



Bellevue

Excellence in Healthcare
Investments

Healthcare Observer



Marketing material

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Dear investors,

Generative artificial intelligence (AI) is being adopted across the healthcare industry. The application of AI analytics and algorithms during drug discovery is shortening the time it takes to identify suitable lead molecules for clinical trials. Health services providers are using AI to save working hours and make administrative processes more efficient, and in the medtech segment AI has long been a crucial factor for imaging diagnostics products or the latest generation of surgical robots. Equally groundbreaking is the progress that is being made in the treatment of obesity. In the US, the treatment regimens for obesity and diabetes with novel medications that are covered by health insurers are likely to experience another wave of innovation following the definition of a new health condition known as CKM syndrome. Obesity, type 2 diabetes, chronic kidney disease and cardiovascular disease are closely linked health issues that call for preventive treatment options. AI and obesity are also highlighted in this Healthcare Observer – and we were an early mover in launching our own investment vehicles to address these themes. We hope you enjoy reading our latest issue of Healthcare Observer.

Sincerely, Dr. Cyrill Zimmermann, Head Healthcare Funds & Mandates

Generative AI represents a new investment opportunity

Generative artificial intelligence (GenAI) is capable of much more than drafting or polishing a written text. The targeted deployment of GenAI will bring unprecedented technology-driven change to a wide variety of industries. One industry that will clearly benefit from GenAI is healthcare – that was one of the findings of a study recently published by PwC. AI can help to eliminate glaring inefficiencies and speed up innovation processes. A huge data pool makes this possible. Investors, too, can benefit from these developments.

Alliances between large healthcare companies and tech leaders have particularly promising prospects because they align access to valuable health-related data with GenAI technology. What's more, the current data landscape in healthcare is complex and inefficiently structured, but also fertile ground for deep learning applications.

Much of the healthcare system is characterized by intricate challenges and system complexities as well as a high degree of systemic inefficiency. This is particularly true in drug development and in healthcare services, where administrative tasks are a heavy burden. Successful and precise deployment of artificial intelligence requires access to a vast amount of data. Most healthcare companies today already have Big Data pools, accumulated through many years of clinical studies and other R&D activities as well from large amounts of historical patient data. However, the current data landscape in the healthcare industry is extremely complex and very inefficiently structured. Deep learning applications in GenAI will enable companies to leverage the full potential that this data offers. We are convinced that companies that make artificial intelligence a centerpiece of their business strategy will build a decisive competitive advantage that will serve them well for years to come. Alliances between large healthcare companies and tech leaders have particularly promising prospects because they align access to valuable health-related data with GenAI technology.

and systematically, and development risks will be reduced. Today the entire drug development process typically takes 10-15 years and costs 1-4 bn dollars. GenAI will unleash significant optimization potential for drug developers. Companies such as Amgen are relying on „generative biology“ approaches and have already halved the average time required for target identification and verification while doubling the success rate. Treatment outcomes will also be significantly improved as R&D methods improve. For example, GenAI is being successfully deployed in imaging diagnostics and in AI-guided ultrasound scans of the heart and enabling the early detection of heart failure. The potentially enormous reduction in administrative costs should not be underestimated either – doctors and nurses could free up as much as 25% of their working time by utilizing GenAI for administrative tasks. UnitedHealth, America's largest health insurer, is working on GenAI-powered tools to detect and avoid unnecessary treatments in advance. A more detailed snapshot of these three GenAI leaders is provided below.

In view of the tremendous potential that GenAI holds, we have crea-



Three areas stand to benefit the most from the use of GenAI. First and foremost, drug development, where the current failure rate is in a high range of 80-90%. Medicines will be developed more quickly



ted an investment fund that helps investors to benefit from this trend. Bellevue AI Health is an actively managed global equity fund that is invested in 50-70 healthcare stocks as well as selected tech companies that do considerable business with the healthcare industry. Its portfolio is focused on liquid mega and large caps and rounded out with carefully selected mid-cap stocks. Bellevue’s proprietary AI Affinity Score is used to identify potential investment candidates. It measures to what extent a company is utilizing GenAI and investing in the necessary resources. We are screening for companies that have already made GenAI an integral part of their business models. The portfolio’s estimated annual sales growth over the next three to four years is currently 9% and estimated average EPS growth is 16%.



Three healthcare companies that are benefiting from generative artificial intelligence

Amgen – faster and more successful thanks to «generative biology»

Biotech giant Amgen invests more than USD 4.5 bn dollars a year in its drug discovery and development operations. It is the leader in “generative biology” and had already established a partnership with Google in the field of generative AI back in 2018. Amgen is using generative AI to improve protein structure generation and prediction in lead discovery and NME development processes and to optimize the design and outcomes of its clinical trials. David Reese, Amgen’s Chief Technology Officer and AI Lead, has said that the company’s generative biology approach has already cut antibody discovery timelines in half while doubling the success rate. This, in turn, has sped up the overall development process and reduced the associated R&D risks, which gives Amgen a huge competitive advantage. Amgen is now building a generative AI platform that will use an in-house supercomputer to simulate molecular dynamics.



GE Healthcare is making ultrasound examinations easier to perform

GE HealthCare is one of the world’s leading manufacturers of medical ultrasound systems. Ultrasound is a safe and highly effective diagnostic tool. Mastering it, however, takes years of specialist training. There can be significant differences in image quality, though, not least due to the scarcity of well-trained sonographers. As a result, the benefits of ultrasound have not yet been fully recognized or harnessed. GenAI is now making it possible to “locate” the position of the ultrasound handset and then “navigate” it to precisely the right spot with the help of real-time image recognition and processing. This enables a wide range of healthcare professionals to capture reliable diagnostic-quality ultrasound images using AI as a guide through each step of the scan and image acquisition process in real time. In the future these ultrasound tools will ensure consistently high levels of quality and care.



UnitedHealth – much more than a health insurance company

UnitedHealth is a leader in data- and technology-enabled healthcare services. It has been estimated that more than USD 300 bn is wasted annually in the US healthcare system alone. Late detection of diseases, suboptimal coordination of care and inappropriate treatment lead to additional healthcare costs. The care provided might also be billed incorrectly or fraudulently. This is one area where UnitedHealth is leveraging its AI know-how. As a vertically integrated company specializing in health insurance solutions, care delivery services, and data capture and analysis, UnitedHealth has been investing in Big Data applications for decades. It is now striving to make its tools more effective and easier to use. For example, GenAI is being utilized to monitor patient data and predict hospital stays, readmission rates and disease progression. Preventive measures can be taken as well and gaps in care can be identified and closed. This can have a positive impact on clinical decision-making, which ultimately lowers overall costs and increases efficiency.



Interview



Dr. Terence McManus
Portfolio Manager

«40% of US adults have CKM syndrome»

Portfolio manager Dr Terence McManus outlines how a new definition of cardio-metabolic disorders will enlarge the future universe of novel innovative treatments.

Last year, the American Heart Association (AHA) unveiled the term cardiovascular-kidney-metabolic syndrome (CKM) as a new defined health disorder. Will this trigger the development of new treatments?

Dr. Terence McManus: Actually I think it was a response to new treatments, and how the build-up of clinical trial data helps us understand the commonality between the causes of these diseases. CKM is a syndrome with underlying symptoms, implying a shared underlying pathophysiology. By creating the term CKM, the AHA has underscored the connection between obesity, type-2 diabetes, chronic kidney disease (CKD) and the cardiovascular (CV) diseases. Starting in early age, the progression of CKM is determined by a combination of genetic as well as social factors such as an unhealthy lifestyle. Approximately 40% of the adult population in the US has CKM, so there is a very large patient population and commercial opportunity should treatments be developed which can target the root cause, or more likely, causes.

Are there new early interventions for CKM?

The GLP-1 agonists and SGLT-2 inhibitors could be seen as the first drug classes which address several drivers of early CKM, both of which originally starting in diabetes. The SELECT study in obesity conducted by Novo Nordisk with GLP-1 agonist Wegovy showed a reduced risk of CV disease by 20%. The FLOW study found that patients taking Wegovy reduced the risk of CKD progression as well as CV and kidney death by 24%. The SGLT2 inhibitors such as Farxiga have moved beyond diabetes treatment and into heart failure and CKD treatment. While less in the headlines than the GLP-1s because they do not induce weight-loss, the SGLT2 inhibitors could form a backbone with other CKM drugs. Indeed, AstraZeneca is doing a lot of work on such oral combination therapies, for example zibotentan/Farxiga.

Taking a step back, what remains the first step in treating CKM?

Along with treating obesity, which is very important, LDL cholesterol control remains an issue. While the statin class of drugs, for example Lipitor, have been available in cheap generic forms for many years, millions of patients either cannot tolerate the side effects or are not compliant with treatment. Actually, 16 million US patients taking statins are still not at LDL target! This therefore represents a high-unmet need and large potential market opportunity. We see Novartis as well placed with its 6-monthly PCSK-9 siRNA injection Leqvio. In the pipeline, we would also point to AstraZeneca's oral PCSK9 called AZD0780, which is in mid-stage development.

Beyond obesity and LDL cholesterol, are there any new targets for early CKM intervention?

There is a lot being investigated, but within the CV part of this syndrome, we would point to lipoprotein(a). Novartis and Ionis pharmaceuticals are testing the hypothesis that lowering lipoprotein(a) or Lp(a) when it is elevated, will result in reduced CV events with a drug called pelacarsen. Many epidemiological and genetic studies have demonstrated that Lp(a) is an important genetically determined causal risk factor for CV disease. An estimated 20% of the world's population have elevated Lp(a) levels. As it has not been shown so far that lowering Lp(a) is beneficial, the pivotal clinical trial in 2025 will be an important catalyst for Novartis. Amgen are also targeting Lp(a) in clinical trials, but are a few years behind. Unlike high LDL cholesterol, Lp(a) is not related to lifestyle or exercise, therefore should the link with CV events be proven, the need for pharmacological treatment will be clear.

Could there be other diseases associated with CKM?

Sure, fatty liver is something seen as a consequence of CKM. Again, the GLP-1 agonists are being investigated here, along with several other mechanisms. In addition, the first clinical trials are underway to investigate the effects of CKM on the development of neurodegenerative diseases like Alzheimer's disease decades before their progression.



BIOTECHNOLOGY

The biotech sector had a positive start to 2024, buoyed by expectations that interest rate cuts were imminent.

However, a series of mixed economic signals caused it to reverse direction, despite brighter funding trends for biotech firms. After 55 new drug approvals in the US in 2023, the second-highest number ever, regulatory action continued to support and promote sector innovation. Obesity treatment is becoming an increasingly important segment for the biotech sector. Novo Nordisk bought Catalent for USD 16 bn to ease production bottlenecks for its weight-loss drugs.

Zealand Pharma presented impressive liver fibrosis results in patients with MASH/NASH after treatment with survodutide. Novo Nordisk's FLOW trial demonstrated a 24% reduction in the risk of death in patients with diabetes (T2D) and chronic kidney disease (CKD). Viking Therapeutics released promising early data on its dual GLP-1/GIP receptor agonist which showed a weight loss of 14.7% in patients after 13 weeks of treatment. In oncology, C4 Therapeutics gained on early data from its trial of a degrader medicine in multiple myeloma. A bispecific antibody under development at Merus Pharma could become the new standard combination therapy in patients with head and neck cancer.

Dr. Christian Lach, Portfolio Manager



MEDTECH & SERVICES

The Medtech & Services sector (+2.1%) developed positively over the course of the year, while the Bellevue Medtech & Services Fund Lux (+7.1%) performed even better.

The broader healthcare market (+7.9%) also developed even more strongly. Performance among the various subsectors varied. Medtech investments (+4.6%) delivered a pleasing gain, while healthcare services (-1.1%) weighed on the fund's performance.

Happily, medtech companies reported consistently good quarterly earnings. They are benefiting from a burst of innovation that has created completely new blockbuster markets. The sharp increase in surgical procedures has also benefited hospital chain operators, while some US health insurers were surprised by the high growth rates and will be raising their premium rates next year to remedy the situation.

Stefan Blum, Portfolio Manager



PHARMA & GENERICA

The strong share price momentum in GLP-1 agonist manufacturers Novo Nordisk and Eli Lilly continued over the last 6 months.

Along with impressive prescription data, and quarterly sales, supportive data in comorbidities has helped expand the TAM (total addressable market) and drive share prices. This includes presentation of positive FLOW study data for Novo Nordisk's Wegovy in chronic kidney disease (CKD), and positive SURMOUNT-OSA study data in obstructive sleep apnea (OSA) with Eli Lilly's Zepbound.

We note the general solid performance for generics names over the last 6 months, which we see as benefiting from a stabilization in pricing, removal of opioid litigation overhang, and an improving US biosimilar market. Finally, we would like to point to mid-cap European pharma as a source of diversification, with UCB, Ipsen, and Recordati showing strong recent performances supported by new product launches.

Dr. Terence McManus, Portfolio Manager



ASIEN & EMERGING MARKETS

The healthcare sector in Asia was unable to keep up with the broader market during the past few months, despite positive fundamental news flow.

This can be blamed on geopolitical tensions that continue to cast a shadow over market activity. Washington is specifically targeting Chinese medical services companies active in the biotech industry with the proposed "Biosecure Act". It would prohibit US companies from contracting with Chinese services companies due to national security concerns. When this ban would take effect has not yet been determined.

Proponents of the proposed law claim that the genetic information of American patients is being collected and used for military purposes. The bill currently singles out five Chinese companies that allegedly have ties to the Chinese military: Wuxi Apptec, Wuxi Biologics, BGI, MGI and Complete Genomics. We assume that the bill will become law by the end of 2024, if not sooner. These latest developments put pressure not only on the shares of the 5 aforementioned companies but also on many other Chinese healthcare stocks.

Oliver Kubli, CFA, Portfolio Manager

News

Alarming increase in obesity

More than a billion people worldwide, about 880 million adults and 159 million children, were living with obesity in 2022, which is double the number from 1990. Among children and adolescents 5 to 19 years of age, obesity has quadrupled over the same period. These numbers are from a study published by The Lancet, a world-leading medical journal.

Two diabetes medicines, Novo Nordisk's semaglutide and Eli Lilly's tirzepatide, show promise as a treatment for obesity. At its investor day in March, Novo expressed optimism about its next-gen oral weight loss drug candidates such as cagrisema and amycretin. After that event, estimated global sales of diabetes/obesity drugs in 2035 quickly rose to USD 165 bn. Roche is hoping to muscle its way back into the weight-loss market through its USD 2.7 bn acquisition of Carmot Therapeutics, which comes after its own weight-loss pill Xenical generated disappointing sales.

Biotech firms are staking out a position in the weight-loss market too. Viking Therapeutics, a California biotech, chalked up a win in late February when it published positive results from its trial of VK2735. Patients with obesity showed a reduction in body weight of up to 15% after 13 weeks of treatment. If the topline data is subsequently confirmed, the drug could be more effective than Zepbound and Wegovy. Viking's stock more than doubled in value in the initial market reaction at the end of February. Its recent weakness has only fueled speculation that the company could be a takeover target.

Intuitive Surgical's da Vinci 5 – a new surgical robot platform that is future-ready for AI applications

Intuitive Surgical's da Vinci 5 (dV5), its latest-generation robotic surgical system, has 10 000 times more computing power than its predecessor, the da Vinci Xi. This puts Intuitive Surgical in a position to develop groundbreaking AI-based applications that will offer hospitals even more value. The day is rapidly approaching when robotic-assisted surgery will be standard practice in the operating room.

dV5 – a surgical robot with a sense of touch

Surgical instruments used with the new dV5 can be equipped with force and tactile sensing capabilities that mimic the sense of pressure and touch and thus provide direct haptic feedback to operating surgeons in real time. This technology enables surgeons to feel the push and pull forces exerted on tissue at the tips of the robotic instruments during an operation. This gives them greater confidence which, in turn, expedites their work. What's more, throughout the operation, data is being captured through sensors and images. This data can then be used for objective performance measurements and to benchmark surgical performance, which in turn can lead to suggestions for improvement or individual training plans. With time, the stored data will be used to devise more complex AI applications that can recognize different tissue types or offer precise recommendations to surgeons during surgery, for example.

Also impressive: dV5's upgraded hardware

Images taken inside the body are displayed in a console mounted on a flexible arm that looks like an augmented-reality device. The advanced visual display provides surgeons with images in greater anatomical detail. A wide range of optional instruments such as an insufflator can be easily added to the system. An insufflator is used to increase body cavity pressure to give surgeons more space for the surgical instruments, which improves and quickens their direct control of the surgical robot. Thanks to the system's advanced AI features, surgeons can consistently obtain superior surgical outcomes in less time and steadily improve their skills.

Intuitive Surgical's widens its competitive lead even more

Medtronic, Intuitive Surgical's closest competitor, is still waiting for the FDA to clear its Hugo robotic surgical platform for the US market. Hugo was already inferior to Intuitive's older Xi generation surgical system and it has not gained a notable share of the European market. Compared to dV5, Hugo is even less of a match. Johnson & Johnson, the potential number three player in the surgical robots market, is still in the process of developing its system Ottava.

Intuitive Surgical's line of surgical robots gives it a marketing advantage

Intuitive Surgical will continue to market its previous-generation da Vinci Xi platform and can thus establish different price segments for robotic surgical systems. This, in turn, will enable its management to pursue a flexible approach if at some point competing, inferior systems are marketed at cut-throat prices, rather than sell the company's top-of-the-line product for less than it's worth. Intuitive Surgical is operating from a position of strength and does not want to jeopardize the potential success of its new robotic surgical system. dV5 will be placed with only a few customers in the US in 2024 so that any bugs or issues can be quickly addressed. It will then be launched in markets outside the US in 2025.

Investment case even more compelling now

Leasing arrangements that give customers an option to switch to a different system mean buyers of the well-known da Vinci Xi system can later upgrade to the new dV5 system. Therefore we do not expect Intuitive to report a temporary dip in growth due to a wait-and-see attitude by some customers; quite the opposite. It's conceivable that Intuitive will be able to place the near-new da Vinci Xi systems that customers return in more price-conscious markets at attractive terms. This would accelerate the expansion of its installed base, which in turn drives Intuitive's overall business: 80% of Intuitive's total revenues stem from the sale of surgical instruments. In summary, the dV5 is expected to boost the company's growth rates and lead to both higher unit sales prices and profit margins. Intuitive Surgical has a head start of 20 years, an installed base of 9 000 systems and the largest R&D budget in the business, while penetration rates are still low – robotic surgical systems are used in only about 30% of total potential procedures.

Outlook

Clinical advances for difficult-to-treat tumors

At the 2024 ASCO meeting, early but significant progress was reported with investigational immunotherapies in solid tumors, which are still more difficult to treat compared to hematologic cancers. A handful of data on bispecific antibodies and CAR-T cell therapies in solid tumors was presented in Chicago. These treatment regimens are designed to overcome the immunosuppressive microenvironment of certain tumors.

Presentations on CAR-T cell therapies targeting GPC3 in liver cancer that showed promising early results were one of the highlights of the meeting. In the field of bispecific antibodies, approaches targeting immune cells in a novel manner by means of dual checkpoint inhibitors or costimulatory receptors that enhance T-cell activity against solid tumors were presented. These presentations draw attention to the efforts being made to integrate advanced immunotherapies into treatment regimens for solid tumors. Such developments point to a brighter future and could lead to better treatment outcomes and new hope for patients with difficult-to-treat tumors.

A wave of innovation is sweeping through the medtech sector and creating new blockbuster markets

Robotic-assisted surgical systems (see our article about Intuitive Surgical's new da Vinci 5) and treatments for diabetes such as continuous glucose monitors and insulin pumps, which can now be integrated into fully automated insulin delivery systems, are two of the most attractive areas of innovation in the medtech space today. These are both markets with low market penetration rates, which signals high double-digit growth potential over the long-term horizon. Dexcom and Abbott were recently granted FDA approval for their new continuous glucose monitors that are available to all people without a prescription. The global market for continuous glucose monitors could grow to more than USD 20 bn by 2028, and Abbott and Dexcom are projected to command a combined market share of about 90%. Insulin pump manufacturers such as Insulet should likewise benefit from this high market growth.

Treatments for structural heart disease are another major growth trigger, especially treatments for heart valve problems. Minimally invasive procedures have become the gold standard for aortic valve replacement, and the market for transcatheter aortic valve replacement could grow to USD 10 bn by 2028. The recent US approval of Evoque from Edwards Biosciences, the world's first transcatheter tricuspid valve replacement system, has opened up a completely new market. Meanwhile in the field of mitral valve surgery, where repair procedures such as Abbott's MitraClip or Edwards Biosciences Pascal for MR are dominant, an alternative solution involving mitral valve replacement could soon be granted marketing authorization. Exciting data from Edwards Biosciences trial of its Sapien M3 transcatheter mitral valve system could be released already early next year.

Treatment options for cardiac arrhythmia, atrial fibrillation in particular, have been enhanced with the emergence of pulsed field ablation (PFA) solutions. This new ablation technology is likely to supplant conventional methods because it is safer and faster. Thanks to the advantages PFA offers, this market volume is forecast to grow from currently zero to USD 6 bn by 2028. Boston Scientific and Medtronic are both marketing products backed by excellent clinical trial data. Two other industry heavyweights, Johnson & Johnson and Abbott, are about to enter the market with their own PFA products.

There are many other notable innovations in the medical technology sector beyond the aforementioned indication areas, too, for example in ophthalmology. RxSight offers intraocular lenses for cataract surgery whose focusing power can be easily adjusted after they are implanted. In summary, the medical technology sector boasts a wide range of impressive innovations that represent attractive opportunities for investors. With the Bellevue Medtech & Services Fund, we offer a well-diversified vehicle to capture these opportunities.

Healthcare costs and the US election cycle

In contrast to previous elections going back two decades, government health policy is not a major concern for US voters in the current election cycle. In a recent Gallup survey of voter concerns, healthcare ranked a distant 16th, well behind the first four most important issues of immigration, the government, the economy, and inflation. Whoever wins the US presidential election in November will nevertheless have to address spiraling healthcare costs in view of the federal government's record budget deficit this year. In contrast to his stance in past years, Donald Trump is no longer vowing to repeal and replace the Obama administration's Affordable Care Act (ACA). Democrats and Republicans are both in favor of putting certain caps on drug prices. A law passed in 2022 with that in mind allows Medicare, the US government's health insurance program, to negotiate lower prices for 10-15 prescription drugs every year. The first negotiated prices will become effective beginning in 2026. Consolidation trends in clinical services are increasing the pressure on medical clinics to operate more profitably. These issues are also known to the broader public. It therefore appears unlikely that healthcare sector stocks will experience higher levels of as the US elections approach.



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