VOLUME 9, ISSUE 32 | OCTOBER 15, 2013

Orthopedics This Week

WEEK IN REVIEW

BREAKING NEWS

For all news that is ortho, read on

Orthopedic Power Rankings

Robin Young's Entirely Subjective Ordering of Public Orthopedic Companies

THIS WEEK: LANX is sold for $147 million. LDR's IPO jumps 30% on the first day of trading. Since the first of the year Globus Medical is up $640 million, NuVasive is up $440 million, Alphatec is up $25 million (oh well). In Wall Street's view spine is looking like the most attractive gal at the dance—which may actually be saying more about the other sectors of healthcare than about spine.

RANK	LAST WEEK	COMPANY	TTM OP MARGIN	30-DAY PRICE CHANGE	COMMENT
1	1	Zimmer	29.28%	7.20%	Cuts a deal with Matt Songer (Frontier Medical) for an innovative lateral MIS interbody implant. Very cool.
2	10	Exactech	10.05	7.77	Huge jump this week as Wall Street is suddenly enamored with this 18-year-old integrated orthopedic manufacturer.
3	3	Conmed	10.57	5.39	By its trading pattern it appears as though Wall Street expects CNMD to beat EPS estimates this quarter.
4	6	Medtronic	28.78	1.66	What a statement at NASS! Cautious, conservative, lumbering MDT actually grew a pair. Seriously, it was a classy leadership move.
5	2	Smith & Nephew	20.78	1.32	Big win for SNN against Arthrex. Court orders Arthrex to stop selling Bio-SutureTak and PEEK SutureTak products in the U.S.
6	4	Stryker	18.71	0.92	Closing and absorbing MAKO will occupy management for the next several quarters. Outlook cloudy for a while.
7	7	Globus Medical	28.53	4.12	The thing about Wall Street is that it is all about the cycle. Spine companies appear to be back in favor. But for how long?
8	8	NuVasive	6.30	7.01	2013 has been a very good year for investors in NUVA. Operationally, NUVA's global expansion is proceeding well.
9	9	Johnson & Johnson	26.68	0.25	JNJ remains one of the all-time great profit machines. This quarter, for example, profits will be $3.8 billion.
10	NR	Integra LifeSciences	11.70	5.95	Back on the Power Rankings after a brief respite. IART's presence at NASS was greater than expected. Good sign.

Robin Young's Orthopedic Universe

TOP PERFORMERS LAST 30 DAYS

	COMPANY	SYMBOL	PRICE	MKT CAP	30-DAY CHG
1	MAKO Surgical	MAKO	$29.85	$1,404	83.02%
2	MiMedx Group	MDXG	$4.86	$468	23.66%
3	Bacterin Intl Holdings	BONE	$0.70	$36	17.65%
4	CryoLife	CRY	$7.49	$207	17.03%
5	TiGenix	TIG.BR	$0.37	$46	14.51%
6	Exactech	EXAC	$20.25	$273	7.77%
7	Tornier N.V.	TRNX	$21.15	$1,011	7.36%
8	Zimmer Holdings	ZMH	$86.66	$14,693	7.20%
9	NuVasive	NUVA	$26.27	$1,171	7.01%
10	Integra LifeSciences	IART	$43.12	$1,211	5.95%

WORST PERFORMERS LAST 30 DAYS

	COMPANY	SYMBOL	PRICE	MKT CAP	30-DAY CHG
1	Baxano Surgical Inc	BAXS	$1.37	$62	-19.41%
2	Orthofix	OFIX	$20.00	$389	-14.53%
3	RTI Biologics Inc	RTIX	$3.93	$221	0.00%
4	Johnson & Johnson	JNJ	$89.45	$252,077	0.25%
5	Stryker	SYK	$70.22	$26,552	0.92%
6	Symmetry Medical	SMA	$8.47	$316	1.19%
7	Smith & Nephew	SNN	$62.14	$11,139	1.32%
8	Alphatec Holdings	ATEC	$1.98	$192	1.54%
9	Medtronic	MDT	$54.99	$54,851	1.66%
10	Wright Medical	WMGI	$27.47	$1,293	3.08%

LOWEST PRICE / EARNINGS RATIO (TTM)

	COMPANY	SYMBOL	PRICE	MKT CAP	P/E
1	Orthofix	OFIX	$20.00	$389	8.03
2	Zimmer Holdings	ZMH	$86.66	$14,693	14.00
3	Medtronic	MDT	$54.99	$54,851	14.94
4	Smith & Nephew	SNN	$62.14	$11,139	15.28
5	Globus Medical	GMED	$17.95	$1,667	15.92

HIGHEST PRICE / EARNINGS RATIO (TTM)

	COMPANY	SYMBOL	PRICE	MKT CAP	P/E
1	NuVasive	NUVA	$26.27	$1,171	93.82
2	Symmetry Medical	SMA	$8.47	$316	33.88
3	RTI Biologics Inc	RTIX	$3.93	$221	29.28
4	ArthroCare	ARTC	$36.33	$1,026	24.62
5	CryoLife	CRY	$7.49	$207	21.40

LOWEST P/E TO GROWTH RATIO (EARNINGS ESTIMATES)

	COMPANY	SYMBOL	PRICE	MKT CAP	PEG
1	Globus Medical	GMED	$17.95	$1,667	1.06
2	Orthofix	OFIX	$20.00	$389	1.15
3	Exactech	EXAC	$20.25	$273	1.30
4	Conmed	CNMD	$35.18	$967	1.38
5	Zimmer Holdings	ZMH	$86.66	$14,693	1.53

HIGHEST P/E TO GROWTH RATIO (EARNINGS ESTIMATES)

	COMPANY	SYMBOL	PRICE	MKT CAP	PEG
1	NuVasive	NUVA	$26.27	$1,171	9.88
2	CryoLife	CRY	$7.49	$207	5.35
3	Symmetry Medical	SMA	$8.47	$316	2.82
4	Johnson & Johnson	JNJ	$89.45	$252,077	2.79
5	Medtronic	MDT	$54.99	$54,851	2.32

LOWEST PRICE TO SALES RATIO (TTM)

	COMPANY	SYMBOL	PRICE	MKT CAP	PSR
1	Symmetry Medical	SMA	$8.47	$316	0.77
2	Orthofix	OFIX	$20.00	$389	0.84
3	Alphatec Holdings	ATEC	$1.98	$192	0.98
4	Bacterin Intl Holdings	BONE	$0.70	$36	1.06
5	Exactech	EXAC	$20.25	$273	1.22

HIGHEST PRICE TO SALES RATIO (TTM)

	COMPANY	SYMBOL	PRICE	MKT CAP	PSR
1	MiMedx Group	MDXG	$4.86	$468	17.31
2	MAKO Surgical	MAKO	$29.85	$1,404	13.67
3	TiGenix	TIG.BR	$0.37	$46	11.30
4	Globus Medical	GMED	$17.95	$1,667	4.32
5	Baxano Surgical Inc	BAXS	$1.37	$62	4.25

PSR: Aggregate current market capitalization divided by aggregate sales and the calculation excluded the companies for which sales figures are not available.

Study: NO Intentional Bias in Medtronic BMP Studies//$2 Million Grant for Penn//Massive Study Looks at Sports Injury Patterns

BY ELIZABETH HOFHEINZ, M.P.H., M.ED.

Study Finds NO Intentional Medtronic BMP Bias His national database work was nominated for "Best Clinical Paper" at NASS. Kern Singh, M.D. an orthopedic surgeon with Midwest Orthopaedics at Rush who says that he has NO involvement with Medtronic, has found no intentional bias on the part of the company or in the studies it sponsored. Dr. Singh tells *OTW*,

Photo Creation by RRY Publications LLC/Morguefile and Alvimann

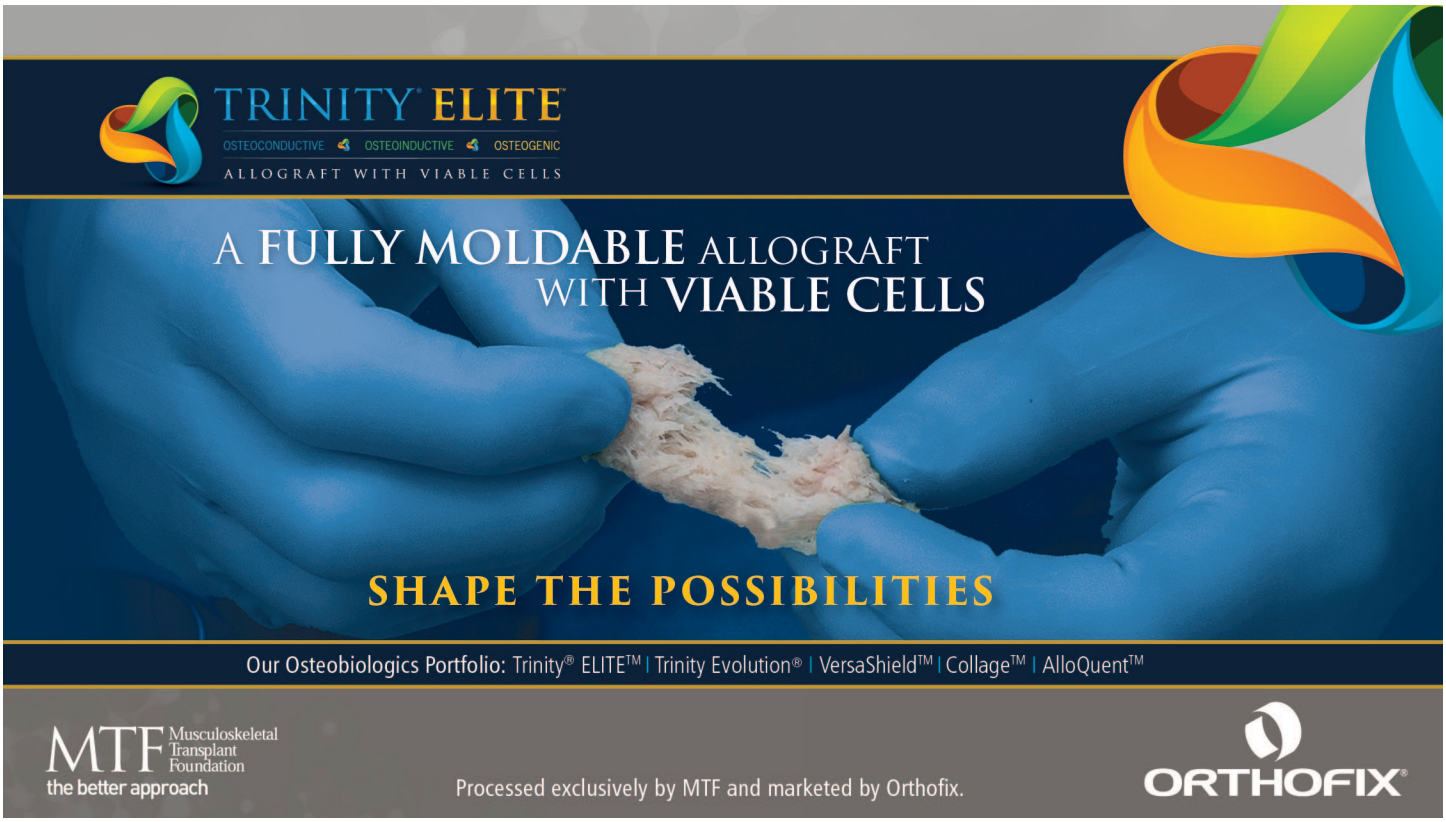
> "My colleagues and I used Medicare data, as well as a hospital database registry to look at trends in BMP from 2000-2011. This work, published recently in *Spine*, revealed a dramatic increase in the utilization of off-label BMP in back and neck surgeries. It was clear that after the FDA warning letter of 2008 there was a downward trend in the use of BMP in the cervical spine. Due to litigation concerns we are seeing a downturn in all uses of BMP because doctors are afraid that they would be sued for using it despite its effectiveness."
>
> "Then we decided to look at cost. Oddly, we saw an increase in the cost of BMP to hospitals from 2002 to 2011…even though the pricing of BMP had not changed. We had assumed that it would be viewed as a commodity with time, i.e., it would experience a valuation decrease, but that was not the case. Then we examined things from a different perspective. We conducted a systematic review of all BMP papers as related to spine from all possible angles—front, side, lateral—and did an analysis and categorization of the papers. We looked to see if the study was sponsored by Medtronic, if the surgeon was paid by Medtronic, and compared it to the date from non-conflicted studies."
>
> "To our surprise, we found that the complication rates were similar whether or not there was a conflict of interest. Essentially, from the published papers we did not find any intentional bias in the reporting of complications whether the surgeon had Medtronic relationships or not. This is contrary to the subtle innuendos that have been implied.'"
>
> "The bottom line is that Medtronic probably did not do as good a job of elucidating potential complications. Some of this may have been due to the FDA limitations of a company discussing off-label applications. At this point, unfortunately, this debate has developed into more of a personal attack as opposed to a scientific debate. And we can't ignore this question: 'Why, as BMP has become more of a commodity, has the price not decreased?' From a neutral and unbiased perspective no one party is damned, but all of these things happening in concert has resulted in this negative situation."

Massive Study Looks at Sports Injury Patterns To get to the bottom of sport-specific injury patterns you need large numbers…like 10,958. Researchers from Kaiser Permanente Medical Cen-

ter in California have reached this lofty "N" by combining two ACL reconstruction registry cohorts, from Norway and the United States, from 2004 to 2011. Gregory Maletis, M.D., an orthopedic surgeon with Kaiser Permanente, told *OTW*,

> "This is the first time that a study has been able to look at these injuries using such a large cohort. My colleagues and I set out to see if sports injury patterns associated with knee injuries after certain sports would be different. Our hypothesis was that they would be because of the differing forces on the knees in various sports."
>
> "We found that soccer was the most common sport to involve an injury thus that became our reference point. We found that basketball players sustained more lateral meniscus tears and cartilage injuries as compared to soccer players; American football players were more likely to experience multiple ligament injuries. The reason for the difference is most likely the forces on the knee at the time of injury."
>
> "While we suspected some differences would emerge, we did not anticipate the differences between basketball and soccer injuries. Many basketball injuries occur when the player lands on a hard surface—especially when the player is off balance. That mechanism of injury is more likely to involve a compression type injury causing damage to the cartilage and meniscus; soccer typically involves a noncontact injury where the player is running and suddenly pivots."

$1 Million to Jefferson Orthopedics for Joint Research A team of researchers in Philadelphia has received a major grant from the Department of Defense (DoD) in order to help create new treatments that could promote recovery and restoration of joint function for members of the military who sustain traumatic combat or combat-related injuries. In 2008, Jefferson researcher Andrzej Fertala, Ph.D., and colleagues discovered an antibody that curtailed the production of collagen fibrils after trauma. Now, he and his team will engage in this pre-clinical study to examine the effectiveness of the antibody in models that mimic post-traumatic joint stiffness. The models will post-operatively receive the antibody and will then be evaluated for its effectiveness through the measurements of collagen content and ROM of analyzed joints. Appropriate controls, which include a group treated with control antibody and a group treated with an anti-inflammatory agent, will be also employed. The team notes that the long-range objective is to reduce the joint stiffness-associat-



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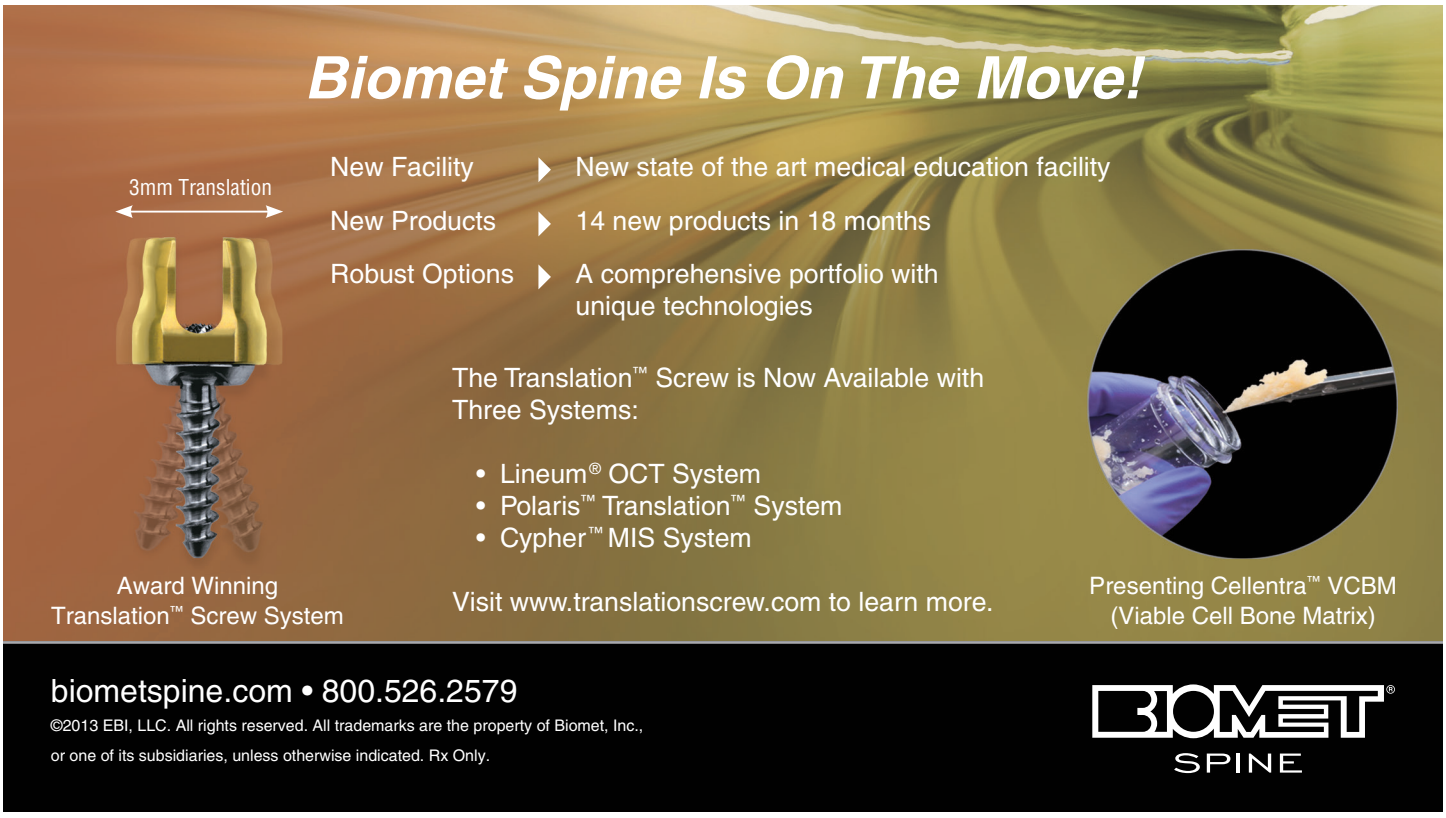
ed fibrosis that will help maintain the correct range of motion following joint trauma, and also prevent a long-term risk of developing osteoarthritis for the men and women of the military who sustain traumatic combat and combat-related injuries during their service. Dr. Fertala told *OTW*, "Our first priorities are to install a bioreactor to produce inhibitory antibodies. In addition, we will soon begin the animal-based studies; during this process participating surgeons will establish a rabbit-based experimental model."

$2 Million to Penn for Advanced Transplantation Vascularized joint transfers and other vascular tissue transfers from living donors…these things just got closer to reality. A team of researchers from Hospital of the University of Pennsylvania and the Children's Hospital of Philadelphia have been awarded a $2 million grant from the U.S. Department of Defense. The grant is part of the Restorative Transplantation Research Cooperative Agreement (RTR)—a $9.3 million consortium led by researchers at Emory University provided through the DoD's Clinical and Rehabilitative Medicine Research Program. L. Scott Levin M.D., FACS is chair of Orthopaedic Surgery at the University of Pennsylvania. Dr. Levin, Professor of Surgery (Plastic Surgery), tells *OTW,*

"These funds will help us push forward in the area of vascularized composite allo-transplantation (VCA), a procedure which gives those who have lost limbs a new lease on life. But the world of VCA is complex, and requires a seamless collaboration amongst transplant, trauma, orthopedic, and plastic surgeons."

"While at this time there are few orthopedic surgeons involved in VCA, there is, however, an enormous potential for this technology. Even with the typical immunosuppressive issues there remains a great opportunity for reconstructive surgery to aid in, for example, a destroyed elbow in a young person…something for which we currently have no good options. Conventional allograft has problems, and implant arthroplasty will not hold up long term. If we can transplant a living joint that could be a lifelong solution."

"These operations rely heavily on microsurgical skills—something that is waning in orthopedics. My hope is that once we perfect VCA beyond hand and arm, then my orthopedic colleagues will again turn their attention toward microvascular surgery. We and others have had great success with VCA procedures, thus the ultimate goal for this new research will be to elevate VCA to the level of an established therapy." ♦



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Injured by a Goat (and Other Stories From the Uganda Spine Surgery Mission) PART II

BY I LIEBERMAN, J TEICHMAN AND D LIEBERMAN

On their first day at the Mbarara hospital, the team and its leader, Dr. Isador (Izzy) Lieberman, were confronted with power outages during surgery and inadequate anesthesia. The next day proved to be as remarkable and unpredictable as the first day. In situations like this, it's really back to basics and each team member finds out what they're made of.

(Excerpts from the team blog)

Why Would You Tie Yourself to a Goat?

Sixty-seven patients later, we were done for the day. On the drive back to the hotel, we reflected on some of the cases from that day, including Bernadette, a 45-year-old woman who injured her back while pulling a goat tethered to her waist. One team member wondered aloud why anyone would tie themselves to a goat.

Quote of the day: "If you haven't mutton-busted, you haven't lived." Rob's response to the question "why would anyone tie themselves to a goat?"

Our first two surgeries were sobering examples of the importance of thinking on your feet. When things don't go as planned, improvise. Teams of longstanding colleagues (like the Texas team) work like well-oiled machines. They anticipate each other's moves, communicate effectively, share expectations and have standard procedures that help things move smoothly. Perhaps today's anesthetic troubles were not from a lack of competence, but rather from miscommunication and incongruent standard practices.

Courtesy of Ethical Sector Communications

Waiting Measured in Years, Not Weeks or Months

The first day at Mbarara was a long one for everyone, but most especially for the patients and their families. The patients sat for hours on a bench in a dark, hot, narrow hallway with minimal food and water. Many of them had travelled long distances to Mbarara just to be seen by Dr. Lieberman.

When the patients began to push their way into the small examining room, we explained sympathetically that we were moving as fast as we could. They would simply have to wait longer. I was astonished by their patience and resilience.

As the day dragged on we began to appreciate a specific luxury of North American medical care: the process of waiting. To Canadians like me and Zvi, waiting a month to see a specialist elicits a groan and some exasperated comment about "the drawbacks of universal healthcare." Waiting over an hour in an air-conditioned waiting room with cushioned seats and a Starbucks in the lobby prompts a similar reaction. Many of these Ugandan patients had lived for over 20 years with back pain. We

Uganda Spine Surgery Mission

saw teenagers and 20-somethings with spine deformities that in North America would have been corrected within the first two decades of their lives. Here, "waiting" is measured in years rather than weeks or months.

The next morning almost felt routine.

Sherri and Rob immediately started setting up the operating room and went hunting for yesterday's tools that we had sent for sterilization.

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Izzy, Zvi, Dr. Deo and I went to visit our two surgical patients from the day before. The patient's ward was in a much older, smaller building. It consisted of 8-10 private rooms which flanked a dim, narrow hallway which opened up on either end to two large common rooms. The perimeter of each large room was lined with cots draped in sheets of all patterns, colours and sizes, leaving a narrow isle down the centre. The colours were so distracting that one could easily miss the patients sprawled on the beds.

Entire families were camped out on mats between and underneath the cots. Children squat and eat from containers of food prepared at home and brought to the hospital. (The Mbarara hospital does not provide meals to admitted patients, save for malnourished children.) The cots and mats were many family's surrogate homes.

The pathologies in the surgical ward are as diverse as the bed sheets: limb amputations from motor vehicle accidents and gangrene, bowel obstructions, tuberculosis, breast cancers, malnourishment and most disturbing, and young girls with severe burns after acid was thrown on their faces. The contrast between this dilapidated surgical ward and the pristine operating theatres of the new building was astonishing.

After a quick visit with Muhamoud, our patient from yesterday afternoon, we left the surgical ward for the ICU where Amina, our first patient was recovering. We found Amina alert and sitting upright in her bed. Other than some pain around her surgical site, Amina was in fantastic shape. Our first patient, an 85-year-old woman who could barely walk a day before, would live out her remaining years with a greatly improved quality of life.

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Flat-lined in the OR

Back in the operating room, the anesthesia team was prepping our first patient of the day.

Twenty-eight-year-old Naboth was a young man who had survived a motor vehicle accident only to develop post-traumatic kyphosis (a forward bend of the spine across the collapsed bone). His surgery began dramatically. After positioning young Naboth face down on the operating table, his monitor suddenly flat-lined. Acting quickly, we flipped him over and Dr. Emmanuel (the anesthesiologist) began chest compressions while a local nursing student and I began bagging (manually ventilat-

Uganda Spine Surgery Mission

ing him with what looks like a whoopee cushion).

Then we found the problem. The canister that removes Naboth's expired carbon dioxide from his breathing gases was leaking because someone had overfilled it with soda lime beads. This meant that while Naboth was effectively blowing off carbon dioxide, he wasn't getting any oxygen in return. To make matters worse, Naboth's pulse oximeter (the device that measures his oxygen saturation) had been disturbed when he was flipped onto his belly, which meant the team could not effectively monitor his oxygen saturation (amount of oxygen in his blood).

It took a few tense moments to figure all of this out and to restore Naboth's breathing and proper ventilation. We continued with the operation as planned.

While the OR settled down, the skies outside were getting ready to burst. Before Naboth's surgery was completed a heavy thunderstorm began blowing sheets of rain down on the hospital (the first rain Mbarara has seen this dry season and therefore a cause for excitement amongst our Ugandan colleagues). Not surprisingly, Dr. Lieberman had to operate through multiple power outages all day long. Thankfully, the ventilator is on an emergency power generator. It

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1. Roche MW, Coon T, Pearle AD, Dounchis J. Two year survivorship of robotically guided medial MCK onlay. 25th Annual Congress of ISTA; October 3-6, 2012; Sydney, Australia.
2. Padgett DE, Thompson MT, Conditt MA, et al. Accuracy of robotic arm assisted acetabular cup implantation. 6th Annual MIRA Congress; May 11-13, 2011; Athens, Greece.

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was in the midst of this downpour that Dr. Lieberman, Danielle and I held our lunchtime clinic in the open-air corridor outside the operating wing.

Although punctuated by frequent power outages, the second surgery of the day went surprisingly smoothly. This was the second step for Muhamoud, our patient from the previous day. Where his first operation used an anterior (frontal) approach to carve out his necrotic bone tissue, today's operation would use a posterior (from the back) approach to stabilize and straighten his spine with screws and rods.

The Children

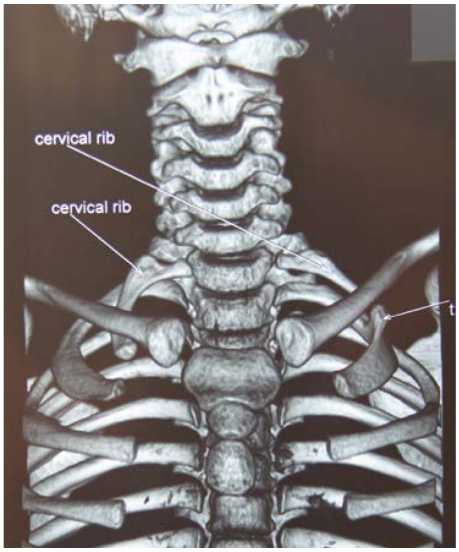
For some patients, their long-awaited visit with Dr. Lieberman brought bittersweet news: they were candidates for surgery, but would have to wait even longer. Kenneth, a short 18-year-old with a pockmarked face and a big smile, was born with severe scoliosis and has developed restrictive lung disease as a result of his rigid spine. He walks stooped over to the right because his scoliosis forces his left shoulder upwards. Unable to work with his deformity, Kenneth was hoping that an operation would restore his physical mobility and give him "purpose," as he put it. But to treat Kenneth's condition the spine surgery team would need three weeks in Uganda, and we only have six operating days here. Dr. Lieberman explained to Kenneth that he would have to wait until next year when there is the possibility of a longer mission.

Uganda Spine Surgery Mission

Prudence is a beautiful six-year-old girl who'd been born with a cervical rib, an extra rib that sits on top of the first rib and can cause the patient considerable pain.

The surgical plan was to remove the articulation (where two bones meet) between the cervical and first ribs. Dr. Lieberman would approach the rib from the left side of Prudence's neck, very close to some of the most critical nerves and vessels of the upper body. While the team prepped the operating room, I stood and chatted with our little patient. She loves to play football (American soccer) and to watch television cartoons. She used to have four siblings, but her little brother passed away last year at age one from a "hole in his heart." She was a brave little girl, staring up at the ceiling from her gurney and concentrating hard on hiding any fears about the operation.

Shortly after the surgery began, Dr. Lieberman encountered his first challenge of the day: a branch of the brachial plexus, the meshwork of nerves that provide motor and sensory function to the upper limbs and trunk, traveled directly above the anomalous cervical rib. This would require meticulously careful dissection to avoid leaving Prudence with a neurological problem following surgery. Dr. Lieberman navigated his way around the nerve and the neighbouring external jugular vein, found the cartilage and bone spicule of the articulation and resected without complication.



Uganda Spine Surgery Mission

When I went to visit Prudence in the surgical wards that afternoon, she was awake, talking, and most importantly, able to wiggle the fingers of her left hand!

At dinner that night, the team discussed some of the mishaps over the last two days and discussed how "old school" is still very important. The ability to adapt to the situation and circumstances at hand, and revert to basic skills is critical to success.

Quote of the day; "it's a good life!" Lieberman after seeing Amina on morning rounds

End of Part II
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Brief summary of contraindications and warnings:

- OP-1 IMPLANT/OP-1 PUTTY is contraindicated in patients who (1) are pregnant (2) have or have had a malignancy (3) are skeletally immature (4) are pregnant or want to become pregnant within 2 years of treatment (5) have a known hypersensitivity to the active substance or to collagen (6) have an autoimmune disease or immune suppression (7) have been previously treated with OP-1 IMPLANT or OP-1 PUTTY.
- The use of OP-1 IMPLANT/ OP-1 PUTTY may result in (1) the formation of localized ectopic or heterotopic bone outside of the treatment site (2) development of an immune response against BMP-7 or Type I collagen.
- There are no adequate well controlled studies of OP-1 IMPLANT/OP-1 PUTTY in (1) pregnant women (2) patients with autoimmune disease or immune suppression (3) patients with renal impairment.

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Who's in Charge of Safety: The FDA or Anthem Blue Cross?

BY ROBIN YOUNG

There came a point in the design of the five-year, 286 patient Pro-Disc-L clinical study where the FDA decided that patients with greater than Level 1 spondylolisthesis should not receive the implant. Here is the specific FDA guidance to physicians.

ProDisc-L is for "spinal arthroplasty in skeletally mature patients with degenerative disc disease (DDD) at one level from L3-S1. DDD is defined as discogenic back pain with degeneration of the disc confirmed by patient history and radiographic studies. These DDD patients should have **no more than Grade 1 spondylolisthesis at the involved level." (Emphasis added.)**

That was in 2006.

That particular guidance is part of the FDA's Summary of Safety and Effectiveness Data guidance for physicians.

Apparently, Anthem Blue Cross has a different point of view.

On May 13, 2013 Anthem Blue Cross issued a clinical guidance document (# CG-SURG-33) which is at best confused and at worst contradicts FDA guidance. Here's a direct quote:

> "Lumbar artificial intervertebral disc (LAID) implantation is considered **medically necessary** when **ALL** (emphasis **theirs**) of the following criteria are met:
>
> 1. Spondylolisthesis with **1 or more** of the following:
>   a. Progressive or severe neurologic deficits (for example, bowel or bladder dysfunction); or
>   b. Adults (age greater than 18) with persistent and significant symptoms, despite an adequate trial of at least 6 months of conservative care with low-grade spondylolisthesis demonstrated on x-ray;
> 2. Degenerative disc disease is limited to the single spinal level at which the LAID is planned; **AND**
> 3. An FDA approved LAID device is used in accordance with FDA labeling (including any label requirement regarding the degree of spondylolisthesis); **AND**
> 4. A single level in the lumbar spine will be treated with an LAID device; **AND**
> 5. The individual is skeletally mature; **AND**
> 6. There are no contraindications to lumbar AID device implantation, (including those listed in the FDA labeling) including, but not limited to, the following:
>   a. Active systemic infection or infection localized to the site of implantation; or
>   b. Osteopenia or osteoporosis (defined as DEXA bone density measured T-score less than -1.0); or
>   c. Bony lumbar spinal stenosis; or
>   d. Isolated radicular compression syndromes, especially due to disc herniation; or
>   e. Pars defect; or
>   f. Clinically compromised vertebral bodies at affected level due to current or past trauma; or
>   g. Lytic spondylolisthesis or degenerative spondylolisthesis of grade greater than 1"

Photo Creation by RRY Publications LLC/ FDA logo

Evidence-Based Medicine

The FDA required ProDisc L to undergo a five-year, 17 center, 286 patient, 35

surgeon clinical study. Furthermore, the study had to meet with FDA approved design characteristics including being preoperatively blinded, randomized and to incorporate an independent data analysis in order to assure that the information provided would be both clinically relevant and accurate. The effort required to meet the FDA criteria was enormous and required literally hundreds of people and tens of millions of dollars.

Anthem Blue Cross' May 13 guidance to physicians was so contrary to the ProDisc clinical study that one of the principal investigators in that study, Dr. Jack Zigler, penned the following open letter.

An Open Letter to the FDA:

Anthem Blue Cross Defies the FDA on ProDisc-L Indications

The Medical Device Amendments to the Food, Drug, and Cosmetic Act were enacted in 1976 to "provide for the safety and effectiveness of medical devices intended for human use."[1] With this direct mandate from the US Congress, the FDA's responsibility ultimately evolved into an active oversight role in the scientific testing of Class III devices, which, since 1996, have largely consisted of multicenter prospective randomized control trials comparing outcomes of an investigational device compared to an FDA-approved control device or procedure.

ProDisc-L underwent such a clinical study beginning in 2001 (PMA# P050010), ultimately resulting in FDA approval for commercialization of the product in 2006.

Concomitant with their approval of the ProDisc-L, FDA published a Summary of Safety and Effectiveness Data that is available on their website[2]. This document lists indications for use as extrapolated from the inclusion and exclusion criteria used in the multicenter prospective study. The SS&E data are used in formulating labeling which guides use of the device by medical professionals, and, until recently, by the insurance industry.

Despite FDA approval of the ProDisc-L for single level on-label usage in 2006, several major insurance companies have non-scientifically and arbitrarily continued to internally define its use as "experimental and investigational", frustrating surgeons who have watched two-year and five-year long-term outcomes data reported publicly at international meetings and then ultimately published in the peer-reviewed scientific literature[3],[4]. With no clear oversight to the insurance industry, and very poor political support from their national organizations, surgeons have fought an individual and frustrating effort against these indefensible insurance industry practices which have denied access to care for their patients.

[Insurance companies have employed other means to deny access to this FDA-approved technology to patients. Besides designing internal and self-serving definitions of "experimental and investigational," they have relied on "guidelines" which appeared, without benefit of sci-

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entific validation or review by spine surgeons or their societies. The Milliman Guidelines and the ACOEM [American College of Occupational and Environmental Medicine] Guidelines are but two examples which selectively "review" the scientific literature and then make "recommendations" for treatment algorithms that are adopted as dictum by insurance companies. These guidelines frequently rely heavily on older literature, while ignoring the more scientifically valid Level 1 data generated by FDA IDE [investigational device exemption] studies demonstrating the efficacy of both fusion and arthroplasty in appropriately-selected patients who have failed conservative care.

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Another mechanism has been the insurance industry's shift to internal peer review. Previously, second opinions were rendered by community surgeons who would interview and examine patients, review their imaging studies, and offer an independent opinion. Because this removed any control the insurance company may have had over the direction of the case, a quiet movement began in the late '90's and early 2000's, uniform across the insurance industry, which brought second opinions "in-house" with insurance company-contracted physicians.

A cadre of physicians and surgeons of uncertain qualification were retained by the insurance company to make telephone contact with the treating surgeon within a narrow window of time. In a typical phone call contact, the review physician briefly allows the surgeon to present the case, but then parrots the insurance company's policy while denying the request for surgical authorization. These often poorly-informed review physicians (not really a peer, because they are very frequently not same-specialty physicians) then offer a further appeal process so the request can be reviewed by an "in-specialty" physician, with an additional built-in time delay. When that physician again repeats the company policy and denies the procedure as "experimental and investigational," a third level of appeal can be invoked, again with a more onerous time delay to the patient. By this time, many patients have become frustrated and give up, accepting medical pain management or a lumbar fusion.]

Most recently, an even more egregious ruse has placed the insurance company above the FDA in determining indications for devices which have successfully navigated the PMA process. Anthem Blue Cross, after settling a class-action lawsuit brought by its California members for failing to authorize use of the ProDisc-L, has resorted to this new tactic. Usurping the mandate of the FDA, the insurance industry has now explored new territory with Anthem's May 2013 decision to change the inclusion criteria listed in the SS&E document for ProDisc-L, in effect changing the labeling of the ProDisc-L device[5],[6].

In the SS&E document for the ProDisc-L single level study, indications are for "spinal arthroplasty in skeletally mature patients with degenerative disc disease (DDD) at one level from L3-S1." The SS&E goes on to state "DDD is defined as discogenic back pain with degeneration of the disc confirmed by patient history and radiographic studies. **These DDD patients should have no more than Grade 1 spondylolisthesis at the involved level**." (The emphasis is mine).

Every spine surgeon understands that patients should have either no spondylolisthesis, or at worst, no more than Grade 1. Many surgeons don't realize the rationale for this inclusion, since degenerative anterior spondylolisthesis is typically a primary disease of the facet joints, causing instability and stenosis, both contraindications to ProDisc-L. This aspect of the inclusion criteria was actu-

ally placed to capture patients with less than one grade of posterior retrolisthesis, which is not infrequently seen with disc space collapse, especially at L5-S1. Degenerative retrolisthesis is the result of height loss and capsulo-ligamentous laxity, which can both be improved by mobilization and disc height restoration during ProDisc-L implantation. There was certainly no **requirement** in the IDE study for a patient to have spondylolisthesis as a condition of enrollment!

Anthem's Clinical Guideline for medical necessity of the ProDisc-L (referred to internally by Anthem as a lumbar artificial intervertebral disc (LAID) device) **now require spondylolisthesis to even consider approval of the procedure** (emphasis mine). This new requirement bypasses the scientific scrutiny used by the FDA in its approval process, over-riding it by a business decision made by insurance company executives and their internal medical directors. All the time, money, and work effort that went into a 17 center, 286 patient, 35 surgeon effort with clinical and administrative support by hundreds of other personnel now over more than 10 years of clinical follow-up has been superseded by a business decision.

Anthem Blue Cross now REQUIRES SPONDYLOLISTHESIS AS A CONDITION FOR ARTHROPLASTY. This is absolutely NOT part of the IDE study design, or its data analysis for success, nor it's labeling, nor is it contained in the FDA's SS&E statement. Anthem Blue Cross MADE THIS UP! They are, in essence, ignoring the FDA's labeling and are essentially creating their own. Should an insurance company have the right to twist the results of an IDE study and the FDA's labeling, and change the indications?

Is this a precedent we want to go unchallenged? Should an insurance company have the right to alter the labeling of any device? Is the FDA willing to allow this to happen, despite its mandate from Congress that it should be the body with responsibility to "provide for the safety and effectiveness of medical devices"?

This is a first effort by the insurance industry to blatantly overstep the boundaries of FDA labeling. I would hope the FDA will not allow this to go on without investigation. As a surgeon who has participated in FDA trials, worked with FDA on site audits, and written several scientific papers reporting on these hard-fought databases, I ask the FDA to act in the interests of our patients to protect their access to care that has been vetted through a rigorous scientific process with layers of oversight, producing some of the best scientific evidence ever generated. The scientifically proven benefits of this technology, in the appropriately-selected patient, should not be denied to patients based on non-scientific fiat by the insurance industry.

Jack E. Zigler, M.D., FACS, FAAOS
Medical Director, Texas Back Institute
Former Clinical Professor of
Orthopaedic Surgery
USC School of Medicine

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3. Zigler J et al: Results of the Prospective, Randomized, Multicenter Food and Drug Administration Investigational Device Exemption Study of the ProDisc-L Total Disc Replacement Versus Circumferential; Fusion for the Treatment of 1-Level Degenerative Disc Disease. **Spine** 32: No. 11, 1155-1162, 2007
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5. ProDisc-L SS&E Indications pages 1-2
6. Anthem Guidelines for LAID pages 1-2 ♦

Suspended and Booted From AAOS

BY WALTER EISNER

Characters portrayed are fictional and no relation to the article. / Source: leadingwithquestions.com/Kicked-Out

The Board of Directors of the American Academy of Orthopaedic Surgeons (AAOS) kicked Alfred R. Massam, M.D., out of the Academy at their June 8, 2013 meeting. They also suspended three other surgeons, including two separate suspensions for Ronald M. Krasnick, M.D. over an expert witness complaint.

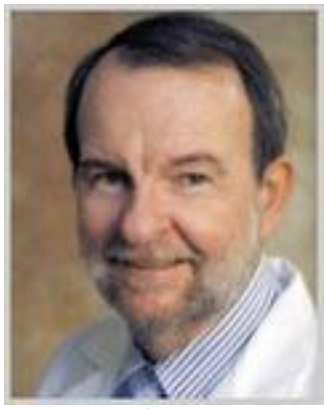
Since 2005, 29 Fellows or members have been kicked out of the Academy. What's it take to get the boot from AAOS?

Massam Expelled

According to an article in the September issue of *AAOS Now*, Massam, of Sebring, Florida, was expelled after he was found guilty in federal court of felony, theft, and embezzlement of employee benefit funds. He was sentenced to 24 months in federal prison.

Getting the boot from the Academy is a rare event. Most disciplinary actions result in suspensions and stem from surgeons failing to comply with professional sanctions imposed on them by their individual state boards.

But the most contentious disciplinary actions arise when Academy members file a grievance about expert testimony provided by one member against the other in medical malpractice cases, as was the situation with Krasnick. More on that below.



Alfred R. Massam, M.D.

We asked the Academy about their record in expelling and suspending members.

Suspensions and Expulsions

Since the Academy's Professional Compliance Program (PCP) was established in 2005, over 150 grievances have been filed. To date, less than 23% have resulted in official compliance action by the AAOS Board, including 24 membership suspensions. Seven of those suspended Fellows or members have been reinstated to full membership.

No one has been expelled from membership as a result of a professional compliance grievance. The PCP is governed by the Article VIII of the Association Bylaws and the Standards of Professionalism (SOP).

The Board has also taken compliance action in matters unrelated to the SOP. These include loss of or restrictions on license to practice medicine or license to dispense medication; felony conviction; guilty plea or no contest plea to felony charge(s). Twenty-nine Fellows or members have been expelled and 32 have been suspended. Seven Fellows or members have been reinstated to full membership status.

"The Board of Directors is obligated to take such measures in order to ensure high standards of professionalism in the field of orthopedic surgery," said AAOS President Josh Jacobs, M.D.

Josh Jacobs, M.D./AAOS President

The detailed report of Krasnick's suspensions in *AAOS Now* provides a rare insight into disciplinary actions taken behind closed door.

Krasnick Double Suspension

Krasnick of Mount Laurel, New Jersey, was suspended for violating the SOP for Orthopaedic Expert Witness Testimony after accusing fellow AAOS members of deviating from standards of care. The members (Grievants) then filed grievances against Krasnick.

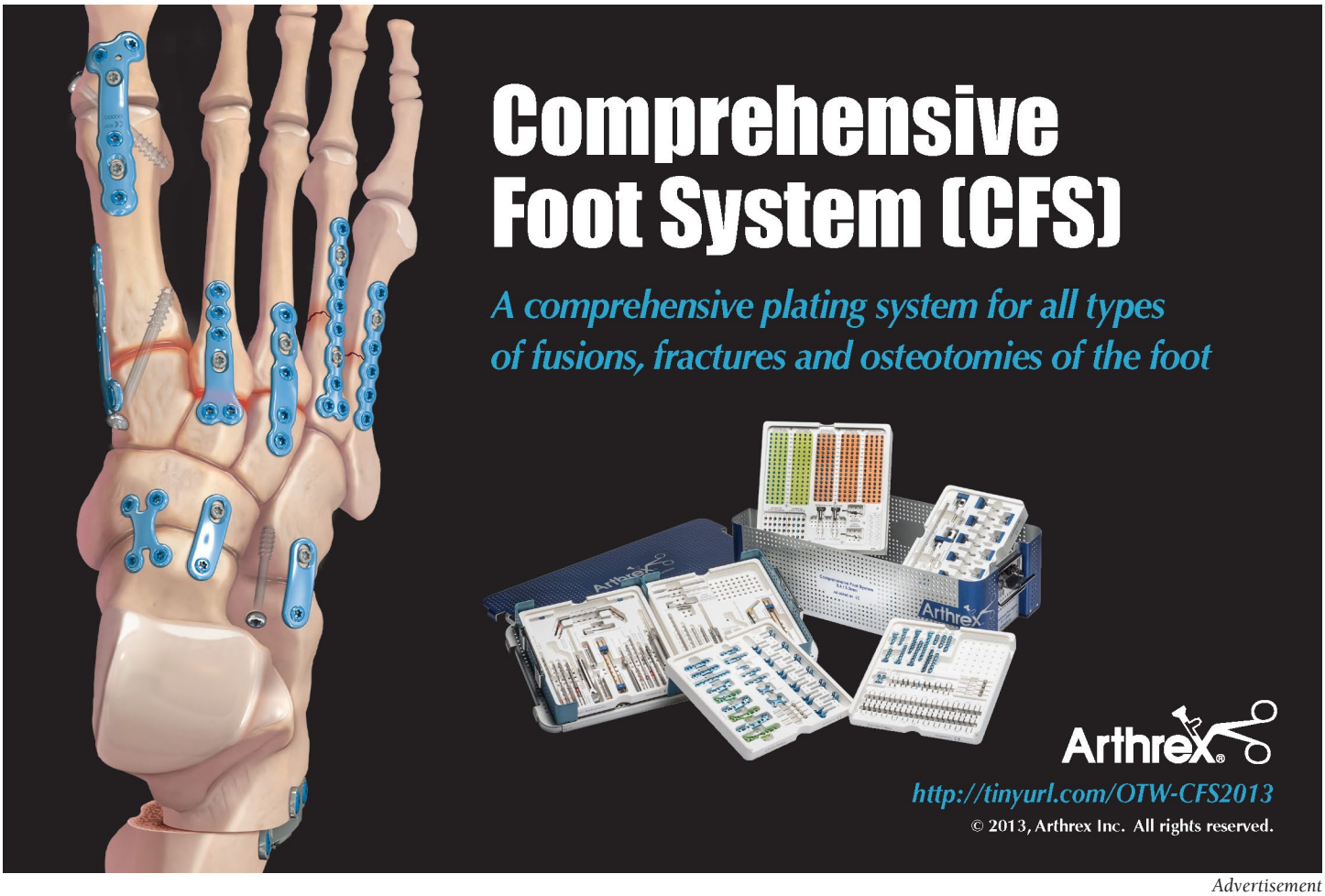
The Academy's Grievance Panel found Krasnick's conclusions erroneous and determined he was guilty of failing to evaluate the patients' medical conditions and care in light of the generally accepted standards at the time. The Panel also noted that Krasnick failed to produce any scientific literature to support his conclusions.

First Grievance

The first grievance was filed on October 7, 2011, for statements Krasnick made during deposition testimony on behalf of a plaintiff in a medical liability lawsuit. The plaintiff-patient alleged that she received second-degree burns during an arthroscopic shoulder procedure performed by the Grievant. The lawsuit was dismissed with prejudice after a settlement was reached.

According to *AAOS Now*, the patient underwent right shoulder arthroscopy and arthroscopic subacromial decompression for rotator cuff tendinitis. At the first postoperative visit, the patient had a burn with blistering over the top of the shoulder. The surgeon broke the blister, removed the superficial dead skin, and applied Silvadene.

The Grievant did not know how the patient sustained the burn. The skin was washed after the surgical proce-



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dure and the area had not been taped. He speculated that an allergic reaction might be the cause. The patient was to return four days later, but did not return until three weeks later, at which time the burn appeared to be healing nicely.

In the interim, the patient had seen a dermatologist, who also treated the burn with Silvadene. The dermatologist had diagnosed second-degree burns, possibly related to contact with a hot instrument during surgery.

In his expert report, Krasnick stated that a burr, a shaver, or a trocar may have caused the burn. He opined that the burr will get hot enough to cause second-degree burns because of the "phenomenal" speed of rotation.

He stated that the trocar could get hot from sterilization, immersion in a hot fluid, or exposure to a heat source. However, he later acknowledged that the instruments used in the patient's surgery had been autoclaved two to four days prior to the procedure and could not have caused the burn.

He added that the shaver's light attachment could have burned the patient's skin or could have been put down for a split second, thus branding the skin.

Krasnick testified that the Grievant deviated from the standard of care by not referring the patient to a plastic surgeon for the treatment of her burn and by breaking the blister, which aggravated the situation and had consequences in terms of a greater scar.

Grievance Hearing

During a July 20, 2012, grievance hearing, the Grievant was asked about possible scenarios for the burn. He confirmed the type of dressing used and said that no electrocautery was used during the procedure; that the draping was very wide; and that it is his practice to personally prep the shoulder, suture the incision, clean the shoulder, and place the dressings and slings in arthroscopic shoulder procedures.

When asked by about the heat generated by the burr's rotation, Krasnick replied that he did not have any scientific data, but that the rotating burr gets very hot and if it is put against the skin, it will cause a burn. He continued that a burn of this size and significance was a deviation from the standard of care. He added that he had performed the occasional shoulder arthroscopy, but that most of his experience had been with knees.

The Panel found that Krasnick violated two standards of the SOP. He was not found to violate a third standard.

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They also considered Krasnick's erroneous conclusion that the Grievant must have deviated from the standard of care because the patient experienced a thermal injury as a complication of the surgery, even though he could not determine with any degree of certainty how this may have occurred. Krasnick provided no literature to support his statements that the burr could reach the boiling point and brand the patient.

The Panel recommended that Dr. Krasnick be suspended from the AAOS for one year. On June 8, 2013, the Board upheld the findings.

Second Grievance

A second grievance was filed by two Fellows against Krasnick on August 11, 2011. The grievance arose from statements Krasnick made in a lawsuit that involved complications following bilateral total hip arthroplasty (BTHA). The lawsuit was concluded through an arbitration proceeding, which found the defendants not negligent.

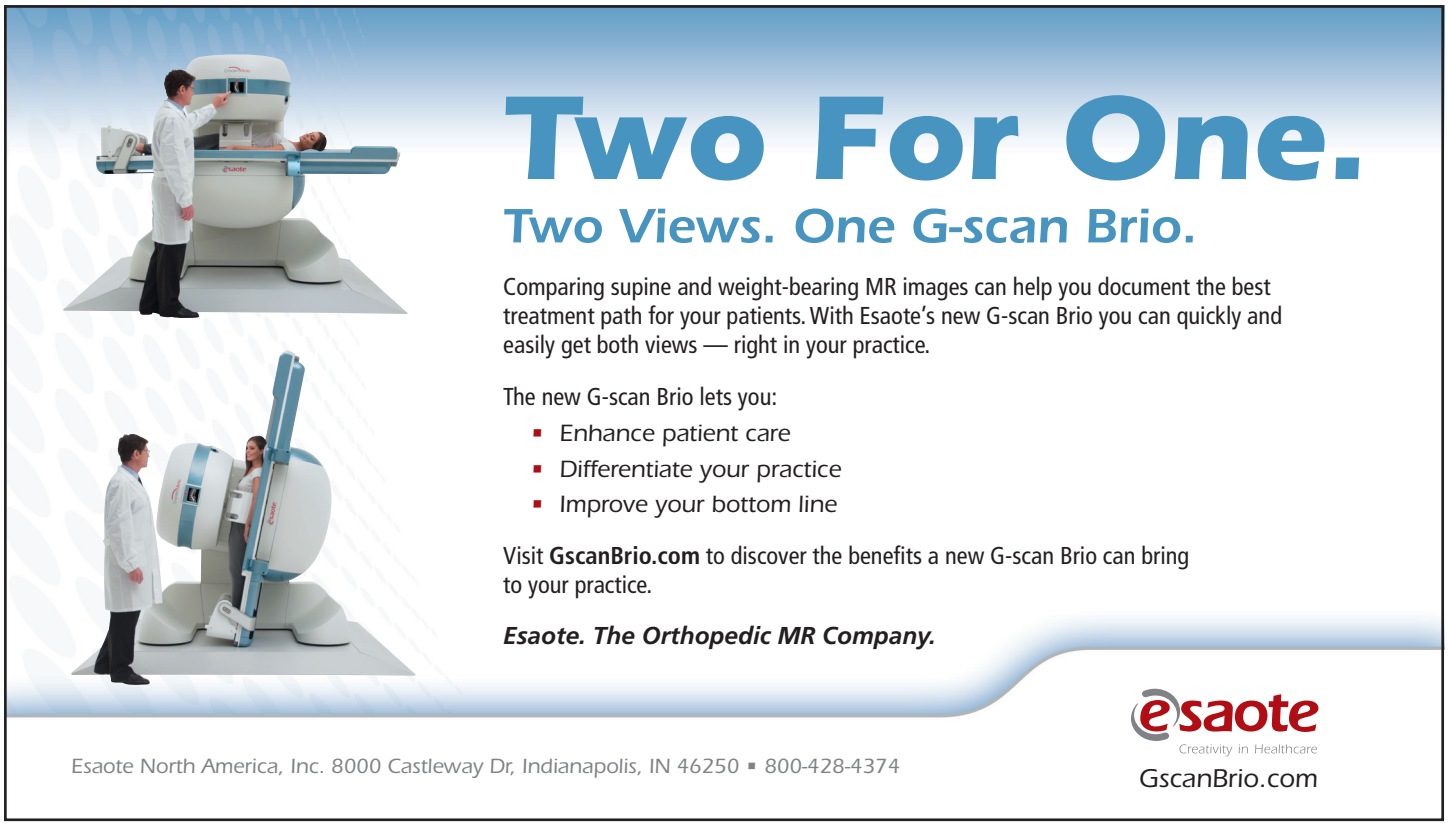
According to *AAOS Now*, the patient was first examined by Grievant #1 for bilateral hip pain and restricted function, for which oral medication was minimally effective. Although an appropriate candidate for BTHA, the patient deferred surgery for three years. On her discharge to the rehab facility, postoperative incisions were clean and dry with scant drainage from the left hip. She returned to the emergency department (ED) later that day and was diagnosed with toxic metabolic encephalopathy secondary to her current medications.

The patient returned to the ED five days later due to increased swelling and incisional drainage. Her temperature was 98.5F. Three days later, Grievant #2 performed bilateral irrigation and débridement, exchanged the acetabular liners, and exchanged the right femoral head to correct slight instability.

Gram stains were negative for bacteria, and the wound fluid was serosanguinous and not purulent. Cultures later grew Enterococcus faecalis from broth only from the right hip and very light growth from the left hip. The left hip responded well to treatment, but increasing swelling and erythema developed in the right hip.

Grievant #1 removed the components from the right hip and inserted an antibiotic-impregnated cement spacer. A revision procedure was reportedly anticipated for six to eight weeks later, but the patient elected to transfer her care to a third surgeon for the revision.

Krasnick stated in his expert report that Grievant #1 was quick to recommend and schedule hip replacement surgery and did not offer the patient nonsur-



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gical treatment options. He further opined that the patient should not have been discharged due to the presence of drainage, which is a known sign of infection.

He also stated that the diagnosis of toxic metabolic encephalopathy can indicate an ongoing infection and that the surgeon was negligent in not obtaining an infectious disease consultation at the time. He said that upon the second admission, the patient had a 103F fever and bilateral hip drainage. He further opined that the patient's ongoing complications resulted from the negligent treatment provided by the Grievants and other healthcare providers.

The Panel found Krasnick in violation of four Standards of the SOP on Orthopaedic Expert Opinion and Testimony.

Grievance Panel Determination

The Panel determined that Krasnick's testimony was not fair and impartial. On multiple occasions, the medical records contradicted his opinions regarding informed consent, timing of surgery, notification of the surgeon at re-admission, characteristics of wound drainage, patient's temperature, and timing of the diagnosis of the wound infection.

The Panel also found that Krasnick did not have appropriate knowledge of the standard of care and was uninformed about issues such as wound drainage, indications for infectious disease consultations, and appropriate surgical care of early postoperative infection. He also did not give creditable explanations for his opinions or why they varied from accepted practices.

The Panel recommended that Krasnick be suspended from the AAOS for two years. The AAOS Board upheld those findings.

While physicians enjoy a broad immunity from being sued for their expert testimony, that immunity does not prevent discipline by the AAOS. The lessons from the Krasnick case should inform surgeons who to testify against their colleagues. ♦

For more information on the AAOS Professional Compliance Program, visit www.aaos.org/profcomp

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COMPANY

DePuy Settles California Bellwether ASR Suit

DePuy Orthopaedics, Inc. has confirmed to *OTW* that a notice of settlement has been filed in the Robert Ottman ASR metal-on-metal case that was scheduled to go to trial October 15, 2013, in the Superior Court of California, County of San Francisco.

The amount of the settlement was not disclosed.

A company spokesperson told us in an email that "ASR Hip System lawsuits are examined individually in light of the individual nature of the claims. In individual cases, the company may consider the appropriateness of settlement."

Ottman alleged that his metal-on-metal ASR hip implant caused him to suffer from several alleged side effects, including the need for revision surgery because of device failure. Ottman's case was to be the first trial in the California consolidation of ASR cases, set to begin in a couple weeks, according to court documents (DePuy ASR Hip System Cases; CJC-10-004649, San Francisco Superior Court, Calif.). Settlement details were not available.

"A settlement is encouraging," said Rochelle Rottenstein, principal of the Rottenstein Law Group. "If DePuy and J&J are interested in settling these cases, and they are offering reasonable settlement amounts, then victims might see money to compensate them for injuries much sooner than if each person has to take his or her case to trial."

According to documents filed October 1, 2013, the parties have two months to file a request to dismiss the case.

In addition to the California bellwether hearing, other ASR trials are scheduled take place in state courts in New Jersey, Florida, Chicago and Los Angeles in the coming year. Each of the 11,500 plaintiffs who filed a DePuy hip lawsuit would have the right to refuse a settlement and opt for a trial if they believe a jury verdict may be higher than the proposed accord amount.

In March, a California state court jury awarded $8.3 million to ASR implant recipient Loren Kransky. The Kransky case was the first trial regarding the DePuy ASR. In April, an Illinois jury ruled in favor of DePuy in the second trial. Meanwhile, rumors persist that the company is contemplating a $3 billion global settlement of pending cases. The rumored settlement would resolve up to 11,500 ASR lawsuits, suggesting the average settlement would be about $300,000 per case.

—WE (October 10, 2013)

RRY Publications LLC.

Biomet Reports Profits and Acquires Lanx

Biomet, Inc. reported making a profit in the last quarter and doubled down on the spine business.

The day after announcing the $147 million acquisition of Lanx, Inc., the company reported a 3.3% increase in 2014 first quarter revenue to $730.7 million. Excluding currency, net sales increased 4.3%. Net income was $31.1 million versus a $31.5 million loss in the previous year's first quarter. The company also reported paying $5 million for the medical device tax during the quarter and $6 million for litigation. Net debt increased slightly for the previous quarter to $5.62 billion.

Binder: "A Great Start"

Jeff Binder, Biomet's president and CEO, said on October 8, 2013, that the company had a great start to their fiscal year. He cited an uptick in first quarter hip and knee sales with worldwide constant currency growth at 4% and 5%, respectively, despite having one less selling day in the quarter. "Our sports, extremities and trauma (S.E.T.) sales remained strong during the quarter with double digit growth worldwide. And, we started this week on a high note with yesterday's press release announcing the signing of a definitive agreement to acquire Lanx, Inc., a leader in minimally invasive spine technologies."

On a reported basis, knees and hips were up 3.5% and 1.9%, respectively. S.E.T. sales climbed 17.4%. Spine, however, declined by 6.6%.

Lanx, Inc.

Adam Johnson, president of Biomet Spine, Bone Healing & Microfixation, said the agreement to acquire Lanx is "a key step in the fulfillment of our strategic plan. The resulting increase in scale, expansion of our product portfolio and infusion of talent will accelerate our efforts to be the partner of choice in spine for distributor partners, hospitals and the spine surgeons we serve."

Biomet, Inc. Corporate Headquarters

Biomet 1Q 2014	Sales $ in million	% Change
Total Reported Sales	**730.7**	**3.3%**
Knees	225.1	3.5%
Hips	149.7	1.9%
Sports, Extremities, Trauma	149.5	17.4%
Spine & Bone Healing	101.6	down 6.6%
Dental	53.9	down 5.4%
Biologics and Other	50.9	2.0%

Source: Biomet, Inc.

Wells Fargo analyst Larry Biegelsen estimates that Lanx likely has between $80 million to $100 million in annual sales. "We estimate that Biomet had worldwide spine sales of approximately $160 million during fiscal 2013 (ended May) which represents close to 2% market share. We believe the combined company will have about 3% share of the $9 billion worldwide spine market."

Healthy Markets

Bank of America analyst Bob Hopkins said he took away three things from the quarterly conference call with the company.

One, the hip, knee and extremities markets are healthy. Despite competitive launches from Zimmer Holdings, Inc. and Johnson & Johnson, Hopkins said Biomet's same day knee sales growth went from 0% to over 6% over the previous quarter.

Two, Biomet isn't acting like a company that is about to be sold. "Indeed Biomet's recent deals in trauma and spine suggest a company likely to remain independent.

No Robots

And three, Hopkins said Biomet outlined a new knee technology today that it believes can improve the patient's experience with total knees by leveraging the high level of patient satisfaction with its Oxford knee, which is derived in large part from preservation of the ACL. "Biomet plans on creating a bicruciate-preserving arthroplasty category and expects to introduce this new innovation for its Vanguard platform at AAOS (American Academy of Orthopaedic Surgeons) in early 2014 and launch the new system in fiscal year 2015."

Hopkins said this announcement is particularly interesting in light of Stryker Corporation's deal for MAKO Surgical,

Inc. "Because outcomes are already so good in hips and knees long term, innovation in ortho going forward is likely to come from technologies that reduce patient recovery times and increase the reproducibility of the procedure. Biomet believes that can be done without a large piece of capital and with new knee approaches like the one described above, while Stryker clearly sees the robot as the best way to drive this type of innovation."

—*WE (October 13, 2013)*

ISTO Cartilage Regeneration Trial Completes Enrollment

ISTO Technologies, Inc., one of the companies in search of the Holy Grail of orthopedics—cartilage regeneration—has completed enrollment of its Phase 2 NuQu clinical trial. The trial is evaluating the efficacy and safety of NuQu, a cell-based therapy for the treatment of degenerative spinal discs.

"Promising and Transformational"

Domagoj Coric, M.D., of Carolina Neurosurgery and Spine Associates and principal investigator of the trial said, "As a cell-based technology, NuQu is very promising and is potentially transformational for a large patient population, enabling pain relief without an invasive surgical procedure. It is the goal of the therapeutically-diverse investigators involved in the trial to evaluate this potential therapy for patients who do not respond to conservative treatment."

Alternative to Surgery

According to the company, 12.5 million Americans experience chronic back pain each year. Approximately 70% or 8.5 million of those require surgery to correct disc herniation and/or relatively advanced vertebral deterioration. The remaining 30%, or 4 million people, experience less severe deterioration, and are not yet considered surgical candidates. Of these, 85% respond well to repetitive, continued conservative therapy, while the remainder, approximately 10-15%, do not respond to conservative therapy and are excellent candidates for NuQu.

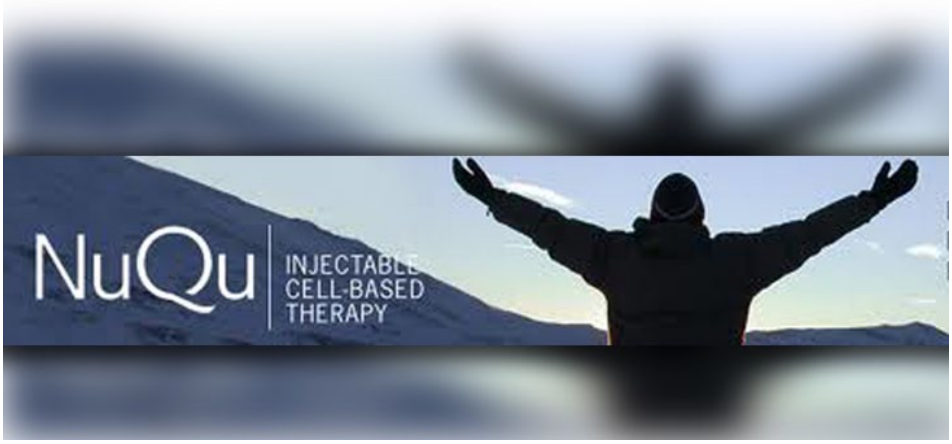
NuQu is currently delivered in clinical trials in a single-use, minimally invasive, out-patient procedure, and it is anticipated that this will remain unchanged upon commercialization. ISTO Technologies believes that the potential regenerative characteristics of NuQu and its "patient-friendly" method of delivery will be viewed favorably by insurance payors as a viable and cost-effective alternative to surgical procedures for those suffering from chronic back pain.

Many patients with back pain show degeneration of cartilage in their intervertebral disc. Typically, says the company, therapeutic treatment begins with conservative measures, such as bed rest, chiropractic care, physical therapy, spinal injections and/or medications including opioids. All of these methodologies are geared toward facilitating movement and relieving pain, but none restore the biology of the disc, and in many patients, will not prevent advancement of disability and the eventual need for surgical correction.

Roger Härtl, M.D., of Weill Cornell Medical College and a NuQu clinical investigator, said "As a regenerative therapy, NuQu marks the beginning of an exciting era. Because it is aimed at restoring cartilage in the disc, without altering the structure of the vertebral column, NuQu may not only heal degeneration, but may also prevent progression of spinal disease to multiple levels."

NuQu – Juvenile Cartilage Cells

ISTO's cell-platform technology harnesses the potency of juvenile cartilage cells, called chondrocytes. Scientific data has demonstrated that when compared to adult cells, cartilage produced by juvenile chondrocytes shows 100-fold higher content of proteoglycan, which is a type of protein critical for the development of cartilage connective tissue. This results in greater cartilage matrix production, and maximizes the opportunity to heal cartilage injuries in a variety of clinical settings.



NuQu/ISTO Technologies, Inc.

Mitchell Seyedin, Ph.D., president and CEO of ISTO, said, "NuQu utilizes juvenile cartilage cells that are not only remarkably prolific, but are programmed to produce cartilage in the spinal disc, an environment with no vascular supply. This is not possible with other cell types."

The company's October 7, 2013 announcement directs readers to clinicaltrials.gov for updates. But, of course, with new clinical trials and new device submissions held hostage by the government shutdown, the site is not current.

—*WE (October 8, 2013)*

Advertisement

MAKO Swallows Manufacturing Partner

MAKO Surgical Corp. is buying Pipeline Biomedical Holdings, Inc., before being acquired by Stryker Corporation.

Pipeline has been MAKO's partner since 2010. The company has developed and supplied advanced implant technologies for use with MAKO's RIO Robotic-Arm Interactive Orthopedic system, including the proprietary MAKO-branded RESTORIS PST Cup and Tapered Stem hip implant system for use with the RIO's MAKOplasty Total Hip Arthroplasty software application.

The acquisition, according to an October 2, 2013 announcement includes substantially all of Pipeline's business dedicated to the design, development, manufacture and commercialization of orthopedic devices and related instruments for use with both robotic devices and manual medical procedures.

MAKO makes money not only through maintenance agreements, but also by selling implants and instrumentation for each procedure performed. So it makes sense to own the business which makes those implants.

The purchase price for the transaction consists of a credit for a cash down payment previously paid to Pipeline in the amount of $2.5 million and the issuance of an aggregate of 3,953,771 unregistered shares of common stock of MAKO. Stryker agreed to pay $30 per share for MAKO in a deal worth almost $1.7 billion. The provision for that deal included the issuance of another roughly 4 million MAKO shares, presumably to consummate the Pipeline deal.

Stryker's acquisition announcement stated that the shares would be issued "in connection with an anticipated acquisition which Stryker expects MAKO will consummate as part of MAKO's normal course of business."

The transaction was expected to be completed immediately.

—*WE (October 8, 2013)*

MAKO Surgical Corp.

LEGAL

Shutdown Halts FDA Submission and New Clinical Trials

"Due to a lapse in funding, the U.S. federal government has shut down."

That's the message people get when trying to get updated information from the FDA and the Department of Health and Human Services (HHS).

While Medicare will continue to pay hospitals and physicians, device manufacturers and patients relying on new devices and therapies will not see progress from the FDA during the shutdown.

eyeonfda.com

New Clinical Trials Postponed

According to an *ABC News* blog, a shutdown will mean that NIH (National Institutes of Health) will not be able to accept new patients into clinical trials nor will new trials be able to begin. Per another posting, this means 640 trials will not be accepting new patients.

Submissions Halted

The agency has furloughed 6,620 employees and until operations resume, will NOT collect any 2014 user fees and will NOT be able to accept any new regulatory submissions that require a fee payment.

According to an October 1, 2013 "Industry Notification: Furlough" posting on the agency's website:

"In the absence of either an FY 2014 appropriation or a Continuing Resolution for FDA, beginning on October 1 and continuing until the date of enactment of an FY 2014 appropriation or Continuing Resolution ("lapse period"), agency operations will be limited to the following:

- *Emergency work involving the safety of human life or the protection of property;*
- *Criminal law enforcement work; and*
- *Activities funded by carryover user fee balances, including user fee balances under the Prescription Drug User Fee Act (PDUFA), Generic Drug User Fee Amendments (GDUFA) , Medical Device User Fee Amendments (MDUFA), Animal Drug User Fee Act (ADUFA), Animal Generic Drug User Fee Act (AGDUFA), and Family Smoking Prevention and Tobacco Control Act. Carryover user fee balances will only be spent on activities for which the fees are authorized under the Federal Food, Drug, and Cosmetic Act (FD&C Act).*

"With respect to medical product user fees, during the lapse period, FDA will not have legal authority to accept user fees assessed for FY 2014 until an FY 2014 appropriation for FDA is enacted. This will mean that FDA will not be able to accept any regulatory submissions for FY 2014 that require a fee payment and that are submitted during the lapse period."

Routine Safety Activities Halted

In an HHS contingency plan for the shutdown, the FDA will be "unable to support the majority of its food safety, nutrition, and cosmetics activities. FDA will also have to cease safety activities such as routine establishment inspections, some compliance and enforcement activities, monitoring of imports, notification programs (e.g., food contact substances, infant formula), and the majority of the laboratory research necessary to inform public health decision-making."

As information about specific regulatory submissions, cancelled agency meetings, impacts on clinical trials and inspections come available, we will report them to our readers.

—WE (October 3, 2013)

LARGE JOINT

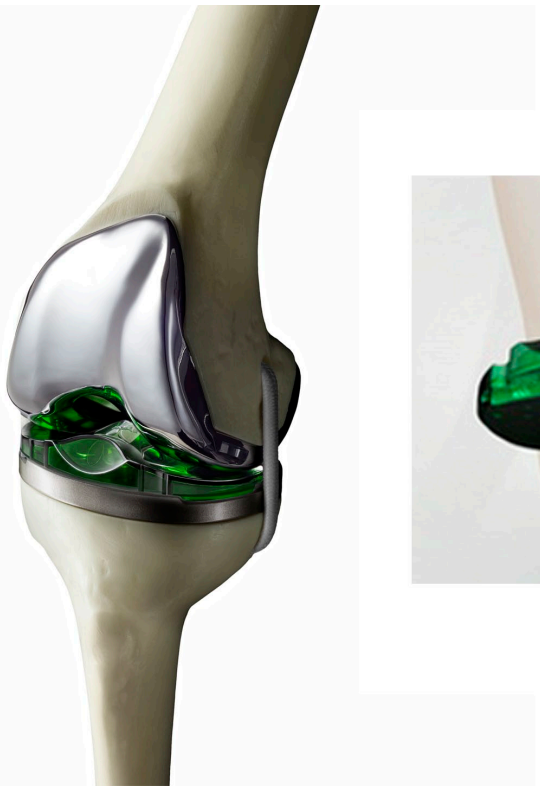
Europe Approves Verasense Knee System

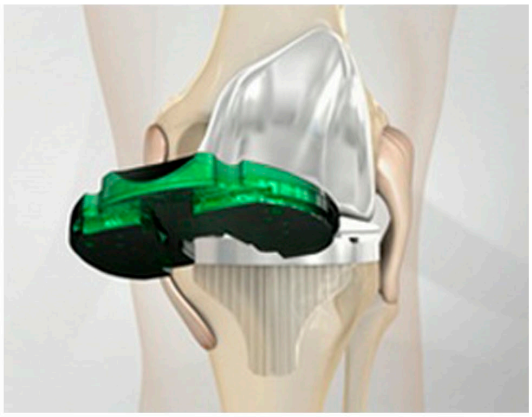
OrthoSensor, Inc. has received the CE Mark approval for its Verasense Knee System and is planning to soon launch its product in European markets. The Verasense Knee System is a single-use instrument system that, according to company officials, replaces the standard plastic tibial trial spacer used during knee replacement surgery. Company officials claim that the system's proprietary software and sensor and data communications technologies empower surgeons to make evidence-based decisions regarding component placement, limb alignment and soft tissue balance to achieve balance and stability through a full range of motion. Verasense integrates seamlessly into the surgical workflow and is compatible for use with multiple leading knee implant systems.

"We're pleased to have successfully achieved CE Mark for our Verasense technology. This enables us to provide OrthoSensor's innovative technology to orthopaedic surgeons and patients in markets outside the US and creates significant growth opportunities for our business," said company President and CEO Jay Pierce. "It's a vital step toward expanding our business internationally."

OrthoSensor, Inc. develops and commercializes intelligent orthopedic devices and data services that provide quantitative feedback to surgeons and hospitals during surgery and post-operatively.

—BY (October 8, 2013)





Courtesy OrthoSensor, Inc.

Exercise, Alone, Didn't Cut It

Which is better—diet or exercise—in the treatment of knee osteoarthritis? Diet came out better than did either alone for obese patients, according to an 18 month trial conducted by Stephen P. Messier, Ph.D. of Wake Forest University, Winston-Salem, North Carolina. However, joint inflammation, pain, function, and quality of life all significantly favored those who followed the combined approach of diet and exercise.

Wikimedia Commons and Elpadawan

According Crystal Phend, Senior Staff Writer, *MedPage Today* the trial included 454 community-living participants ages 55 and older who had mild or moderate knee osteoarthritis and a body mass index in the 27 to 41 kg/m^2 range. The analysis included the 399 participants (88%) who stuck out the program to month 18.

The mean weight loss of the participants was 11.4% of body weight in the combined diet and exercise group compared with 9.5% in the diet-alone group and 2% in the exercise-alone group, Phend reported. The goal for all groups was a weight loss of 10% or more. All of the patients had a sedentary lifestyle at the beginning of the trial.

Amanda E. Nelson, M.D., MSCR, a rheumatologist at the University of North Carolina at Chapel Hill, told *MedPage Today* "This gives us some real guidelines for what kind of change needs to happen to be meaningful. We can tell patients if they're going to lose 10% of their body weight, they can expect these kinds of benefits and in order to do that the kind of diet restrictions and the kind of exercise regimens that are required."

Most of the patients in the trial had relatively mild pain at baseline (a mean of 6.5 on a 20-point scale), which left little room for improvement. However the pain was sufficient to lead the researchers to believe it helped the participants adhere to the exercise regimen.

—BY (October 3, 2013)

California's Reference Pricing Cuts Charges

Until recently there has been little incentive for hospitals to reduce the fees they charge for procedures such as hip and knee replacements. Then, about one year ago, the California Pubic Employees Retirement System took on hospitals in the state in regard to the fees they were charging for replacements. It did that through a program called "reference pricing", adopted in 2011. As reported by Peter Ubel, in *Pharma & Healthcare*, the administration told California public employees that they could use any hospital and any orthopedic surgeon they wanted for a hip or knee replacement but their insurance would cover only $30,000 of the hospital expenses.

If an employee wanted to use a hospital and surgeon who charged more than the $30,000, he was free to do so but he would have to pay the extra cost himself. The results have been dramatic with the price of implant procedures dropping by more than 25%. Hospitals known as "high price hospitals" lost more than 20% of their implant business from the public employee population. Lower price hospitals saw their business go up.

Ubel reported that, in response to their lost business, high-priced hospitals dramatically reduced their fees. Not surprisingly, the new fees came in just under $30,000. Reference pricing may turn out to be one of the most powerful ways to reduce the price of healthcare in the U.S., Ubel suggested.

—BY (October 3, 2013)

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EXTREMITIES

Nerve Repair Device Study Completed

Just completed is a two-year follow-up of a controlled, randomized, blind multi-center study of peripheral nerve repair using Integra LifeSciences Holding Corporation's NeuraGen Nerve Guide. The Nerve Guide is a semi-permeable, resorbable Type 1 collagen tube designed for nerve repair. The study compared the NeuraGen Nerve Guide to direct suture in patients who had traumatic injuries to their median or ulnar nerves.

Integra Life Sciences Holding Corporation

Thirty-two patients, who were routinely examined for sensory and motor electrophysiological function, post-operative pain assessments and overall hand function, completed the two-year post-operative period.

Results of the study showed that operation time using the collagen conduit was significantly shorter than was performing a conventional repair. Patients who received NeuraGen Nerve Guide had lower post-operative pain than those treated with direct suture repair. The overall study conclusion was that entubulation nerve repair using the NeuraGen Nerve Guide was as effective

a method of joining severed nerves as was direct microsurgical suture.

Integra's Chief Scientific Officer Simon Archibald said, "The successful completion of the NeuraGen Nerve Guide clinical trial is the culmination of over 30 years of basic science and clinical translation efforts by a wide range of industrial and academic collaborations across Europe and the United States. The clinical follow-up of nerve repair is a long and exacting task; the entire team is to be congratulated on completing this 10-plus year investigation."

Michel Boeckstyns, M.D., and colleagues, presented the study titled *A Collagen Conduit vs. Microsurgical Neurorrhaphy. Two-Year Follow up of a Prospective Blinded Clinical and Electrophysiological Multicenter RCT, , at the Annual Meeting of the American Society for Surgery of the Hand in the Best Papers segment at the 68th Annual Meeting of the American Society for Surgery of the Hand*, October 3-5, 2013, San Francisco, California.

—BY (October 8, 2013)

TRAUMA

Repeating BMD Tests Shows Little Benefit

Repeating bone mineral density (BMD) tests after four years provides little clinical benefit when assessing bone fracture risk in seniors age 75 and older, according to a recent study led by researchers at the Harvard Medical School-affiliated Institute for Aging Research at Hebrew SeniorLife. The study appears in the September 25 online issue of *JAMA*.

Currently, there are no established guidelines for the appropriate time interval between BMD tests. Medicare pays for BMD screening every two years without restricting the number of repeat tests and regardless of baseline test results.

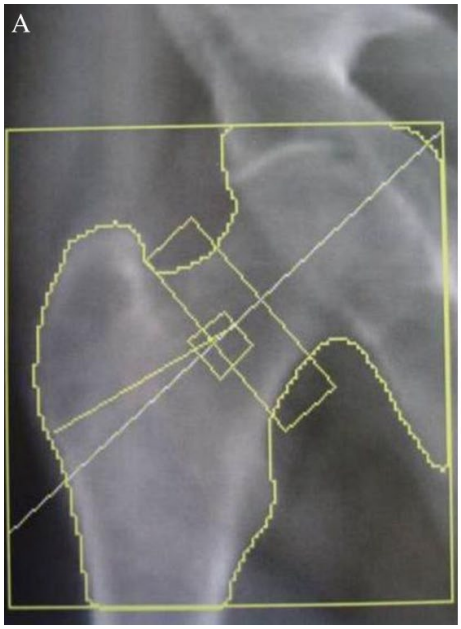
"Given the drive to control health care costs while improving quality of care, we wanted to determine whether repeating a BMD screening test is useful," explained Sarah Berry, M.D., M.P.H., the study's lead author, in the September 24, 2013 news release.

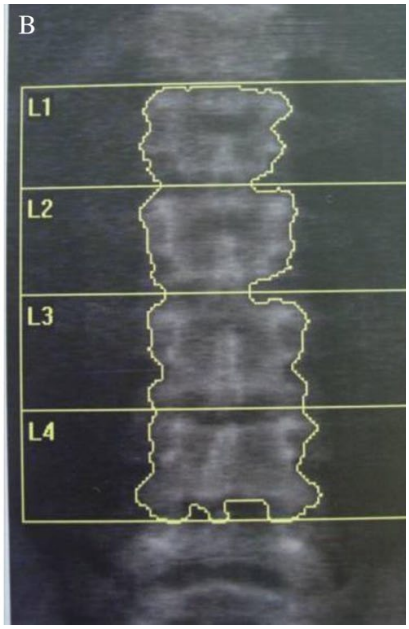
Dr. Berry and her colleagues studied 310 men and 492 women whose BMD was assessed twice between 1987 and 1999 as part of the Framingham Osteoporosis Study. This ancillary study of the Framingham Heart Study was led by Dr. Douglas P. Kiel, one of Dr. Berry's co-authors.

"Our research, which was made possible through the routine clinical examinations performed as part of the Framingham Heart Study, tells us that the initial BMD test does a very good job of identifying people at risk for fracture," Berry said. "The current clinical practice of repeating the test every two years may not be necessary in adults over age 75 who aren't being treated for osteoporosis."

BMD is included in the Fracture Risk Assessment Tool (FRAX), a widely used calculator that estimates the 10-year risk of major fracture related to osteoporosis. The tool also considers clinical characteristics, such as age and fracture history, which are fracture risk factors. "Instead of repeating the BMD test, we recommend that providers update the patient's clinical characteristics in the tool at the time of the visit to reassess fracture risk," Dr. Berry said.

—EH (September 30, 2012)





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SPINE

Cartilage Regeneration Technology Awarded Patent Protection

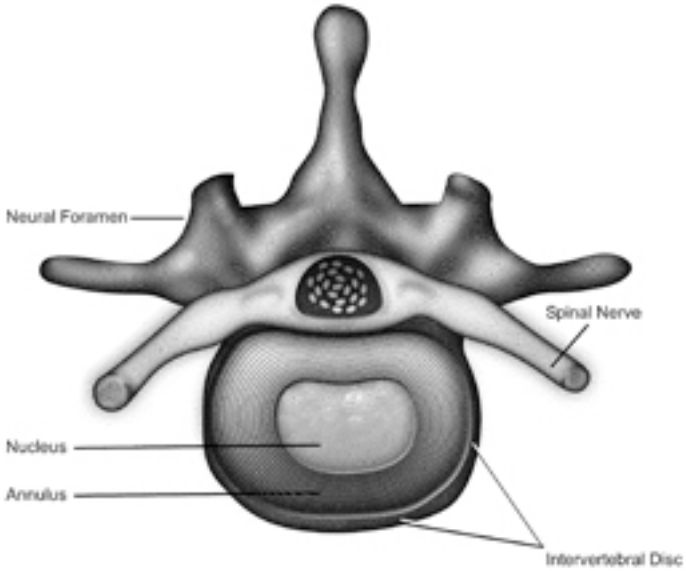
A Houston-based spinal technology company focused on autologous regrowth of the spinal disc nucleus using human dermal fibroblasts, has received a Notice Of Acceptance on its patent application from the Australian Patent Office. The company is SpinalCyte, LLC, founded in 2007 to develop a cartilage regeneration technology using autologous dermal cells harvested from the patient.

The title of the patent application is "Methods and Compositions for Repair of Cartilage Using An In Vivo Bioreactor" to regrow the spinal disc, using human dermal fibroblasts. The allowed claims include the use of human dermal fibroblasts from the patient's own body, to regrow the nucleus of the spinal disc in vivo.

"This is the sixth international patent in our growing patent portfolio and it distinguishes SpinalCyte as a world leader for regeneration of the spinal disc," said Chief Executive Officer Pete O'Heeron. "This is our second Australian Patent and we are excited the Australian Patent Office continues to validate the uniqueness of our technology. Regenerative medicine is leading the rapidly growing movement toward biologics, cell therapy and gene therapy and we believe our focus on autologous regrowth of cartilage will provide an eventual cure for all forms of cartilage degradation."

The nucleus pulposus is a gelatinous material which consists of chondrocytes, collagenfibrils, and proteoglycan aggrecans. It acts as a cushion or shock absorber to the spinal column, functioning to distribute hydraulic pressure in all directions within each disc under compressive loads.

—BY (October 7, 2013)



Courtesy of SpinalCyte, LLC

PEOPLE

John Brown Receives First-Ever AdvaMed Lifetime Achievement Award

Stryker Corporation Chairman Emeritus John Brown has received the first-ever AdvaMed Lifetime Achievement Award.

John Brown/Stryker Corporation

The award was presented during AdvaMed's annual MedTech Conference in Washington, D.C. on September 25, 2013.

Brown graduated from Auburn University and began his career in 1957 as an engineer for the aluminum manufacturer Ormet Corporation, before moving on to the Thiokol Corporation, where he worked on rocket propellants. After an industry slump, he moved to Squibb Corporation, where he assumed a variety of positions and in 1972 became president of one of its subsidiaries, Edward Weck & Company—which, at the time, was a struggling medical device manufacturer. During his five-year tenure, he doubled its sales and tripled its profits.

Stryker Corporation

His success at Edward Weck & Company brought him to the attention

of Homer Stryker, M.D. In 1977 he became Stryker's president and chief executive officer. Brown immediately set out three goals that would determine the future of the company—to take Stryker public, to grow earnings per share 20% every year, and to drive growth through acquisitions and operational excellence—all of which he accomplished. In his first year at Stryker, Brown developed the strategy that would drive the company to achieve the longest sustained profit growth of any medical technology company.

In May 1980, after the death of Homer Stryker, Brown was named chairman of the board. Although he retired as company CEO in 2004, he remained chairman until 2009, and today serves as chairman emeritus.

"It is an honor to be recognized by fellow peers and colleagues throughout the medical technology industry. It is my hope that this recognition will serve to inspire future generations of medical technology executives to appreciate that, with a commitment to saving lives and creating jobs, our industry is of unmatched value to America," said Brown.

AdvaMed Lifetime Achievement Award

The Lifetime Achievement Award highlights the contributions and accomplishments of a senior executive who has made significant advancements for the medical technology industry, its employees, and its patients. An AdvaMed statement said Brown's award is in recognition of his unparalleled and sustained activity in industry leadership, medical innovation, public engagement, and corporate philanthropy.

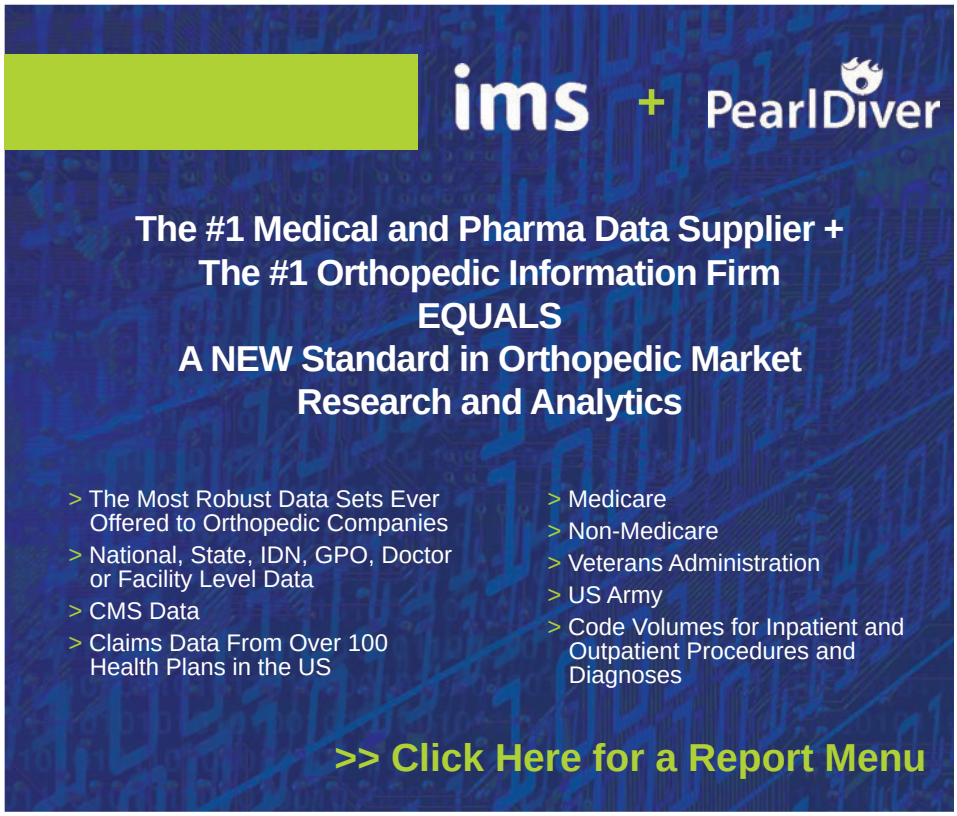
"AdvaMed is extremely proud to honor John Brown with the AdvaMed Lifetime Achievement Award," said Stephen J. Ubl, AdvaMed president and CEO. "America's medical technology industry is the beneficiary of John's legacy of leadership as the longest serving board member in the Association's history. His vast accomplishments have greatly impacted the industry and the advancement of medical technology as an essential part of America's economy." Brown served on the boards of both AdvaMed and the Health Industry Manufacturers Association, the predecessor to AdvaMed.

"Importantly, while John Brown is often viewed as a business visionary, he also is a man of unmatched character making him a clear choice for AdvaMed's first Lifetime Achievement Award," Ubl added.

Brown is a director of the American Business Conference, a coalition of Chief Executive Officers of mid-size, high-growth companies. He is also a director of St. Jude Medical, a global cardiovascular device company. He also serves as a governor-appointee on the Michigan Economic Development Committee and is a member of the Board of Directors of the Auburn University Foundation.

Brown currently lives in Kalamazoo, Michigan, with his wife, Rosemary Kopel Brown. They have two daughters and four grandchildren.

—*WE (October 3, 2013)*



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