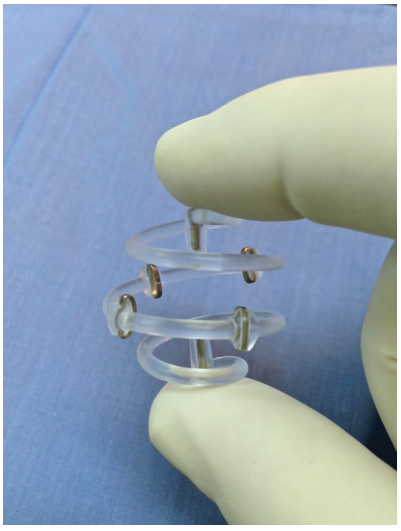
Given the personalized and complex decision-making processes taking place during the preoperative evaluation and surgical planning stages, the need for tight coordination and communication between all physicians is clear. Most of these decisions involve many factors that must be considered simultaneously and they must be communicated to the patient sensitively in language she understands so that she can participate in the decision-making process. Thus, oncoplastic surgery is not only a new paradigm of breast cancer treatment, it also encompasses a new model for cooperation between medical disciplines that accords with evolving requirements from CMS and other payers.

Oncoplastic Surgery & Post-Surgical Radiation Treatment

Oncoplastic surgery has downstream implications for the radiation oncologist because unlike the manner in which traditional breast conservation treatment is performed—where the tumor is simply removed and the surgical opening closed—oncoplastic surgery involves extensive tissue relocation and/or rearrangement. This makes it more challenging for the treatment planners and radiation oncologist to identify where the tumor was located and the area to be treated.

However, these challenges should be viewed in context. Precisely identifying the location of the tumor site can be problematic even with a traditional lumpectomy, i.e., without the tissue location factors of oncoplastic surgery. This is because the conventional marking methods, e.g., titanium clips and seroma, are notoriously unreliable, as is documented in the literature.[10-12] The clips can migrate and are merely marking the perimeter of the lumpectomy cavity; the tumor may have occupied an eccentric location in the space. Similarly, the seroma may only loosely correspond with the tumor-site location. As a result, treatment planners may inadvertently overestimate the treatment volume, resulting in excess radiation dosing of the patient.

Ideally, of course, the radiation oncology team wants to treat no more tissue than is necessary, to minimize the overall dose for the patient, and to avoid, if possible, irradiating adjacent healthy tissues and structures, such as the heart, skin, and lungs. At our cancer program, we've found it helpful to use a new technology in conjunction with oncoplastic surgery—a small surgical implant (BioZorb, Focal Therapeutics/Aliso Viejo, Calif.), which is a marker that is sutured directly to the tumor site. This technology precisely delineates the tumor site, no matter how much tissue has been moved or removed, eliminating the issues created by tissue relocation and/or rearrangement.



3D BioZorb device with titanium clips.

The marker, which comes in multiple sizes and configurations to conform to breast size and/or clinical circumstances, has an open framework structure with six titanium clips in a fixed array. The framework is made of a bioabsorbable material that is slowly resorbed by the body over time—generally 12 to 18 months. The clips, which remain after the framework is resorbed, identify the tumor site in three dimensions.

Thus, the site can be clearly seen by radiation treatment planners for precise radiation treatment. The marker is also useful for contour radiation dosing, as well as more precise targeting of boost radiation. The implant's three-dimensional array of clips identifies the site for long-term follow-up imaging, too. Because the device is sutured to the site and the clips create a 3D image, there is little question about the precise location of the site, long after implantation of the device.

In our program, the BioZorb device has enhanced our surgical planning for oncoplastic surgery. Without the device, the radiation oncology team might be misled by the seroma created by the surgical tract and choose to irradiate a large area that includes the surgical tract, just to be on the safe side. The device eliminates that kind of overestimation because it is sutured to the tumor site. No matter where the surgical tract begins and ends, the radiation oncologist knows where to target the dose. This creates multiple cosmetic advantages, from incision location to more precise treatment.

The device also has another advantage for both breast conservation treatment and oncoplastic surgery. The framework fills up much of the space left behind by the tumor removal, so there is less chance of the divot that often occurs with ordinary lumpectomies. Eliminating the divot not only improves the cosmesis of the breast that was operated on but

also improves post-surgical breast symmetry. The device provides a scaffolding for the ingrowth of new tissue, as well. This helps account for the excellent cosmetic outcomes that have been reported by multiple users since the device was first introduced in 2012 and that we've seen with our patients at the Roper St. Francis Cancer Center. In many cases, the cosmetic result is so significant, that the mammography techs cannot find the locations of our incisions at the time of subsequent mammograms.

Finally, there are early indications that because it allows more precise radiation, the device may enable radiation oncologists to employ a shorter course of radiation than usual with early breast cancer patients, reducing the normal six-week course to four weeks or less.[13,14] This shorter Canadian radiation protocol could open the way for more women to choose breast conservation treatment and oncoplastic surgery, because the pragmatic difficulties of arranging work and home schedules around a six-week radiation course can discourage some women from choosing breast conservation.

Final Considerations

There are multiple reasons why community cancer programs should consider adding specialists who are familiar with onco-

Oncoplastic Surgery: A Patient's Story

When J.H. was diagnosed with breast cancer in May 2015, her mind raced with fear—and a sense of inevitability. Her mother had died of late-stage breast cancer in 1999 at age 68, shortly after being diagnosed. The feeling that J.H.'s family history had caught up with her was reinforced a week later when her older sister was also found to have breast cancer. (J.H. and both of her sisters had previously taken the BRCA test, and the results were negative for all three women.)

Ever since her mother's diagnosis, J.H. had diligently undergone annual mammograms. Because of that diligence J.H.'s cancer was detected at an early stage and that turned out to make a big difference in her treatment options. J.H., who is married with two grown children, lives in Mount Pleasant, S.C., near Charleston. Her breast surgeon and radiation oncologist for her treatment were the Charleston-based authors of this article, Paul Baron, MD, FACS, and Josh Mondschein, MD. Dr. Baron told J.H. that her prognosis was favorable because she had stage 1 disease and it was growing slowly. She briefly considered getting a mastectomy but after further discussion with Dr. Baron, decided to have oncoplastic surgery instead.

Dr. Baron performed J.H.'s cancer excision. During the surgery, he sutured a 3D bioabsorbable marker (discussed on page 45) to the tumor site. The marker was placed to serve several purposes. On the surgical side, it supported the cosmetic goals of the oncoplastic approach by filling the space left by the lumpectomy and providing a scaffolding for tissue ingrowth. The marker placement also made it possible for Dr. Mondschein to target the post-surgical radiation treatments more accurately because the tumor site was marked clearly in three dimensions. J.H. was able to receive a short, four-week course of radiation therapy because her tumor was low-risk and met specific criteria outlined by the American Society for Radiation Oncology (ASTRO).

J.H. was pleased and surprised at how quick and efficient her radiation treatment was. She felt good throughout the process, so she was able to keep up her exercise regimens of walking, biking, and swimming. She also felt energetic enough to continue her work as an office manager for a private school, which she fit in around the treatment schedule. The fact that her treatment had so little impact on her daily life helped her stay optimistic about the eventual outcome. She called the treatment "a piece of cake."

J.H. is confident that the decision to have oncoplastic surgery and radiation treatment instead of a mastectomy was the right one. She's also pleased that using the 3D marker improved the radiation treatment planning and targeting, which protected her healthy tissue from radiation exposure. She has no visible scar, wears the same size bra as before her diagnosis, and can't see or feel the marker. She says, "If you didn't know I'd had breast cancer, you wouldn't be able to tell."

plastic surgery to their breast cancer services if they haven't already done so. Those reasons start with the fact that no cancer program can remain competitive unless it offers state-of-the-art treatment of the highest quality. With respect to breast cancer, that means offering oncoplastic surgery, which provides improved cosmetic outcomes without comprising cancer control. That said, cancer programs should understand all that is implied by the term oncoplastic surgery. It is a mindset about breast cancer surgery in addition to a method and technique. To provide oncoplastic surgery is to consider the cosmetic outcome at every stage of the treatment process, starting with the preoperative evaluation and surgical planning and continuing through the post-operative radiation treatment. Every one of these stages can affect the eventual cosmetic results so the oncoplastic surgery mindset must guide every decision made throughout the chain of events that comprise the total treatment process. The holistic, comprehensive nature of oncoplastic surgery should be reflected in the way the oncoplastic surgery program is organized, as well. The end goal of treatment is determined by the patient's desires as she expresses them to her doctors. So the cancer program must foster excellent communication between the patient and all the medical specialists involved, as well as between the specialists themselves.

As mentioned above, oncoplastic surgery programs vary in how the actual surgery is accomplished. A breast surgeon can work in tandem with a plastic surgeon to achieve the optimal results. Alternatively, a breast surgeon can receive advanced training in oncoplastic surgery and perform both the excision and the reconstruction. The first configuration is an excellent way for a cancer program to begin its oncoplastic surgery program. As the program develops, the breast surgeon may then want to train in oncoplastic surgery and eliminate the need for a plastic surgeon to be involved in many of the surgical cases. As an example, the co-author of this article, Dr. Paul Baron, performs most of the oncoplastic surgery on his patients. However, he works in tandem with a plastic surgeon in those cases undergoing mastopexies (breast lifts) and reductions following breast conservation treatment, and reconstructions following skin or nipple-sparing mastectomies.

While oncoplastic surgery has the reputation in some quarters of making post-operative radiation treatment planning challenging, we have found that use of new technology (the innovative 3D marker described above), overcomes the imprecision issue with both breast conservation treatment and oncoplastic surgery, while also providing other advantages that may improve cosmetic outcomes. Accordingly, we suggest that this technology be considered in conjunction with an oncoplastic surgery program and for patients receiving breast conservation treatment. OI

Paul Baron, MD, FACS, is a board certified general surgeon for Roper St. Francis Physician Partners in Charleston, S.C. who completed a Fellowship in Surgical Oncology at Memorial Sloan Kettering Cancer Center, and is a clinical associate professor of Surgery at the Medical University of South Carolina. He is a Fellow of the American College of Surgeons and the Society of Surgical Oncology and an active member of the American Society of Breast Surgeons. Josh Mondschein, MD, MSCI, is a board certified radiation oncologist at Roper St. Francis Healthcare in Charleston, S.C. who completed a residency in Radiation Oncology at Vanderbilt University, and is a clinical assistant professor of Radiation Oncology at the Medical University of South Carolina.

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Implementation of a Health Disparities & Equity Program at the Duke Cancer Institute

BY NADINE J. BARRETT, PHD, MA, MS; TRACEY VANN HAWKINS, MA; JULIUS WILDER, MD, PHD; KEARSTON L. INGRAHAM, MPH; REBECCA REYES, MA; MARITZA CHIRINOS, MD; PATRICIA WIGFALL, PHD; WILLIAM ROBINSON; AND STEVEN R. PATIERNO, PHD

Health disparities in cancer are a national problem with local implications, requiring a deep and clear understanding of community needs while implementing and leveraging programs and partnerships that can address disparities long term.[1-3] Given the changing landscape of the healthcare industry—coupled with the growing diversity of our patient and community populations—the need for strategic and integrated priority setting, collaborations, and partnerships is paramount.[4] Across the cancer spectrum significant disparities exist where negative outcomes disproportionately impact underserved communities, including race and ethnic minorities, the poor, the uninsured and underinsured, and low resource communities in both rural and urban settings.[5]

The Issue in Brief

Traditionally the underserved have worse cancer outcomes, where minorities are more likely to die from most cancers compared to their white counterparts regardless of incidence.[1-5] For example, in the case of prostate cancer, men of African American descent exhibit a 1.6-fold higher incidence of the disease and a 2.4-fold higher mortality rate.[5] Moreover, while participation in cancer research and clinical trials is lagging at 9 percent of those eligible to participate, minorities participate at even lower rates, ranging from 2 percent to 5 percent nationally.[7,8] Racial and ethnic minorities, the poor, and those who live in rural or low resourced communities are less likely to be involved in clinical research due to numerous factors, including distance, fear, cost, and simply not being asked to participate.[9]

Contributors to poor cancer outcomes and lack of participation in research are multifaceted and reflect community and health system wide challenges. Significant contributors to poor cancer outcomes in minority populations include:[9-11]

- Lack of access to cancer screenings or treatment
- Lack of transportation
- Costs and/or insurance barriers
- Fear
- Distrust of the medical establishment
- Language barriers
- Delayed timeliness to diagnosis and treatment
- Lack of effective provider and patient communication.

A myriad of psychosocial, healthcare system, community, and individual factors all contribute to cancer disparities, requiring a localized, multipronged approach to identifying and addressing the issue.[3]

Barriers that prohibit access and utilization of cancer services vary by community, so providers must first understand local needs to be able to develop effective strategies to overcome these barriers.[12]

An Opportunity to Collaborate

Today's cancer programs are required to both identify and address key needs in their community and patient population through the community assessment process. Community assessments create an opportunity for cancer programs to engage in authentic partnerships between medical and academic entities, grassroots community stakeholders, and community-based health organizations. At a time when expectations are increasing for academic and medical research institutions to partner with community cancer programs to conduct meaningful and useful community assessments; engage the community; improve patient care; and increase research participation, the development of integrated and strategic programming, offices, or departments to address health disparities is critical and timely. A myriad of psychosocial, healthcare system, community, and individual factors all contribute to cancer disparities, requiring a localized, multipronged approach to identifying and addressing the issue.[3]

Addressing health disparities across the entire cancer care spectrum is of paramount importance, particularly within the context of community and population health improvement.[3] Cancer programs have a unique opportunity to positively and significantly impact the health of target populations by leveraging a range of community resources and partnerships to address community health needs and the broader social determinants of

health. Salient to these efforts are both understanding the needs in a given population and aligning the priorities of partner organizations to build capacity through strategic collaborations designed to address cancer disparities and improve population health.[3,11] Although improving population health is fundamentally the right thing to do for any community, health systems also benefit through shared resources across multiple sectors converging to impact the community and population health with nominal costs. Community partnerships across rural and urban areas are needed to address all facets of cancer disparities in the context of cancer screening, diagnosis, care, treatment, access to care, and utilization of services. Obtaining, maintaining, and sustaining these relationships are a key linchpin to improving population health, and cancer programs are particularly well positioned to engage and lead these efforts.[3]

Accrediting entities and funding agencies are increasingly implementing policies reflecting heightened accountability around community engagement, community health assessments, research participation, and health disparities and equity. Among many accountability measures, cancer programs are expected to:

- Identify, assess, and respond to community and patient needs.
- Increase participation and retention in research and clinical trials, particularly for underserved populations.
- Ensure patients do not fall through the gaps in care.

According to a 2010 American Hospital Association survey, only 7 percent of hospitals actually use their community assessments to develop programs or interventions to address identified needs and priorities.[12] For Duke Health, the creation of a coordinated effort to engage the community and patients in outreach, delivery of healthcare, and research has been a longstanding priority, and in 2012 the newly re-organized Duke Cancer Institute launched the Office of Health Equity and Disparities (OHED). Next, Duke Cancer Institute hired a director to lead OHED and develop a cancer health disparities and equity agenda that fully engaged both the local community and the Duke University Health System.

In this article, we share the experience of the Duke Cancer Institute initiative to expand its capacity to engage the community and the health system towards achieving improved population and patient health outcomes. This initiative includes development and implementation of a coordinated and comprehensive strategy to address local health disparities through our comprehensive community assessment process. We provide examples and practical models to help other cancer programs:

- Meet multiple organizational expectations
- Leverage community health assessments to address needs and gaps in healthcare delivery
- Engage in community outreach and cancer screening activities
- Increase participation in clinical research.

The capacity to address disparities varies from one cancer program to another, so we provide adaptable and strategic examples that can be implemented in either community or comprehensive cancer centers based on capacity and the resources available.

Program Development: Background & Need

In 2010 Duke Medical Center, Durham, N.C., reorganized its extensive cancer programs, launching a restructured Duke Cancer Institute as the integrating umbrella for cancer clinical care, research, education, and outreach. New senior leadership was appointed in 2011-12 and the Office of Health Equity and Disparities became a part of Duke Cancer Institute's new long-term vision. Several factors triggered the identification of health disparities as a key strategic priority under this new vision. Under its new leadership, Duke Cancer Institute embarked on a new model of research and patient care: a coordinated effort to engage with our local community in outreach, education, and screening efforts, and with our patients in the provision of both personalized cancer treatment and supportive care, while working to increase diverse participation in clinical research. Duke Cancer Institute also sought heightened attention and increased accountability around:

- The use of community assessments to understand and effectively respond to community and patient needs.
- Increased minority accrual and retention in research and clinical trials.
- Engagement of our patients and the community in health disparities research.
- Increased focus on diverse representation and work culture among staff and faculty in medical settings.

> Cancer programs can develop and leverage relationships with local residents and patients to provide insight and support when developing and implementing programs and engaging in research...[3,11]

Through collaborative community partnerships and based on recommendations from community organizations and leaders, researchers, clinicians, caregivers, and patients, the OHED built a dynamic integrated platform and infrastructure to facilitate programs and research. As a result, the cancer program has developed a co-created community and academic health disparities strategic plan that highlights a health system/academic and community partnered platform to serve the community, patients, and clinicians through programs and research.

Five-Step Strategic Process

Cancer programs can develop and leverage relationships with local residents and patients to provide insight and support when developing and implementing programs and engaging in research, including clinical trials.[3,11] Moreover, with collaboration from the onset, programs intended to increase screening; ensure access and utilization of services by traditionally under-represented groups; and increase and diversify clinical trial participation are more likely to be implemented and sustained.[9,10] The following five steps describe Duke Cancer Institute's strategic process to leverage our existing local and statewide resources and partnerships to:

- Improve the breadth, scope, and utility of our community assessment process.
- Develop and implement a health equity agenda to address community and patient needs through the OHED.
- Raise the bar in meeting our internal and external reporting and accreditation guidelines to address health disparities.

Step 1. Create an Engaged & Diverse Community Advisory Council

To ensure community and patient perspectives are incorporated in Duke Cancer Institute's research, programs, and services, in 2012 the OHED established a Community Advisory Council, engaging community partners, leaders, organizations, patients, and caregivers to serve as experts and advocates in the development of a health equity agenda. The Council is a dynamic and vital component of Duke Cancer Institute's health disparities work and is comprised of 22 to 25 individuals, offering diverse perspectives across the cancer spectrum. Members are representatives from public and private agencies at the state and county levels, community residents, and persons concerned with cancer needs and disparities in our urban and rural communities. Collectively, the Community Advisory Council is made up of educators, health professionals, researchers, faith leaders, grassroots organizers, cancer survivors and patients, community advocates, and more, while representing diversity across race, ethnicity, socio-economic class, religion, geography, sexuality and identity, and many other perspectives. These partners access and engage their broader community constituency based on programming and research priorities. The Community Advisory Council meets monthly and plays a critical role in Duke Cancer Institute's community health assessment process, programming and services, and research. The roles and responsibilities of the Council include but are not limited to:

Dr. Barrett facilitates a community conversation on health, well-being, and cancer risks at the Annual Women's Health Awareness Day. Courtesy of Duke Health Photography.

- Serve as liaisons between the Duke Cancer Institute, our community, and our patients.
- Actively advocate and participate in the development and implementation of Duke Cancer Institute initiatives.
- Function as a "think tank" for OHED and Duke Cancer Institute activities.
- Continually align community and patient priorities with Duke Cancer Institute and OHED activities.
- Identify and connect local resources to enhance Duke Cancer Institute and our community partners' capacity to meet identified priorities.
- Partner and collaborate in grant writing and research across the Duke Cancer Institute.

Our Community Advisory Council—along with an extensive network of community partners—was instrumental in the development of the OHED community assessment and strategic plan, and as a result of our assessment, several sub-committees formed to address specific areas of OHED work. The following subcommittees address key priorities identified from the Community Health Assessment and support the development and implementation of OHED programs and activities across specific populations:

1. ***Asian Outreach & Research Committee.*** Eight Asian community organizations partner with the Duke Cancer Institute to conduct focus groups and cancer needs assessments within the diverse Asian community. The committee is currently developing a collaborative research agenda for the long-term partnership.
2. ***Patient & Community Advocates in Research Committee.*** This diverse group of patients, caregivers, researchers, and advocates ensures the patient's perspective is present; proactively shapes research at multiple levels; and provides insight and feedback to increase minority participation in research.
3. ***Latino Interfaith Leadership Committee.*** A group of faith leaders from Hispanic- and Latino-serving faith organizations addresses cancer needs and other health priorities within their organizations and participates in specialized health programming and research with the Hispanic and Latino community.
4. ***Diversity & Inclusion Committee.*** A team of Duke Cancer Institute employees from multiple levels and programs implement activities and training to enhance and promote diversity and inclusion in hiring practices, and interactions among colleagues and our patients.

Each committee meets to address key priorities identified in the ongoing community health assessments and plays a critical role in the development and implementation of programs and research. Additionally, OHED has well-established relationships with the African American community—including faith organizations, and grassroots community-based organizations—many of which are represented on the Community Advisory Council.

Step 2. Conduct a Robust Community Health Assessment & Disseminate Findings

Between 2012 to 2013, Duke Cancer Institute partnered with the Community Advisory Council and other community partners to develop and execute a community health assessment to better understand our community and patients' needs and recommendations around cancer outreach, education, screening, treatment, survivorship, and research participation. Our initial assessment was comprehensive. We conducted focus groups and analyzed data from the local cancer registry, Susan G. Komen Community Profile, the NC Cancer Plan, and the Durham County Health Assessment, to both qualitatively and quantitatively examine the scope and need in cancer services for the community, patients, and caregivers, as well in healthcare service delivery across the cancer continuum of care. We also sought to ascertain community perceptions, priorities, and recommendations to enhance cancer services.

Duke Cancer Institute held 10 sessions, reaching more than 130 participants, including community laypersons, diverse faith leaders, social agencies, patients, survivors, and caregivers representing the Latino and Hispanic, African American, Asian, white, and rural communities. Four overarching questions guided our sessions:

1. What factors facilitate or hinder access and utilization of cancer services from education, outreach, and screening to survivorship?
2. What factors impact access and participation of minorities and underserved populations in research and clinical trials?
3. What suggestions and/or recommendations might address the barriers to outreach, screening, treatment, and access to clinical trials?
4. What groups and organizations are critical partners to help address the identified needs in the community assessment?

The community assessment—coupled with Duke Cancer Institute organizational priorities—led to the development of the OHED strategic plan. Four primary and integrated themes were identified and became the core focus areas of the OHED:

(continued on page 54)

Table 1. Community Needs & Recommendations

PSYCHOSOCIAL, FINANCIAL & COMPETING PRIORITIES
• Cost of cancer screenings and treatment remains an ongoing challenge. Competing priorities can impact access and utilization of services for the uninsured and underinsured.
• Transportation, childcare, and lack of available services after-hours make it difficult to access cancer screening and care.
• Make psychosocial and financial resources readily available for patients seeking care, especially those who are more likely to fall through the gaps.
PRACTICAL EDUCATION & AWARENESS
• People in the community do not know when and where they should get screened for cancer.
• Create survivorship education support groups, workshops, and community-based survivorship resources to educate patients and caregivers on factors related to treatment and survivorship.
• Develop workshops for caregivers and cancer survivors to begin a dialogue on how to address the burden of cancer, including survivorship.
FEAR & CULTURE
• Fear takes on two roles in the community: 1) fear of a cancer diagnosis, which is often viewed as a death sentence and 2) fear of engaging in a complex healthcare system—of which some in the community do not trust historically.
• Provide bilingual services when engaging with the community, patients, and caregivers.
• Work with diverse faith leaders to increase awareness and support across the cancer care continuum for members within faith organizations.
• Understand the role of spirituality and reliance on faith for both caregivers and patients and how spirituality can influence screening and treatment choices, as well as survivorship outcomes.
• Provide training on the use of non-western remedies to address health concerns and/or treatment options and their influence on cancer care decisions, especially within the Asian and Latino communities.
• Hire healthcare providers and clinicians who reflect the community and patient demographic.
PARTICIPATION & RETENTION IN RESEARCH & CLINICAL TRIALS
• Create opportunities to increase health literacy and awareness about cancer research and clinical trials through community leaders in diverse communities.
• Provide culturally tailored educational resources around cancer research, clinical trials, research participation, genetic testing, and bio (tissue) banking.
• Cancer patients want to be informed of clinical trials even if the trials might not be an option for them or they do not qualify.
• Information and education about cancer and clinical trials is a critical need and interest in all race and ethnic groups.
COMMUNICATION
• Improve clinician communication with patients and caregivers about cancer screening, diagnosis, treatment plan, survivorship, and clinical trial participation.
• Cancer patients do not always fully understand their diagnosis or their treatment plan.
• Cancer survivors highlight lack of understanding about what they should do once they have completed active treatment, which leads to a sense of disconnectedness and fear.
BUILD COLLABORATIONS: CONNECT CANCER CENTERS TO THE COMMUNITY
• Connect cancer survivors to resources to address their cancer care and support service needs in their local community rather than in a hospital setting.
• Partner with community-based organizations and diverse faith leaders to share resources, increase cancer screenings, and build programs linking the health system to the community.
• Provide psychosocial support to help community members and patients navigate the healthcare system from outreach though survivorship.

(continued from page 52)

1. Develop and sustain community engagement and programs to promote optimal outcomes in cancer education, screening, treatment, survivorship, and research in underserved communities.
2. Improve minority education and participation in research and clinical trials.
3. Conduct health disparities education, training, and research.
4. Increase and enhance diversity and inclusion in the workforce.

In partnership with the community and clinical faculty, the OHED presented the focus group findings and strategic plan to approximately 321 people, including patients, community representatives, clinicians, researchers, and staff at an event entitled, *Community Voices on Cancer*. A report on our findings (with the same title) was provided at this event.

Our assessments are an ongoing and dynamic process designed to sustain community engagement and reduce cancer disparities through service delivery and research. Duke Cancer Institute employs several effective strategies to conduct these ongoing assessments and gauge diverse community and patient perspectives on cancer across the spectrum, and to serve as communication outlets to disseminate findings and solicit feedback. Listening sessions, town hall meetings, focus groups, community forums, local cancer support groups, and county meetings are all viable sources to identify needs and determine what activities are most useful for our patients, caregivers, and the broader community.

Based on the recommendations gleaned from our initial focus groups, the OHED developed an infrastructure that provided a framework for sustainable, long-term program and research activities to reduce cancer disparities and improve population health. We presented our findings to numerous groups across the health system and in the community; to date Duke Cancer Institute has reached more than 100 organizations and more than 2,000 stakeholders. From these activities Duke Cancer Institute continues to identify partners whose mission and priorities align with OHED goals, leading to new partnerships in the fight to reduce cancer disparities and improve health. Currently, OHED has 42 active community partners engaged in programs and/or research.

Step 3. Establish Program & Research Priorities

The OHED examined and categorized the assessment data, identifying key needs and recommendations from the broader community, patients, and caregivers. Perceived needs and recommendations include:

- Psychosocial and financial challenges
- Education and awareness
- Culture and fear
- Research
- Communication
- Potential opportunities to collaborate and address community and patient needs.

The OHED categorized priorities and recommendations to illustrate themes, establish priorities, and easily identify potential alignment with existing Duke Cancer Institute programs, services, research, or collaborations with key partners to address specific priorities and goals. For a summary of themes derived from the community assessment see Table 1, page 53.

Step 4. Develop or Enhance Partnered Programming & Research in Alignment with Priorities

Integrating organizational priorities with community assessment outcomes informed both the development and enhancement of collaborative programs, research, and activities to meet patient and community needs. Leveraging multi-sector partnerships is critical to reducing health disparities and improving population health. The OHED increased our capacity to implement community and patient programming through our extensive community engagement activities, leading to a portfolio of collaborative programming and research activities. An overview of key collaborative programs and research activities are described below. These directly align with key priorities identified from the community assessment (Table 1, page 53).

Longitudinal patient navigation—from community outreach to survivorship. Duke Cancer Institute's patient navigation program is a cornerstone to all outreach, screening, treatment, and survivorship activities. With a multicultural and bilingual staff, Duke Cancer Institute addresses the needs of diverse patient and community populations. Community navigators work to eliminate barriers to cancer screening and follow-up, essentially getting people through the front door to needed services. Patients diagnosed with cancer are then transitioned to treatment and survivorship navigators. These navigators support patients throughout their cancer journey, working to eliminate or reduce psychosocial and financial barriers to care.

Transportation program. In collaboration with local community partners, volunteers, and the American Cancer Society (ACS), this program meets one of the most pressing needs in healthcare—transportation. Free transportation is provided for patients to get to their cancer treatment. This program includes gas vouchers and volunteers to provide transportation for patients on active treatment. Duke Cancer Institute also has valet and free parking for patients on treatment.

Men's Health Initiative. This free health screening program is held the third weekend in September as a longstanding partnership between Duke Health and Lincoln Community Health Center. A network of collaborators, including Duke's Heart Center; Durham County Department of Public Health; the North Carolina Department of Health and Human Services, Cancer Control Branch; and the Durham Diabetes Coalition provide free health education and services. More than 300 men receive prostate cancer, diabetes, and hypertension education and screening at this one-day event. Duke Cancer Institute patient navigators follow-up on all abnormal results until each case is resolved. To date the program has screened about 950 men and received approximately $40,000 in outreach and

screening support from pharmaceutical companies and government agency funding. The program is provided during non-traditional hours, increasing access to services to underserved, high-risk populations.

Women's Health Initiative. The National Institutes of Environmental Health Sciences hosts an annual Women's Health Initiative at which the OHED leads the cancer track, providing cancer education, screening, and assessments in thyroid, lung, and breast cancer, and radon exposure testing kits to more than 400 attendees with follow-up services. Duke Cancer Institute faculty and staff volunteers and community partners, such as the Lung Cancer Initiative, participate in the program together to conduct a cancer workshop titled, "Everything You Want to Know about Cancer but Didn't Ask."

Community Health Ambassador Program. This collaborative and interactive cancer and clinical trials training program reaches out to diverse members of the community, including faith organizations. Ambassadors are selected by faith or community leaders to be trained at a one-day, six-hour course that educates participants about cancer risk factors, symptoms, screenings, and the psychological effects of cancer. Upon completion, Ambassadors are equipped with knowledge and tools to implement cancer awareness activities within their own organizations. Ambassadors are directly connected to Duke Cancer Institute patient navigators, who serve as a resource and a link to the healthcare system for those needing cancer screening or other services. The program has received funding from several foundations and funding agencies, including Susan G. Komen for the Cure and the NC Department of Health and Human Services, Cancer Control Branch. Twenty Ambassadors have been trained to date.

Duke Cancer Institute Speaker Bureau. To meet the speaking demands from our programs and requests from our community partners, Duke Cancer Institute developed a Speaker Bureau to align research, faculty, and staff expertise with outreach engagements in the community. All programs have simultaneous interpretation services to remove language barriers for non-English speakers. The Speaker Bureau provides a means for staff and faculty to engage the community and is designed to be a mutually beneficial learning experience. Currently, the Speaker Bureau has 84 active members available to speak in a variety of community settings, averaging two to five speaking engagements monthly.

The "Just Ask" Minority Participation in Research Program. To ensure patients are aware and knowledgeable about research and clinical trial participation and that researchers are well equipped with the necessary skills to communicate with diverse populations, the OHED established the "Just Ask" program. The program provides individual and group consulting support to research teams and clinical staff to improve minority enrollment in research. The OHED provides health communications and cultural competency training, and develops interventions to recruit and retain minorities in research. Through the Patient Advocates in Research Program and the Duke Cancer Institute Community Advisory Council, OHED increases awareness about research and clinical trials in our community.

Angel Romero, volunteer from the Duke LATCH program, speaks with a participant at the Men's Health Initiative. Courtesy of Duke Health Photography.

Diversity & Inclusion in Patient Care & the Workplace. This program provides training and education to faculty and staff around bias, diversity, and inclusion. Training segments vary and are tailored to specific audiences to include:

- Understanding the prism of differences
- Social determinants of health
- Understanding and valuing diversity, power, and privilege
- Patient and community engagement
- Hiring from a diverse pool of candidates
- Assessing our own comfort and discomfort with "difference."

The program provides strategies to help individuals and teams communicate effectively to enhance patient care and the work environment.

OHED Research Program & Funding Support. Since 2013 the OHED has collaborated with community and institutional partners, leading to 11 funded programs. Funded programs are diverse, supporting services and research across the cancer care continuum. Research collaborations cover a host of factors related to cancer, including:

- A project examining race differences in prostate cancer screening and active surveillance
- Colon cancer screening and patient navigation
- Race and ethnic differences in breast cancer and adjuvant therapy
- Community and patient perspectives on precision medicine
- The development of a faith-based program to increase breast cancer awareness and screenings.

Partnered proposal development is part of our growing research and funding portfolio.

Step 5. Evaluation & Outcomes

OHED programs and activities are consistently evaluated and modified using process and impact outcomes to ensure goals and objectives are being met and are consistent with metrics to reduce cancer disparities and improve population health. As an example, between 2013 and 2015, our navigators connected to 42 com-

munity partners and outreach programs, screened 1,155 participants, and educated more than 5,408 people, of which about 2,300 received clinical trials and research education. During that same time period, Duke Cancer Institute faculty and staff participated in 67 speaking engagements.

Program Metrics. Measuring the impact of programs, services, and research provides insight on the effectiveness of both the process and the impact of an initiative and how best to move forward. The OHED uses RedCap, a software program designed to capture and report program evaluation data. Common metrics in the OHED evaluation plan includes tracking the:

- Number of patients screened
- Number of re-engaged patients after no-shows
- Number of encountered barriers
- Types of barriers encountered
- Number of resources used
- Time to diagnosis
- Number of patients provided education
- Number of Ambassadors
- Number of Ambassador sites
- Number of lectures, trainings, and seminars
- Number of community partners
- Quality of community partnerships
- Number of clinical trial consults
- Number of grant applications submitted and funded
- Increase in minority accrual in research and trials.

Strategic Roles & Impact. The OHED uses a robust community assessment process to proactively shape priorities to improve cancer services across the care continuum. This process is particularly salient for patients and communities that have been traditionally underserved with tenuous relationships with health systems and research institutions. The assessment provides end-user perspectives and insight on the effectiveness of current services and opportunities to best meet community and patient needs. We develop strategic programs and interventions to address identified needs through internal and external collaborations. Our vigorous and comprehensive assessment is designed to effectively capture our community and patients' needs and is an example of how to meet and potentially exceed the growing expectations for cancer programs and health systems to conduct community assessments, as mandated in accreditation guidelines established by a variety of governing bodies.

For example, the Commission on Cancer (CoC) requires cancer programs to conduct needs assessments as part of the accreditation process. Likewise, relatively new CoC guidelines required all cancer programs to implement a patient navigation process by January 1, 2015. Patient navigation programs should, in part, be designed based on community needs assessments. Lastly, increasingly community cancer centers are expected to engage in research, creating opportunities for patients to participate in studies—regardless of where they live and seek care. Through focus groups with patients, cancer programs can identify critical needs in cancer care, while also increasing research participation.

COURTESY OF DUKE PHOTOGRAPHY.

Duke employee and volunteer Jane Worrell, RN, discusses lung cancer risks and provides radon test kits at the Annual Women's Health Awareness Day.

OHED partnerships have led to additional opportunities for Duke Cancer Institute to engage in integrated efforts to reduce cancer disparities and improve community and population health across the state. For example, the Deputy Director of the Durham County Department of Public Health serves on the Duke Cancer Institute Community Advisory Council. Every three years, the county completes a community assessment report on chronic disease and the social determinates of health in the county. As part of our ongoing partnership, the Duke Cancer Institute Community Assessment is used as the data for the cancer component and the OHED director is a co-author of this important report. Similarly, the Deputy Director of the Duke Cancer Institute and the Director of the OHED both serve in leadership roles in the state Access to Care and Early Detection Subcommittees (respectively), to execute the state cancer control plan and meet the colon cancer screening goals set forth nationally by the American Cancer Society. Collectively, these activities keep the Duke Cancer Institute community assessment and our partnerships relevant and vibrant as key contributors to the reduction of cancer disparities in the community.

Closing Thoughts

OHED's five-step process provides a roadmap to conducting health assessments that have the ability to meet multiple organizational needs, with the primary goal of reducing cancer disparities and improving community and population health through collaborations and partnerships. As part of our strategic process, Duke Cancer Institute leveraged our collaborative community assessment to identify and address local priorities through collaborative research and programming. The organic development of strategic community councils and committees allows the cancer program to stay in tune with community and patient needs and perspectives. Capitalizing on diverse perspectives and guidance, Duke Cancer Institute is able to:

- Engage in a proactive effort to improve access to cancer screenings and services
- Enhance the delivery of patient care

- Increase minority engagement in research
- Strengthen community and health system relationships across diverse communities.

For cancer programs looking to develop a similar health equity agenda, Duke Cancer Institute has found these factors to be key to our success:

- A patient navigation program that spans across the continuum of care from outreach and screening to survivorship to ensure patients have what they need to find their way through the complex health system.
- Community screening programs and faith initiatives that keep OHED's work relevant to addressing access to cancer screenings and information.
- An outreach program that serves as a gateway to educate the community about clinical trials so as to normalize the conversation while providing culturally sensitive strategies for research teams to more effectively engage patients in research and standard care.
- Diversity and Inclusion Program staff and faculty who can develop strategies to diversify their hiring pools while providing diversity and implicit bias training and education to more effectively engage and communicate with diverse patients, the community, and colleagues.

The five-step process outlined in this article is adaptable to suit any cancer program—regardless of size—either executed as a comprehensive strategy or by selecting and implementing facets based on a cancer program's identified needs, priorities, capacity, and resources. Given the depth and significance of cancer health disparities, it is important for all cancer programs to focus on the needs of the underserved, identifying strategies to address local health disparities in cancer and improve population health. OI

Nadine J. Barrett, PhD, MA, MS, is director, Office of Health Equity and Disparities, Duke Cancer Institute, Durham, N.C. Tracey Vann Hawkins, MA, is special projects and research coordinator and Kearston L. Ingraham, MPH, is community and patient navigation coordinator, Office of Health Equity and Disparities, Duke Cancer Institute, Durham, N.C. Julius Wilder, MD, PhD is a medical instructor, Duke Clinical Research Institute, Durham, N.C. Rebecca Reyes, MA, is program coordinator, Latino Health Services, Duke University Health Systems, Durham, N.C. Maritza Chirinos, MD, is personal health navigator, El Centro Hispano, Durham, N.C. Patricia Wigfall, PhD, is professor of Public Administration and Public Policy, North Carolina Central University, Department of Public Administration, Durham, N.C. William Robinson is founder, Black Men's Health Initiative, Durham, N.C. Steven R. Patierno, PhD, is deputy director, Duke Cancer Institute, Durham, N.C.

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Training Community Nurses & Administrators to Implement Cancer Clinical Trials

BY REGINA CUNNINGHAM, PHD, RN, AOCN, FAAN;
MARCIA GRANT, PHD, RN, FAAN;
MARISA CORTESE, PHD, FNP-BC;
ROBIN HERMANN, MSN, RN, CCRP; AND
DENICE ECONOMOU, MN, RN, CHPN

Death from cancer in the U.S. declined 20 percent from 1991 to 2010, from 214.1 deaths per 100,000 to 171.8 deaths per 100,000, respectively.[1] This dramatic improvement in cancer survival is directly attributable to the remarkable findings coming out of clinical trial research,[2] which serves to highlight the need for the continued creation, support, and completion of cancer clinical trials. While today's clinicians recognize the value clinical trials offer in conquering cancer and improving quality of life of cancer patients undergoing treatment,[2] many community cancer programs have not been able to improve clinical trial accrual for their cancer patients.[3]

To help in the effort to improve access to clinical trials in the community setting, the American College of Surgeons Commission on Cancer (CoC) established new accrual goals as part of its *Cancer Program Standards 2012: Ensuring Patient-Centered Care*.[4] Standard 1.9 requires "a percentage of patients be accrued to cancer-related clinical trials each year. The clinical trial coordinator or representative reports clinical trial participation to the cancer committee yearly."[4] The standard states that the community cancer program must accrue 2 percent of their annual analytic cases to clinical trials by 2015 to meet the standard; it requires 4 percent of the analytic cases for commendation. The comprehensive community cancer program requires a minimum of 4 percent accrual, with 6 percent necessary for commendation.

Implementation of this CoC standard requires that community cancer programs build an adequate clinical trials infrastructure staffed by qualified administrative, nursing, and data management personnel. Unfortunately, many community cancer programs do not have the infrastructure, institutional resources, or qualified personnel to carry out the myriad tasks involved in accruing and maintaining patients on cancer clinical trials. Accordingly, the National Cancer Institute (NCI), among other organizations, is looking to provide support for these programs. For example, in 2012, nurse researchers from the Hospital of the University of Pennsylvania, City of Hope, and the Mount Sinai Hospital received an NCI-funded R25 grant to support the education of both clinical trial nurses and administrators to meet CoC Standard 1.9, through a two-day curriculum that would be provided twice a year for three years, with an additional course in year four. Courses began in 2013 and continued through the spring of 2016, with a total of seven courses held. This article describes the program curriculum and participant evaluations for courses one through three; Course 1 was held May 18-19, 2013, Course 2 was held October 5-6, 2013, and Course 3 was held June 5-6, 2014.

The Program

The aim of the program, *Training Community Nurses & Administrators to Implement Cancer Clinical Trials*, was to develop and administer a curriculum that can be used to train community-based nurses and administrators to implement clinical trials and increase accrual to meet CoC accreditation standards. The curriculum was built on the foundations of the:[5-7]

- Oncology Nursing Society (ONS) Clinical Trials Nurse Competencies
- International Conference on Harmonization Good Clinical Practice
- Institute of Medicine report on building a clinical trials system for the 21st Century
- Code of Federal Regulations.

Participants were recruited through a variety of approaches. For example, researchers collaborated with CoC leadership to obtain email contact information for cancer program administrators from accredited programs. Researchers also contacted the ONS special interest group for clinical trials nurses, as well as other multicultural focused nursing groups: the American Black Nurses Association, the National Association of Hispanic Nurses, and the Philippine Nurses Association of America. The participant application included demographic and professional information, statements of interest, and a list of three goals to be implemented by participants when returning to their care setting.

Historically, the education of clinical research nurses and those administratively responsible for the conduct of clinical trials was often limited to "on the job" training experiences.[3] In the current research environment, this approach is less than optimal. The increased complexity of trial design, the exponential increase in regulatory demands, advances in informatics, and the need for patient protection make a compelling case for a more formal,

systematic approach to the education and skill maintenance of cancer clinical research personnel.

Quality cancer research requires highly competent clinical research personnel with knowledge of:

- Research methods
- Regulatory and compliance issues
- Oncology-specific reimbursement and patient management.

The framework identified in Figure 1 (below) shaped the development of the content presented in the educational program and identified the teaching strategies to be used.

The two-day curriculum was developed by investigators and content experts from around the country, using teaching methods that were based on adult learning principles and performance improvement strategies, including lectures, discussion, small group work, and individual participation activities.[8] Table 1, below, describes the education approaches used to apply the conceptual framework to the education program. A sample of the two-day agenda is provided in Table 2, right.

Separate workshops were held simultaneously for administrators and nurses, and focused on specific aspects of their roles in cancer clinical trials. Additionally participants were asked to submit three goals that they planned to implement in their own cancer programs over the 18 months post course. Evaluation of

Figure 1. Conceptual Framework for Curriculum Planning

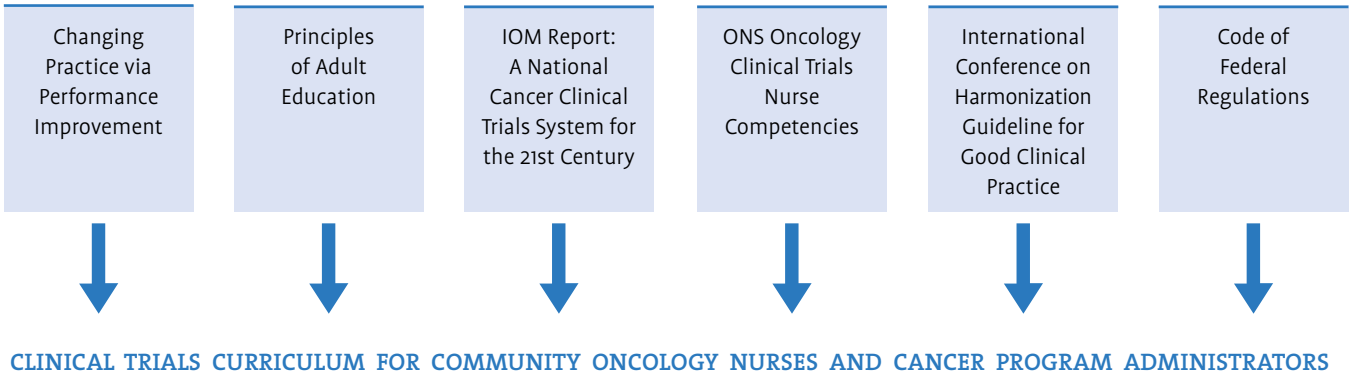


Table 1. Application of Conceptual Framework to Curriculum Development

Changing Practice via Performance Approval	• Pre- & post-clinical trials knowledge test • S.M.A.R.T. goal follow-up
Principles of Adult Education	• Mixed didactic presentations • Small group breakouts • Conference call follow-up
IOM Report: A National Cancer Clinical Trials System for the 21st Century	• Presentations: Why do Clinical Trials?, Overview of History and Background of Clinical Trials Research, Ensuring Quality in Clinical Trials, and Keys to Success in the Community Setting
ONS Oncology C.T. Competencies	• Didactic lectures to improve knowledge and prepare for competency exam
International Conference on Harmonization Guideline for Good Clinical Practice	• Presentations: Overview of Protocol Development, Regulatory & Legal Issues, Roles & Responsibilities, and Patient Management
Code of Federal Regulations	• Presentations: Responsible Conduct of Research and Why do Clinical Trials?

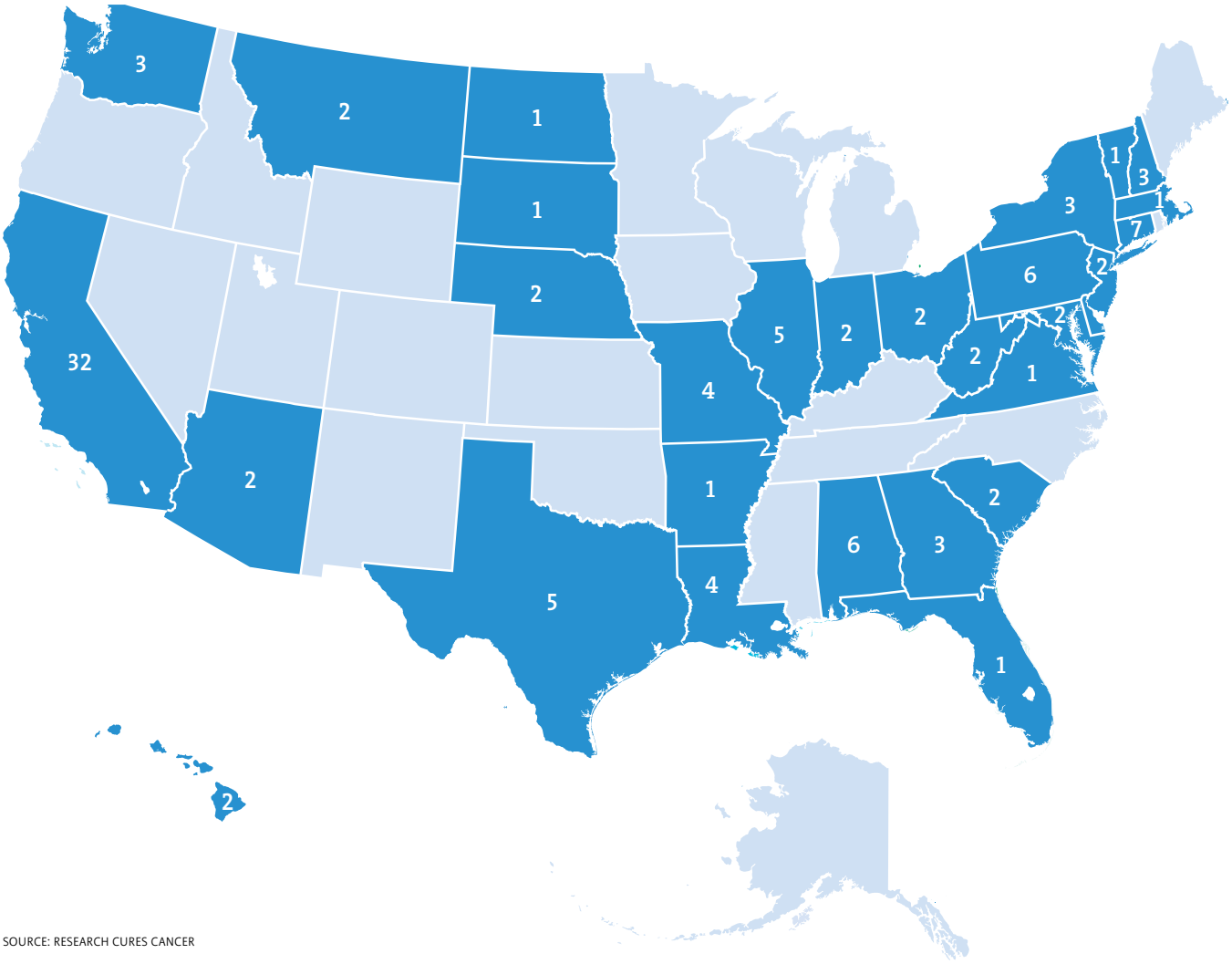
Table 2. Training Community Nurses & Administrators to Implement Cancer Clinical Trials

AGENDA: DAY 1	
Welcome & Overview	All
Pre-Test & Completion of Involvement in Clinical Trials Survey	All
Why Do Clinical Trials? Research Cures Cancer	All
Overview of the History & Background of Clinical Research	All
Break	All
Overview of Clinical Trials Designs	All
Overview of a Clinical Trial Protocol	Clinical participants
Protocol Development	Administrative participants
Regulatory & Legal Issues	All
Lunch	All
Roles & Responsibilities of the Research Team	All
Clinical Trial-Related Communication	All
Break	All
Goal Refinement, Completion of Day 1 Course Evaluation	All
Networking & Poster Session	All
AGENDA: DAY 2	
Barriers to Recruitment & Retention of Subjects in a Culturally Diverse World	All
Clinical Trials Patient Management: Pre-Study, Active, and Follow-Up Phases	Clinical participants
Clinical Trials: Administrative Workshop	Administrative participants
Break	All
Data Management	Clinical participants
Working with Sponsors	Administrative participants
Lunch	All
Ensuring Quality in Clinical Trials: Good Clinical Practices, SOPs, Audits	All
Capitalizing on Clinical Trials: Keys to Success in the Community Setting	All
Q&A, Post-Test, Goal Finalization, Completion of Day 2 Course Evaluation	All

goal achievement provided a way to document changes in practice patterns. Goals were reviewed by program staff and principal investigators at 6, 12, and 18 months post course. An additional mechanism to allow for interaction among participants and principal investigators included monthly conference calls over the four months following the two-day course. During these calls, participants discussed their goal-focused activities, as well as asked for and shared additional resources and information related to clinical trials program development barriers and facilitators. Faculty participated in the calls to provide support for participants' individual questions or concerns.

Program resources included a binder with the syllabus content consisting of an overview, objectives, a content outline, slides, references, and resources for each agenda topic. Additional resources such as the NCI Clinical Trials Booklets and other clinical trials-focused resources were available for participants

Figure 2. Course Participants by State



SOURCE: RESEARCH CURES CANCER

to review and obtain if relevant to their settings. A program participation announcement letter allowed attendees to share their course completion with hospital leadership. Participants also received a CD with overview slides and statistics to help them deliver an in-service session on clinical trials and marketing strategies at their individual cancer programs.

Results

The first three courses had 108 participants, including 56 nurses and 52 administrators from 29 states (Figure 2, above). Participant credentials, positions, setting characteristics, patient culture, and ethnicity were documented, see Table 3, pages 63–64.

Pre- and post-knowledge tests were used to evaluate administrators and nurses before and immediately after the course. The knowledge scores of nurse participants showed a statistically significant increase from pre- to post-testing (p=0.01) with a change in score from 65.49 percent to 70.03 percent. The same approach was used to evaluate administrator knowledge scores, which also showed a statistically significant increase from pre- to post-testing (p=0.00) with a change in score from 71.47 percent to 76.77 percent.

Overall course evaluations (range 1=lowest to 5= highest) for day 1 and day 2 were as follows:

- What was your overall opinion of this conference? Ranged from 4.5 to 4.89.
- Was the information stimulating and thought provoking? Ranged from 4.53 to 4.94.
- To what extent did the course meet the objectives and your expectations? Ranged from 4.22 to 4.85.

Descriptions of faculty average evaluations (range 1=lowest to 5=highest) for day 1 and day 2 are provided in Table 4, page 65.

(continued on page 65)

Table 3. Participant Demographics

POSITION DESCRIPTION	N=108	%
Administrators	52	48.1
Nurses	56	51.8
GENDER OF PARTICIPANTS	**N=95**	**%**
Female	86	90.5
Male	9	9.5
ETHNICITY OF PARTICIPANTS	**N=90**	**%**
Not Hispanic or Latino	82	91
Hispanic	8	8.9
RACE OF PARTICIPANTS	**N=90**	**%**
American Indian or Alaskan Native	0	0
Asian	7	7.8
Black or African American	2	2.2
Native Hawaiian or Pacific Islander	0	0
White	80	88.9
More than one race	1	1.1
Other	0	0
TYPE OF INSTITUTION	**N=96**	**%**
Academic Medical Center	15	15.6
Community Hospital	64	66.7
Integrated Health System	12	12.5
Community Cancer Center/Ambulatory Care	1	1
VA	4	4.2
Pediatric Hospital	0	0
Other	1	1.1
ACCREDITED BY AMERICAN COLLEGE OF SURGEONS	**N=95**	**%**
Yes	89	93.6
No	6	6.3
ACCREDITATION DESIGNATION	**N=92**	**%**
Academic Comprehensive Cancer Program	17	18.9
Community Cancer Program	18	20.0
Comprehensive Community Cancer Program	43	47.8
Freestanding Cancer Center Program	1	1.1
Integrated Network Cancer Program	1	1.1
NCI-Designated Comprehensive Cancer Program	4	4.4
Pediatric Cancer Program	2	2.2
Veterans Affairs Cancer Program	2	2.2
Other	1	1.1

table continued on page 64

Table 3. Patient Demographics, *continued from page 63*

ETHNICITY OF PATIENT POPULATION	%
Not Hispanic or Latino	81.36
Hispanic	16.55
RACE OF PATIENT POPULATION	**%**
American Indian or Alaskan Native	1.04
Asian	5.29
Black or African American	12.28
Native Hawaiian or Pacific Islander	1.95
White	73.43
Other	5.93

Attendees at the two-day course, *Training Community Nurses & Administrators to Implement Cancer Clinical Trials*, participate in a breakout session.

(continued from page 62)

Going Forward

Education for cancer professionals is one approach to addressing the challenges of increasing participation in cancer clinical trials. Based on these data, the *Training Community Nurses & Administrators to Implement Cancer Clinical Trials* curriculum was well received by attendees. Further, participants had the opportunity to interact with peers from across the country—both during the workshop and in the months following the workshop.

During the interactive sessions, participants indicated that this education was needed because many were new to their role or their departments were new to clinical research. When attendees left the two-day program, they had the support and mentorship of the faculty. Faculty made four monthly phone calls to participants immediately after the course; long-term follow-up involved evaluating achievement of individual goals at 6, 12, and 18 months post course. As goals are followed up and analysis is completed, faculty will be able to identify any institutional changes that have occurred and whether this professional education has made an impact on increasing accrual and retention of patients to cancer clinical trials—the ultimate outcomes of this program. Currently post-course goal analysis is in progress, and results will be submitted for publication once follow-up is completed. (NCI funding-1R25CA 168551-01). OI

Regina Cunningham, PhD, RN, AOCN, FAAN, is chief nurse executive/associate executive director at the Hospital of the University of Pennsylvania, Philadelphia, Pa., and adjunct professor at the University of Pennsylvania, School of Nursing. Marcia Grant, PhD, RN, FAAN, is distinguished professor in Nursing Research at the City of Hope, Duarte Calif. Marisa Cortese, PhD, FNP-BC, is the associate director of the Cancer Clinical Trials Office at Mount Sinai School of Medicine, New York, N.Y. Robin Hermann, MSN, RN, CCRP, is the manager of Nursing Research at the Hospital of the University of Pennsylvania. Denice Economou, MN, RN, CHPN, is a senior research specialist at the City of Hope and the Project Director for Training Community Cancer Centers to Implement Clinical Trials.

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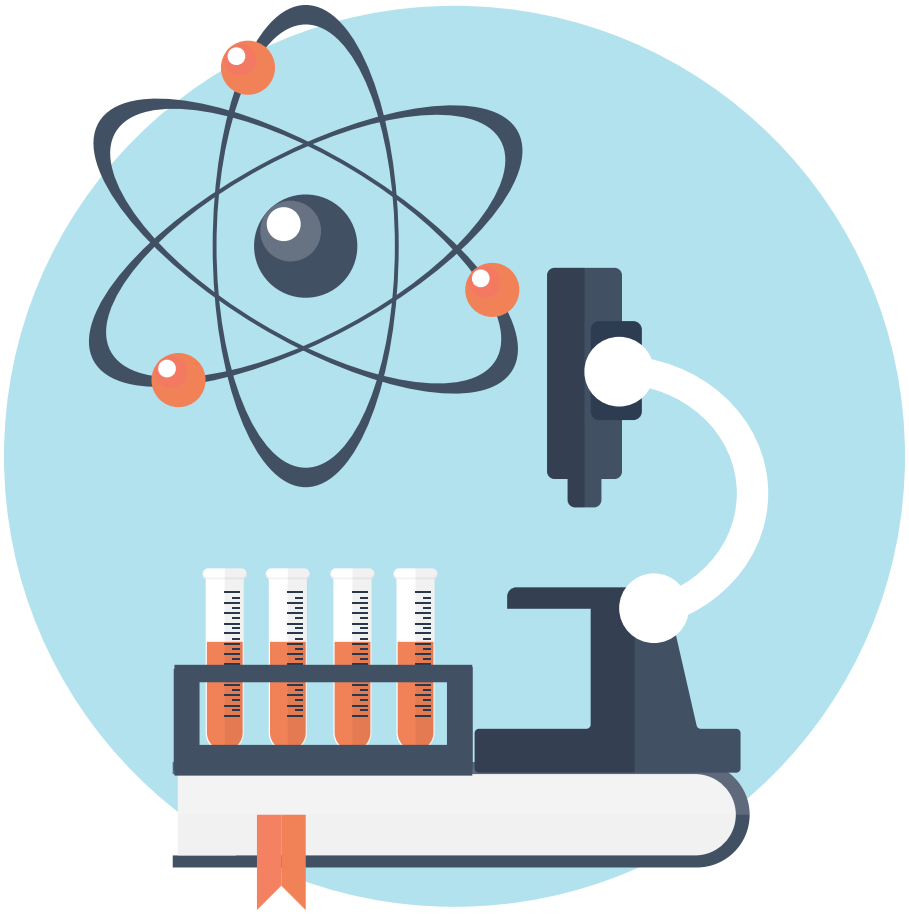
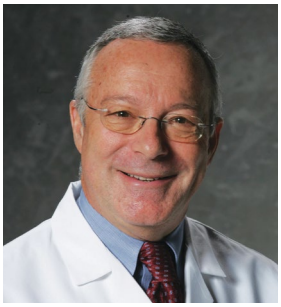
Table 4. Overall Course & Faculty Evaluations

COURSE EVALUATIONS OVERALL	RANGE (1=Lowest to 5=Highest)		
	COURSE 1	COURSE 2	COURSE 3
Overall opinion of this course	4.50	4.85	4.50
Was the information stimulating and thought provoking?	4.50	4.94	4.52
To what extent did the course meet the objectives and your expectations?	4.20	4.85	4.20
FACULTY EVALUATIONS OVERALL	**RANGE (1=Lowest to 5=Highest)**		
	COURSE 1	COURSE 2	COURSE 3
Clarity of presentation	3.78–4.95	3.59–4.86	4.71–4.96
Quality of content	3.72–4.95	3.81–4.79	4.69–5.00
Value to you as a clinician	3.94–4.95	3.91–4.75	4.70–4.95



Best of ASCO 2016

BY CARY A. PRESANT, MD, FACP, FASCO



THE 2016 ASCO ANNUAL MEETING WAS FILLED WITH INFORMATION, practice advice, and exciting results that will change oncology for the coming year. Several themes emerged: genomics, immunotherapeutics, targeted oncology products, and practice management issues. Here are my thoughts about the best of ASCO 2016.

The impacts of sequestration and proposed ASP reductions in payment may be devastating for practices by pushing more oncology drugs "under water" and necessitating consideration of alternate sites of administration or alternative treatment plans.

Practice Management Issues

At the pre-ASCO session on Economics of Cancer Care, presentations focused on patient financial burdens and the impact of patient bankruptcy, which is associated with shortened survival; the new ASCO practice survey results; and experience with shared savings models.

In "Palliative Care Alongside Oncology: Better Care at a Cost We Can Afford," Thomas J. Smith, MD, FACP, FASCO, FAAHPM, reported that considerable healthcare savings were realized by implementing early palliative care, which may be important in programs that are participating in alternative payment models (APMs) where there are shared risk and savings arrangements.

In "Impacts of Changes in Part B Drug Payment Policy," Andrew Mulcahy, PhD, MPP, emphasized how much chemotherapy has shifted to the hospital outpatient site (now 41%). The impacts of sequestration and proposed ASP reductions in payment may be devastating for practices by pushing more oncology drugs "under water" and necessitating consideration of alternate sites of administration (e.g., hospital outpatient departments) or alternative treatment plans.

Acronym Legend

ACA: Affordable Care Act
ALL: Acute lymphoblastic leukemia
AML: Acute myeloid leukemia
APM: Alternative payment model
ASP: Average sales price
CIPN: Chemotherapy induced peripheral neuropathy
CLL: Chronic lymphocytic leukemia
CMS: Centers for Medicare & Medicaid Services
CR: Complete response
DFS: Disease-free survival
dMMR: Deficient mismatched DNA repair
EFS: Event-free survival
ESMO: European Society for Medical Oncology
GDP: Gross domestic product
HR: Hazard ratio
ICER: Institute for Clinical and Economic Review
MACRA: Medicare Access and CHIP Reauthorization Act of 2015
MIPS: Merit-Based Incentive Payment System
NCCN: National Comprehensive Cancer Network
NCI: National Cancer Institute
NSCLC: Non-small cell lung cancer
OS: Overall survival
PARP: Poly ADP ribose polymerase
PFS: Progression-free survival
PQRS: Physician Quality Reporting System
QOPI: Quality Oncology Practice Initiative
QRUR: Quality and Resource Use Reports
RR: Relative risk
TNBC: Triple negative breast cancer
TTP: Time to progression

ASCO was urging participation in the QOPI and PCOP programs, although it is unclear if these programs will be accepted in part—or at all—by CMS as quality measures or as APMs for 2017.

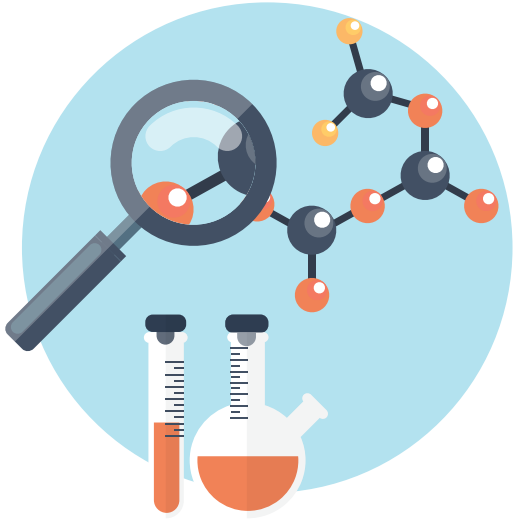
Ron Kline, MD, from the Center for Medicare & Medicaid Services (CMS), gave an update on the Oncology Care Model (OCM), which will impact many practices across the country.

In "The Economics of Cancer Care: The Impact of MACRA," Philip J. Stella, MD, Chair, Rapid Response Taskforce, reminded attendees that all oncology programs will, by law, be impacted by MACRA and MIPS starting in 2017. His takeaway: physicians and administrators must know *now* the metrics that are already being collected on physicians and practice patterns to determine what changes must be made. Know your PQRS, meaningful use, and QRUR scores, and review the cms.gov website to understand how you are doing.

At other education meetings, ASCO was urging participation in the QOPI and PCOP programs, although it is unclear if these programs will be accepted in part—or at all—by CMS as quality measures or as APMs for 2017.

Editor's Note: Proposed Medicare Outpatient Prospective Payment System and Physician Fee Schedule rules came out in July; final rules are expected in November 2016 for implementation in 2017. Be sure to read *Oncology Issues* and other journals, visit accc-cancer.org, reach out to your state oncology societies, and leverage ASCO resources to be fully prepared for new requirements.

Robin Zon, MD, vice president and senior partner at Michiana Hematology-Oncology, PC, in South Bend, Indiana, emphasized several important preparations that oncology practices should make over the next months. Her suggestions:



- Participate in PQRS (the CMS quality reporting system)
- Improve your meaningful use performance by having patients use your portal
- Reduce hospitalizations when possible
- See when you can use generics in place of single-source drugs
- Code for all ICD-10 comorbidities in each patient so that CMS knows the complexity of your patients
- Have a practice leadership team (physician, nurse, administrator, and medical assistant) to get ready for 2017.

Value continued to be an underlying theme at ASCO 2016. In "Quality and Value: Measuring and Utilizing Both in Your Practice," Lowell E. Schnipper, MD, PhD, discussed the ASCO equation for value determination. Net health benefit was equal to clinical benefit (80% of the benefit as measured by Phase III studies of survival, PFS, response plus extended survival plus symptom control minus toxicity) divided by cost to the system and the patient. Examples were provided. No corrections are made according to the perceived value to the individual patient, although adjuvant-treated patients value individual therapies differently from palliative-treated patients. Of course the ASCO model is not the only value framework; ESMO, NCCN, ICER, and the DrugAbacus are others. Bottom line: we do not know how insurers and health systems will respond to these innovative value determinations, but they likely will affect which treatments will be available for our patients, and how we and our profession will be viewed by patients and the public.

Health Science Research

- ***Abstract LBA6500,*** Goldstein et al. showed that in the U.S., the retail price of patented drugs was $8,694 per month, compared to $654 per month for generic drugs. But in other countries, the retail price of patented drugs was $1,500-$3,100 per month, while generic drugs were $120-$530 per month. Looking at a percent of GDP per capita, patented drugs were 192% in U.S. vs. 288% in China and 313% in India.
- Kehl and colleagues ***(Abstract 6503)*** found that after the ACA, while 94% of networks covered by the ACA nationally had a CoC-approved hospital in network, only 40% had at least one NCI-approved comprehensive cancer center. Only two-thirds of states with ACA national networks had an NCI-approved comprehensive cancer center located in the state. Only 30% of HMO networks had an NCI-approved comprehensive cancer center in their network.
- ***Abstract 6505,*** Neubauer et al. showed that in practices that used value-based NCCN pathways compared to practices not using such pathways, there was adherence to pathways in

84% with 93% patient satisfaction, increased use of hospice of 57%, and savings of 20% in chemotherapy, 15% in inpatient care, and overall savings of 18.5%.

- Wong and colleagues ***(Abstract 6506)*** evaluated the time costs of getting oral anticancer drugs approved by insurance. Financial assistance was necessary in 43%, with 5 calls per patient, and 5 days (range 0-45 days) to get authorization, and 11.6 days (range 1-66 days) to actually receive the drugs.
- ***Abstract 6507,*** Patel showed that using lay health workers to help patients navigate a VA health system resulted in cost savings of $11,000 (9%) per patient and increased use of hospice 40% vs. 23%, with equal survival.
- Veenstra and colleagues ***(Abstract 6508)*** reported that 55% of working patients lose their jobs while receiving chemotherapy for stage III colorectal cancer. This percentage was less in patients with employer-provided health insurance, who were men, Caucasian, or married, and who had fewer co-morbidities.

Breast Cancer

- ***Abstract LBA1,*** Goss et al. reviewed hormonal adjuvant trial MA.17R. After 5 years of letrozole (+/- tamoxifen for the first 5 years), patients continuing letrozole for 5 more years had improved DFS HR 0.66 (p=0.01). Contralateral cancer diagnosis was reduced HR 0.42 (p=0.001). OS was equal. Distant recurrence was reduced 1.1%. However, fractures were increased to 14% vs. 9% in placebo control (p=0.001), and osteoporosis was 11% vs. 6% (p=0.001). Discussant Ian Smith pointed out that if letrozole was continued, an IV bisphosphonate should be given, and that continued therapy might be best used for high risk patients (e.g., larger tumors).
- Hurwitz and colleagues ***(Abstract 500)*** showed in neoadjuvant therapy, TCH pertuzumab was superior to trastuzumab emtansine plus pertuzumab CR 56% vs 44% (p=0.01), but was more toxic.
- ***Abstract 504,*** Urreticoechea et al. showed addition of pertuzumab to trastuzumab plus capecitabine resulted in non-significant increased PFS by 2 months and OS by 8 months in patients progressing on trastuzumab.
- Blum and colleagues ***(Abstract 1000)*** reported on the adjuvant combination ABC trial (USOR 06-090 + NSABP 46 + NSABP 49). Four-year invasive DFS favored doxorubicin combination (TaxAC) compared to TC; 90.7% vs 88.2% (p=0.04), HR 1.20. Leukemia so far has been seen in 0.24% of TaxAC patients, none in TC. Four-year OS was equal. This may change therapy, especially in ER positive 4+ nodes positive patients.
- ***Abstract 1002,*** Bergh et al. showed dose dense epirubicin cyclophosphamide was superior to Q3W FEC with 5-year EFS, HR 0.79 (p=0.04).
- ***Abstract 1005,*** Soran et al. showed that mastectomy improved survival in patients presenting with de novo stage IV breast cancer; OS HR 0.66 (p=0.005).
- Giuliano and colleagues ***(Abstract 1007)*** showed in patients with 1-2 positive sentinel nodes, complete axillary node dissection was not necessary, 10-year OS equal.
- Adams and colleagues ***(Abstract 1009)*** found a CR+PR rate of 71% in patients with ≤ 3 prior regimens with atezolimumab plus nab-paclitaxel.
- ***Abstract 1012,*** Zhimim et al. showed that adding capecitabine to docetaxel + FEC in adjuvant breast cancer produced better distant DFS; 94.3% vs 89.3% (p=0.02) in TNBC.
- Freedman and colleagues ***(Abstract 1024)*** showed that in adjuvant Alliance breast cancer trials, there were only 17% of patients over 65, and only 7% over 70.
- ***Abstract 11578,*** Reinbolt et al. showed genetic mutations in 100 breast cancer patients having comprehensive genetic profiles. There was a median of 5 mutations per patient (0-13 range). Other than for drugs already FDA-approved for breast cancer, researchers found a drug, which had already been FDA-approved for other cancers to be associated with the mutations found in breast cancer genes in 77/100 patients; 41% of reports suggested a change in therapy, and in half of those the physician followed the change advice.

Colorectal Cancer

- ***Abstract 3503,*** Morris et al. reported a 24% RR in patients with squamous cell cancer of the anus with nivolumab.
- Venook and colleagues ***(Abstract 3504)*** found that right-sided cancers had better outcomes when bevacizumab was given, but left-sided cancers had better outcomes when cetuximab was given (if KRAS wild type).
- ***Abstracts 3505*** (Schrag et al.) and ***3506*** (Lee et al.) reported outcomes of right-sided colon cancer were better than left-sided.

Gastrointestinal & Pancreatic Cancer

- ***Abstract 103,*** Le et al. found that PFS from pembrolizumab was longer in patients with deficient mismatched DNA repair (dMMR) vs. those with no dMMR HR 0.135 (p<0.0001); OS was also longer HR 0.25 (p-0.001).

- Strosberg and colleagues *(Abstract 4005)* showed that treatment of recurrent midgut neuroendocrine tumors had longer PFS with 177-Lu-DOTATATE compared to octreotide LAR; RR was 18% vs 3% (p=0.0008).
- *Abstract LBA 4006,* Neoptolemos et al. reported on ESPAC-4. OS for gemcitabine/capecitabine was superior to gemcitabine alone median survival time (MST) 28.0 months vs 25.5 months; HR 0.82 (p=0.032).

Genitourinary Cancer

- McDermott and colleagues *(Abstract 4507)* showed that renal cell cancer patients on nivolumab had a 5-year OS of 41% and 5-year OS of 34%.
- *Abstract 4515,* Dreicer et al., showed that atezolizumab had RR of 28% in bladder cancer patients with high PDL1 levels, with 15% CR, and 12-month OS of 37%. 19% of progressing patients had responses after progression.
- Nelson and colleagues *(Abstract 5009)* found that in metastatic prostate cancer, 11% of patients had deficient DNA repair mutations in germline analysis, suggesting increased use of olaparib or other PARP inhibitors.

Glioblastoma

- *Abstract LBA2,* Perry et al., showed that patients over age 65 treated with RT 40 Gy over 3 weeks with temozolamide had 9.3 months survival and 10% 2-year survival, vs 7.6 months and 2% 2-year survival without temozolamide.

Gynecologic Cancer

- *Abstract 5501,* Ledermann et al. showed that olaparib maintenance after response to platinum-based induction chemotherapy in ovarian cancer patients with 2 or more prior therapies offered longer PFS 8.4 months vs. 4.8 months compared to control patients, HR 0.35 (p<0.0001), with better OS 29.8 months vs. 27.8 months, HR 0.73 (p=0.02), and best in BRCA mutated patients 34.9 months vs. 30.2 months, HR 0.62 (p=0.02).
- Gershenson and colleagues *(Abstract 5502)* found that hormonal maintenance therapy after surgery for low-grade serous cancer was better than no therapy after surgery; TTP 81 months vs. 29.9 months (p<0.001).
- *Abstract 5505,* Pignata et al. showed that in patients with ovarian cancer relapsing in 6-12 months, platinum re-induction therapy was better than non-platinum; OS 24.5 months vs. 21.8 months, HR 1.38 (p=0.06).

Head and Neck Cancer

- *Abstract 6007,* Zhang reported that patients with nasopharyngeal cancer showed superiority of gemcitabine/cisplatin vs. 5FU/cisplatin with PFS 7.0 months vs. 5.6 months, HR 0.55, and OS 29.4 months vs. 20.9 months, HR 0.62 (p=0.0002).
- Soulieres and colleagues *(Abstract 6008)* showed that after 1 prior line of platinum taxane therapy, buparlisib (an oral PIK3 inhibitor) plus paclitaxel was better than paclitaxel with PFS 4.6 months vs. 3.5 months, HR 0.65, and OS 10.4 months vs. 6.5 months, HR 0.72 (p=0.04). RR in HPV-negative patients was 39% vs. 11%.

Leukemia, Myelodysplastic Syndrome

- Turtle and colleagues *(Abstract 102)* showed CAR-T responses in ALL at 100% CR; NHL at 44% CR, and CLL at 45% CR. Cytokine release syndrome was common with 70-90% needing hospitalization.
- *Abstract 7000,* Lancet et al., showed that liposomal cytarabine + daunorubicin was superior to standard therapy in patients with AML age 60-75, CR (complete response) 37% vs 25%, and increase OS HR 0.69 (p=0.005).
- Frey and colleagues *(Abstract 7002)* and Park and colleagues *(Abstract 7003)* reported successful results of CA19 CAR-T cell therapy of ALL; CR 70-90%.
- Lin and colleagues *(Abstract 7007)* showed venetoclax in relapsed AML showed CR 54% and 1 year OS 58%.

Lung Cancer

- *Abstract 100,* Antonia et al. reviewed the results of Checkmate 032 nivolumab plus ipilimumab in patients with recurrent NSCLC. Only 24% of patients were PDL1 positive. Depending on dose, 1 year OS was 33% to 43% with some long survival in the follow-up "tails."
- Rudin and colleagues *(Abstract LBA8505)* showed patients with SCLC, treated with the DLL-3 targeted antibody drug conjugate rovalpituzumab teserine, had an RR of 25%, but RR was 91% if they were DLL-3 positive. In third line DLL-3 positive patients, RR was 70%.
- Wakelee and colleagues *(Abstract 9001)* showed that in 36% of NSCLC patients the EGFR mutation T790M was present in urine but not in tumor tissue, so urine, plasma, and tumor tissue should all be tested.
- *Abstract 9004,* Gomez et al., treated patients with oligometastatic NSCLC (3 or fewer metastases) without progression on chemotherapy, with either local surgery and RT or continued chemotherapy. PFS was longer with local therapy, 11.9 months

vs. 3.9 months, HR 0.36 (p=0.01). OS is being evaluated but patients on the chemotherapy arm are crossing over to local therapy.

- Nokihara and colleagues ***(Abstract 9008)*** showed that in patients with ALK- positive NSCLC, alectinib was better than crizotinib, PFS 20.3 months vs. 10.2 months, HR 0.34 (p<0.0001).

Melanoma

- ***Abstract 9505,*** Wolchok et al. updated the Checkmate 067 trial. Nivolumab plus ipilimumab gave longer PFS than nivolumab alone or ipilimiumab alone, 11.5 months vs 6.9 vs. 2.9 months.

Multiple Myeloma

- ***Abstract LBA4,*** Palumbo et al., showed that in the CASTOR trial daratumumab with Vd (bortezomib plus decadron) was better than Vd with PFS >12 months vs 7.2 months (p<0.0001), 1 year PFS 67% vs. 26%.
- Cavo and colleagues ***(Abstract 8000)*** showed early transplant was superior to late transplant PFS HR 0.76 (p=0.01).
- ***Abstract 8002,*** Lacy et al., showed a 77% response rate with all oral therapy ixazomib, cyclophosphamide, and dexamethasone (ICd).

Precision Medicine

- Zill and colleagues ***(Abstract LBA11501)*** found that circulating tumor DNA showed agreement with tissue analyses in 87% of 15,000 patients. They found actionable changes in patients with insufficient tumor tissue for analysis, patients with tumor progression without tissue biopsies, and patients with TNBC but mutations in HER2 on tumor progression.
- ***Abstract LBA11511,*** Hainsworth et al., showed a RR of 14/74 in patients (with non-trastuzumab approved tumors) who showed alterations in the HER2 pathway and who were treated with anti-HER2 therapy. Also, 7/31 RR occurred in the patients found to have a BRAF mutations treated with anti-BRAF therapy.

Patient & Survivor Care

- ***Abstract 10001,*** Hershman et al. reported that risk for chemotherapy induced peripheral neuropathy (CIPN) from paclitaxel was worse in diabetics (25%) vs. 12% without diabetes. It was less in patients with autoimmune disease 10% vs. those without autoimmune disease 20%.
- Greenlee and colleagues ***(Abstract 10002)*** found that CIPN was increased in obese patients and less if patients had 5 hours per week of exercise, suggesting a therapy, or preventive strategy. Kleckner and colleagues ***(Abstract 10000)*** also showed reduced CIPN with exercise.
- ***Abstract 10006,*** Knestrick et al. showed use of physician orders for scope of treatment vs. standard advanced directives resulted in increased hospice use 54% vs. 27%, and reduced in-hospital deaths 11% vs 30%.
- Hanai and colleagues ***(Abstract 10022)*** reported on reduced paclitaxel CIPN by use of frozen gloves and socks. Objective CIPN was reduced from 81% in controls to 28% in contralateral extremities treated by frozen gloves or socks (p<0.01).

Pediatric Cancer

- ***Abstract 10507,*** Minard-Colin et al. found that adding rituximab to standard chemotherapy in high-risk non-Hodgkin's lymphoma patients resulted in increased PFS at 1 year 94% vs. 81% without rituximab (p<0.001). OI

Cary A. Presant, MD, FACP, FASCO, is assistant clinical professor, City of Hope Medical Center; Professor of Clinical Medicine, University of Southern California Keck School of Medicine; Chairman of the Board, Medical Oncology Association of Southern California; and past-president of ACCC.

ACCC Launches Optimal Care Coordination Model for Lung Cancer Patients on Medicaid Project

Each year more than 220,000 Americans are diagnosed with lung cancer and about 160,000 die of the disease, making it the leading cause of cancer deaths in the nation. These dismal statistics are worse for minorities and those who are socio-economically disadvantaged, who not only have a higher incidence of lung cancer but also higher mortality rates. Studies have shown that Medicaid patients with cancer experience worse survival rates than those with private insurance or no coverage at all. These patients also face higher cancer incidence rates and later stage diagnosis.

In the U.S. today, providers and patients continue to grapple with a fragmented healthcare system. While navigating across the cancer care continuum is challenging for all patients, patients on Medicaid face additional barriers to accessing care across the disease trajectory from screening through diagnosis and treatment.

ACCC and its membership are committed to health equity and ensuring patient access to quality cancer care. To take action on improving care for this vulnerable patient population, ACCC has launched a project to develop an Optimal Care Coordination Model for Lung Cancer Patients on Medicaid. The work is supported by a three-year grant from the Bristol-Myers Squibb Foundation (BMSF).

The optimal care coordination model will seek to overcome identified social, financial, and institutional barriers to care. In developing the model, ACCC will engage Cancer Program Members, community health centers, patient advocacy organizations, health system leadership, and other stakeholders to streamline patient access across the lung cancer continuum of care.

With 65 percent of cancer patients in the U.S. now being treated in the community setting, the development of a comprehensive care coordination model will provide ACCC members with a critical resource to address the unique needs of Medicaid patients with lung cancer, leading the charge for health equity.

Project Components

In developing an Optimal Care Coordination Model for Lung Cancer Patients, ACCC planned a three-phase approach. During project year one, ACCC conducted an environmental scan and has identified five Development Sites to help lay the foundation for the model development.

The environmental scan included a literature review as well as the insights of the project's Advisory Committee members, a lung cancer survivor and patient advocate, and staff from two ACCC Cancer Program Members gathered in interviews conducted in April and May 2016. The scan and bibliography are available on the ACCC website at accc-cancer.org/carecoordination. Key findings from the scan include:

- The financial and social barriers that Medicaid beneficiaries face in pursuing lung cancer treatment are significant, detrimental to outcomes, and largely unaddressed.
- Medicaid beneficiaries have unequal access to high quality care.
- Increasing patient engagement is critical to improving outcomes but will require a tailored approach given the unique challenges Medicaid beneficiaries face.
- Integration of patient navigators into care teams can promote Medicaid beneficiaries' access to timely, high quality care.
- Multidisciplinary teams are key to improving care coordination. There may be opportunities to strengthen and build on the team approach to lung cancer care.
- Improvement is needed in timely access to supportive services for Medicaid patients including attention to biopsychosocial needs, palliative care needs, survivorship issues, hospice, and end of life care.

Five ACCC Cancer Program Members have been selected from a robust pool of applicants to serve as Development Sites for the care coordination model. Through a data collection and onsite interview process, these sites will help ACCC document the current state of care coordination for Medicaid patients with lung cancer. Information gleaned from the Development Sites will help in formulating draft principles to guide the development of the optimal care coordination model.

During year two the optimal care coordination model will be drafted and Testing Sites will be identified from among ACCC Cancer Program membership. In project year three, the model will be tested at the Testing Sites. For more information on the project and a listing of the Development Sites, visit accc-cancer.org/carecoordination. OI

GEAR UP FOR ACCC MEETINGS

ACCC meetings offer bright ideas to help you grow, excel, and succeed. Come away with innovative approaches to business, economic, and programmatic challenges, and help your cancer program maximize new opportunities. Benefit from the latest "how-to" knowledge, real-world examples, and tools for the delivery of effective cancer care across oncology disciplines. Please share these opportunities with your entire cancer care team.

For details on all ACCC meetings, visit accc-cancer.org/meetings

ONCOLOGY REIMBURSEMENT MEETINGS provide a fresh perspective on coding and billing trends, financial toxicity, reimbursement challenges, Medicare payment models, and a legislative and regulatory update.

- **Thursday, November 17, 2016**
  Baltimore, MD
- **Tuesday, December 13, 2016**
  Costa Mesa, CA

accc-cancer.org/ReimbursementMeeting

43RD ANNUAL MEETING, CANCERSCAPE provides the latest insight on the evolving healthcare policy landscape, alternative payment models, data collection and quality standards, 340B drug pricing, value-based frameworks, and more! Represent your cancer program—and your patients—during Capitol Hill Day to advocate for access to quality cancer care.

- **March 29–31, 2017**
  Washington, D.C.

accc-cancer.org/cancerscape

FINANCIAL ADVOCACY NETWORK (FAN) CASE-BASED WORKSHOPS offer innovative solutions to strengthen your financial assistance program and broaden your services. Learn strategies to communicate with your patients, maximize external assistance, optimize patient coverage, and improve the collections process.

- **Thursday, September 29, 2016**
  Philadelphia, PA

accc-cancer.org/FAN

INSTITUTE FOR CLINICAL IMMUNO-ONCOLOGY (ICLIO) NATIONAL CONFERENCE is the ONLY conference to prepare the multidisciplinary cancer care team for the complex implementation of immuno-oncology. Go beyond the clinical side to explore how immunotherapy operations will impact your practice.

- **Friday, September 30, 2016**
  Philadelphia, PA

accc-iclio.org

33RD NATIONAL ONCOLOGY CONFERENCE delivers practical ideas, solutions, and strategies to implement in your cancer program. How-to sessions focus on proven approaches to real-world challenges.

- **October 19 – 21, 2016**
  St. Louis, MO

accc-cancer.org/oncologyconference

ACCC
Association of Community Cancer Centers

Association of Community Cancer Centers
These programs are a benefit of membership.

ACCC Welcomes its Newest Members

Oncology San Antonio, P.A.
San Antonio, Tex.
Delegate Rep: Patrick Magallanes
Website: oncologysa.com

WellSpan Good Samaritan Sechler Family Cancer Center
Lebanon, Pa.
Delegate Rep: Kelly Smith, MS, RN, OCN
Website: wellspan.org/offices-locations/cancer-centers/sechler-family-cancer-center

Siteman Cancer Center
St. Louis, Mo.
Delegate Rep: Susan Fleecs
Website: siteman.wustl.edu

New ACCC Health System Member
Mercy Health Cincinnati System
Website: e-mercy.com

- **Mercy Health Anderson**
  Cincinnati, Ohio
  Delegate Rep: Nancy Pace, BSN, RN
  Website: e-mercy.com/mercy-hospital-anderson.aspx
- **Mercy Health Clermont**
  Batavia, Ohio
  Delegate Rep: Deb Vickers, AND
  Website: e-mercy.com/clermont-hospital.aspx
- **Mercy Health Fairfield**
  Fairfield, Ohio
  Delegate Rep: Ellen Hensler, BSN
  Website: e-mercy.com/mercy-hospital-fairfield.aspx
- **Mercy Health West**
  Cincinnati, Ohio
  Delegate Rep: Rob Brown, MHA
  Website: e-mercy.com/west-hospital.aspx

New ACCC Health System Member
Meridian Health System
Website: meridianhealth.com

- **Bayshore Community Hospital**
  Holmdel, N.J.
  Delegate Rep: Susan Labus
  Website: bayshorehospital.org
- **Riverview Medical Center**
  Red Bank, N.J.
  Delegate Rep: Nancy Zimmerman
  Website: riverviewmedicalcenter.com
- **Southern Ocean Medical Center**
  Manahawkin, N.J.
  Delegate Rep: Arlette Lowe
  Website: southernoceanmedicalcenter.com

SAVE THE DATE! Oncology Reimbursement Meetings

Free to ACCC members, these meetings offer a comprehensive look at oncology reimbursement issues, tools to strengthen your program, and information to help you weather market changes. At these one-day sessions:

- Hear the latest trends in oncology coding and billing
- Gain strategies to overcome reimbursement obstacles
- Learn strategies to optimize your patients' insurance coverage.

November 17, 2016
Baltimore, Md.
Hyatt Regency Baltimore Inner Harbor

December 13, 2016
Costa Mesa, Calif.
Hilton Orange County/Costa Mesa

April 13, 2017
Minneapolis, Minn.
Hyatt Regency Minneapolis

April 25, 2017
Tampa, Fla.
The Westin Tampa Harbour Island

May 18, 2017
Omaha, Nebr.
Embassy Suites by Hilton Omaha Downtown Old Market

Register online at: accc-cancer.org/reimbursementmeeting.

ASSESS. CHANGE. TEST.

ACCC, LUNGevity, CHEST, and CAP have partnered on a process improvement toolkit for molecular testing programs for Non-Small Cell Lung Cancer (NSCLC).

This online process improvement initiative for the multidisciplinary team draws from the experiences of community cancer centers who participated in workshops to assess, change, and improve molecular testing processes at their programs.

The interactive toolkit includes:

- Assessment tools to measure current performance and turnaround times
- Webinars on process improvement, identifying specific areas for change
- A Plan-Do-Study-Act tool to create a plan of action and measure the impact of changes
- A worksheet to capture results and demonstrate success—and share with your peers!

Get started today at accc-cancer.org/elearning

Look for an upcoming CAP TODAY commercial webinar that explores the challenges of molecular testing faced by teams in practice settings. ACCC will support the live broadcast to provide insights on the update to the CAP/AMP/IASLC Guidelines.

LUNGEVITY
Find it. Treat it. Live.

CHEST
AMERICAN COLLEGE of CHEST PHYSICIANS

CAP TODAY

Pfizer Oncology

Funding and support provided by Pfizer Oncology.

Since 2012, ACCC has developed tools and resources to ensure that cancer programs are optimizing biomarker testing processes with a focus on supporting programs in the community setting, with funding and support from Pfizer Oncology. A.C.T. on Molecular Testing is the culmination of these initiatives. For questions, please contact resources@accc-cancer.org

careers

CHIEF CLINICAL OFFICER
Winchester, Virginia

Blue Ridge Hospice seeks a Chief Clinical Officer to direct the clinical and operational activities of our home hospice and 8-bed inpatient facility.

Responsibilities:
- Directs clinical services in accordance with hospice, governmental, and other regulatory standards.
- Ensures compliance with accreditation, quality assurance, legal, and other regulatory requirements.
- Assists in development of the organization's financial plan; monitors the allocation of clinical resources.
- Develops organization and clinical goals and objectives in consultation with the CEO and CMO.
- Responsible and accountable for developing staffing plans.
- Monitor and improve the quality and appropriateness of care.

Qualifications:
A Master's Degree in Nursing; RN or NP with 7+ years of nursing experience, including 5 years of supervisory level experience; hospice experience preferred; current BLS certification.

Interested candidates should contact Ellen Hicks at: ehicks@blueridgehospice.org.

CLINICAL ONCOLOGY MANAGER
Hyannis, Massachusetts

Cape Cod Healthcare seeks an individual to manage overall operation of the Oncology Program. Major responsibilities include:
- Oversees day-to-day operation of Oncology to include scheduling of patient, physician, and treatment visits.
- Assists in establishing new programs; sets up policies/procedures/standards for any new programs, including evaluative measures.
- Assists Administrative Director with developing unit operating and capital budgets, reviews periodic performance reports to the budget, maintains expenditures within allocated resources.
- Identifies recommends and justifies any additional departmental needs, i.e., space requirements, equipment, and staff to the Administrative Director; assists the Administrative Director with physician recruitment process as needed.

Requirements:
Bachelor's degree in nursing (Master's degree preferred); certification in oncology; current MA license to practice; 3-5 years oncology nursing experience; 2+ years of management and/or supervisory experience (previous experience managing an oncology program preferred.)

Interested candidates should email: njberardi@capecodhealth.org.

DIRECTOR, RADIATION THERAPY
Seattle, Washington

Swedish Medical Center is looking for a Director to work at our Swedish First Hill Campus in Seattle. The Director provides management and leadership for all administrative, technical, and clinical operations for all Swedish radiation therapy services.

Responsibilities:
- Responsible for the daily operations and personnel, as well as: financial & business planning, business & new program development, marketing & communications, physician relations for all areas.
- Serve as site administrator and radiation therapy liaison for assigned cancer treatment centers within the Swedish network.
- Manage budgets for radiation therapy services.
- Serve as a disease site service line manager for assigned sites.

Required qualifications
BA/BS with related degree (Master's degree preferred); minimum 5 years management or supervisory experience; in-depth work experience in the radiation therapy field; strong communication and leadership skills; RRT certification preferred.

Apply online at: http://swedish.jobs.
Reference job number 126589.

ONCOLOGY SERVICE LINE DIRECTOR
Tulsa, Oklahoma

Oklahoma Cancer Specialists and Research Institute seeks a Service Line Director to facilitate the effective planning, operation, and growth of hospital-based oncology services in collaboration with St. John Medical Center leadership, and support the development of an effective continuum of care for all oncology services with St. John Health Systems and Oklahoma Cancer Specialists and Research Institute. This work will result in service line growth, operational excellence, cost effectiveness, and high quality patient services. This position will work in close partnership with physician, nursing, and administrative leadership, and other clinical leadership to ensure coordination of care and achieve regional network development.

Qualifications:
Master's degree in Business Administration, Public Health or Health Care Administration required. Minimum of 7 years' experience in progressive administrative leadership roles. At least 3 years of progressive administrative and operational experience in oncology, where the position has required in-depth knowledge of planning, marketing, operations, finance, information systems, and physician collaboration.

Forward resumes to Human Resources Department at: jobs@OCSRI.org or fax to: 918.505.3256.

IMMUNO-ONCOLOGY: The future is here. Where are you?

ICLIO | INSTITUTE FOR CLINICAL IMMUNO-ONCOLOGY

ICLIO is the only one-stop hub addressing immuno-oncology implementation in the community.

- Enhanced e-Newsletters with targeted content for clinicians, fellows, and the supportive care team.
- Publications with strategies to improve payer, provider, and patient communication on immuno-oncology value, methods of action, and coverage.
- ACCC Learning Portal, an online education platform will offer on-demand module courses focused on administrative and operational issues.
- Webinars led by experts specializing in real-world implementation strategies.
- Podcast commentary from tumor-specific collaborative working groups to help identify and outline best practices and strategies.
- ICLIO National Conference addresses challenges and opportunities in treatment and delivery.

More resources at accc-iclio.org

ICLIO is made possible by a charitable donation from Bristol-Myers Squibb and supported by an educational grant from Merck & Co., Inc.

Bristol-Myers Squibb MERCK

AN INSTITUTE OF ACCC Association of Community Cancer Centers

California's Smoking Signals

BY ENZA ESPOSITO-NGUYEN, RN, MSN, ANP-BC

On June 9, 2016, California increased the legal smoking age from 18 to 21; restricting the use of e-cigarettes and vaping devices in public places, and expanding the non-smoking areas at public schools. This move sends a loud and clear "smoking signal" to tobacco companies that the war on cigarettes and other nicotine containing addictive products still thrives in this state. The aim of these laws is to curtail the number of underage teens and children from ever starting this addictive habit, and to further restrict the use of these products in public places.

Known as Tobacco 21, these laws make California the second state, after Hawaii, to raise the smoking age from 18 to 21. These laws are being backed by the American Cancer Society, the American Heart Association, and the California Medical Association, among others, and represent a huge victory in public health and cancer prevention.

According to recent data released in 2015 by the California Department of Public Health, smoking rates in the State of California are consistently lower than that for the nation as a whole. California monitors smoking rates among high school age children utilizing the California Student Tobacco Survey.[1]

Between 2002 and 2010, smoking rates among California teens wavered between 13 percent and 16 percent with a significant decline in 2012 to 10.5 percent. This decrease is attributed to the FDA's ban on the marketing of flavored cigarettes, as well as the passage of the federal Family Smoking Prevention and Control Act in 2009. The report found that smoking prevalence goes up as children get older, with 12th graders having higher smoking rates than 10th or 8th graders.[1]

As many as 90 percent of tobacco users start before the age of 21 and nearly 80 percent try their first tobacco product before age 18, according to a national study reported by the *LA Times* in May 2016.[2]

In early 2015, the Institute of Medicine presented data on studies that demonstrate that raising the smoking age from 18 to 21 would decrease smoking prevalence by 12 percent, and that raising the smoking age to 25 would represent a 16 percent decrease in prevalence.[3]

These laws are being adopted at a pivotal time for those of us involved in thoracic oncology. Just 18 months ago, the Centers for Medicare & Medicaid Services approved low-dose CT screening for heavy lifetime smokers to detect early lung cancers. These screenings are also a great opportunity for healthcare providers to discuss smoking cessation or abstinence from tobacco products.

Here in our cancer center and affiliated facilities, smoking cessation sessions are tailored to the patient's needs. We offer group sessions that meet for one hour, for five consecutive weeks. Most patients find this support-group-like meeting very helpful; they feel more encouraged and reassured that they are not alone in their fight to "kick the habit."

Some patients, due to work schedules or other constraints, feel that one-on-one sessions or telephone sessions provide enough support and guidance.

Typically smoking cessation therapies have one of two approaches: to treat tobacco dependence as an addiction, where pharmacological therapy is at the center of therapy; or approach dependency as a habit, where behavior modification is at the center of therapy and pharmacological agents are used as adjuncts to treatment. Anecdotally, this mode of therapy has higher success rates.

One can only hope that more states—and perhaps other countries where smoking is more prevalent than the U.S.—will soon adopt similar laws to protect their young, vulnerable children against deceiving advertisement. OI

Enza Esposito-Nguyen, RN, MSN, ANP-BC, is a thoracic/urology nurse navigator/nurse practitioner at The Center for Cancer Prevention and Treatment, St. Joseph Hospital, Orange, Calif.

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1. California Department of Public Health. California Tobacco Facts and Figures 2015. Available online at: cdn.shopify.com/s/files/1/0121/4032/files/2015_California_Facts_and_Figures.pdf. Last accessed: July 29, 2016.

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3. Bonnie R, et al. IOM report: Public Health Implications of Raising the Minimum Age of Legal Access to Tobacco Products. Available online at: nap.edu/catalog/18997/public-health-implications-of-raising-the-minimum-age-of-legal-access-to-tobacco-products. Last accessed: July 29, 2016.

Xtandi® (enzalutamide) 40 mg capsules

XTANDI® (enzalutamide) capsules for oral use
Initial U.S. Approval: 2012
BRIEF SUMMARY OF PRESCRIBING INFORMATION

The following is a brief summary. Please see the package insert for full prescribing information.

INDICATIONS AND USAGE

XTANDI is indicated for the treatment of patients with metastatic castration-resistant prostate cancer (CRPC).

CONTRAINDICATIONS

Pregnancy

XTANDI can cause fetal harm when administered to a pregnant woman based on its mechanism of action and findings in animals. XTANDI is not indicated for use in women. XTANDI is contraindicated in women who are or may become pregnant. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, apprise the patient of the potential hazard to the fetus and the potential risk for pregnancy loss.

WARNINGS AND PRECAUTIONS

Seizure

In Study 1, which enrolled patients who previously received docetaxel, 7 of 800 (0.9%) patients treated with XTANDI experienced a seizure and no patients treated with placebo experienced a seizure. Seizure occurred from 31 to 603 days after initiation of XTANDI. In Study 2, 1 of 871 (0.1%) chemotherapy-naive patients treated with XTANDI and 1 of 844 (0.1%) patients treated with placebo experienced a seizure. Patients experiencing seizure were permanently discontinued from therapy and all seizure events resolved. There is no clinical trial experience re-administering XTANDI to patients who experienced seizure.

Limited safety data are available in patients with predisposing factors for seizure because these patients were generally excluded from the trials. These exclusion criteria included a history of seizure, underlying brain injury with loss of consciousness, transient ischemic attack within the past 12 months, cerebral vascular accident, brain metastases, and brain arteriovenous malformation. Study 1 excluded the use of concomitant medications that may lower the seizure threshold, whereas Study 2 permitted the use of these medications.

Because of the risk of seizure associated with XTANDI use, patients should be advised of the risk of engaging in any activity where sudden loss of consciousness could cause serious harm to themselves or others. Permanently discontinue XTANDI in patients who develop a seizure during treatment.

Posterior Reversible Encephalopathy Syndrome (PRES)

There have been reports of posterior reversible encephalopathy syndrome (PRES) in patients receiving XTANDI. PRES is a neurological disorder which can present with rapidly evolving symptoms including seizure, headache, lethargy, confusion, blindness, and other visual and neurological disturbances, with or without associated hypertension. A diagnosis of PRES requires confirmation by brain imaging, preferably magnetic resonance imaging (MRI). Discontinue XTANDI in patients who develop PRES.

ADVERSE REACTIONS

Clinical Trial 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.

Two randomized clinical trials enrolled patients with metastatic prostate cancer that has progressed on androgen deprivation therapy (GnRH therapy or bilateral orchiectomy), a disease setting that is also defined as metastatic CRPC. In both studies, patients received XTANDI 160 mg orally once daily in the active treatment arm or placebo in the control arm. All patients continued androgen deprivation therapy. Patients were allowed, but not required, to take glucocorticoids.

The most common adverse reactions (≥ 10%) that occurred more commonly (≥ 2% over placebo) in the XTANDI-treated patients from the two randomized clinical trials were asthenia/fatigue, back pain, decreased appetite, constipation, arthralgia, diarrhea, hot flush, upper respiratory tract infection, peripheral edema, dyspnea, musculoskeletal pain, weight decreased, headache, hypertension, and dizziness/vertigo.

Study 1: Metastatic Castration-Resistant Prostate Cancer Following Chemotherapy

Study 1 enrolled 1199 patients with metastatic CRPC who had previously received docetaxel. The median duration of treatment was 8.3 months with XTANDI and 3.0 months with placebo. During the trial, 48% of patients on the XTANDI arm and 46% of patients on the placebo arm received glucocorticoids.

Grade 3 and higher adverse reactions were reported among 47% of XTANDI-treated patients and 53% of placebo-treated patients. Discontinuations due to adverse events were reported for 16% of XTANDI-treated patients and 18% of placebo-treated patients. The most common adverse reaction leading to treatment discontinuation was seizure, which occurred in 0.9% of the XTANDI-treated patients compared to none (0%) of the placebo-treated patients. Table 1 shows adverse reactions reported in Study 1 that occurred at a ≥ 2% higher frequency in the XTANDI arm compared to the placebo arm.

Table 1. Adverse Reactions in Study 1

	XTANDI N = 800		Placebo N = 399	
	Grade 1-4[a] (%)	Grade 3-4 (%)	Grade 1-4 (%)	Grade 3-4 (%)
General Disorders				
Asthenic Conditions[b]	50.6	9.0	44.4	9.3
Peripheral Edema	15.4	1.0	13.3	0.8
Musculoskeletal And Connective Tissue Disorders				
Back Pain	26.4	5.3	24.3	4.0
Arthralgia	20.5	2.5	17.3	1.8
Musculoskeletal Pain	15.0	1.3	11.5	0.3
Muscular Weakness	9.8	1.5	6.8	1.8
Musculoskeletal Stiffness	2.6	0.3	0.3	0.0
Gastrointestinal Disorders				
Diarrhea	21.8	1.1	17.5	0.3
Vascular Disorders				
Hot Flush	20.3	0.0	10.3	0.0
Hypertension	6.4	2.1	2.8	1.3
Nervous System Disorders				
Headache	12.1	0.9	5.5	0.0
Dizziness[c]	9.5	0.5	7.5	0.5
Spinal Cord Compression and Cauda Equina Syndrome	7.4	6.6	4.5	3.8
Paresthesia	6.6	0.0	4.5	0.0
Mental Impairment Disorders[d]	4.3	0.3	1.8	0.0
Hypoesthesia	4.0	0.3	1.8	0.0
Infections And Infestations				
Upper Respiratory Tract Infection[e]	10.9	0.0	6.5	0.3
Lower Respiratory Tract And Lung Infection[f]	8.5	2.4	4.8	1.3
Psychiatric Disorders				
Insomnia	8.8	0.0	6.0	0.5
Anxiety	6.5	0.3	4.0	0.0
Renal And Urinary Disorders				
Hematuria	6.9	1.8	4.5	1.0
Pollakiuria	4.8	0.0	2.5	0.0
Injury, Poisoning And Procedural Complications				
Fall	4.6	0.3	1.3	0.0
Non-pathologic Fractures	4.0	1.4	0.8	0.3
Skin And Subcutaneous Tissue Disorders				
Pruritus	3.8	0.0	1.3	0.0
Dry Skin	3.5	0.0	1.3	0.0

Table 1. Adverse Reactions in Study 1 (cont.)

Respiratory Disorders				
Epistaxis	3.3	0.1	1.3	0.3

a CTCAE v4
b Includes asthenia and fatigue.
c Includes dizziness and vertigo.
d Includes amnesia, memory impairment, cognitive disorder, and disturbance in attention.
e Includes nasopharyngitis, upper respiratory tract infection, sinusitis, rhinitis, pharyngitis, and laryngitis.
f Includes pneumonia, lower respiratory tract infection, bronchitis, and lung infection.

Study 2: Chemotherapy-naive Metastatic Castration-Resistant Prostate Cancer

Study 2 enrolled 1717 patients with metastatic CRPC who had not received prior cytotoxic chemotherapy, of whom 1715 received at least one dose of study drug. The median duration of treatment was 17.5 months with XTANDI and 4.6 months with placebo. Grade 3-4 adverse reactions were reported in 44% of XTANDI-treated patients and 37% of placebo-treated patients. Discontinuations due to adverse events were reported for 6% of XTANDI-treated patients and 6% of placebo-treated patients. The most common adverse reaction leading to treatment discontinuation was fatigue/asthenia, which occurred in 1% of patients on each treatment arm. Table 2 includes adverse reactions reported in Study 2 that occurred at a ≥ 2% higher frequency in the XTANDI arm compared to the placebo arm.

Table 2. Adverse Reactions in Study 2

	XTANDI N = 871		Placebo N = 844	
	Grade 1-4[a] (%)	Grade 3-4 (%)	Grade 1-4 (%)	Grade 3-4 (%)
General Disorders				
Asthenic Conditions[b]	46.9	3.4	33.0	2.8
Peripheral Edema	11.5	0.2	8.2	0.4
Musculoskeletal And Connective Tissue Disorders				
Back Pain	28.6	2.5	22.4	3.0
Arthralgia	21.4	1.6	16.1	1.1
Gastrointestinal Disorders				
Constipation	23.2	0.7	17.3	0.4
Diarrhea	16.8	0.3	14.3	0.4
Vascular Disorders				
Hot Flush	18.0	0.1	7.8	0.0
Hypertension	14.2	7.2	4.1	2.3
Nervous System Disorders				
Dizziness[c]	11.3	0.3	7.1	0.0
Headache	11.0	0.2	7.0	0.4
Dysgeusia	7.6	0.1	3.7	0.0
Mental Impairment Disorders[d]	5.7	0.0	1.3	0.1
Restless Legs Syndrome	2.1	0.1	0.4	0.0
Respiratory Disorders				
Dyspnea[e]	11.0	0.6	8.5	0.6
Infections And Infestations				
Upper Respiratory Tract Infection[f]	16.4	0.0	10.5	0.0
Lower Respiratory Tract And Lung Infection[g]	7.9	1.5	4.7	1.1
Psychiatric Disorders				
Insomnia	8.2	0.1	5.7	0.0
Renal And Urinary Disorders				
Hematuria	8.8	1.3	5.8	1.3
Injury, Poisoning And Procedural Complications				
Fall	12.7	1.6	5.3	0.7
Non-Pathological Fracture	8.8	2.1	3.0	1.1
Metabolism and Nutrition Disorders				
Decreased Appetite	18.9	0.3	16.4	0.7
Investigations				
Weight Decreased	12.4	0.8	8.5	0.2
Reproductive System and Breast Disorders				
Gynecomastia	3.4	0.0	1.4	0.0

Table 2. Adverse Reactions in Study 2 (cont.)

a	CTCAE v4
b	Includes asthenia and fatigue.
c	Includes dizziness and vertigo.
d	Includes amnesia, memory impairment, cognitive disorder, and disturbance in attention.
e	Includes dyspnea, exertional dyspnea, and dyspnea at rest.
f	Includes nasopharyngitis, upper respiratory tract infection, sinusitis, rhinitis, pharyngitis, and laryngitis.
g	Includes pneumonia, lower respiratory tract infection, bronchitis, and lung infection.

Laboratory Abnormalities

In the two randomized clinical trials, Grade 1-4 neutropenia occurred in 15% of patients treated with XTANDI (1% Grade 3-4) and in 6% of patients treated with placebo (0.5% Grade 3-4). The incidence of Grade 1-4 thrombocytopenia was 6% of patients treated with XTANDI (0.3% Grade 3-4) and 5% of patients treated with placebo (0.5% Grade 3-4). Grade 1-4 elevations in ALT occurred in 10% of patients treated with XTANDI (0.2% Grade 3-4) and 16% of patients treated with placebo (0.2% Grade 3-4). Grade 1-4 elevations in bilirubin occurred in 3% of patients treated with XTANDI (0.1% Grade 3-4) and 2% of patients treated with placebo (no Grade 3-4).

Infections

In Study 1, 1% of patients treated with XTANDI compared to 0.3% of patients treated with placebo died from infections or sepsis. In Study 2, 1 patient in each treatment group (0.1%) had an infection resulting in death.

Falls and Fall-related Injuries

In the two randomized clinical trials, falls including fall-related injuries, occurred in 9% of patients treated with XTANDI compared to 4% of patients treated with placebo. Falls were not associated with loss of consciousness or seizure. Fall-related injuries were more severe in patients treated with XTANDI and included non-pathologic fractures, joint injuries, and hematomas.

Hypertension

In the two randomized trials, hypertension was reported in 11% of patients receiving XTANDI and 4% of patients receiving placebo. No patients experienced hypertensive crisis. Medical history of hypertension was balanced between arms. Hypertension led to study discontinuation in < 1% of patients in each arm.

Post-Marketing Experience

The following additional adverse reactions have been identified during post approval use of XTANDI. Because these reactions were reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate the frequency or establish a causal relationship to drug exposure.

Neurological Disorders: posterior reversible encephalopathy syndrome (PRES)

DRUG INTERACTIONS

Drugs that Inhibit CYP2C8

Co-administration of a strong CYP2C8 inhibitor (gemfibrozil) increased the composite area under the plasma concentration-time curve (AUC) of enzalutamide plus N-desmethyl enzalutamide by 2.2-fold. Co-administration of XTANDI with strong CYP2C8 inhibitors should be avoided if possible. If co-administration of XTANDI with a strong CYP2C8 inhibitor cannot be avoided, reduce the dose of XTANDI.

Drugs that Induce CYP3A4

Co-administration of rifampin (strong CYP3A4 inducer and moderate CYP2C8 inducer) decreased the composite AUC of enzalutamide plus N-desmethyl enzalutamide by 37%. Co-administration of strong CYP3A4 inducers (e.g., carbamazepine, phenobarbital, phenytoin, rifabutin, rifampin, rifapentine) with XTANDI should be avoided if possible. St John's wort may decrease enzalutamide exposure and should be avoided. If co-administration of a strong CYP3A4 inducer with XTANDI cannot be avoided, increase the dose of XTANDI.

Effect of XTANDI on Drug Metabolizing Enzymes

Enzalutamide is a strong CYP3A4 inducer and a moderate CYP2C9 and CYP2C19 inducer in humans. At steady state, XTANDI reduced the plasma exposure to midazolam (CYP3A4 substrate), warfarin (CYP2C9 substrate), and omeprazole (CYP2C19 substrate). Concomitant use of XTANDI with narrow therapeutic index drugs that are metabolized by CYP3A4 (e.g., alfentanil, cyclosporine, dihydroergotamine, ergotamine, fentanyl, pimozide, quinidine, sirolimus and tacrolimus), CYP2C9 (e.g., phenytoin, warfarin) and CYP2C19 (e.g., S-mephenytoin) should be avoided, as enzalutamide may decrease their exposure. If co-administration with warfarin cannot be avoided, conduct additional INR monitoring.

USE IN SPECIFIC POPULATIONS

Pregnancy– Pregnancy Category X.

Risk Summary

XTANDI can cause fetal harm when administered to a pregnant woman based on its mechanism of action and findings in animals. While there are no human data on the use of XTANDI in pregnancy and XTANDI is not indicated for use in women, it is important to know that maternal use of an androgen receptor inhibitor could affect development of the fetus. Enzalutamide caused embryo-fetal toxicity in mice at exposures that were lower than in patients receiving the recommended dose. XTANDI is contraindicated in women who are or may become pregnant while receiving the drug. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, apprise the patient of the potential hazard to the fetus and the potential risk for pregnancy loss. Advise females of reproductive potential to avoid becoming pregnant during treatment with XTANDI.

Animal Data

In an embryo-fetal developmental toxicity study in mice, enzalutamide caused developmental toxicity when administered at oral doses of 10 or 30 mg/kg/day throughout the period of organogenesis (gestational days 6-15). Findings included embryo-fetal lethality (increased post-implantation loss and resorptions) and decreased anogenital distance at ≥ 10 mg/kg/day, and cleft palate and absent palatine bone at 30 mg/kg/day. Doses of 30 mg/kg/day caused maternal toxicity. The doses tested in mice (1, 10 and 30 mg/kg/day) resulted in systemic exposures (AUC) approximately 0.04, 0.4 and 1.1 times, respectively, the exposures in patients. Enzalutamide did not cause developmental toxicity in rabbits when administered throughout the period of organogenesis (gestational days 6-18) at dose levels up to 10 mg/kg/day (approximately 0.4 times the exposures in patients based on AUC).

Nursing Mothers

XTANDI is not indicated for use in women. It is not known if enzalutamide is excreted in human milk. Because many drugs are excreted in human milk, and because of the potential for serious adverse reactions in nursing infants from XTANDI, a decision should be made to either discontinue nursing, or discontinue the drug taking into account the importance of the drug to the mother.

Pediatric Use

Safety and effectiveness of XTANDI in pediatric patients have not been established.

Geriatric Use

Of 1671 patients who received XTANDI in the two randomized clinical trials, 75% were 65 and over, while 31% were 75 and over. No overall differences in safety or effectiveness were observed between these patients and younger patients. Other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

Patients with Renal Impairment

A dedicated renal impairment trial for XTANDI has not been conducted. Based on the population pharmacokinetic analysis using data from clinical trials in patients with metastatic CRPC and healthy volunteers, no significant difference in enzalutamide clearance was observed in patients with pre-existing mild to moderate renal impairment (30 mL/min ≤ creatinine clearance [CrCL] ≤ 89 mL/min) compared to patients and volunteers with baseline normal renal function (CrCL ≥ 90 mL/min). No initial dosage adjustment is necessary for patients with mild to moderate renal impairment. Severe renal impairment (CrCL < 30 mL/min) and end-stage renal disease have not been assessed.

Patients with Hepatic Impairment

Dedicated hepatic impairment trials compared the composite systemic exposure of enzalutamide plus N-desmethyl enzalutamide in volunteers with baseline mild, moderate, or severe hepatic impairment (Child-Pugh Class A, B, or C, respectively) versus healthy controls with normal hepatic function. The composite AUC of enzalutamide plus N-desmethyl enzalutamide was similar in volunteers with mild, moderate, or severe baseline hepatic impairment compared to volunteers with normal hepatic function. No initial dosage adjustment is necessary for patients with baseline mild, moderate, or severe hepatic impairment.

OVERDOSAGE

In the event of an overdose, stop treatment with XTANDI and initiate general supportive measures taking into consideration the half-life of 5.8 days. In a dose escalation study, no seizures were reported at ≤ 240 mg daily, whereas 3 seizures were reported, 1 each at 360 mg, 480 mg, and 600 mg daily. Patients may be at increased risk of seizure following an overdose.

NONCLINICAL TOXICOLOGY

Carcinogenesis, Mutagenesis, Impairment of Fertility

Long-term animal studies have not been conducted to evaluate the carcinogenic potential of enzalutamide.

Enzalutamide did not induce mutations in the bacterial reverse mutation (Ames) assay and was not genotoxic in either the *in vitro* mouse lymphoma thymidine kinase (Tk) gene mutation assay or the *in vivo* mouse micronucleus assay.

Based on nonclinical findings in repeat-dose toxicology studies, which were consistent with the pharmacological activity of enzalutamide, male fertility may be impaired by treatment with XTANDI. In a 26-week study in rats, atrophy of the prostate and seminal vesicles was observed at ≥ 30 mg/kg/day (equal to the human exposure based on AUC). In 4-, 13-, and 39-week studies in dogs, hypospermatogenesis and atrophy of the prostate and epididymides were observed at ≥ 4 mg/kg/day (0.3 times the human exposure based on AUC).

Manufactured by: Catalent Pharma Solutions, LLC, St. Petersburg, FL 33716

Manufactured for and Distributed by: Astellas Pharma US, Inc., Northbrook, IL 60062

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Medivation, Inc., San Francisco, CA 94105

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Rx Only

076-1200-PM

Xtandi® (enzalutamide) 40 mg capsules

XTANDI (enzalutamide) capsules is indicated for the treatment of patients with metastatic castration-resistant prostate cancer (CRPC).

Important Safety Information

Contraindications

XTANDI is not indicated for women and is contraindicated in women who are or may become pregnant. XTANDI can cause fetal harm when administered to a pregnant woman.

Warnings and Precautions

Seizure In Study 1, conducted in patients with metastatic castration-resistant prostate cancer (CRPC) who previously received docetaxel, seizure occurred in 0.9% of XTANDI patients and 0% of placebo patients. In Study 2, conducted in patients with chemotherapy-naive metastatic CRPC, seizure occurred in 0.1% of XTANDI patients and 0.1% of placebo patients. There is no clinical trial experience re-administering XTANDI to patients who experienced a seizure, and limited safety data are available in patients with predisposing factors for seizure. Study 1 excluded the use of concomitant medications that may lower threshold; Study 2 permitted the use of these medications. Because of the risk of seizure associated with XTANDI use, patients should be advised of the risk of engaging in any activity during which sudden loss of consciousness could cause serious harm to themselves or others. Permanently discontinue XTANDI in patients who develop a seizure during treatment.

Posterior Reversible Encephalopathy Syndrome (PRES) In post approval use, there have been reports of PRES in patients receiving XTANDI. PRES is a neurological disorder which can present with rapidly evolving symptoms including seizure, headache, lethargy, confusion, blindness, and other visual and neurological disturbances, with or without associated hypertension. A diagnosis of PRES requires confirmation by brain imaging, preferably MRI. Discontinue XTANDI in patients who develop PRES.

Adverse Reactions

The most common adverse reactions (≥ 10%) reported from two combined clinical studies that occurred more commonly (≥ 2% over placebo) in XTANDI patients were asthenia/fatigue, back pain, decreased appetite, constipation, arthralgia, diarrhea, hot flush, upper respiratory tract infection, peripheral edema, dyspnea, musculoskeletal pain, weight decreased, headache, hypertension, and dizziness/vertigo.

In Study 1, Grade 3 and higher adverse reactions were reported among 47% of XTANDI patients and 53% of placebo patients. Discontinuations due to adverse events were reported for 16% of XTANDI patients and 18% of placebo patients. In Study 2, Grade 3-4 adverse reactions were reported in 44% of XTANDI patients and 37% of placebo patients. Discontinuations due to adverse events were reported for 6% of both study groups.

- Lab Abnormalities: Grade 1-4 neutropenia occurred in 15% of XTANDI patients (1% Grade 3-4) and 6% of placebo patients (0.5% Grade 3-4). Grade 1-4 thrombocytopenia occurred in 6% of XTANDI patients (0.3% Grade 3-4) and 5% of placebo patients (0.5% Grade 3-4). Grade 1-4 elevations in ALT occurred in 10% of XTANDI patients (0.2% Grade 3-4) and 16% of placebo patients (0.2% Grade 3-4). Grade 1-4 elevations in bilirubin occurred in 3% of XTANDI patients (0.1% Grade 3-4) and 2% of placebo patients (no Grade 3-4).
- Infections: In Study 1, 1% of XTANDI patients compared to 0.3% of placebo patients died from infections or sepsis. In Study 2, 1 patient in each treatment group (0.1%) had an infection resulting in death.
- Falls (including fall-related injuries), occurred in 9% of XTANDI patients and 4% of placebo patients. Falls were not associated with loss of consciousness or seizure. Fall-related injuries were more severe in XTANDI patients, and included non-pathologic fractures, joint injuries, and hematomas.
- Hypertension occurred in 11% of XTANDI patients and 4% of placebo patients. No patients experienced hypertensive crisis. Medical history of hypertension was balanced between arms. Hypertension led to study discontinuation in < 1% of all patients.

Drug Interactions

Effect of Other Drugs on XTANDI Avoid strong CYP2C8 inhibitors, as they can increase the plasma exposure to XTANDI. If co-administration is necessary, reduce the dose of XTANDI.

Avoid strong CYP3A4 inducers as they can decrease the plasma exposure to XTANDI. If co-administration is necessary, increase the dose of XTANDI.

Effect of XTANDI on Other Drugs Avoid CYP3A4, CYP2C9, and CYP2C19 substrates with a narrow therapeutic index, as XTANDI may decrease the plasma exposures of these drugs. If XTANDI is co-administered with warfarin (CYP2C9 substrate), conduct additional INR monitoring.

Please see adjacent pages for Brief Summary of Full Prescribing Information.

astellas MEDIVATION

94% of insured patient lives are covered for XTANDI*[2]

*As of February 2015. A product's placement on a plan formulary involves a variety of factors known only to the plan and is subject to eligibility.

To learn more, please visit **XtandiHCP.com**

Xtandi® (enzalutamide) 40 mg capsules

XTANDI (enzalutamide) capsules is indicated for the treatment of patients with metastatic castration-resistant prostate cancer (CRPC).

Rx

Start XTANDI at disease progression to metastatic CRPC for your patients on GnRH therapy*[1]

*Or after bilateral orchiectomy.[1]

94% of insured patient lives are covered for XTANDI†[2]

†As of February 2015. A product's placement on a plan formulary involves a variety of factors known only to the plan and is subject to eligibility.

To learn more, please visit **XtandiHCP.com**

Select Safety Information

XTANDI is not indicated for use in women. XTANDI is contraindicated in women who are or may become pregnant.

Seizure occurred in 0.9% of patients receiving XTANDI who previously received docetaxel and in 0.1% of patients who were chemotherapy-naive. Permanently discontinue XTANDI in patients who develop a seizure during treatment.

There have been post approval reports of **posterior reversible encephalopathy syndrome** (PRES), a neurological disorder which can present with rapidly evolving symptoms and requires confirmation by brain imaging. Discontinue XTANDI in patients who develop PRES.

References: 1. XTANDI [package insert]. Northbrook, IL: Astellas Pharma US, Inc. **2.** Data on file, Medivation, Inc.

Please see inside page for additional Important Safety Information.
Please see adjacent pages for Brief Summary of Full Prescribing Information.