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A good day.
It’s no accident.

Solesta: a unique treatment for FI

- An injectable, biocompatible gel
- Nonsurgical, in-office procedure
- No anesthesia required
- May preclude need for more invasive surgical procedures

Durable efficacy with Solesta

Number of episodes/14 days

<table>
<thead>
<tr>
<th>Months</th>
<th>0</th>
<th>5</th>
<th>10</th>
<th>15</th>
<th>20</th>
<th>25</th>
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<tr>
<td>Baseline</td>
<td>15.0</td>
<td>8.6</td>
<td>6.2</td>
<td>7.0</td>
<td>7.0</td>
<td></td>
</tr>
</tbody>
</table>

P=0.001

n=136

Important Safety Information about SOLESTA

SOLESTA® (hyaluronic acid/dextranomer) is contraindicated in patients with active inflammatory bowel disease, immunodeficiency disorders or ongoing immunosuppressive therapy, previous radiation treatment to the pelvic area, significant mucosal or full thickness rectal prolapse, active anorectal conditions (including abscess, fissures, sepsis, bleeding, proctitis, or other infections), anorectal atresia, tumors, or malformation, rectocele, rectal varices, presence of existing implant (other than SOLESTA) in anorectal region, or allergy to hyaluronic acid-based products.

SOLESTA must not be injected intravascularly as injection of SOLESTA into blood vessels may cause vascular occlusion. Injection in the midline of the anterior wall of the rectum should be avoided in men with an enlarged prostate.

SOLESTA should only be administered by physicians experienced in performing anorectal procedures and who have successfully completed a comprehensive training and certification program on the SOLESTA injection procedure.

The most common adverse reactions with SOLESTA (incidence >4%) in the clinical study were proctalgia, anorectal hemorrhage, injection site hemorrhage, pyrexia, injection site pain, diarrhea, and anorectal discomfort.

Find out more at solestainfo.com.

Indication

Solesta is indicated for the treatment of fecal incontinence in patients 18 years and older who have failed conservative therapy (e.g., diet, fiber therapy, anti-motility medications).
Solesta®

Brief Summary
Please consult Package Insert for full prescribing information.

Indication for Use
Solesta is indicated for the treatment of fecal incontinence in patients 18 years and older who have failed conservative therapy (e.g., diet, fiber therapy, anti-motility medications).

Contraindications
Solesta is contraindicated in patients with the following conditions:

- Active inflammatory bowel disease
- Immunodeficiency disorders or ongoing immunosuppressive therapy
- Previous radiation treatment to the pelvic area
- Significant mucosal or full thickness rectal prolapse
- Active anorectal conditions including: abscess, fissures, sepsis, bleeding, proctitis, or other infections
- Anorectal atresia, tumors, stenosis or malformation
- Rectocele
- Rectal strictures
- Presence of existing implant (other than Solesta) in anorectal region
- Allergy to hyaluronic acid based products

Warnings
Do not inject Solesta intravascularly. Injection of Solesta into blood vessels may cause systemic toxicity.

- Injection in the midline of the anterior wall of the rectum should be avoided in men with enlarged prostate.

Precautions
General precautions
- Solesta should only be administered by physicians experienced in performing anorectal procedures and who have successfully completed a comprehensive training and certification program in the Solesta injection procedure.

- The safety and effectiveness of Solesta have not been investigated in patients with complete external sphincter disruption or significant chronic anorectal pain.

- The safety and effectiveness of Solesta have not been investigated in patients with previous procedures in the anorectal region: rectal prolapse ≤12 cm from anal verge, anorectal surgery within previous 12 months, hemorrhoid treatment with rubber band within 3 months, anorectal implants and previous injection therapy, Stapled Transanal Rectal Resection (STARR) or stapled hemorroidectomy.

- The safety and effectiveness of Solesta have not been studied in patients under the age of 18 years.

- The safety and effectiveness of Solesta have not been studied in pregnant or breastfeeding women.

- The durability of Solesta has not been studied past 12 months.

- The safety and effectiveness of Solesta have been studied in patients who received one or two treatments. In the Pivotal study, the majority of patients received two treatments, four weeks apart.

Patient related precautions
- Patients with bleeding diathesis or patients using anticoagulant or antplatelet agents, as with any injection, may experience increased bleeding at injection sites.

- Patients should be counseled that a repeated Solesta injection procedure may be required to achieve a satisfactory level of improvement in incontinence.

Procedure related precautions
- Adequate bowel preparation of the rectum using enema is required prior to injection. The enema should be given immediately prior to the procedure to ensure evacuation of the anorectum. It is recommended that additional cleansing of the injection area with an antiseptic be performed prior to injection. Use of prophylactic antibiotics is recommended.

- Solesta should be injected slowly to avoid undue stress on the Luer-lock connection which could cause leakage of the gel.

- After injection of Solesta, hold the needle at the injection site for an additional 15-30 seconds to minimize leakage of Solesta.

- Injection too close to the dentate line or too deep in the tissue might cause excessive pain.

- Injection should be stopped if excessive bleeding or pain occurs.

- One sterile needle should be used per syringe and injection.

Device related precautions
- The use of needless other than those supplied may impede injection of Solesta due to the properties of the gel and may cause device malfunction.

- Solesta is supplied ready to use in a prefilled syringe with a Luer-lock fitting. Carefully examine the unit to verify that neither the contents nor the package has been damaged in shipment. Do not use if damaged.

- Solesta is supplied sterile and is intended for single use only. Do not re-sterilize as this may damage or alter the product.

- In the event of accidental contamination of a needle, discard the needle.

- Never mix Solesta with other products.

- Solesta is to be stored at up to 25°C (77°F), and used prior to the expiration date printed on the label. Do not expose Solesta to either sunlight or freezing, as this may damage or alter the product.

- Care should be taken when handling the glass syringes and disposing of broken glass to avoid laceration on or injury.

- After use, syringes and needles should be handled as potential biohazards. Dispose should be in accordance with accepted medical practice and applicable local, state and federal requirements.

Adverse Events
Potential adverse events include: abdominal discomfort, abdominal distension, abdominal pain, lower abdominal pain, abdominal rigidity, alopecia, anal abscess, anal fissure, anal hemorrhage, anal prolapse, anal pruritus, anorectal discomfort, back pain, constipation, C-reactive protein increased, colon distension, darkening of urine, diarrhea, device dislocation, distension, dyspareunia, escherichia bacteremia, fecal incontinence, feces hard, fatigue, gastrointestinal motility disorder, gastrointestinal pain, genitral discharge, genital prolapse, hematochezia, hematospermia, hemorrhoids, infection, injection site abscess, injection site discomfort, injection site hematoma, injection site hematoma, injection site inflammation, injection site irritation, injection site nodule, injection site pain, injection site pustule, injection site swelling, infection site ulcer, intestinal mass, malsea, mucosal inflammation, musculoskeletal pain, perianal abscesses, nausea, edema, pain, painful defecation, pelvic mass, perineal pain, proctalgia, proctitis, pyrexia, rectal abscesses, rectal discharge, rectal hemorrhage, rectal erosion, rectal obstruction, rectal prolapse, rectal spasms, rectal tenesmus, rectovaginal septum abscesses, urinary retention, vaginal discharge, vulvovaginal pain. The adverse event profile of Solesta beyond 18 months is not known, but is under investigation in post-market studies.

Safety Data
The safety evaluation of Solesta in the treatment of fecal incontinence (FI) is based on the results from the Pivotal clinical study, and is supported by the Open-Label multicenter clinical study and one single site Proof-of-Concept study. The analysis of safety was based on the safety cohort of all 206 patients treated in the Pivotal study with either Solesta or Sham. Safety data for Solesta are available from 359 treatments in 197 total patients followed for up to 18 months post treatment (i.e., 136 subjects from the blinded phase and 61 subjects from the open phase).

The primary safety data set includes data from 206 patients treated with either Solesta or Sham in the Pivotal study. The data show that a total of 232 treatment-related adverse events for either Solesta or Sham were reported up to 18 months after treatment. Three (3) adverse events assessed as related to Solesta, or 1.3% of the treatment-related adverse events, were deemed serious by the investigators. These three (3) serious adverse events occurred in three (3) patients, including one case of an E. coli bacteremia, and two (2) cases of rectal abscesses (one event per patient). All of these serious adverse events resolved following treatment without any sequela within approximately 30 days of treatment.

Overall, 96% of the 203 Solesta treatment-related adverse events in the Pivotal study were of mild to moderate intensity and 97% of the events required no intervention or required medical or simple non-invasive interventions, including application of local pressure, silicone ointment, water irrigation and warm baths. Seven (7) events required more invasive procedures including: personal drainage of abscesses (4 events), one (1) case of rubber band ligation of an anal prolapse, one (1) case of lancing of a hemorrhoid, and one (1) case of a Kenalog injection in a pre-existing anal scar. The most frequent adverse events following Solesta treatment pertained to post-treatment proctalgia, minor anal or rectal bleeding, post-treatment fever, abdominal complaints (such as diarrhea and constipation), and events potentially related to peri-operative infection.

Patient Counseling Information
The patient should be advised that Solesta treatment is not effective for all patients with fecal incontinence and that repeat treatment might be required for treatment effect. It should also be made clear to the patient that the available clinical study data are not sufficient to predict in whom Solesta treatment will be effective. The patient should be informed about post-treatment care and potential adverse events. The patient should also be made aware that the implants might be detected during future anorectal examinations and radiographic imaging of the pelvis. Patients should be instructed to inform all future treating physicians about the presence of Solesta gel.

If there should be a need for future surgery (e.g., hemorrhoidectomy) the Solesta implant can be resected.

Directions for Use
Solesta should be administered by qualified physicians with experience in the treatment of anorectal conditions and who have successfully completed a comprehensive training and certification program in the Solesta injection procedure. Solesta should only be used after a thorough physical evaluation of the patient to exclude treatable underlying disorders.

Please consult Package Insert for full directions for use and method of administration.

Post-treatment care
1. The patient should be instructed to avoid taking hot baths during the first 24 hours post-treatment.
2. The patient should be informed of the risk of infections and bleeding.
3. The patient should be instructed to contact the clinic or physician’s office immediately if symptoms of rectal bleeding, bloody diarrhea, fever, tenesmus or problems with urinating occur.
4. Anti-diarrheal drugs should not be used for one week after treatment.
5. Stool softeners may be used until the first defecation occurs.
6. Analgesics other than Non-steroidal Anti-Inflammatory Drugs (NSAIDs) may be prescribed.
7. The patient should be instructed to:
   - Avoid physical activity for 24 hours
   - Avoid sexual intercourse and strenuous physical activity for one week (e.g., horse back riding, bicycling and jogging, etc.)
   - Avoid anal manipulation for one month (e.g., insertion of suppositories or enemas and rectal temperature recording)

Re-treatment procedure
1. If the patient does not have an adequate response to Solesta after the first injection, a re-injection procedure should be performed.
2. Use a maximum of 4 mL Solesta can be administered in each injection site after the first injection.
3. The re-treatment procedure and all pretreatment preparations are performed the same way as the initial treatment procedure. All pretreatment preparations and injection procedures should be performed as described in “Methods of Administration” above. However, the patient of injection should be made in between the initial injections, shifted one-eighth of a turn (e.g., left posteroanterior, left anterodorsal, and right anterodorsal) and right posteroanterior.

How Supplied
Solesta is supplied in a glass syringe with a standard Luer-lock fitting containing 1 mL gel. Each syringe is terminally moist heat sterilized in a pouch. Four pouches, each containing one syringe are packed in a carton together with five Sterican needles (21G x 4 inches, 0.80 mm x 120 mm), patient record labels and a package insert. The needles are sterilized by ethylene oxide.

Storage
Store at a temperature up to 25°C (77°F) and protect from sunlight and freezing.

To report adverse events, a product complaint, or for additional information, call: 1-800-508-0024.

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Health Management Institute
Through the Center for Preventive Health and Center for Continuity of Care (Chronic Illness), the NAMCP Health Management Institute is led by an Executive Leadership Council of medical directors that develops tools to prevent disease, assess and reduce risk and help improve patient outcomes!

Prevention & Lifestyle Institute
The purpose of the Lifestyle Institute is to promote and advocate a healthy lifestyle. The majority of chronic illness comes from unhealthy behaviors and lifestyles. We encourage implementation and interventions to prevent chronic illness. This is done through our Preventive Health Record and education on the principles of a healthy lifestyle!

Oncology Institute
The purpose of the Medical Directors Oncology Institute is to provide updated and pertinent information and resources to Medical Directors from Purchasers, Health Plans and Provider Systems in the area of Oncology. The Institute is currently looking for medical directors that are interested in serving on the Oncology Institute Executive Leadership Council (ELC).

To learn more about the NAMCP Oncology Institute, or to become involved in the Executive Leadership Council, please contact Katie Eads at 804-527-1905 or keads@namcp.org.

For more information on the institutes, visit www.namcp.org.
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Humana
Breast cancer is the most commonly diagnosed cancer among women in the United States with approximately 200,000 new cases every year. Forty thousand women die due to metastatic breast cancer each year in the United States. The vast majority are those relapsing after having received adjuvant treatment for early stage disease. In general, most relapses occur in the first five years, but can occur at any time. Up to one in five relapses occurs after 10 years. Sadly, between 1 and 5 percent of women with breast cancer have metastatic disease at presentation.

Currently, metastatic breast cancer (MBC) is treatable, but not curable. The median survival with MBC is two to three years. Five to 10 percent of patients will survive for five or more years and 2 to 5 percent may survive more than 10 years. Since it is not curable, the goals for treating MBC are maintaining quality of life, prolonging survival, maintaining activity, and managing pain and treatment side effects.

In recent years, it has been recognized that breast cancer is a heterogeneous disease. The luminal cells inside the breast ducts give rise to luminal A and B type cancers, whereas the basal cells surrounding the breast ducts give rise to basal types. Other cells within the breast give rise to the other types including human epidermal growth factor receptor 2 positive (HER-2+) and triple negative. These different types of breast cancers have different molecular signatures that dictate tumor biology and predict outcome. Thus, treatment is chosen based on the biology of the tumor (Exhibit 1). Breast cancer can be divided into three general categories – hormone receptor positive, HER-2+, or triple negative – which are all treated differently.

<table>
<thead>
<tr>
<th>Summary</th>
</tr>
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<tbody>
<tr>
<td>Although not considered curable, metastatic breast cancer can be treated with multiple lines of therapy, which all provide a modest survival advantage. The choice of therapy will depend on the underlying tumor biology. Therapy for metastatic disease continues to evolve as the understanding of the mechanisms of growth and treatment resistance are understood and treatments targeting those issues are developed.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Key Points</th>
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</thead>
<tbody>
<tr>
<td>• Metastatic breast cancer is treatable, but not curable.</td>
</tr>
<tr>
<td>• Underlying tumor histology and genetics dictate prognosis, choice of therapy, and response to therapy.</td>
</tr>
<tr>
<td>• Hormone response disease is treated primarily with antiestrogen therapies.</td>
</tr>
<tr>
<td>• HER-2 positive disease is treated with targeted therapies in addition to chemotherapy.</td>
</tr>
<tr>
<td>• Triple negative disease is treated with chemotherapy.</td>
</tr>
</tbody>
</table>

**BREAST CANCER IS THE MOST COMMONLY**

**diagnosed cancer among women in the United States with approximately 200,000 new cases every year.** Forty thousand women die due to metastatic breast cancer each year in the United States. The vast majority are those relapsing after having received adjuvant treatment for early stage disease. In general, most relapses occur in the first five years, but can occur at any time. Up to one in five relapses occurs after 10 years. Sadly, between 1 and 5 percent of women with breast cancer have metastatic disease at presentation.

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In recent years, it has been recognized that breast cancer is a heterogeneous disease. The luminal cells inside the breast ducts give rise to luminal A and B type cancers, whereas the basal cells surrounding the breast ducts give rise to basal types. Other cells within the breast give rise to the other types including human epidermal growth factor receptor 2 positive (HER-2+) and triple negative. These different types of breast cancers have different molecular signatures that dictate tumor biology and predict outcome. Thus, treatment is chosen based on the biology of the tumor (Exhibit 1). Breast cancer can be divided into three general categories – hormone receptor positive, HER-2+, or triple negative – which are all treated differently.
Hormone receptor positive [estrogen (ER) or progesterone receptor (PR) positive] disease is generally biologically less aggressive than other types, but it can recur at any point. By gene expression testing, these are typically luminal A or B type. Luminal B tends to have higher proliferation rates and relapse rates. The mainstay of treatment is antiestrogen therapy (Exhibit 1). Options include a selective estrogen receptor modulator (SERM, tamoxifen), an estrogen receptor antagonist [fulvestrant (Faslodex®)], aromatase inhibitors [AI, anastrozole (Arimidex®), letrozole (Femara®), exemestane (Aromasin®)] and ovarian ablation using surgical removal, medication, or radiation.

Chemotherapy may also be an option for some patients. Consider the example of a 60-year-old female with a 2.3 cm invasive mammary carcinoma, no special type, low grade, low proliferative rate, and one out of five positive lymph nodes. In addition to the type of tumor, treatment would be cho-
sen based on her risk of recurrence. Using Adjuvant Online, she has a 40 percent risk of relapse with no other treatment after surgical removal (www.adjuvantonline.com). Five years of therapy with an AI would reduce her risk to 20 percent. In her case, chemotherapy would only have a modest benefit of 5 percent reduction in recurrence risk. On the other hand, if she had a high grade tumor, her risk of relapse with surgery alone is 66 percent. In this situation, the addition of chemotherapy would provide a 10 percent benefit. The key point is that histologic grade significantly impacts the risk of recurrence and the choice of treatment.

After multiple lines of therapy, many women with hormone responsive MBC will develop hormone resistance. Strong evidence links hormone resistance to cross-talk between signal transduction pathways and ER signaling. One of the mechanisms of endocrine resistance appears to be aberrant signaling of mammalian target of rapamycin (mTOR), a key regulator of cell growth and proliferation. Thus, targeting it is a rational approach in hormone resistance.

Everolimus is an oral, potent inhibitor of mTOR recently FDA approved for MBC. In the BOLERO-2 study, everolimus in combination with exemestane was compared with placebo/exemestane in 724 postmenopausal women with ER-positive refractory MBC (with recurrence or progression following prior therapy with letrozole or anastrozole). The analysis of progression-free survival (PFS) based on independent central radiological assessment showed a 2.6-fold prolongation in median PFS (10.58 months versus 4.14 months), resulting in a 64 percent risk reduction of progression or death (HR 0.36). The addition of everolimus to exemestane prolongs PFS in patients with ER+ breast cancer refractory to initial nonsteroidal aromatase inhibitors. The benefits were observed in all subgroups. Adverse events were consistent with previous experience with everolimus, including stomatitis, fatigue, noninfectious pneumonitis, and hyperglycemia. Everolimus is the first agent shown to enhance the clinical benefit of hormonal therapy in refractory ER+ patients. The results of Boler-2 represent a paradigm shift in the management of patients with hormone receptor-positive breast cancer.

Another approach to hormone resistance would be to combine two hormonal agents with different mechanisms of action. The combination of anastrozole and fulvestrant has been studied and appears to be better than either alone in the setting of resistance. Thus, when a patient progresses on one hormonal agent, a second agent may be added.

Twenty to 25 percent of breast cancers overexpress HER-2. Tumors that overexpress HER-2 are typically poorly differentiated tumors, markers of high proliferation, worse disease-free survival (DFS) and overall survival (OS). The median survival with HER-2 overexpression is three years versus six to seven years with normal HER-2 expression. The most developments in the last few years have been with this type of breast cancer.

Trastuzumab (Herceptin®) was the first targeted therapy approved for this type of breast cancer. It is a monoclonal antibody to the HER-2 protein on the tumor cell surface. It prolongs survival of patients with MBC by five to seven months. A significant percentage of patients with HER-2+ disease recur

Exhibit 2: Comparing BRCA-1 and TNBC

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Hereditary BRCA1</th>
<th>Triple Negative/Basal Like</th>
</tr>
</thead>
<tbody>
<tr>
<td>ER/PR/HER2 status</td>
<td>Negative</td>
<td>Negative</td>
</tr>
<tr>
<td>TP53 status</td>
<td>Mutant</td>
<td>Mutant</td>
</tr>
<tr>
<td>BRCA1 status</td>
<td>Mutational inactivation*</td>
<td>Diminished expression*</td>
</tr>
<tr>
<td>Gene-expression pattern</td>
<td>Basal like</td>
<td>Basal like</td>
</tr>
<tr>
<td>Tumor histology</td>
<td>Poorly differentiated (high grade)</td>
<td>Poorly differentiated (high grade)</td>
</tr>
<tr>
<td>Chemosensitivity to DNA-damaging agents</td>
<td>Highly sensitive</td>
<td>Highly sensitive</td>
</tr>
</tbody>
</table>

*BRCA1 dysfunction due to germline mutations, promoter methylation, or overexpression of HMG or ID4.
or progress on trastuzumab treatment. The mechanisms of resistance and methods to circumvent this resistance are under intense investigation. Current treatment options beyond trastuzumab include lapatinib, pertuzumab, and T-DM1.

Dual blockade of signaling may be more effective than the single-target inhibition provided by trastuzumab. Lapatinib (Tykerb®) is a small molecule tyrosine kinase inhibitor that binds to both the intracellular ATP binding site of epidermal growth factor receptor (EGFR) and her-2 on the cell surface, preventing phosphorylation and activation. It blocks downstream signaling through homodimers and heterodimers of EGFR and HER-2. Lapatinib in combination with capecitabine increased the median time to progression compared with placebo/capecitabine (8.4 vs 4.4 months). Pertuzumab (Perjeta®) is the most recent addition in the fight against her-2+ disease. It is a HER dimerization inhibitor that prevents HER-2 from partnering with HER-3. In combination with trastuzumab and docetaxel as first line therapy in HER-2+ disease, the addition of pertuzumab improved PFS (18.4 vs 12.3 months) and preliminary OS. Using this combination that targets both the inside and outside of the cancer cell is a way for patients to avoid chemotherapy.

Pertuzumab (Perjeta®) is the most recent addition in the fight against HER-2+ disease. It is a HER dimerization inhibitor that prevents HER-2 from partnering with HER-3. In combination with trastuzumab and docetaxel as first line therapy in HER-2+ disease, the addition of pertuzumab improved PFS (18.4 vs 12.3 months) and preliminary OS. Using this combination that targets both the inside and outside of the cancer cell is a way for patients to avoid chemotherapy.
line therapy for HER-2+ metastatic disease.

T-DM1 (Kadcyla®) is a combination of trastuzumab and emtansine (DM1), which is a derivative of maytansine, a very effective but highly toxic chemotherapy. Combined with trastuzumab, the emtansine enters the HER-2+ cell only. T-DM1 has been compared with capecitabine/lapatinib. T-DM1 treatment resulted in an improvement in PFS (9.6 vs 6.4 months) and OS (30.9 vs 25.1 months) compared with the combination.10 T-DM1 has also been compared with trastuzumab plus docetaxel in the first-line setting. There is an improvement of PFS but no difference in OS. The combination of trastuzumab/docetaxel is no longer the standard of care. There is an ongoing trial of T-DM1 versus T-DM1/pertuzumab versus paclitaxel/trastuzumab.

Some tumors do not have estrogen, progesterone, or HER-2 receptors and are thus termed triple negative breast cancer (TNBC). This is typically a more aggressive breast cancer with higher proliferation rates, higher histologic grades, larger tumors, higher recurrence rates, and lower survival than ER+ disease. About 15 percent of new cases of breast cancer will be triple negative. It is more common in younger, Hispanic, and African American women. TNBC recurrences tend to occur early with peak rates at one to two years and almost all recur within five years. If someone with TNBC has lived eight years without a recurrence, they are most likely cured. Recurrences occur more often in visceral organs compared to ER+ disease.

Not all TNBCs are the same. TNBC is defined based on lack of expression of ER/PR/HER-2 on immunohistochemistry. Based on gene-expression profiling, most TNBCs are basal-like tumors. The gene expression of these tumors share characteristics with basal epithelial cells including high EGFR expression, proliferation genes, and basal clusters (CK 5, 14, and 17). Most basal-like tumors are triple negative, but 25 percent will express ER/PR/HER-2 by IHC. On gene-expression profiling, 25 percent of TNBCs do not have basal-like patterns. They express epithelial-mesenchymal transition genes and stem cell-like patterns.

Poor prognosis associated with TNBC is likely driven by the majority of tumors with basal-like biology. Basal-like cancers have a worse prognosis than the overall breast cancer population or TNBC subgroup. Because molecular profiling is not widely available, triple negative phenotype is a clinical surrogate, but all TNBC may not have a poor prognosis.

Because no validated targets have been identified for TNBC, chemotherapy is the treatment of choice. Numerous agents have been studied in TNBC. The search is ongoing for specific targets that may prove beneficial in this subset of breast cancer.

Exhibit 2 illustrates how TNBC shares clinical and pathologic features with breast cancer gene mutation one (BRCA-1) related breast cancer.11-14 Base excision repair through polyadenosine diphosphate-ribose polymerase 1 (PARP1) is one of the two major mechanisms for repairing cellular DNA damage caused by environmental causes and carcinogens (Exhibit 3).15 Homologous recombination through BRCA is the other major mechanism of DNA repair. When a patient is treated with chemotherapy, DNA damage is the desired outcome of therapy but PARP or BRCA can “fix” the effects of chemotherapy.

Because BRCA is nonfunctional in BRCA mutation disease, these tumors rely on PARP1 to repair DNA damage. PARP inhibitors that circumvent DNA repair after chemotherapy have shown activity in BRCA+ disease. Single-agent oral olaparib 400 mg BID has substantial activity in heavily pretreated BRCA1/2 carriers with advanced breast/ovarian cancer but is still investigational. Veliparib is another PARP inhibitor under study.

PARP is upregulated in most TNBC thus blockade may enhance the efficacy of chemotherapy. Although the studies with PARP inhibitors in TNBC have not been highly successful, selecting patient populations for trials may be the issue. TNBC needs to be sliced thinner and only those with the same gene expression profiles should be studied together.

Because TNBC is composed of a number of subtypes, the challenge in effective treatment is recognizing which subtypes are targetable. Clinical trials are underway to target TNBC by gene expression profiles, but it is important to select patients rationally, not just “TNBC” patients.

Conclusion
Breast cancer is a heterogeneous disease; its different subsets (ER+, HER-2+, triple negative) are associated with markedly distinct outcomes and respond to different treatments. New targeted therapies are likely to continue to improve outcomes. Tumor biology is the most important factor in treatment and survival. Thus, future improvements in treatment require identifying more relevant targets and understanding mechanisms of resistance.

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References
THE COMPLICATIONS OF DIABETES ARE well known. It is the leading cause of new cases of blindness among adults aged 20 to 74 years. Diabetes is the leading cause of kidney failure, accounting for 44 percent of all new cases. Approximately 60 to 70 percent of people with diabetes have mild to severe forms of nervous system damage. More than 60 percent of nontraumatic lower-limb amputations occur in people with diabetes. Additionally, diabetes contributes to over 200,000 deaths each year. Importantly, diabetes does not cause complications; poorly controlled disease does.

The total costs of diagnosed diabetes in the United States in 2012 were $245 billion, which included $176 billion for direct medical costs and $69 billion in reduced productivity. After adjusting for population age and gender differences, average medical expenditures among people with diagnosed diabetes were 2.3 times higher than expenditures would be in the absence of diabetes. One way to reduce the significant costs of this disease is greater glycemic control (Exhibit 1).

Glucose levels are not the only important issue in type 2 diabetes, but good glycemic control is essential. Blood pressure and lipid control are two other essentials to preventing complications. As blood pressure rises, so do the risks of complications. Over time, the risk of cardiovascular disease (CVD) significantly increases in patients with diabetes even with high-normal blood pressure. The general goal for blood pressure is 140/80 mm Hg or less. Exhibit 2 compares the benefits of glucose control and blood pressure control. Lipid goals include achieving a low-density lipoprotein cholesterol (LDL-C) of 100 mg/dl or less (without cardiovascular disease) or less than 70 mg/dl with CVD. High-density lipoprotein (HDL) goals are greater than 40 mg/dl in men and greater than 50 mg/dl in women. Triglycerides should be maintained at 150 mg/dl or less. Statins are extremely effective in achieving these lipid goals with minimal adverse effects.

Many effective medications exist to manage glucose in patients with type 2 diabetes, with combination therapy being quite effective. The choice of...
therapy depends on an understanding of the pathophysiology of type 2 diabetes, the adverse effects, the nonglycemic effects of therapy, the method of delivery, and the cost of the medications.

For lowering postprandial glucose, the newer kids on the block are the glucagon-like peptide-1 (GLP-1) agonists and the dipeptidyl peptidase-4 (DPP-4) inhibitors. GLP-1 stimulates the release of insulin, suppresses glucagon release, reduces glucose production, slows gastric emptying and promotes satiety. GLP-1 is released in response to a meal, but this release is reduced in people with diabetes. GLP-1 is metabolized by DPP-4. Thus, GLP-1 can be increased by either delivering an agonist or inhibiting DPP-4.

GLP-1 agonists include exenatide (Byetta®), liraglutide (Victoza®) and exenatide LA (Bydureon®). These agents do require subcutaneous injection, which some patients may be afraid to do. The most common side effect is nausea, and these agents are associated with weight loss.

The available DPP-4 inhibitors [sitagliptin (Januvia®), saxagliptin (Onglyza®), linagliptin (Tradjenta®)] are oral agents that are very well tolerated and are weight neutral. Exhibit 3 compares the hemoglobin A1C (AIC) lowering of various agents as monotherapy.

There have been some concerns about possible
adverse effects of these newer agents. Pancreatitis in patients treated with exenatide was first reported by the FDA in 2006. The first FDA report of pancreatitis associated with sitagliptin was announced in 2009.

Several analyses have been published examining the possible risk of pancreatitis. One analysis of the FDA’s database of reported adverse events from 2004 to 2009 found an increased risk with exenatide of 10.7-fold and sitagliptin of 6.7-fold compared with other agents for diabetes. The high rate of reported cases of pancreatitis may have been due to both these agents being first in class agents where clinicians were looking for adverse effects and thus reported them. Insurance claims database analyses and cohort studies found no relationship between use of exenatide and the risk of pancreatitis. Similarly, no increased risk of pancreatitis was found in patients treated with sitagliptin. A cohort study using retrospective study of claims data from over 30,000 patients found no increased risk with either exenatide or sitagliptin. A more recent case-controlled analysis of an administrative database using 2005 to 2009 data found a twofold increased risk of pancreatitis. Thus, pancreatitis is a possible, but likely rare, adverse effect of these two classes of diabetes therapy.

Pancreatic cancer is another possible but controversial concern with these agents. An analysis of the FDA adverse effect database found an almost three-fold increased risk with exenatide. A retrospective case-controlled cohort analysis of 209,306 patients found no increased risk with exenatide. In a case-controlled study that examined a small number of pancreas tissue samples from patients who received GLP agents, approximately a 40 percent increase in pancreatic mass, increased exocrine cell proliferation and dysplasia, α cell hyperplasia and microadenomas were found. At this time, a definitive link between use of GLP-1 agents has not been established.

Insulin is the most feared therapy for many people but is powerful and effective without significant issues when used appropriately. In one study, 60 percent of patients were able to achieve an A1C less

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### Exhibit 3: Efficacy of Monotherapy in Type 2 Diabetes

<table>
<thead>
<tr>
<th>Agent</th>
<th>A1C Reduction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sulfonylureas</td>
<td>1.5 - 2.0</td>
</tr>
<tr>
<td>Secretagogue</td>
<td>1.0 - 2.0</td>
</tr>
<tr>
<td>Metformin</td>
<td>1.5 - 2.0</td>
</tr>
<tr>
<td>TZD</td>
<td>0.6 - 1.9</td>
</tr>
<tr>
<td>Alpha glucosidase inhibitors</td>
<td>0.5 - 1.0</td>
</tr>
<tr>
<td>DPP-IV inhibitors</td>
<td>0.6 - 0.8</td>
</tr>
<tr>
<td>GLP-1</td>
<td>0.8 - 1.2</td>
</tr>
</tbody>
</table>

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### Exhibit 4: Legacy Effect of Better Glycemic Control

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>1997</th>
<th>2007</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any T2D-related event</td>
<td>RRR:</td>
<td>P:</td>
</tr>
<tr>
<td></td>
<td>32%</td>
<td>0.0028</td>
</tr>
<tr>
<td>Diabetes-related death</td>
<td>RRR:</td>
<td>P:</td>
</tr>
<tr>
<td></td>
<td>42%</td>
<td>0.017</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>RRR:</td>
<td>P:</td>
</tr>
<tr>
<td></td>
<td>39%</td>
<td>0.01</td>
</tr>
<tr>
<td>Mortality by any cause</td>
<td>RRR:</td>
<td>P:</td>
</tr>
<tr>
<td></td>
<td>36%</td>
<td>0.01</td>
</tr>
</tbody>
</table>
than 7% with insulin therapy. Nighttime dosing of insulin, which minimizes adverse effects, is a good way to start. The use of analog insulin also minimizes the risk of hypoglycemia.

Premixed insulin analogs, which improve patient convenience, are available. There are advantages and disadvantages of premixed insulins. The premixed formulations provide rapid- and intermediate-acting insulin in one injection without the need to mix insulins. These formulations are administered twice each day and cover insulin requirements throughout most of the day. Pen devices with the mixtures are available, which make injections even easier for patients. Disadvantages of premixed formulations include requirements for a relatively consistent meal and exercise pattern and the ratio of rapid to intermediate insulin is fixed. There is a greater likelihood of nocturnal hypoglycemia from peak effects of presupper NPH and fasting hyperglycemia as presupper NPH wears off.

Early control of glucose is important. The United Kingdom Prospective Diabetes Study (UKPDS) study taught us that diabetes is progressive. In the UKPDS study, over approximately 10 years, the metformin treatment group had a mean A1C of 7.0% versus a mean of 7.9% in the standard care group. The lower A1C in the metformin group led to a 25 percent reduction in microvascular endpoints, 39 percent reduction in amputation, 29 percent reduction in eye-related laser therapy, and 10 percent reduction in amputation, 29 percent reduction in microvascular endpoints, 39 percent reduction in amputation, and average age of 62 (30 to 82 years). Mean A1C at baseline was 8.2%. As compared with standard therapy, the use of intensive therapy for 3.7 years to target a A1C level below 6% reduced five-year nonfatal myocardial infarctions but increased five-year mortality. Two other large studies found no impact on cardiovascular risk with late aggressive treatment.

Since early aggressive control is beneficial, everyone with type 2 diabetes should meet their A1C goals but many are not under control. The progressive nature of diabetes is one reason for lack of control. Keeping all things equal, glycemic control worsens over time because pancreatic beta cells continue to fail over time. Additional therapy is needed to keep even; therefore, providers need to advance therapy over time.

Primary care providers are slow to advance therapy. In an analysis of a Kaiser database, physicians waited over one year to add a second oral agent after A1C was over 8%. Additionally, physicians who are slow to add oral agents are also slow to add insulin. Fifty percent of physicians in one survey preferred to delay initiation of insulin until absolutely essential. Almost half question the efficacy of insulin. In one trial, at insulin initiation, the average patient had five years with an A1C greater than 8% and 10 years with A1C greater than 7%. Doctor-centered contributors for failing to advance therapy include overestimation of care provided, perception of improving, applicability of guidelines to a particular patient, concerns of potential side effects/interactions, and concern about patients’ concerns (real or imagined). Patient-based issues include adherence, adverse effects (real or imagined), cultural beliefs, health care beliefs – more medications means they are sicker, economics, limitations on lifestyle, and lack of immediate benefit. The more adherent a patient is the more likely their therapy will be advanced.

There are also health care system factors, including a system designed for acute care rather than chronic care. The starting dose or single agent therapy for diabetes is often not adequate and glycemia will worsen over time. Rapid follow-up is often not practical on a large-scale basis, so it is reserved only for the most concerning patients. Patients are usually not enlisted to do dosage acceleration. Numerous other system problems contribute to inadequate management of diabetes and many other chronic conditions including the lack of effective information sharing between provider and specialist, lack of a team to assist primary care providers, systems that depend on the provider not missing anything and addressing all issues without assistance or reminders, and, lastly, systems that require providers to address each advancement of therapy as a “new” decision process.

Improving therapy advancement requires several things to occur. Physicians need to understand the goals of therapy – what they are trying to achieve and how to achieve it.
Additionally, patients need to understand the goals of therapy and why it is important to achieve and maintain these goals. A health care infrastructure needs to exist in order that therapy is advanced in a relatively simple process.

Conclusion
Poorly controlled type 2 disease leads to well-known complications. Early aggressive glycemic control has been shown to have a long-lasting effect on complication reduction. To improve diabetes control, changes need to be made to the health care system to make it easier for providers to set appropriate goals for individual patients and prescribe and advance therapy to achieve appropriate goals.

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References
PULMONARY HYPERTENSION (PH) IS SIMPLY high blood pressure within the pulmonary vascular bed which can have many causes. PH can be divided into five groups: pulmonary arterial hypertension (PAH), pulmonary hypertension associated with left heart disorders, pulmonary hypertension associated with intrinsic lung diseases and/or hypoxemia, chronic thromboembolic pulmonary hypertension, and pulmonary hypertension due to miscellaneous and/or multifactorial causes. Identifying the appropriate group is important for prognosis and for choosing therapy.

The focus of this article is PAH, which without treatment has a mean survival of less than three years. PAH is a disorder of increased pulmonary vascular resistance (PVR) as a consequence of structural changes to the pulmonary arteries. The pulmonary pressures by right heart catheterization which classify someone as having this condition are an increased mean pulmonary arterial pressure (mPAP, ≥ 25 mm Hg), a normal pulmonary capillary pressure, and increased PVR.1,2 Symptoms, morbidity, and mortality are determined by the effects of the increased resistance on right ventricular function and the ability to maintain cardiac output (CO). In response to the increased PVR, some people develop right ventricular hypertrophy and can maintain their CO for a significant period of time. Others, in response to the PVR, develop dilation, the ventricle fails faster, and symptoms occur early.

PAH can be idiopathic, heritable, drug induced, or as the result of another disease or condition.3 People with the genes that have been identified as associated with PAH have a much higher risk of developing the condition, but usually development of PAH requires a trigger. Fenfluramine and dexfen-
Fluramine were common causes of drug-induced PAH in the past but have since been removed from the market. Currently, methamphetamine is the most common cause of drug-induced PAH. Diseases associated with PAH include connective tissue diseases (i.e., scleroderma), HIV infection, portal hypertension, congenital heart diseases, schistosomiasis, and chronic hemolytic anemia.

The symptoms of PAH develop and progress as the ability to maintain or increase cardiac output is compromised and the right ventricle progressively fails (Exhibit 1). The initial signs and symptoms include dyspnea on exertion, fatigue, presyncope, edema, dizziness, and angina. The nonspecific nature of these complaints can lead to confusion with other conditions and a significant delay in establishing the diagnosis. Also, patients can present at various points during the progression of this condition. Most people do not seek care until the symptoms truly bother them.

There has been little progress over the last 25 years in reducing the time from symptom onset to an accurate diagnosis. It still takes more than two years to get a diagnosis.5-7 Sadly, the majority of patients are being diagnosed at later stages of the disease (WHO class three or four).

The evaluation of someone suspected of having PAH will include the patient’s history, a physical, laboratory tests, a chest x-ray, an electrocardiogram, and pulmonary function tests. Evaluation may also include a ventilation-perfusion lung scan, a pulmonary angiography, an echocardiogram (at rest, and/or with exercise), an exercise test (including an assessment for arterial oxygen desaturation during exertion), a sleep study, and right heart catheterization.

In PAH, the most frequent symptom is dyspnea on exertion. If symptoms occur during exertion, and the resting evaluation is not informative, the patient should be evaluated during exertion to detect early disease and establish a diagnosis. The evaluation, in this case, will include post-exercise pulmonary function tests, cardiopulmonary exercise test, exercise echocardiogram, and exercise during right heart catheterization.

Right heart catheterization is required for almost every patient with suspected pulmonary hypertension and establishes the diagnosis. It is used to exclude congenital heart disease and/or coronary artery disease, to measure pulmonary capillary wedge pressure, and to establish the severity and prognosis of PAH. Very importantly, it is also used to test the effect of vasodilator therapy. Vasodilator response to a calcium channel blocker (CCB) is defined as a decrease in mean PAP by at least 10 mm Hg, reduction in PA pressures to an absolute mean PAP less than 40 mm Hg, and unchanged or increased CO.3

In PAH, the major determinants of symptoms, risk of progression, and survival are markers of right...

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Exhibit 1: Hemodynamic Changes Correlate with Disease Progression

![Exhibit 1](https://example.com/exhibit1.png)

- **CO** = cardiac output
- **PAP** = pulmonary arterial pressure
- **PVR** = pulmonary vascular resistance
- **RAP** = right atrial pressure.

<table>
<thead>
<tr>
<th>Stage</th>
<th>Hemodynamics</th>
<th>PAP = PVR x CO</th>
</tr>
</thead>
<tbody>
<tr>
<td>Presymptomatic/</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Compensated</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Symptomatic/</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Decompensating</td>
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<td></td>
</tr>
<tr>
<td>Worsening/</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Decompensated</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

CO = cardiac output
PAP = pulmonary arterial pressure
PVR = pulmonary vascular resistance
RAP = right atrial pressure.
ventricular function (and not the pulmonary arterial pressures). At this point, there are no therapies that target or support right ventricle function. Risk factors for progression and shorter survival include clinical evidence of right ventricular failure, rate of progression, WHO class, six-minute walk distance, cardiopulmonary exercise testing results, echo findings, hemodynamics, and brain natriuretic peptide (BNP) levels. Exhibit 2 illustrates low- and high-risk values for each of these factors.2

The goals in managing PAH are numerous. They include improve survival, prevent worsening, improve hemodynamics, improve exercise capacity, maintain or improve functional class, and improve daily functioning and quality of life. Additionally, reversal of vascular injury, improvement in right ventricular function, and normalization of pulmonary pressures will hopefully be achieved.

Medications should be started once the diagnosis is confirmed. No data support a “wait-and-see” approach to treating diagnosed PAH. Data suggest that patients assigned to placebo in randomized controlled trials may fail to “catch-up” when enrolled into long-term observational arms.

General medical management of PAH includes oxygen which may be required at rest, with exertion and/or at night, warfarin (if not otherwise contraindicated), diuretics, and digoxin (if the right ventricle is dilated and/or depressed). Anticoagulation is recommended because the high prevalence of microthrombotic lesions results in high risk for venous thromboembolic disease. Multiple studies in PAH (predominately idiopathic PAH) have shown that using warfarin anticoagulation has a beneficial effect on survival.2

Numerous lifestyle adjustments are also necessary. Those with PAH need to avoid stimulants and decongestants that contribute to vasoconstriction. They should be on a low-salt diet and may need fluid restriction. Additionally, avoidance of pregnancy in women is recommended. Women with PAH who try to carry a pregnancy to term have a 30 percent chance of dying.

Years ago, patients were counseled to avoid exercise. Studies have since shown benefits. Exercise training significantly improves six-minute walk distance in PAH.8 However, weight lifting and other exercise that can cause a Valsalva effect need to be avoided.

The small percentage of patients who have a positive vasodilator response will be treated with a calcium channel blocker with vasodilatory properties such as nifedipine. It is essential to follow patients treated with CCBs closely to make sure the clinical response is as anticipated, to make sure there are no side effects of therapy and, very importantly, to
Lots of altered pathways and mediators have been identified that contribute to the cell proliferation and vasoconstriction in PAH, which ultimately ends in vascular remodeling. Targets of current PAH specific therapies include the prostacyclin, endothelin, and nitric oxide pathways (Exhibit 3). Targeting each of these pathways results in vasodilation and antiproliferative effects in the pulmonary vasculature. The FDA approved therapies for PAH by class include:

- Prostacyclin analogues – continuous IV infusion epoprostenol (Flolan®, generic), continuous IV infusion thermostable epoprostenol (Veletri®), continuous SC or IV infusion treprostinil (Remodulin®), inhaled iloprost (Ventavis®), inhaled treprostinil (Tyvaso®)
- Endothelin receptor antagonists – oral bosentan (Tracleer®), oral ambrisentan (Letairis®)
- Phosphodiesterase type 5 inhibitors – oral or IV sildenafil (Revatio®, generic), oral tadalafil (Adcirca®)

Selection of initial PAH specific medication will depend on severity of symptoms, rate of progression, evidence of right-sided heart failure, six-minute walk distance, and BNP levels. The dosage form selected will also depend on the capability of the patient to manage inhaled or parenteral therapy. Parenteral therapy is first-choice therapy in rapidly progressing and advanced disease. Other issues to consider include drug–drug interactions, adverse events, co-morbid conditions (e.g., diabetes), dosing, and cost. The American College of Cardiology Foundation/American Heart Association (ACCF/AHA) guidelines recommendations are shown in Exhibit 4.

Therapy should be escalated or changed when there is failure to improve on monotherapy. If the patient has improved, but not to the satisfaction of the patient and/or the physician (by objective end points, symptoms, QOL, etc.) or has improved for a period of time, but is now deteriorating, therapy needs to be changed either to another single agent or combination therapy.

Combination therapy is somewhat controversial, but there are some justifications for utilizing it. Combining different mechanisms of action medications targets multiple pathogenic pathways, thereby achieving synergistic effects. Combination therapy potentially allows dose reduction of one or more of the therapies, thereby reducing the toxicities of full-dose monotherapy. Lastly, combination therapy is the standard of care in most chronic medical conditions such as heart failure and diabetes. One study found an improvement of survival compared to historical controls when bosentan was combined with either sildenafil or iloprost.
Conclusion
An early and accurate diagnosis of PAH is crucial. Once a diagnosis is established, therapy should be instituted. The initial therapeutic choice(s) depends upon the patient's clinical co-morbidities, clinical circumstance, and their functional status. Treatment must be individualized and ongoing reassessment of the patient's clinical status and response to therapy is mandatory. If the patient does not meet treatment goals, switching to an alternative agent or adding a second (or perhaps a third agent) may be appropriate. Referral to an experienced pulmonary hypertension center should be considered for all patients and may be necessary for parenteral therapies and involvement in clinical trials.

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References
INFLAMMATORY BOWEL DISEASE (IBD) is a chronic imbalance between pro- and anti-inflammatory events where the immune system is attacking the intestinal tract. Normally, the immune system will down-regulate after an inflammatory event. In those with IBD, there is no down-regulation so they have chronic inflammation. IBD can be divided into two major types — Crohn’s disease (CD) and ulcerative colitis (UC).

The goals of treating IBD include inducing remission, maintaining remission, mucosal healing, preventing disease and therapy-related complications, limiting the need for surgery, and improving quality of life. Because the immune system in IBD is genetically programmed to attack the individual, if medications keeping the immune system in check are stopped the uncontrolled inflammation will return. Thus, maintaining remission requires maintaining medications.

IBD remission can be defined as the absence of disease or the impact upon disease upon the patient. The definition of remission has changed as therapies have improved. With the newer medications, many patients have a complete absence of symptoms, whereas, in the past, remission might have been considered living with minimal symptoms. Remission can be considered equivalent to perfection (to the extent that nonperfection is due to active disease). Asking the patient how they are should elicit no problems, they should say everything is perfect.

Exhibit 1 shows the current therapeutic pyramid for both forms of IBD. Therapy is started based on the disease severity.

Aminosalicylates that include 5-aminosalicylate, mesalamine, and sulfasalazine are typically the first therapy approved for mild to moderate UC but are also used in mild to moderate CD. These agents work topically by contact with the mucosa of the bowel wall and are not intended to be absorbed.

There is a great deal of misunderstanding about the selection of aminosalicylate products. Clinicians need to match the location of disease to the specific release mechanism of the various mesalamine prod-
ucts. Exhibit 2 shows the area of release within the bowel and the release mechanism of agents by brand name. It is important to note that from a formulary standpoint, these products are not all interchangeable because they work in different areas of the intestinal tract. Additionally, some of the products require multiple tablets dosed several times daily. This can significantly impact adherence and therapy outcomes. Although the acquisition cost may be higher, adherence will be better with products that only have to be dosed once a day such as mesalamine extended release (Apriso®).

Antibiotics are used for specific circumstances in IBD. In Crohn’s Disease, they are used in perianal disease, penetrating disease that has gone outside the bowel wall, and sometimes in stricturing. In UC, antibiotics are limited to treating pouchitis. Antibiotics may need to be used long term in CD, thus they should not be stopped. Antibiotics decrease luminal bacterial concentrations, selectively eliminate bacterial subsets, reduce tissue invasion and microabscesses, and prevent systemic dissemination of bacteria. Ciprofloxacin and metronidazole are most commonly used and may also have some anti-inflammatory effects.

Corticosteroids will be needed to manage disease flare-ups but should be discontinued as soon as possible. Oral, parenteral, and topical (rectal) steroids are effective in inducing remission but are ineffective in maintaining remission. Additionally, they cause prohibitive adverse effects. Clinicians need an exit plan for stopping steroids, which requires starting a remission therapy at the same time as the steroids.

Budesonide is a high-potency steroid with extensive hepatic first-pass metabolism that reduces many of the systemic adverse effects of corticosteroids. Newer products with targeted delivery to the bowel for UC and CD are now available. A controlled ileal release product (Entocort®-EC) has release characteristics for CD. Sixty to 70 percent of this product is absorbed in the ileal and ileocecal area with only 10 percent of a dose entering the systemic circulation. Older patients can have typical steroid adverse effects with long-term use of the ileal release product. There is also a once-a-day product customized for UC - budesonide multi-matrix release (Uceris®). This product has a pH-resistant coating that delays release till a pH of 7 so it releases in the colon.

Patients with Crohn’s disease are at risk for osteoporosis, largely due to the combination of disease activity and systemic corticosteroid exposure. The effects of budesonide and prednisolone on bone mineral density (BMD) were compared in a two-year, open-label, randomized trial. At baseline, osteopenia or osteoporosis was evident in 58 percent of corticosteroid-dependent patients, 44 percent of those previously exposed but now corticosteroid-free, and 34 percent of corticosteroid-naïve patients.
For patients administered budesonide extended release, there was no substantial loss in BMD at two years compared to baseline. Among 98 corticosteroid-naïve patients, those treated with prednisolone lost more bone mass than those treated with budesonide, particularly during the first six months of therapy. The study also showed that the overall incidence of treatment-emergent side effects was significantly lower for budesonide than prednisolone (51% vs 71%; P < .001).  

Budesonide, while preferred over other steroids, is still not a long-term plan for CD. As shown in Exhibit 3, at one year there is no benefit of this therapy.  

The next step in the treatment pyramid is immunomodulators (purine analogues and methotrexate). The purine analogues (6-mercaptopurine [6-MP] and azathioprine) are effective in maintaining in adults and children with CD and UC. They are safe long-term choices but are typically underdosed and underused. Additionally, they are available generically, are inexpensive, and are dosed once a day. The purine analogues do have a slow onset of effect (3 to 6 months) but wear off slowly (i.e., the patient can skip some doses). As long as they are working, the immunomodulators should be continued because stopping therapy can lead to a relapse.

Methotrexate is an option in CD, but it is used little. It has to be used as an injectable because oral therapy is not as effective. It is another inexpensive option given as a once-a-week subcutaneous injection.

The game changers in iBD have been the biologic agents. Biologic agents approved for iBD include the TNF blockers [infliximab (Remicade®), adalimumab (Humira®), certolizumab (Cimzia®), and golimumab (Simponi®)] and Natalizumab (Tysabri®). Natalizumab, humanized monoclonal antibody against the cell adhesion molecule α4-integrin, is only FDA approved for CD. The biologics are “game changers” in IBD patients because they work fast, work well, can be used long term for maintenance. Like immunomodulators, they should not be stopped if working and initiation should not be delayed too long. FDA approval is for moderate to severe disease. In the past, these agents have been reserved for severe disease but should be used for moderate disease when the potential impact is higher.

Over time, patients with IBD will develop stricture or penetrating disease, which leads them toward surgery. The impact of therapy will depend on the degree of structural damage and the velocity of progression in the individual (Exhibit 4). The time to make most impact in IBD is to start therapy early in the disease process when the patient is in the inflammatory phase.

Biologic response rates are highest if they are started early in the disease course. For CD, this needs to be before stricture or penetration through the intestines occurs and in UC before chronic inflammation leads to a tubular colon. Studies have been shown improved remission rates with early use. There is a 50 percent higher remission rate when biologics are used within the first two years of CD onset. Step-up therapy has been the traditional treatment path. When compared to step-down therapy (aggressive early treatment with biologics and aza-
there is a significantly higher rate of remission (61.5% versus 42.2% at one year) with step-down therapy.8

Unlike treatment of rheumatoid arthritis with biologics, induction loading doses of biologics are required. This is likely a result of IBD patients losing the medication through the inflamed bowel. Induction dosing increases remission rates.9 Once the patient is in remission with biologics, therapy needs to be continued. Many trials have shown that if therapy is stopped, relapse will occur.

A controversial area is whether biologics should be given in combination with immunomodulators or alone. When given with an immunomodulator, the rate of development of anti-biologic antibody development is significantly lower.10-13 Some antibodies are neutralizing, which make the biologics ineffective, whereas other antibodies cause infusion reactions. One in seven patients will develop neutralizing antibodies if given infliximab alone versus one in 100 patients if infliximab is used along with azathioprine. Because IBD patients have to be treated for many years, preserving the efficacy of the limited number of medications by using com-

| Exhibit 3: Lack of Oral Budesonide Maintenance Efficacy² |

<table>
<thead>
<tr>
<th>days to relapse</th>
<th>% relapse @ 1 year</th>
</tr>
</thead>
<tbody>
<tr>
<td>Budesonide 6 mg</td>
<td>178*</td>
</tr>
<tr>
<td>Budesonide 3 mg</td>
<td>124*</td>
</tr>
<tr>
<td>Placebo</td>
<td>39</td>
</tr>
</tbody>
</table>

| Exhibit 4: Impact of Therapy Depends on Degree of Structural Damage and Velocity of Progression⁴ |

<table>
<thead>
<tr>
<th>Cumulative Probability (%)</th>
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<tbody>
<tr>
<td>Cumulative Probability (%)</td>
</tr>
<tr>
<td>0 12 24 36 48 60 72 84 96 120 144 180 216 240</td>
</tr>
<tr>
<td>High Impact</td>
</tr>
<tr>
<td>Progression Toward Surgery</td>
</tr>
<tr>
<td>Penetrating</td>
</tr>
<tr>
<td>Inflammatory</td>
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<td>Stricturing</td>
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A controversial area is whether biologics should be given in combination with immunomodulators or alone. When given with an immunomodulator, the rate of development of anti-biologic antibody development is significantly lower.10-13 Some antibodies are neutralizing, which make the biologics ineffective, whereas other antibodies cause infusion reactions. One in seven patients will develop neutralizing antibodies if given infliximab alone versus one in 100 patients if infliximab is used along with azathioprine. Because IBD patients have to be treated for many years, preserving the efficacy of the limited number of medications by using com-
Combination therapy is important. Although initial clinical trials of combination therapy in IBD did not show success, more recent trials have. Exhibit 5 shows the improvement in remission and mucosal healing rates with combination therapy in CD. Similar results are seen in UC.

Biologics in IBD have significant benefits. They are fast acting, efficacious, work for induction and maintenance of remission, and are steroid, hospitalization, and surgery sparing. There are some downsides to the use including possible adverse effects and significant acquisition costs.

There have been concerns about the effects of biologics on infection risk. In an analysis from the Therapy, Resource, Evaluation and Assessment Tool (TREAT) registry, although the unadjusted analysis showed an increased risk for infection with infliximab use in CD, multivariate logistic regression analysis suggested that infliximab was not an independent predictor of serious infections (OR, 0.99; 95% CI, 0.64–1.54). Factors independently associated with serious infections included prednisone use (OR, 2.21; 95% CI, 1.46–3.34; P<.001), narcotic analgesic use (OR, 2.38; 95% CI, 1.56–3.63; P<.001), and moderate-to-severe disease activity (OR, 2.11; 95% CI, 1.10–4.05; P=.024).

The authors concluded that the increased risk for serious infection observed with infliximab likely was owing to disease severity and prednisone use. Five-year follow-up data from the TREAT registry showed similar findings.

Additionally from the TREAT registry data, the hazard ratio for death was significantly higher in those with CD treated with prednisone or narcotic analgesics. The mortality rate was similar for those receiving infliximab and other treatments. Thus, corticosteroids can be considered the most dangerous class of medication used in treating IBD.

Another concern with the biologics has been the risk for cancer. Again from the TREAT registry, the rate of malignancies is no higher in those with CD receiving infliximab compared with those receiving other treatments. In another analysis, the rate of non-Hodgkin’s lymphoma in those receiving a TNF inhibitor and an immune modulator was higher than the standardized incidence ratio from the Surveillance Epidemiology and End Results (SEER) database [6.1 per 10,000 patient years vs. 3.23]. The authors of this analysis concluded that the use of anti-TNF agents with immunomodulators is associated with an increased risk of non-Hodgkin’s lymphoma in adult CD patients, but the absolute rate of these events remains low and should be weighed against the substantial benefits associated with treatment.

Although the acquisition costs of the biologics is significant, the overall health care costs related to use of these agents must be considered. Infliximab use has been shown to decrease utilization of hospitalizations and surgeries, decrease overall costs, decrease disability, increase full-time employment, and increase part-time employment. In comparison with other widely accepted medical interventions, the cost utility of infliximab in CD is significantly lower.

Many clinicians have concerns about running out of treatment options if therapy is started “too early.” Patients with IBD are typically young (av-
erage at age diagnosis is 22), have a chronic, relapsing disease, but also have a normal or near normal life expectancy. Thus, they will have to live many years with this disease. Starting biologics early maximizes the chance biologics will work and using combination therapy maximizes the chances biologic efficacy will last.

The previous treatment paradigm was a bottom-up approach with conservative use of immunomodulators. The new treatment paradigm is an early aggressive approach with earlier use of immunomodulators and biologics. Under this new paradigm, additional goals are possible. These include disease modification, mucosal healing, and choosing the most cost-effective therapy.

**Conclusion**

Choosing the most appropriate therapy for IBD is important in achieving good clinical outcomes. In those with mild disease, the location of the inflammation and the release characteristics of amino-salicylates are used to select appropriate products. Corticosteroids are important for inducing remission, but should not be used for maintenance of remission. Budesonide is the preferred agent, but it still should be used for the shortest time possible. In moderate to severe disease, immunomodulators and biologics are extremely effective and safe for maintaining long-term remission but are under-used. Using these two in combination is especially efficacious but does possibly increase risk of non-Hodgkin’s lymphoma. The future of managing IBD includes using a step-down approach to aggressively manage inflammation early in the disease course.

**References**

OVERACTIVE BLADDER (OAB) IS A PREVALENT symptom complex of urgency, frequency, and urgency urinary incontinence (UUI), which has enormous impact on those affected (Exhibit 1). Urgency is the sudden compelling desire to void that is difficult to defer, whereas frequency is defined as eight or more micturitions in 24 hours. Patients may also complain of nocturia.

Urgency is often referred to as the cornerstone symptom of OAB. Urgency is not the same as urge, a sensation that everyone feels at times. Urge can be deferred until there is a socially acceptable time or place to void, but urgency cannot be easily deferred. Patients with OAB may experience an urgency episode early in the bladder filling phase. This usually results in a void, whether voluntary or involuntary. This void is also associated with a reduced volume voided because it occurs early in the bladder filling phase.

There are several possible reasons why a person with OAB has urgency. In the detrusor muscle, increased afferent nerve activity may result from an enhanced reaction to stretching of the detrusor cells or by an increase in urothelial signaling to suburothelial nerves. In the central nervous system (CNS), there may be a tonic inhibition of afferent signals. A decrease in this tonic inhibition could result in the initiation of detrusor activity during the bladder filling phase. In addition, certain conditions (such as stroke) could lead to loss of voluntary control of micturition. Several disorders associated with detrusor overactivity, whether neurogenic damage, aging, bladder outflow obstruction, or idiopathic detrusor overactivity, may result in increased sensitivity of the bladder smooth muscle.

The most common risk factor for OAB is increasing age. Other common risk factors include obesity, Caucasian race, and hormone replacement therapy. Neurogenic OAB may be secondary to multiple sclerosis, Parkinson’s disease, dementia, spinal cord injury, cerebrovascular accident, and diabetes.

OAB negatively affects various components of quality of life (QOL). OAB symptoms compromise many aspects of QOL, including physical, occupa-
tional, sexual, psychological, domestic, and social aspects. For example, occupationally, OAB can lead to absence from work and, therefore, decreased productivity. Socially, OAB reduces social interaction and can limit travel, or at least hinder travel so it must be planned around accessibility to a toilet. OAB can also affect sexual QOL because it might lead to avoidance of sexual contact and intimacy. Psychologically, OAB can negatively affect the patient by causing guilt or depression, loss of self-esteem, and fear of being a burden. Patients also may fear that lack of bladder control may cause them to have an odor of urine.

Individuals with OAB have higher health care resource utilization than people without OAB. Resource utilization includes physician visits, medications, tests, and incontinence management supplies.

The impact of OAB goes beyond the impact on QOL and the economic impact. There is morbidity associated with this syndrome. OAB is associated with falls, fractures, and depression. OAB related UUI increases risk of falls by 26 percent and fractures 34 percent. Early diagnosis and treatment can potentially prevent or decrease falls and fractures. OAB places people at greater risk for urinary tract infections (UTIs) and perineal dermatitis. UUI increases risk of hospitalization (30% increased risk for women, 50% for men) and of the elderly being admitted to nursing homes. 

Even though this condition has significant financial, social, and personal impact, it is undertreated. Few OAB sufferers get diagnosed and few are treated. There are many reasons for this. Patients don’t discuss the condition with a physician because of embarrassment, fear of invasive procedures or the need for surgery, and a perceived lack of available treatment. Many people, particularly women, believe incontinence is inevitable. Physicians do not ask about OAB symptoms because they are busy, lack time to add another screening, and do not understand the impact. Additionally, this is a not life-threatening. Many physicians feel that patients will bring it up if bothered.

Two easy questions to screen for OAB include “Is your bladder causing you any problems?” and “Do you have trouble controlling your urine?” The impact of symptoms on an individual is important. Many patients have minor symptoms, are not significantly impacted, and may not wish to be treated.

Certain patients should be referred to an urologist for further evaluation. Indications for referral include hematuria, significant pelvic organ prolapse, recurrent urinary tract infections, increased post-void residual, failure to improve with medical therapy, and prior pelvic surgery.

Treatment of OAB is a combination of education, behavioral modification, medications, and surgical procedures. First-line therapy is education about normal bladder function and appropriate expectations and behavioral interventions. OAB is a symptom complex with a variable and chronic course. Patients need to understand they will not be cured. Treatment improves symptoms but usually does not totally eliminate symptoms or incontinence episodes. Thus, patients need appropriate treatment expectations. Patient set goals are typically task oriented instead of number oriented. For example, they may wish to watch a movie without interruption rather than have two fewer episodes of micturition daily.

Various forms of behavioral modification can be helpful in the management of OAB. Useful strategies

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Exhibit 1: The Overactive Bladder Complex

- Frequency – 8 or more micturitions per day
- Urgency – sudden compelling desire to void that is difficult to defer
- Nocturia – awakening at night 1 or more times to void
- Urges Incontinence – incontinence associated with urgency

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for behavioral modification include patient education, timed or delayed voiding, and positive reinforcement of any changes made. Bladder diaries can help to characterize symptoms, fluid intake, and when accidents are happening. Simply doing a bladder diary is a form of behavioral treatment. It helps patients be tuned into what causes their symptoms. Pelvic floor exercises have been found useful for women, primarily those with stress urinary incontinence. Dietary changes to avoid bladder irritants (spicy foods, citrus fruits and juices, tomato-based foods, alcohol and caffeine) can also help in the management of OAB. Managing caffeine and fluid intake are especially important. It is important to educate patients to not fluid restrict to the point of dehydration and concentrated urine which is a bladder irritant. Behavioral therapy is generally equivalent to or superior to medications in reducing incontinence episodes, improving voiding parameters and quality of life, and is relatively low cost.7

Medications are considered second-line therapy after behavioral interventions do not adequately control symptoms. There are now two classes of medications for managing OAB. The antimuscarinics have been around for many years. Newly approved are beta agonists. Most patients will require a combination of behavioral therapy and medications, which has been shown to be more efficacious than either alone.8

Antimuscarinics work by antagonizing receptors in the detrusor muscle of the bladder. In the detrusor, the postjunctional muscarinic M3 receptor is the predominant subtype mediating contraction. M3 receptor antagonism stabilizes the detrusor muscle, increases bladder capacity, diminishes frequency of involuntary bladder contractions, and delays initial urge to void.9

All six available antimuscarinics (oxybutynin, tolterodine, solifenacin, darifenacin, fesoterodine, trospium chloride) are effective for OAB symptom management.7,10 The majority of comparison studies of these agents are non-inferiority studies. A Cochrane group review found no major differences in efficacy.11

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**Exhibit 2: Pearls in Treating Patients with OAB**

- Identify the most bothersome symptom.
- Make sure patient’s expectations are realistic.
- Start low and titrate up as needed.
- Most patients will see some benefit within 2 weeks, but it will often take at least 4 weeks for maximum response – patients need to modify behavior also.
- Be proactive about preventing/treating side effects.
- If a patient has failed prior antimuscarinic therapy, start with an agent that has more than one dose.
- Night-time dosing may help decrease adverse effects but should not be used with trospium chloride.
- Patients who are refractory to behavioral and medical therapy should be evaluated by an appropriate specialist.

**Exhibit 3: Identifying Anticholinergic Agent Failure**

- Is the failure due to lack of efficacy or intolerable side effects?
- Is the patient using the highest tolerable dose?
- Is behavioral therapy being utilized?
- Have you identified the patient’s expectations?
- Are the patients expectations realistic?
Because comparative efficacy is lacking, the pharmacokinetic and pharmacologic profiles of each agent are considered when selecting the ideal antimuscarinic agent for a particular patient. There are some differences in method of delivery, dose flexibility, and tolerability which may impact persistence with therapy. For example, transdermal oxybutynin (patch or gel) causes less dry mouth than oral forms of oxybutynin. The transdermal formulation bypasses first pass metabolism through the liver. One of the liver metabolites of oxybutynin is more likely to cause dry mouth.

Exhibit 2 lists some pearls of treating OAB. With antimuscarinics, patients can expect up to a 90 percent reduction in UUI, a reduction in micturition frequency, and an increase in dry rates. The endpoint for micturition frequency is not zero but normalization – about two to three less voids per day. Dry rates will vary with baseline severity. Typically with therapy 50 to 64 percent of patients will be dry. The rate will be less with more severe UUI and greater with less severe UUI. Patients should have some benefit within two weeks of starting therapy with continued improvement out to six weeks.

Expectations about treatment efficacy and side effects are the most important considerations in discontinuing OAB medications for most patients. In one study, 11 percent of subjects noted general aversion to taking medication. Thus, interventions to promote realistic expectations about medication efficacy and side effects may enhance adherence and persistence.

Constipation and dry mouth are the most common adverse effects of antimuscarinics. The American Urological Association guidelines state that clinicians should manage constipation and dry mouth before abandoning effective antimuscarinic therapy.

To proactively manage bowel function, baseline function should be assessed before antimuscarinic therapy is started. Many patients fluid restrict in hopes of decreasing frequency and incontinence, but this can worsen or cause constipation. If constipation occurs, increasing fluid intake, dietary fiber, and adding an osmotic laxative can be helpful.

Educating patients that dry mouth can occur and how to manage this adverse effect may help some people adhere to antimuscarinic therapy. Some tips for managing dry mouth include sipping cool water throughout the day or drinking milk to lubricate the oral mucosa. Caffeine and alcohol both cause dry mouth so they should be restricted. There are many other medications that can cause dry mouth so the patient’s regimen should be examined to identify any that possibility could be discontinued. Sugar-free gum can be used to stimulate saliva flow. Lastly, products such as saliva substitutes, dry mouth toothpaste, or dry mouth mouthwash or mouth spray can be used.

The treatment guidelines recommend using caution in prescribing antimuscarinics in frail OAB patients (mobility deficits, weight loss and weakness without medical cause and who may have cognitive deficits). The use of OAB medications may have a lower therapeutic index and a higher adverse drug event profile in this patient group. If used, antimuscarinics should be prescribed at the lowest possible dose and increased slowly.

If a patient fails an antimuscarinic agent, the reasons for the failure should be identified (Exhibit 3). Alternatives for a true failure include trying another anticholinergic agent, adding or optimizing behavioral therapy, or trying a beta agonist.

Mirabegron (Myrbetriq) is a selective beta-3 adrenoceptor agonist which activates the beta-3 adrenoceptors on the bladder detrusor muscle to facilitate filling of the bladder and storage. Different from antimuscarinics, the agent does not affect detrusor contractility. Mirabegron is a first-line agent like the antimuscarinics but can also be used if those agents fail. This agent is effective in reducing symptoms within eight weeks. This agent decreases incontinence episodes, micturition episodes, and increases voided volume at similar efficacy to antimuscarinics.

One unique adverse effect of this agent that may occur is increased blood pressure. In one study, the rate of dry mouth with mirabegron was equivalent to placebo, whereas 10 percent of subjects that received tolterodine developed dry mouth. Overall, treatment-emergent adverse effects were similar between placebo, mirabegron, and tolterodine.

Solabegron is another beta agonist under evaluation. Phase I and II studies have been completed, but the Phase III trials have not yet been initiated.

Third-line therapies include sacral neuromodulation, which requires surgery to place the stimulator, percutaneous tibial nerve stimulation, and botulinum toxin injection into the bladder muscle. Each of these is an option for patients who do not get sufficient efficacy with behavioral therapy and medications. Bladder augmentation is the last line of therapy.

Antimuscarinic therapy has been compared with botulinum toxin injection. In a multicenter, randomized, double-blind trial comparing solifenacin daily with botulinum toxin injection in women with moderate to severe UUI (5 or more UUI episodes on 3 day diary), the mean reduction in UUI episodes/day was similar (3.4 episodes/day in anticholinergic group vs. 3.3 in botulinum group). The reduction in daily UUI episodes was main-
tained in both groups for the six-month active treatment phase. In this study, a higher baseline frequency of UUI episodes/day was associated with greater reduction in UUI episodes (p<0.01). The botulinum toxin group was more likely to report complete resolution of UUI (27% vs 13%, p=0.003). QOL and patient-reported outcome parameters improved in both groups.

Because it significantly decreases detrusor muscle contractility, botulinum toxin injections can lead to urinary retention that can last six months, which is the typical duration of therapeutic efficacy of an injection series. In the study discussed above, 5 percent of the patients in the botulinum group required self catheterization. The rate of retention requiring catheterization decreased to 3 percent at four months and 1 percent at six months. Because of the need for catheterization, more women in the botulinum toxin group had UTI (33% vs 13%, p<0.001).

**Conclusion**

OAB remains a highly prevalent, underdiagnosed and undertreated condition. Despite the impact on QOL and associated morbidities, patients are afraid to bring it up and doctors often don’t ask about bladder problems. There are effective treatments for this condition. Despite improvements in OAB symptoms, persistence with antimuscarinics remains limited. Care should be used in treating frail elderly patients with antimuscarinics. Mirabegron is a newer oral OAB therapy with a different MOA from antimuscarinics. Third-line therapies include percutaneous tibial nerve stimulation, sacral nerve stimulation, and botulinum toxin.

**References**


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Recent Advances in the Treatment and Management of Metastatic Melanoma

Evan J. Lipson, MD

Summary
The treatment of metastatic melanoma continues to evolve. Exciting treatments that include vemurafenib and ipilimumab are producing durable responses in some patients. Additional treatments that continue to extend survival are under investigation.

Key Points
- Chemotherapy results in a very low response rate that only lasts briefly.
- Vemurafenib treatment produces about a 40 percent response rate, but resistance develops quickly.
- Ipilimumab treatment produces about a 20 percent response rate.
- Those who respond to ipilimumab typically have a durable response of several years.
- Combination treatments to overcome vemurafenib resistance and additional immunotherapies are under investigation.

MELANOMA IS A RISING THREAT. IN THE Western world, the incidence of melanoma is increasing more rapidly than any other cancer. The lifetime risk of an individual American developing melanoma is now near one in 70, compared with one in 1,500 in the 1930s.1

Many patients will develop metastatic disease, which is considered incurable. The treatment of metastatic melanoma includes chemotherapy, oncogenic pathway inhibitors, and immunotherapy. In addition to these treatments, the National Comprehensive Cancer Network (NCCN) guidelines include clinical trials as a preferred therapy.2

FDA approved chemotherapy includes dacarbazine, temozolomide (Temodar®), and platinum. Standard chemotherapy is curative in some cancers (e.g., testicular, some lymphomas). In general, melanoma is not one of them. Response rates are low and typically brief. Given the well-known adverse effects and low response rates, chemotherapy has a somewhat limited role in the treatment of this disease, usually used for patients with a poor performance status or whose disease has progressed on other therapies.

Discovery of genetic mutations that drive melanoma has led to development of targeted therapy with oncogenic pathway inhibitors. About 50 percent of melanoma tumors have BRAF mutations that cause cell proliferation. Currently, only one selective BRAF inhibitor is available – vemurafenib (Zelboraf®). Vemurafenib shuts down tumor growth in cells with a mutation. In a Phase III randomized clinical trial comparing vemurafenib with dacarbazine in 675 patients with untreated, metastatic V600E mutant melanoma, the overall response rate was 48.4 percent with vemurafenib or 5.5 percent with dacarbazine.3 Vemurafenib was FDA approved in August 2011 for metastatic melanoma harboring a BRAF V600E mutation. In practice, it is effective in patients with other BRAF mutations.

Adverse effects of vemurafenib are not insignificant. Arthralgia, rash, fatigue, alopecia, keratoacanthoma or squamous cell carcinoma, significant photosensitivity, nausea, and diarrhea are all common.
In a study of vemurafenib, 38 percent of patients required dose modification because of side effects. Vemurafenib therapy often works quickly and effectively; it is good for patients who need an immediate response. In general, responses are not durable; resistance often develops after six to eight months of therapy.

Two immunotherapies include ipilimumab and interleukin-2. Immunotherapy is almost the ideal cancer treatment for several reasons. Melanoma is perhaps the most immunogenic human cancer. The human immune system can attack with virtually unlimited precision. Unlike targeted therapy, the human immune system can adapt to ongoing tumor mutations and avoid drug resistance. Additionally, responses to immunotherapy are often durable (immune memory). An example is lifelong protection against measles after vaccination.

Interleukin-2 was the first immunotherapy approved for metastatic melanoma. It stimulates the production of T-cells. The use of interleukin-2 is limited by the need to administer it in the intensive care unit during a five-day stay; approximately 100 centers in the United States administer this agent. There is a 15 to 20 percent response rate, which depends on the location of the disease. Disease limited to skin and lymph nodes tends to respond better to interleukin than disease in visceral organs. About 5 percent of patients obtain a durable complete remission and are long-term survivors. The adverse effects of interleukin-2 include hypotension, tachycardia, capillary leak syndrome, and altered mental status. Patients have to be fairly healthy to tolerate this therapy, which is another factor limiting its use.

Another target of immunotherapy is cytotoxic T-lymphocyte–associated antigen 4 (CTLA-4), an immune checkpoint molecule that down-regulates pathways of T-cell activation. Ipilimumab (Yervoy®) is a fully human monoclonal antibody (IgG1) that blocks CTLA-4 to promote antitumor immunity. It was FDA approved for the treatment of metastatic melanoma in 2011 after a 676-patient randomized study demonstrated improved overall survival. This was the first randomized trial to demonstrate improved overall survival in metastatic melanoma. The difference in survival at a year was significant (44% versus 25%, Exhibit 1). At 24 months, there is a plateau where the survival curve stays fairly level. If patients respond, they are likely to maintain that response for several years.

This agent is given over a nine-week course. There are some data supporting a repeat course of therapy if the disease regrows.

This agent does lead to some serious adverse effects. In the trials, serious (grade 3-4) drug-related adverse events occurred in 17 to 23 percent of patients, with a 2 percent mortality rate. The adverse event rate with this agent is almost as high as the re-
response rate. Immune-related adverse events include colitis (diarrhea, abdominal pain, blood in stool), hepatitis, dermatitis (pruritus, rash, rare toxic epidermal necrolysis), hypophysitis (headache, endocrine dysfunction), nephritis (creatinine rise), and neuropathies (numbness, weakness, paresthesias). These immune-related adverse events all come from the mechanism of action of this agent.5 In the normal immune system, T-cells are regulated to prevent them from attacking normal cells. Ipilimumab blocks the regulation pathway leading to attack on the colon, liver, or other body parts.

Patients have to be monitored very closely for the immune-related adverse effects. Management for most immune-related adverse effects is based on severity. In general, for grade 1-2, supportive care, plus possibly withholding the ipilimumab, is recommended. For grade 3-4, corticosteroids and discontinuation of the ipilimumab are recommended. Severe enterocolitis requires permanently discontinuing ipilimumab and systemic corticosteroids. Infliximab treatment may be required for refractory enterocolitis. For patients with complete or partial resolution of adverse reactions (Grade 0-1) who are receiving less than 7.5 mg/day prednisone or equivalent, ipilimumab can be restarted every three weeks until administration of all four planned doses or 16 weeks from the first dose, whichever occurs first.

As noted previously, resistance to BRAF inhibition occurs within six to eight months of initiating therapy. To overcome BRAF resistance, therapies blocking additional growth pathways are under study. Dabrafenib, a BRAF inhibitor, is being studied in combination with trametinib, a mitogen-activated protein kinase (MEK) inhibitor. Median progression-free survival in the combination group (BRAF+MEK) was 9.4 months, as compared with 5.8 months in the monotherapy group (BRAF alone).6

Another immunotherapy, nivolumab, is also under study. This is targeting the programmed death (PD-1) pathway. This is another negative regulatory pathway of the immune system to protect normal tissues from immune attack. Early data indicates some success with this approach. Thirty-one percent of patients responded. In patients with one year or more follow-up, 52 percent of the responses lasted over a year.7 This agent is also being studied in renal cell carcinoma and non-small cell lung cancer.

Conclusion

This is an exciting time for those who treat patients with metastatic melanoma. Ipilimumab and vemurafenib are two agents that prolong survival, and there are many more promising agents on the horizon.

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References

there were more than 200,000 new cases of lung cancer in 2013. Forty percent of those cases were metastatic at presentation. In 2012, lung cancer caused 160,000 deaths, a figure comparable to prostate, pancreas, breast, and colon cancer deaths combined. Five-year survival rates depend on the stage of disease at diagnosis. The five-year relative survival rate for patients with distant-stage disease is only 3.7 percent.

Lung cancer arises in different parts of the lung, resulting in different histologic types. Small cell and non-small cell are the two major divisions. Non-small cell lung cancer (NSCLC) is further divided into squamous cell, adenocarcinoma, large cell, and not otherwise specified. Immunohistochemistry is used to distinguish the different types and genetic testing is done to identify the increasing number of known genetic mutations that drive cancer growth.

Screening for lung cancer is not inexpensive because smokers need to be sequentially followed with low-dose CT, but it is effective. The number needed to screen to detect one case is approximately 300 people, which is similar to mammography. The benefit of screening is a 20 percent reduction in lung cancer mortality and about an 8 percent overall reduction in risk of death. It is recommended by the American Society of Clinical Oncology and the American College of Chest Physicians. Only a specific population needs to be screened – those with significant smoking history and aged 50 to 75 years. The screening should be conducted at an experienced institution. The rate of false positives with this screening is very high without an experienced radiologist interpreting the results.

Exhibit 1 compares stage at diagnosis for breast and lung cancer. Even with screening, the majority of patients have advanced disease at diagnosis. This is because of the biology of this disease.

Stage I and II disease (isolated to lung) is treated with surgery in operable patients, radiotherapy for inoperable or borderline patients, and adjuvant che-

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**Summary**

Advanced NSCLC is treated with chemotherapy and targeted agents. The choice of first-line therapy is driven by histology and/or tumor mutational status. Second-line therapy choices depend on performance scores, prior treatment, current organ function, tumor histology and molecular variables. Progress continues to be made with survival in this deadly disease.

**Key Points**

- The majority of patients already have metastatic disease at time of diagnosis.
- First-line therapy in advanced disease is selected based on tumor histology and mutational status in addition to patient factors.
- Patients with squamous disease should not receive bevacizumab.
- Pemetrexed is most efficacious in nonsquamous disease.
- Patients who have tumors with EGFR mutations should receive tyrosine kinase inhibitors and those with ROS1 or EML4-ALK fusion genes should receive crizotinib.
- Resistance develops relatively quickly to the targeted therapies.

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THERE WERE MORE THAN 200,000 NEW cases of lung cancer in 2013. Forty percent of those cases were metastatic at presentation. In 2012, lung cancer caused 160,000 deaths, a figure comparable to prostate, pancreas, breast, and colon cancer deaths combined. Five-year survival rates depend on the stage of disease at diagnosis. The five-year relative survival rate for patients with distant-stage disease is only 3.7 percent.

Lung cancer arises in different parts of the lung, resulting in different histologic types. Small cell and non-small cell are the two major divisions. Non-small cell lung cancer (NSCLC) is further divided into squamous cell, adenocarcinoma, large cell, and not otherwise specified. Immunohistochemistry is used to distinguish the different types and genetic testing is done to identify the increasing number of known genetic mutations that drive cancer growth.

Screening for lung cancer is not inexpensive because smokers need to be sequentially followed with low-dose CT, but it is effective. The number needed to screen to detect one case is approximately 300 people, which is similar to mammography. The benefit of screening is a 20 percent reduction in lung cancer mortality and about an 8 percent overall reduction in risk of death. It is recommended by the American Society of Clinical Oncology and the American College of Chest Physicians. Only a specific population needs to be screened – those with significant smoking history and aged 50 to 75 years. The screening should be conducted at an experienced institution. The rate of false positives with this screening is very high without an experienced radiologist interpreting the results.

Exhibit 1 compares stage at diagnosis for breast and lung cancer. Even with screening, the majority of patients have advanced disease at diagnosis. This is because of the biology of this disease.

Stage I and II disease (isolated to lung) is treated with surgery in operable patients, radiotherapy for inoperable or borderline patients, and adjuvant che-
motherapy in those with positive nodes or larger tumor size. In Stage I or II disease, adjuvant chemotherapy provides an absolute improvement in five-year overall survival of 11 percent (67% vs 56%) with the benefit persisting for nine or more years.5

Stage III (locally advanced) is treated with combined modality therapy. This locally advanced cancer can be cured with chemotherapy and radiation together; surgery is not necessary. In Stage III disease, there is a higher cure rate for combined chemotherapy and radiotherapy compared with radiotherapy alone. There is ongoing controversy regarding optimal chemotherapy and the role of surgery. Finally, Stage IV (metastatic) is treated with systemic therapy (chemotherapy, targeted agents) and palliative radiotherapy and surgical procedures as appropriate.6

Factors correlated with adverse prognosis in NSCLC are presence of pulmonary symptoms, large tumor size (>3 cm), nonsquamous histology, metastases to multiple lymph nodes, and vascular invasion. For patients with inoperable disease, prognosis is adversely affected by poor performance scores and weight loss of more than 10 percent. Advanced age alone has not been shown to influence response or survival with therapy at any stage of disease.

Even though most cases of metastatic disease cannot be cured, there are multiple reasons to treat advanced NSCLC. A meta-analysis of eight trials (778 patients) using older therapies found an absolute improvement in survival of 10 percent at one year.7 Even with toxic chemotherapy, quality of life (QOL) is uniformly superior with chemotherapy versus no treatment. Lung cancer is a very symptomatic disease; therefore, controlling the disease growth is important for QOL.

Some patients with metastatic NSCLC are curable. They have solitary metastatic disease in the brain, adrenal, or bone. They are treated with local therapy (surgery, stereotactic radiation, conventional radiation) and chemotherapy. Patients need extensive metastatic workup before therapy to make sure they only have a solitary metastases.

Considerations in selecting first-line therapy in advanced disease include performance scores, age, organ function, nutritional status, histology, and molecular variables. First-line therapy has changed significantly since 2005 with many new, better tolerated agents. Exhibit 2 provides an algorithm of selecting first-line therapy in advanced NSCLC.

The histology of the tumor has been shown to be important for efficacy and adverse effects with select therapies. Bevacizumab, a VEGF inhibitor, is indicated for advanced nonsquamous NSCLC. Those with squamous cell carcinoma should not receive this agent because of potential for fatal hemoptysis. An example of histology making a difference in efficacy is with pemetrexed. It is more effective in nonsquamous disease.

Genetic mutations are also important in selecting therapy. Lung cancer is different from other cancers in that carcinogen associated epithelial cancers (colon, lung, melanoma) are exceedingly genetically complex. Around the late 1990s, when the first epidermal growth factor receptor (EGFR) inhibitor agents were developed, some patients had dramatic responses. It was found that these agents worked best in those who were never smokers, be-
cause they develop a different type of cancer than smokers. Ten to 15 percent of lung cancer cases are in never or distant smokers. EGFR receptor mutations are most common in the never smokers. These mutations are also more common in Asians. One-third of lung cancers in Asia are in never smokers. Gefitinib and erlotinib, EGFR tyrosine kinase inhibitors, are both more effective in patients with EGFR mutations than chemotherapy. Even with the most active drugs, the response to treatment is on average less than a year.

Approximately 4 percent of NSCLC tumors have echinoderm microtubule-associated protein-like 4–anaplastic lymphoma kinase (EML4–ALK) translocation fusion that is an oncogene. This mutation is primarily found in adenocarcinoma cases. Crizotinib [Xalkori®] is an ALK inhibitor, which has shown dramatic results in patients with this gene fusion. Nearly all patients have initial benefit with this agent but, unfortunately, resistance does develop to this agent.

Crizotinib has also been shown to be effective in tumors with ROS1 fusions. Signaling downstream of ROS1 fusions results in activation of cellular pathways known to be involved in cell growth and cell proliferation.

Rat sarcoma virus (RAS) mutations occur in 15 to 20 percent of NSCLC, with greater than 90 percent of these involving KRAS (Kristen rat sarcoma virus). KRAS mutations are associated with smoking and adenocarcinoma tumors. The role of KRAS, as either a prognostic or predictive factor in NSCLC, is unknown at this time. Very few prospective randomized trials have been completed using KRAS as a biomarker to stratify therapeutic options in the metastatic setting. Currently, there are no direct anti-KRAS therapies available.

Many other genetic abnormalities have been or are being identified in both nonsquamous and squamous NSCLC. Trials of targeted therapies for many of these mutations are already under way.

For second-line therapy in NSCLC, no combination chemotherapy has proven benefit over single agents. Numerous factors have to be considered when selecting further lines of therapy including previous therapy, histology, performance status, and organ function. EGFR TKIs are an option comparable to chemotherapy which are less toxic and result in better QOL. Survival rates are similar for EGFR TKIs and chemotherapy. In many cases, the question is not whether a patient will receive a particular drug, but when and in what sequence.

Conclusion
Advanced NSCLC is a prevalent and deadly cancer. Several chemotherapy and targeted agents have been approved in recent years as first-line therapy. The choice of therapy is driven by histology and/or mutational status (i.e., EGFR and possibly others). Second-line therapy choices depend on performance scores, prior treatment, current organ function, tumor histology and molecular variables. Many patients do not respond to or relapse on exist-
ing therapies; however, there are promising agents under investigation that are hoped will continue to prolong survival in NSCLC.

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References
Prostate cancer is the number one cancer in men by incidence and is projected to remain first. After initial definitive treatment, many men will develop recurrent or advanced cancer which will eventually become castrate-resistant prostate cancer (CRPC). For specifically managing CRPC, several different therapies are available and are used at different stages (Exhibit 1).

For individuals with recurrent or advanced prostate cancer at diagnosis, hormonal therapy is the first step of therapy. The most common hormone therapies in this setting are the gonadotropin-releasing hormone (GnRH) agonists (leuprolide [Lupron®], goserelin [Zoladex®]) and antagonist (degarelix, [Firmagon®]) which decrease the production of testosterone. In patients with metastatic disease to the bone, premedication is required with an androgen receptor blocker to prevent a disease flare-up when a GnRH agonist is used. To avoid this issue, the GnRH antagonist can be used. After one month, the risk of a flare-up declines and the androgen blocker is not necessary.

If a patient on a GnRH agent has a rising prostate specific antigen (PSA) level, which suggests cancer cell growth, initially a testosterone level will be checked. If they have a non-castrate testosterone level (<20-50ng/dL) is present, an androgen receptor blocker can be added to block the action of any residual testosterone. Up to 40 percent of testosterone is derived from adrenal precursors. Three androgen...
receptor blockers are used in the setting of recurrent or advanced prostate cancer – flutamide (Eulexin®), bicalutamide (Casodex®), and nilutamide (Nilandron®).

Three large studies suggested that maximal androgen blockade (MAB) with the combination of a GnRH agent and an androgen receptor blocker conferred a survival advantage. The Prostate Cancer Trialists' Collaborative Group conducted a meta-analysis of 27 randomized trials including 8275 men with metastatic or locally advanced prostate cancer. The five-year survival rate was 25.4 percent with MAB versus 23.6 percent with androgen suppression alone. Because there is a higher rate of adverse effects with MAB, most clinicians will start with monotherapy and add the receptor blocker if the PSA level rises.

Patients can also have rising PSA while on MAB. The first option in this case is to stop the androgen receptor blocker, while continuing the GnRH agent. When MAB is changed back to monotherapy, PSA decreases in about 30 percent of patients for about a three-month duration. The androgen receptor blockers, in the setting of emerging resistance, actually act as an agonist. When that fails, alternative therapies would be considered.

For patients with metastatic prostate cancer on hormonal therapy, the median progression-free survival ranges from 12 to 30 months. Once the state of androgen independency (CRPC) occurred, historically the median overall survival was only eight to 16 months from the time of its appearance.

CRPC is defined by disease progression despite androgen deprivation therapy and castrate levels of testosterone (< 20ng/dL). This presents as a spectrum of disease, ranging from increasing PSA levels without metastases or symptoms despite androgen deprivation therapy, to metastases and significant debilitation from cancer symptoms.

CRPC does not necessarily imply hormonal resistance altogether. The tumor has learned to grow despite lowered testosterone levels, but there is a molecular basis underlying retained hormone sensitivity in CRPC. Amplification of the androgen receptor (AR) occurs in approximately 30 percent of CRPC tumors, but not in tumors prior to therapy. Enhanced intracellular conversion of adrenal androgens to testosterone and dihydrotestosterone may occur in cancer cells. There can be intra-tumor androgen synthesis, increased expression of AR messenger RNA, and ligand-independent AR activation. Because androgen receptors remain active in most patients with CRPC, the National Comprehensive Cancer Network (NCCN) and others recommend that ADT be continued in patients with CRPC.

More than 90 percent of patients with metastatic CRPC develop bone metastases and decreased bone integrity. Patients are at significant risk of developing skeletal-related events (SREs), including fracture, bone pain, and spinal cord compression, which significantly impacts quality of life (QOL). Additionally, bone loss is associated with ADT, which further increases the risk of fracture. To prevent SREs, all patients on ADT should get vitamin D and calcium supplementation. Several guidelines recommend zoledronic acid (Reclast®) or denosumab (Xgeva®) to preserve bone health and prevent SREs in CRPC patients with bone metastases, whether asymptomatic or symptomatic. Zoledronic acid, a bisphosphonate given intravenously every three to four weeks, is recommended in men with CRPC and bone metastases to prevent...
Denosumab is a RANK ligand inhibitor given subcutaneously every four weeks. Both have been shown to decrease SREs. The NCCN guidelines recommend denosumab as an alternative to zoledronic acid for prevention of SREs. Exhibit 2 compares major outcomes and adverse effects with zoledronic acid and denosumab. In a cost-effective analysis from a U.S. payer perspective, denosumab resulted in fewer estimated SREs (-0.241; 1036 vs 1.277), more QALYs (0.0074; 0.9306 vs 0.9232), and lower SRE-related costs (-$2,340; $4,424 vs $11,164) than zoledronic acid. Those benefits came at a higher drug-related cost ($10,181; $23,144 vs $12,963) and higher total costs ($7,841; $31,968 vs $24,127).

sipuleucel-t (Provenge®) is FDA approved for asymptomatic or minimally symptomatic metastatic CRPC. This is the first immunotherapy specifically for prostate cancer. A course of sipuleucel-t treatment consists of three basic steps. A patient’s white blood cells, primarily antigen-presenting cells (APCs), are extracted in a leukapheresis procedure. The blood product is sent to the factory and incubated with a fusion protein (PA2024) consisting of two parts, the antigen prostatic acid phosphatase (PAP), which is present in 95 percent of prostate cancer cells, and an immune signaling factor granulocyte-macrophage colony-stimulating factor (GM-CSF) that helps the APCs to mature. The activated blood product (APC8015) is returned to the infusion center and infused into the patient to cause an immune response against cancer cells carrying the PAP antigen. A complete sipuleucel-t treatment repeats three courses, with two weeks between successive courses. The cost is about $31,000 per infusion and $93,000 for a complete treatment. Acute infusion reaction is the most common adverse effect and was reported in 71.2 percent of clinical trial patients. Patients are premedicated with oral acetaminophen and an antihistamine such as diphenhydramine to prevent the reaction. Sipuleucel-T provides a median of 4.1 month survival benefit over placebo. Historically, docetaxel (Taxotere®, generic) has been the next step in therapy once someone with CRPC became symptomatic, providing about two month survival benefit. Docetaxel does cause some significant adverse effects. There are multiple studies ongoing examining the combination of this agent with many different therapies to improve the survival response.

Cabalitaxel (Jevtana®) was FDA approved in 2010 for metastatic CRPC in patients who have failed docetaxel. In one study, the median overall survival (OS) was 15.1 months in the cabazitaxel group compared with 12.7 months in the mitoxantrone group (HR 0.70; 95% CI 0.59–0.83; P<0.0001). Mitoxantrone is a chemotherapy agent that is no longer commonly used in prostate cancer treatment.

Beyond chemotherapy, there has been a research focus on targeting the androgen receptor. Two agents – abiraterone (Zytiga®) and enzalutamide (Xtandi®) - target the androgen receptor in different ways and have been FDA approved. Several more agents like each of these are under investigation.

Abiraterone is a CYP17 modulator that inhibits steroidogenesis. CYP17 is essential for biosynthesis of androgens and adrenal hormones and implicated in aberrant intratumoral androgen production. This agent provides more potent and durable androgen suppression than ketoconazole, another CYP17 in-

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<td>Denosumab N = 1,026</td>
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<td>Renal toxicity</td>
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<td>Osteonecrosis of jaw</td>
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hibitor. The FDA approved this agent in 2011 for patients with progression after docetaxel. In late 2012, the FDA expanded approval to treat men with late-stage (metastatic) CRPC prior to receiving chemotherapy. The cost of this agent is approximately $5,000 per month.

Because of the adrenal metabolic pathways altered by this agent, it must be given with daily prednisone. Adrenal insufficiency can occur if daily steroid dosing is interrupted, or during times of infection or stress. Other common adverse effects with abiraterone include fatigue, joint swelling or discomfort, edema, hot flush, diarrhea, vomiting, anemia, hypercholesterolemia, hyperglycemia, increased liver function tests, hyperphosphatemia, and hypokalemia.

The most commonly observed difference between CRPC cells and hormone sensitive prostate cancer cells is androgen receptor overexpression. Enzalutamide is a second-generation androgen receptor antagonist with no agonist activity in the setting of androgen receptor overexpression. It was FDA approved in 2012 and is indicated for patients with metastatic CRPC with prior docetaxel treatment.

Over time, this agent will be used earlier in therapy because it is a better androgen blocker than the currently used agents. It acts through three different pathways within a cancer cell to block the effects of testosterone. This agent costs $7,450 per month, wholesale.

Compared with placebo in a randomized, double-blind study in metastatic CRPC patients previously treated with at least two chemotherapy agents, enzalutamide resulted in a 4.8 month difference in median overall survival. Median OS was 18.4 months (95% CI, 17.3 to not yet reached) in the enzalutamide group and 13.6 months (95% CI, 11.3 to 15.8) in the placebo group. At the time of pre-specified interim analysis, enzalutamide use resulted in a 37 percent reduction in risk of death as compared with placebo (HR for death, 0.63; 95% CI, 0.53 to 0.75; P<0.001). The OS benefit was consistent across all subgroups, including age, baseline pain intensity, geographic region and type of disease progression at entry. Enzalutamide was also better than placebo for all the secondary endpoints - PSA-level response rate, soft-tissue response rate, QOL, time to PSA progression, radiographic progression-free survival, and time to first skeletal-related event.

Enzalutamide does have significant potential for serious drug–drug interactions. Reported adverse effects of this agent include asthenia/fatigue, back pain, diarrhea, arthralgia, hot flush, peripheral edema, musculoskeletal pain, muscular weakness, dizziness, insomnia, hematuria, paresthesia, anxiety, and increased blood pressure. One unique adverse effect of enzalutamide is seizure.

Many patients with CRPC will have pain related to bone metastases. Radiotherapy and strontium 89 are two options for treating metastases. Strontium 89 is a beta-emitter that has a higher affinity for tumor containing bone than normal bone. Its half-life in normal bone (14 days) is considerably shorter than in tumor containing bone (50 days). It results in similar pain reduction when compared with radiotherapy. Most frequently observed toxicities are associated with bone marrow suppression, occurring in more than 50 percent of patients. Blood counts return to normal within eight weeks and rarely cause Grade 3 or 4 toxicity when given to patients with normal hematological parameters.

Radium 233, an investigational agent, is the first bone-targeted therapy to show an increase in OS compared to placebo (median 3.6 months). The other bone targeting agents are used to prevent SRs or reduce pain, but this agent may be used to improve survival. It is an alpha-particle-emitting radionuclide that mimics calcium and is incorporated in osteoblastic bone lesions. Radium 233 delivers short range, high energy radiation that spares the bone marrow thus decreasing myelotoxicity.

Another investigational therapy for prostate cancer is another immunotherapy, Prostvac-VF®. This is different from Provenge in that it is a vaccine regimen containing the transgenes for PSA and multiple T-cell costimulatory molecules (TRICOM). The PSA-TRICOM vaccines infect antigen-presenting cells (APCs) and generate proteins that are expressed on the surface of the APCs in an immune context. This procedure leads to the development of killer T-cells that attack the tumor. In a Phase II trial of this agent, safety was demonstrated but no significant effect on time to disease progression was seen. Prostvac-VF treated patients experienced longer median survival of 8.5 months, compared to controls (25.1 vs. 16.6 mos, p=0.0061) and extended three-year survival (30% vs 17%).

Conclusion
Prostate cancer remains the most common cancer in men. Treatment of prostate cancer, even CRPC, has resulted in improved survival rates. Hormonal therapy remains first-line therapy in advanced prostate cancer; however, with time, most patients will progress despite castrate levels of testosterone. Several new agents, which have unique mechanisms of action and indications, have recently been approved for the management of CRPC and many more are on the horizon. Patients with CRPC will ultimately require multiple agents over time. The cost of man-
agement of CRPC is not without significant economic consequences.

Pamela Ellsworth, MD is a Professor of Urology at UMass Memorial Medical Center/University of Massachusetts Medical School.

References
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Not for your patient.

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- When a patient with metastatic cancer fails to respond as expected to treatment
- If there is atypical presentation or discordant findings
- When a basic IHC panel does not yield a definitive diagnosis
- When evaluation costs need to be managed
- When family members fear genetic links to certain cancers

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REFERENCES

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RG-24.0.0.15 Rev3 8/14
Introduction
GIVEN THE UNSUSTAINABLE COSTS OF U.S. health care, universal agreement exists among payers, regulatory agencies, and private and public health care stakeholders that reform must include substantial improvements in the quality and value of health care treatment options. Low back pain disorders and lumbar fusion are particularly costly and are under critical scrutiny in all evolving models of health care delivery. Evidence is mounting that proves the effectiveness of lumbar fusion for degenerative spinal conditions and is beginning to balance the high cost of spine fusion in the health care value equation.1-3 As the relative value (quality/cost) of lumbar fusion is established in the emerging value-based purchasing paradigm, hospital systems, payers, and health care purchasers are increasingly demanding evidence to demonstrate value added before adoption of new treatment options. Moving forward, novel fusion approaches must either demonstrate reduced cost or surgical morbidity while providing equivalent patient-centered effectiveness.

Minimally invasive techniques of lumbar fusion are one example of novel surgical approaches that may provide increased value over traditional surgical treatments for lumbar disorders.4-11 Axial presacral lumbar interbody fusion is a minimally invasive alternative to obtain L5-S1 interbody fusion when used with percutaneous pedicle screw or facet screw fixation.10-13 This approach requires only a small perineum incision for interbody bone grafting and small sub-centimeter incisions for percutaneous spinal fixation, theoretically reducing soft tissue injury, recovery time, and surgical morbidity. Despite these theoretical advantages, no comparative studies have examined whether this approach offers an advantage over traditional fusion with respect to quality, cost, or health care value. Indications for interbody fu-
sion include, but are not limited to, spondylolisthesis, symptomatic degenerative disc disease, recurrent disc herniation, and augmentation of long posterior fusion constructs in the setting of deformity surgery.

We set out to review the literature to date on the axial presacral approach for lumbar interbody fusion in order to determine whether reported surgical morbidity, hospital course, and outcomes are equivalent to those reported for a standard open fusion technique. Furthermore, we set out to determine if clinical factors that drive health care cost and value differ in the reported literature to date for axial presacral versus open transforaminal interbody fusion.

**METHODS**

We conducted a systematic literature review of all studies published to date (October 2012) assessing axial presacral lumbar interbody fusion in order to
qualitatively and quantitatively assess the evidence to date on the safety and effectiveness of this approach to one-level fusion for degenerative spinal conditions. Since open transforaminal lumbar interbody fusion (TLIF) has been accepted as a gold standard for an effective and durable approach for one-level lumbar interbody fusion for over a decade, we also reviewed all studies published to date assessing the safety and effectiveness of single-level TLIF approach for degenerative spinal conditions.

We sought to address the following clinical questions based on the outcomes reported in the literature to date: Is the axial presacral approach versus open TLIF approach for single-level lumbar interbody fusion associated with comparable: 1) intra- and perioperative outcomes; 2) rate of 90-day global period surgical morbidity; 3) improvements in back pain and functional disability; and, 4) fusion rates? Lastly, does comparative analysis of the cumulative evidence to date suggest that this minimally invasive approach offers quality improvement and economic value to health care stakeholders based on current cost estimates?

### Literature Review

Three independent reviewers conducted a review of the current English literature in the month of October 2012 using Google Scholar and PubMed Internet libraries. The goal was to identify all published studies reporting perioperative or postoperative outcomes on the axial presacral lumbar approach or open TLIF approach for single-level lumbar interbody fusion for degenerative lumbar disease. Search terms in these libraries included, “interbody fusion,” “transforaminal fusion,” “lumbar fusion,” “TLIF,” “AxialLIF,” “axial presacral,” “axial lumbar interbody fusion,” “transacral fixation,” “axial fixation,” and “minimally invasive fusion.”

All titles obtained using these search terms were reviewed. Biomechanical studies, non-English studies, and animal studies were excluded. The abstracts of all remaining studies were reviewed. The full-text articles of all clinical abstracts reporting any clinical results of axial presacral fusion or open TLIF procedures were reviewed in entirety. Only studies reporting perioperative measures
or outcomes data for single-level interbody fusion were included. Studies that clearly described their surgical technique as an open incision for standard transforaminal interbody grafting with pedicle screw fixation were considered open TLIF cohorts. Studies that clearly described their surgical technique as minimally invasive axial presacral interbody fixation performed as standalone or in conjunction with percutaneous pedicle screws or facet fixation were considered axial presacral cohorts. Studies of presacral fusion as adjuvants to multilevel fusion, in conjunction with open posterior procedures, or for indications other than elective single-level lumbar degenerative disease were not included.

### Data Collection
For each included study, we recorded the reported patient sample size, mean operative time, mean estimated blood loss, mean length of hospital stay (for U.S. hospital studies), incidence of surgical morbidity, baseline and postoperative back pain (VAS), baseline and postoperative physical disability (ODI), mean baseline and postoperative VAS and ODI scores were similar between the surgical approaches. Both approaches to single level interbody fusion resulted in improvement in pain and disability. Cumulative analysis of evidence to date demonstrated similar post-operative back pain (VAS: 2.8 vs. 2.8) and post-operative physical disability (ODI: 22.9 vs. 18.9) six-24 months after surgery between axial presacral fusion and open TLIF, respectively.

### Exhibit 3: Patient Reported Outcomes Utilized in the Literature

<table>
<thead>
<tr>
<th>AxiaLIF Cohort</th>
<th>Cohort Size</th>
<th>Pre-Op VAS</th>
<th>Follow-up VAS</th>
<th>Pre-Op ODI</th>
<th>Follow-up ODI</th>
<th>COhort Size</th>
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<th>Follow-up VAS</th>
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<td>All Studies</td>
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<th>Open TLIF Cohort</th>
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<td>21.7</td>
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<tr>
<td>Yan et al 2008</td>
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<td>2.8</td>
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<td>Rihn et al 2009</td>
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<td>3.6</td>
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<td>Gong et al 2010</td>
<td>21</td>
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<td>2.2</td>
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<tr>
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<td>43</td>
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<tr>
<td>Adogwa et al 2011</td>
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<td>8.9</td>
<td>4.3</td>
<td>36.0</td>
<td>19.5</td>
</tr>
<tr>
<td>Kotil et al 2012</td>
<td>60</td>
<td>7.2</td>
<td>2.2</td>
<td>52.1</td>
<td>10.5</td>
</tr>
<tr>
<td>Lee et al 2012</td>
<td>72</td>
<td>6.3</td>
<td>2.4</td>
<td>44.4</td>
<td>20.7</td>
</tr>
<tr>
<td>Wang et al 2012</td>
<td>39</td>
<td>6.0</td>
<td>1.5</td>
<td>40.2</td>
<td>17.4</td>
</tr>
<tr>
<td>All Studies</td>
<td>n = 559</td>
<td>7.2</td>
<td>2.8</td>
<td>46.9</td>
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</tr>
</tbody>
</table>
gocele, hardware failure, hematoma, persistent/worsening symptoms). The evidence reported to date for each variable for both surgical approaches were cumulatively summated and compared.

**Cost Estimation**

For both the hospital and payer perspectives, variability in length of hospital stay, incidence of surgical morbidity, re-admission, and incidence of long-term re-operation (often from symptomatic pseudoarthrosis) are the major factors that drive cost variance for lumbar fusion. Therefore, utilizing our cumulative analysis of the literature to date, we estimated the economic impact associated with variation in hospital stay, surgical complication rate, and pseudoarthrosis between the reviewed surgical approaches. Based on 2012 private payer norms, cost per hospital day was estimated as $1,800 (Health Care Blue Book14). To estimate private payer cost per complication, 2012 Medicare DRG fee schedule was used for lumbar fusion with complication (DRG 459: $42,118) and lumbar fusion without complication (DRG 460: $23,074)15. To estimate private payer cost per case of pseudoarthrosis requiring reop-

---

**Exhibit 4: Fusion Rates Reported in the Literature**

<table>
<thead>
<tr>
<th>AxiaLIF Series</th>
<th>Cohort Size</th>
<th>Fusion Rate (%)</th>
<th>Mean Last Follow-up (months)</th>
<th>Open TLIF Series</th>
<th>Cohort Size</th>
<th>Fusion Rate (%)</th>
<th>Mean Last Follow-up (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carl et al 2006</td>
<td>1</td>
<td>100</td>
<td>12</td>
<td>Hee et al 2001</td>
<td>50</td>
<td>96</td>
<td>24</td>
</tr>
<tr>
<td>Aryan et al 2008</td>
<td>31</td>
<td>93.5</td>
<td>12</td>
<td>Salehi et al 2004</td>
<td>12</td>
<td>100</td>
<td>16.9</td>
</tr>
<tr>
<td>Gerszten et al 2011</td>
<td>26</td>
<td>100</td>
<td>24</td>
<td>Villavicencio et al 2005</td>
<td>18</td>
<td>100</td>
<td>12</td>
</tr>
<tr>
<td>Tobler et al 2011</td>
<td>155</td>
<td>93.5</td>
<td>24</td>
<td>Cutler et al 2006</td>
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<td>15.1</td>
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<td>1</td>
<td>100</td>
<td>6</td>
<td>Houten et al 2006</td>
<td>32</td>
<td>100</td>
<td>11</td>
</tr>
<tr>
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<td>99</td>
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<td>24</td>
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<td>89</td>
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<tr>
<td>Tender et al 2011</td>
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<td>100</td>
<td>12</td>
<td>Weiner et al 2006</td>
<td>27</td>
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<td>Dhall et al 2008</td>
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<td>34</td>
<td>Yan et al 2008</td>
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<td>43</td>
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<td>Goyal et al 2009</td>
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<td>Rihn et al 2009</td>
<td>48</td>
<td>96</td>
<td>19.4</td>
<td>Sethi et al 2009</td>
<td>19</td>
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<tr>
<td>Fujibayashi et al 2010</td>
<td>12</td>
<td>100</td>
<td>6</td>
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<td>6</td>
<td>Aoki et al 2012</td>
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<td>Xue et al 2012</td>
<td>31</td>
<td>96.8</td>
<td>25.3</td>
<td></td>
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</tbody>
</table>

All Studies n = 315 | 94% | 21.7 | All Studies n = 728 | 96.6% | 20.3
eration, 2012 Medicare DRG fee schedule was used for lumbar fusion without complication (DRG 460: $23,074) 15. Per standard macro-costing methods, private payer cost was estimated as 1.7x Medicare.1

**RESULTS**

**Literature Review**

A PubMed search using the defined search terms to identify axial presacral interbody fusion resulted in 43 studies. An additional 19 studies were identified through Google Scholar Internet search library. Of the 62 axial presacral interbody fusion studies identified, six were excluded based on title review (biomechanical, animal study, technical report only). Full abstracts of the remaining 56 studies were reviewed. Forty-five published studies did not meet inclusion criteria (review articles, multi-level fusion, presacral fixation in conjunction with long posterior or open constructs, or no clinical evidence reported). A total of 11 studies with data on single-level axial presacral interbody fusion were included in the quantitative analysis.

A PubMed search for open TLIF literature using the defined search terms resulted in a total of 9,348 potential studies. After title review and exclusion, a total of 212 studies were clinical reports on lumbar interbody fusion and abstracts reviewed. Of these, 177 studies were excluded (review articles, multiple-level fusion, minimally invasive TLIF studies, and biochemical/radiological studies). A total of 35 studies reporting perioperative outcomes data on single-level open TLIF were included in the quantitative analysis.

**Perioperative Measures**

There were eight single-level axial presacral lumbar fusion studies that reported intra- and perioperative measures, comprising a total of 180 patients. There were twenty-five single-level open TLIF studies that reported intra- and perioperative measures comprising a total of 771 patients (Exhibit 1). Cumulative analysis of published evidence to date demonstrated that operative time (83.3 vs. 178.4 mins), mean estimated blood loss (68.8 vs. 444.7 ml), and mean length of hospital stay (1.9 vs. 4.1 days) are less for axial presacral fusion compared to open TLIF when attempting a one-level lumbar fusion (Exhibit 1).

**Surgical Morbidity and Safety**

There were seven single-level axial presacral lumbar fusion studies reporting morbidity and safety data, comprising a total of 407 patients. There were 14 single-level open TLIF studies reporting morbidity and safety data, comprising a total of 653 patients (Exhibit 2). Cumulative analysis of published evidence to date demonstrated a lower surgical complication rate (3.2% vs. 8.7%) for axial presacral fusion compared to open TLIF (Exhibit 2).

**Patient-Reported Outcomes**

There were seven single-level axial presacral lumbar fusion studies utilizing patient-reported outcomes, comprising a total of 301 patients. There were 13 single-level open TLIF studies utilizing patient-reported outcomes, comprising a total of 559 patients (Exhibit 3). Cumulative analysis of evidence to date demonstrated similar six to 24 month postoperative outcomes with regard to back pain (VAS: 2.8 vs. 2.8) and physical disability (ODI: 22.9 vs.
18.9) between axial presacral fusion and open TLIF, respectively (Exhibit 3). Both treatment approaches resulted in significant reduction in low back pain and disability.

Fusion Rates
There were seven single-level axial presacral lumbar fusion studies reporting fusion rates, comprising of 315 patients. There were 20 single-level open TLIF studies reporting fusion rates, comprising of 728 patients (Exhibit 4). Cumulative analysis of evidence to date demonstrated a similar fusion rate (94% vs. 96.6%) between axial presacral fusion and open TLIF, respectively (Exhibit 4).

Estimated Cost Benefit
A minimally invasive approach (Axial presacral approach) versus open TLIF approach for single-level fusion for degenerative spine pathology was associated with a mean 2.2 day reduction in hospital stay per case in the literature to date. Based on current market cost standards, this hospital stay reduction can lead to cost-savings of $396,000 per 100 surgeries performed, or $3,960 per patient treated. The axial presacral approach versus open TLIF approach was also associated with a 4.8 percent reduction in 90-day surgical morbidity (3.2% vs. 8.7%) in the literature to date. Based on private payer cost estimates from 2012 DRG medicare fees, this 4.8 percent reduction in surgical complication can lead to cost savings of up to $178,061 per 100 surgeries performed, or $1,781 per patient treated. However, axial presacral approach was associated with a 2.6 percent higher rate of pseudoarthrosis compared to open TLIF (6.0% vs. 3.4%) in the literature to date. Based on private payer cost estimates from 2012 DRG medicare fees, this 2.6 percent increase in the rate of pseudoarthrosis can lead to an additional cost expenditure of up to $101,987 per 100 surgeries performed, or $1,020 per patient treated.

Given the reported benefits in length of hospital stay and surgical morbidity but slightly higher rate of pseudoarthrosis reported with the axial presacral approach for single-level fusion, a cost savings of up to $472,074 per 100 surgeries ($4,721 per patient) may be realized by hospital systems or payers adopting this approach over traditional posterior lumbar fusion approaches. Our results demonstrate equivalent effectiveness for a reduced cost of care, and suggest that minimally invasive approaches such as axial presacral interbody fusion may offer increased health care value over traditional surgical options.

Discussion
In a systematic review of the literature on single-level axial presacral and open transforaminal lumbar interbody fusion (TLIF) for degenerative spine disease, studies consistently reported estimated blood loss, operative times, length of hospital stay, and surgical morbidity rates for the axial presacral approach that were lower than those reported for the open TLIF approach. Six to twenty-four month outcomes did not differ between surgical approaches in the literature, suggesting equal effectiveness. Successful fusion occurred in the vast majority of cases reported in the literature for both approaches (94% vs 96.6%). Based on the cumulative outcomes reported to date, a minimally invasive fusion approach (axial presacral interbody fusion) was associated with improved perioperative quality metrics (length of stay, blood loss, morbidity) while achieving equivalent fusion rates and clinical effectiveness up to two years as reported in the literature. When considering the potential economic impact of these clinical benefits, cost savings as great as $4,721 per patient may be experienced by hospital systems or payers adopting this approach over traditional posterior lumbar fusion approaches. Although reduced operative times were reported in the literature with the axial presacral approach, we did not include operative time as a cost driver in our economic estimation. Hence, for hospital–payer contracts that pass along added costs of prolonged operative time, the cost savings of axial presacral approach may be even greater than estimated here. Avoiding a perioperative blood transfusion can also save $522 to $1,183 per Unit. We did not estimate cost savings associated with reduced blood loss since number of transfusions was not reported in the literature. However, it is very likely that the nearly 400c lower EBL reported in the literature was associated with reduced rate of transfusion. Lastly, we encountered the largest report to date on over 9,000 patients focusing on complications with AxialF by Gundanna et al. Surgical morbidity data in this report were collected as part of a voluntary postmarketing surveillance report and were <2% incidence. This paper was not included since it did not meet full inclusion criteria. However, this postmarketing
surveillance report suggests that surgical morbidity may be even lower than our review suggests. It is important to note that these cost estimates serve as approximations based on the reported evidence to date on specific clinical variables that are surgical cost drivers, so hospital systems experiencing greater complications and readmissions, or non-representative length of hospital stays for either surgical approach may experience greater or less economic value with minimally invasive approaches to single-level lumbar fusion. Nevertheless, the body of evidence available in the literature to date suggests that the clinical outcomes reported here are representative of current care norms.

The difference in implant cost is relevant when assessing value between these two surgical approaches. The cost analysis here intentionally avoided estimating implant costs in the equation, especially given their pricing variability in real-world care. However, including surgical and all related costs allow for a better valuation when determining cost-gain trade-offs of implant purchases. Hospitals and payers that negotiated similar implant prices for open TLIF interbody grafts and axial presacral fixation may experience the full cost savings estimated here (over $4,000 per case). However, hospitals purchasing an axial presacral device for $4,500 more than the TLIF interbody cage for open TLIF may have a budget neutral investment, but still gain from the patient-centered perspective of reduced complication rate and reduced hospital stays. Cost estimations performed from a literature review are not accurate enough to provide granular detail on absolute cost numbers, but do provide an accurate context on valuation of novel surgical approaches and technology for health care stakeholders.

The perspective of the decision maker should always be considered when assessing the value or cost-benefit of a treatment option. Across the spectrum of patient, hospital, payer, and societal perspectives, the clinical benefits observed in our literature review are relevant to all. Decreased surgical complications are paramount to patient-centered quality improvement. The lower morbidity rates and equivalent long-term effectiveness observed in our literature review serve the interest of the patient first and foremost. From an economic decision maker perspective, the hospital and the payer both gain from reduced hospital stays and reduced surgical morbidity. While the relative proportion of cost savings and value realized will vary based on each hospital system – payer contract, in all scenarios, reduced hospital stay will help hospital systems deliver quality care while helping drive sustainable profitability. The economic benefit of reduced complications will likely be shared between payer and hospital system with the relative proportion of economic risk sharing determining who gains the most from this quality improvement. However, as payer policies shift away from reduced payment to no payment for surgical complications, these economic benefits may swing entirely to the hospital side. Lastly, the scope of our review and economic modeling does not address the societal perspective. Without including work productivity losses, caregiver burden, long-term resource utilization, and health state utility scores, one cannot begin to quantify the economic effect that minimally invasive approaches such as axial presacral fusion may have on U.S. society. However, less invasive alternatives to fusion that allow for quicker recovery may offer their greatest value to society, where accelerated return to work offers the greatest potential for economic impact.

Several weaknesses of this study should be considered when interpreting its findings. There have been no direct comparison studies to date between the axial presacral and open TLIF approaches to interbody lumbar fusion (Level I, II, or III evidence). The cumulative analysis performed here is based on single cohort studies and represents Level IV evidence.18 Prospective comparative effectiveness studies utilizing patient reported outcome instruments and standardized cost measurement tools are required to draw firm cost-utility conclusions. Furthermore, we utilized macro-costing techniques to estimate cost differences between treatments. This technique can be well suited for the societal and payer perspective but may be less accurate for the hospital perspective. Nevertheless, our findings suggest the minimally invasive fusion approaches (such as axial presacral interbody fusion) may serve as an example of quality improvement advancement for lumbar fusion with increased health care value and warrants a prospective cost-utility study.

Conclusions
In a systematic review of the literature to date, there are no studies directly comparing the minimally invasive approach of axial presacral lumbar interbody fusion to the traditional open approach of transforaminal lumbar interbody fusion. The outcomes reported for each of these approaches to single-level fusion for degenerative lumbar disease suggest that both are highly effective at improving patient reported pain and disability and achieving successful fusion. Although the literature to date revealed that the axial presacral approach was associated with a 2.6 percent higher rate of pseudoarthrosis compared to open TLIF; the minimally invasive axial presacral approach was also associated with decreased blood
loss, operative times, length of hospital stay, and re-
duced surgical morbidity reported in the literature,
which are all factors that drive health care cost. Cost
estimation suggests that the benefits of minimally
invasive fusion may allow for cost savings for hospi-
tals and payers.

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at Vanderbilt University Medical Center and director of the Spinal Col-
umn Surgical Quality and Outcomes Research Laboratory.

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and Spine Associates and Adjunct Research Associate Professor at the
University of North Carolina at Chapel Hill.

Conflicts of Interest
Matthew J. McGirt, MD serves as a Consultant for TranS1, Inc., Wilms-
ton, NC.

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Summary
We compared total costs of care in patients aged 18 to 63 years beginning renal replacement therapy for end-stage renal disease (ESRD) with peritoneal dialysis (PD) or hemodialysis (HD) between January 1, 2005 and December 31, 2008 (“study period”). PD patients were matched to HD patients using propensity scoring to control for differences in baseline characteristics between the two groups. Levels of health care utilization and billed charges in the year following dialysis initiation then were compared between the two groups. We identified 139 patients who began dialysis during the study period (PD, n=26; HD, n=113); after matching, the final study sample consisted of 26 PD patients and 26 HD patients. Mean age of study subjects was 55 years, 58 percent were men, and 72 percent were African American. Over the 12 months, mean billed charges were nominally higher in HD patients ($156,464 vs $127,981 for PD patients; p=0.21). In sensitivity analyses in which patients who began dialysis in hospital were included in the study sample, mean billed charges were significantly higher for HD ($188,340 vs 127,981 for PD; p=0.01). Further study is needed to understand the extent to which these findings derive from differences in dialysis modalities versus the characteristics of patients who receive them.

Key Points
• Dialysis (i.e., hemodialysis [HD], peritoneal dialysis) is the mainstay of treatment for end-stage renal disease (ESRD)
• Total health care costs over one year were nominally higher in patients who received HD versus PD.
• Results from our study are consistent with prior research from the United States and other countries.

Introduction
KIDNEY TRANSPLANTATION IS GENERALLY VIEWED TO BE THE OPTIMAL TREATMENT FOR PATIENTS with end-stage renal disease (ESRD), due to superior clinical outcomes (e.g., survival) as well as lower costs of care in comparison with dialysis. Unfortunately, the supply of donor kidneys is limited, and many ESRD patients are relatively poor candidates for surgery. Thus, the great majority of these patients are maintained on dialysis—either hemodialysis or peritoneal dialysis. Hemodialysis can be administered at a dialysis center or at home, and is typically performed three times weekly. Peritoneal dialysis, in contrast, utilizes the lining of the abdomen instead of an extracorporeal dialyzer to filter the blood. With peritoneal dialysis, patients typically either self-administer dialysis solution into their abdomen about three to five times daily, or use an automated cycler that performs three to five exchanges during the night. Hemodialysis and peritoneal dialysis are thought to be equally effective.1

We previously reported on methods that we developed to identify patients in health care claims databases who were receiving peritoneal versus hemodialysis,2 as well as a comparison of health care utilization and costs between these patients over a one-year period following therapy initiation.3 Our findings indicated that patients who began renal re-
placement therapy with peritoneal dialysis had lower costs of care—principally as a result of a lower risk of hospitalization and emergency department visits than those starting hemodialysis, even after controlling for differences in baseline characteristics with propensity-score matching—and were consistent with data from the United States Renal Data System (USRDS).4

Our prior work had some important limitations, however. Foremost among them is the fact that our earlier study was based on analyses of health care claims data, and the accuracy of the methods that we used to distinguish between patients who received peritoneal dialysis versus hemodialysis was

<table>
<thead>
<tr>
<th>Exhibit 1: Demographic and clinical characteristics of unmatched patients initiating peritoneal dialysis versus hemodialysis</th>
</tr>
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<tbody>
<tr>
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</table>
unknown. Therefore, some patients may have been incorrectly designated as receiving peritoneal dialysis or hemodialysis (i.e., “false-positives”), while others who were indeed receiving such treatment may have been missed by the algorithms that we used (i.e., “false-negatives”). The actual magnitude of misclassification is unknown and impossible to quantify, since the methods could not be validated against a “gold standard” (e.g., patient medical records). Moreover, while we used techniques of propensity score matching in our prior study to attempt to control for important differences in baseline characteristics between peritoneal dialysis and hemodialysis patients, many potentially important

<table>
<thead>
<tr>
<th></th>
<th>20 (76.9)</th>
<th>76 (67.3)</th>
<th>0.48</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drug dependency/abuse</td>
<td>0 (0.0)</td>
<td>3 (2.7)</td>
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</tr>
<tr>
<td>HIV/AIDS</td>
<td>1 (3.8)</td>
<td>1 (0.9)</td>
<td>0.34</td>
</tr>
<tr>
<td>Hypertension</td>
<td>26 (100.0)</td>
<td>107 (94.7)</td>
<td>0.59</td>
</tr>
<tr>
<td>Pretreatment healthcare utilization</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Medications, No. %</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ACE Inhibitors</td>
<td>8 (30.8)</td>
<td>27 (23.9)</td>
<td>0.46</td>
</tr>
<tr>
<td>ARBs</td>
<td>9 (34.6)</td>
<td>26 (23.0)</td>
<td>0.22</td>
</tr>
<tr>
<td>Erythropoietin-stimulating agents</td>
<td>5 (19.2)</td>
<td>20 (17.7)</td>
<td>0.78</td>
</tr>
<tr>
<td>Vitamin D analogues</td>
<td>11 (42.3)</td>
<td>44 (38.90</td>
<td>0.83</td>
</tr>
<tr>
<td>Phosphate binders</td>
<td>9 (34.6)</td>
<td>41 (36.3)</td>
<td>&gt; 0.9</td>
</tr>
<tr>
<td>Antibiotics</td>
<td>9 (34.6)</td>
<td>35 (31.0)</td>
<td>0.82</td>
</tr>
<tr>
<td>IV iron</td>
<td>0 (0.0)</td>
<td>2 (1.8)</td>
<td>&gt; 0.99</td>
</tr>
<tr>
<td>Hospitalizations</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patients, No. %</td>
<td>8 (30.8)</td>
<td>75 (66.4)</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>Number of admissions</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>0.6 (1.1)</td>
<td>1.2 (1.3)</td>
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</tr>
<tr>
<td>Median (IQR)</td>
<td>0 (0 - 1)</td>
<td>1 (0 - 2)</td>
<td></td>
</tr>
<tr>
<td>Outpatient services</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Physician office visits</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patients, No. %</td>
<td>26 (100.0)</td>
<td>105 (92.9)</td>
<td>0.35</td>
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<td>Mean (SD)</td>
<td>10.5 (4.3)</td>
<td>9.7 (8.9)</td>
<td>0.52</td>
</tr>
<tr>
<td>Median (IQR)</td>
<td>10 (8 - 13)</td>
<td>8 (4 - 12)</td>
<td></td>
</tr>
<tr>
<td>Emergency room visits</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patients, No. %</td>
<td>13 (50.0)</td>
<td>39 (34.5)</td>
<td>0.18</td>
</tr>
<tr>
<td>Number of visits</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>0.9 (1.30)</td>
<td>0.6 (1.1)</td>
<td>0.3</td>
</tr>
<tr>
<td>Median (IQR)</td>
<td>1 (0 - 1)</td>
<td>0 (0 - 1)</td>
<td></td>
</tr>
<tr>
<td>Pretreatment healthcare costs</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>43,218 (28,489)</td>
<td>67,138 (93,323)</td>
<td>0.02</td>
</tr>
<tr>
<td>Median (IQR)</td>
<td>33,418 (25,528 - 49,520)</td>
<td>43,351 (24,949 - 68,224)</td>
<td></td>
</tr>
</tbody>
</table>

*Value closest to date of dialysis initiation. Some patients had missing data for lab values (PD patients: 4 [15.4%] for BMI, 10 [38.5%] for hemoglobin A1c, 1 [3.8%] for serum creatinine, 4 [15.4%] for serum albumin; HD patients: 23 [20.4%] for BMI, 50 [44.3%] for hemoglobin A1c, 2 [1.8%] for hematocrit, 3 [2.7%] for serum creatinine, 7 [6.2%] for serum albumin, 2 [1.8%] for hemoglobin, 2 [1.8%] for SBP, and 2 [1.8%] for DBP)

confounders (e.g., albumin levels) are not available in health care claims data. These issues are nontrivial, as the validity of findings regarding utilization and costs is entirely dependent upon the accuracy of the methods used to identify study subjects, and the extent to which potential confounders were ade-

quately controlled.

As a result of these potential limitations of earlier work, we undertook a new retrospective study to compare health care utilization and costs between patients who received peritoneal dialysis versus hemodialysis, using information on both electronic medi-

---

### Exhibit 2: Demographic and clinical characteristics of propensity-matched patients initiating peritoneal dialysis versus hemodialysis

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>PD (N = 26)</th>
<th>HD (N = 113)</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean (SD), y</td>
<td>54.4 (9.0)</td>
<td>55.4 (8.6)</td>
<td>0.43</td>
</tr>
<tr>
<td>Male, No. %</td>
<td>15 (57.7)</td>
<td>15 (57.7)</td>
<td>&gt; 0.99</td>
</tr>
<tr>
<td>Race, No. %</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>African American</td>
<td>18 (69.2)</td>
<td>19 (73.1)</td>
<td>0.77</td>
</tr>
<tr>
<td>White/other</td>
<td>7 (26.9)</td>
<td>7 (26.9)</td>
<td></td>
</tr>
<tr>
<td>BMI, kg/m2*</td>
<td>31.8 (9.8)</td>
<td>34.3 (8.6)</td>
<td>0.19</td>
</tr>
<tr>
<td>Serum creatinine, mg/dL*</td>
<td>5.6 (1.5)</td>
<td>6.4 (3.7)</td>
<td>0.23</td>
</tr>
<tr>
<td>Hemoglobin, g/dL*</td>
<td>3.5 (0.6)</td>
<td>3.6 (0.06)</td>
<td>0.45</td>
</tr>
<tr>
<td>SBP, mmHg*</td>
<td>142.9 (22.3)</td>
<td>144.8 (29.4)</td>
<td>0.92</td>
</tr>
<tr>
<td>DBP, mmHg*</td>
<td>78.5 (13.6)</td>
<td>71.7 (13.9)</td>
<td>0.17</td>
</tr>
<tr>
<td>Comorbidity, No. %</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alcohol dependency/abuse</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>-</td>
</tr>
<tr>
<td>Anemia</td>
<td>26 (100.0)</td>
<td>26 (100.0)</td>
<td>-</td>
</tr>
<tr>
<td>Cancer</td>
<td>0 (0.0)</td>
<td>1 (3.8)</td>
<td>0.32</td>
</tr>
<tr>
<td>Cigarette smoking</td>
<td>2 (7.7)</td>
<td>3 (11.5)</td>
<td>0.64</td>
</tr>
<tr>
<td>Congestive heart failure</td>
<td>9 (34.6)</td>
<td>6 (23.1)</td>
<td>0.36</td>
</tr>
<tr>
<td>Coronary artery disease</td>
<td>6 (23.1)</td>
<td>4 (15.4)</td>
<td>0.49</td>
</tr>
<tr>
<td>Depression</td>
<td>4 (15.4)</td>
<td>3 (11.5)</td>
<td>0.69</td>
</tr>
</tbody>
</table>
cal records and administrative databases from a large integrated health system. We limited our attention to patients aged 18 to 63 years, as our principal interest was in persons who were not Medicare beneficiaries.

**METHODS**

**Data Source.** This retrospective study was conducted at Henry Ford Health System (HFHS), a comprehensive health system that provides medical care to approximately 800,000 residents of Detroit, Michigan, and the surrounding areas. In any given year, approximately 200,000 of these persons are enrolled in the Health Alliance Plan (HAP), a wholly owned, not-for-profit health maintenance organization within HFHS. Study subjects were drawn from the population of

<table>
<thead>
<tr>
<th>Pretreatment healthcare costs</th>
<th>Mean (SD)</th>
<th>Median (IQR)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean (SD)</td>
<td>43,218 (28,489)</td>
<td>45,478 (41,360)</td>
</tr>
<tr>
<td>Median (IQR)</td>
<td>33,418 (25,528 - 49,520)</td>
<td>39,362 (18,396 - 50,966)</td>
</tr>
</tbody>
</table>

*Value closest to date of dialysis initiation. Some patients had missing data for lab values (PD patients: 4 [15.4%] for BMI, 10 [38.5%] for hemoglobin A1c, 1 [3.8%] for serum creatinine, 4 [15.4%] for serum albumin; HD patients: 2 [7.7%] for BMI, 11 [42.3%] for hemoglobin A1c, 2 [7.7%] for serum albumin)

persons enrolled in HAP, nearly 20 percent of whom are aged ≥65 years.

HFHS uses a comprehensive multi-dimensional electronic medical records (EMR) system that provides clinicians and researchers with real-time access to computerized medical records (“carePlus”). HFHS also maintains a large administrative data warehouse containing information on all encounters with HFHS providers and facilities, including ambulatory care visits, hospital admissions, health care services provided at non-HFHS sites, billing records generated within inpatient and outpatient settings, and outpatient prescription claims (for all members of HAP).

Information in CarePlus, while stored electronically, is not searchable and cannot be harvested in digital format; it therefore was extracted manually onto hard-copy case-report forms that we developed.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>PD (N = 26)</th>
<th>HD (N = 113)</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Medications, No. %</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ACE Inhibitors</td>
<td>10 (38.5)</td>
<td>8 (30.8)</td>
<td>0.56</td>
</tr>
<tr>
<td>ARBs</td>
<td>6 (23.1)</td>
<td>8 (30.8)</td>
<td>0.54</td>
</tr>
<tr>
<td>Erythropoietin-stimulating agents</td>
<td>19 (73.1)</td>
<td>20 (76.9)</td>
<td>0.75</td>
</tr>
<tr>
<td>Vitamin D analogues</td>
<td>15 (57.7)</td>
<td>18 (69.2)</td>
<td>0.39</td>
</tr>
<tr>
<td>Phosphate binders</td>
<td>17 (65.4)</td>
<td>15 (57.7)</td>
<td>0.57</td>
</tr>
<tr>
<td>Antibiotics</td>
<td>17 (65.4)</td>
<td>18 (69.2)</td>
<td>0.77</td>
</tr>
<tr>
<td>IV iron</td>
<td>4 (15.4)</td>
<td>0 (0.0)</td>
<td>0.04</td>
</tr>
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<td>Hospitalizations</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Patients, No. %</td>
<td>11 (42.3)</td>
<td>14 (53.8)</td>
<td>0.41</td>
</tr>
<tr>
<td>Number of admissions</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>1 (1.6)</td>
<td>1.4 (2.2)</td>
<td>0.33</td>
</tr>
<tr>
<td>Median (IQR)</td>
<td>0 (0 - 1)</td>
<td>1 (0 - 2)</td>
<td></td>
</tr>
<tr>
<td>Days in hospital</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>11.5 (9.5)</td>
<td>19.7 (21.4)</td>
<td>0.15</td>
</tr>
<tr>
<td>Median (IQR)</td>
<td>8 (4 - 17)</td>
<td>12 (7 - 29)</td>
<td></td>
</tr>
<tr>
<td>Outpatient services</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Physician office visits</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patients, No. %</td>
<td>26 (100.0)</td>
<td>26 (100.0)</td>
<td>-</td>
</tr>
<tr>
<td>Number of visits</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>12.4 (8.4)</td>
<td>16.6 (9.7)</td>
<td>0.05</td>
</tr>
<tr>
<td>Median (IQR)</td>
<td>12 (6 - 17)</td>
<td>15 (10 - 22)</td>
<td></td>
</tr>
<tr>
<td>Emergency room visits</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patients, No. %</td>
<td>12 (46.2)</td>
<td>14 (53.8)</td>
<td>0.58</td>
</tr>
<tr>
<td>Number of visits</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>1.1 (2.0)</td>
<td>1.3 (2.1)</td>
<td>0.69</td>
</tr>
<tr>
<td>Median (IQR)</td>
<td>0 (0 - 1)</td>
<td>1 (0 - 2)</td>
<td></td>
</tr>
</tbody>
</table>

oped specifically for use in this study. To ensure patient confidentiality and compliance with the Health Insurance Portability and Accountability Act (HIPAA) of 1996, no patient-identifying information was extracted. The study was approved by the HFHS Institutional Review Board.

**Study Subjects.**

The source population for the study consisted of all persons, aged 18 to 63 years as of the beginning of the study period, who were members of HAP anytime between January 1, 2005 and December 31, 2008 (“study period”). The source population was limited to those who were enrolled in HAP since information on health care utilization outside of HFHS facilities is available only for these persons. Since information in CarePlus is not readily searchable, it was infeasible to identify patients receiving dialysis based on medical record review. To improve the efficiency of case finding, we began by identifying all persons with evidence of dialysis-related encounters in administrative data during the study period, using Current Procedural Terminology (CPT) codes, International Classification of Disease, Ninth Revision, Clinical Modification (ICD-9-CM) diagnosis and procedure codes, and Healthcare Common Procedure Coding System (HCPCS) procedure codes (Appendix). The date of each such patient’s earliest dialysis-related encounter, as reflected in administrative data systems, was designated the “anchor date”.

We then scanned CarePlus (i.e., the electronic medical record [EMR]) for evidence of receipt of dialysis during the 18-month period beginning six months prior to the anchor date (as defined above) and ending one year subsequent to this date. Patients without evidence of receipt of dialysis in CarePlus during this period were excluded from the analysis population. For patients with such evidence in the medical record, the earliest date of actual receipt of dialysis during the study period (i.e., January 1, 2005 through December 31, 2008) was designated the “index date”. Patients were then classified into treatment groups based on the dialysis modality noted on the index date (i.e., peritoneal dialysis or hemodialysis).

Patients with evidence of receipt of dialysis prior to the beginning of the study period were excluded from the analyses, as were patients who were not continuously enrolled in HAP over the six-month period preceding their index date (“pre-index period”), as gaps in enrollment could result in inaccurate assessment of pretreatment health care utilization and costs. We also excluded patients with evidence of receipt of dialysis for reasons other than ESRD (e.g., acute kidney injury due to trauma), which we ascertained based on medical record review, as well as those who underwent renal trans-
plantation within one month of beginning dialysis.

A preliminary review of data for our study subjects revealed that some hemodialysis patients were hospitalized on their index date and thus most likely initiated dialysis in hospital. Since these patients may differ in important respects from patients who began renal replacement therapy on a more routine basis, we also excluded patients who were hospitalized as of their index date.

Measures.
Various measures of health care utilization were examined over the 12-month period following initiation of dialysis, as were billed total health care charges since reimbursed amounts were unavailable. Because it is often difficult to accurately attribute receipt of particular services to specific disease conditions, health care utilization and charges were examined on an overall basis.

Analyses.
Demographic and clinical characteristics that were compared between peritoneal dialysis and hemodialysis patients included age, sex, race, comorbidities, laboratory data, and health care utilization and billed charges during the pretreatment period. Presence of comorbid conditions was ascertained based on information in CarePlus.

To control for potentially important differences in these pretreatment characteristics, we matched peritoneal dialysis and hemodialysis patients using techniques of propensity scoring. Briefly, multivariate logistic regression was used to generate a probability ("propensity score") that each patient had received peritoneal dialysis; covariates entered into the model included age, gender, race, occurrence of a hospitalization, occurrence of an emergency room (ER) visit, and number of physician office visits. Once a propensity score had been generated for each patient in the study sample, each peritoneal dialysis patient was matched to a hemodialysis patient in stepwise fashion (without replacement), minimizing the absolute difference in propensity scores for each match to <0.1 (i.e., caliper matching was employed).

We then compared pretreatment characteristics between matched peritoneal dialysis and hemodialysis patients to assess the adequacy of matching. Health care utilization and total billed charges were then compared between the two groups of matched patients over the 12-month period following the index date. Kaplan-Meier methods were used to examine time to hospitalization during follow-up. Statistical significance of differences between peritoneal dialysis and hemodialysis patients was assessed using paired t-tests for continuous variables and McNemar’s tests for categorical measures.

We also undertook a sensitivity analysis in which we did not exclude patients who initiated dialysis in hospital to explore how their inclusion in the study sample might have affected our findings. With the larger number of patients available to us in this anal-
In the primary analysis, we used 1:2 matching (i.e., each peritoneal dialysis patient was matched to two hemodialysis patients), rather than 1:1 matching as was used in the primary analysis.

**Results**

We identified a total of 427 patients with evidence of dialysis-related encounters in HFHS administrative data stores during the study period. Among these persons, 344 had evidence of receipt of dialysis in CarePlus within the 18-month period beginning six months prior to the anchor date and ending one year subsequent to this date. Approximately 53 percent of patients were excluded because they did not meet study inclusion/exclusion criteria, including evidence of receipt of dialysis prior to the beginning of the study period (35%), initiation of dialysis for reasons other than ESRD (16 percent),

### Exhibit 6: Utilization of selected health care services during follow-up among propensity-matched patients initiating peritoneal dialysis versus hemodialysis: Sensitivity analysis including patients hospitalized on index date

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>PD (N = 26)</th>
<th>HD (N = 113)</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Medications, No. %</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ACE Inhibitors</td>
<td>10 (38.5)</td>
<td>19 (36.5)</td>
<td>0.87</td>
</tr>
<tr>
<td>ARBs</td>
<td>6 (23.1)</td>
<td>17 (32.7)</td>
<td>0.36</td>
</tr>
<tr>
<td>Erythropoietin-stimulating agents</td>
<td>19 (73.1)</td>
<td>41 (78.8)</td>
<td>0.57</td>
</tr>
<tr>
<td>Vitamin D analogues</td>
<td>15 (57.7)</td>
<td>37 (71.2)</td>
<td>0.2</td>
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<td>Phosphate binders</td>
<td>17 (65.4)</td>
<td>38 (73.1)</td>
<td>0.53</td>
</tr>
<tr>
<td>Antibiotics</td>
<td>17 (65.4)</td>
<td>35 (67.3)</td>
<td>0.86</td>
</tr>
<tr>
<td>IV iron</td>
<td>4 (15.4)</td>
<td>0 (0.00)</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td><strong>Hospitalizations</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patients, No. %</td>
<td>11 (42.3)</td>
<td>35 (67.3)</td>
<td>0.03</td>
</tr>
<tr>
<td><strong>Number of admissions</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>1 (1.6)</td>
<td>2.0 (2.8)</td>
<td>&lt; 0.05</td>
</tr>
<tr>
<td>Median (IQR)</td>
<td>0 (0 - 1)</td>
<td>1 (0 - 2)</td>
<td></td>
</tr>
<tr>
<td><strong>Days in hospital</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>11.5 (9.5)</td>
<td>19.4 (21.0)</td>
<td>0.55</td>
</tr>
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<td>Median (IQR)</td>
<td>8 (4 - 17)</td>
<td>11 (6 - 29)</td>
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</tr>
<tr>
<td><strong>Outpatient services</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Physician office visits</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patients, No. %</td>
<td>26 (100.0)</td>
<td>52 (100.0)</td>
<td>-</td>
</tr>
<tr>
<td><strong>Number of visits</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>12.4 (8.4)</td>
<td>17.2 (10.0)</td>
<td>0.01</td>
</tr>
<tr>
<td>Median (IQR)</td>
<td>12 (6 - 17)</td>
<td>18 (10 - 23)</td>
<td></td>
</tr>
<tr>
<td>Emergency room visits</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patients, No. %</td>
<td>12 (46.2)</td>
<td>33 (63.5)</td>
<td>0.09</td>
</tr>
<tr>
<td><strong>Number of visits</strong></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>1.1 (2.0)</td>
<td>2.1 (2.9)</td>
<td>0.04</td>
</tr>
<tr>
<td>Median (IQR)</td>
<td>0 (0 - 1)</td>
<td>1 (0 - 3)</td>
<td></td>
</tr>
</tbody>
</table>

and the remainder due to lack of continuous enrollment during the six-month period preceding the index date (2%). Among the 162 patients who satisfied these entry criteria, 139 (86 percent of all such patients) were not hospitalized as of their index date; the other 23 patients were dropped from the sample. The final study sample therefore consisted of 139 patients—26 receiving peritoneal dialysis, and 113 receiving hemodialysis. For almost all patients, the date of initiation of dialysis in medical records was within three months of the anchor date (peritoneal dialysis: 100%; hemodialysis: 89%).

The demographic and clinical characteristics of unmatched peritoneal dialysis and hemodialysis patients are presented in Exhibit 1. Patients in the two groups were similar in terms of age, gender, race, and BMI. There were statistically significant differences, however, in baseline hemoglobin (mean [SD] = 11.2 [1.2] g/dL for peritoneal dialysis vs 10.0 [1.5] g/dL for hemodialysis; p<0.01). Approximately 66 percent of hemodialysis patients had been hospitalized during the six-month period preceding their index date, while only 31 percent of peritoneal dialysis patients had been hospitalized during this period (p<0.01). The mean number of hospitalizations per patient during this period also was approximately twice as high among hemodialysis patients (1.2 [1.3] vs 0.6 [1.1] for peritoneal dialysis patients; p=0.02). Consistent with these observations concerning health care utilization, mean total health care charges during the six-month pre-index period also were significantly higher among hemodialysis patients ($67,138 [893,323] vs $43,218 [28,489] for patients receiving peritoneal dialysis; p=0.02).

Four patients switched from hemodialysis to peritoneal dialysis within 90 days of initiating dialysis; no patient switched from peritoneal dialysis to hemodialysis during this period. We did not examine modality switching after 90 days.

The demographic and clinical characteristics of peritoneal patients in the matched sample (n=26) were comparable to those of their propensity-matched HD counterparts (n=26) (Exhibit 2).

Utilization of selected health care services over the 12-month period following initiation of dialysis is presented in Exhibit 3 for propensity-matched patients. While there were no statistically significant differences in any of these measures, the percentage of patients hospitalized at one year was nominally higher among those receiving hemodialysis (53.8% vs 42.3% for peritoneal dialysis; p=0.41) (Exhibit 4). Mean numbers of emergency room (ER) visits and physician office visits during follow-up also were nominally (but not significantly) higher in hemodialysis patients (ER visits: 1.3 vs 1.1 respectively; p=0.69; physician office visits: 16.6 vs 12.4; p=0.05). Mean total billed charges over 12 months also was nominally higher in hemodialysis patients ($156,464 vs $127,981 for peritoneal dialysis; p=0.21)—a difference largely attributable to higher inpatient charges (Exhibit 5).

In a sensitivity analysis in which we included
(rather than excluded) patients who initiated dialysis in hospital, and used 1:2 matching of peritoneal dialysis patients to hemodialysis patients, patients were well-matched with respect to all pretreatment characteristics other than hemoglobin levels, which differed between the two groups (10.2 [1.6] for hemodialysis vs 11.2 [1.2] g/dL vs for peritoneal dialysis; p<0.001) (data available upon request). Approximately 67 percent of hemodialysis patients, and 42 percent of peritoneal dialysis patients, were hospitalized over the 12-month follow-up period (p=0.03). Hemodialysis patients also averaged more ER visits (2.1 [2.9] vs 1.1 [2.0]; p=0.01) and physician office visits (17.2 [10.0] vs 12.4 [8.4]; p=0.01) over 12 months (Exhibit 6). Total billed charges were significantly higher among hemodialysis patients than those receiving peritoneal dialysis ($188,340 vs $127,981, respectively; p=0.01) (Exhibit 7).

Discussion
In a previous study, we compared health care utilization and costs in ESRD patients beginning peritoneal dialysis versus hemodialysis, using data from a large U.S. health care claims database. An important limitation of our earlier work was uncertainty about the accuracy of the algorithms used to identify patients who were receiving hemodialysis versus peritoneal dialysis, which were based exclusively on diagnosis and procedure codes that were used for billing purposes. Our present study was undertaken to address some of the limitations of our earlier work.

Our study population consisted of a total of 139 ESRD patients—26 (19%) initiating treatment with peritoneal dialysis, and 113 (81 percent) beginning therapy with hemodialysis. (If hemodialysis patients in hospital on the date of initiation of dialysis are included, peritoneal dialysis patients represent only 16 percent of the sample.) Prevalence of peritoneal dialysis in our study population is substantially higher than that reported based on analyses of data from the USRDS (11% between 1996 to 1997, decreasing to 7% between 2002 to 2003 [p<0.001 for trend]). The discrepancy between URDS data and ours may be due to small sample size and/or unique characteristics of the setting in which our study was conducted.

Patients who begin therapy with peritoneal dialysis have been reported to be younger, less likely to be African American, and healthier than those who initiate therapy with hemodialysis. In our study, while mean age of peritoneal dialysis and hemodialysis patients was approximately the same, the former were generally in better health than the latter. Peritoneal dialysis patients had a significantly lower incidence of hospitalization and lower total billed charges in the pretreatment period. We used propensity score matching to control for these differences, which yielded relatively well-balanced groups.

In the primary analysis, we found that total billed charges over 12 months were nominally lower among patients who began renal replacement therapy with peritoneal dialysis ($127,981 vs $156,464 for hemodialysis; p=0.41). In a sensitivity analysis in which patients who began dialysis in hospital were included in the study sample, there was a $60,359 difference favoring peritoneal dialysis (p<0.01). The magnitude of relative differences in total health care charges that we observed (i.e., between patients receiving peritoneal dialysis vs hemodialysis) is consistent with findings from the USRDS, which has reported—in both matched and unmatched analyses—that costs are approximately 25 percent higher in patients receiving HD in comparison with those receiving PD.

We therefore believe that the lack of statistical significance in our main analyses is principally a reflection of our small sample size. The power of our study to detect a significant difference in total health care charges of the magnitude that we observed was only 13 percent; a fivefold larger sample would have been required to attain conventional levels of statistical power (e.g., 80%).

Approximately one in seven patients in our study began renal replacement therapy in hospital, suggesting a relatively rapid—and most likely suboptimal—initiation of dialysis due to sudden changes in medical status and/or lack of appropriate pre-dialysis care. All such patients received hemodialysis, although there is evidence suggesting that “urgent-start” peritoneal dialysis is both feasible and safe. Thus, our decision to eliminate from consideration patients who began hemodialysis in hospital and to focus exclusively on patients who initiated renal replacement therapy on an outpatient basis may represent more of an “apples-to-apples” comparison.

Optimal transitions to dialysis are planned and preceded by “early” (e.g., >1 year) referral to a nephrologist, discussion of treatment options, creation of an appropriate dialysis access (i.e., arteriovenous fistula, peritoneal catheter), and possibly also arrangements for availability of equipment and supplies (e.g., dialyzer, dialysate solution) either for in-center or at home use. Only 37 percent of patients in the U.S. who begin hemodialysis have an appropriate permanent vascular access ready for use at the time of treatment initiation, however. Notably, patients whose pre-dialysis care is optimized in this fashion have been reported to have better clinical outcomes than those for whom care is suboptimal. In one study of 339 patients initiating renal replacement therapy at 10 Canadian
centers, patients deemed to have “optimal initiation” of dialysis (n=134) were approximately one-half as likely as those with “suboptimal initiation” (n=205) to experience death, transfusion, or subsequent hospitalization (hazard ratio = 0.47; 95% confidence interval = 0.32 - 0.68); Ninety-four percent of patients who began renal replacement therapy with peritoneal dialysis were deemed to have had an optimal start versus only 20 percent of those who initiated therapy with hemodialysis.19 The degree to which patients report substantial involvement in therapeutic decision making with respect to choice of renal replacement therapy also differs by dialysis modality. In the USRDS Morbidity and Mortality Study, which surveyed 2,400 patients initiating dialysis, 84 percent of those who began renal replacement therapy with peritoneal dialysis reported substantial involvement in the decision versus only 47 percent among those beginning hemodialysis.20

In a recent examination of the number of invasive interventions required to maintain dialysis access, almost one-half of patients deemed eligible for either hemodialysis or peritoneal began treatment in hospital (20% of study sample) or did not receive at least four months of pre-dialysis care (28%).21 In addition to the costs of the admission during which dialysis began, patients with unplanned initiation of renal replacement therapy (predominantly hemodialysis) also were more likely to have begun treatment with a temporary vascular access, necessitating the creation of a second—and likely permanent—access at a later date. In another examination of 152 patients who began renal replacement therapy, mean annual per-patient costs associated with dialysis access were more than twice as high among hemodialysis patients who began treatment with a tunneled cuffed catheter versus an arteriovenous fistula (€4208 vs €1555) (the corresponding value among patients who began treatment with peritoneal dialysis was €1172).22 Only about one-third of hemodialysis patients (37%) initiate renal replacement therapy with an appropriate permanent vascular access, such as an arteriovenous fistula or graft.23 Consequently, the €60,000 difference in total health care costs in the year following initiation of dialysis that we observed in our sensitivity analysis in fact may represent potential cost savings to third-party payers associated with the provision of optimal pre-dialysis care and/or changing the paradigm of care for unplanned starts to include PD.16,21-23

However, since all “unplanned starts” in our study involved hemodialysis, we effectively were precluded from examining the degree to which choice of dialysis modality among these patients might impact subsequent health care costs.

Our study has several limitations. While our findings are similar to those of our previous study, and even expand upon them by leveraging information heretofore unavailable, the relatively small sample sizes—especially of patients receiving peritoneal dialysis—warrant caution. We tallied health care utilization and charges during the one-year period following initial receipt of dialysis, irrespective of modality (i.e., our perspective was “intent-to-treat”). Prior research has indicated that a large proportion of patients switch modality following initiation of dialysis. The USRDS Annual Data Report indicated that in 2013, the hemodialysis population at day 90 was more than 10 percent smaller than at therapy initiation, while the peritoneal dialysis population in contrast had grown.4 Shih et al reported that peritoneal dialysis patients who did not switch to hemodialysis had lower annual costs that those who switched (€48,446 vs €68,531); similarly, hemodialysis patients who did not switch to peritoneal dialysis had lower costs than those who switched (€68,209 vs €76,007).24 More recently, Chui and colleagues examined patients who received peritoneal dialysis only (n=208), hemodialysis followed by peritoneal dialysis (n=120), and hemodialysis only (n=1005); cumulative mean (95% CI) total health care costs over a three-year period for these three groups were €58,724 ($44,123 - $73,325), €114,503 ($96,318 – 132,688), and €175,996 ($134,787 - $217,205), respectively (all estimates reported in 2010 Canadian dollars).25 Because our examination of modality switching was limited to the 90-day period following initiation of dialysis, we could not conduct an “as-treated” analysis as others have done.

Our propensity score model was limited to variables included in our data. Although we believe that we adjusted for the key variables, any omitted variables that would both render patients more likely to receive one modality versus the other and also be correlated with health care costs could confound our results. We also note that we used billed charges rather than reimbursed amounts, since the latter were not available in the database; while it is reasonable to expect similar directionality (i.e., higher charges likely equate to higher reimbursed amounts), the difference in reimbursement between patients initiating hemodialysis versus peritoneal dialysis is unknown.

Our findings were based on 139 patients with ESRD who were enrolled in a single health maintenance organization in Detroit, Michigan and the surrounding areas. In 2010, the mean age at which patients began dialysis in the U.S. was 63 years, and only 6.4 percent of such patients resided in the upper
Midwest (the geographic area that includes Michigan). The generalizability of our findings to other settings and areas is unknown.

In summary, costs of renal replacement therapy over one year were nominally and consistently (but not always significantly) higher in patients who received HD versus PD; our results were sensitive, however, to patient-selection criteria. Further study would be needed to understand the extent to which our findings derive from differences in dialysis modalities versus the characteristics of patients who receive them.

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References
### Appendix. Dialysis-related procedure/diagnosis codes

<table>
<thead>
<tr>
<th>Code</th>
<th>Code Type</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>996.56</td>
<td>ICD-9-CM Diagnosis</td>
<td>Mechanical complication due to peritoneal dialysis catheter</td>
</tr>
<tr>
<td>996.68</td>
<td>ICD-9-CM Diagnosis</td>
<td>Infection and inflammatory reaction due to vascular device, implant and graft (due to peritoneal dialysis catheter)</td>
</tr>
<tr>
<td>V56.2</td>
<td>ICD-9-CM Diagnosis</td>
<td>Fitting and adjustment of peritoneal dialysis catheter</td>
</tr>
<tr>
<td>V56.32</td>
<td>ICD-9-CM Diagnosis</td>
<td>Encounter for adequacy testing for peritoneal dialysis</td>
</tr>
<tr>
<td>V56.8</td>
<td>ICD-9-CM Diagnosis</td>
<td>Other dialysis—peritoneal dialysis</td>
</tr>
<tr>
<td>49420</td>
<td>CPT-4</td>
<td>Insertion of intraperitoneal cannula or catheter for drainage or dialysis; temporary</td>
</tr>
<tr>
<td>49421</td>
<td>CPT-4</td>
<td>Insertion of intraperitoneal cannula or catheter for drainage or dialysis; permanent</td>
</tr>
<tr>
<td>90945</td>
<td>CPT-4</td>
<td>Dialysis procedure other than hemodialysis (eg, peritoneal dialysis, hemofiltration, or other continuous renal replacement therapies), with single physician evaluation</td>
</tr>
<tr>
<td>90947</td>
<td>CPT-4</td>
<td>Dialysis procedure other than hemodialysis (eg, peritoneal dialysis, hemofiltration, or other continuous renal replacement therapies), requiring repeated physician evaluations, with or without substantial revision of dialysis prescription</td>
</tr>
<tr>
<td>A4653</td>
<td>HCPCS</td>
<td>Peritoneal dialysis catheter anchoring device, belt, each</td>
</tr>
<tr>
<td>A4671</td>
<td>HCPCS</td>
<td>Disposable cycler set used with cycler dialysis machine, each</td>
</tr>
<tr>
<td>A4672</td>
<td>HCPCS</td>
<td>Drainage extension line, sterile, for dialysis, each</td>
</tr>
<tr>
<td>A4673</td>
<td>HCPCS</td>
<td>Extension line with easy lock connectors, used with dialysis</td>
</tr>
<tr>
<td>A4719</td>
<td>HCPCS</td>
<td>Y set tubing for peritoneal dialysis</td>
</tr>
<tr>
<td>A4720</td>
<td>HCPCS</td>
<td>Dialysate solution, any concentration of dextrose, fluid volume greater than 249cc, but less than or equal to 999cc, for peritoneal dialysis</td>
</tr>
<tr>
<td>A4721</td>
<td>HCPCS</td>
<td>Dialysate solution, any concentration of dextrose, fluid volume greater than 999cc but less than or equal to 1999cc, for peritoneal dialysis</td>
</tr>
<tr>
<td>A4722</td>
<td>HCPCS</td>
<td>Dialysate solution, any concentration of dextrose, fluid volume greater than 1999cc but less than or equal to 2999cc, for peritoneal dialysis</td>
</tr>
<tr>
<td>A4723</td>
<td>HCPCS</td>
<td>Dialysate solution, any concentration of dextrose, fluid volume greater than 2999cc but less than or equal to 3999cc, for peritoneal dialysis</td>
</tr>
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<td>A4724</td>
<td>HCPCS</td>
<td>Dialysate solution, any concentration of dextrose, fluid volume greater than 3999cc but less than or equal to 4999cc, for peritoneal dialysis</td>
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<tr>
<td>A4725</td>
<td>HCPCS</td>
<td>Dialysate solution, any concentration of dextrose, fluid volume greater than 4999cc but less than or equal to 5999cc, for peritoneal dialysis</td>
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<td>A4726</td>
<td>HCPCS</td>
<td>Dialysate solution, any concentration of dextrose, fluid volume greater than 5999cc, for peritoneal dialysis</td>
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<tr>
<td>A4727</td>
<td>HCPCS</td>
<td>Dialysate solution, non-dextrose containing, 500 ml</td>
</tr>
<tr>
<td>A4760</td>
<td>HCPCS</td>
<td>Dialysate solution test kit, for peritoneal dialysis, any type, each</td>
</tr>
<tr>
<td>A4765</td>
<td>HCPCS</td>
<td>Dialysate concentrate, powder, additive for peritoneal dialysis, per packet</td>
</tr>
<tr>
<td>A4766</td>
<td>HCPCS</td>
<td>Dialysate concentrate, solution, additive for peritoneal dialysis, per 10 ml</td>
</tr>
<tr>
<td>A4860</td>
<td>HCPCS</td>
<td>Disposable catheter tips for peritoneal dialysis, per 10</td>
</tr>
<tr>
<td>A4880</td>
<td>HCPCS</td>
<td>Storage tanks utilized in connection with water purification system, replacement tanks for dialysis</td>
</tr>
<tr>
<td>A4900</td>
<td>HCPCS</td>
<td>Continuous ambulatory peritoneal dialysis (capd) supply kit</td>
</tr>
<tr>
<td>A4901</td>
<td>HCPCS</td>
<td>Continuous cycling peritoneal dialysis (ccpd) supply kit</td>
</tr>
<tr>
<td>A4905</td>
<td>HCPCS</td>
<td>Intermittent peritoneal dialysis (ipd) supply kit</td>
</tr>
<tr>
<td>E1632</td>
<td>HCPCS</td>
<td>Wearable artificial kidney, each</td>
</tr>
<tr>
<td>E1592</td>
<td>HCPCS</td>
<td>Automatic intermittent peritoneal dialysis system</td>
</tr>
<tr>
<td>E1594</td>
<td>HCPCS</td>
<td>Cycler dialysis machine for peritoneal dialysis</td>
</tr>
<tr>
<td>E1630</td>
<td>HCPCS</td>
<td>Reciprocating peritoneal dialysis system</td>
</tr>
<tr>
<td>E1634</td>
<td>HCPCS</td>
<td>Peritoneal dialysis clamps, each</td>
</tr>
<tr>
<td>E1638</td>
<td>HCPCS</td>
<td>Heating pad, for peritoneal dialysis, any size, each</td>
</tr>
<tr>
<td>E1640</td>
<td>HCPCS</td>
<td>Replacement components for hemodialysis and/or peritoneal dialysis machines that are owned or being purchased by the patient</td>
</tr>
<tr>
<td>38.95</td>
<td>ICD-9-CM procedure</td>
<td>Venous catheterization for renal dialysis</td>
</tr>
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<td>39.27</td>
<td>ICD-9-CM procedure</td>
<td>Arteriovenostomy for renal dialysis</td>
</tr>
<tr>
<td>39.42</td>
<td>ICD-9-CM procedure</td>
<td>Revision of arteriovenous shunt for renal dialysis</td>
</tr>
<tr>
<td>39.43</td>
<td>ICD-9-CM procedure</td>
<td>Removal of arteriovenous shunt for renal dialysis</td>
</tr>
<tr>
<td>39.95</td>
<td>ICD-9-CM procedure</td>
<td>Hemodialysis</td>
</tr>
<tr>
<td>458.21</td>
<td>ICD-9-CM procedure</td>
<td>Hypotension of hemodialysis</td>
</tr>
<tr>
<td>v56.0</td>
<td>ICD-9-CM procedure</td>
<td>Extracorporeal dialysis</td>
</tr>
<tr>
<td>v56.1</td>
<td>ICD-9-CM procedure</td>
<td>Fitting and adjustment of extracorporeal dialysis catheter</td>
</tr>
<tr>
<td>v56.31</td>
<td>ICD-9-CM procedure</td>
<td>Encounter for adequacy testing for HD</td>
</tr>
<tr>
<td>36145</td>
<td>CPT-4</td>
<td>Arteriovenous shunt created for dialysis (cannula, fistula, or graft)</td>
</tr>
<tr>
<td>36800</td>
<td>CPT-4</td>
<td>Insertion of cannula for hemodialysis, other purpose (separate procedure); vein to vein</td>
</tr>
<tr>
<td>36810</td>
<td>CPT-4</td>
<td>Insertion of cannula for hemodialysis, other purpose (separate procedure); arteriovenous, external</td>
</tr>
<tr>
<td>36815</td>
<td>CPT-4</td>
<td>Insertion of cannula for hemodialysis, other purpose (separate procedure); arteriovenous, external revision, or closure</td>
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<tr>
<td>36931</td>
<td>CPT-4</td>
<td>Thrombectomy, open, arteriovenous fistula without revision, autogenous or nonautogenous dialysis graft</td>
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<tr>
<td>36932</td>
<td>CPT-4</td>
<td>Revision, open, arteriovenous fistula; without thrombectomy, autogenous or nonautogenous dialysis graft</td>
</tr>
<tr>
<td>36833</td>
<td>CPT-4</td>
<td>Revision, open, arteriovenous fistula; with thrombectomy, autogenous or nonautogenous dialysis graft</td>
</tr>
<tr>
<td>36838</td>
<td>CPT-4</td>
<td>Distal revascularization and interval ligation, upper extremity hemodialysis access (steal syndrome)</td>
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<td>90935</td>
<td>CPT-4</td>
<td>Hemodialysis procedure requiring repeated evaluation(s) with or without substantial revision of dialysis prescription</td>
</tr>
<tr>
<td>90939</td>
<td>CPT-4</td>
<td>Hemodialysis access flow study to determine blood flow in grafts and arteriovenous fistulae by an indicator dilution method, hook-up; transcutaneous measurement and disconnection</td>
</tr>
<tr>
<td>90940</td>
<td>CPT-4</td>
<td>Hemodialysis access flow study to determine blood flow in grafts and arteriovenous fistulae by an indicator dilution method, hook-up; measurement and disconnection</td>
</tr>
</tbody>
</table>
93990  CPT-4  Duplex scan of hemodialysis access (including arterial inflow, body of access and venous outflow)
99512  CPT-4  Home visit for hemodialysis
A4674  HCPCS  Chemicals/antiseptics solution used to clean/sterilize dialysis equipment, per 8 oz
A4680  HCPCS  Activated carbon filter for hemodialysis
A4690  HCPCS  Dialyzer (Artificial kidneys), all types/sizes, for hemodialysis
A4700  HCPCS  Dialyzer (Artificial kidneys), all types/sizes, for hemodialysis
A4705  HCPCS  Bicarbonate dialysate solution, each
A4706  HCPCS  Bicarbonate concentrate, solution, for hemodialysis, per gallon
A4707  HCPCS  Bicarbonate concentrate, powder, for hemodialysis, per packet
A4708  HCPCS  Acetate concentrate solution, for hemodialysis, per gallon
A4709  HCPCS  Acid concentrate solution, for hemodialysis, per gallon
A4712  HCPCS  Water, sterile, for injection, per 10 ml
A4714  HCPCS  Treated water (deionized, distilled, or reverse osmosis) for peritoneal dialysis, per gallon
A4730  HCPCS  Fistula cannulation set for hemodialysis
A4740  HCPCS  Shunt accessory, for hemodialysis, any type
A4750  HCPCS  Blood tubing, arterial or venous, for hemodialysis
A4755  HCPCS  Blood tubing, arterial and venous combined, for hemodialysis
A4770  HCPCS  Blood collection tube, vacuum, for dialysis, per 50
A4774  HCPCS  Ammonia test strips, for dialysis, per 50
A4780  HCPCS  Sterilizing agent for dialysis equipment, per gallon
A4790  HCPCS  Cleansing agents for equipment for dialysis only
A4800  HCPCS  Heparin for dialysis and antidote, any strength, porcine or beef, up to 1000 units, 10-30 ml (for parenteral use see b4216)
A4801  HCPCS  Heparin, any type, for hemodialysis, per 1000 units
A4802  HCPCS  Protamine sulfate, for hemodialysis, per 50 mg
A4820  HCPCS  Hemodialysis kit supplies
A4850  HCPCS  Hemostats with rubber tips for dialysis
A4870  HCPCS  Plumbing and/or electrical work for home hemodialysis equipment
A4890  HCPCS  Contracts, repair and maintenance for hemodialysis equipment
A4918  HCPCS  Venous pressure clamp, for hemodialysis
A4919  HCPCS  Dialyzer holder, each
A4929  HCPCS  Turniquet for dialysis, each
E1510  HCPCS  Kidney, dialysate delivery syst. kidney machine, pump recirculating, air removal system, flowrate meter, power off, heater and temperature control with alarm, i.v. poles, pressure gauge, concentrate container
E1520  HCPCS  Heparin infusion pump for hemodialysis
E1530  HCPCS  Air bubble detector for hemodialysis, each, replacement
E1540  HCPCS  Pressure alarm for hemodialysis, each, replacement
E1550  HCPCS  Bath conductivity meter for hemodialysis
E1560  HCPCS  Blood leak detector for hemodialysis, each, replacement
E1575  HCPCS  Transducer protectors/fluid barriers, for hemodialysis, any size, per 10
E1580  HCPCS  Unipuncture control system for hemodialysis
E1590  HCPCS  Hemodialysis machine
E1600  HCPCS  Delivery and/or installation charges for hemodialysis equipment
E1610  HCPCS  Reverse osmosis water purification system, for hemodialysis
E1615  HCPCS  Deionizer water purification system, for hemodialysis
E1620  HCPCS  Blood pump for hemodialysis, replacement
E1625  HCPCS  Water softening system, for hemodialysis
E1635  HCPCS  Compact (portable) travel hemodialyzer system
E1636  HCPCS  Sorbent cartridges, for hemodialysis, per 10
792.5  ICD-9-CM diagnosis  Cloudy (hemodialysis) (peritoneal) dialysis effluent
E879.1  ICD-9-CM diagnosis  Other procedures, without mention of misadventure at the time of procedure, as the cause of abnormal reaction of patient, or of later complication, kidney dialysis
V45.1  ICD-9-CM diagnosis  Renal dialysis status
90920  CPT-4  End stage renal diseases related services per full month; for patients between twelve and nineteen years of age to include monitoring for the adequacy of nutrition, assessment of growth and development, and counseling of parents
90921  CPT-4  End stage renal diseases related services per full month; for patients twenty years of age and older to include monitoring for the adequacy of nutrition, assessment of growth and development, and counseling of parents
90924  CPT-4  End stage renal diseases related services (less than a full month), per day; for patients between twelve and nineteen years of age
90925  CPT-4  End stage renal diseases related services (less than a full month), per day; for patient twenty years of age and over
90989  CPT-4  Dialysis training, patient, including helper where applicable, any mode, completed course
90993  CPT-4  Dialysis training, patient, including helper where applicable, any mode, course not completed, per training session
90999  CPT-4  Unlisted dialysis procedure, inpatient or outpatient
A4736  HCPCS  Topical anesthetic, for dialysis, per gram
A4737  HCPCS  Injectable anesthetic, for dialysis, per 10 ml
A4771  HCPCS  Serum clotting time tube, for dialysis, per 50
A4772  HCPCS  Blood glucose test strips, for dialysis, per 50
A4773  HCPCS  Occult blood test strips, for dialysis, per 50
A4910  HCPCS  Non-medical supplies for dialysis, (i.e., scale, scissors, stopwatch, etc.)
A4911  HCPCS  Drain bag/bottle, for dialysis, each
A4912  HCPCS  Gomco drain bottle
A4913  HCPCS  Miscellaneous dialysis supplies, not otherwise specified
A4914  HCPCS  Preparation kits
A4920  HCPCS  Harvard pressure clamp, each
<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>A4921</td>
<td>Measuring cylinder, any size, each</td>
</tr>
<tr>
<td>A4927</td>
<td>Gloves, non-sterile, per 100</td>
</tr>
<tr>
<td>A4928</td>
<td>Surgical mask, per 20</td>
</tr>
<tr>
<td>A4930</td>
<td>Gloves, sterile, per pair</td>
</tr>
<tr>
<td>A4931</td>
<td>Oral thermometer, reusable, any type, each</td>
</tr>
<tr>
<td>A4932</td>
<td>Rectal thermometer, reusable, any type, each</td>
</tr>
<tr>
<td>C1750</td>
<td>Catheter, hemodialysis/peritoneal, long-term</td>
</tr>
<tr>
<td>C1752</td>
<td>Catheter, hemodialysis/peritoneal, short-term</td>
</tr>
<tr>
<td>C1881</td>
<td>Dialysis access system (implantable)</td>
</tr>
<tr>
<td>E1500</td>
<td>Centrifuge, for dialysis</td>
</tr>
<tr>
<td>E1570</td>
<td>Adjustable chair, for esrd patients</td>
</tr>
<tr>
<td>E1637</td>
<td>Hemostats, each</td>
</tr>
<tr>
<td>E1639</td>
<td>Scale, each</td>
</tr>
<tr>
<td>E1699</td>
<td>Dialysis equipment, not otherwise specified</td>
</tr>
<tr>
<td>G0257</td>
<td>Unscheduled or emergency dialysis treatment for an esrd patient</td>
</tr>
<tr>
<td>G8076</td>
<td>ESRD patient with documented dialysis dose of URR less than 65% (or Kt/V less than 1.2)</td>
</tr>
</tbody>
</table>

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Introduction
ACCORDING TO THE CENTERS FOR DISEASE CONTROL AND PREVENTION (CDC), THE OVERALL PREVALENCE OF HYPERTENSION AMONG U.S. ADULTS AGED ≥18 YEARS FROM 2003 TO 2010 WAS 30.4 PERCENT OR APPROXIMATELY 66.9 MILLION ADULTS. AMONG THOSE WITH HYPERTENSION, AN ESTIMATED 35.8 MILLION (53.5%) DID NOT HAVE THEIR HYPERTENSION CONTROLLED. AMONG THESE, AN ESTIMATED 14.1 MILLION (39.4%) WERE NOT AWARE OF THEIR HYPERTENSION AND 5.7 MILLION (15.8%) WERE AWARE OF THEIR HYPERTENSION BUT WERE NOT RECEIVING PHARMACOLOGIC TREATMENT.1 OF THE 35.8 MILLION U.S. ADULTS WITH UNCONTROLLED HYPERTENSION, 89.4 PERCENT REPORTED HAVING A USUAL SOURCE OF HEALTH CARE AND 85.2 PERCENT REPORTED HAVING HEALTH INSURANCE, INDICATING POTENTIAL MISSED OPPORTUNITIES BY INDIVIDUALS, HEALTH CARE PROVIDERS, AND HEALTH CARE SYSTEMS TO IMPROVE HYPERTENSION CONTROL. AS STATED BY THE CDC, IMPROVED HYPERTENSION CONTROL REQUIRES AN EXPANDED EFFORT AND INCREASED FOCUS ON HYPERTENSION FROM PATIENTS, HEALTH CARE SYSTEMS, AND CLINICIANS.2

In addition to barriers to hypertension control, the risks of uncontrolled blood pressure (BP) are often underscored by providers. Moreover, even modest elevations in BP increase the risk for car-

Impacting Hypertension: Support for a Remote Lifestyle and Home Blood Pressure Monitoring Intervention

Kristine S. Calderon, PhD, CHES, Anthony N. Akosa, MD, MBA, Susan Meece-Hinh, MPH, CHES, CCP

Summary
THE EXISTENCE OF AN ESTIMATED 35.8 MILLION AMERICANS WITH UNCONTROLLED HYPERTENSION COUPLED WITH BARRIERS OF CONTROLLING BLOOD PRESSURE (BP) AMONG PAYERS, CLINICIANS AND HEALTH CARE SYSTEMS, IS PLACING A GROWING NUMBER OF HEALTH PLAN MEMBERS NOT ONLY AT CARDIOVASCULAR RISK BUT WITH POTENTIAL FOR INCREASED HEALTH CARE SPEND. WITH THE INCREASING HYPERTENSION INCIDENCE, STRONG EVIDENCE FROM LIFESTYLE MANAGEMENT GUIDELINES FOR BP CONTROL AND GROWING EFFICACY FOR SELF-BLOOD PRESSURE MONITORING, AN INTERVENTION COMBINING THESE ELEMENTS IS NEEDED. THE PURPOSE OF THIS PILOT STUDY WAS TO DETERMINE IF A REMOTE LIFESTYLE INTERVENTION WITH PROVISION OF A BLOOD PRESSURE MONITOR WOULD IMPACT BP, ASSOCIATED METRICS AND LIFESTYLE BEHAVIORS, AS WELL AS COST SAVINGS AMONG HYPERTENSIVE PLAN MEMBERS.

Key Points
• This 12-month study examined BP, weight, BMI, exercise, sodium intake and perceived stress among 102 enrolled hypertensive plan members.
• After enrollment, members were mailed a BP monitor to their home as well as an educational incentive and information for each quarterly follow-up.
• Final analysis included 58 participants with complete data with significant baseline to 12-month follow-up comparisons including decreases in weight (t = 2.49, p = 0.03) and perceived stress (t = 3.15, p = 0.02) and near significant differences in diastolic BP (t = 1.86, p < 0.08) and daily sodium intake (t = 1.96, p < 0.09).
• Claims analysis revealed a 28 percent higher average increase in medical spend among a random sample of 499 hypertension-only non-participants in the plan as compared to program participants.
• It is recommended that the study intervention be implemented on a larger scale and that enrolled members are tracked for multiple years to show long-term health care spend savings.
For every 20-mmHg increase in SBP beginning at 115 mmHg, or 10-mmHg increase in DBP beginning at 75 mmHg, mortality from ischemic heart disease and stroke are doubled. Furthermore, nearly 30 percent of adults with uncontrolled hypertension who are aware of their hypertension and pharmacologically treated have Stage 2 hypertension (SBP ≥160 mmHg or DBP ≥100 mmHg), placing them at even higher risk for adverse cardiovascular events. 2

It is without question that increased focus on BP from clinicians and health care systems is essential for not only improving hypertension control but also decreasing cardiovascular risk. In addition to usual treatment strategies to improve hypertension control such as use of evidence-based clinical practice guidelines and improving medication adherence, individuals also can play an important role in achieving control by monitoring their own BP and following lifestyle behaviors such as consuming a lower-sodium diet.

As more guidelines recommend that adults with hypertension self-monitor or self-measure their blood pressure; Uhlig et al, 2013 summarized evidence about the effectiveness of self-measured blood pressure monitoring among adults with hypertension. Over 50 prospective comparative studies revealed that BP monitoring lowers BP compared with usual care with efficacy beyond 12 months remains uncertain. However, educational and clinical support added to BP monitoring did show to enhance the BP-lowering effect. 3

According to the 2013 American Heart Association/American College of Cardiology Lifestyle Management Guidelines, there is strong evidence for adults who would benefit from lowering BP to 1) follow a dietary plan such as the DASH diet, 2) lower sodium intake, and 3) engage in regular aerobic physical activity. 4 Following a dietary plan such as the DASH diet emphasizes intake of vegetables, fruits, and whole grains; includes low-fat dairy products, poultry, fish, legumes, non-tropical vegetable oils and nuts; and limits intake of sodium, sweets, sugar-sweetened beverages and red meats. In terms of sodium intake specifically, it is recommended that individuals with hypertension consume no more than 2,400 mg/day with a reduction of sodium to 1,500 mg/day for even greater reduction in BP. For physical activity, it is recommended that hypertensive individuals engage in three to four sessions a week, lasting on average 40 minutes per session, and involving moderate-to-vigorous intensity physical activity. 5 Hence, lifestyle interventions including these components are needed for optimum BP lowering effect among hypertensive individuals.

A recent survey examined how managed care payers implement disease management programs, design programs to target patients, and engage them in the management of their own health. All payer participants reported addressing the “big five” chronic conditions, which included chronic heart failure (CHF), diabetes, chronic obstructive pulmonary disease (COPD), asthma and coronary artery disease (CAD). 6 However, few if any payers, specifically targeted hypertension. This data supports how hypertension often falls below the radar in terms of chronic disease targets, thereby perpetuating the ever-increasing incidence of uncontrolled hypertension.

The missed target of hypertension among payers, clinicians and health care systems, coupled with barriers of controlling BP, will continue to lead to more cardiovascular events, thereby placing more individuals in the higher risk and higher cost categories. The purpose of this pilot study was to determine if a remote lifestyle intervention with provision of a blood pressure monitor would impact BP, associated metrics and lifestyle behaviors, as well as cost savings among hypertensive plan members.

Methods

A remote lifestyle program targeting hypertension was offered to health plan members with a diagnosis of only hypertension. Two waves of 2,000 “hypertension-only” members were randomly selected for recruitment. Members who decided to participate registered via an online member health portal upon which they agreed to an IRB-approved consent form prior to enrollment. The methodology and consent form was submitted to and approved by the NAMCP Research Institutional Review Board for inclusion as a pilot study in the Center for Preventive Health and Lifestyle Medicine.

Recruitment and Enrollment

Health plan members with a diagnosis of only hypertension were sent a postcard to their home address inviting them to participate in the program. The postcard directed members to enroll in an online portal after which they were sent a home blood pressure monitor. All members who registered in the online member health portal were enrolled in the study. For enrollment, members had to provide consent, baseline assessment data for both clinical and behavioral measures and demographic information via the member health portal. After creating their data “profile” in the system, members could go back into their profiles to enter subsequent data or track blood pressure at any time over the course
of the program year. Members were sent both electronic (email) and mailed reminders to their home each quarter to share data.

**Demographic and Clinical Measures**

Within the member health portal, demographic measures including age and gender were collected along with address, email and phone number for contact information. Clinical measures collected included height and weight upon which body mass index (BMI) automatically calculated and appeared. Data fields were present for systolic BP, diastolic BP and pulse as well as a question asking whether or not the member is taking medication for hypertension.

Members were mailed a BP monitor to their home after enrollment as the first incentive to start the program. Participants received a fully automatic Health Sense home BP monitor along with a large adult cuff (standard size cuff is included with the monitor) and, if requested, an extra-large arm cuff for BP monitoring. They were also sent the 2012 American Heart Association (AHA) “Blood Pressure Tracker–Instructions” which instructs participants how to take their BP as well as lists the AHA recommended BP levels.

**Behavioral Measures**

**Weekly Activity Fitness Scale (WAFS)**

Though physical steps are important for daily movement, purposeful exercise that raises the heart rate and produces cardiovascular benefit is needed to impact hypertension. To simply measure purposeful exercise, the Weekly Activity Fitness Scale or WAFS was used. The WAFS is a modified version of the NASA Activity Scale (NAS). The NAS has been used in several exercise studies by the Johnson Space Center. In one study with men, the zero-order correlations between peak oxygen uptake and percentage body fat \( r = -0.62 \) and NAS \( r = 0.58 \) were significant \( P < 0.05 \). In a follow-up study with women, the zero-order correlations between peak oxygen uptake and % body fat \( r = -0.742 \) and NAS \( r = 0.626 \) were also significant \( P < 0.05 \). In terms of scale validation, both these studies indicate that self-report exercise from the NAS was related to actual physiological measures among participants. In the scale, participants are asked one question, “Check the box next to one of the following responses that best describes your exercise habits.” The scale ranges from a score of “0” – “no regular exercise/no physical activity outside of work” to a score of “10” – “regular exercise/weekly average of more than 11 hours per week.”

**Sodium Intake (FFQ-S)**

To measure sodium intake, a Food Frequency Questionnaire for Sodium or FFQ-S containing 38 commonly consumed food items in the current market in four categories of sodium levels – over 1000mg (high sodium), over 750mg (moderate sodium), over 375mg (lower sodium), and over 25mg (recommended sodium level) was developed. Participants were asked to insert the number of days per week that these food items are consumed. Based on the four sodium categories, the member health portal calculates total sodium intake for the week and divides by seven days for the daily average sodium intake. This average daily sodium intake is then shown to the participants in the member health portal.

**Perceived Stress Scale (PSS)**

As stress is strongly related to hypertension, the Perceived Stress Scale (PSS) was used to measure current (each quarter) perceived stress among participants. The PSS is the most widely used psychological instrument for measuring the perception of stress and is a measure of the degree to which situations in one’s life are appraised as stressful. Items are designed to tap how unpredictable, uncontrollable, and overloaded respondents find their lives. The scale also includes a number of direct queries about current levels of experienced stress. The 10 questions in the PSS ask about feelings and thoughts during the last month. In each case, respondents are asked how often they felt a certain way. Higher PSS scores have been associated with failure to quit smoking; failure among diabetics to control blood sugar levels; and greater vulnerability to stressful life-event-elicited depressive symptoms. Cohen et al. have shown correlations with PSS and various stress, self-reported health and health services, health behavior, smoking status, and help seeking measures.

All program metrics were collected each quarter as prompted by a quarterly mailed letter with an incentive tool and an educational piece. Members that provided valid email addresses were also emailed a reminder to enter their data.

**Participant Feedback Survey**

At the end of the program, all participants were mailed a feedback survey in a generic facility-addressed, stamped envelope to return anonymously. Participants were told to rate how strongly they agreed or disagreed with six items regarding impact of the program. They were also asked to openly write about what they liked, did not like and would recommend for improvement. Lastly, participants were asked to rank in order of preference the way
in which they would like to receive information to improve their health.

**Education and Incentive Tools**
For each subsequent quarter from baseline enrollment, participants were mailed an incentive tool along with educational sheet. Exhibit 1 outlines the incentive tools and education. With each mailing, participants were asked to re-visit their portal profile for purposes of entering their data for the given quarter.

**Program Data Analysis**
The examination of program data included comparisons between baseline and 12-month (4th quarter) follow-up among the program participants for all relevant metrics including weight, BMI, systolic BP, diastolic BP, WAFS, FFQ-S, and PSS scores. These metric comparisons were made using paired t-tests for statistical analyses. Average scores and preference rankings were also calculated for the program feedback survey.

**Claims Analysis**
To determine medical spend savings as a result of program participation, annual claims were compared between program participants and a random sample of 499 hypertension-only, non-participants (matched for average age and gender split from the same health plan) between the program year and prior year. For this analysis, the average dollar amount for medical spend was calculated for both the participant group and non-participant comparison group to calculate differences between program and prior years. Members in both groups identified as “critical” risk, based on prospective risk scores, were eliminated from the analysis due to high dollar “critical incident cost” creating outlier costs in both group averages. However, all remaining members in both participant and non-participant comparison groups classified as low, medium, and high risk were kept in the analyses.

<table>
<thead>
<tr>
<th>Metric</th>
<th>Baseline Mean (SD)</th>
<th>12-month F/U Mean (SD)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight</td>
<td>229.1 (49.4)</td>
<td>195.9 (41.8)</td>
<td>0.03*</td>
</tr>
<tr>
<td>BMI</td>
<td>31.3 (6.2)</td>
<td>29.9 (6.8)</td>
<td>0.59</td>
</tr>
<tr>
<td>Systolic BP</td>
<td>130.4 (15.5)</td>
<td>125.6 (13.6)</td>
<td>0.63</td>
</tr>
<tr>
<td>Diastolic BP</td>
<td>82.7 (11.5)</td>
<td>73.7 (11.4)</td>
<td>0.08**</td>
</tr>
<tr>
<td>FFQ-S (Daily Sodium)</td>
<td>2,715 (1,328.8)</td>
<td>2,198.6 (1,009.8)</td>
<td>0.09**</td>
</tr>
<tr>
<td>WAFS</td>
<td>4.5 (2.7)</td>
<td>5.4 (2.9)</td>
<td>0.28</td>
</tr>
<tr>
<td>PSS</td>
<td>11.5 (5.3)</td>
<td>9.5 (4.9)</td>
<td>0.02*</td>
</tr>
</tbody>
</table>

* Significant (p < 0.05)
** Near significance (p < 0.10)

Note: WAFS is exercise frequency score - a higher score indicates more frequent exercise performed in a given week. PSS is perceived stress score - a higher score indicates higher perceived stress at given time.
Results
Baseline program data included 102 participants who enrolled in the program. However, from these 102 participants only 58 participants entered data for all three follow-up quarters. Hence, only these 58 participants with complete data were included in the final analyses.

The average age for the 58 participants, which included 20 males and 38 females, was 51 years. About 85 percent or 49 participants reported taking medication for their hypertension throughout the study, leaving only nine or 15 percent who reported not taking medication. No participants reported change in medication status throughout the study year. Exhibit 2 shows averages and comparison p values for all metric comparisons including weight, BMI, systolic BP, diastolic BP, WAFS, FFQ-S and PSS scores.

As shown in Exhibit 2, significant baseline to 12-month follow-up comparisons included decreases in weight (t = 2.49, p = 0.03) and perceived stress (t = 3.15, p = 0.02). Near significant differences included diastolic BP (t = 1.86, p < 0.08) and daily sodium intake via the FFQ-S (t = 1.96, p < 0.09).

As described earlier, participants rated the impact of the program via six questions on the program feedback survey. With available scoring from 1 to 4 for each item, scores ranged from 3.5 to 3.9. The average scores listed for all items are shown in Exhibit 3.

In addition to these feedback items, participants ranked the order in which they prefer to receive health information. The most preferred delivery method was a mailed, printed newsletter and/or sheets, with the least preferred being a phone call with a care coach or educator. The rankings were listed as follows:
- Mailed printed newsletter and/or sheets
- Face-to-face with your health care provider
- Local workshop (at your worksite or a health facility)
- Emailed newsletter and/or information
- Webcast – viewable on a computer or tablet
- Podcast – viewable on your smart phone or mobile device
- Phone call with care coach or educator

In terms of claims analysis for determination of medical spend differences, 51 of the 58 program participants and 480 of the 499 randomly selected non-participants remained in the analyses after elimination of those members identified as “critical risk.” The average medical spend as well as risk score for each group is depicted in Exhibit 4. As shown, the average increase in medical spend between years was 28 percent higher among non-participants than program participants.

Discussion
The purpose of this pilot study was to determine if a remote lifestyle intervention with provision of a blood pressure monitor would impact blood pressure and associated lifestyle behaviors and metrics, as well as cost savings among hypertensive-only plan members. Significant improvements were seen in both weight and perceived stress with near significant differences in diastolic BP and daily sodium intake. In addition, participating members gave very positive feedback regarding the impact of the program.

As stated previously, BP monitoring by itself can be considered an intervention. Hence, it is likely that simple awareness of BP readings led to some lifestyle behavior change. In feedback surveys, several participants made comments regarding the positive impact of increased awareness of BP due to provision of BP monitors.
With the resulting significant difference in weight and near significant difference in daily sodium intake, it is likely that members were eliminating high sodium (and often coinciding) high calorie foods over the course of the program year. This effect is often seen in nutrition and weight-loss interventions where participants are told to reduce sodium knowing that elimination of high sodium foods will also eliminate many high calorie foods.

In terms of cost savings, the average increase in medical spend between the intervention year and prior years was 28 percent higher among non-participants (59% increase in medical spend) than program participants (31% increase in medical spend). With the assumption that the participants would have also incurred a 59 percent increase in medical spend without intervention, the average spend per member per year (PMPY) in the intervention year could have been $7,153 PMPY instead of the current $5,888 PMPY (cited in Exhibit 4). With this assumption, one could argue that the estimated cost savings equals approximately $1,265 PMPY.

The first year cost savings is certainly promising toward a possible trend of long-term cost containment and even decrease in spend. Other hypertension-targeted interventions have shown similar cost savings. Most recently, one health plan-based study analyzed cost-effectiveness of a patient hypertension education intervention that provided patient education through interactive voice response (IVR) technology and distribution of automated BP monitors to high-risk plan members with uncontrolled hypertension. Using data on activity based program costs and changes in hypertension control, this study modeled the intervention’s cost-effectiveness relative to no intervention. Across 534 participants in one year, 0.3 cardiovascular events were avoided and 2.77 life years were gained (LYG). The incremental cost-effectiveness ratio (ICER) for the intervention compared with no intervention was $767 per person brought under BP control. If the gains in hypertension control from the first year investment were assumed to last 10 years, the 10-year ICER relative to no intervention would be $1,857 per LYG.

In addition, health and wellness and health risk interventions targeting hypertension have shown cost savings. Johnson & Johnson’s Health and Wellness Program has seen a long-term impact on controlling health care costs, reporting a $225 PMPY savings each year (in a four year study) through its policy, environmental, and education components addressing lifestyle risks for both hypertension and hyperlipidemia. Moreover, Henke et al. has indicated that a 1 percent reduction in health risks such as weight, blood pressure, glucose, and cholesterol risk factors would save $83 to $103 annually in medical costs per person, much of which could accrue to employers in reduced premiums.

Limitations and Recommendations

With the small scale of this pilot study, limitations certainly exist in generalizability; however, the positive results warrant several recommendations to replicate the intervention on a larger scale. Given that only a postcard was sent to a random sampling of hypertensive-only plan members for recruitment and that over 100 members chose to enroll, it is assumed that a much larger number of members would enroll in such an intervention with more communication and marketing channels.

One such channel for participation recruitment could be referral via providers in the payer network. It is likely that if members who are enrolled...
in the hypertension intervention share results with their provider not only would they, themselves, have further improvement in outcomes as encouraged by their provider, but those providers may recommend other hypertensive patients to participate as well.

Another limitation of the study is that the data is self-report. Though differences were seen in real claims spend, it would be ideal to have actual biometric and real-time behavior data to support the self-report measures. For instance, participation in the intervention could be tied to pre-post intervention biometric screenings along with exercise measured via accelerometer devices and diet measured daily or weekly via real-time food trackers. In terms of further promoting behavior change, participants could be required to view videos on controlling BP. Infusing education supporting the soon-to-be released FDA revised food labels highlighting sodium content, would be of particular value. 13

A final study limitation is that only the most current year of medical claims data could be compared with the previous program year at this point in time. Though differences are currently seen between participants and non-participants in terms of increase in medical spend, further claims tracking will be needed to see intervention sustainability throughout subsequent plan years.

In conclusion, the results of this study show a positive trend in clinical, behavioral, and medical spend outcomes for a lifestyle intervention with self-blood pressure monitoring among hypertensive plan members. It is recommended that the study intervention be implemented on a larger scale and that enrolled members are tracked for multiple years to show maximum efficacy.

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References

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