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Medical Supplies & Technology
**North America**

# Citi's Clinic at the Clinic

## The 2014 Edition

- **Conclusion(s)** — Our 9th annual Clinic at the Clinic sessions didn't point to an alleviation of cost pressures and the implementation of episodic care will likely require significant changes in provider's models. Pharma/Biotech again dominated the debate, but we heard more skepticism this year on the prospects for some pipeline drugs and a greater need to deliver cost effectiveness.

- **Biotechnology** — Several speakers provided disappointing commentary that either revolved around skepticism whether novel products will succeed in development or forecasted disappointing use of expensive/undifferentiated drugs as cost effective critical care pathways are adopted. We heard positive comments on the PCSK9 space broadly, STX-100 and simtuzumab, Imbruvica, Otezla and dupilumab, and PARPs, mixed comments on Tecfidera, Alprolix/Eloctate, and negative comments on anti-LINGO, Eylea, Xtandi/Zytiga, idelalisib, and Gilenya. We believe AMGN and REGN fared the best while BGEN and MDVN fared the worst.

- **Pharmaceuticals** — While the ongoing roll-out of episodic/accountable care needs to be considered, Pharma again took center stage at this event behind new therapeutics for HF, cholesterol management and immuno-oncology. The Clinic's feedback points to NVS (LCZ696) and SASY's (PCSK9) being clear winners and MRK a loser (IMPROVE-IT, anacetrapib, DPP-IV heart failure signal). LLY is the potential 'dark horse' in PCSK9 and with evacetrapib.

- **Medical Technology & Tools** — The med tech sessions were once again focused on cost control as the Clinic is attempting to lower implant/disposable costs and improve efficiency. In orthopedics, SYK seems to be in a good position and there is an interesting pilot program underway for Medicare payments. MDT fared well in cardiology and while BAX, VAR, and ZMH had a tougher go of it in other sessions.

- **Managed Care** — We again heard about how much the Clinic believes the health care model will change, but little has actually changed, as less than 10% of the Clinic's reimbursement is derived from capitated contracts with health plans, consistent with recent years.

- **Healthcare Technology** — Layering on top of the Clinic's IT infrastructure was a key theme this year. Data analytics to assist in population health management, transparency tools to allow patients access to procedure pricing, and portability across intra- and inter- health systems are key opportunities for HCIT vendors.

- **Healthcare Facilities** — The Cleveland Clinic continues to see price transparency and narrow networks as a risk to their future reimbursement levels and hospital systems slowly evolving towards assuming population health risk

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See Appendix A-1 for Analyst Certification, Important Disclosures and non-US research analyst disclosures.

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# Pharmaceuticals & Biotechnology

## Alzheimer's Disease – High Unmet Need But Expectations Still Low

We hosted an Alzheimer's session for the first time this year to gain an update on current thinking, following recent high profile failures and ahead of key data read outs for a number of assets through 2014-16. The incidence of dementia in 85-90 year olds is 50%, with demographics driving an expected quadrupling of AD patients by the middle of the century (>10m in US by 2050 with current cost of disease estimated at >$200bn). AD is a global issue with the population expected to double by 2020 in US/EU, and more than double in Brazil, India and Pakistan over the same period.

The advances being made in therapeutic areas such as cancer are being driven by an improved understanding of the molecular biology of the disease. With the debate still raging amongst the "BAPtists" and "TAUists" (see below) regarding the cause of AD we await evidence that current therapies can prevent, slow or reverse progression before carrying significant pipeline forecasts. Our speaker, a director of a neurological institute, was hopeful rather than optimistic that the more recent and rationally designed B-amyloid studies involving Lilly's solenuzumab, Roche's gantenerumab and Genentech's crenezumab would prove successful in slowing/reversing the development of Alzheimer's Disease in early stage (prodromal) patients. Other therapeutic approaches being pursued include BACE inhibitors, anti-tau, vaccines, inhaled insulin, and the role of neuroinflammation in AD, as well as identification of better biomarkers and imaging techniques.

While all cases of AD involve amyloid plaques, it is still unclear whether these are part of the primary process, or secondary effects of AD. BAPtists advocate that B-amyloid is part of the pathophysiology and cite pathology, clinical data, and genetics as supporting evidence. BAPtists argue that the failed phase III trials for bapineuzumab and solenuzumab were due to the disease not being targeted at an early stage. Our speaker doesn't believe there is much differentiation with respect to the anti-amyloid betas currently in clinical development, which are targeting prodromal patients (earlier stage versus mild to moderate AD) and using amyloid PET imaging scans as well as CSF lumbar puncture assessments as clinical trial entry criteria. However, we note crenezumab is an IgG4 antibody (others are IgG1), thereby reducing the risk of microhemorrhage and neuroinflammation and allowing higher doses to be tested in the hope of improved efficacy (as defined by amyloid plaque clearance). TAUists support the role of Tau based on evidence suggesting the number of neurofibrially tangles, made up of Tau proteins, correlates with the severity of AD. While this may be the case our speaker highlighted the genetic evidence to support the Tau theory was not strong. Anti-tau agents are in early clinical development though we note the focus to date has been more on FTD (frontotemperal dementia).

Interest in the BACE inhibitor class remains despite Lilly terminating its program due to liver toxicity, and Roche suspending its program. We await data on Merck's MK-8931 though note an additional phase III study was initiated last year in a pro-dromal (earlier stage) population, in addition to the ongoing phase II/III EPOCH study in mild to moderate patients. Our speaker noted Merck is still investigating MK-8931 in the mild to moderate AD population, based on animal model systems that have not been shown to be particularly predictive. Other therapeutic areas being investigated include inhaled insulin, anti-Tau and the role of neuroinflammation in the pathophysiology of the disease. Unmet needs include improving diagnostic accuracy, the monitoring of treatment response and predictive tools regarding the development of dementia.

The development of vaccines to combat AD continues to be explored, despite numerous failures historically due to neurocomplications. We note both Glaxo and Pfizer have ongoing vaccine programs that incorporate better adjuvant systems and less frequent injections. Our speaker noted he is hearing current vaccine programs in the clinic are having problems eliciting a strong immunological response. The use of inhaled insulin as an approach to AD is based on increasing glucose uptake in brain cells, thereby reducing neuronal death. With respect to neuroinflammation mutations of TREM2 and CD33 genes are strongly linked with increased inflammation of the brain.

Current tools allow for accurate prognosis though the cost of amyloid PET imaging remains high ($5,000) and is not reimbursed. Our speaker noted finding new biomarkers remains an important area of research to improve diagnostic accuracy, as well as monitor treatment response, guide best treatment, and help better predict the development of dementia. Current biomarkers include genetics, and Amyloid-b/Tau levels in cerebrospinal fluid. While CSF assessment is good to assess risk (low amyloid beta/high-Tau patients more likely to progress to MCI - mild cognitive impairment), it is not good for monitoring progression of AD and is a relatively invasive procedure.

### Breast Cancer – PARP Inhibitors Are Promising in BRCA+

The speaker, a director of the breast oncology program, believes that BRCA+ is ~5% of all breast cancer patients while TN- are 15% of all patients and HER2+ 20%-25% of all patients.

The expert is excited about the PARP inhibitors in breast cancer and believes that these drugs will find use in BRCA+ patients. He was impressed with data from ph 2 trial of Olaparib in patients with metastatic BRCA breast cancer, where single-agent olaparib resulted in ORR of 40% and mPFS of about six months. The PARP inhibitor field is getting exciting with several trials being conducted in various populations. ABT-888 or veliparib is being tested in neo-adjuvant setting. AbbVie is doing a Ph3 trial of taxol/carbo/veliparib vs. taxol/carbo vs. taxol in triple negative, neo-adjuvant setting.

AstraZeneca is testing olaparib vs. chemo in a phase III trial in BRCA+ patients with 1st/2nd prior lines of therapy. BMN-673 is being tested in Ph 1/2 triple negative with carbo/taxol/BMN-673 vs. carbo/taxol. Both BMN-673 and Tesaro's niraparib are in phase III testing these drugs head to head vs chemo in patients with 0-2 prior lines of therapy. The doc noted that olaparib and niraparib look similar in potency while BMN-673 might be more potent. He noted that all 3 drugs should be able to beat chemo in their head to head studies.

### Cardiovascular Therapeutics - LCZ696 wows, Increasingly Bullish on PCSK9, Tough Year Ahead Expected for Merck, Lilly the Dark Horse

We again hosted two cardiovascular sessions to provide an update on important developments across a wide range of areas. Key takeaways included unbridled enthusiasm for both Novartis' LCZ696 in chronic heart failure and the cholesterol lowering anti-PCSK9 class (Amgen seen as the leader). Other topics included serelaxin, CETP inhibitors, Brilinta - PEGASUS, Vytorin - IMPROVE-IT, darapladib, obesity drugs, cangrelor, and addressing FDA concerns on CV safety with insulin degludec and the DPP-IV class, as well as theoretical CNS concerns with PCSK9.

The recent announcement that the LCZ696 phase III study in preserved chronic heart failure had been stopped early "wow-ed" our speaker (an opinion leader in cardiovascular medicine) given it essentially implies the trial has shown a mortality

benefit on top of a CV benefit. LCZ696 (combo drug - nep/ARB inhibitor) was tested against an ACE inhibitor. The only potential wrinkle in the data (expected to be presented at ESC or AHA) is if the ACE dose used in the comparator trial was lower than prior outcome studies using enalapril. While surprised it worked our speaker was highly encouraged and, given the people behind the clinical program, he would be surprised if low ACE dosing in the comparator trial becomes an issue. The potential for LCZ696 in indications outside of heart failure now needs to be considered, and includes anything that is currently treated using an ARB or ACE inhibitor (e.g. treatment resistant hypertension). We currently forecast risk adjusted sales of just $5bn. Our speaker moved on to discuss serelaxin for acute heart failure. While believing the drug to be approvable Novartis will probably need to make changes to the ongoing phase III study.

Our experts are increasingly bullish on the PCSK9 class and expect them to show long-term outcome benefit and will be using it in patients who are unable to control their LDL levels or intolerant to statins (17-21m patient population across US/EU5. They are of the opinion that PCSK9 injections are very acceptable to patients and LDL cholesterol reduction itself has an anti-inflammatory effect. They believe that there are differences in design of outcomes trials, Amgen has fixed dose, Regeneron has flexibility with dose escalation, and Pfizer is doing a dose reduction strategy if the LDL reduction reaches a certain threshold. Pfizer's SPIRE phase III outcomes studies might need more patients or long-term follow up for events and is a risky strategy. There have been no safety issues with ultra-low LDL levels and the experts believe that the neurocognitive safety issues are overblown and FDA is being cautionary. Bococizumab SPIRE outcome trial data is expected in August, 2017. Evolocumab FOURIER outcome study data is expected in February, 2018. Alirocumab ODYSSEY outcomes data is expected in January, 2018. Our expert believes Eli Lilly is a "dark horse" with their phase II PCSK9 asset LY3015014. The current program is testing six injections per year (versus 13-26 for competition), and while a number of years behind the leaders, could prove financially attractive to physicians wishing to administer the drug to patients in their office.

GAUSS-2 is testing patients who failed 2 statins at least (half failed 3+ statins) and has a very strict definition of statin intolerant patients. GAUSS-3 is enrolling now and will test atorvastatin/placebo cross over design on a blinded fashion. ODYSSEY alternative is testing alirocumab vs. statin vs. placebo in statin intolerant patients.

Our expert believes that at present compliance is 35%-50% on orals and this will reduce by 50% with injectables. He expects that 10% of patients will get treated with PCSK9 class and will increase over time, with an annual treatment cost >$6,000. The success of the CETP inhibitor class, and potential failure of Merck's IMPROVE-IT study would have negative sentiment read across for the PCSK9 class We note Amgen is doing a large IVUS study in an attempt to demonstrate PCSK9 use can lead to regression of coronary disease.

The expert does not expect IMPROVE-IT (Zetia on top of high dose statin Zocor) to be positive and believes that the odds are stacked against it due to poor trial design. Merck randomized ACS patients early, which seems odd given all early events in this population are thrombotic and therefore not impacted by drug. Also, Lipitor went generic during the middle of the trial, leading cross over and patient retainment issues. Lastly, Merck appears to have stacked the deck against themselves by looking for a difference whose starting LDL-C levels were already relatively low. If we see a trend, which is not statistically significant, we will need to understand the trial population and see what the dropout rate was and whether the dose was maintained. If the IMPROVE-IT is a true negative or detrimental study it is not clear if can generalize to all LDL lowering therapies.

Our speaker believes the future of CETP inhibitors, as potential therapeutic agents, hinges on Lilly's evacetrapib. This, along with a potential PCSK9 and branded basal insulin asset makes Lilly somewhat of a dark horse with respect to future CV/diabetes therapeutics, especially given modest expectations. Pfizer's torcetrapib and Roche's dalcetrapib have already failed in phase III, with our speaker believing Merck's anacetrapib will follow. While the efficacy of anacetrapib, with respect to LDL-lowering/HDL-raising ability, remains to be seen the drugs prolonged half-life (3-4 years post drug cessation) is seen as a significant issue that skews the risk reward profile.

When discussing obesity, our speaker recognized the limited success of therapeutics to date, but noted a treatment gap exists between lifestyle modification (3-5% weight loss from baseline) and bariatric surgery (>15%). The experience physicians had historically with phen phen and sibutamine explains why Vivus' Qsiva (phentermine and topiramate) has been a flop despite best in class weight loss for an oral at -14%. Arena's Belviq (lorcaserin) is not perceived to be effective though Orexigen's Contrave (bupropion naltrexone - weight loss -5-10%) is considered approvable. Victoza is seen as approvable but our speaker found it difficult to get excited given the need for injection and expensive price (>$20/day).

Despite the Medicine Company's Cangrelor recently receiving a Complete Response Letter our speaker put this down to poor trial design, the company seeking too broad a label, and the regulatory bar at FDA being raised. The speaker believes the drug is approvable, despite Plavix being a difficult drug to beat when given properly. In the original phase III studies administration of Plavix was delayed thereby favouring the cangrelor arm. Our speaker cited registrational studies for Lilly's Efient and AZN's Brilinta doing the same.

AZN's PEGASUS-TIMI 54 trial is critical to improving the commercial outlook for Brilinta, and is expected to read out in 1Q15: our speaker rates the chances of success at 50%. While the trial has been designed correctly and targets the right patients, current clinical practice has seen the event rate in this post-ACS setting decline, thereby creating tension in this 21,000 patient population. Current treatment guidelines for acute coronary syndrome (ACS) patients recommend dual antiplatelet therapy for up to 12 months post-event, followed by longer-term treatment with aspirin alone. PEGASUS is studying the long-term efficacy (>12 months treatment) and safety of Brilinta in patients who have sustained a heart attack from one to three years prior to enrolment.

A negative view on GSK's darapladib was reiterated, both in terms of the efficacy seen to date in phase III but more importantly the "stink problem" experienced by patients using the drug. The second phase III study, SOLID-TIMI 52 will evaluate the effects of darapladib in 13,000 patients with acute coronary syndrome. Results from this trial, which our speaker believes will be negative, are expected in Q2.

ETC1002 is a dual ATP citrate lyase inhibitor/AMP kinase activator. It showed 25%-40% reduction vs. placebo in phase IIa trial and looks promising.

Finally, our speaker offered strong views with respect to addressing potential safety issues associated with insulin degludec and the DPP-IV class. On the former he believes Novo Nordisk has been hard done by FDA, and does not believe insulin degludec has a CV safety signal. With respect to the oral anti-diabetic DPP-IV class he believes there is cause for concern regarding a potential link with heart failure.

### Hematological Malignancies: NHL, CML, Myeloma – Constructive on Imbruvica, Limited Opportunity for Kyprolis

Our expert, a department chair in hematological oncology, in this session was seeing 50% reimbursement for CLL when Johnson & Johnson/Pharmacyclics' Imbruvica was approved for NHL. Following CLL approval he is not seeing any issues with reimbursement of Imbruvica for either NHL or CLL. Our expert prefers to use single agent Imbruvica vs. combination of Rituxan+ Idelalisib unless Idelalisib is priced much cheaper. Imbruvica does not have a label in low grade lymphoma and the expert will try to use it off-label, but he also believes that it makes sense to use idelalisib + Imbruvica in combination if possible to get reimbursed.

Our expert is of opinion that Kyprolis will be a short term use agent due to its side effect profile and the need to bring in patients for infusions. He prefers Velcade as it can be used long term as it can be given subcutaneously.

He believes that Takeda/Millennium's MLN9708 is as tolerable as Velcade and would prefer it by virtue of once daily oral dosing.

### Hemophilia- Switching Will Depend on Less Frequent Dosing Intervals

As per our speaker (a practicing physician in the hematologic oncology department) the key question with long-acting recombinant factors is whether the dosing interval is sufficiently long to justify switching between drugs. When patients on plasma-derived factors moved to recombinant factors, there was transient inhibitor formation. But currently, there is no significant risk of inhibitor formation when switching between recombinant products and so this historical experience can help provide some comfort that switching to newer long acting drugs will not result in major safety issues.

Biogen's Eloctate (long acting factor 8) can be dosed twice per week with an ABR of zero. The spectrum of dosing interval can range from twice per week to once every four days to once very week in a minority of patients. According to the expert, about ~1/3rd of patients in the phase III trial had a longer interval of dosing than twice per week. The expert noted that there will be a very wide range of adoption of the drug as some physicians will be early adopters but many will wait until there is more experience and safety data with the drug before using it broadly. Eloctate is not a game changer in his view but many patients are very educated and he does anticipate that some patients will want to switch to this drug. Over time, he sees new patients going on the long acting drugs as they offer fewer injections. In his view, there is little differentiation at this point between the different long acting factor 8 drugs in terms of clinical data and Biogen is clearly in the lead.

Patients starting therapy with the new long acting drugs will be on an individualized regimen as it could offer the least frequent injection schedule. The expert believes that there is need to do that PK monitoring once to optimize the dosing frequency. So this is easy enough and could become a part of the standard care over time. Currently switching between factors is infrequent. His patients are currently split evenly between on demand vs. prophylaxis. The expert does not expect that adult patients will change immediately. He expects that with time the proportion of patients could shift to 20% on demand vs. 80% on prophylaxis.

The experts believes that Novo's N8-GP data looks good and can be dosed once every four days with an ABR of 1.3. Rixubis (BAX326) is a BDD un-modified recombinant FVIII. He believes that advantages of this factor are questionable as the drug is not a long-acting drug. BAY 94-9027 can be dose once every five days with an annual bleed rate (ABR) of 1.9 and can be dosed every 7 days with an ABR of 3.9. CSL recombinant factor IX has a half-life of 94 hours and has an ABR of 1.4.

Biogen's Kids A-LONG study included previously treated patients for both prophylaxis and surgery. This will enable dosing kids who were previously treated. Currently, 20%-25% of kids on prophylaxis develop inhibitors in the first 20-50 days of treatment with recombinant factors and then decrease. Most adult hemophilia patients should remain inhibitor free. Most of new factors are B-domain deleted factor 8, as this structure increases the manufacturing yields of the product but does not impair in vitro or in vivo functionality. Based on meta-analysis it was suggested that there is 10x increase in inhibitor development with BDD vs. full domain. But the individual studies were small sized and therefore the data is not reliable.

In hemophilia B, Pfizer's BeneFIX has recovery and unpredictability problems. Hence, Biogen's Alprolix has an edge which could lead to faster switching as it offers a once weekly dosing frequency which is clearly preferable.

Gene therapy with AAV2 virus historically led to liver function test (LFT) elevations in the initial gene therapy trials. But since then newer viruses have resolved this issue. AAV8 virus based gene therapy can be given intravenously. Due to prior anti-AAV antibodies, patients need to be given steroids to suppress their anti-viral immune responses. The paper on gene therapy published in NEJM included 6 hemophilia patients and this provided proof of concept for this promising approach. Data from animal models have showed hepatomas as the main risk factor. But as the adenovirus does not integrate into DNA, this should not lead to new tumor formation and the hepatomas were only found in a few animal models. In his view, gene therapy is a very promising approach.

### Idiopathic Pulmonary Fibrosis– Several Options on Horizon

Fibrosis is caused by abnormal wound healing and the speaker (a practicing physician in a respiratory institute) estimates that there are 100,000 to 200,000 patients with idiopathic pulmonary fibrosis and 50,000 new patients are diagnosed each year with mortality of 40,000 patients each year. He believes that IPF is a heterogeneous disease with some patients progressing faster than others and includes patients with slow decline, patients that die quickly, and patients that see no change. IPF is diagnosed by both clinical and radiologic evidence of pulmonary function deterioration including radiologic evidence via CT/xray imaging which shows a characteristic histopathology pattern known as usual interstitial pneumonia (UIP), which could be of fibroblastic focus or honeycombing.

IPF disease pathology involves epithelial injury followed by epithelial remodeling leading to disruption of the basement membrane, formation of provisional matrix, and recruitment of pro-fibrotic mediators. These lead to fibroblastic foci formation that than advance to "feed-forward" progression. Feed-forward progression is found in other fibrotic processes as well and is not just limited to IPF.

Biogen's STX-100 is a humanized monoclonal antibody to integrin αvβ6. It acts by blocking the activation of a key anti-fibrotic cytokine, TGFβ, selectively at sites of tissue injury. TGFβ is only expressed in parts of lung where fibrosis is occurring. STX-100 exhibits significant anti-fibrotic activity in preclinical models of lung, kidney, and liver disease. STX-100 has completed Ph1 trial and Ph2 trial in patients with IPF is wrapping up in next few months. Each cohort of this trial has a higher dose and the trial is assessing both safety and efficacy, with FEV1 decline as primary endpoint. The study is ongoing and is currently testing the higher doses which we conclude to mean that the lower doses likely were safe.

The expert was enthusiastic about the potential for this drug, albeit we have to note that he was optimistic about all the drugs in development. As both pirfenidone and Boehringer Ingelheim's nintedanib recently showed robust phase III data, he argued that the treatment of IPF is on the cusp of revolutionary change. Hence, he was also very optimistic about the anti-fibrotic drugs in development. As STX-100, anti-CTGF, and simtuzumab have yet to be fully validated in clinical studies, we note that some caution is warranted although we note his enthusiasm for these drugs as their mechanism of action makes sense.

Gilead's simtuzumab is a humanized monoclonal antibody that binds to Lysyl oxidase-like 2 (LOXL2) and acts as an anti-fibrotic agent. Ph2 study of Simtuzumab in mild to severe IPF is ongoing with primary endpoint of PFS defined as time to all-cause mortality or decline in force vital capacity % predicted. LOXL2 is over expressed in lungs of patients with IPF and causes "feed-forward" progression. It is possible that Simtuzumab potentially reverses IPF and not just slows progression, as noted in animal models

InterMune's Pirfenidone should be available late this year or early next year in U.S. The drug is already approved in many ex-US markets including China, Japan, and Europe. Pirfenidone recently showed positive phase III data in it's ASCEND study. The data looks impressive in his view and this drug will be a viable option. However, pirfenidone does have some noticeable side effects that require careful monitoring.

Tyrosine kinase inhibitors play a role in fibrosis. Boeringher Ingelheim's Nintedanib recently achieved its primary endpoints in the phase III INPULSIS studies. Hence, there will be tough competition between the 2 drugs.

There are a number of other agents in pipeline. In the near term most are targeted inhibitors. In the longer term, the strategy would be to use body's mechanism and switch from fibrotic pathway to non-fibrotic pathway. Among those strategies are antioxidants / NOX4 agents that target prevention of AEC injury. IL13 targets AEC proliferation and inhibits apoptosis. Anti-thrombotic target the coagulation cascade / thrombin. Pirfenidone / CGTF target inhibition of fibroblasts.

The expert believes that within next year, we will have 2 agents available for treating IPF that will rapidly become the standard of care agents. He expects that within 5 years, there will be several additional agents approved to treat IPF. The expert believes that due to the impact of additional therapeutic options, the key will be to understanding which patients are most likely to benefit from each drug. This will require better biomarkers and more in-depth understanding of the disease.

### Multiple Sclerosis – Tecfidera Has a Higher Drop Out, Gilenya is a Teratogen, Excitement for Ocrelizumab and Skepticism for Lemtrada/LINGO

Our speaker (the medical director of an MS unit) began his session recognizing the relative paucity of novel therapeutics for the treatment of MS, especially progressive MS (50% of 2.1m MS population), and the fact injectable therapies are losing market share to the orals at a slower than expected rate. The expert noted that Biogen's Tecfidera continues to be very popular and the clinical experience has been very good. Thus far, the side effects have been as expected from the phase III studies, but the frequency and magnitude of the GI and rash side effects is higher than was in the phase III. Hence, the dropout rate is 15%-20% and is higher than the 13% rate in the phase III studies. While Biogen has guided the Street to expect this dropout rate, the actual dropout rate was initially lower and seems to have been creeping up with time. Our speaker is seeing patients move back to Novartis'

Gilenya, though also noted the first reported case of teratogenicity associated with the use of Gilenya (side effect concern currently reserved for Sanofi's Aubagio). Aubagio continues to be viewed as having the weakest efficacy and de minimis use given equivalent efficacy to ABCR injectables.

With respect to pipeline oral therapies our speaker noted Novartis' once weekly S1P receptor modulator BAF312 was originally designed to have an improved dosing and CV profile versus Gilenya. The fact it is being developed for the treatment of secondary progressive MS, versus relapse remitting, suggests the CV profile is little different versus Gilenya. With respect to the first dose monitoring requirements for Gilenya, our speaker noted the CV risks were overblown in his view given the typical patient initating treatment is young and healthy. Finally, our speaker beliefved Receptos' RPC1063 has not demonstrated compelling evidence to show a lower affinity S1P receptor spared the cardiac side effect profile associated with the class.

Teva's laquinimod is basically an antiinflammatory that reduces MRI lesions in MS patients by 45% (versus 50-80% for Gilenya) with data in a small number of patients showing demonstrating a slowdown in both atrophy and disability progression. Our speaker noted it is unclear presently how predictive atrophy slowing is in terms of slowing disabiltiy profession. There remains a potential use in progressive MS though we note our speaker gave laquinamod a lukewarm reception.

With respect to injectable therapies our speaker made a brief comment on three times a week Copaxone, noting not all payors were embracing the convenience advantage, with a major push from payors expected once generic Copaxone arrives. Our consultant was bearish on Biogen's Plegridy as it does not offer much benefit over weekly Avonex. Plegridy is dosed every 2 weeks. Comfort with Biogen's Tysabri continues to increase, with use and duration of use continuing in "low risk" JCV +ve patients (antibody index for PML risk raised to 1.2-1.3) due to enhancements to the predictive value of Tysabri's JCV assay.

As was the case last year, our speaker was excited by the prospects for Roche's Ph III asset ocreluzimab, given the efficacy seen in phase II as well as dosing advantage versus Tysabri. The key question remains whether the side effect profile is manageable.

Our speaker was less optimistic on the outlook for Biogen/Abbvie's daclizumab due to a clinical profile that offers similar efficacy to existing orals, with significant toxicities (rash, hair loss, increase in lymphnodes size and breast nodules reported in 3/20 patients treated at John Hopkins off-label with Zenapax, an older formulation of daclizumab). Similarly, our speaker was downbeat on Sanofi's Lemtrada (alemtuzumab), believing the drug was efficacious but the side effects were worrying and required blood monitoring requirements will be burdensome. He noted Sanofi's recent re-filing with FDA is most likely to be based on incremental safety data, and/or further data stratification. Either way, the efficacy profile is perceived as inferior to other biologics in late stage development such as ocreluzimab. Our speaker viewed Opexa's Tcelna as a drug trying to look for a disease based on fact MS is not driven by the immune system, so why use a T-cell modulator to treat the disease.

Our expert was not very enthusiastic about the potential of remyelinating agents like Acorda's rHIgM22 and Biogen's anti-LINGO. Acorda's rHIgM22 molecule is in phase I development and is still early, whereas Biogen's Anti-LINGO phase II RENEW data in optic neuritis is expected in 2H14 and phase II SYNERGY in MS is expected in 2H15. He believes that anti-LINGO will have an uphill struggle.

The expert is pessimistic that remyelinating agents will work in primary progressive disease and in RRMS. In his view, in optic neuritis, the opportunity is limited since steroids are very effective and he is worried that it will be tough to show a benefit in resolution of an attack. Based on his experience, most MS patients recover well from a single relapse and he believes that it will be difficult to show benefit in the study. The good news is that most patients recover within 12 weeks from an optic neuritis attack and hence a 24 week study has sufficient length to detect a benefit.

In RRMS, Biogen's is testing a new neurocognitive and physical composite endpoint at 72 weeks in the SYNERGY phase 2 study evaluating Avonex +/- anti-LINGO. The key area of concern for the doc is that the endpoint is not validated and that demyelination may not be the main culprit of deterioration (as opposed to atrophy) in RRMS. Hence, he is not convinced that the SYNERGY study will be successful.

### Ophthalmology- Excited about Anti-VEGF/Anti-PDGF Combination Therapy in wet AMD

For wet AMD our ophthalmology expert's view suggests that Allergan's DARPin (in phase II development) may face an uphill battle if ultimately approved in a competitive space for treating wet AMD. Based on data presented at AAO (in November 2013), DARPin seems to confer little differentiation on the efficacy front over Lucentis, although the drug showed increased levels of inflammation (potentially tied to ongoing improvements in the manufacturing process). It was unclear to speaker (a founding director in the eye institute) as to how a new entrant could differentiate itself from Lucentis and/or Eylea, other than on price.

The expert noted that he believes that the usage of Avastin will increase dramatically at the Cleveland Clinic from current levels of 40-50% to 80% over time as the institution moves towards a capitated, episodic care model under the Affordable Care Act. Under this backdrop, with the potential for low-priced Avastin usage increasing, this could further present a considerable headwind for DARPin as the drug will need to differentiate itself on price. This new model will also reduce usage of both Eylea and Lucentis as they are expensive and offer little benefit over Avastin.

The expert generally uses Eylea and Lucentis in most of his patients who have good insurance and Avastin is used in the rest of patients. But that is not the mainstream at the Clinic where Avastin is oftentimes used ahead of the branded drugs. The Clinic has its own Avastin compounding lab and so they are not worried about the risk of infections.

The expert is a big fan of Eylea for RVO and DME, 2 conditions where there is a need for chronic injections as the role of VEGF is more pronounced than in AMD. Hence Eylea will be the preferred drug once approved and he was bullish on the DME segment for that drug. This is because Eylea offers tangible benefits over both Avastin and Lucentis in terms of greater potency, fewer injections, and better safety.

Our ophthalmology expert saw steroid implants (including Allergan's Ozurdex and Alimera's Iluvien) playing an important role for treating diabetic macular edema (DME). While anti-VEGF therapies (namely Roche's Avastin and Lucentis and Regeneron's Eylea) will likely still be utilized ahead of longer acting steroids in the expert's treatment regimen, molecules injected into the vitreous have a brief intraocular half-life, limiting the potential therapeutic window per treatment and requiring frequent injections. Steroids could provide a more potent, longer lasting alternative, and the physician felt implantable therapies confer a significant compliance benefit by limiting physician visits, particularly important amongst younger patients. The expert also believed that implants could be used

concomitantly with intravitreal injections. While the expert noted that spikes in intraocular pressure (IOP) remained a concern with longer-lasting steroids due to the link between elevated IOP and an increased risk of glaucoma, he believed that the risk was manageable through glaucoma medication or surgery. The KOL's view supports our view that Ozurdex (which has shown a high durability of 4-6 months) will be an important addition to physicians' armamentarium in the DME population that is poorly controlled on anti-VEGF therapies.

The expert was excited about the potential offered by anti-VEGF/anti-PDGF combination therapy as an emergent treatment paradigm for treating wet AMD. He did not believe that the administration of one injection vs. two injections provided a significant compliance benefit given the marginal ease of administering an additional injection while the ocular area was already numb. Instead, he preferred the optionality of combining an anti-PDGF injection with an anti-VEGF of choice (mostly likely Avastin in the physician's practice). He also believed that combination therapy would be mechanistically favorable to anti-PDGF monotherapy due to anti-VEGF's anti-fibrotic benefits. So in essence, he noted that Opthotech's FOVISTA is promising as the data showed a consistent improvement in vision over time and may reduce the need for chronic anti-VEGF injections. In his view Regeneron will be wise to have a combo of Eylea with their anti-PDGF antibody in order to be able to control the price of the combo. At this point, it is not clear whether combining an anti-VEGF drug with anti-PDGF or with anti-Ang is preferable.

The expert was skeptical over Roche's anti-Factor D data for geographic atrophy dry AMD as it was based on a success in a segment of the population. The biggest issue is that only 20% of his patients will be willing to have chronic injections into the eye given that the disease is asymptomatic.

### Psoriasis/Atopic Dermatitis- Otezla Will Find Use in Milder Patients

Our speaker (a physician within the dermatology program) believes that biologics are safe in psoriasis and further long term data on cardiovascular safety and outcomes should further promote usage and uptake. There is MTX vs. TNFs study evaluating cardiac outcomes since patients with autoimmune disease have higher rates of cardiovascular events. In dermatology the safety profile for biologics is different than in other autoimmune disease. In her practice, the expert is treating healthier patients with biologics. Patients typically have side effects during the first year and then the drugs are well tolerated afterwards. Biologics are comparatively safer in dermatology than in rheumatoid arthritis or irritable bowel disease.

Patients stay on Humira/Enbrel for several years, but 40%-50% of patients are still not adequately controlled. Stelara is being used as a second line biologic and the expert has had good experience with the drug as efficacy is same as anti-TNFs. Simponi had PAS75I score reduction of 70%. Cimzia had PASI75 reduction of 75%-83%. The expert believes that anti-IL17 drugs will initially be used as 3rd line biologic. She believes that the drugs are very potent and have been safe in ph 3 so far. But adoption will be slow once approved as there are other good options. Voclosporin (ISA247) is safer than Cyclosporin but less effective.

In psoriasis 20% of patients are on anti-biologics and the expert believes that Otezla may get 10% share.

IL-17/23 is up regulated in psoriasis, this prevents secondary infections. Down regulation of IL-17/23 leads to candidiasis/ staph aureus infections.

Celgene's Otezla has been approved for psoriatic arthritis. There was very little talk about Otezla at AAD and this was surprising for her. She has a moderate level of interest in Otezla as it is not a very potent drug but is very safe and is oral. She believes that the drug will do well in the community dermatology settings where docs are busy and risk averse. In her view, many psoriasis patients are chronic under treated or not treated at all and Otezla could be a viable options for milder patients. She is of opinion that 25% of patients could benefit from an oral drug for milder patients.

Otezla in a small, open label trial without control in atopic dermatitis (n=16) improved pruritus/DLQI. The expert believes that Otezla has good potential in atopic dermatitis and could be used ahead of biologic injectables. She also believes that it will be easier sell to patients as it is an oral drug.

Atopic dermatitis is caused due to hypersensitivity and is common in kids. Up to 50% of kids who have the disease will also have symptoms as adults. Typically atopic dermatitis is treated with moisturizers, soap, topical steroids. In the black population it is worse and is more common. Systemic steroids work well in atopic dermatitis and patients can be tapered and not get a flare up like in psoriasis. Kids with atopic dermatitis will require chronic therapy for 2-4 years, whereas adults have a waxing/waning disease. Some of the patients will have tough disease and require chronic therapy. Biologics do not work well in atopic dermatitis. The expert is impressed with Regeneron/Sanofi's dupilumab data but believes that it will be tough to inject as a SQ weekly for kids. Overall, the doc believes that Otezla and dupilumab will be used in up to 10% of patients with moderate/severe AD.

### Prostate Cancer - Bearish On Xtandi in Pre-Chemo

The expert (the chairman in the solid oncology tumor division) was of opinion that Xtandi will find substantial use in pre-chemo space driven by the statistically significant survival benefit, but is cautious about uptake by community urologists as most urologists prefer doing office based procedures for which they get paid and are not incentivized monetarily to prescribe Zytiga or Xtandi. He expects that in community urology practices, Xtandi will move to pre-chemo over time since it does not require much monitoring and there is no need to give steroids. Currently, Xtandi is mostly used in post-chemo and that will change once it is approved in pre-chemo. The expert is a thought leading oncologist and started using Zytiga in pre-chemo a year ahead of approval and almost all his pre-chemo patients are on Zytiga.

In terms of movement of Xtandi and Zytiga into the pre-chemo segment, he was very cautious on the uptake by community urologists as most urologists prefer doing office based procedures for which they get paid and are not incentivized monetarily to prescribe Zytiga or Xtandi. Furthermore, the need for monitoring patients for side effects from prednisone is leading to low uptake. He does not expect this to change as active monitoring is an issue which urologists do not want to deal with. Instead, he believes that oncologists will be the main prescribers for these drugs in pre-chemo.

In his view, the PREVAIL study was positive but he does not believe that it will lead Xtandi to replace Zytiga. This is because Zytiga's data essentially also showed an OS benefit even though it technically missed the high statistical bar. Since Zytiga is already widely used and is a very good drug, he believes that both drugs will compete in pre-chemo and that Xtandi will not replace Zytiga.

The expert expects value-based critical care pathway to be used more frequently over the next 2-3 years, which will require data about how to sequence Zytiga and Xtandi. These critical care pathways will have a big focus on reducing costs. In that situation, generic Zytiga will be preferable over branded drugs.

The early data does show that there is some overlapping resistance between Zytiga and Xtandi and so the drug that will be used first will have a much long duration of benefit. Hence, new studies are underway to look at sequencing. The phase III MD Anderson/Intergroup study in pre-chemo metastatic prostate cancer patients testing Zytiga+Xtandi vs. Xtandi will attempt to pivot Xtandi to be the standard of care and will evaluate whether combo with Zytiga is preferable over Xtandi alone.

The presenter was bearish on Johnson & Johnson's ARN-509 since it is hard to compete with Xtandi. The 2 drugs are now locked in a race to the M0 population. The doc noted that the magnitude of EFS should be meaningful and a greater than a 6 months benefit is required to stimulate adoption. Hence, these studies will take a long time and are challenging. The doc did not believe that the TERRAIN or STRIVE phase II studies testing Xtandi vs. Casodex are meaningful as they are phase II and are widely expected to beat Casodex. But cost is remains a key factor and there will not be reimbursement for Xtandi based on these data. In general, the doc was worried about the cost of Xtandi in M0 and so will need to see a big benefit to justify its high cost.

Our presenter is using Bayer's Xofigo in some of his patients. In his view, Xofigo is a very good drug and is easy to use once the initial set up process is established. The drug is used post Zytiga or Xtandi but before chemo in patients who have bone mets.

The speaker was bearish on Exelixis' cabo as the DSMB did not stop the trial early. Hence, he envisions that the drug is likely not that potent.

### Rheumatic Diseases - Anti-TNFs to Remain 1st line Biologic Option. IL6 and IL17 Classes Crowded and Offer Limited Differentiation

Our speaker (a sector head within the rheumatic disease unit) gave a comprehensive overview and update on the various therapeutic classes, and pipeline assets, to treat rheumatic diseases. While the competitive landscape is set to intensify anti-TNFs are expected to remain the mainstay first line biologic therapy of choice, given physician experience and comfort with the class as well as the expected arrival of biosimilars later this decade. Other headline take away from our speaker included the belief there is limited differentiation amongst players in the IL-6 and IL-7 class, Otezla will only have a modest penetration in PsA, with UCB's epratuzumab remaining the most interesting pipeline asset for lupus.

Despite significantly different market shares, and breadth of indications, the anti-TNFs are viewed as offering limited clinical differentiation amongst each other. The recent launch of Johnson & Johnson's Simponi ARIA (IV formulation) provides great dosing flexibility and is expected to win further share from Remicade. UCB's Cimzia will benefit from label expansion (PsA and AS) with our speaker believing the drug does work more quickly than its competitors (within 12 weeks). Trials to demonstrate this are ongoing but, if proven, it provides UCB an opportunity given 35-40% of patients are resistant/intolerant to anti-TNF therapy. Our speaker now cycles though just 2 anti-TNFs before considering alternative biologic therapies, and will only consider a second anti-TNF in the event the patient has failed therapy due to toxicity, rather than efficacy issues.

Our speaker likes the clinical profile of the anti-IL-6 class, given its 'at least' comparable efficacy to anti-TNFs, fast onset of action and manageable side effect profile. Incremental X-ray data for Roche's Actemra as well as CV safety data in an ongoing head to head study versus Amgen's anti-TNF Enbrel could further help.

# Med Tech & Life Science Tools/Diagnostics

## Cardiac Rhythm Management – MDT Has Some New Opportunities

We came away incrementally more positive on Medtronic's prospects in CRM following this year's session, which we did not expect heading into the session, and it came areas we may have underestimated. Both Boston Scientific - behind the opportunity for the S-ICD and St. Jude Medical – with a strong position in the US for quadripolar leads – did also receive some positive commentary.

For the market overall, the commentary was more muted as the Clinic had been seeing ICD volumes growing above market rates – which have been relatively flat in the US – but now sees minimal growth. It appears that the difference is more pronounced in replacements as our speaker (an opinion leader in the field of electrophysiology) believes the improvement in battery longevity (especially in CRT-D systems) has led to a reduction in replacement volume. On the flip side, the decline being seen in pacemaker implants a year ago has turned into modest growth. Hence, overall CRD implant rates appear to be showing modest growth. The Clinic has seen a sizable increase in remote monitoring follow up – it is rising about 15%, which does suggest they will get most of the replacements once the longevity extension runs its course.

In terms of new data, the updated MADIT-CRT data presented at the American College of Cardiology meeting two weeks ago was viewed as an incremental positive as it showed it is important to reduce right ventricular (RV) pacing and QRS duration and left bundle branch block (LBBB) can be separate issues. While this is unlikely to actually increase the number of patients that receive an ICD – it was noted that it could actually improve patient selection and narrow the indication a bit – it appears to be another strong statement that there is less value in dual-chamber ICDs which could drive more implants of premium-priced CRT-D devices.

The discussion of the MADIT-CRT results led to another discussion which surprised us – the value of Medtronic's recently approved Adaptive CRT technology. The Adaptive CRT algorithm was launched as part of the Viva XT CRT-D line which was launched in Europe in 2012 and in the US this past summer. While we have normally not focused on new ICD algorithms as they seem to pop up quite frequently, we may have underestimated this one. Adaptive CRT measures AV conduction every minute and attempts to minimize RV pacing which has been shown in prior studies (e.g., DAVID) to potentially have negative effects in patients with HF. MDT conducted a 522 patient randomized, prospective study of Adaptive CRT which showed improved LV pacing response rates and is estimated to reduce HF hospitalizations by 21%. Follow on data presented this past September at the HFSA meeting showed the algorithm reduced the risk of atrial fibrillation (AF) by 46% at 24 months. Our speaker noted that this algorithm is unique to Medtronic and we don't know of any clinical trials underway by the competition. Medtronic also has a 2,900 global clinical trial planned for a mid-2014 start called ADAPT RESPONSE that will be powered to show superiority of the Adaptive CRT algorithm vs. traditional CRT-D pacing. While Medtronic still lacks a quadripolar lead in the US – the timing is estimated at 12-15 months away – and should give Medtronic a very strong position in the 40% of the market that is currently represented by CRT-D implants.

We came away with more appreciation for the upside opportunity for its recent acquisition of Tyrx (see our 01/06/14 note Medtronic Inc (MDT) - Pushing The Envelope) where Medtronic plans on running a global 6,600 patient, 100-200 center, prospective, randomized trial for the company's Aigsrx R bioabsorbable ICD envelope. To date, three separate clinical studies – COMMAND, CENTURION, and one by Vanderbilt University – have shown that the Tyrx pouches reduce infection

rate risk on ICD implants to 0-1% from 2-3%. Given that our speaker noted the mortality rate for an infection was around 25% and the cost ranges from $70-125K, cutting the rate down by over 50% would be a significant advantage. The trial is expected to start in 2014 and assuming enrollment takes 9 months, we could see some data in 2015 (the prior trials were all 6 months or less in duration) as our understanding is that infection rates will be tracked at 1,3,6, and 12 months. If the prior non-randomized results hold up in this trial, our speaker noted this could be a significant differentiating point for Medtronic among high risk patients (e.g., replacements) as the company would likely only package the products with its ICDs. At $750-1,000 each for the Aigisrx R, this would also likely give Medtronic more pricing power in addition to share gains.

For the S-ICD, the commentary was also a bit more bullish than we expected as our estimate of a 5% capture of the current US ICD market and a 5% expansion was viewed as achievable and possible conservative. The primary population being targeted is patients with vascular access issues including young patients, those on dialysis, those that have chronic ports inserted (other than for dialysis) and have renal insufficiency. On the flip side, it was estimated that 60% of the market was not an option for the device today based on CRT-D usage, a lack of anti-tachycardial pacing (ATP) and remote telemetry. The next generation S-ICD is expected to launch in Europe later this year and in addition to being smaller could also offer some level of remote telemetry.

The comments on leadless pacemakers were more cautious than we expected. While St. Jude's Nanostim has been released in Europe, the limited data – it was approved with clinical data on just 30 patients – was seen as a concern. In addition to the limited data, the first generation devices take a lot off the table in the way of atrial pacing/sensing, telemetry, and offer limited programming. It was also noted that most patients in the US receive dual-chamber devices but this is well understood. Given the limited data and US experience, our speaker did not see much difference between Nanostim and Medtronic's Micra. Longer-term, the speaker expected dual-chamber options to include 2 implants that communicate and a combination technology with a subcutaneous ICD (although Medtronic and St. Jude are well behind on subcutaneous ICDs and Boston is well behind in a leadless pacemaker). Concerns were also voiced about the price point of leadless pacemakers as our speaker was concerned the industry may try to charge a premium to not just single chamber devices, but dual chamber devices as well.

For Durata, the speaker noted that the registry data and prospective trial results continue to look good and concerns of the OPTIM coating have died down. It was also noted that the biggest concern he had – the risk of internal abrasion causing a short – has been dealt with after the launch of the Dynamic Tx algorithm over the summer.

Finally, it was noted that MRI-compatible ICDs should not be overlooked although it will be a while before they are released in the US (Medtronic's trial should be starting soon). While we thought pacemaker recipients were more likely to be at risk than an ICD patient (based primarily on a higher average age), it was noted that cardiac MRIs (especially for patients with ventricular tachycardia risk) are more likely to occur for ICD patients.

### General Surgery & Robotics – Still Waiting for Outcomes

We hosted two events this year surrounding general surgery and robotics to provide different perspectives on the use of MIS in bariatrics in particular and general surgery overall.

**Bariatic co-morbidity data with diabetes is growing, but insurer coverage is slow to adapt**. In bariatrics, the hurdles that have been noted in the past – insurance coverage, patient perception, referrals, and the $20-25K cost – were highlighted again this year. Overall, it was noted that procedure volumes were largely flat globally in 2013 although it was noted that the Ohio market has been growing the past 2 years. We believe the market has actually showed some modest growth post the unveiling of the STAMPEDE trial in early 2012 which was led by the Cleveland Clinic and showed a significant improvement in body weight reduction and several type 2 diabetes metrics including HbA1c and the percent of patients using insulin. At the most recent ACC meeting, the 3-year results of STAMPEDE were released and showed an even more significant improvement in these metrice (including increases in HbA1c and insulin injections for the control arm but not the 2 surgery arms).

In addition the STAMPEDE follow up, a recent Australian study was published in the LANCET showing better results with the gastric band (which is considered less efficacious than gastric bypass or gastric sleeve surgeries) and more studies are expected in 2014. While most insurance companies do not cover the procedure for patients with BMI's under 35 this has remained an issue for adoption hurdle given the vast majority of type 2 diabetic patients have a BME in the 25-35 range. However, given the growing evidence base, the Clinic has decided this year to lower its threshold to a BMI of 30 for its employee health network (over 100K lives) which could set a precedent for other payors. While more evidence needs to be built to get insurers to lower this bar, the strong clinical data momentum still suggests bariatric procedures could very well see an increase in growth in the coming years..

In terms of procedures, it was noted that gastric sleeve continues to take share from gastric banding which was not a surprise and our speaker believes the gastric sleeve procedure now makes up 35% off all bariatric procedures.

Similar to prior years, our speaker (an assistant professor in a baratrics institute) remains hopeful that new technologies either in clinicals or development can provide a less invasive option. Our speaker was optimistic on the EndoBarrier, which is in clinicals looking at improving blood sugar control, Apollo's Overstitch (PROMISE Trial – currently enrolling) but remained cautious on the prospects for neuromodulation and intragastric balloons.

**Views on robotics remains mixed.** Moving on to robotics, the Clinic has added 2 Intuitive Surgical DaVinci systems from last year (10 total; 8 in clinical use, 2 for training purposes) and physician opinions remain mixed given the limited clinical data, higher cost and increased procedure time. However, utilization is increasing on the systems (80-100%) and demand high between the urology, gynecology, and general surgery department.

Within general surgery, we focused specifically on the bariatric and colorectal use. Within bariatrics, the department performs 800 cases a year with roughly a 1/3 of all procedures using robotics with our speaker citing patient safety, surgeon comfort and slightly shorter LOS as the main benefit offsetting the higher costs (+$300-500). That said, it was very clear that this was not the norm as the majority of the bariatric procedures being done were either revisions or gastric bypasses. For revisions, this is largely the domain of expert institutions such as the Clinic and both revisions and gastric bypass use significantly fewer staplers where the DaVinci system can get cost prohibitive (they rely much more on sutures). We also got the feeling that the high level of expertise at the Clinic has led to only a modest difference in procedure times.

In colorectal, it was noted that for complex procedures such as lower anterior resection but for most colorectal cases the DaVinci doubles the procedure time. It was also noted that while there is a consistent theme that there are too many open colorectal procedures being performed today, our speaker noted that there will always be about 20-30% that will remain open as the tumor being removed is just too large. The same logic of when to use robotics in the colorectal specialty is being applied to other areas of general surgery where the Clinic performs complex procedures such as a whipple but largely skips robotics where current MIS techniques deliver good outcomes. It was also noted that the Clinic does not get any special carve outs for reimbursement by insurers for using DaVinci (we have heard this being the case in some hospital systems) which means the procedures are less profitable.

In terms of the Clinic's appetite for spending more on robotic systems or accessories, the commentary was a bit of a downer. While the just released Xi did offer some improvement in quadrant coverage over the current Si, it was not viewed as a significant addition and it was also noted that it requires new instruments and lacks FDA approval to be used with the vessel sealing and stapling components. Hence, the fact that Xi is not backward compatible is an issue in the Clinic's eyes as the budget for capital equipment remains tight – it was noted that the Clinic finally added in vessel sealing to its DaVinci systems as the roughly $80K cost of the generators turned into a lengthy purchasing battle and the addition of the stapler has still not been approved. Consistent with what we have heard in the past, the launch of a true single-site module (which was shown at the recent SAGES meeting) is considered a significant improvement if the arms are flexible but the timeline on this component looks to be 2 years from approval. Finally, it sounds as if the Clinic has not adopted Novadaq's Firefly technology either with DaVinci or as a stand-alone system due to a lack of clinical data justifying the higher cost.

### Interventional Cardiology – A Unique Way to Drive Down TAVR Costs

Transcatheter aortic valve replacement (TAVR) was once dominated the conversation during the interventional cardiology session as our speaker (a director within the interventional cardiology program) focused on the recent Medtronic high risk Corevalve results from the recent ACC meeting. Our speaker was surprised by the mortality benefit and thought it likely stemmed for the lower 18F of Corevalve vs. the 22-24F Sapien due to a much higher percentage of patients requiring a more invasive "cut down" procedure to insert the device. It was also noted that the PARTNER 1A trial there was a trend toward a mortality benefit at one year for Sapien (22.2% vs. 26.4%, p=0.25) in the transfemoral only component of the trial which is what Medtronic showed in the high-risk trial, making an argument for a possible class effect. However, this spread largely disappeared at 2 years while the Corevalve data appears to be holding up.

While the STS score was meaningfully lower in Corevalve high risk compared to the PARTNER 1A, 1B, and 2B studies, our speaker doesn't think it was due to a "class effect" as the patient frailty was indeed worse in the Corevalve study. On stroke rates, the speaker agreed that the higher rates in the Corevalve trial (both for Corevalve and the surgical valve arm) was due to better identification of stroke as Corevalve investigators had neurological assessments on a routine basis.

Commenting on the higher paravalvular leak (PVL) seen in the PARTNER 2B study, our speaker reiterated (similar to last year) that determination of mid/moderate is highly subjective and the conflicting data on mild/moderate PV leak impact on mortality signifies the difference in core labs "mild" definition. In fact, the speaker noted that there was quite a bit of clinical data presented (including the recent

CHOICE trial) that suggested a higher rate of PVL for Corevalve vs. Sapien XT. While an initial Edward's PARTNER clinical site, our speaker noted that the Clinic plans on adding Corevalve and is currently training for the valve (they have been referring 2-3 patients a month to other Corevalve sites). The specific advantages noted for Corevalve were similar to what we heard in the past: 1) smaller and easier to deliver, 2) better sizes available for patients with a larger annulus, 3) and a better fit for calcified valves.

Overall, TAVI volume has been growing slightly the Clinic and around 150 cases were performed last year vs. 1,500 surgical valve (SVR) surgeries. As the data expands and off-label use is tricky given there are no hard metrics on patient groups, volumes should creep into the intermediate risk population which our speakers sees as around 15% of SVR volumes (high risk at 10%; low risk the remaining 75%). However, it's too early to see how TAVR will do in the broader, low-risk patient pool given lack of durability data and the low mortality for AVR.

Given the influx of next-generation US clinical trials that have either started (Edward's Sapien 3) or are expected to begin soon (Boston's Lotus, Medtronic's Evolute R, St. Jude's Portico, and Direct Flow's system), our speaker noted that the Cleveland Clinic believes it can largely cover its TAVR patients as part of clinical trials (an estimated 85-90% of patients). The key here is that the speaker noted that clinical use valves typically cost $5-10K less than commercial valves, which is critical given that the Clinic is apparently still losing money on TAVR procedures. Given that these studies will cover all the key patient groups – extreme, high, and intermediate risk – and will have control arms that are either approved TAVR devices or surgical valves, this does seem to be a plausible strategy. While we didn't think about this before this session, we suspect there are at least 30 other centers in the US that could also likely adopt a similar strategy (if they haven't done so already).

Once trained on Corevalve (and assuming an injunction is not in place), the biggest factor dictating share will be on the cost front given the tough reimbursement environment (currently losing money on TAVI) – he believes Medtronic's higher pacemaker rates and its impact on procedure economics will matter. While the higher pacemaker rate issue seemed to be largely viewed as a non-event at the ACC, for hospital systems such as the Cleveland Clinic where costs are being heavily scrutinized, this did sound a bit more ominous.

For Edward's Sapien XT, the delay in approval is not believed to be due to the higher PVL rate seen in PARTNER 2B at one year or any issues with the longer-term data. Instead it was viewed to be due to increased scrutiny on the 29mm valve (which was included in the submission) give the lack of randomization (was a nested registry), small patient population (only 107 total patients in registry; Corevalve likely had over 500 patients each for its 29 and 31mm valve) and the novelty of the valve (not an iterative approval; 23/26mm valve was approved for original Sapien valve). That said, we do get the sense that the PARTNER 2B data is getting a more rigorous analysis, although it may be just in order to get published in a major clinical journal.

For the next-generation valves, our speaker believed that Direct Flow and Sapien 3 are significantly more advanced than the current Sapien and even the Sapien XT and Corevalve. Hence, the Clinic is either putting these patients in the current Sapien 3 trials and/or holding patients until Direct Flow trial starts. Views on Sapien 3 and the potential for a very low PVL rate were particularly bullish.

We also briefly discussed Mitral Clip where our speaker's opinion largely agreed with our prior thinking – the high cost of the clip ($25-30K) and unfavorable reimbursement ($18K) plus a narrow indication (have only done 6 cases that have fit the symptomatic, degenerative, MR>+2 patient criteria) has limited adoption at the Clinic.

While the commentary on renal denervation was hopeful and similar to what we heard at the ACC – technique, patient selection, and the device were all likely issues – our sense was that this has significantly narrowed the opportunity if it does recover. It was also interesting to note that during the cardiovascular therapies section it was noted that Medtronic's HTN-3 trial was a perfect example of why the more onerous US system of device approvals is better than the relatively easy hurdle put up by the EU.

### Orthopedics – A New Model for Medicare Payment

Similar to prior years, our orthopedics dinner focused on a lack of innovation and the changing dynamics in pricing, sales, and service. We did ask about procedure volumes given all the concern about the impact of the bad weather seen in the US in 1Q and our speakers did not a seasonally slow quarter. However, they noted that this could have been equally related to a continued shift of more procedures in 4Q and less in 1Q and some pull forward in front of the ACA impact on coverage starting in 2014 than just the weather.

In terms of the market, our speakers (practicing physicians within the orthopedic and spine institute) remained skeptical about Mako's Rio system even under Stryker's umbrella given its lack of clinical data, the surgeon skill level at the Cleveland Clinic, and the high cost of the system. At this point, the Clinic still does not have a Rio system. The Clinic still utilizes shelf pricing for hip and knee implants and all the major vendors are on the shelf. That said, even though the surgeons noted a lack of differentiation among the major players it does sound as if Johnson & Johnson and Stryker are still the more prominent vendors due in part to their success in prior contract negotiations and overall market share. With the Clinic's reconstructive contract coming up again for renewal this year, we expect pricing concessions may be a bit more aggressive than the current contract given that everyone decided to meet the shelf price in the last go around. It was interesting to note that if Stryker would structure its offerings in a way that included a lease model for Rio, this could offer a differentiated play in the upcoming contract negotiations.

This year we added spinal implants into the discussion and there are some notable differences. First, the contracting was different as there are two primary vendors – Medtronic and Stryker – vs. the shelf pricing model. Second, the "exceptional technology" carve out is a lower hurdle in spine as there are just more types of implants used and therefore more room for some differentiation (e.g., cervical discs. This contract is also coming up for renewal this year. In terms of procedure volumes, the Clinic is still seeing insurer pushback from commercial insurers and workman's compensation to get precertification to treat degenerative disc disease (DDD) but our speaker noted that their ability to get approval is improving as they have learned the key criteria for 3$^{rd}$ party review and buzzwords. It was also interesting to note that last year's OIG "special fraud alert" on physician owned distributors (PODs) led the Clinic to aggressively get its surgeons in compliance on this front. While the Clinic is considered a hospital system where physicians are employees, there are some cases of physicians being in private practice and spine is one of these areas. Given that we estimate 20% of the US spinal implant market share is held by PODs, tough policies such as the Clinic's recent moves suggest room for share gains by the industry's larger players.

Another new area of focus was in Medicare payment structure. The Clinic recently received approval and started a pilot program where one of its hospitals is employing a risk-based model with Medicare to get a flat payment for 30 days of episodic care for hip and knee replacement. This will include the surgery, hospital stay, post-acute care, and any readmissions over this time period and includes all patients no matter what the risk level. Based on the Clinic's data analysis of its Medicare patient costs, management believes they can turn a roughly 50% profit on these cases vs. what was essentially a breakeven or money losing outcome. It was estimated that Medicare patients represented 25% of hip and knee implants at this hospital (not including Medicare Advantage which is not part of the program).

What was interesting to note was that the primary way the Clinic appears to be managing the post-acute care costs – which can be the single biggest expense in the process – by either directly owning the post-acute care facility and/or setting up partnerships. This has also put more pressure on the surgeons and staff to maximize OR efficiency and stay on top of the patient and/or their family to speed up the recovery time. While the program is still in its early stages, it's gone well so far and it sounds as if there will be a move to expand the program to more of its hospitals in 2015. Down the road, we could see the program move into Medicare Advantage (not part of the current program) and even commercial plans but there does not appear to be a rush here as they both offer reimbursement levels that are more favorable than standard Medicare.

### Radiation Oncology – Several Long-term Headwinds Highlighted

While reimbursement pressures have subsided for the near-term for the radiation/oncology space, many of the longer-term headwinds facing the US market (saturated market, clinical data needed, lack of innovation) still remain. The market shift towards SRS/SBRT-based treatment continues as the ACA is setting up incentives towards shorter-treatment schedules (moving towards 1-2 weeks vs. 7 week courses) - our speaker (a practicing physician and the previous head of a radiation oncology program) expected 80% of treatment to be delivered in these shorter, higher dose settings over the next 5 years (up from 20% currently) even though hospital workflow/infrastructure changes will be needed to accommodate this shift.

On the reimbursement front, we should expect increased payor scrutiny and a continued trend of gradual reductions in radiation/oncology rates as bundling proposals become inevitable. It was noted that just this year, United Healthcare has begun requiring "prior authorization" for high end, IMRT, SRS/SBRT treatments which raises the standard for utilizing these expensive treatments – while volumes haven't slowed yet, the speaker believes other payors will roll-out similar documentation requirements which will likely reduce volumes to only necessary cases. While the Clinic plans on purchasing a Varian Edge System for the main campus and one for its Florida facility, he sees the total radiosurgery suite as a high-end product likely regulated only to niche opportunities.

Given the increasingly cost consciousness of hospital customers, building a robust clinical framework has been a focus for radiation oncology of late and while the recent European SPCG-4 Trial published in New England Journal of Medicine (NEJM) demonstrated favorable mortality benefits for surgical intervention vs. watchful waiting, the studies impact on US clinical practice remains uncertain given the differences in screening environments between the US and EU (lack of broad PSA screening in EU likely led to later-stage tumors being diagnosed vs. early-stage tumor in the US).

Software development has also garnered renewed attention for Varian (cited as a $2B+ opportunity), however our speaker has seen little change in radiation therapy workflow and was more cautious on the reality of RT data/analytics being integrated within the wide hospital ecosystem. Overall the US looks to remain a challenged market, though our speaker was more positive on the turnaround story of Accuray (though they have yet to purchase a system) as operational improvements and the SRS/SBRT shift will likely strengthen its competitive position against Varian/Elekta.

### Wellness – Less Smoking, Less Stress and More Wearables

For the second straight year we hosted a session on health and wellness given that the Cleveland Clinic has a dedicated Wellness Institute. Similar to last year, it was noted that 4 factors contribute to 75% of chronic disease and it is estimated that 84% off all US health care spending is to treat chronic diseases. The speaker (the chief of a wellness institute) also noted that the reason the US has the highest per-capita health care spend is because chronic health care costs are 2x the rest of the developed world. The four factors noted were: 1) smoking; 2) diet (portion control and food choice); 3) physical activity; and 4) stress. At this year's session there was more focus on stress and smoking as these are considered the primary two drivers of chronic risk.

The update on smoking – deemed the #1 culprit in health care costs - included new information on second-hand smoke (more of a risk than previously determined), how it adds an extra 18 years to the average person's time spent with a disability; increases costs when not addressed (seen in Ohio when the state budged for prevention was cut) and surprisingly can be 100% reversed if you quit before the age of 35. It was also noted the e-cigarettes were considered less harmful than smoking but could end up targeting younger populations and eventually shift them to cigarettes. It was also noted that loosening regulations on marijuana could be problematic as it is considered worse than cigarettes both for the smoker and for second-hand smoke. Similar to last year, stress was considered an underappreciated risk of chronic disease as it increases the release of cortisol, increases fat, increases inflammation, and decreases brain size. The Clinic has set up an online system dubbed Stress Free Now to help reduce employee stress and the data thus far has been encouraging.

One new area that got a bit of attention year was the potential for "wearables" in the health care environment. While there already are plenty of applications for phone, computers and tablets and several wireless devices such as activity counters (FitBit, Basis, FuelBand), heart rate monitors, scales and blood pressure monitors, the speaker noted that today they are primarily used by younger, healthier patients. The view at the Clinic is that usage will eventually shift to people with chronic conditions as hardware the hardware will become a commodity and devices will be able to monitor multiple health metrics. Our sense is that there was an implication in these comments that not only will wearables be consumer driven but will also likely be embraced by insurers/payors/employers to help lower health care spending.

Finally, our speaker gave an explanation on why he believes health care spending growth has slowed the past 3 years. In addition to economic pressure and higher deductible plans leading to lower admission trends, the following were also noted as having an impact and/or positive signs for the longer-term: 1) people appear to be consuming more fruits and vegetables, 2) it is getting harder to sell tobacco (more stores are banning sales), 3) childhood obesity appears to be on the decline; and 4) there is a shift in fast good consumption toward healthier alternatives.

# Health Care Services

## Managed Care – Still No Real Activity on Payor/Provider Relationships

For the fourth consecutive year, we heard about how much the Clinic believes the health care model will change, but for the fourth consecutive year, we also heard how little has actually changed to this point. As we noted last year, one of the consistent themes that's been around since the passage of health reform is the idea of providers taking on more risk from health insurers, with providers learning how to effectively manage a population of patients to produce better outcomes at a lower cost, rather than being as productive as possible to manipulate a fee for service system that only rewards volume. It's quite striking to us that the Cleveland Clinic, one of the most sophisticated hospital systems in the country, receives less than 10% of its reimbursement from capitated arrangements with health plans, relatively unchanged from last year[1]. Moreover, the capitated business the Clinic has is largely comprised of a longstanding relationship with WellPoint covering around 30,000 Medicare Advantage lives in the area, rather than something that has grown out of health reform.

Our biggest takeaway from the Clinic this year is the same conclusion we had last year, which is that while there's certainly a lot of discussions about how the relationship between managed care and providers can evolve over the next few years, at this point, there's not a lot of actual activity we can point to, and hospitals still have a number of significant obstacles to overcome before this vision can become reality. One is that taking on risk likely entails generating less profitability. So to start the process, hospitals first have to convince themselves that the alternative of doing nothing would be even worse financially at some point in the future.

There's a structural issue for hospitals to confront, which is that most health care cost savings initiatives target the reduction of inpatient utilization as the primary goal. That's kind of problematic if you run a hospital and inpatient utilization is the primary source of revenue. Put differently, it's a lot easier for a managed care plan to approach a group of doctors and set up a successful capitated or risk sharing arrangement. If the doctors are able to reduce the number of people visiting the hospital, both the plan and the doctor group win. Setting up the same kind of arrangement with a hospital is more difficult, since the savings from lower inpatient utilization comes directly out of hospital revenue. Hospitals may get to share in the savings from the lower level of utilization, but most of the time, that isn't going to be a financial positive, unless hospitals can do something about the large amount of fixed infrastructure expense they currently have.

Other highlights from the discussion:

- **The Cleveland Clinic isn't technically an academic medical center, but it has a lot of similar characteristics, and academic medical centers and narrow network exchange products wouldn't seem to have a lot of natural overlap.** Narrow network exchange products have a primary goal of offering a pre-established set of benefits for the lowest possible price by focusing primarily

[1] Capitation is a payment methodology that offers a fixed payment amount, rather than reimbursing on a fee for service basis. As a hypothetical example, WellPoint could pay the Cleveland Clinic $850 per member per month (PMPM) for each one of the roughly 30,000 lives covered under their capitated arrangement, or about $305 million. If the Clinic is able to keep the costs of these members under $305 million, the Clinic gets to keep the difference as profit. However, if the Clinic is unable to manage medical costs and the actual expenses come in above $305 million, the earnings hit falls directly to the bottom line of the Clinic. Clearly, a very different way of paying providers than the normal fee for service arrangement, through which WellPoint would pay the Clinic a set amount for every procedure performed, which gives providers the incentive to do more in order to increase their revenue and earnings.

on lower cost providers. Academic medical centers are usually some of the highest priced providers in the market. The Cleveland Clinic is part of the exchange network offered by Medical Mutual, while WellPoint has an exchange relationship with University Hospitals, which is affiliated with Case Western Reserve University. To this point, the Clinic hasn't been required to discount its normal rates to any meaningful extent in the exchange product, but the Clinic is cognizant that may not always be the case. One potential way of achieving a lower price point would be to include only certain Clinic facilities in the exchange network, rather than the broad spectrum.

- **The Cleveland Clinic was an early investor in Castlight, and sat on the company's board before it went public.** That said, even as an early investor, the Cleveland Clinic didn't provide its pricing data to Castlight. The Clinic acknowledges that some form of transparency is a reasonable goal, but the Clinic also faced the reality that many of the services it provides are largely commodities, even though the Clinic charges a premium price for them.

- **Given its price points, the Cleveland Clinic was quite interested the reference based pricing program CalPERS introduced for joint replacement.** CalPERS established a predetermined price that it would pay for joint replacement, and a list of facilities that would provide the joint replacement for less than that amount. Members were free to go anywhere they wanted for the procedure, but if it cost more than the reference price, the difference would come out of the member's pocket. After the program was implemented, something around a third of the business immediately moved away from the high cost facilities and many providers decided to lower their price. The state of Ohio is working through a similar program, which means that the Cleveland Clinic needs to demonstrate that there is an improvement in value through their higher priced service.

- **There was some discussion of moving Cleveland Clinic employees into a private exchange, but the discussion didn't progress too far.** One of the challenges faced by the Clinic was that it broadly has two groups of employees, including the professional employees and the lower paid workers. Each group has different financial motivations and different trade-offs they are willing to make.

### HC Technology – Room for Layering on Top of the Foundation

We again hosted the Clinic's Associate Chief Medical Information Officer to share his views on health care technology, trends, and where the Clinic is spending HCIT resources. It also offers us a great opportunity to hear about privately-held Epic, one of the largest vendors in the space that competes against Cerner (CERN), with the Cleveland Clinic being a marque client. This year, we also hosted dinner with the senior management team of Explorys, a HCIT data analytics firm spun off from the Cleveland Clinic and now working with 300+ hospitals encompassing 45 million unique patients nationwide.

Our takeaways were evolutionary than revolutionary, but still useful. They validated some of our views as remaining very relevant, added viewpoints on the competitive landscape, and offered some new areas of interest that we'd like to do more work on in the future. We highlight some of them below:

**Population health management is still in its infancy**. The Clinic's mission is to use its IT infrastructure to drive down the cost of care while improving quality. Also important going forward, the Clinic knows it needs to better use technology to understand and influence the manner in which it delivers care through data analytics.

We didn't observe a noticeably improved tone in specific "apps" the Clinic was overlaying to accomplish these tasks than before, but note that companies such as Cerner and arguably Athenahealth should be best positioned to benefit from this trend going forward. Worth pointing out is that the clinic in the past has gone so far as to fund startups in the healthcare data analytics space, with Explorys being a prime example of the Clinic's more prominent investments within the 'big data' space.

Our dinner with Explorys simply amplified the need that providers have for analytics capabilities. One anecdote from the company's co-founder and CSO (not disputed by the health plan senior executive also in attendance) we thought was insightful is that the new reimbursement models discussed between health plans and hospitals are in some ways like a game of poker…but some providers are placing bets without being able to see their hand much less understand it. Given the demand Explorys has seen since its inception in 2009, it only recently began establishing a modest sales force earlier this year.

**Looking beyond Epic**. We've frequently sited that within larger hospital systems, it's increasingly a two-horse race between Epic and Cerner. But especially given Epic's very low profile and discreet demeanor with the Street, our best data come from providers such as our event last week.

The Clinic, as an Epic systems client on the clinical side, continues its work in extracting data to meet its population health objectives. However, it seemed to us that Epic hasn't made material progress on this front since last year. Our impression was that such projects remain in-house, or with upstarts such as Explorys. To the extent this remains an opportunity, it can benefit multiple HCIT vendor bases such as:

- Other inpatient HCIT vendors as Cerner or Allscripts that offer EMR-agnostic population management 'apps'
- Current outpatient HCIT vendors looking to enter the inpatient setting; specifically, Athenahealth with its Enterprise Communicator offering currently in alpha phase.
- New or recent 'big data' startups as Explorys and Health Catalyst.

**Displacement opportunities are not over**. In recent years, there's been a 'land grab' by clinical system vendors as a combination of factors including the start of Meaningful Use incentives, provider consolidation, regulatory requirements, and even vendors sunsetting IT platforms, all leading to providers selecting or displacing their clinical systems. But with over 60% of Medicare- & Medicaid-eligible professionals, and over 80% of eligible hospitals, having made a financial commitment to an eligible Electronic Health Record, we view displacement opportunities decreasing relative to the last couple years.

However, this is the second time in as many months that we've heard displacement opportunities as still being robust. (See our Feb. 27 note "HIMSS-HIMSS…Hooray! The Healthcare IT Boom Continues…"). And during our Clinic visit, displacement opportunities preoccupying vendors was an unexpected theme brought up during our conversations.

**Revenue cycle opportunities remain, but are not immediate**. The Clinic recognizes the significance of an interoperable clinical and financial system able to effectively communicate between claims and financial data in our view. Unlike its clinical system that revolves around Epic, it seems there are some disparate legacy systems from prior hospital acquisitions that have yet to be integrated. So, there could be some ripe opportunities to consolidate financial systems.

But our sense was that there is nothing immediate in the Clinic's HCIT roadmap, at least for the next 12 months. The Clinic had successfully worked to ensure ICD-10 compliance across all its hospitals until the ~1 year delay announced less than two weeks prior to our visit, and we suspect the Clinic is still deliberating its financial systems plans. Should the Clinic decide to invest more in its financial systems, its clinical vendor Epic would be a natural contender to take on more work. Among our coverage universe, MedAssets could benefit from its collection of revenue cycle offerings. And longer term, even possibly Athenahealth, with its enterprise coordinator offering that is designed to operate on top of a hospitals' clinical and financial systems.

**Telehealth, visualization, and infrastructure are this year's buzzwords**. We rarely have time to fully discuss all the various topics within a hospital's IT roadmap, but three buzzwords this year we noted were telehealth, visualization, and infrastructure.

- Telehealth is not new, but something that's still in its infancy and a focus of the Clinic. As the word implies, it's the use of IT and telecommunication technologies to support long distance health care. The clinic has set up what appears to be a beta system to deliver such care, but work continues.

- Visualization, through the examples during our talks, seems to be data analytics-related tools to assist physicians in analyzing and identifying trends. It also included Google-Oculus like tools to conduct telehealth.

- Infrastructure is merely recognizing that the advent of 'eHospitals' is eating up bandwidth; proper networks, support, and overall infrastructure are critical and requires proper planning. While these terms may seem mundane, vague, or farther out, it's still worth noting when it's from such a premier provider organization and something we'll monitor going forward.

### Health Care Facilities – Evolution Toward Population Health Risk

As a high cost, heavily subsidized academic medical center, the Cleveland Clinic continues to see price transparency (note the Clinic was an investor and board member of Castlight, but refused to provide the Clinic's own price information to Castlight) and narrow networks as a risk to their future reimbursement levels. In addition, the Clinic continues to see hospital systems slowly evolving towards assuming population health risk. Along that spectrum, Ohio Medicaid is moving towards episode payment bundles for five common, high-cost diagnoses in 2015. As we also noted earlier, the hip and knee pilot program at one of the Clinic's hospital systems for a 30-day total episodic care payment from Medicare seems to be working and could be expanded to more hospitals in the system in 2015.

Note: Names of all the experts and speakers mentioned in this note are available upon request.

## Covered companies

Allergan, Inc. (AGN.N; US$120.89; 1); Amgen Inc (AMGN.O; US$111.94; 1); Athenahealth, Inc. (ATHN.O; US$139.13; 1); AstraZeneca PLC (AZN.L; £37.81; 2); Baxter International Inc (BAX.N; US$71.98; 2); Bayer AG (BAYGn.DE; €92.81; 1); Biogen Idec Inc (BIIB.O; US$274.00; 1); Bristol Myers Squibb (BMY.N; US$48.83; 1); Boston Scientific Corp (BSX.N; US$12.69; 2); Celgene Corp (CELG.O; US$136.90; 1); Cerner Corp. (CERN.O; US$52.11; 1); Gilead Sciences Inc (GILD.O; US$66.03; 1); Google Inc. (GOOGL.O; US$537.76; 1); InterMune Inc (ITMN.OQ; US$28.16; Not Rated); Johnson & Johnson Inc (JNJ.N; US$96.87; 1); Eli Lilly (LLY.N; US$58.45; 1); MedAssets, Inc. (MDAS.O; US$23.19; 1); Allscripts Healthcare Solutions, Inc. (MDRX.O; US$15.78; 2); Medtronic Inc (MDT.N; US$59.20; 1); Medivation, Inc (MDVN.O; US$55.08; 1); Merck & Co (MRK.N; US$55.92; 2); Novartis AG (NOVN.VX; SFr72.90; 1); Novo Nordisk A/S (NOVOb.CO; Dkr231.40; 1); Pfizer (PFE.N; US$29.86; 1); Regeneron Pharmaceuticals (REGN.O; US$288.36; 1); Roche Holding AG (ROG.VX; SFr250.70; 1); Sanofi SA (SASY.PA; €74.39; 2); St Jude Medical Inc (STJ.N; US$61.64; 3); Stryker Corp (SYK.N; US$79.36; 2); Teva Pharmaceutical Industries Ltd. (TEVA.N; US$50.33; 1); WellPoint (WLP.N; US$95.05; 2); Zimmer Holdings Inc (ZMH.N; US$91.50; 3)

# Appendix A-1

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