Debjit Chattopadhyay: ROTH Capital, in general, has a very strong healthcare presence, and currently follows almost 80 companies in this sector. This gives us a very robust view of what's happening in micro-, small- and mid-cap companies across medical devices, diagnostics, immuno-oncology, regenerative medicine and specialty pharma. This diversity gives us a very unique view as to what's happening in the sector, how development in larger companies is impacting valuations in the micro- and small-cap range, and which technologies are of interest from licensing, partnering and acquisition perspectives.

TLSR: You mentioned a broad range of sectors within healthcare. Can you highlight some of the technologies that pique your interest?

DC: To answer that question, we need to take a step back and look at what's happening with the population. With 10,000 (10K) baby boomers turning 65 every day for the next 15 years, there will be 2 million (2M) additions to that population over those years. In addition, 33% of the country is potentially obese, and over 50% of the country is overweight. Aging and obese populations are prone to multiple diseases and comorbidities, compared to younger populations and populations that are more fit.

"Watch out for NeoGenomics Laboratories: it is significantly undervalued given the opportunities that lie ahead."

Given these significant trends, one can envision which diseases these populations are most likely to be impacted by. For the aging population, the first thing that comes to mind is oncology. In fact, the rate of cancer is 10 times greater for those 65 years and older compared to those under 55. With the aging demographic, 17% or 18% of the population will be susceptible to higher rates of malignancies over the next 10–15 years. Companies focused on targeted therapeutics and diagnostics are addressing this need.
On the other hand, the obese population is at increased risk for cardiovascular, metabolic and orthopedic disorders. For example, statins have benefited patients with hypercholesterolemia. With these drugs going off patent, PCSK9 inhibitors, which block a gene that regulates production of low-density lipoprotein (bad cholesterol), may represent the next generation of treatment. For orthopedic disorders, regenerative medicine will see the use of stem cells to rebuild cartilage, potentially reducing incidences of knee replacement surgery.

Finally, diagnostics are going to play a huge role in both sectors, by targeting each therapeutic to the patient population most likely to respond.

**TLSR:** Do you see consistent growth in healthcare, or are there social and political factors impacting the sector these days?

**DC:** For a long-term investor, I think the healthcare sector offers unique opportunities, as short-term, macro-induced volatility is likely to present investment opportunities. As long as individuals have insurance, underlying chronic or acute conditions have to be treated, unless patients want those conditions to balloon into something much more serious. In an economic downturn, you avoid big-ticket consumer purchases and elective procedures. As long as the employment market remains stable, chronic and/or serious medical conditions have to be addressed.

Overall, in my opinion, healthcare is a growth sector. Furthermore, despite the robust stock performance during 2013, the sector is far from being overvalued. This is especially true for commercial-stage companies where forward price/earnings ratios are supported by earnings growth. Sure, some biotechnology companies are going to blow up because of study failures, but that's where investors must do their research and identify the companies or the technologies most likely to succeed.

**TLSR:** Can you comment on the growing trend linking cancer therapeutics and diagnostics?

**DC:** This trend is a result of the aging population directing the sector. With the projected growth in cancer cases, are you going to treat everybody with a targeted therapy, not knowing what mutation or specific translocation that person has? For example, Genentech/Roche Holding AG's (RHHBY:OTCQX) Herceptin is almost a $7 billion ($7B) global franchise, but only 20-30% of all breast cancer patients are positive for HER2 (human epidermal growth factor receptor 2), and will respond to the therapy. Are you going to give Herceptin to 100% of breast cancer patients, or are you going to be selective and give Herceptin to the few who will respond? With Herceptin therapy costing about $75K, the cost of performing the IHC (immunohistochemistry) and FISH (fluorescence in situ hybridization) tests are more than justified.

Herceptin is an example of an approved therapeutic. What about therapies currently under development? An increasing number of companies are screening patients for relevant gene mutations before enrolling them in clinical trials. These emerging drugs are likely to be approved with companion diagnostics. The pharmacoeconomic benefit to the system and society in general is large. Instead of spending $100K on a drug for a patient who won't respond, spending a few thousand on a diagnostic test is truly meaningful, and the patient is spared from significant adverse events.

**TLSR:** There was resistance to the concept of personalized medicine, at least early on, because pharma companies would like to sell their drugs to as many people as possible. But if a company can select subpopulations likely to be responders, then that company has a whole class of nonresponders for whom it can develop
An increasing number of companies are screening patients for relevant gene mutations before enrolling them in clinical trials. These emerging drugs are likely to be approved with companion diagnostics.

DC: Yes. But it's not just about developing additional therapies. It's also about the time to market, and the probability of success in a clinical trial. If you identify the right patient population, the probability that your trial will succeed is much higher than if you conduct the trial with a random population, where 20% of the patients might benefit. Additionally, by preselecting patients, you can potentially do smaller trials that cost less. Coupling a smaller trial with a potentially shorter time to market, the net present value for a product is a lot higher than conducting a random, 5,000-patient trial and hoping the product works.

TLSR: Please tell me about some of the companies you follow.

DC: In oncology, I cover MacroGenics Inc. (NASDAQ:MGNX) and CTI BioPharma (CTIC:NASDAQ). In the rare disease segment, I follow Sarepta Therapeutics Inc. (SRPT:NASDAQ), Prosensa Holding N.V. (RNA:NASDAQ) and PTC Therapeutics Inc. (PTCT:NASDAQ). On the cancer diagnostic front, I follow NeoGenomics Laboratories (NEO:NASDAQ).

TLSR: What makes NeoGenomics stand out against other companies developing cancer diagnostic technologies?

DC: Let's start with the management team. The CEO, Doug VanOort, has been on board for the last four years, and has done a stellar job in positioning the company. VanOort, during his tenure with Corning Life Sciences Inc., was instrumental in acquiring, merging and rationalizing over 100 different companies. These were eventually spun out as Quest Diagnostics (DGX:NYSE) and Covance Inc. (CVD:NYSE). He has an enormous amount of expertise in merger and acquisition (M&A) strategy and operations. That makes NeoGenomics unique compared to its peers.

In addition, the whole sector has experienced rate cuts from the Centers for Medicare and Medicaid Services. Since 2012, NeoGenomics has seen its average revenue per test decline by over $130. However, it has managed to reduce average cost per test by more than that number, resulting in rising gross margin. The company has a market cap of more than $250M right now, but a couple of weeks ago the market cap was $130–140M. For a company of this size to manage that level of rate cuts through improved efficiency shows VanOort's expertise in managing through adversity. The company has seen significant volume growth because it is being perceived as a one-stop shop in cancer diagnostics. NeoGenomics is well positioned to drive operating leverage, and we see significant earnings growth during 2015.

NeoGenomics is also a reference laboratory, so does not depend on one product for revenue and is not dependent on the feast-or-famine model. It is also in the process of developing proprietary assays, much like Genomic Health Inc. (GHDX:NASDAQ). NeoGenomics is in the process of developing a urine/plasma based-diagnostic for prostate cancer, which it has recently started making available to clinicians as a part of its clinical development program. This is a lab-developed test, so does not need U.S. Food and Drug Administration (FDA) blessing. We think this is the Holy Grail for prostate cancer, and moves the needle away from unnecessary
biopsies. The preliminary data looks very promising, and the test can discriminate between benign prostatic hyperplasia and prostate cancer, as well as predict the aggressiveness of the disease. The test should be ready for commercial launch by the American Society for Clinical Oncology (ASCO) meeting in 2015, and if it lives up to the preliminary data, we think NeoGenomics could be a highflier. Its core business is growing at about 15-25% per year and we expect 20–28% revenue growth for the next two years, with catalysts such as the prostate cancer test not factored into these numbers.

Finally, NeoGenomics has a deal with Covance to be Covance's sole molecular diagnostic service provider for its clinical oncology reference lab segment. Covance is one of the world's largest contract research organizations, with about $2.5B in revenue and about $300–350M of that derived from late-stage oncology testing. Covance never had the capabilities that NeoGenomics has, so the combination of NeoGenomics and Covance is actually helping Covance increase its penetration into the segment. This, in turn, benefits NeoGenomics by providing a third source of revenue. Watch out for this company, because I think it is significantly undervalued given the opportunities that lie ahead.

TLSR: You also mentioned MacroGenics and CTI BioPharma. These are both therapeutics companies.

DC: The CTI BioPharma story is simple to understand. This company has gone through a lot due to bad regulatory experiences with its lead compound, Pixuvri (pixantrone; for treatment of refractory B-cell non-Hodgkin lymphomas). Pixuvri is now approved in Europe. What is more interesting is the 2010-2011 acquisition of pacritinib from Onyx Pharmaceuticals Inc. This myelofibrosis drug is in competition with Jakafi (ruxolitinib), which was developed in collaboration by Incyte Corp. (INCY:NASDAQ) and Novartis AG (NVS:NYSE). Onyx divested because the ruxolitinib data was presumed to be so good that there was no sense competing. CTI BioPharma has advanced pacritinib into a Phase 2b clinical program, and its advantage over the competition is its tolerability profile.

A primary pathology associated with myelofibrosis is thrombocytopenia (low platelet count). Jakafi and an additional product, momelotinib, under development by Gilead Sciences Inc. (GILD:NASDAQ), suffer from exacerbation of the thrombocytopenia problem because they are JAK1 (Janus kinase 1) inhibitors. JAK1 inhibition is known to exacerbate thrombocytopenia. About 37% of the current myelofibrosis patient population cannot tolerate these products, or will receive suboptimal dosages to minimize thrombocytopenia, thus limiting the therapeutic benefits. Pacritinib does not have issues with thrombocytopenia because it specifically inhibits JAK2 and FLT3 (Fms-like tyrosine kinase 3) without binding to JAK1, thus explaining the CTI BioPharma tolerability profile advantage.

CTI BioPharma is now codeveloping pacritinib with Baxter International Inc. (BAX:NYSE). Two Phase 3 studies (PERSIST 1 and 2) are underway. PERSIST 1 is fully enrolled, with a six-month follow-up. This is an all-comers trial, reflecting real-world clinical settings, and not an enriched population as was investigated in the ruxolitinib study. We anticipate data during Q1/15. PERSIST 2 will compare pacritinib directly against ruxolitinib in a population with low platelet counts. In this population, the ruxolitinib dose is almost 75% lower than the Phase 3 dose based on which it was approved. Hence, a head-to-head comparison, if favorable for pacritinib, will be a big commercial differentiator, and could drive higher reimbursement. PERSIST 2 data may not come till late 2015, but we anticipate a rolling new drug application (NDA) filing should PERSIST 1 be positive.

TLSR: What about MacroGenics?
Despite the robust stock performance during 2013, the sector is far from being overvalued.

MacroGenics is an earlier-stage company, with Phase 3 data likely in the 2017–2018 timeframe. That said, the company is developing multiple platform technologies, including dual affinity receptor targeting (DART). DART is similar to Amgen Inc.'s (AMGN:NASDAQ) bispecific T-cell engager (BiTE) platform. These technologies target two different cell surface receptors at the same time. They have the ability to use antibodies to simultaneously downregulate cellular growth promoters and upregulate immunologic pathways, such as T-cell activation. That combination provides T cells to help out while shutting off a pro-stimulatory pathway on the cell surface.

Recently, Amgen announced that its lead BiTE product received breakthrough therapy designation from the FDA. However, there are problems with the BiTE technology stemming from its reliance on electrostatic interactions, instead of covalent linkages, to assemble the heavy and light antibody chains. The DART constructs are more stable due to covalently bound components. Overall, this results in DART constructs having much stronger affinities for their respective targets, thus providing better immune responses. An added advantage of the covalent linkages relates to simpler manufacturing with a predictable chemical outcome.

In head-to-head animal models comparing DART to BiTE, DART has shown much better efficacy, and is now advancing to the clinic for treatment of acute myeloid leukemia (AML). If Amgen's BiTE can get a breakthrough therapy designation, I would expect MacroGenics to pursue the breakthrough therapy designation pathway as well. This designation will allow the company to file a new drug application post-Phase 2b, and significantly accelerate time to market.

Finally, MacroGenics has identified and screened over 100 different DART molecules so far. It has partnerships with a number of pharma companies. Committed dollars to the MacroGenics DART program total about $5B. Currently, one DART molecule is in the clinic and MacroGenics plans to advance another one to the clinic later this year. We would expect some preliminary updates by ASCO 2015. Phase 2/2b is unlikely to be initiated until H2/15.

Another MacroGenics platform is Fc optimization. That program is currently in a Phase 2b study in breast cancer patients who express low levels of HER2 and are not eligible for current HER2-based therapies. If the technology works, it represents a big breakthrough in this sector, leading to more potent antibody-based therapeutics. MacroGenics has two Fc-optimized antibodies in the clinic, and we anticipate data from the breast cancer study during Q1/15. MacroGenics has initiated a Phase 3 study in gastric/gastro-esophageal cancers in patients who have high HER2-expressing tumors (by IHC/FISH). However, data may not be mature till 2018. The second Fc-optimized compound targets B3-H7 overexpressed on cancer cells, and is in the same axis as PD-1 and PD-L1 (programmed cell death 1 and programmed cell death ligand 1). However, the receptor for B3-H7 has not yet be identified, so the data (expected during ASCO 2015) will be eagerly anticipated. MacroGenics is targeting melanoma and prostate cancer in this 90+-patient Phase 1 trial.

MacroGenics is focused on discovery and development, while CTI is focused on acquisition and development. What do you feel are the pros and cons related to these business models?
DC: Not everybody has the infrastructure to execute a research and development (R&D)-based business model. Most often, R&D companies have platform technologies. Examples include antibody companies such as MacroGenics, antisense companies such as Isis Pharmaceuticals Inc. (ISIS:NASDAQ) and RNA interference companies such as Alnylam Pharmaceuticals Inc. (ALNY:NASDAQ). These companies have robust platform technologies from which they can develop multiple therapeutic options for a range of disorders.

CTI, on the other hand, was a drug development company. While Pixuvri is approved in Europe, its patent life is limited and reimbursement in Europe is not as attractive compared to U.S. markets. Furthermore, CTI is required to do a postmarketing study. If it doesn't demonstrate efficacy in that study, Pixuvri's marketing authorization could be pulled. Having learned from that experience, and having been opportunistic and savvy enough to acquire pacitinib in light of problems with competing products, CTI avoided years of research and obtained that product for approximately $0.20 on the dollar. The CTI CEO is a transplant physician, so he understood the differences between the products. The MacroGenics and CTI business models are unique, and each company is doing fairly well in its own space.

TLSR: Sarepta is an RNA therapeutics company, and Alnylam is in similar space. One could argue that pursuit of RNA therapeutics is a risky venture, because no products have been successfully launched in this area.

DC: There are three challenges in the RNA space—delivery, specificity and side effects. Though the challenges are based on the underlying chemistry, they have to be overcome to deliver a specific drug at the right concentrations to induce either a knockdown or an amplification of select gene expression. In this area, Sarepta has carved out a niche for itself by starting with a very different chemistry platform. Departing from the current heavily researched platforms, Sarepta invested in its phosphorodiamidate morpholino oligomer (PMO) chemistry platform. This platform's major disadvantage relates to limited manufacturing expertise in this area, rendering development of Sarepta PMO-based antisense nucleotides cumbersome and expensive.

However, the safety profile of this charge-neutral platform has been remarkable thus far. The company has treated 38 Duchenne muscular dystrophy (DMD) patients with varying doses of its lead compound, eteplirsen, and the drug's safety profile is stellar.

With just 38 patients treated (at various dose levels) thus far, Sarepta intends to file an NDA seeking accelerated approval for eteplirsen. Phase 2 data pointed to a correlation between novel dystrophin expression (a surrogate for clinical benefit) and a clinical endpoint (change in distance walked over six minutes). Since the Phase 2b study was unblinded at week 48, patients have been followed in an open-label format, and as of week 120, continue to demonstrate remarkable stability in their walking ability, versus an expected decline of 20–30% compared to baseline. The recent, 144-week data did show a deterioration in some patients, which has caused the stock to sell off.

However, given the magnitude of eteplirsen's clinical benefit, supported by robust evidence of de novo dystrophin expression, and the progressive and fatal course of this disease, we rate the probability of eteplirsen's H2/15 approval at ~50%. The FDA has indicated to Sarepta that an NDA (for accelerated approval) should be...
filable with additional efficacy data from existing studies, augmented by initial safety
data from the planned pivotal study. To increase the odds of a favorable review,
Sarepta intends to include any or all of the following: 142-week follow-up efficacy
data from the open-label portion of the Phase 2b study, drug exposure data from the
confirmatory trial that is expected to begin during Q3/14, data from a fourth biopsy
from some or all of the 12 patients enrolled in the Phase 2b study, pulmonary
function tests, extensive review of the dystrophin characterization, performed in
collaboration with the FDA, and 164-week efficacy data, post-NDA submission.

Sarepta has also begun preparing for several additional clinical studies, which
together comprise a comprehensive clinical development program for eteplirsen
and other follow-on theropoulos. While the FDA may choose to grant full approval to
eteplirsen during H2/15, Sarepta, based on guidance from the FDA, is planning an
open label, historically-controlled study with eteplirsen in ambulatory DMD patients,
and a second, placebo-controlled study with a follow-on exon-skipping compound,
powered on a clinical endpoint, like a six-minute walk test.

A successful outcome from either of these two studies is likely to be the basis for
eteplirsen’s full approval (assuming only accelerated approval is granted during
H2/15). Moreover, if the randomized trial delivers a positive readout, it could amount
to two simultaneous approvals (eteplirsen and exon 45- or 53-targeting
compounds), which encompasses about 21% of the DMD population. We estimate
that the treatment-amenable patient population (ambulant and non-ambulant) for the
company's first eight therapies to be about 7,000 patients in the U.S.

**TLSR:** Thank you for your time.

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