Work force shortage projections climb

Three reports predict declining number of urologists, increasing demand

Lisette Hilton | UT CORRESPONDENT

National Report—If medical specialties were competing for which would have the most dire shortage of practicing physicians by 2025, urologists would likely win.

Urologists have for years sounded the alarms about work force issues. But a new nationwide report looking at all medical specialties, including primary care, singles out urology as one of the biggest areas of concern.

The physician work force report, released April 5 by the Association of American Medical Colleges (AAMC), suggests that the United States will experience a shortage of 61,700 to 94,700 physicians in the next decade. The report goes on to say that under virtually every health care scenario, the supply of surgical specialists, including urologists, is projected to decline by 2025. In contrast, the supply of primary care physicians, medical specialists, and other specialists is expected to increase but not enough to meet the demand, according to Janis M. Orlowski, MD, AAMC’s chief health care officer and an author of the report.

It gets worse.

“In particular, we note in the report that for urology, we see the number of people leaving the field of urology, meaning those retiring and dying, is greater than the number of new people who are entering the field of urology,” Dr. Orlowski told Urology Times.

The only other specialty to stand out in a similar way is ophthalmology, according to Dr. Orlowski.

Two additional reports—an abstract presented at the 2016 AUA annual meeting by University of North Carolina researchers and the recently released 2015 AUA Annual Census—also provide concerning data about the present

Does specialty affect sling complication rate?

Slightly fewer complications seen with urologists vs. gynecologists

Mac Overmyer | UT CONTRIBUTING EDITOR

Munich, Germany—Gynecologists derive higher complication rates than urologists during the first 30 days following sling procedures for urinary incontinence, according to a multicenter study presented at the European Association of Urology annual congress in Munich, Germany.

However, the difference was small and most complications were slight—primarily post-procedure urinary tract infections.

The authors arrived at these findings by delving into data amassed by the American College of Surgeons National Surgical Quality Improvement Program (NSQIP). They reviewed 10,508 sling procedures for stress urinary incontinence conducted between 2006 and 2013.

Procedures performed by gynecologists (5,970) were associated with a higher rate of
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Perspective

Urologists, GYNs demonstrate slings’ safety

An abstract authored by Löppenberg et al is an interesting analysis of information from a respected prospective database examining variations in the quality of care provided to patients undergoing sling placement by gynecologists and urologists. An article discussing the research appears in this issue of Urology Times (see page 1). A significant limitation of this study is its inability to evaluate complications beyond 30 days postoperatively. Outcomes associated with sling placement, such as obstruction, delayed pelvic pain, mesh exposure/extrusion, recurrent UTIs, dyspareunia, and persistent incontinence can declare themselves in the extended recovery period and would not be captured in the National Surgical Quality Improvement Program database. Many of these complications are what trigger ultimate reoperation in this patient population. That being said, considering the large cohort studied, there is very little evidence to be made about the quality of surgical care offered by gynecologists or urologists in terms of early complications of sling placement. Patients and referring physicians should feel comfortable that a knowledgeable urologist or gynecologist will have minimal complications in the first 30 days. This work confirms that sling insertion is safe, low risk, and carries minimal complications in the first 30 days, with essentially no difference between gynecologists and urologists during this early time period.

In a larger context, the American Board of Medical Specialties recognized female pelvic medicine and reconstructive surgery as a separate subspecialty in 2011, with accreditation of training programs by the American Board of Obstetrics and Gynecology. This represents a standardization in training for pelvic floor specialists, with a foundational goal of ensuring these surgeons, whether from urology or gynecology backgrounds, have the same surgical skill sets and provide uniform quality care. It is the hope that such training will eliminate disparities of any kind in outcomes of pelvic floor surgical interventions studied in the future.

Seth A. Cohen, MD, and Shlomo Raz, MD

Dr. Cohen is a fellow in female pelvic medicine and reconstructive surgery and Dr. Raz is professor of surgery (urology), UCLA School of Medicine, Los Angeles. Dr. Raz is a member of the Urology Times Editorial Council.

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AACC LEGISLATIVE UPDATE

States attempt to limit importance of MOC

Maintenance of certification has become a time-consuming, expensive, and unnerving exercise. At the federal level, definitions of quality and payment increasingly depend on board certification. State legislators, urged on by grassroots physician activists, are taking the opposite approach, rejecting re-certification as a factor in reimbursement and staffing.

READ THE AACC’S ANALYSIS OF STATEWIDE ACTIONS AT: urologytimes.com/MOC-states

BLOG

Marijuana and me: One urologist’s experience

Henry Rosevar, MD, practices medicine in Colorado, where the state’s ongoing experiment with legal recreational marijuana has provided him a significant amount of professional experience with the drug. Its impact on urology is wide ranging, he says, affecting areas as diverse as fertility and anesthesia.

urologytimes.com/Rosevar

Dr. Rosevar

BLOG

SUO 2015: Bladder Ca variants, renal Bx, and more

Highlights of the 2015 Society of Urologic Oncology meeting included new findings about two bladder cancer variants, how the economy affects prostate cancer diagnosis, the role of renal mass biopsy in management, and more. Read our full coverage, provided exclusively by urologic oncology fellows from across the country.

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Dr. Rosevar

BLOG

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Always there.
Botulinum formulations show slight outcomes differences

Stefanie Petrou Binder, MD
UT CORRESPONDENT

Munich, Germany—A new comparative study showed that the use of intradetrusor injections of abobotulinum toxin A (Dysport) for urinary incontinence due to neurogenic detrusor overactivity (NDO) provided results that were similar to or superior to those seen with onabotulinum toxin A (Botox), depending on the dosage of the latter.

Urinary incontinence due to NDO in adults who have an inadequate response to or are intolerant of anticholinergic therapy has been shown to be responsive to onabotulinum toxin A. Although an increasing number of reports support the efficacy of abobotulinum toxin A for urinary incontinence, few studies have compared the two in NDO patients.

The current retrospective case-control study was carried out by first author Benoit Peyronnet, MD, a urologist at Rennes University Hospital in Rennes, France, and his team of specialists, and was presented at the European Association of Urology annual congress in Munich, Germany. It was subsequently published online in Neurourology and Urodynamics (March 31, 2016 [Epub ahead of print]).

The study included 211 NDO patients who were treated in three consecutive periods of time. The first time period extended from 2004 to 2006 and included the treatment of 80 patients who received onabotulinum toxin, 200 U. The second period spanned the years 2011 to 2014 and studied 53 patients who received onabotulinum toxin, 200 U. The third time period extended from 2007 to 2008 and included the treatment of 2004 to 2006 and included the treatment of 200 U.

Study authors compared urodynamic and clinical parameters among the three groups with regard to the first intradetrusor injections of three botulinum toxin formulations. The primary endpoint was the rate of success defined as the combination of urgency, urinary incontinence, and detrusor overactivity resolution.

Success rates compared

Dr. Peyronnet and his team noted that the success rates were similar—65.4% versus 55.6% (p=0.16)—when comparing combined urgency, urinary incontinence, and detrusor overactivity resolution among patients who received either abobotulinum toxin or onabotulinum toxin (any dose, 200 U or 300 U), respectively (n=133).

The patients who were treated with abobotulinum toxin, 750 U had a higher success rate when compared to the success rate seen in those patients receiving onabotulinum toxin, 200 U (65.4% vs. 41.5%; p=0.007). By contrast, there were similar success rates in the abobotulinum toxin, 750 U, and onabotulinum toxin, 300 U groups (65.4% vs. 65%; p=0.91).

However, the investigators noted a trend toward longer time intervals between the first and the second injections in the onabotulinum toxin, 300 U group compared to the abobotulinum toxin, 750 U group (12.4 vs. 9.3 months; p=0.09), suggesting a longer duration of action of onabotulinum toxin, 300 U.

“Success rates of abobotulinum toxin 750 U and onabotulinum toxin 300 U were similar but interval between injections tended to be longer with onabotulinum toxin 300 U,” Dr. Peyronnet and colleagues wrote.

Onabotulinum toxin, 200 U treatments were associated with higher complication rates than were seen in onabotulinum toxin, 300 U, and abobotulinum toxin, 750 U patients. These included seven cases of urinary tract infection (13.2%) and one case of fatigue in onabotulinum toxin 200 U patients. Complications in the other two groups affected under 4% of the study patients.

The side effects of anticholinergic therapy have led to poor compliance with long-term use. Fortunately, patients with an unsatisfactory response to anticholinergic therapy no longer need to face invasive surgical interventions. The low complication rates observed in this study seem to bode well for long-term applications of botulinum toxin for NDO.

Brain activity in OAB patients characterized in study

Supraspinal control altered in overactive bladder patients, researcher reports

Stefanie Petrou Binder, MD
UT CORRESPONDENT

Munich, Germany—Preliminary findings of a Swiss study revealed that the brain activity associated with the desire to void in response to the automated, repetitive filling and distention of the bladder with body warm saline differed greatly between healthy patients and patients with non-neurogenic overactive bladder (NNOAB).

OAB is characterized by urinary urgency and frequency. Supraspinal control and specifically sensory processing become altered in patients with OAB, according to first author Matthias Walter, MD, research fellow in neuro-urology at the University of Zürich, Balgrist University Hospital, Zürich, Switzerland.

The study, which was presented at the European Association of Urology annual congress in Munich, Germany, included 24 right-handed female participants, of whom 12 had a diagnosis of OAB and 12 were healthy subjects who were matched for age and gender. This was a block design functional magnetic resonance imaging (fMRI) study that acquired neuroimaging data with the use of a 3 Tesla MR scanner. The scan paradigm comprised automated, repetitive bladder filling of 100 mL body warm saline within 15 s.

Please see OAB, page 8
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Undetectable PSA nadir predicts recurrence-free survival
Salvage HIFU shows promise in post-RT PCa patients

Wayne Kuznar
UT CORRESPONDENT
San Francisco—High-intensity focused ultrasound (HIFU) as salvage therapy allows for intermediate-term disease control in selected patients with recurrence following radiation therapy for prostate cancer.

Data from a prospective database reveal that an early predictor of recurrence-free survival in this setting is an undetectable PSA nadir achieved at a median of 3 months post-HIFU, Canadian researchers reported at the Genito-Urinary Cancers Symposium in San Francisco.

The data are interesting and hypothesis-generating but with the series of patients studied being relatively small, “I think that the evidence to support widespread utilization of HIFU for this indication is not there yet,” first author Shawn Dason, MD, told Urology Times. The findings “suggest that salvage HIFU may be promising as a salvage modality with reasonable intermediate-term biochemical control outcomes and limited toxicities,” added Dr. Dason, a urology resident at McMaster University, Hamilton, Ontario, working with Bobby Shayegan, MD, and colleagues.

Local failure rates are as high as 32% following electron beam radiation therapy for prostate cancer, and one-third of patients receiving 81Gy radiotherapy have positive biopsies. To date, local salvage options include salvage prostatectomy, cryotherapy, and brachytherapy. Dr. Dason’s group investigated HIFU in 24 patients with localized radio-recurrent prostate cancer, defined as both a PSA nadir + 2 ng/mL and a positive biopsy.

Study participants were treated with a single session of whole-gland HIFU ablation, with the primary endpoint being recurrence-free survival, defined as a composite endpoint of PSA progression, receipt of any further salvage therapy, receipt of androgen deprivation therapy, clinical progression, or death.

Median PSA level at study entry was 4.02 ng/mL. The treated prostate volume was 23.8 cc. Median follow-up was 31 months. Many patients experienced a sizable decline in PSA from HIFU, with three being PSA non-responders. The median time to PSA nadir was 3 months after treatment, and the median post-HIFU PSA nadir was 0.04 ng/mL.

The 2-year and 5-year recurrence-free survival rates were 66.3% and 51.6%, respectively. An undetectable PSA nadir was a strong predictor of recurrence-free survival (HR 0.07; 95% CI: 0.02 to 0.29; p<.001).

Who benefits from which modality unknown
No comparative data exist between the different forms of nonsurgical salvage therapies, said Dr. Dason, and which patients specifically would benefit from each modality is not certain.

“The reality is that the use of any one of these modalities for salvage therapy will depend on availability. All of these therapies should really only be administered as part of an experimental protocol since the data we have on toxicities and long-term outcomes is not mature enough for widespread adoption,” Dr. Dason said.

While all nonsurgical options avoid the medical risks of surgery and seemingly have lower rates of rectal injury and incontinence, some toxicities appear to be unique to nonsurgical therapies, such as rectourethral fistulae and osteitis pubis.

Urethral strictures are seen with both surgical and nonsurgical therapies, but are probably more common with the latter, he said. In the series presented here, the rate of toxicity was low, with no rectal complications and no cases of osteitis pubis.

“Other series have reported these complications after salvage HIFU but also suggest that they are rare. These findings suggest that salvage HIFU may be promising as a salvage modality with reasonable intermediate-term biochemical control outcomes and limited toxicities,” Dr. Dason said.

In looking at absolute numbers, the biochemical recurrence-free survival in this small series appears to be similar to published series on salvage prostatectomy and other nonsurgical salvage options, he indicated.

“Future randomized controlled trials will be important in confirming these promising results,” he said.

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Functional MRI ‘a powerful tool,’ author says

The patients were catheterized and their bladders were pre-filled until a persistent desire to void was reported from each subject. Using SPM8, the blood-oxygenation-level-dependent signal change during bladder filling was compared to the level at rest; ie, the pre-filled bladder.

Dr. Walter and his colleagues observed bilateral activation in the frontal and prefrontal areas in healthy subjects, including in the inferior frontal gyrus pars triangularis (BA45), pars orbitalis (BA47), and medial frontal gyrus (BA10 and 46).

Activation patterns in NNOAB patients included the right hemisphere: insula, supramarginal gyrus (BA40), Rolandic operculum (BA44), and the postcentral gyrus (primary somatosensory cortex); the left hemisphere: superior frontal gyrus (BA8), caudate, angular gyrus (BA39); and thalamus, as well as bilateral activation patterns: middle cingulate cortex (BA24).

No group differences on whole-brain analysis
Furthermore, no group differences were detected on whole-brain analysis. The regions of interest (ROI) analyses revealed significantly stronger activations in the right posterior insula, left middle cingulate cortex, and left cerebellum for NNOAB patients compared to healthy subjects.

“These differences might reflect the abnormal and unpleasant sensation of urinary urgency and fear of leakage, since both the right dorsal insula and the middle cingulate cortex have been associated with the processing of complex somatosensory information involving emotions and sensory discomfort,” Dr. Walter explained.

The second-level random effects analysis included a sample t-test for each group. Within-group results are shown at a voxel-threshold at p=.05 familywise error rate (FWE) and at p<.001 using the false discovery rate correction, with a strict cluster threshold correction of p<.05 (cluster extend: k>42 voxels) to adjust for multiple comparisons using Monte Carlo simulations.

For group comparisons, whole-brain analyses as well as ROI analyses were computed. The whole-brain analysis was conducted for a comprehensive overview. The ROI approach was performed to explore regional differences between both groups. Thus, the ROIs were included as a mask in order to restrict the voxel-by-voxel statistical analysis (including FWE correction) to pre-specified brain areas. ROIs were generated using the WFU Pickatlas.

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Greater long-term side effect risk with intermittent ADT
Higher incidence of ischemic, thrombotic events observed vs. continuous ADT

Wayne Kuznar
UT CORRESPONDENT

New York—In men with metastatic prostate cancer, those assigned to intermittent androgen deprivation therapy (ADT) have more ischemic and thrombotic events than those assigned to continuous androgen deprivation, according to Columbia University researchers.

The finding comes from linking data from the randomized SWOG 9346 clinical trial to corresponding Medicare claims. This method has the advantage of random assignment for study-specific comparisons of late effects, which limits confounding, said first author Dawn L. Hershman, MD, MS.

Observational studies have linked ADT to sexual dysfunction, osteoporosis and bone fracture, cardiovascular disease, metabolic complications, diabetes, and cognitive changes. Much of these data come from linked databases such as the Surveillance, Epidemiology, and End Results Medicare database, in which a tumor registry is combined with claims-based data.

“Our objective was to evaluate the late effects by treatment arm on men randomized to intermittent versus continuous androgen deprivation therapy who were enrolled in SWOG 9346 for metastatic prostate cancer,” Dr. Hershman said of the study, which was presented at the 2015 American Society of Clinical Oncology annual meeting in Chicago and subsequently published in JAMA Oncology (2016; 2:453-61).

SWOG 9346 had a non-inferiority study design in which men with newly diagnosed metastatic hormone-sensitive prostate cancer and a PSA level ≤5.0 ng/mL received induction therapy with goserelin acetate (Zoladex) plus bicalutamide (Casodex) for 7 months. If the PSA level declined to <4.0 ng/mL, patients were randomized to either continuous or intermittent ADT.

Men randomized to the intermittent-therapy group discontinued ADT and had monthly PSA, and resumed ADT based on pre-specified criteria.

Non-inferiority not reached in median OS
Intermediate ADT failed to reach non-inferiority with respect to median overall survival. The median duration of protocol therapy was 19 months in the intermittent arm and 17 months in the continuous arm. Intermittent therapy was associated with better erectile function and mental health at month 3 but not thereafter. There was no significant difference between the groups in the number of treatment-related high-grade adverse events.

“Only patients without a given prior toxicity were considered at risk for experiencing new toxicity. That means that if a patient had a prior bone fracture, it would not be included in the bone fracture analysis,” said Dr. Hershman, professor of epidemiology at Columbia University’s Mailman School of Public Health and professor of medicine at Columbia University Medical Center, New York.

Toxicity was determined for any hospital claim or at least two outpatient claims at least 30 days apart. The toxicities evaluated were ischemic thrombotic events, endocrine/sexual dysfunction, dementia, and depression.

Of the overall SWOG 9346 study population, 636 (56%) of trial participants had ≥1 year of continuous Medicare Parts A and B coverage. Of these, 311 received continuous ADT and 325 received intermittent ADT. Their mean age was approximately 71 years.

At 5 years, the cumulative incidence of ischemic/thrombotic events was 25% in the intermittent group and 14% in the continuous group, and at 10 years, the cumulative incidence was 33% and 23%, respectively, for an hazard ratio (HR) of 0.68 (p=.02) with continuous ADT on multivariable regression analysis.

For ischemic events alone, the 5-year cumulative rates were 9% and 4% in the intermittent versus continuous arms, and the 10-year rates were 12% and 7%, respectively, for an HR of 0.55 (p=.005) on multivariable regression.

The results were unchanged when two sensitivity analyses were conducted by treatment duration variability.

Cycling of coag. cascade may increase risk
“One might ask, why would ischemic-thrombotic events be lower for patients on continuous ADT? We know there is an increased risk of diabetes and certain cardiovascular diseases with any exposure to ADT. Consulting with my hematology colleagues, they pointed out that the cycling of the coagulation cascade may increase risk, as it does for women on hormone replacement therapy or on birth control pills.

“The risk is highest in the first 6 months, after initiation of ADT. So, it may increase with each initiation of treatment,” Dr. Hershman said.

Compared with no ADT, the incidence of vertebral fractures increased by 40% in men receiving ADT. Prospective studies of bone mineral density in men on intermittent ADT have shown heterogeneity in bone mineral density recovery as patients go off treatment. Many patients enrolled in SWOG 9346 have been followed with bone density measurements and may have been treated with bisphosphonates for any change in bone density, she said.

“Given the failure of SWOG 9346 to prove non-inferiority, clinicians should be cautious about using intermittent ADT,” Dr. Hershman said.
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RP shows worse biochemical failure, less clinical failure than EBRT, brachytherapy

Wayne Kuznar
UT CORRESPONDENT

San Francisco—Treatment options for high-risk prostate cancer perform similarly. In a single-institution study, radical prostatectomy was associated with worse biochemical failure, less clinical failure, and superior prostate cancer-specific mortality compared with radiation therapy and brachytherapy, reported Jay P. Ciezki, MD, at the Genitourinary Cancers Symposium in San Francisco.

More ‘onco-lore’ than ‘onco-data’

“If you look at biochemical relapse-free survival, clinical relapse-free survival, or prostate cancer-specific mortality, there’s not much that’s different amongst [treatment methods].”

JAY P. CIEZKI, MD

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More ‘onco-lore’ than ‘onco-data’

“If you look at biochemical relapse-free survival, clinical relapse-free survival, or prostate cancer-specific mortality, there’s not much that’s different amongst the lot,” said Dr. Ciezki, a radiation oncologist at Cleveland Clinic. “The reason it’s potentially surprising is because there has been ‘onco-lore,’ more than ‘onco-data,’ saying that when you have high-risk prostate cancer and you’re going to use brachytherapy, you have to combine it with external beam.”

His group looked at 2,736 high-risk prostate cancer patients treated at Cleveland Clinic from 1996 to 2012, who were part of an inception cohort study. High-risk prostate cancer was defined as clinical stage T3, a biopsy Gleason score—pretty much the same across all of them.”

JAY P. CIEZKI, MD

Radical prostatectomy PSA value ≥0.4 ng/mL and a post-radiotherapy PSA value ≥2.0 ng/mL above the PSA nadir value. Clinical failure was defined as either local failure (recurrence of cancer within the prostate or prostate bed) or distant failure (cancer metastasized to another site of the body). Cause-specific survival was defined as death from prostate cancer. Patient follow-up data were collected from a review of their electronic medical record and were entered into a database.

“The majority of patients who underwent external beam radiation therapy were treated prior to 2002 because of our growing preference for radical prostatectomy and brachytherapy over time,” said Dr. Ciezki.

Radical prostatectomy was performed in 54% of patients (n=1,487), external beam radiation therapy in 27% (n=734), and brachytherapy in 19% (n=515). No patient received external beam radiation therapy plus brachytherapy, and 44% received androgen deprivation therapy.

The biggest difference among patient groups was in clinical stage. About one-fourth (25.8%) of patients who underwent radical prostatectomy had clinical stage T3 compared with 13.8% undergoing external beam radiation therapy and 0.4% undergoing brachytherapy.

Median follow-up was 4.6 years overall: 3.8 years for patients undergoing radical prostatectomy, 7.7 years for those receiving radiotherapy, and 4.1 years for those who were treated with brachytherapy.

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RP patients at higher risk of PSA failure

Biochemical relapse-free survival at 10 years was 53% in the external beam radiation group, 52% in the brachytherapy group, and 48% in the radical prostatectomy group. On multivariable analysis, radical prostatectomy patients were at higher risk for biochemical failure versus external beam (hazard ratio [HR]: 1.316; p=.008).

Clinical relapse-free survival at 10 years was 73% in the external beam radiation group, 76% in the brachytherapy group, and 76% in the radical prostatectomy group. On multivariable analysis, brachytherapy patients (HR: 1.771; p=.0029) and external beam patients (HR: 1.353; p=.0030) were at higher risk for clinical failure than radical prostatectomy patients.

Prostate cancer-specific mortality at 10 years was 11.5% in the external beam radiation group, 3.6% in the brachytherapy group, and 7.2% in the radical prostatectomy group, and at 15 years, it was 16.3% in the external beam radiation group, 3.6% in the brachytherapy group, and 10.2% in the radical prostatectomy group.

On multivariable analysis, external beam patients (HR: 1.511; p=.0007) were at higher risk for prostate cancer-specific mortality compared to radical prostatectomy patients, while there was no significant difference between radical prostatectomy and brachytherapy (HR: 1.173; p=.6366).

All multivariable analyses were adjusted for clinical stage, biopsy Gleason score, pretreatment PSA, and duration of ADT.

“Clinical stage doesn’t seem to track very much with the outcomes—a little but not quite as strongly as Gleason score, for which there was no real difference between the modalities, and that’s one of its strengths,” Dr. Ciezki said. “One of the major prognostic variables—Gleason score—was pretty much the same across all of them.”

UT Table

<table>
<thead>
<tr>
<th>Outcomes of treatments for high-risk PCa</th>
<th>External beam radiation therapy</th>
<th>Brachytherapy</th>
<th>Radical prostatectomy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Biochemical relapse-free survival at 10 years</td>
<td>53%</td>
<td>52%</td>
<td>48%</td>
</tr>
<tr>
<td>Clinical relapse-free survival at 10 years</td>
<td>73%</td>
<td>76%</td>
<td>76%</td>
</tr>
<tr>
<td>Prostate cancer-specific mortality at 10 years</td>
<td>11.5%</td>
<td>3.6%</td>
<td>7.2%</td>
</tr>
<tr>
<td>Prostate cancer-specific mortality at 15 years</td>
<td>16.3%</td>
<td>3.6%</td>
<td>10.2%</td>
</tr>
</tbody>
</table>

Source: Jay P Ciezki, MD
No link between PDE-5 use, prostate Ca recurrence

Study data appear to refute earlier study findings suggesting higher risk

Wayne Kuznar
UT CORRESPONDENT

San Francisco—No significant relationship was found between use of a phosphodiesterase type-5 inhibitor (PDE-5) and prostate cancer recurrence after treatment in a nested case-control study.

“Our results from a population-based setting suggest against an increased risk of biochemical recurrence among men using PDE-5 after prostate cancer treatment,” said lead investigator Stacy Loeb, MD, MSc, at the Genitourinary Cancers Symposium in San Francisco. The findings were also published online in European Urology (Dec. 29, 2015).

No change in clinical practice regarding the use of PDE-5 inhibitors after prostate cancer treatment is therefore warranted, Dr. Loeb said.

The results corroborate recent findings from Italian investigators, who found no significant association between number of PDE-5 inhibitor pills taken and biochemical recurrence in 2,579 patients who underwent nerve-sparing radical prostatectomy (Eur Urol 2015; 68:750-3). An earlier study from the Martini-Clinic Prostate Cancer Center in Hamburg, Germany suggested a higher risk of prostate cancer recurrence using PDE-5 inhibitors (J Urol 2015; 193:479-83).

The German study “was a huge surprise to the urological community and caused concern given how commonly these medications are used,” said Dr. Loeb, assistant professor of urology and population health at New York University, New York.

“Our study was meant to be the tie-breaker.”

Given the frequency with which PDE-5 inhibitor medications are used, an association with prostate cancer oncologic outcomes would have important consequences.

Dr. Loeb’s group used data from the National Prostate Cancer Register of Sweden linked to the National Prescribed Drug Register and identified 293 men who had radiation therapy or radical prostatectomy and had biochemical recurrence after treatment. For each case, 20 controls were identified who were free of biochemical recurrence. One hundred fifty (51%) of the cases and 3,334 (58%) of the controls used oral PDE-5 inhibitor medication after treatment.

Biochemical recurrence was defined as two PSA measurements ≥0.2 ng/mL for men undergoing radical prostatectomy and two PSA measurements ≥2 ng/mL over the nadir for radiation therapy, with the date of the first such measurement considered the date of biochemical recurrence.

PDE-5 not linked to recurrence after RP, RT

The use of a PDE-5 inhibitor was not associated with biochemical recurrence either in the men who underwent radical prostatectomy (odds ratio [OR] 0.78, 95% confidence interval [CI]: 0.59–1.03) or radiation therapy (OR: 0.98, 95% CI: 0.49-1.97).

Higher PSA level and higher biopsy Gleason grade were significant predictors of biochemical recurrence after prostatectomy and radiation therapy. Clinical stage T2 (compared with T1) and >33% positive biopsy cores were also significant predictors of biochemical recurrence after prostatectomy.

Dr. Loeb noted that a greater number of cumulative PDE-5 inhibitor pills after treatment was associated with a slightly lower risk of recurrence, a finding that lost significance after adjusting for pathologic features.

On stratification by exposure risk, there was no association between PDE-5 inhibitor exposure and risk of biochemical recurrence. Men whose cumulative number of PDE-5 inhibitor pills was above the median had a slightly lower risk of biochemical recurrence in the clinical model (OR: 0.68) and no difference in biochemical recurrence risk after adjustment for prostatectomy features (OR: 0.73).

“I hope that these findings will help to reassure patients who are using these medications for erectile dysfunction after prostate cancer treatment,” Dr. Loeb said.

Dr. Loeb has received honoraria from and is a consultant/adviser for Bayer. She has also received travel, accommodations, and expenses compensation from Sanofi.

Family history of PCa may predict improved outcomes

Significantly increased 10-year survival in men with positive family history

Cory Hugen, MD
SPECIAL TO UROLOGY TIMES

Washington—A positive family history for prostate cancer may predict pathologic and clinical outcomes following radical prostatectomy.

According to new research presented at the 2015 Society of Urologic Oncology annual meeting in Washington, men with a positive family history for prostate cancer are more likely to have lower risk disease at diagnosis, organ-confined disease at the time of surgery, and improved cancer-specific and overall survival.

Researchers from Mayo Clinic in Rochester, MN identified 16,472 men who underwent radical prostatectomy between 1987 and 2010. Of these men, 5,323 reported a positive family history of prostate cancer. When pathologic outcomes were compared, men with a positive family history of prostate cancer were more likely to have low-risk disease at the time of diagnosis (47.7% vs. 43.0%, p<.0001) and organ-confined disease at the time of radical prostatectomy (79.2% vs. 74.4%, p<.0001) compared with men without a family history of prostate cancer.

When the authors compared differences in survival, they found that men with a positive family history of prostate cancer had significantly increased 10-year cancer-specific survival (99% vs. 97%, p<.001) and overall survival (92% vs. 85%, p<.001) compared with men with a negative family history.

Association seen on multivariable analysis

The data were then analyzed using multivariable analysis, and family history retained statistical significance and demonstrated reduced cancer-specific mortality (HR: 0.65, 95% CI: 0.500-0.832, p=.0007) and all-cause mortality (HR: 0.68, 95% CI: 0.622-0.745, p<.0001).

“This study shows that men with a positive family history of prostate cancer who undergo radical prostatectomy have improved cancer-specific and overall survival. We believe that family history information could be used to improve risk stratification and preoperative counseling for men considering surgery for prostate cancer,” said first author Mary E. Westerman, MD, urology resident at Mayo Clinic, Rochester, MN, who worked on the study with Stephen Boorjian, MD, and colleagues.

Whether the differences seen between men with and without a positive family history of prostate cancer are due to earlier diagnosis and stage migration due to increased screening was not evaluated in this study and would certainly warrant further investigation.
The Affordable Care Act: How it has impacted men’s health

The ACA provides a framework to help men embrace their health concerns, but more work is needed

Joel J. Heidelbaugh, MD

The Affordable Care Act (ACA) has provided a substantial benefit for millions of Americans who otherwise wouldn’t have been able to afford or have access to primary and specialty health care. Going to the doctor, however, still can be very costly for men who lack health insurance, which in many cases has resulted in avoidance of health care or overutilization of emergency department services. The ACA is a large step forward in allowing men to embrace their health concerns, and for health care practitioners to understand men and the challenge of help seeking, masculinity, and disparity in their quest for wellness (Men’s Health in Primary Care [Current Clinical Practice]. Switzerland: Springer International Publishing, 2016).

An estimated 41.3 million uninsured people became eligible for new health insurance coverage under the ACA, the majority of whom were adult men. Prior to the installation of the ACA, approximately 33% of American Indian and Alaska Native men, 25% of Hispanic men, 20% of African-American men, and 12% of Caucasian men did not have health insurance, while notably 25% of men between the ages of 19 and 25 years had no health insurance, according to the Centers for Medicare & Medicaid Services (CMS).

Pre-ACA figures from the first half of 2013 showed that 31% of men aged 25 to 34 years went without insurance, as opposed to 22% of women in the same age group. In addition, 26% of men never saw a doctor in 2012, compared to only 13% of women.

Disparities in coverage identified

Early critics of the ACA pointed out disparities in coverage between women and men. While the law expanded contraception coverage for women (eg, oral and implantable contraceptives, tubal ligations), not all insurance companies have covered vasectomies, and most do not cover condoms. Similarly, all insurance companies cover screening for sexually transmitted infections in women, yet only for high-risk men, including human immunodeficiency virus screening. To date, not all health insurance companies cover gonorrhea testing in men.

Wellness and preventive care are provisions that should be equally provided to men and women of all ages throughout their lives. To date, there remains a disparity in coverage across many major insurance plans, although this gap has narrowed in the last few years. Through the ACA, individual states have the opportunity to expand Medicaid coverage to

These disparities have led to an outcry in the male community, citing "sexism" in the ACA, as reported by change.org. Another point of disparity that has led to claims of gender bias in the ACA is domestic violence screening. Women have full coverage for screenings at no cost, yet men do not, while the rates of domestic violence against men are rising in both opposite-sex and same-sex relationships.

To date, there are no federal health offices with specific provisions to adequately address male-specific health issues. The ACA lists 134 references to women’s health, yet has only two references to men’s health without a clear definition or plan for these references. The law even has a specific chapter dedicated to women’s health but nothing dedicated to men’s health ("The Affordable Care Act, Section by Section" [hhs.gov] and “Shining a Light on Health Insurance Rate Increases” [cms.gov]).

The ACA dedicates an entire section to breast cancer, but gives no attention to prostate cancer, while a substantial disparity exists between men and women when it comes to spending on cancer research (figure 1). The importance of wellness and comprehensive care for men across the lifespan seems to have been marginalized, other than to offer a simple entry point to the health care system.

Wellness and preventive care are provisions that should be equally provided to men and women of all ages throughout their lives. To date, there remains a disparity in coverage across many major insurance plans, although this gap has narrowed in the last few years. Through the ACA, individual states have the opportunity to expand Medicaid coverage to

SECTION EDITOR

Steven A. Kaplan, MD, is professor of urology at the Icahn School of Medicine at Mount Sinai and director of benign urologic diseases, Mount Sinai Health System, New York. Follow him on Twitter at @MaleHealthDoc.
INDICATION
ZYTIGA® (abiraterone acetate) in combination with prednisone is indicated for the treatment of patients with metastatic castration-resistant prostate cancer (mCRPC).

IMPORTANT SAFETY INFORMATION
Contraindications—ZYTIGA® is not indicated for use in women. ZYTIGA® can cause fetal harm (Pregnancy Category X) when administered to a pregnant woman and is contraindicated in women who are or may become pregnant.

Hypertension, Hypokalemia, and Fluid Retention Due to Mineralocorticoid Excess—Use with caution in patients with a history of cardiovascular disease or with medical conditions that might be compromised by increases in blood pressure, hypokalemia, or fluid retention. ZYTIGA® may cause hypertension, hypokalemia, and fluid retention as a consequence of increased mineralocorticoid levels resulting from CYP17 inhibition. Safety has not been established in patients with LVEF <50% or New York Heart Association (NYHA) Class III or IV heart failure (in Study 1) or NYHA Class II to IV heart failure (in Study 2) because these patients were excluded from these randomized clinical trials. Control hypertension and correct hypokalemia before and during treatment. Monitor blood pressure, serum potassium, and symptoms of fluid retention at least monthly.

Adrenocortical Insufficiency (AI)—AI was reported in patients receiving ZYTIGA® in combination with prednisone, after an interruption of daily steroids and/or with concurrent infection or stress. Use caution and monitor for symptoms and signs of AI if prednisone is stopped or withdrawn, if prednisone dose is reduced, or if the patient experiences unusual stress. Symptoms and signs of AI may be masked by adverse reactions associated with mineralocorticoid excess seen in patients treated with ZYTIGA®. Perform appropriate tests, if indicated, to confirm AI. Increased dosages of corticosteroids may be used before, during, and after stressful situations.

mCRPC = metastatic castration-resistant prostate cancer; ADT = androgen-deprivation therapy.

Please see additional Important Safety Information on the next pages. Please see brief summary of full Prescribing Information on subsequent pages.
In the final analysis of the pivotal phase 3 trial*...

**ZYTIGA®** + prednisone achieved a median OS of almost 3 years (34.7 months) after a median 4 years (49 months) of follow-up†

- 4.4 months improvement in median overall survival—34.7 months with ZYTIGA® + prednisone vs **30.3 months** with placebo + prednisone (active compound)‡
  - **Co-primary end point**—median OS: hazard ratio (HR)=0.81; 95% CI: 0.70, 0.93; *P*=0.0033
  - **Co-primary end point**—at the prespecified rPFS analysis, median not reached for ZYTIGA® + prednisone vs a median of 8.28 months for placebo + prednisone; HR=0.425; 95% CI: 0.347, 0.522; *P*<0.0001§

**IMPORTANT SAFETY INFORMATION**

**Hepatotoxicity**—Monitor liver function and modify, withhold, or discontinue ZYTIGA® dosing as recommended (see Prescribing Information for more information). Measure serum transaminases [alanine aminotransferase (ALT) and aspartate aminotransferase (AST)] and bilirubin levels prior to starting treatment with ZYTIGA®, every two weeks for the first three months of treatment, and monthly thereafter. Promptly measure serum total bilirubin, AST, and ALT if clinical symptoms or signs suggestive of hepatotoxicity develop. Elevations of AST, ALT, or bilirubin from the patient’s baseline should prompt more frequent monitoring. If at any time AST or ALT rise above five times the upper limit of normal (ULN) or the bilirubin rises above three times the ULN, interrupt ZYTIGA® treatment and closely monitor liver function.

**Adverse Reactions**—The most common adverse reactions (≥10%) are fatigue, joint swelling or discomfort, edema, hot flush, diarrhea, vomiting, cough, hypertension, dyspnea, urinary tract infection and contusion.

The most common laboratory abnormalities (>20%) are anemia, elevated alkaline phosphatase, hypertriglyceridemia, lymphopenia, hypercholesterolemia, hyperglycemia, elevated AST, hypophosphatemia, elevated ALT and hypokalemia.

**Drug Interactions**—Based on in vitro data, ZYTIGA® is a substrate of CYP3A4. In a drug interaction trial, co-administration of rifampin, a strong CYP3A4 inducer, decreased exposure of abiraterone by 55%. Avoid concomitant strong CYP3A4 inducers during ZYTIGA® treatment. If a strong CYP3A4 inducer must be co-administered, increase the ZYTIGA® dosing frequency only during the co-administration period [see Dosage and Administration (2.3)]. In a dedicated drug interaction trial, co-administration of ketoconazole, a strong inhibitor of CYP3A4, had no clinically meaningful effect on the pharmacokinetics of abiraterone.

*continued on next page*
Prespecified secondary end point\textsuperscript{\textregistered}†
ZYTIGA\textsuperscript{\textregistered} + prednisone significantly delayed median time to initiation of cytotoxic chemotherapy

ZYTIGA\textsuperscript{\textregistered} + prednisone vs placebo + prednisone:

\textbf{25.2 vs 16.8 MONTHS}

Secondary end point—HR=0.580; 95\% CI: 0.487, 0.691; \textit{P}<0.0001

**IMPORTANT SAFETY INFORMATION—continued**

Drug Interactions—continued

ZYTIGA\textsuperscript{\textregistered} is an inhibitor of the hepatic drug-metabolizing enzymes CYP2D6 and CYP2C8. Avoid co-administration with CYP2D6 substrates with a narrow therapeutic index. If alternative treatments cannot be used, exercise caution and consider a dose reduction of the CYP2D6 substrate drug. In a CYP2C8 drug interaction trial in healthy subjects, the AUC of pioglitazone, a CYP2C8 substrate, was increased by 46\% when administered with a single dose of ZYTIGA\textsuperscript{\textregistered}. Patients should be monitored closely for signs of toxicity related to a CYP2C8 substrate with a narrow therapeutic index if used concomitantly with ZYTIGA\textsuperscript{\textregistered}.

Use in Specific Populations—Do not use ZYTIGA\textsuperscript{\textregistered} in patients with baseline severe hepatic impairment (Child-Pugh Class C).

OS = overall survival; rPFS = radiographic progression-free survival.

\textsuperscript{\textregistered}Study Design: ZYTIGA\textsuperscript{\textregistered}, in combination with prednisone, was evaluated in a phase 3, randomized, double-blind, placebo-controlled, multicenter trial in patients with mCRPC who had not received prior chemotherapy (N=1,088). Patients were using a luteinizing hormone-releasing hormone (LHRH) agonist or were previously treated with orchiectomy. In the ZYTIGA\textsuperscript{\textregistered} arm, patients received ZYTIGA\textsuperscript{\textregistered} 1,000 mg orally once daily + prednisone 5 mg orally twice daily. In the placebo arm, patients received placebo orally once daily + prednisone 5 mg orally twice daily. In this study, the co-primary efficacy end points were OS and rPFS. Select exclusion criteria included aspartate aminotransferase (AST) and/or alanine aminotransferase (ALT) $\geq 2.5X$ ULN, liver metastases, moderate or severe pain, opiate use for cancer pain, prior ketoconazole treatment for prostate cancer, a history of adrenal gland or pituitary disorders, and visceral organ metastases. Concurrent use of spironolactone was not allowed during the study period.

\textsuperscript{\textregistered}At a prespecified final analysis for OS, 65\% (354/546) of patients treated with ZYTIGA\textsuperscript{\textregistered} + prednisone compared with 71\% (387/542) of patients treated with placebo + prednisone had died.

\textsuperscript{\textregistered}Prednisone, as a single agent, is not approved for the treatment of prostate cancer.

\textsuperscript{\textregistered}rPFS was assessed with the use of sequential imaging studies and was defined by bone scan identification of 2 or more new bone lesions with confirmation (Prostate Cancer Working Group 2 [PCWG2] criteria) and/or modified Response Evaluation Criteria in Solid Tumors (RECIST) criteria for progression of soft tissue lesions. Analysis of rPFS utilized centrally reviewed radiographic assessment of progression.

\textsuperscript{\textregistered}At the prespecified rPFS analysis, 150 (28\%) of patients treated with ZYTIGA\textsuperscript{\textregistered} + prednisone and 251 (46\%) of patients treated with placebo + prednisone had radiographic progression.

\textsuperscript{\textregistered}The secondary efficacy analysis presented here is as of the December 20, 2011, cutoff date.\textsuperscript{1}


Learn more today at [www.zytigahcp.com](http://www.zytigahcp.com)
ZYTIGA® (abiraterone acetate) Tablets
Brief Summary of Prescribing Information.

INDICATIONS AND USAGE
ZYTIGA is a CYP17 inhibitor indicated in combination with prednisone for the treatment of patients with metastatic castration-resistant prostate cancer.

CONTRAINDICATIONS
Pregnancy: ZYTIGA can cause fetal harm when administered to a pregnant woman. Use in women. ZYTIGA is contraindicated in women who are or may become pregnant. If this drug is used during pregnancy, use ZYTIGA with caution in these patients. Pregnancy: ZYTIGA is not indicated for use in women. ZYTIGA is contraindicated in women.

WARNINGS AND PRECAUTIONS
Hypertension, Hypokalemia and Fluid Retention Due to Mineralocorticoid Excess: ZYTIGA may cause hypertension, hypokalemia, and fluid retention as a consequence of increased mineralocorticoid levels resulting from CYP17 inhibition [see Clinical Pharmacology (12.1) in full Prescribing Information]. In the two randomized clinical trials, grade 3 to 4 hypertension occurred in 2% of patients, grade 3 to 4 hypokalemia in 4% of patients, and grade 3 to 4 edema in 1% of patients treated with ZYTIGA. Co-administration of a corticosteroid suppresses adrenocorticotropic hormone (ACTH) drive, resulting in a reduction in the incidence and severity of these adverse reactions. Use caution when treating patients whose underlying medical conditions might be compromised by increases in blood pressure, hypokalemia or fluid retention, e.g., those with heart failure, recent myocardial infarction or ventricular arrhythmia. Use ZYTIGA with caution in patients with a history of cardiovascular disease. The safety of ZYTIGA in patients with left ventricular ejection fraction $<$50% or New York Heart Association (NYHA) Class III or IV heart failure (in Study 1) or NYHA Class II to IV heart failure (in Study 2) was not established because these patients were excluded from these randomized clinical trials [see Clinical Studies (14) in full Prescribing Information]. Monitor patients for hypertension, hypokalemia, and fluid retention at least once a month. Control hypertension and correct hypokalemia before and during treatment with ZYTIGA.

Adrenocortical Insufficiency: Adrenal insufficiency occurred in the two randomized clinical trials in 0.5% of patients taking ZYTIGA and in 0.2% of patients taking placebo. Adrenocortical insufficiency was reported in patients receiving ZYTIGA in combination with prednisone, following interruption of daily corticosteroids and/or with concurrent infection or stress. Use caution and monitor for symptoms and signs of adrenocortical insufficiency, particularly if patients are within 14 days of dose reduction of corticosteroids, or experience unusual stress. Symptoms and signs of adrenocortical insufficiency may be masked by adverse reactions associated with mineralocorticoid excess seen in patients treated with ZYTIGA. If clinically indicated, perform appropriate tests to confirm the diagnosis of adrenocortical insufficiency. Increased dosages of corticosteroids may be indicated before, during and after stressful situations [see Warnings and Precautions].

Hepatotoxicity: In the two randomized clinical trials, grade 3 or 4 ALT or AST increases (at least 5X ULN) were reported in 4% of patients who received ZYTIGA, typically during the first 3 months after starting treatment. Patients whose baseline ALT or AST were elevated were more likely to experience liver test elevation than those beginning with normal values. Treatment discontinuation due to liver enzyme increases occurred in 1% of patients taking ZYTIGA. No deaths clearly related to ZYTIGA were reported due to hepatotoxicity events.

Measure serum transaminases (ALT and AST) and bilirubin levels prior to starting treatment with ZYTIGA, every two weeks for the first three months of treatment and monthly thereafter. In patients with baseline moderate hepatic impairment receiving a reduced ZYTIGA dose of 250 mg, measure ALT, AST, and bilirubin prior to the start of treatment, every week for the first month, every two weeks for the following two months of treatment and monthly thereafter. Promptly measure serum total bilirubin, AST, and ALT if clinical symptoms or signs suggestive of hepatotoxicity develop. Elevations of AST, ALT, or bilirubin from the patient’s baseline should prompt more frequent monitoring. If at any time AST or ALT rise above five times the ULN, or the bilirubin rises above three times the ULN, interrupt ZYTIGA treatment and closely monitor liver function. Re-treatment with ZYTIGA at a reduced dose level may take place only after return of liver function tests to the patient’s baseline or to AST and ALT less than or equal to 2.5X ULN and total bilirubin less than or equal to 1.5X ULN [see Dosage and Administration (2.2) in full Prescribing Information]. The safety of ZYTIGA re-treatment of patients who develop ALT or AST greater than or equal to 20X ULN and/or bilirubin greater than or equal to 10X ULN is unknown.

ADVERSE REACTIONS
The following are discussed in more detail in other sections of the labeling:
- Hypertension, Hypokalemia, and Fluid Retention due to Mineralocorticoid Excess [see Warnings and Precautions].
- Adrenocortical Insufficiency [see Warnings and Precautions].
- Hepatotoxicity [see Warnings and Precautions].

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 clinical practice.

ZYTIGA® (abiraterone acetate) Tablets
Two randomized placebo-controlled, multicenter clinical trials enrolled patients who had metastatic castration-resistant prostate cancer who were using a luteinizing hormone-releasing hormone (LHRH) agonist or were previously treated with orchiectomy. In both Study 1 and Study 2 ZYTIGA was administered at a dose of 1,000 mg daily in combination with prednisone 5 mg twice daily in the active treatment arms. Placebo plus prednisone 5 mg twice daily was given to control patients.

The most common adverse reactions (≥10%) reported in the two randomized clinical trials that occurred more commonly (≥2%) in the abiraterone acetate arm were fatigue, joint swelling or discomfort, edema, hot flush, diarrhea, vomiting, cough, hypertension, dyspnea, urinary tract infection and contusion.

Table 1 shows adverse reactions on the ZYTIGA arm in Study 1 that occurred with a ≥2% absolute increase in frequency compared to placebo or were events of special interest. The median duration of treatment with ZYTIGA was 8 months.

Table 1: Adverse Reactions due to ZYTIGA in Study 1

<table>
<thead>
<tr>
<th>System/Organ Class</th>
<th>Adverse reaction</th>
<th>ZYTIGA with Prednisone (N=791)</th>
<th>Placebo with Prednisone (N=394)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All Grades</td>
<td>Grade 3-4</td>
<td>All Grades</td>
<td>Grade 3-4</td>
</tr>
<tr>
<td>Musculoskeletal and connective tissue disorders</td>
<td>Joint swelling/discomfort</td>
<td>29.5</td>
<td>4.2</td>
</tr>
<tr>
<td></td>
<td>Muscle discomfort</td>
<td>26.2</td>
<td>3.0</td>
</tr>
<tr>
<td>General disorders</td>
<td>Edema</td>
<td>26.7</td>
<td>1.9</td>
</tr>
<tr>
<td></td>
<td>Vascular disorders</td>
<td>19.0</td>
<td>0.3</td>
</tr>
<tr>
<td></td>
<td>Hypertension</td>
<td>8.5</td>
<td>1.3</td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td>Diarrhea</td>
<td>17.6</td>
<td>0.6</td>
</tr>
<tr>
<td></td>
<td>Dyspepsia</td>
<td>6.1</td>
<td>0</td>
</tr>
<tr>
<td>Infections and infestations</td>
<td>Urinary tract infection</td>
<td>11.5</td>
<td>2.1</td>
</tr>
<tr>
<td></td>
<td>Upper respiratory tract infection</td>
<td>5.4</td>
<td>0</td>
</tr>
<tr>
<td>Respiratory, thoracic and mediastinal disorders</td>
<td>Cough</td>
<td>10.6</td>
<td>0.5</td>
</tr>
<tr>
<td>Renal and urinary disorders</td>
<td>Urinary frequency</td>
<td>7.2</td>
<td>0.3</td>
</tr>
<tr>
<td></td>
<td>Nocturia</td>
<td>6.2</td>
<td>0</td>
</tr>
<tr>
<td>Injury, poisoning and procedural complications</td>
<td>Fractures</td>
<td>5.9</td>
<td>1.4</td>
</tr>
<tr>
<td>Cardiac disorders</td>
<td>Arrhythmia</td>
<td>7.2</td>
<td>1.1</td>
</tr>
<tr>
<td></td>
<td>Chest pain or chest discomfort</td>
<td>3.8</td>
<td>0.5</td>
</tr>
<tr>
<td></td>
<td>Cardiac failure</td>
<td>2.3</td>
<td>1.9</td>
</tr>
</tbody>
</table>

1 Adverse events graded according to CTCAE version 3.0
2 Includes terms Arthritis, Arthralgia, Joint swelling, and Joint stiffness
3 Includes terms Muscle spasms, Musculoskeletal pain, Myalgia,
Musculoskeletal discomfort, and Musculoskeletal stiffness
4 Includes terms Edema, Edema peripheral, Pitting edema, and Generalized edema
5 Includes all fractures with the exception of pathological fracture
6 Includes terms Arthralgia, Tachycardia, Atrial fibrillation, Supraventricular tachycardia, Atrial tachycardia, Ventricular tachycardia, Atrial flutter, Bradyarrhythmia, Atrioventricular block complete, Conduction disorder, and Bradycardia
7 Includes terms Angina pectoris, Chest pain, and Angina unstable.
Myocardial infarction or ischemia occurred more commonly in the placebo arm than in the ZYTIGA arm (1.3% vs. 1.1% respectively).
8 Includes terms Cardiac failure, Cardiac failure congestive, Left ventricular dysfunction, Cardiogenic shock, Cardiomegalic, Cardiomyopathy, and Ejection fraction decreased.
Table 2 shows laboratory abnormalities of interest from Study 1. Grade 3-4 low serum phosphorus (7%) and low potassium (5%) occurred at a greater than or equal to 5% rate in the ZYTIGA arm.

Table 3: Adverse Reactions in ≥5% of Patients on the ZYTIGA Arm in Study 2

Table 4: Laboratory Abnormalities in >15% of Patients on the ZYTIGA Arm in Study 2

Cardiovascular Adverse Reactions: In the combined data for studies 1 and 2, cardiac failure occurred more commonly in patients treated with ZYTIGA compared to patients on the placebo arm (2.1% versus 0.7%). Grade 3-4 cardiac failure occurred in 1.6% of patients taking ZYTIGA and led to 5 treatment discontinuations and 2 deaths. Grade 3-4 cardiac failure occurred in 0.2% of patients taking placebo. There were no treatment discontinuations and one death due to cardiac failure in the placebo group.

In Study 1 and 2, the majority of arrhythmias were grade 1 or 2. There was one death associated with arrhythmia and one patient with sudden death in the ZYTIGA arm and no deaths in the placebo arms. There were 7 (0.5%) deaths due to cardiorespiratory arrest in the ZYTIGA arms and 3 (0.3%) deaths in the placebo arms. Myocardial ischemia or myocardial infarction led to death in 3 patients in the placebo arms and 2 deaths in the ZYTIGA arms.

Post Marketing Experience
The following additional adverse reactions have been identified during post approval use of ZYTIGA. 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.

DRUG INTERACTIONS
Drugs that Inhibit or Induce CYP3A4 Enzymes: Based on in vitro data, ZYTIGA is a substrate of CYP3A4.

In a dedicated drug interaction trial, co-administration of rifampin, a strong CYP3A4 inducer, decreased exposure of abiraterone by 55%. Avoid concomitant use of these agents in patients taking ZYTIGA. If a strong CYP3A4 inducer must be co-administered, increase the ZYTIGA dosing frequency [see Dosage and Administration (2.3) and Clinical Pharmacology (12.3) in full Prescribing Information].

In a dedicated drug interaction trial, co-administration of ketoconazole, a strong inhibitor of CYP3A4, had no clinically meaningful effect on the pharmacokinetics of abiraterone [see Clinical Pharmacology (12.3) in full Prescribing Information].

Effects of Abiraterone on Drug Metabolizing Enzymes: ZYTIGA is an inhibitor of the hepatic drug-metabolizing enzymes CYP2D6 and CYP2C8. In a CYP2D6 drug-drug interaction study, the Cmax and AUC of dextromethorphan (CYP2D6 substrate) were increased 2.8- and 2.9-fold, respectively, when dextromethorphan was given with abiraterone acetate 1,000 mg daily and prednisone 5 mg twice daily. Avoid co-administration of abiraterone acetate with substrates of CYP2D6 with a narrow therapeutic index (e.g., thioridazine). If alternative treatments cannot be used, exercise caution and consider a dose reduction of the concomitant CYP2D6 substrate drug [see Clinical Pharmacology (12.3) in full Prescribing Information].

In a CYP2C8 drug-drug interaction trial in healthy subjects, the AUC of pioglitazone (CYP2C8 substrate) was increased by 46% when pioglitazone was given together with a single dose of 1,000 mg abiraterone acetate. Therefore, patients should be monitored closely for signs of toxicity related to a CYP2C8 substrate with a narrow therapeutic index if used concomitantly with ZYTIGA [see Clinical Pharmacology (12.3) in full Prescribing Information].

USE IN SPECIFIC POPULATIONS
Pregnancy: Pregnancy Category X [see Contraindications:]. ZYTIGA can cause fetal harm when administered to a pregnant woman based on its mechanism of action and findings in animals. While there are no adequate and well-controlled studies with ZYTIGA in pregnant women and ZYTIGA is not indicated for use in women, it is important to know that maternal use of a CYP17 inhibitor could
**Patients with Renal Impairment:** In a dedicated renal impairment trial, the mean PK parameters were comparable between healthy subjects with normal renal function (N=8) and those with end stage renal disease (ESRD) the mean PK parameters were comparable between healthy subjects with normal renal function and those with end stage renal disease.

**Nursing Mothers:** ZYTIGA is not indicated for use in women. It is not known if abiraterone acetate 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 ZYTIGA, 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 ZYTIGA in pediatric patients have not been established.

**Geriatric Use:** Of the total number of patients receiving ZYTIGA in Phase 3 trials, 73% of patients were 65 years and over and 30% were 75 years and over. No overall differences in safety or effectiveness were observed between these elderly 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 Hepatic Impairment:** The pharmacokinetics of abiraterone were examined in subjects with baseline mild (N=8) or moderate (N=8) hepatic impairment (Child-Pugh Class A and B, respectively) and in 8 healthy control subjects with normal hepatic function. The systemic exposure (AUC) of abiraterone after a single oral 1,000 mg dose of ZYTIGA increased by approximately 1.1-fold and 3.6-fold in subjects with mild and moderate hepatic impairment compared to subjects with normal hepatic function.

In another trial, the pharmacokinetics of abiraterone were examined in subjects with baseline severe (N=8) hepatic impairment (Child-Pugh Class C) and in 8 healthy control subjects with normal hepatic function. The systemic exposure (AUC) of abiraterone increased by approximately 7-fold and the fraction of free drug increased 2-fold in subjects with severe baseline hepatic impairment compared to subjects with normal hepatic function. No dosage adjustment is necessary for patients with baseline mild hepatic impairment. In patients with baseline moderate hepatic impairment (Child-Pugh Class B), reduce the recommended dose of ZYTIGA to 250 mg once daily. Do not use ZYTIGA in patients with baseline severe hepatic impairment (Child-Pugh Class C). If elevations in ALT or AST >5X ULN or total bilirubin >3X ULN occur in patients with baseline moderate hepatic impairment, discontinue ZYTIGA treatment [see Dosage and Administration (2.1) and Clinical Pharmacology (12.3) in full Prescribing Information].

For patients who develop hepatotoxicity during treatment, interruption of treatment and dosage adjustment may be required [see Dosage and Administration (2.2) in full Prescribing Information, Warnings and Precautions, and Clinical Pharmacology (12.3) in full Prescribing Information].

**Patients with Renal Impairment:** In a dedicated renal impairment trial, the mean PK parameters were comparable between healthy subjects with normal renal function (N=8) and those with end stage renal disease (ESRD) on hemodialysis (N=8) after a single oral 1,000 mg dose of ZYTIGA. No dosage adjustment is necessary for patients with renal impairment [see Dosage and Administration (2.1) and Clinical Pharmacology (12.3) in full Prescribing Information].

**OVER Dosage**

**Human experience of overdose with ZYTIGA is limited.** There is no specific antidote. In the event of an overdose, stop ZYTIGA, undertake general supportive measures, including monitoring for arrhythmias and cardiac failure and assess liver function.

**Storage and Handling:** Store at 20°C to 25°C (68°F to 77°F); excursions permitted in the range from 15°C to 30°C (59°F to 86°F) [see USP controlled room temperature].
all uninsured adults aged 19 to 64 years with incomes up to 133% of the federal poverty level. In those states expanding Medicaid coverage, many parents and single and childless adults are now eligible for health care coverage.

Financial assistance available
Additionally, financial assistance to help pay for monthly premiums and lower out-of-pocket costs can be available to men applying for health care coverage through the marketplace, CMS reports. Notably, the ACA plans have resulted in drastic increases in premium prices for men in nearly every state, raising the question of how men can sustainably afford such coverage (figure 2).

Over a decade ago, prior to embarking on writing an evidence-based men’s health textbook, I asked a random male patient in my practice to give me his views of men’s health. His reply was, “Guy problems. You know, prostate and genital problems. They die of heart attacks and strokes mostly... Oh yeah, some cancers too. And stupid, risky behaviors. Guys like to take chances, and don’t always think about what might happen to them. We should know better.” (“Clinical Men’s Health: Evidence in Practice.” Philadelphia: Saunders/Elsevier, 2008).

Substantial opportunities exist to improve upon multidisciplinary men’s health now that the ACA is in place.

It became clear to me that many men struggle to understand the key health care provisions that they should receive, while many lack access to health care. The ACA has provided the portal, yet in many cases, unequally for men.

What needs to be done
Substantial opportunities exist to improve upon multidisciplinary men’s health now that the ACA is in place. An updated report analyzing the current state of men’s health in the United States is desperately needed to outline where efforts should be directed to decrease morbidity and mortality from preventable illness. An office of men’s health at the National Institutes of Health with efforts dedicated to understanding the unique needs of men and to close the gap in disparities would help improve the health of men and families in our communities, similar to the efforts provided by the existing office for women’s health.

The future of men’s health sits on opportunistic ground. Who owns the domain of men’s health? There is no clear answer, yet collaborative efforts across medical disciplines including primary care, urology, andrology/endocrinology, cardiology, and mental health need to band together in research, guideline development, and health policy to foster more accessible and cost-effective strategies to care for men.

U.S. medical schools continue to see a decline in interest in students entering primary care, with less than 10% of graduating students matching in family medicine. Most of those matching in internal medicine will choose to be specialists or hospitalists. Most students matching in family medicine are women, many of whom will choose to focus on women’s health. Nurse practitioners and physician assistants can’t be minted fast enough to compensate for the deficit in primary care to care for our male patients.

Now is the time to invest in men’s health, build upon the framework of the ACA, and improve the health care of men and our communities.
PQRS success challenging but doable for urologists

Careful selection of measures, reporting method is crucial to meet program requirements

Q We are really struggling with the Physician Quality Reporting System (PQRS) codes. Our Medicare remittance is telling us 3016F is not a reportable code, but I have called and verified the code is billable. I also understand that we need to be reporting nine measures across three categories. Can you help clarify this?

A Your question does not have a simple answer. We will try to break down the parts of the question into a few separate answers.

The first part of your question, in relation to code 3016F not being a reportable code, is confusing. In fact, 3016F is a valid code and can be used as part of reporting measure 173. However, based on your question, we can safely assume that you submitted this code on a claim. Measure 173 is not eligible for claims-based reporting but can only be reported via a registry. Therefore, the claim processing system will reject the code as it cannot be processed. The rejection notice is not very descriptive.

If you look under the PQRS measure section on the AUA Coding Today website (www.auacodingtoday.com), you can find all measures. Each measure will list in the body of the measure what methods are acceptable for reporting.

Regarding the second part of your question: You are required to report at least nine individual measures across three National Quality Strategy domains, one of which must be a cross-cutting measure, or a single measures group. The issue we have seen with measures groups for urology is a lack of a measures group that truly fits the specialty. It can be done, but you will have to collect some information that is likely not in your process.

The issue we have seen with PQRS measures groups for urology is a lack of a measures group that truly fits the specialty.

Reporting can be done using any of several methods; however, you will need to select your measures and method of reporting with the method of reporting in mind. Here are the methods you can choose from:

- Medicare Part B claims
- qualified PQRS registry
- direct electronic health record (EHR) using certified EHR technology (CEHRT)
- CEHRT via data submission vendor
- qualified clinical data registry.

Finally, once the method and measures are selected and matched, you will need to set up the practice actions, documentation, and reporting to meet the reporting requirements. In the end, PQRS is doable but it does require both planning and execution.

The AUA has a “PQRS Toolkit” online with resources including recommended urology measures and information on reporting options; see bit.ly/PQRStoolkit for more.

If you are still have difficulty with PQRS, resources like Physician Reimbursement Systems can provide in-depth assistance, but please contact us directly to discuss options.

Q If a patient was referred to a subspecialist to only do the surgery and then returns to the local physician for the follow-up care, how is that coded? The physicians are not in the same practice, but since there is a global period, how does that work?

A Theoretically and the correct way to report from a coding standpoint, the “urologist specialist/surgeon” that is performing the procedure would append the 56-Preoperative Management Only and 54-Surgical Care Only modifiers to the procedure code.

The “local physician” would then submit the same procedure code and append the 55-Postoperative Management Only modifier. The carrier would then split the overall value appropriately to the appropriate physicians. (Also see, “Modifier 54, 55, and 56 definitions,” page 17.)

The “local physician” is basically purchasing (taking over) the postoperative planning and execution.

 Send coding and reimbursement questions to Ray Painter, MD, and Mark Painter c/o Urology Times, at UT@advanstar.com.

Questions of general interest will be chosen for publication. The information in this column is designed to be authoritative, and every effort has been made to ensure its accuracy at the time it was written. However, readers are encouraged to check with their individual carrier or private payers for updates and to confirm that this information conforms to their specific rules.

Business of Urology

THE BOTTOM LINE
18 Is a ‘perfect storm’ heading for urology?

MONEY MATTERS
21 This trust could benefit special needs individuals
care package and should be getting reimbursed up front for that portion of the procedure. Since the local physician has now purchased, or been paid for the postoperative care, that physician is also tied to any global period issues.

However, this requires cooperation among all the providers involved as well as prior knowledge and agreement on transfer of care among the providers involved. We have seen a few roadblocks in reporting the services provided correctly.

First is the agreement for transfer of care among the providers. Often, the operating physician does not wish to return care of the patient to another physician after the surgery has been completed and asks that the patient return for follow-up. In these cases, there is not agreed-upon transfer of care for follow-up. Therefore, each provider is left to report the services each provides separately, the surgeon reporting the surgical services without the modifiers and the local physician reporting services provided under evaluation/management codes without modifiers relative to the surgery provided.

The second common issue is that the providers do not communicate the intention to transfer care to billing staff. If the bill for the surgeon/specialist does not include the modifiers, the local physician billing, with a procedure code and the 55 modifier, will be denied as the global service will have been paid in full to the other.

In either case, the lack of understanding for all involved is an issue that will interrupt payment. Most at this point will take the path of least resistance in coordination of care, reporting only the services each provides and ignoring the split billing required by the coding system. In this scenario, the local physician providing the postoperative care will charge for each service provided without a modifier.

Longer term, the payers will begin to recognize that they are overpaying for coordinated care. When coupled with the fact that changes in health care are increasing the number of cases that are treated with coordinated care, it is apparent that payers will eventually look into these cases. We would encourage you to consider all aspects of coordinated care when reporting these services.

**Q** A friend stated that you had made the statement at one of your seminars that I could charge based on time when I see a consult at the hospital. Is that true, and are there any restrictions?

**A** Charging by time is an option only if you spend over 50% of the time in counseling or coordinating care. The good news is that in a facility setting, you can count total “floor time” as opposed to only counting face-to-face time in the office or other outpatient setting. That means you can count not only the time you spend discussing the patient’s options with the patient and the family, but also the time you spend discussing with the nurse or other physicians the care of the patient, scheduling surgery, etc. The documentation guidelines quoted below specifically state counseling or coordinating care must dominate the visit and that you must document the time spent and what was done:

“In the case where counseling and/or coordination of care dominates (more than 50%) of the physician/patient and/or family encounter (face-to-face time in the office or other outpatient setting or floor/unit time in the hospital or nursing facility), time is considered the key or controlling factor to qualify for a particular level of E/M services.”

Documentation Guideline: “If the physician elects to report the level of service based on counseling and/or coordination of care, the total length of time of the encounter (face-to-face or floor time, as appropriate) should be

Please see PQRS, page 18

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**Modifier 54, 55, and 56 definitions**

**54-Surgical Care Only:** When one physician performs a surgical procedure and another provides preoperative and/or postoperative management, surgical services may be identified by adding modifier 54 to the usual procedure number.

**55-Postoperative Management Only:** When one physician performs the postoperative management and another physician performs the surgical procedure, the postoperative component may be identified by adding modifier 55 to the usual procedure number.

**56-Preoperative Management Only:** When one physician performs the preoperative care and evaluation and another physician performs the surgical procedure, the preoperative component may be identified by adding modifier 56 to the usual procedure number.
Is a ‘perfect storm’ heading for urology?

ICD-10 specificity, MIPS, changing buy and bill formula could significantly impact specialty

The perfect storm” is a commonly and perhaps overused metaphor that describes an effect of combined circumstances to produce an unusually strong effect. Independent urologists have absorbed remarkable change at a remarkable pace in the last 10 years—change in the understanding of urologic disease and treatment, change in adoption of technology, change in insurance reform, change in health care reimbursement, and change in the cost of operating a medical practice.

The next few years may bring more change in a more compressed time frame than ever before. Could a perfect storm be brewing, and what should you be doing about it?

ICD-10 flexibility set to expire

On Oct. 1, 2015, the Centers for Medicare & Medicaid Services and other payers stopped accepting ICD-9 codes and began rejecting claims without valid ICD-10 codes. The transition brought dire predictions of interruptions in cash flow, drawing on lines of credit, practices shutting down, and information systems crashing. In retrospect, the transition was relatively smooth and has been compared to the Y2K “non-event.”

Perhaps lost in the memory of this successful management of change is the “flexibility” that CMS issued in July 2015 regarding the specificity of codes (bit.ly/ICD10guidancestatement): “For 12 months after ICD-10 implementation, Medicare review contractors will not deny physician or other practitioner claims billed under the Part B physician fee schedule through either automated medical review or complex medical records review based solely on the specificity of the ICD-10 diagnosis code as long as the physician/practitioner used a valid code from the right family.”

Meaningful use as a stand-alone program is scheduled to end in 2019, but until then, practices need to consider the financial implications of successful participation in the program.

In other words, starting Oct. 1, 2016, urologists face claims rejections if they choose a nonspecific code or an incorrect code from the same family when a specific code exists. A good indication of your practice’s compliance in this regard would be the utilization of C67.9- Malignant Neoplasm of Bladder, unspecified: If you are still using this nonspecific code, it could signal a gap in your adoption of ICD-10 that should be addressed before Oct. 1, 2016.

Negative PQRS pay adjustments

The Physician Quality Reporting System has been around for several years as an incentive program, and has transitioned to a “payment adjustment system.” Many specialists, including urologists, have struggled to find relevance in the available quality measures, and the options for reporting have grown extremely complex (claims submission, EHR reporting, group practice reporting, registry reporting).

There are indirect signs that providers are struggling to successfully attest under this program: In the last few months, CMS extended the period during which physicians could request an informal review of determinations that they would receive a 2016 negative adjustment (based on 2014 performance) (bit.ly/PQRSdeadline); then, in February 2016, CMS extended the deadline for certain 2015 PQRS submissions (bit.ly/PQRSdeadlineextension) (to avoid a 2017 payment adjustment).

Perhaps lost in the complexity of the program is the simple arithmetic that adjustments to payment are implemented 2 years after the submission of measures. In other words, starting Jan. 1, 2017, urologists could face negative payment adjustments based upon their performance in 2015, the results of which are unknown. A good indication of a practice’s likelihood of facing negative adjustments in 2017 could be obtained from reviewing your 2014 Quality and Resource Use Reports (bit.ly/QRURinfo).

If your quality score is more than one standard deviation below the benchmark, you may want to closely monitor your 2016 PQRS measures while there is still time to “improve,” as well as prepare for the possibility of a negative adjustment on Jan. 1, 2017.

Meaningful use still a factor

Meaningful use is still around but changing (www.urologytimes.com/mu-shift). In January 2017, early adopters of meaningful use will have the option of progressing to Stage 3 attestation (mandatory in 2018). Stage 3 will bring higher thresholds for successful attestation of some existing measures, higher standards for exchange of information with public health entities, and a requirement that the EHR be certified to 2015 edition standards, which could mean a technology or software upgrade in some cases.

Furthermore, practices that did not successfully attest to meaningful use in 2015 will face a negative payment adjustment starting Jan. 1, 2017. Meaningful use as a stand-alone program is scheduled to end in 2019, but until then, prac-

Please see PERFECT STORM, page 20
Atezolizumab (MPDL3280A)*: an engineered anti-PDL1 antibody under investigation in bladder cancer

NOW ENROLLING IN BLADDER CANCER

Phase III • NCT02450331 • IMvigor010
A Phase III study of atezolizumab (MPDL3280A) treatment versus observation as adjuvant therapy in patients with PD-L1–positive, high-risk muscle-invasive bladder cancer (MIBC) after cystectomy

SCHEMA

Patients with PD-L1–selected MIBC who are at high risk for recurrence after cystectomy

Estimated enrollment: 440

Randomized

Atezolizumab (MPDL3280A)

Observation

STUDY ENDPOINTS

Primary Outcome Measure:
• Disease-free survival

Secondary Outcome Measures:
• Overall survival
• Disease-specific survival
• Distant metastasis-free survival
• Number of participants with adverse events
• Percentage of anti-therapeutic antibody response to atezolizumab (MPDL3280A)
• Atezolizumab (MPDL3280A) maximum serum concentration
• Score of participant-reported health status in EuroQoL 5-Dimension, 5-Level Version Questionnaire

Sponsor Study Identifier: WO29636   ClinicalTrials.gov Identifier: NCT02450331

*Product under investigation has not been approved for this use in bladder cancer outside of the clinical trial setting. This information is presented only for the purpose of providing an overview of the clinical trials and should not be construed as a recommendation for use of any product for unapproved purposes. Trial consistent with information on ClinicalTrials.gov as of April 4, 2016.
Urologists to be reimbursed under new models
continued from page 18

tices need to consider the financial implications of successful participation in the program.

Changes from MACRA coming

Remember SGR and the “physician fix”? Both were replaced by the Medicare Access & CHIP Reauthorization Act of 2015 (MACRA, bit.ly/MACRAresources), a massive reform to the way physicians are paid under the Medicare program. The legislation is too complex to review in detail here, but providers will be reimbursed under one of two “value” models—the merit-based incentive program (MIPS) or alternative payment model (APM). While many details of this complicated bill have yet to be defined by rule, the schedule for change is set in law (bit.ly/MACRAtimeline), and payment changes begin in January 2019.

If CMS follows precedent, that means performance beginning Jan. 1, 2017 will impact adjustments under the MIPS program in January 2019. It is unlikely that urologists will know with certainty if they will be part of an APM in 2019 before the 2017 performance year begins; they should track details of the MIPS program as they are published to prepare for this sweeping change and the possibility that they will be reimbursed under MIPS in 2019.

I recently reviewed buy and bill (www.urologytimes.com/buy-bill) for urology, and it looks like it is about to change. On March 11, 2016, CMS issued a proposed rule that would significantly change the way physicians are reimbursed for most drugs administered in the office and paid under the Part B program (bit.ly/PartBmodel). Under the first phase of this proposed “demonstration” project—ostensibly designed to test whether the current system incentivizes the administration of higher cost drugs—the ASP + 6% methodology would be replaced by ASP + 2.5% + a flat add-on fee ($16.80) for a significant number of providers in the country. Furthermore, CMS intends to implement this change in “late 2016.”

In other words, by Jan. 1, 2017, urologists could face a new reimbursement methodology that significantly decreases any profit margin (or increases any loss) on expensive drugs they acquire and administer to Medicare patients. Now more than ever, it is critical to understand on a drug-by-drug basis the revenue, acquisition cost, and margin as you decide whether the benefit to patients outweighs the operational risks for this line of service.

Bottom line: The forecast for late 2016/early 2017 includes the possibility of a perfect storm years in the making: ICD-10 “flexibility” expires as specificity requirement goes live, 2015 PQRS and meaningful use payment adjustments begin, the decision looms about whether to go to meaningful use stage 3, MIPS measurement is implemented, and phase 1 of the Part B drug demo begins. Local conditions may affect the weather in your area, but atmospheric disturbances appear likely to affect the entire country.

Practice Pointers

- A confluence of changes in health care reimbursement policy could mean urologists will soon be facing a “perfect storm.”
- Starting Oct. 1, 2016, urologists will face ICD-10 claims rejections if they choose a nonspecific code or an incorrect code from the same family when a specific code exists.
- On March 11, 2016, CMS issued a proposed rule that would significantly change the way physicians are reimbursed for most drugs administered in the office and paid under the Part B program.

MACRA will drive value-based reimbursement momentum

Aubrey Westgate
EXECUTIVE EDITOR, MANAGED HEALTHCARE EXECUTIVE

Across the country, increasing numbers of plans and providers are participating in value-based payment models. In fact, the Centers for Medicare & Medicaid Services (CMS) recently announced it met its target of having 30% of Medicare payments tied to value 11 months ahead of schedule.

While more payers and providers are getting on board with alternative payment models, new legislation is also helping drive the movement.

In April 2015, President Barack Obama signed the Medicare Access and CHIP Reauthorization Act (MACRA) into law. Most known for repealing the sustainable growth rate formula (SGR), the legislation also contains regulations related to physician payment.

During the Advanced Payment Models in Healthcare Conference 2016, held in Orlando, FL, attendees heard more about MACRA’s effects on reimbursement during the keynote session. The session was presented by Matt DoBias and Igor Belokrinitsky of PwC Health Research Institute.

“In many ways, MACRA genuinely reflects Medicare and Medicaid’s drive towards payments that are based on the quality of care physicians deliver rather than the quantity of procedures they perform,” DoBias said.

“The law creates two new payment streams beginning in 2018—one known as the Merit-Based Incentive Payment System (MIPS) and another focused on providers who are in an alternative payment model.”

Both tracks offer built-in bonuses if providers meet and exceed certain quality metrics, said DoBias. For providers who opt for the alternative payment model, the highest performers could achieve a 5% bonus payment on top of the built-in increases in reimbursement.

“It won’t be easy, but the overarching goal is to nudge physicians into a position where they have real money at risk in order to gain substantial rewards,” he said.

On one level, physician practice groups that choose the alternative payment path—or already participate in one, such as the Medicare Shared Savings Program—are fulfilling CMS’s goal to shift providers away from traditional fee-for-service payments, Belokrinitsky said. But MACRA could accelerate this shift.

“One of the benefits of MACRA over, say, the outdated SGR formula, is that it gives physicians both predictability and stability to make decisions for their practices. MACRA boosts physician payments and then offers them a chance to get even more in reimbursement over several years,” Belokrinitsky said.

While many of MACRA’s core changes don’t take place until 2018, executives at provider organizations should prepare now, said DoBias. “The first reporting year is likely to be 2017, which means discussions around what type of payment model best fits the practice’s own core strengths should begin sooner rather than later.”
This trust may benefit special needs individuals

Document ensures disabled individual’s financial needs are met without cutting existing benefits

Q Is there a way to establish a special needs trust that doesn’t reduce potential government assistance?

A Ongoing medical advances, an aging population, and the increase of conditions such as autism are combining to produce a growing need for a particular type of estate-planning tool: the special needs trust.

The aging couple whose adult child has severe autism might want a special needs trust because they are worried about how the child will survive after the parents’ deaths. Or a group of siblings may want to set up a special needs trust for their young sister, who is now a teenager but is expected to need supervision for the rest of her life.

Many people depend on government benefits such as Social Security, Medicaid, rehabilitative care, and transportation assistance available for children and adults with special needs. However, these benefits can be dramatically reduced if an individual’s assets exceed a certain level. If loved ones give the individual too much money or provide assistance in a way that breaks the rules, the person could lose benefits. This is a trap many families fall into.

A special needs trust allows parents (and others who care about someone with a disability) to comply with government regulations yet invest and save money to meet a disabled individual’s financial needs throughout their lifetime. In most cases, a special needs trust is a “stand-alone” document, but it can be part of a will. Assets in a special needs trust are not considered countable assets for purposes of qualifying for government benefits based on need. (Disqualification from government benefits could occur if an individual’s assets hit $2,000 and their annual income reaches $10,000.) Parents and others can bequeath assets to the trust rather than directly to the individual.

Assets in a special needs trust are not considered countable assets for purposes of qualifying for government benefits based on need.

Funds in a special needs trust provide for supplemental care beyond what the government provides, including expenses such as utilities, medical care, special equipment, education, job training, and entertainment. A special needs trust does not belong to the person with the disability, but is established and administered by someone else. The person with the disability is simply nominated as a beneficiary and is usually the only one who receives the benefits. The trustee is given discretion to determine when and how much the person should receive. Many factors must be taken into consideration including assets and debts, estimated spending, life expectancies of the parents and children, and costs of care.

The trust must be carefully worded and show clearly that it:

- is established by the family (persons other than the individual with the disability)
- is managed by a trustee (and successor trustees other than the person with the disability)
- gives the trustee the absolute discretion to provide the assistance required
- never gives the person with the disability more income or resources than permitted by the government.

The trust wording should also define what is meant by “special needs” and list terms related to the unique needs of the disabled person, provide instructions for the individual’s final arrangements, determine who should receive the remainder of the trust after the person dies, provide choices for successor trustees, and protect the trust against creditors or government agencies.

Overall responsibilities of trusteeship include:

- understanding the beneficiary’s situation and needs, doing inventory of trust assets, maintaining records for income and principal transactions, and preparing periodic accountings
- filing federal and state fiduciary income tax returns, obtaining Internal Revenue Service tax registration for the trust, and establishing accounts for the management of trust assets
- monitoring disbursements, hiring and regularly monitoring agents and service providers, communicating with the beneficiary and service providers, and assisting in emergency situations to preserve the beneficiary’s lifestyle.

Consult with your estate-planning attorney about how a special needs trust might benefit your situation. Knowledgeable advisers are vital in making sure a trust complies with all regulations.

Q Is the 10% early withdrawal penalty from an individual retirement account waived in the event of death?

A Amounts withdrawn from an IRA after the IRA owner’s death are always free of the 10% penalty. However, this exception isn’t available for funds rolled over into a surviving spouse’s IRA or if the surviving spouse elects to treat the inherited IRA as his or her own account. If the surviving spouse needs some of the inherited funds, they should be left in the inherited IRA (in other words, the one set up for the deceased spouse). Then, the surviving spouse can withdraw the needed funds from the inherited IRA without a 10% penalty.

The information in this column is designed to be authoritative. The publisher is not engaged in rendering legal, investment, or tax advice.
Corporal rupture (penile fracture) was reported as an adverse reaction in 5 of 1044 (0.5%) XIAFLEX®-treated patients in clinical studies. In other XIAFLEX®-treated patients (9 of 1044; 0.9%), a combination of penile ecchymoses or hematoma, sudden penile detumescence, and/or a penile “popping” sound or sensation was reported, and in these cases, a diagnosis of corporal rupture cannot be excluded. Severe penile hematoma was also reported as an adverse reaction in 39 of 1044 (3.7%) XIAFLEX®-treated patients.

Signs or symptoms that may reflect serious penile injury should be promptly evaluated to assess for corporal rupture or severe penile hematoma which may require surgical intervention.

Because of the risks of corporal rupture or other serious penile injury, XIAFLEX® is available for the treatment of Peyronie’s disease only through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS) called the XIAFLEX® REMS Program.
When Peyronie’s disease is on his mind

THINK XIAFLEX®
FOR YOUR APPROPRIATE PATIENTS

The only FDA-approved nonsurgical treatment option for adult men with Peyronie’s disease with a palpable plaque and curvature deformity of at least 30 degrees at the start of therapy

Your patients may find it difficult to start a discussion about their erectile curvature, which could be Peyronie’s disease.1 You play an integral role in making sure they get help. Upon assessment, be sure to clarify with your patients, “Do you have a curved erection?”

XIAFLEX® should be administered by a healthcare provider experienced in the treatment of male urological diseases.

Get started
Became a trained injector or refer your patients to trained injectors nearest them.

Visit XIAFLEX.com/urot to find trained injectors.

- Because XIAFLEX® contains foreign proteins, severe allergic reactions to XIAFLEX® can occur. Anaphylaxis was reported in a post-marketing clinical trial in one patient who had previous exposure to XIAFLEX® for the treatment of Dupuytren’s contracture. Healthcare providers should be prepared to address severe allergic reactions following XIAFLEX® injections. The safety of more than one treatment course of XIAFLEX® is not known.

- In the XIAFLEX® controlled trials in Peyronie’s disease, 65.5% of XIAFLEX®-treated patients developed penile hematoma, and 14.5% developed penile ecchymosis. Patients with abnormal coagulation (except for patients taking low-dose aspirin, eg, up to 150 mg per day) were excluded from participating in these studies. Therefore, the efficacy and safety of XIAFLEX® in patients receiving anticoagulant medications (other than low-dose aspirin, e.g., up to 150 mg per day) within 7 days prior to XIAFLEX® administration is not known. In addition, it is recommended to avoid use of XIAFLEX® in patients with coagulation disorders, including patients receiving concomitant anticoagulants (except for low-dose aspirin).

- In the XIAFLEX® clinical trials for Peyronie’s disease, the most frequently reported adverse drug reactions (≥25%) and at an incidence greater than placebo included: penile hematoma, penile swelling, and penile pain.

Please see Brief Summary of full Prescribing Information, including Boxed Warning, on following pages.

XIAFLEX® (collagenase clostridium histolyticum) for injection, for intralesional use

**Brief Summary of Prescribing Information**

For complete information, see the full prescribing information for XIAFLEX.

**WARNINGS:**

**CORPORAL RUPTURE (PENILE FRACTURE) OR OTHER SERIOUS PENILE INJURY IN THE TREATMENT OF PERYONIE’S DISEASE**

Corporal rupture (penile fracture) was reported as an adverse reaction in 5 of 1044 (0.5%) XIAFLEX-treated patients in clinical studies. In other XIAFLEX-treated patients (9 of 1044, 0.9%), a combination of penile ecchymosis or hematoma, sudden penile detumescence, and/or a penile “popping” sound or sensation was reported, and in these cases, a diagnosis of corporal rupture cannot be excluded. Severe penile hematoma was also reported as an adverse reaction in 39 of 1044 (3.7%) XIAFLEX-treated patients. [See Warnings and Precautions].

**INDICATIONS AND USAGE**

XIAFLEX® is indicated for the treatment of adult men with Peyronie’s disease with a palpable plaque and curvature deformity of at least 30 degrees at the start of therapy.

**DOSAGE AND ADMINISTRATION**

**Dosing Overview for Peyronie’s Disease**

XIAFLEX should be administered by a healthcare provider experienced in the treatment of male urological diseases, who has completed required training for use of XIAFLEX in the treatment of Peyronie’s disease. XIAFLEX, supplied as lyophilized powder, must be reconstituted with the provided diluent prior to use [see Dosage and Administration (2.2)]. The dose of XIAFLEX is 0.58 mg per injection administered into a Peyronie’s plaque. If more than one plaque is present, inject into the plaque causing the curvature deformity. A treatment course consists of a maximum of 4 treatment cycles. Each treatment cycle consists of two XIAFLEX injection procedures [see Dosage and Administration (2.2)] and one penile modeling procedure [see Dosage and Administration (2.2)]. The second XIAFLEX injection procedure is performed 1 to 3 days after the first. The penile modeling procedure is performed 1 to 3 days after the second injection of the treatment cycle. The interval between treatment cycles is approximately six weeks. The treatment course therefore, consists of a maximum of 6 injection procedures and 4 modeling procedures if the curvature deformity is less than 15 degrees after the first, second or third treatment cycle, or if the healthcare provider determines that further treatment is not clinically indicated, then the subsequent treatment cycles should not be administered.

The safety of more than one treatment course of XIAFLEX is not known.

The table below displays an overview of the volume of sterile diluent for reconstitution and the reconstituted XIAFLEX solution to be used in the intracavernosal injection [see Dosage and Administration (2.2)].

<table>
<thead>
<tr>
<th>Volumes Needed for Reconstitution and Administration</th>
<th>Volume</th>
<th>Volume</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sterile Diluent for Reconstitution</td>
<td>0.39 mL</td>
<td>0.25 mL</td>
</tr>
<tr>
<td>Reconstituted XIAFLEX Solution to be injected</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- **Using a new hubless syringe containing 0.01 mL graduations with a permanently fixed 27-gauge 1/2-inch needle (not supplied), withdraw a volume of 0.25 mL of reconstituted solution (containing 0.58 mg of XIAFLEX).**
- **The penis should be in a flaccid state before XIAFLEX is injected. Place the needle tip on the side of the target plaque in alignment with the point of maximal concavity. Orient the needle so that it enters the edge of the plaque and advance the needle into the plaque itself from the side. Do not advance the needle beneath the plaque nor perpendicular to the corpus cavernosum.**
- **Insert and advance the needle transversely through the width of the plaque, towards the opposite side of the plaque without passing completely through it. Proper needle position is tested and confirmed by careful noting resistance to minimal deformation of the syringe plunger.**
- **With the tip of the needle placed within the plaque, initiate injection, maintaining steady pressure to slowly inject XIAFLEX into the plaque. Withdraw the needle slowly so as to deposit the full dose along the needle track within the plaque.**
- **For plaques that are only a few millimeters in width, the distance of withdrawal of the syringe may be very minimal. The goal is always to deposit the full dose entirely within the plaque.**
- **Upon complete withdrawal of the needle, apply gentle pressure at the injection site. Apply a dressing as necessary.**
- **Discard the unused portion of the reconstituted solution and diluent after each injection. Do not store, pool, or use any vials containing unused reconstituted solution or diluent.**
- **The second injection of each treatment cycle should be made approximately 2 to 3 mm apart from the first injection.**

**Penile Modeling Procedure for Peyronie’s Disease**

Penile modeling helps relieve curvature deformity and straighten the penile shaft. As a follow-up visit 1 to 3 days after the second injection of each treatment cycle, perform a penile modeling procedure (as described below) on the flaccid penis to stretch and elongate the treated plaque:

- Administer suitable local anesthetic, if desired.
- Wear gloves, grasp the plaque or indurated portion of the flaccid penis about 1 cm proximal and distal to the injection site. Avoid direct pressure on the injection sites.
- Using the target plaque as a fulcrum point, apply firm, steady pressure to elongate and stretch the goal. The goal is to gradually create bending opposite to the patient’s penile curvature, with stretching to the point of moderate resistance. Hold pressure for 30 seconds then release.
- After a 30 second rest period, repeat the penile modeling technique for a total of 3 modeling attempts at 30 seconds each for each attempt.

In addition to the in-office penile modeling procedure, patients should be instructed to self-perform penile modeling activities at home each day for the 6-week period following the investigator penile plaque modeling visit of each treatment cycle as follows:

- During spontaneous erections, gently attempt to straighten the penis without producing pain and hold the penis in a straightened position for 30 seconds.
- The flaccid penis should be gently stretched three times daily. Slow, gentle force should be used without producing pain.

**CONTRAINDICATIONS**

XIAFLEX is contraindicated in:

- the treatment of Peyronie’s plaques that involve the penile urethra due to potential risk to this structure.
- patients with a history of hypersensitivity to XIAFLEX or to collagenase used in any other therapeutic application or application method [see Warnings and Precautions].

**WARNINGS AND PRECAUTIONS**

**Corporal Rupture (Penile Fracture) or Other Serious Injury to the Penis in the Treatment of Peyronie’s Disease**

Corporal rupture was reported as an adverse reaction after XIAFLEX injections in 5 of 1044 (0.5%) XIAFLEX treated patients in the controlled and uncontrolled clinical trials in Peyronie’s disease. In other XIAFLEX-treated patients (9 of 1044, 0.9%), a combination of penile ecchymosis or hematoma, sudden penile detumescence, and/or a penile “popping” sound or sensation was reported, and in these cases, a diagnosis of corporal rupture cannot be excluded. These patients were managed without surgical intervention, but the long-term consequences of corporal rupture were not evaluated.

Severe penile hematoma was also reported as an adverse reaction in 39 of 1044 patients (3.7%) in the controlled and uncontrolled clinical trials in Peyronie’s disease [see Adverse Reactions].

Signs or symptoms that may reflect serious penile injury should be promptly evaluated to assess for possible corporal rupture or other serious penile injury. Signs or symptoms that may reflect serious penile injury include:

- Sudden penile detumescence, and/or a penile “popping” sound or sensation was reported, and in these cases, a diagnosis of corporal rupture cannot be excluded. These patients were managed without surgical intervention, but the long-term consequences of corporal rupture were not evaluated.
- Severe penile hematoma was also reported as an adverse reaction in 39 of 1044 patients (3.7%) in the controlled and uncontrolled clinical trials in Peyronie’s disease [see Adverse Reactions].
- Signs or symptoms that may reflect serious injury to the penis should be promptly evaluated in order to assess for possible corporal rupture or severe penile hematoma, which may require surgical intervention.
- Injection of XIAFLEX into corpora containing structures such as the corpora cavernosa of the penis may result in damage to those structures and possible injury such as corporal rupture (penile fracture). Therefore, XIAFLEX should be injected only into the Peyronie’s plaque and care should be taken to avoid injecting into the urethra, nerves, blood vessels, corpora cavernosa or other collagen-containing structures of the penis.

**XIAFLEX REMS Program**

Because of the risks of corporal rupture (penile fracture) or other serious penile injury in the treatment of Peyronie’s disease, XIAFLEX is available for the treatment of Peyronie’s disease only through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS) called the XIAFLEX REMS Program [see Warnings and Precautions].

**Identification of Treatment Area for Peyronie’s Disease**

- Prior to each treatment cycle, identify the treatment area as follows:
  - Induce a penile erection. A single intracavernosal injection of 10 or 20 micrograms of alprostadil may be used for this purpose. Apply anesthetic at the site of the injection and allow the skin to dry prior to the intracavernosal injection.
  - Locate the plaque at the point of maximum concavity or focal point) in the bend of the penis.
  - Mark the point with a surgical marker. This indicates the target area in the plaque for XIAFLEX deposition.

**Injection Procedure for Peyronie’s Disease**

- The reconstituted XIAFLEX solution should be clear. Inspect the solution visually for particulate matter and discoloration prior to administration. If the solution contains particulates, is cloudy, or is discolored, do not inject the reconstituted solution.
- Apply anesthetic at the site of the injection and allow the skin to dry.
- Administer suitable local anesthetic, if desired.
Patients with abnormal coagulation (except for patients taking low-dose aspirin, e.g., up to 150 mg per day) were excluded from participating in these studies. Therefore, the efficacy and safety of XIAFLEX in patients receiving anticoagulant medications (other than low-dose aspirin, e.g., up to 150 mg per day) within 7 days prior to XIAFLEX administration is not known. In addition, it is recommended to avoid use of XIAFLEX in patients with coagulation disorders, including patients receiving concomitant anticoagulants (except for low-dose aspirin).

ADVERSE REACTIONS

The following serious adverse reactions in patients with Peyronie’s disease are discussed in greater detail elsewhere in the labeling:

- Corporal rupture (penile fracture) and severe penile hematoma [see Warnings and Precautions].
- In other XIAFLEX-treated patients, a combination of penile ecchymoses or hematoma, sudden penile detumescence, and/or a penile “popping” sound or sensation was reported, and in these cases, a diagnosis of corporal rupture cannot be excluded [see Warnings and Precautions].

Clinical Studies Experience in Patients with Peyronie’s Disease

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

In the controlled and uncontrolled clinical studies of XIAFLEX in Peyronie’s disease, 1044 patients received a total of 7468 XIAFLEX injections.

Corporal Rupture and Other Serious Penile Injury

Corporal rupture was reported as an adverse reaction after XIAFLEX injections in 5 of 1044 (0.5%) XIAFLEX treated patients.

- In other XIAFLEX-treated patients (9 of 1044, 0.9%), a combination of penile ecchymoses or hematoma, sudden penile detumescence, and/or a penile “popping” sound or sensation was reported, and in these cases, a diagnosis of corporal rupture cannot be excluded. These patients were managed without surgical intervention, but the long-term consequences are unknown.
- Severe penile hematoma was also reported as an adverse reaction in 39 of 1044 patients (3.7%) in the controlled and uncontrolled clinical trials in Peyronie’s disease [see Adverse Reactions].

The data described below are based on two identical, pooled, randomized, double-blind, placebo-controlled, multi-center trials through Day 365 in patients with Peyronie’s disease (Studies 1 and 2). These trials included 632 patients of whom 551 and 281 received XIAFLEX and placebo, respectively. In these trials, patients were given up to 4 treatment cycles of XIAFLEX or placebo. In each cycle, two injections of XIAFLEX or two injections of placebo were administered 1 to 3 days apart. A penile modeling procedure was performed at the study site on patients 1 to 3 days after the second injection of the cycle. The treatment cycle was repeated at approximately 6-week intervals up to three additional times, for a maximum of 8 total injection procedures and 4 total modeling procedures [see Clinical Studies in the full Prescribing Information].

The majority of Peyronie’s patients experienced at least one adverse reaction (92% XIAFLEX-treated patients, 61% placebo-treated patients). Most adverse reactions were local events of the penis and groin and the majority of these events were of mild or moderate severity, and most (79%) resolved within 14 days of the injection. The adverse reaction profile was similar after each injection, regardless of the number of injections administered.

The most frequently reported adverse drug reactions (≥ 25% of patients receiving XIAFLEX clinical trials in patients with Peyronie’s disease were penile hematoma, penile swelling, and penile pain. The table below shows the most frequently reported adverse drug reactions (≥ 25% of patients receiving XIAFLEX in patients with coagulation disorders, including patients receiving concomitant anticoagulants (except for low-dose aspirin).

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>XIAFLEX N=551</th>
<th>Placebo N=281</th>
</tr>
</thead>
<tbody>
<tr>
<td>All Adverse Reactions</td>
<td>84.2%</td>
<td>36.3%</td>
</tr>
<tr>
<td>Penile hematomaa</td>
<td>65.5%</td>
<td>19.2%</td>
</tr>
<tr>
<td>Penile swellingb</td>
<td>55.0%</td>
<td>3.2%</td>
</tr>
<tr>
<td>Penile painc</td>
<td>45.4%</td>
<td>9.3%</td>
</tr>
<tr>
<td>Penile ecchymosesd</td>
<td>14.5%</td>
<td>6.8%</td>
</tr>
<tr>
<td>Blood blister</td>
<td>4.5%</td>
<td>0</td>
</tr>
<tr>
<td>Penile blister</td>
<td>3.3%</td>
<td>0</td>
</tr>
<tr>
<td>Pruritus genital</td>
<td>3.1%</td>
<td>0</td>
</tr>
<tr>
<td>Painful erection</td>
<td>2.9%</td>
<td>0</td>
</tr>
<tr>
<td>Erectile dysfunction</td>
<td>1.8%</td>
<td>0.4%</td>
</tr>
<tr>
<td>Skin discoloration</td>
<td>1.8%</td>
<td>0</td>
</tr>
<tr>
<td>Procedural pain</td>
<td>1.6%</td>
<td>0.7%</td>
</tr>
<tr>
<td>Injection site vesicles</td>
<td>1.3%</td>
<td>0</td>
</tr>
<tr>
<td>Localized edema</td>
<td>1.3%</td>
<td>0</td>
</tr>
<tr>
<td>Dyspareuni</td>
<td>1.1%</td>
<td>0</td>
</tr>
<tr>
<td>Injection site pruritus</td>
<td>1.1%</td>
<td>0</td>
</tr>
<tr>
<td>Nodule</td>
<td>1.1%</td>
<td>0</td>
</tr>
<tr>
<td>Suprapubic pain</td>
<td>1.1%</td>
<td>0</td>
</tr>
</tbody>
</table>

- Includes: injection site hematoma and penile hematoma were reported with the verbatim term of penile bruising or injection site bruising in 51% of subjects.
- Includes: injection site swelling, penile edema, penile swelling, local swelling, scrotal swelling, and injection site edema.
- Includes: injection site pain, penile pain, and injection site discomfort.
- Includes: contusion, ecchymoses, penile hemorrhage, and injection site hemorrhage.
- Includes: corporal rupture (penile fracture) and severe penile hematoma reported in 33/551 (6.0%) of XIAFLEX-treated patients and 0/281 (0%) of placebo-treated patients.

There were no clinically meaningful differences in the incidence of adverse events following treatment with XIAFLEX based on the severity of baseline erectile dysfunction or concomitant phosphodiesterase type 5 (PDE5) inhibitor use. XIAFLEX was not associated with shortening of penile length in clinical trials in the treatment of Peyronie’s disease.

Immunogenicity

During clinical studies in Dupuytren’s contracture and Peyronie’s disease, patients were tested at multiple time points for antibodies to the protein components of XIAFLEX (AUX-I and AUX-II). In the Peyronie’s disease clinical studies, at 6 weeks after the first treatment cycle of XIAFLEX 0.58 mg, approximately 75% of patients had antibodies against AUX-I and approximately 65% of patients had antibodies against AUX-II. Six weeks after the eighth injection (fourth treatment cycle) of XIAFLEX, ~96% of XIAFLEX-treated patients developed high titer of antibodies to both AUX-I and AUX-II. Neutralizing antibodies were assayed for a subset of 70 samples selected to be representative of high and low titer binding antibody responses at week 12 of treatment. For each subject in whom a Week 12 sample was selected, the corresponding Week 6, 18, 24, and 52 samples were assayed if they were also binding antibody positive. Neutralizing antibodies to AUX-I and AUX-II were detected in 60% and 51.8%, respectively, of patients tested. In patients treated for these two indications, there was no apparent correlation of antibody frequency, titer levels, or neutralizing status to clinical response or adverse reactions.

Since the protein components in XIAFLEX (AUX-I and AUX-II) have some sequence homology with human matrix metalloproteinases (MMPs), anti-product antibodies could theoretically interfere with human MMPs. In vitro studies showed no evidence of cross-reactivity between anti-drug-antibody reactive patient sera and a series of relevant MMPs. In addition, no clinical safety concerns related to the inhibition of endogenous MMPs have been observed.

Immunogenicity assay results are highly dependent on the sensitivity and specificity of the assay used in detection and may be influenced by several factors, including sample handling, timing of sample collection, and use of different antibody screening and confirmation assays.

Animal Data

Human pharmacokinetic studies showed that XIAFLEX levels were not quantifiable in the systemic circulation following injection in a Dupuytren’s cord. Low levels of XIAFLEX were quantifiable in the plasma of evaluable male subjects for up to 30 minutes following administration of XIAFLEX into the penile plaque below subjects with Peyronie’s disease (see Clinical Pharmacology in the full Prescribing Information). Almost all patients develop anti-product antibodies (anti-AUX-I and anti-AUX-II) after treatment with XIAFLEX, and the clinical significance of anti-product antibody formation on a developing fetus is not known [see Adverse Reactions].

Immunogenicity assay results are highly dependent on the sensitivity and specificity of the assay used in detection and may be influenced by several factors, including sample handling, timing of sample collection, and use of different antibody screening and confirmation assays.

Drug Interactions

Anticoagulant drugs: XIAFLEX should be used with caution in patients receiving concomitant anticoagulants (except for low-dose aspirin) [see Warnings and Precautions].

Use In Specific Populations

Pregnancy

Pregnancy Category B

There are no adequate and well-controlled studies of XIAFLEX in pregnant women. Because animal reproduction studies are not always predictive of human response, XIAFLEX should be used during pregnancy only if clearly needed.

Risk Summary

Based on animal data, XIAFLEX is not predicted to increase the risk for major developmental abnormalities in humans. Human Data

Human pharmacokinetic studies showed that XIAFLEX levels were not quantifiable in the systemic circulation following injection in a Dupuytren’s cord. Low levels of XIAFLEX were quantifiable in the plasma of evaluable male subjects for up to 30 minutes following administration of XIAFLEX into the penile plaque below subjects with Peyronie’s disease (see Clinical Pharmacology in the full Prescribing Information). Almost all patients develop anti-product antibodies (anti-AUX-I and anti-AUX-II) after treatment with XIAFLEX, and the clinical significance of anti-product antibody formation on a developing fetus is not known [see Adverse Reactions].

Immunogenicity assay results are highly dependent on the sensitivity and specificity of the assay used in detection and may be influenced by several factors, including sample handling, timing of sample collection, and use of different antibody screening and confirmation assays.

Animal Data

Reproduction studies have been performed in rats with intravenous exposures up to approximately 11 times the maximum recommended human dose (MRHD) of XIAFLEX on a mg/m2 basis, and have revealed no evidence of impaired fertility or harm to the fetus due to collagenase clostridium histolyticum. Nursing Mothers

It is not known whether collagenase clostridium histolyticum is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when XIAFLEX is administered to a nursing woman.

Pediatric Use

The safety and effectiveness of XIAFLEX in pediatric patients less than 18 years old have not been established.

Geriatric Use

Of the 551 XIAFLEX-treated patients in the double-blind, placebo-controlled, clinical trials in Peyronie’s disease (Studies 1 and 2), 100 (18%) were 65 years of age or older and 5 (0.9%) were 75 years of age or older. No overall differences in safety or effectiveness of XIAFLEX were observed between these patients and younger patients.

OVERDOSAGE

The effects of overdose of XIAFLEX are unknown. It is possible that multiple simultaneous or excessive doses of XIAFLEX may cause more severe local effects than the recommended doses including serious adverse reactions in the injected area (e.g., tendinopathies or corporal rupture dependent on the injection site). Supportive care and symptomatic treatment are recommended in these circumstances.

Manufactured and Distributed by:

Auxilium Pharmaceuticals, Inc.

Malvern, PA 19355

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Revised 05/2015

XP-03921
The dangers of writing off patient copays

Physicians pledge to protect their patients’ health, but they also have legal responsibilities

It comes naturally to want to help your patients, especially the ones struggling to get by on a meager income or retirement. At first blush, it may make sense to waive the patient portion of a medical bill after the insurance has paid. But before you waive a patient’s financial responsibility, consider the legal consequences of doing so.

Nowadays, patient discounts, if given incorrectly, can run awry of insurance regulations or even violate federal anti-kickback statutes. John Meigs, Jr., MD, has practiced as a solo, family physician in rural Alabama for over 30 years. During that time he says the business of medicine has changed drastically. Prior to the institution of health insurance, physicians would often discount their services for patients who struggled to pay or even give free care for the worst cases.

Now, however, waiving the patient portion of a physician’s fee could potentially land a kind-hearted physician in hot water, as failing to collect insurance copays and deductibles could violate contracts with private and federal insurance companies. It could also negatively impact a practice’s bottom line.

“To be legal, you can’t charge less than what Medicare would pay. Obviously, if you discounted everybody you couldn’t stay in business. You have to collect,” said Dr. Meigs, who is now an employed physician at Bibbs Medical Associates, a rural health clinic in Bibbs County, AL.

Legal considerations

In its “Code of Medical Ethics, Opinion 8.03, Conflicts of Interest,” the AMA writes, “Under no circumstances may physicians place their own financial interests above the welfare of their patients. … If a conflict develops between the physician’s financial interest and the physician’s responsibilities to the patient, the conflict must be resolved to the patient’s benefit.”

But as a businessman or woman who has also entered into legal contracts with multiple insurance payers and the federal government, this ethical dictate is not always as simple as physicians might wish.

Attorney Michael Sacopulos, JD, founder and president of Terre Haute, IN-based Medical Risk Institute, says in the vast majority of cases, the physicians he works with are not intent on defrauding payers or the government. “You’ve got a group of people that care about others, or they wouldn’t have gone into health care, and they want to provide services,” he said.

Several reasons not to waive copays

But the impulse to help patients by waiving copays is one a physician should resist for several reasons, says Sacopulos. Patient cost sharing is viewed as an important component of holding down the rising cost of medical care by commercial and government payers. The insurance companies reason if patients have more “skin in the game,” they may make better informed decisions about when and where to seek medical treatment, and potentially reduce their demands for expensive diagnostic testing and procedures that may not be necessary.

Aside from the fact that collecting copays and deductibles is a contractual obligation for physicians, if a physician were to routinely waive the patient portion of his fee, the insurance company could take that to mean that his usual and customary fee was really “x” percent less than originally stated. There have been cases, says Sacopulos, where insurance companies have sued physicians for fraud and won.

“[Payers and physicians] entered into a contract where they said these are the fees you normally charge… and in fact, what you have done is systematically ignored that. And that is a breach of contract… so you’ve defrauded [the payer],” he said.

Another pitfall that could trip up physicians is violating the federal Anti-Kickback Statute (AKS). There is no lack of news about shady physicians or medical suppliers who exchange
patients to afford services. Patients may feel unable or unwilling to pay their copays and/or deductibles or skip out on necessary treatment or testing, says Dr. Meigs. When patients do not pay their insurance premiums, health exchange insurance companies are asking physicians for refunds for services already rendered, Dunn says, leaving practices to collect from patients who have already demonstrated that they cannot pay.

In cases of true financial hardship, practices can discount treatment. The key, Dunn says, is not to make it a regular practice; it must be an isolated incident that is documented in the patient chart.

“As long as you bill out the full amount, you can discount anybody’s bill. Just document that the patient has a hardship, and therefore they would discount the patient portion by ‘x’ number of dollars,” she said.

To protect your practice’s revenue stream, comply with contractual obligations, and make your front-desk/billing staff’s job easier, it is vital to establish a clear financial policy that spells out provisions for collecting patient copays and deductibles and establishes your policy on patient discounts and charity care.

Doing it right

It doesn’t need to be “pages and pages in a policy manual,” says Sacopulos. “But, I think if [practices] are ever intending to waive off copays and deductibles, it should be done pursuant to a policy with documentation.” He says many consultants can provide a template that practices can adopt for their own use.

Here are a few guidelines to follow when creating your own financial policy:

● Develop, publish, and train staff on your practice’s financial policy. Establish the circumstances and qualifying criteria when your practice will discount patient care, and disseminate that information to staff. By outlining your policies on helping low-income patients, patients without insurance, or cancer patients who may need expensive treatments, for example, staff will have a consistent policy to follow and will treat all patients the same. This will also protect your practice from embezzlement disguised as waived copays or discounts to staff friends and family members.

● Make sure that a section is devoted to your policy on professional courtesy. It used to be a common occurrence to extend discounts to physician colleagues as a professional courtesy, says Dr. Meigs. But given contractual obligations to collect patient copays, that tradition has fallen by the wayside for many practices. The key, says Dunn, is to make sure that waiving copays is not a routine policy.

“In today’s medical environment, [physicians] are really hurting themselves [if they don’t collect] because a lot of times the insurance company is paying less than the copay.”

BARBARA DUNN
MedRecovery Solutions

Discounting staff treatment

Providing practice staff with “insurance only” medical care (waiving the patient copay and accepting the insurance reimbursement as payment in full) would likely violate the practice’s insurance contracts. However, practices do sometimes discount staff care as a professional courtesy or an employee benefit. While the custom is well-meaning, it can be problematic, according to Michael Sacopulos, a health care attorney.

“I think [discounting care] is an employee benefit; I’ve not seen anyone have trouble with that. The question is do you have to report it as compensation? Technically you are giving them the value of [treatment],” he said.

One way for practices to help staff with medical expenses and avoid running afoul of the IRS is to fund a financial vehicle like a Medical Expense Reimbursement Plan that reimburses staff for a portion of their out-of-pocket medical expenses like copays and deductibles, experts say.

“More times I see that [practices] will take that patient portion and discount it. And that discounted part is a professional courtesy, but there is still a balance that is billed to the patient,” she said.

● Institute a system to consistently make a fair effort at collecting outstanding patient accounts. A typical policy is to send out three patient statements, says Dunn. If there is no patient response, follow statements with a phone call and/or a collection letter and document your efforts in the patient chart.

If done properly and consistently, your practice may safely write-off uncollectible copays and/or deductibles, or turn them over to a collections agency. And if the practice is ever audited by Medicare or a private payer, you will have a paper trail easily retrieved from the patient’s chart.
Competition-stifling facility regulations scrutinized nationwide

‘Certificate of need’ reform proposals under consideration in multiple states

n 1964, New York lawmakers enacted the first state statute granting regulators the power to determine a community’s “need” for new hospitals and nursing homes. Ten years later, the federal government stepped in, requiring all 50 states to create an agency to review “capital projects such as building expansions or ordering new high-tech devices,” according to the National Conference of State Legislatures.

Supporters of “certificate of need” (CON) laws argued that limiting new facilities and services would reduce inefficiencies and minimize excess capacity. When the restrictions failed to reduce costs, established providers changed their rationale. They instead argued that the state must limit the growth of specialty hospitals and ambulatory surgery centers to ensure that privately insured patients do not abandon hospital settings, which depend on private payer beneficiaries to make up for losses associated with Medicare and Medicaid reimbursement.

Overwhelmed by insufficient evidence of their usefulness and the tide of Reagan-era deregulation, the federal health facilities planning mandate was repealed in 1987. Within 10 years, 14 states eliminated their certificate of need programs. In the intervening period, most states have tweaked their laws, whether adding new technologies under the CON umbrella or, to loosen the noose, increasing the capital expenditure threshold at which regulators must review a project. But 36 states still impose restrictions in the hope of reducing costs and limiting duplication of services. (For a graphical depiction of CON laws in the U.S., see www.urologytimes.com/CON-laws.)

Imaging tech restricted in 20 states

According to the authors of a January 2016 study of CON laws, at least 20 states restrict the technology needed for three highly demanded imaging services: MRI scans, CT scans, and PET scans. In a Jan. 11, 2016 Wall Street Journal editorial, the researchers assert that patients in states with such restrictions have “between 20% and 30% fewer options for providers of these scans than residents of other states. This leads to fewer scans, a drop of between 30% and 65%, depending on the type.”

Given a lack of significant changes to CON laws in the last 15 years, it is noteworthy that many states are currently considering high-profile proposals to reform the process by which health facility and services projects are reviewed.

Campaign accounts of Georgia lawmakers have benefited from a years-long tussle between established hospital systems and upstart specialty hospitals. Most recently, organizations representing Georgia hospitals and nursing homes defeated a bill that would have shelved the state’s CON process entirely. A review of campaign finance receipts found that contributors employed by those facilities donated more than $2 million to legislators’ war chests over the last 2 years.

South Carolina’s CON program has also been under intense scrutiny for more than 2 years. In 2014, Gov. Nikki Haley (R) eliminated funding for the office that enforced the CON law, thereby effectively ending the program. Hospitals successfully challenged that action in court, but Gov. Haley responded by asking the Federal Trade Commission and U.S. Department of Justice to investigate the law. Those agencies recently recommended that South Carolina repeal its CON laws, having concluded the process is anticompetitive and doesn’t help control costs or improve the quality of health care. The South Carolina House approved a bill in 2015 that would eliminate the program by 2018, but that measure has since stalled in the state Senate.

In Florida, health system and nursing home executives are stridently opposed to legislation (HB 437) making its way through the House that would eliminate the CON altogether. Another proposal in the state Senate (SB 1144) would eliminate the CON, provided the facility demonstrates a “significant, active, and continuing commitment to improved access to care for uninsured and low-income residents…” Likewise, one of at least 15 bills dealing with Virginia’s CON program predicates a facility’s exemption from the review on the provision of a level of care at a reduced rate to indigents, as well as accepting patients requiring specialized care.

Virginia lawmakers are considering two other increasingly common changes to the laws regulating health facility and services expansion. Health System Executive Delegate Chris Stolle, MD, introduced legislation that would exempt diagnostic imaging, as well as radiation and proton beam therapy, services, and equipment from the CON process if an acceptable amount of charity care is provided (HB 1083).

A proposal to exempt medical facilities located in rural areas is also under scrutiny in Virginia (HB 349), while a similar measure failed in neighboring North Carolina last year. Broad reform to North Carolina’s CON program also failed in 2015, but proponents did secure approval of legislation that allows recently closed facilities to reopen without going through the arduous process.

Targeted reforms proposed across the U.S.

Similar targeted reforms are being considered across the country. In Iowa, there’s a proposal to eliminate CON requirements for radiation therapy equipment valued below $5 million. Clinics and offices of advanced practice registered nurses may soon be exempt in Kansas, while kidney disease treatment centers may be freed from intense scrutiny in Washington. Interestingly, Washington lawmakers are proposing to use the CON law to halt industry consolidation. HB 1870 would prohibit the issuance of a CON for the sale, purchase, or lease of an existing hospital to anyone with an investment interest in any other hospital within the state.

A final example of conventional CON reform is embodied in divergent proposals being considered in Nashville and Boston. After rejecting a bill that would have exempted ambulatory surgery centers and diagnostic imaging services...

Please see CON REFORM, page 30
Based on your patient’s individual tumor-based genomics, Decipher® is the only test that delivers a clear answer about treatment recommendations to prevent metastasis after a radical prostatectomy. Its accuracy has been validated in multiple studies with over 2,500 patients, indicating an unprecedented negative predictive value of 98.5%. Its accuracy is so widely accepted that it is the only tissue based genomic test covered by Medicare and many private insurance payers for post-surgery patients.

If your post-surgery patients have adverse pathology, such as pT3, positive margins, bladder neck invasion, or experience a rising PSA, Decipher provides clear guidance on your next move. Decipher accurately identifies which patients may benefit from early or adjuvant radiation and which may be safely managed by observation of PSA levels or delayed radiotherapy, allowing more time for recovery after surgery. Also, for patients with PSA rise or BCR after surgery, Decipher helps you identify patients who will likely do well with salvage radiation alone from those who may require systemic or intensified therapy beyond radiation.

There are many management and treatment options available to patients after a radical prostatectomy. Decipher is the only test that accurately tells you which ones are best suited for each patient, no doubt about it.

How residents can prepare for changes in measurement

Novel data acquisition methods offer opportunities to improve patient care

The judging and measuring started on my first day as a urology sub-intern and hasn’t let up since. Two hours into a radical cystectomy, nervous about my suturing skills, and tired from feverishly reading the night before, the attending finally directed a question my way: “Alan, who performed the lead in this 1977 Broadway classic playing on the radio?”

The notion of being measured and judged is as familiar to urology residents as coffee. Although that process continues beyond training where patients and colleagues form and spread opinions of a doctor’s aptitude, the world of physician measurement is rapidly evolving and residents need to understand the changing landscape.

Recently, a friend right out of training told me how devastated he was over his first negative Yelp review. The patient’s insurance didn’t cover the visit, and that brought down the doctor’s composite score to three of five stars. While online reviews of physician performance are not always that base and crude, they are becoming ubiquitous.

Last summer, ProPublica, a non-profit producer of investigative journalism, published its version of individual surgeon quality metrics using publicly available Medicare claims data. The “Surgeon Scorecard” incorporated case volume and complications to determine which surgeons were “best” at eight common procedures, including radical prostatectomy. ProPublica has come under scrutiny for its limited data scope (most prostatectomies are non-Medicare and thus not included), its non-validated method for risk-adjustment, and the inability to capture “clinically relevant” outcome metrics (such as functional status and quality of life).

Despite the criticism, the Surgeon Scorecard publication attracted national attention on performance measurement and transparency, and the issue isn’t going away; ProPublica is currently working on version 2.0 of the Surgeon Scorecard. While ProPublica uses publicly available data, California-based tech startups are capitalizing on robust private claims data to refine those analyses further.

Quality of data questioned

The major criticism of these approaches, of course, is the quality of the quality data. Insurance claims are a) only as good as the coders/billers and b) limited in their ability to give us information about key components of the patient’s clinical outcomes. To focus performance data around “how do we improve” rather than “who is better,” the Michigan Urological Surgery Improvement Collaborative (MUSIC) links measurement with improvement initiatives. MUSIC, which is supported by Blue Cross Blue Shield of Michigan, is a physician-led consortium of over 40 urology practices designed to improve value in urologic care. The goal of participating practices is to identify actionable targets to improving care, and they have been successful in reducing post-prostate biopsy sepsis, among other endeavors.

This type of high-level performance measurement strategy is an encouraging step in the right direction but is still geographically and topically limited. As trainees, it is essential that we prepare for a world in which our performance will come under intense scrutiny but perhaps without our input into the nuances of that inquiry.

So how can we prepare for these changes? First, we must become informed about the metrics currently in use. Even our most technologically unsavvy faculty can understand Yelp, but what about the Pro Publica score? Being able to address questions like how data are acquired, how risk-adjustment is done, who does it and why, and what metrics are included into a scoring methodology allows us to better communicate with patients and colleagues that may ask about these tools.

Second, we need to get engaged in the measurement discussion. Join a quality improvement collaborative if one exists in your area, join the AUA Quality Registry (AQUA), or work with local and regional colleagues and payers to promote value that is driven by high-quality data.

Finally, advocate. Payers and policymakers are already driving health policy decisions based on quality and value data. As specialists, urologists have faced challenges getting the Centers for Medicare & Medicaid Services and others to adopt relevant metrics that make sense in our realm. Ensuring that policy decisions are based on metrics that represent relevant outcomes and are improvement-oriented is of utmost concern to the young urologist.

Someone recently told me, “The good old days of simply doing right by your patient and being good to your referring docs are gone.” While that may be true, I believe the horizon is bright. Novel data acquisition methods and analytics, information technology, and physician collaboratives based on improving quality open the potential for doing even more “right” by our patients and being even better to our referring docs.

So how do residents prepare for the inevitable changes in physician measurement? Embrace them.

Legislation under consideration in MA, TN

from CON review, the Tennessee legislature is now considering legislation that would increase the amount capital expenditures must exceed before triggering the process. Conversely, lawmakers in Massachusetts have before them a bill to reduce the threshold to $5 million (down from $25 million).

Each of these measures, as well as many more dealing with administrative simplification, physician work force, provider scope of practice, medical liability, and other issues are available for viewing on the AACU website. Please take note of this activity and take action when organizations representing urologists, as well as the patient community, urge you to make your voice heard.
Consider foreign urologists as solution to shortage

The subject of this letter is to propose a solution to the urologist shortage problem in the U.S. As you are aware, the supply of U.S. residency graduates in urology is not sufficient to meet the great demand for this specialty in the country. In addition, many urologists are expected to retire in the next few years, which will only add to this problem. Many hospitals in the nation have been searching for a urologist for many years without success.

Many experts in the field believe that the solution to this shortage is to increase the number of residency slots and by training more PAs/NPs. While increasing the number of urology residency graduates is a step in the right direction, it remains insufficient by itself.

On the other hand, training more PAs/NPs to do the work of MDs will be a step in the wrong direction. Urology is a surgical specialty. Most patients prefer to see an MD, especially when serious health issues are present, such as cancer diagnoses, consultations on surgical treatments, pediatric issues, and infertility.

The solution I propose is to allow foreign urologists with sufficient training who have U.S. clinical experience and good references from U.S. board-certified urologists to be part of the urology family of the U.S. The way to do that is by revising the rules of the American Board of Urology (ABU) so that these foreign urologists would be able to sit for the ABU certification exam if they meet the required case log numbers and have endorsements from U.S. urologists. The current ABU requirements make it virtually impossible for any urologist with foreign residency training to become ABU certified.

By the current ABU regulations, even world-known talented surgeons such as Urs Studer, MD, Peter Wiklund, MD, PhD, and others are unable to sit for ABU exam unless they work in a U.S. academic center for 7 years (why 7?), achieve the rank of a full professor (no academics exist in most U.S. community hospitals where the greatest demand is), and get endorsed from the chair and residency program director.

In addition, extraordinary abilities in research, education, etc. need to be demonstrated. How is extraordinary research ability going to impact a surgeon’s ability to do a good prostatectomy operation?

Take the United Kingdom, for example. In order to sit for the Royal College exam, which is the equivalent of the ABU exam, any candidate needs to have three reference letters from urologists who are actively practicing urology in the UK and registered in the General Medical Council of the UK. Such a requirement is fair! The current ABU regulations are unreasonable and unfair.

There are hospitals in the General Medical Council of the UK that are already overlooking ABU certification and hiring foreign-trained surgeons with adequate General Medical Council of the UK clinical experience and active state medical licenses. Many such urologists are already working in major academic centers in the U.S. and have demonstrated excellent levels of skills and knowledge.

Faris Azzouni, MD
Hays Medical Center
Hays, KS

FDA approves treatment for advanced renal cell carcinoma

The FDA has approved cabozantinib (CABOMETYX) tablets for the treatment of patients with advanced renal cell carcinoma who have received prior anti-angiogenic therapy, Exelixis, Inc. recently announced.

The approval of cabozantinib is based on results of the phase III METEOR trial, which met its primary endpoint of improving progression-free survival. Compared with everolimus (Afinitor), cabozantinib was associated with a 42% reduction in the rate of disease progression or death. Median progression-free survival for cabozantinib was 7.4 months versus 3.8 months for everolimus (HR=0.58, 95% CI: 0.45-0.74, p<.0001). Cabozantinib also significantly improved the objective response rate compared with everolimus. These data were published in The New England Journal of Medicine (2015; 373:1814-23).

RT dose escalation lowers PSA but does not improve OS

In prostate cancer patients undergoing external beam radiation therapy, escalation of the biologically equivalent dose results in improved freedom from biochemical failure up to 10 years, but does not improve what’s really important to many patients, including overall survival, according to a recent study.

Researchers conducted a meta-analysis of 6,884 men with non-metastatic prostate cancer from 12 randomized controlled clinical trials of external beam radiation therapy. The findings were published online in the American Journal of Clinical Oncology (March 24, 2016).

The authors found that increasing biologically equivalent dose correlated with a 10-year improvement in biochemical survival of 9.6% for low-risk and 7.2% for intermediate-risk patients. They also observed that PSA levels decreased as patients received higher doses of radiation, according to a press release from Thomas Jefferson University, Philadelphia, one of the participating institutions. However, the lower PSA scores did not correlate with improvements in overall survival, distant metastasis, or cancer-specific mortality at 5 or 10 years.

Senior author Robert Den, MD, of Thomas Jefferson University, said one of the study’s take-aways is that radiation therapy for prostate cancer can be delivered safely, even at increasing doses. The review also suggests that for men with more aggressive or higher risk disease, the combination of radiation with hormone therapy might be more appropriate and that radiation alone with dose escalation is not necessarily sufficient to improve patient survival.
AUA Census: Urologists putting off retirement
continued from page 1

and projected work force in urology. In particular, the North Carolina study found that, while the overall urology full-time equivalent (FTE) work force (urologists plus advanced practice providers) is expected to increase over the next 20 years, from 14,343 in 2015 to 14,806 in 2035, the number of urologist FTEs is expected to plummet, from 10,772 to 8,505.

Christopher M. Gonzalez, MD, MBA, professor and chairman of urology at University Hospitals Case Medical Center, Case Western University, Cleveland, who has long studied work force issues in the specialty, says age has a lot to do with the shortage. Not only is the general population aging and will need more medical care, but the age of the urology work force is climbing as well.

“We have one of the oldest work force groups of all the surgical specialties,” Dr. Gonzalez said.

With a median age of 53 years, urology represents the second oldest surgical specialty, following on the heels of cardiothoracic surgery, which has a median age 53.6 years, according to the study from the University of North Carolina at Chapel Hill by Raj S. Pruthi, MD, professor and chair of urology, Maxim McKibben, MD, a urology resident, and co-authors.

“About 20% of our specialty is 65 years of age or older. So, 20% could retire very soon,” Dr. Gonzalez said. “With new regulations and practice changes right now, the concern is that many will say, ‘It’s not worthwhile to practice anymore from a financial or quality of life perspective, I am going to retire.’ ”

Shortage is inevitable
In any scenario, there are going to be far greater numbers of urologists retiring than coming through training programs, according to Dr. McKibben.

“The shortage of urologists is inevitable. And even if there are pretty large increases in residency training, it’s probably not going to fill that gap,” he said.

Legislation for change in progress
There are three proposed bills to increase the number of federally funded residency slots:

The Resident Physician Shortage Reduction Act of 2015 (H.R. 2124). This bill, introduced by Reps. Joseph Crowley (D-NY) and Charles Boustany, Jr., MD (R-LA), increases the number of residency slots nationally by 3,000 each year between 2017 and 2021, for a total of 15,000. At least 1,000 newly available slots each year must be used for a shortage specialty residency program as identified in the National Health Care Workforce Commission’s report.

The Resident Physician Shortage Reduction Act of 2015 (S. 1148), introduced by Sens. Bill Nelson (D-FL), Charles Schumer (D-NY), and Senate Democratic Leader Harry Reid (D-NV), this bill also increases the number of residency slots nationally by 3,000 each year between 2017 and 2021, for a total of 15,000. At least 1,500 slots each year must be used for a shortage specialty residency program as identified in the National Health Care Workforce Commission’s report.

(Visit the AAMC website for a side-by-side comparison of the two bills: bit.ly/BillsCompared.)

Training Tomorrow’s Doctors Today Act (H.R. 4774). Introduced by Rep. Kathy Castor (D-FL), this legislation would help to lift the 20-year freeze on Medicare support for a share of residency training costs. The bill aims to provide federal support to help train an additional 3,000 resident physicians a year, while introducing accountability and transparency initiatives for institutions receiving Medicare funding for physician training.

Urologists can learn more on the AUA’s main advocacy page: www.auanet.org/advocacy, and find lists of legislation supported by the AACU and the AUA at www.aacuweb.org/jac365 and www.capwiz.com/aua/issues, respectively.

There could be glimmer of hope concerning retirement age in the specialty. In its 2015 Annual Census, the AUA reported that nearly 30% of the 11,990 practicing urologists in the United States are delaying retirement until at least 71 years of age. That’s compared to 22.7% a year ago.

Other concerns are changing work-life patterns in the specialty and whether young urologists and the increasing numbers of women entering the specialty will work as many hours as the prior generation, according to Dr. Gonzalez.

Women account for about 8% of urologists, but 25% of incoming residents, according to Dr. Pruthi.

“Previous studies, including the AUA Census, have demonstrated that female physicians tend to work fewer hours than their male counterparts. This isn’t to say that we shouldn’t encourage women to enter the field of urology. The feminization of our work force has been an important positive trend in our field, and we should encourage and support further growth at all levels. But, fewer hours potentially affects the effective full-time equivalent urology positions. In addition, young physicians of both genders desire more work-life balance with fewer work hours than the previous generation, and this should be accounted for,” Dr. Pruthi said.

Still another concern that could fuel the shortage is the prevalence of burnout in the specialty, Dr. Gonzalez said.

“We know there could be a higher burnout rate amongst urologists compared to other surgical specialties,” he said. (Also see, “Urologist burnout: Exhaustion jumps, satisfaction slumps,” Urology Times, January 2016, page 1.)

Supply vs. demand gap in rural America
Its 2016 report is the AAMC’s first physician work force report to look at disparities in physician supply and demand. The authors found, overall, that Caucasians in an urban environment will have greater physician access and
greater utilization of physicians than other races and individuals who live in rural communities. In one scenario they studied, the authors looked at how many physicians would have been needed in 2014 if everyone had equal utilization based on insurance, geography, and race. If that were the case, Americans would have needed an additional 96,000 physicians 2 years ago, according to Dr. Orlowski.

In urology, the disparity between urban and rural practice is particularly concerning, according to Dr. Gonzalez.

“The number of urban to rural urologists is about seven to one. The profile of the urologist in an urban setting is going to be younger in age and associated with larger groups, whereas the profile of a urologist in a rural setting is going to be a bit older in age and either in solo practice or with just one other partner,” Dr. Gonzalez said.

“If we have an older work force in the rural populations, which represent about 54 or 55 million people living in the U.S., they’re not going to get covered. And we know right now that over 60% of the counties in the U.S. do not have a urologist.”

Quality of care at stake

Quality of care is a potential consequence of the urologist shortage. Studies have shown that urologist density impacts outcomes and survival in urologic oncology, according to Dr. Pruthi.

“I think, as practitioners, we all went to medical school, and we all have a primary interest in delivering quality of care, and the shortage, which would likely limit access, threatens it,” he said.

Ability to recruit is a side effect of the short-

**“The shortage of urologists is inevitable. And even if there are pretty large increases in residency training, it’s probably not going to fill that gap.”**

MAXIM MCKIBBEN, MD

number of new graduates each year, and the number of available positions is greater than the number of providers looking for positions,” Dr. Rubenstein said. “However, as my practice is in an urban area, we do find it somewhat easier to recruit than available spots in more rural areas. It can be challenging to recruit subspecialists to smaller cities and rural areas.”

About 41% of urology practices have diffic-

Please see WORK FORCE, on page 34
More GME funding, APPs among solutions
continued from page 33

 curing filling urologist vacancies, according to the AUA Census.

Fixing the problem
The time to start fixing the physician shortage is now, according to Dr. Orlowski.

“We believe that it’s critical to address the situation now because, for most of the areas of physician specialty, it takes from 8 to 10 years for individuals to be trained,” she said.

Individual states have examined the physician work force shortage and taken steps to alleviate it. Florida is one example. When it was revealed that the state would face a deficit of levels, which was about 170 slots for urology each year, according to Dr. Gonzalez.

“Now we have about 280, but that’s all coming out of either physicians’ pockets, philanthropy, or hospitals. That’s the only reason [residency slots have] grown. It is a big problem,” Dr. Gonzalez said.

Dr. Pruthi said the University of North Carolina increased the residency spots for urology by one per year.

“And we did it on our clinical dollars,” he said. “That’s the money that pays faculty salaries, research efforts, and other educational endeavors. In what other field do the people doing the job of training the people below them take money out of their own pockets to train more people?”

Even in a more perfect world, increasing the supply is limited in its capacity to help, according to Dr. Pruthi.

“There are about 120 residency programs. If all of them took one more resident a year, that is going to be 120 times about $70,000 which is the direct cost of a resident’s salary [at North Carolina]. And that doesn’t include the indirect expenses. First, we have to get the money to do

“We do have some challenges in recruiting new physicians, as there are only a certain number of new graduates each year, and the number of available positions is greater than the number of providers looking for positions.”

JONATHAN RUBENSTEIN, MD

that. Second, not every residency has the caseload and faculty to train more people. There’s a whole infrastructure behind that. All easier said than done,” Dr. Pruthi said.

Another solution is to pad the work force with advanced practice providers (APPs).

“If you factor in [APPs], the difference in the supply versus demand is not as dire as what has been reported. I think the advanced practice providers are at least going to be a stopgap over the next decade or so, until more urologists graduate from residency programs. Advanced practice providers are invaluable and will even be more so in the future as the number of urologists decreases,” Dr. McKibben said.

There are about 8,000 APPs in urology, and about 62% of urology practices employ them, according to Urological Association of Physician Assistants (UAPA) President Charlene Kreiensieck, PA-C, MPAS.

The work force outlook for APPs is very different from that of physicians, Kreiensieck said.

“Physician assistants and nurse practitioner are among the top ten careers in this country,” she said. “This has led to a vast increase in the number of applicants to these programs. There are currently over 200 PA programs in this country, with more slated to open in the future. There will come a point in time when the supply of APPs will outweigh the demand and the field could be saturated.”

But with urology’s need for additional providers greater than most medical specialties, the demand for APPs could continue to be steady.

“My feeling is that as more and more urology practices successfully integrate advanced practice providers into their offices, the trend will be to follow suit,” said Kreiensieck. “Hopefully, urologists will be willing to provide advanced educational opportunities for both the PAs and NPs interested in the urology specialty. The UAPA is committed to engaging these PAs and providing educational opportunities. There are several urology residency programs for physician assistants, as well.”

While it’s a solution, filling the gaps in urology care with advanced practice providers is only a part of the fix, according to Dr. Gonzalez. It’s a more impactful solution in primary care than in surgical specialties.

“Advanced practice providers can do probably 75% to 80% of what a primary care doctor can do. In urology, it’s probably along the lines of 40% and mostly it’s going to be seeing patients in the clinic,” Dr. Gonzalez said.

What you can do to help
There are bills seeking to lift the freeze on government-paid residency expansions (see “Legislation for change in progress,” page 32).

To help, individual urologists can write to their senators and representatives or work with medical or specialty societies on efforts to pass legislation.

“The bottom line is urologists need to help us in organized urology in our grassroots lobbying efforts,” Dr. Gonzalez said.
ASA score ≥3 among predictors of reoperation

continued from page 1

UTIs (3.6%) compared to the 2.3% rate seen in 4,538 procedures conducted by urologists (OR: 1.55, 95% CI: 1.23-1.97, p<.0001). Gynecologists also had a higher rate of overall complications than urologists: 4.1% vs. 2.9% (OR: 1.42, 95% CI: 1.15-1.76, p=.001).

“Large sample sizes can make small differences statistically significant. The question is whether they are clinically meaningful,” first author Björn Löppenberg, MD, a research fellow at Brigham and Women’s Hospital, Boston, told Urology Times.

The overall complication rate was 3.5%, with the majority (84.3%) of complications being UTIs. Thirty-day postoperative outcomes, including cardiovascular, pulmonary, thrombotic, septic, renal, wound, and bleeding complications, did not differ between the two specialties. Reoperation and readmission rates were also similar.

The above rates were similar despite differing patient characteristics. Patients treated by urologists tended to be older with a greater incidence of comorbidity and higher American Society of Anesthesiologist scores (ASA ≥3, p=.05).

It is possible the complication rates are under-reported, noted Dr. Löppenberg, who worked on the study with Quoc-Dien Trinh, MD, and co-authors.

“The NSQIP database codes only for complications that occur within 30 days of the procedure. We cannot account for long-term adverse events such as chronic pain and erosion, among others,” said Dr. Löppenberg, who explained that these complications would not be registered in the NSQIP database.

Some 17.1% of the patients in the dataset underwent an additional procedure. Gynecologists performed twice as many additional procedures as urologists, 22.2% versus 10.5% (p<.0001), despite the higher comorbidity rates seen among patients being treated by urologists.

“We are not able to identify the underlying reason for this finding. The majority of these additional procedures were cystoscopies, and the majority were performed by gynecologists. It is possible that these findings simply reflect differences in surgical technique and approach,” Dr. Löppenberg said.

Independent predictors of reoperation and readmission rates were ASA scores ≥3 (OR: 1.6%, 95% CI: 1.2-2.0, p=.001), prolonged operative time in the 75th percentile or higher (OR: 1.9, 95% CI: 1.5-2.3), and a gynecologist-conducted procedure (OR: 1.5, 95% CI: 1.2-1.9; p<.0001).

Dr. Löppenberg said the study was prompted when Dr. Trinh and co-author Christian Meyer, MD, were asked to comment on a December 2015 JAMA Surgery article that examined factors associated with synthetic mesh removal following surgical interventions for stress urinary incontinence (study, JAMA Surg 2015; 150:1167-75; comment, 1175-6). That study found that over a 10-year span, complications were not significantly influenced by the specialty of the surgeon conducting the procedure.

Specialists at the Henry Ford Hospital Health System, Vattikuti Institute of Urology, Center for Outcomes Research, Analytics and Evaluation, Detroit, participated in the study. It will be presented again in a poster session at the AUA annual meeting in San Diego. [U]
There’s a lot of talk about the ACA and whether candidates would keep it, revoke it, change it, re-fashion it. But there’s nothing specific.

I don’t like proposals to get rid of the ACA and replace it with a brand-new plan without having anything solid and in place. That’s what I don’t hear from the candidates—exactly what their plan is. All we hear is that ‘the ACA will be thrown out and we’ll come up with a better plan.’ It’s definitely necessary to keep some sort of health care. People realize the ACA serves a good purpose for a patient population that wasn’t being served before. Parts of the plan need to be adjusted, but any massive program like this will go through different iterations until you get to the perfect, or near-perfect, plan. We’ve always seen that: Social Security and Medicare weren’t perfect the first time around. That goes for universal coverage too. That’s been discussed over the last 10 to 20 years, and no one has come up with the perfect plan, so I don’t see how someone could suddenly come up with one now.

The ACA is not perfect, but it’s the best we have and the best put forward in the last 10 years. So we need to work with the current plan and make it work for everybody instead of going back to the drawing board. I’m not sure anybody could come up with a better idea. No one has.”

Robert Laciak, MD
Corvallis, OR

Bernie Sanders makes the most sense because we really need universal health care. I practiced about 2 hours outside of Kansas City in Osage Beach, MO, and a single-payer system is what would work best for providing care in rural areas.

There’s no way I’d vote for Hillary Clinton. I don’t believe anything she has to say about health care or anything else. She says whatever she has to say. I’m afraid she’s going to decrease Medicare and Social Security if elected.

Ted Cruz says he’s going to repeal Obamacare, but he can’t repeal it. It would be disastrous for 15 to 20 million people. My son and daughter-in-law depend on the ACA. Cruz can say whatever he wants; he won’t be able to do anything about Obamacare. Republicans won’t be able to cut Social Security or Medicare because the Democrats would block that.

I really wished Biden would’ve run. I think I’m starting a no-voting campaign—that’s the best solution.”

Robert Brenner, DO
Kansas City, MO

I’m hearing about undoing the Affordable Care Act from Republican candidates, trying to revise health care in a different format, and I’m in favor of that. For the most part, they haven’t proposed anything specific, although Ben Carson had some ideas like health care savings accounts. He had a pretty detailed proposal that sounded like a more logical and affordable plan than the ACA. But he’s not in the race anymore.

Whatever Republicans would come up with would be better than what we have; the one we’ve got is such a bad plan. It’s not affordable in the long term. The cost is much higher for people, and I’m generally against big federally mandated government programs to solve all the problems. It’s a philosophical bias, I guess. I don’t know that it’s helped that many people.

In my view of things, everybody has been covered since I’ve been in practice for 30 years because people who didn’t have insurance still got taken care of; people who had insurance paid more for their premiums. It’s just how you’re spreading the cost of that coverage.”

Wallace Vaught, MD
Florence, SC

I haven’t heard much that I like, but what I really don’t like are the promises that they’re going to revolutionize health care but with no plans to back it up. Trump doesn’t even tell you who his health care policy advisers are. I really don’t think we can just get rid of the ACA. Too many people have gotten insurance and are benefiting from it. Even if it’s not the perfect program, it’s what we have now, and nothing else specific is being proposed.

I don’t know much about the idea of a single-payer system, but I don’t know how you would pay for it. It would be really expensive and whenever the government gets involved in a program, it gets really bogged down.”

Thomas Facelle, MD
Golden, CO
The Department of Urology at the University of Kansas Medical Center is seeking a board certified or eligible urologist. We have full time faculty members in all subspecialty areas and are seeking a urologist specializing in female urology, urinary incontinence, voiding dysfunction, and neurourology.

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The Department of Urology at the University of Kansas is seeking a board certified (or eligible) general urologist.

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Academic rank and salary will be commensurate with experience. Interested applicants should contact Jessica McCullough at jmccullough3@kumc.edu

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About GSU
Garden State Urology was formed in 2008, the result of a merger of five of the busiest urology practices in Morris County. We joined on the principle that by working cooperatively, we could provide more cost-effective and higher quality care than we did individually. Our mission statement, created at our inception, reflects these beliefs and directs our future growth: To provide comprehensive and compassionate urologic care at the highest possible level. By coming together, we have embraced a national trend to coordinate care. Most important to each of the members of Garden State Urology is to keep the practice of medicine patient-focused. We believe in the integrated model of patient care.

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Careers@gsunj.com Please include a cover sheet and salary requirements.
Other information on GSU may be found on our website www.gsunj.com

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CMS halts PSA quality measure—for now

Agency to engage stakeholders to determine future direction

Washington—As a result of strong opposition from organized medicine, including the AUA and patients, the Centers for Medicare & Medicaid Services (CMS) has put on hold its development of a draft plan to penalize physicians for ordering “non-recommended” PSA tests to screen for prostate cancer.

During a month-long comment period on its draft clinical quality measure, “Non-Recommended Prostate-Specific Antigen (PSA)-Based Screening,” CMS received 358 comments from multiple stakeholders, including specialty societies, to determine whether a restructured appropriate use measure concepts to address overuse and patient safety on prostate cancer screening, as well as additional measure gap areas.”

“[The AUA and its members] strongly believe that blanket statements regarding PSA testing directed at the entire male population disregard the published benefits associated with such testing in men who may be at higher risk than the average male.”

J. STUART WOLF, JR., MD

The AUA said it had been notified of the project’s suspension by Rep. Michael Burgess, MD (R-TX), who along with Rep. Phil Roe (R-TN) was instrumental in generating a letter from the GOP Doctors Caucus to CMS conveying concerns about the proposal. Burgess hand-delivered the caucus’ letter to CMS Acting Administrator Andy Slavitt after his testimony during a Dec. 8 hearing last year.

In the AUA’s comments to CMS, J. Stuart Wolf, Jr., MD, chair of the association’s Science & Quality Council, declared that the AUA and its members “strongly believe that blanket statements regarding PSA testing directed at the entire male population disregard the published benefits associated with such testing in men who may be at higher risk than the average male.”

AUA lobbies CMS on Medicare pay model

So having scored at least a temporary victory on the PSA issue, the AUA and other specialty medical groups have turned to Congress once again, this time asking lawmakers to push CMS to withdraw a new Medicare Part B Drug Payment Model proposed March 8.

The AUA signed a letter submitted to CMS by the Alliance of Specialty Medicine. The letter, which also was signed by 11 other specialty groups, argued that the rule would make sweeping changes to Medicare Part B drug reimbursement without sufficient stakeholder input and could affect the care and treatment of Medicare patients with complex conditions.

In a recent Policy & Advocacy blog post, the AUA explained that the proposed Medicare Part B Model is designed “to test different physician and patient incentives... to drive the prescribing of the most effective drugs, and test new payment approaches to reward positive patient outcomes.”

The first phase would test whether reducing the 6% add-on to 2.5% plus a flat fee payment of $616.80 per drug per day would lead to improved quality and value. CMS would update the flat fee annually by the percentage increase in the consumer price index for medical care for the most recent 12-month period. That test is scheduled to begin no sooner than 60 days after the rule is finalized.

The second phase would produce a menu of value-based purchasing options. CMS would consider the following no sooner than Jan. 1, 2017:

- discounting or eliminating patient cost-sharing
- feedback on prescribing patterns and online decision support tools as a resource for providers and suppliers focused on safe and effective use for selected drugs and indications
- indications-based pricing, which would vary the payment for a drug based on the clinical effectiveness for different indications
- reference pricing, which would test the practice of setting a standard payment rate for a group of therapeutically similar drug products

CMS would evaluate the proposed model over 5 years, with the goal of having both phases in full operation during the last 3 years so the changes could be evaluated.

In its letter, the Alliance of Specialty Medicine expressed fear that the initiative would “adversely affect the care and treatment of patients.” The Alliance said that under the proposed payment method, “patients would be forced to navigate a CMS initiative that could potentially lead to a halt in their ongoing treatment. This is not the right way to manage the Medicare program for any beneficiary—let alone patients with serious conditions.”

Fast Facts

A proposed Medicare Part B Drug Payment Model:

- would test whether reducing the 6% add-on to 2.5% plus a flat fee payment of $616.80 per drug per day would lead to improved quality and value
- would produce a menu of value-based purchasing options
- has been opposed by the Alliance of Specialty Medicine, which argues that it could affect the care and treatment of Medicare patients with complex conditions
How to avoid malpractice suits related to APPs

Negligent hiring/supervising of NP, PA are common medicolegal pitfalls to watch out for

Advanced practice providers (APPs), credentialed as physician assistants and nurse practitioners, have had an increased presence in the work force over the past several years. Combined, there are more than 300,000 of these licensed providers in the United States, and they have made their way into more than half of urology practices (Med Econ 2015; 92:43-5; Curr Urol Rep 2015; 16:62).

While training of these providers is relatively uniform, what differs dramatically under various state laws are the roles, responsibilities, and relationships between the provider and the physician. It is imperative that physicians know the law of the state they practice in with regard to their relationship with and responsibility for APPs providing urologic care.

There is rarely a malpractice suit where an NP or PA is named, and not a physician. This is due to the inextricable supervisory relationship between the physician and APP. The most common ways collaborating with an APP can land you as a named defendant in a lawsuit are negligent hiring/training of the APP and failure to properly supervise the APP.

Let’s take each one of these separately to highlight where the risk lies and what you, the physician, can do to prevent it.

Scenario 1: Negligent hiring

PA Harwood has been hired for your busy urology practice to assist in procedures including urodynamics and cystoscopies. He interviews very well and seems like the perfect fit for those physicians who will supervise him. He is hired within days and starts within a week.

In the course of evaluating a patient with a history of dysuria and hematuria, Harwood prescribes antibiotics for a suspected urinary tract infection and sends a urine culture. He does not perform a cystoscopy or communicate with the urologist about this patient or the potential need for a cystoscopy. Harwood was written up by his prior employer for “communication issues” with his supervising physicians, but this was not learned in the course of interviewing him.

Negligent hiring or training of an APP is an avoidable claim. It simply requires the physician or office to do their initial homework and then due diligence when taking on a new APP. When deciding to hire an APP, it is critical to thoroughly review the candidate’s résumé, contact prior employers, and verify their education and certification.

Guidelines and limits for APPs need to be clear, and collaborative two-way communication between physicians and APPs is essential to best reduce liability risk.

A new APP should not “hit the ground running.” Rather, he or she also needs to be trained on applicable policies and procedures of your office, and this needs to be documented to best avoid a failure-to-train claim.

Assume the patient in the above scenario eventually gets diagnosed with bladder cancer and sues for a delay in diagnosis. The physician and PA will not have a strong defense to a negligent hiring claim, as the PA’s communication issues could easily have been discovered. Vetting a potential new APP might seem tedious and time-consuming, but is urged for office managers or administrators that often undertake these activities.

Scenario 2: Improper supervision

An elderly patient presents to his urology clinic for an annual check-up. His PSA is drawn and reveals an elevated value of 7.21 ng/mL, which had risen from the previous year’s PSA of 4.7 ng/mL. The patient sees urology NP Mills in follow-up, who notes the elevated PSA and also notes that the patient’s prostate is enlarged.

However, Mills believes that the patient’s PSA value is within the acceptable range for age-adjusted PSA, a concept that allows for higher PSA values in older men to account for benign growth. The NP recommends no further urologic work-up.

Five months later, the primary care doctor draws another PSA, which now returns a result of 12.9 ng/mL. The patient returns to the urology clinic to see Mills, who still believes the increase in PSA is the result of benign growth and does not believe a biopsy is indicated. Months later, the patient is diagnosed with Gleason 9 prostate cancer, and he dies within the year.

Scenario 2 is rife with potential problems regarding the NP and her collaborating physician. Did the physician review the charting, documentation, and labs of this patient? Was there a physician physically on site when this patient was evaluated by Mills? Some states require this. Did Mills feel like she could or should speak to a collaborating physician about this patient’s PSA values?

The literature supports that an environment of excessive autonomy for APPs, or one in which there is hesitance to “bother” the physician about a patient, are both dangerous (Med Econ 2000; 77:205-8, 215). Each of these situations results from a lack of communication, which can be disastrous for a physician. Guidelines and limits for APPs need to be clear, and collaborative two-way communication between physicians and APPs is essential to best reduce liability risk.

The AUA Consensus Statement on Advanced Practice Providers further details how to identify the skill level of an APP and consequently the level of supervision one might require (bit.ly/AUAAPPstatement). While all APPs, by law, require some degree of supervision or collaboration, extra caution must be taken with those new to urology.

While the purpose of this document “is to provide guidance for urologists on the integration of APPs into the urological care setting,” it is highly recommended that all administrators and/or office managers who have any role in hiring or vetting APPs or have general clinical oversight responsibilities be familiar with this document to best reduce liability risks for physicians and APPs alike.
Pregnancy

CONTRAINDICATIONS

INDICATIONS AND USAGE

Initial U.S. Approval: 2012

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, diarrhea, dizziness/vertigo, headache, hypertension, and dizziness/vertigo. Patients were allowed, but not required, to take glucocorticoids. The most common adverse reactions (≥ 10%) that occurred 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.

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 3 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 a 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.

Nervous System Disorders

General Disorders

Table 1. Adverse Reactions in Study 1

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Table 2. Adverse Reactions in Study 2

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

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<td>prazepam, propoxyphene, promethazine, propoxyphene</td>
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<tr>
<td></td>
<td>propoxyphene, quinidine, sirolimus, tacrolimus, topiramate, trimethoprim</td>
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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.

Fails and Fail-related Injuries
In the two randomized clinical trials, fails including tail-related injuries, occurred in 9% of patients treated with XTANDI compared to 4% of patients treated with placebo. Failures were not associated with loss of consciousness or seizures. Fail-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 CYP3A4
Co-administration of a strong CYP3A4 inhibitor (ketocazole) 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 CYP3A4 inhibitors should be avoided if possible. If co-administration of XTANDI with a strong CYP3A4 inhibitor cannot be avoided, reduce the dose of XTANDI.

Drugs that Induce CYP3A4
Co-administration of rifampin (strong CYP3A4 inducer and moderate CYP2C9 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., 5-methoxyphenyl)

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 taking the drug, as the drug may expose the patient to 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 palate 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 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 toxicity 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- and 13-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

Marketing by: Astellas Pharma US, Inc., Northbrook, IL 60062
Medivation, Inc., San Francisco, CA 94105

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Rx Only
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astellas

MEDIVATION
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 CYP3A4, CYP2C9 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.

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

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.

94% of insured patient lives are covered for XTANDI.†

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To learn more, please visit XtandiHCP.com