Bellevue Healthcare Trust

SEPTEMBER 2022

Factsheet

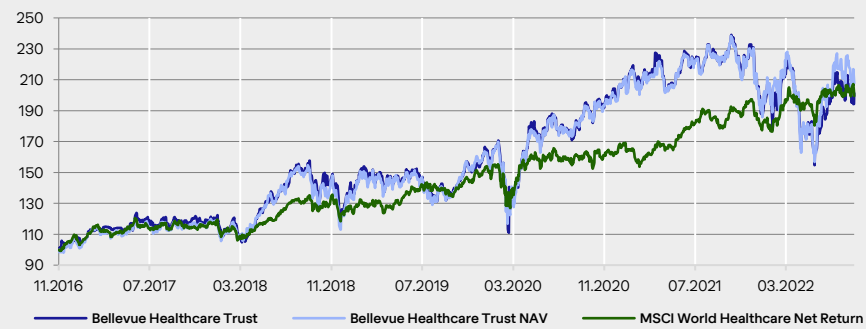
London Stock Exchange (LSE)

Marketing document

Investment focus

Bellevue Healthcare Trust intends to invest in a concentrated portfolio of listed or quoted equities in the global healthcare industry. The investable universe for the fund is the global healthcare industry including companies within industries such as pharmaceuticals, bio-technology, medical devices and equipment, healthcare insurers and facility operators, information technology (where the product or service supports, supplies or services the delivery of healthcare), drug retail, consumer healthcare and distribution. There is no restrictions on the constituents of the fund's portfolio by index benchmark, geography, market capitalisation or healthcare industry sub-sector. Bellevue Healthcare will not seek to replicate the benchmark index in constructing its portfolio. The Fund takes ESG factors into consideration while implementing the afore-mentioned investment objectives.

Indexed performance since launch



Cumulated & annualized performance

Cummulated

	1 M	1 Y	2 Y	3 Y	4 Y	5 Y	ITD
Share	-0.9%	-9.7%	8.7%	47.3%	29.1%	72.5%	101.4%
NAV	-2.4%	-7.7%	12.1%	52.4%	34.2%	81.4%	107.8%
BM	0.3%	9.1%	24.1%	42.7%	48.7%	74.4%	99.4%

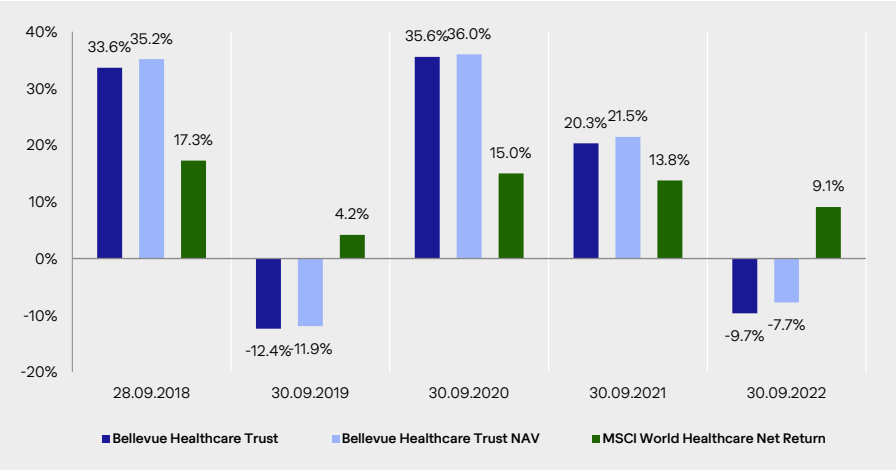
Annualized

1 Y	3 Y	5 Y	ITD
-9.7%	13.8%	11.5%	12.8%
-7.7%	15.1%	12.6%	13.4%
9.1%	12.6%	11.8%	12.6%

Annual performance

	2017	2018	2019	2020	2021	YTD
Share	14.8%	4.9%	22.7%	29.1%	16.6%	-12.8%
NAV	12.7%	8.6%	25.9%	25.7%	15.2%	-8.0%
BM	9.4%	8.8%	18.4%	10.3%	20.8%	1.7%

Rolling 12-month-performance



Fund facts

Share price	GBp 169.00
Net Asset Value (NAV)	GBp 174.13
Market Capitalisation	GBp 991.7 mn
Investment manager	Bellevue Asset Management (UK) Ltd.
Administrator	Sanne Fund Services (UK) Ltd.
Launch date	01.12.2016
Fiscal year end	Nov 30
Benchmark	MSCI World Healthcare Net Return
ISIN code	GB00BZCNLL95
Bloomberg	BBH LN Equity
Number of ordinary shares	586'783'083
Management fee	0.95%
Performance fee	none
Min. investment	n.a.
Legal entity	UK Investment Trust (plc)
EU SFDR 2019/2088	Article 8

Key figures

Beta	1.29
Correlation	0.77
Volatility	30.3%
Tracking Error	20.17
Active Share	92.83
Sharpe Ratio	0.73
Information Ratio	0.34
Jensen's Alpha	3.64

Source: Bellevue Asset Management, 30.09.2022;
Calculation based on the Net Asset Value (NAV) over the last 3 years.

Source: Bellevue Asset Management, 30.09.2022; all figures in GBp %, total return / BVI-methodology

Past performance is not a reliable indicator of future results and can be misleading. Changes in the rate of exchange may have an adverse effect on prices and incomes. All performance figures reflect the reinvestment of dividends and do not take into account the commissions and costs incurred on the issue and redemption of shares, if any. The reference benchmark is used for performance comparison purposes only (dividend reinvested). No benchmark is directly identical to the fund, thus the performance of a benchmark is not a reliable indicator of future performance of the Bellevue Healthcare Trust to which it is compared. There can be no assurance that a return will be achieved or that a substantial loss of capital will not be incurred.

Top 10 positions

Option Care Health	6.7%
Axonics	6.7%
Sarepta Therapeutics	6.6%
Jazz Pharmaceuticals	6.2%
Insmed	5.6%
UnitedHealth Group	5.4%
Apellis Pharmaceuticals	5.4%
Charles River Labs	4.2%
Amedisys	4.1%
Tandem Diabetes Care	4.1%
Total top 10 positions	55.0%

Sector breakdown

Focused Therapeutics	25.3%
Med-Tech	18.1%
Services	15.1%
Diagnostics	10.5%
Managed Care	9.1%
Diversified Therapeutics	6.2%
Healthcare IT	5.9%
Tools	4.9%
Health Tech	4.1%
Dental	1.0%

Geographic breakdown

United States	95.3%
China	2.0%
Canada	1.7%
Switzerland	1.0%

Market cap breakdown

Mega-Cap	14.6%
Large-Cap	8.6%
Mid-Cap	51.6%
Small-Cap	25.3%

Due to rounding, figures may not add up to 100.00%

Source: Bellevue Asset Management, 30.09.2022;
For illustrative purposes only. Holdings and allocations are subject to change. Any reference to a specific company or security does not constitute a recommendation to buy, sell, hold or directly invest in the company or securities. Where the subfund is denominated in a currency other than an investor's base currency, changes in the rate of exchange may have an adverse effect on price and income.

It's October and we are officially bereft of transcendent adjectives that would adequately describe market dynamics and the parlous state of UK Plc. Indeed, the temptation to break with the norms of acceptable business language into a tirade of expletives is almost overwhelming.

One could resort to comedic parody, but we have to live here and live through all of this. Moreover, the very real misery coming down the line for the majority feels like no laughing matter. The last time we were here (2007), Tony Blair won a landslide victory to the pop synth beats of "things can only get better".

Except they didn't, not really. The can got kicked further down the road. As is so often the case, the political solutions on offer were hollow quick fixes. So here we are in late 2022 (or is it 1978 redux? Time will tell). The can is pretty bashed up now and the road is at an end, having taken us to some geopolitical cul-de-sac where it feels very cold indeed.

If we have anything positive to say, it is that our investments will succeed or fail far from these shores, demand for the products is not economically sensitive and our assets are not in sterling. Not so much positive then, as inured from the widespread negatives that swirl around us.

Monthly review

The UK market

Very few things have amused us in recent weeks. However, the assertion from the Labour conference that "hedge funders" must have got a sneak peek at the budget because "they all shorted sterling" made us snigger. It betrays that a failure to understand even the basics of economics and markets is a pervasive failing across the UK political "talent pool".

The jollity was short-lived however. It is very hard to find even a glimmer of long-term optimism amongst such a paucity of vision and talent, although the 1 October reversal of the 45% tax rate abolition does at least suggest this new administration is not completely ideologically focused. All they need now are some policies that might actually help the economy and the long-suffering populace.

It's not as if the problems that ail our ~~sceptred~~ septic isle are new. The Government's professional whatabouterists will of course argue the current crisis is a global, geopolitical calamity fomented by the disorderly post-COVID normalisation and the invasion of Ukraine. This is fair, but only to a point.

It does not address the (ongoing) question of why the UK is so poorly equipped to deal with these, or indeed any, crises versus other comparable Western nations. Our lack of economic resilience is undoubtedly the product of generations of poor management, making all mainstream politicians and parties jointly culpable. For our younger readers, we encourage you to spend some time researching the collapse of the Callaghan administration (Labour) and 1978's 'winter of discontent'. We are old enough to recall its impact and the lessons of that time feel eerily relevant today.

We know that Italy and Greece are not France and Germany and, despite the size of our economy, we probably deserve to sit somewhere in the middle of those EU bookends on a myriad of measures. However, it feels that we are much closer to Italy than Germany (both were yoked to Russian gas).

Moreover, the success of our close neighbour Ireland in tackling multiple crises since 2008 (and Thatcher in 1979-83) surely attests to the ability of even vaguely competent administrations to turn around dire situations of their own making in a service-driven economy. There is no magic either; they turned things around by telling the population the truth and taking tough decisions quickly (huge tax increases, three emergency budgets in a row from 2009-2011). It wasn't pretty, but there is no pretty way to clean a festering wound.

Aside from putting the country back on a sustained GDP recovery and improvement in living standards, this left Ireland with a stronger-than-expected balance sheet and thus some flexibility to manage Brexit and now the energy situation, where it continues to plan interventions targeted at the most needy.

Ireland is not perfect; no country is. However, it does offer a comparator, showing it is still possible to take bold political action to address a crisis, even when you are stuck inside a leviathan bureaucracy and cannot devalue your way out due to the lack of a sovereign currency.

For the UK, what better time to have taken bold action than when you have no EU strictures to adhere to, an 80-seat majority to ram through legislation and two years left on the clock? Instead, we have more fantasy economics that may guarantee the outcome that prompts all this timidity in the first place – electoral suicide (as Callaghan found out). We have used this quote before, but it is so apt that it bears repeating: "A great leader takes people where they don't necessarily want to go, but ought to be".

Like many other countries, the UK stock-market (FTSE All-Share Index) is dominated by a small number of global mega-cap companies. The ten largest companies (two oils, two pharmas, three Consumer Goods, a miner, a bank and a Swiss commodities trader) account for almost 43% of the index by weighting and earn most of their profits abroad.

With sterling falling and the value of foreign profits thus increasing, one would expect these companies to hold up quite well and this was indeed the case. The FTSE All-Share Top-10 declined 3.2% in sterling terms during September, compared to a fall of 5.4% for the MSCI World Index, which is of course dominated by dollar-reporting global multi-nationals.

However, the other facet that the UK market shares with its peers is a long tail of much smaller, more locally focused companies. Although many of these also have foreign/export earnings, they are a barometer of expectations for the wider UK economy and it is no surprise that the picture there has been an ugly one.

The overall All-Share Index declined 7.0% in sterling terms over September. It fell 11.1% when measured in a real currency – the US dollar. If you are looking for some cheer, it was up 6.0% if you measure it in Zimbabwean dollars. Another way of comparing the local with the global is to compare the sterling monthly return of the multi-national-led FTSE-100 Index (-6.3%) with the SMID-Cap FTSE-250 Index (-10.4%).

As UK consumer confidence collapses, that long (and less liquid) tail wags the dog and the market sell-off becomes a self-fulfilling prophecy, especially among retail investors and the elderly, who perhaps cannot afford to take a long-term view on the recovery of their portfolio; why would one remain invested in any asset that feels likely to decline further?

At this point, regular readers might be wondering why we have elected to include a section on the UK market. The reason is this: the liquidation of portfolios ("put me in cash, preferably dollars") sinks all ships and has manifested itself in disorderly sell-off. Another attendant (inevitable?) consequence is that many Investment Trusts have fallen onto greater discounts.

This will often have nothing to do with the quality of the underlying investments; when there are more sellers than buyers, equity prices fall. There is value out there to be sure, but people are shell-shocked and it will likely take a bit of time before we see any meaningful (and careful) dip-buying.

Data from JP Morgan, who are one of the Trust's brokers, suggests that the average discount across the UK Investment Trust sector increased from ~13% at the end of August to closer to 16% at the end of September, and this compares to around 5% at the beginning of 2022. We too have seen an escalation in the discount on Bellevue Healthcare over the month (5.7% as of the end of September), having traded at an average premium of 0.5% from inception to the end of 2021.

What might the managers be able to do about these discounts? Share buybacks by Trusts are one option. In reality, these must be conducted on an arm's length basis and in a manner that does not distort trading. As such, it will seldom have a material impact – the Trust would simply furnish sellers with liquidity and diminish the capital the manager has available to buy cheap assets on behalf of the remaining shareholders. This feels rather unfair, especially when there are some compelling opportunities within the scope of the wider investment environment.

It is deeply frustrating to say so, but we probably need to resign ourselves to higher discounts persisting as a wider phenomenon in the Trust sector until broader confidence in the UK stock market is restored. This will be a function of asset prices being deemed to have fallen far enough or some sort of profound change in the economic outlook for the country.

However, the latter seems fanciful to us. The country is in a mess and there will be difficult months and years ahead. As Ireland amply demonstrates, the pain is unavoidable, and the choice should be one between a short, sharp shock or protracted misery. The UK though seems to have found a third way; prolonged misery through economic policies that do not address the core issues and fail to help the plurality of the populous. All this will achieve is a protracted visit to the electoral wilderness for the Conservative party and, whatever your politics, a weak party in opposition or Government is not good in our system (look at the mess the SNP has made in Scotland).

In this context, we think the best thing a domestic investor can do in the short-term is to focus on under-valued UK-listed equities that are de-coupled from the UK economy and sterling. A global healthcare-focused Investment Trust for example.

The wider market

Amidst a backdrop of pernicious core inflation, rising rates and growing geo-political/energy tensions, September saw a continuation of late August's negative macro-driven sentiment. As noted previously, the MSCI World Index declined 9.5% in dollar terms during September (5.4% when measured in sterling). This is the worst monthly performance year-to-date in what has been a roller-coaster year that has seen the Index decline 26.4% year-to-date in dollars (-10.5% in sterling).

We list the sector performances in Figure 1 below. Every sector was in the red and, given the economic outlook was the key sentiment driver, it is no surprise to see the classically defensive Pharma & Biotech sector declining the least and the remainder of healthcare in second place. As we have noted many times, the drivers of demand for the sector are demographic, not economic.

Indeed, there is very little about the dispersal of returns that is surprising, if your default position is that the economy is slowing. Rising rates will likely further exacerbate consumer caution, especially toward any big ticket purchases such as property or vehicles. A higher rate environment potentially increases profit margins for financial institutions, but only so long as deteriorating credit quality does not become too much of a headwind.

Sector	Monthly perf (USD)
Pharmaceuticals, Biotechnology	-3.2%
Healthcare Equipment & Services	-6.0%
Consumer Services	-6.0%
Insurance	-6.9%
Commercial & Professional Services	-6.9%
Food, Beverage & Tobacco	-8.0%
Banks	-8.2%
Retailing	-8.3%
Food & Staples Retailing	-8.4%
Household & Personal Products	-8.5%
Automobiles & Components	-9.1%
Materials	-9.2%
Telecommunications Serivces	-9.5%
Energy	-9.9%
Diversified Financials	-9.9%
Capital Goods	-10.2%
Software & Services	-11.1%
Utilities	-11.9%
Technology Hardware & Equipment	-11.9%
Media & Entertainment	-12.1%
Real Estate	-13.3%
Consumer Durables & Apparel	-13.5%
Transportation	-13.8%
Semiconductors & Semiconductor Equipment	-14.5%

Source: Bellevue Asset Management, 30.09.2022

Healthcare

As noted previously and per the comments in last month's factsheet about the negative economic sentiment being likely to favour healthcare on a relative performance basis, the dynamic described above delivered the expected relative positive performance. In sterling terms, the MSCI World Healthcare Index rose 0.2%. It declined 4.1% in dollars, well ahead of the MSCI World Index's -9.5% dollar return. However, this is still not a positive overall performance.

Within this broadly defensive sector, the most resilient sub-sectors from a demand perspective are pharmaceuticals (Focused & Diversified Therapeutics), Distributors and Managed Care (health insurers). In constituent value terms, the Conglomerate sub-sector is mostly pharmaceutical exposure.

When viewed in this context, the sub-sector performance data in Figure 2 below is broadly unremarkable, save for Healthcare Technology (diabetes devices) which one might have expected to be closer to the bottom given its consumer discretionary element. However, both Dexcom and Tandem Diabetes Care saw material rallies during the month; Insulet was more of a laggard.

On the other side, one can understand why the focus on rising interest rates would impact higher rated sub-sectors (e.g. Healthcare IT) and those with a consumer discretionary element (Dental) would fare worst. The Facilities (hospitals) sector performance was hurt by KKR walking away from its April 2022 offer to acquire Australian operator Ramsay Health Care. We estimate this impacted the sub-sector performance by ~200bps. These companies also tend to be highly indebted and thus quite sensitive to rising interest rates.

	Weighting	Perf (USD)	Perf (GBP)
Focused Therapeutics	7.4%	-0.2%	4.2%
Diversified Therapeutics	36.5%	-2.0%	2.4%
Conglomerate	12.1%	-2.1%	2.2%
Managed Care	11.9%	-3.6%	0.7%
Healthcare Technology	0.7%	-4.9%	-0.7%
Other HC	1.5%	-6.1%	-1.9%
Tools	9.0%	-7.4%	-3.3%
Distributors	1.4%	-7.5%	-3.4%
Diagnostics	1.6%	-7.6%	-3.5%
Med-Tech	12.7%	-8.1%	-4.0%
Generics	0.4%	-9.3%	-5.3%
Facilities	1.0%	-9.8%	-5.8%
Services	2.5%	-12.8%	-8.9%
Dental	0.5%	-15.2%	-11.4%
Healthcare IT	0.7%	-16.5%	-12.8%
Index perf		**-4.1%**	**0.2%**

Source: Bloomberg/MSCI and Bellevue Asset Management (UK) Ltd. Weightings as of 31.08.2022. Performance to 30.09.2022.

As we move into Q4 and Q3 2022 reporting gets underway, we expect the focus to remain on the resilience of the earnings outlook, with the potential for negative earnings revisions to come from the more discretionary end of the market and in those sectors where there are options to trade down/away from certain product types. We will also be keeping an eye on the impact of the inevitable uptick in COVID-19 cases and the extent to which this will impact the availability of critical care and intensive care beds and thus available bed capacity to support the ongoing recovery in elective procedure volumes.

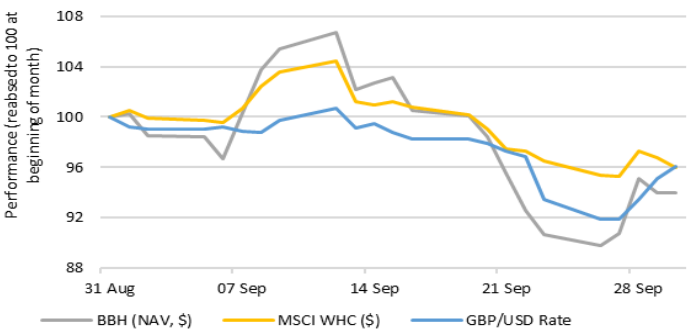
As a final thought, we wanted to come back to our prior observation of SMID-healthcare being unfairly punished versus the broader sector since Q4 2021. We have used the relative performance of the Mid-Cap Russell 2000 Healthcare Index as a proxy for Mid-Cap to show the under-performance compared to Large-Cap.

This trend reversed markedly in July and August (+673bp and +800bp in favour of the Russell respectively when measured in dollars, even though the sector overall declined in August). We found it interesting this outperformance held again through September despite the wider sector going down in dollar terms once again.

However, if we look at the 12-month period to the end of September 2022, the Russell 2000 Healthcare Index is still 23.3% behind the MSCI World Healthcare Index. There is clearly much further to go, but we are somewhat reassured that the return of a more negative overall equities narrative is not leading to the return of this unusual dynamic.

The Trust

The positive relative sector performance and seemingly predictable sub-sector outcomes belie a significant amount of volatility during the month, which actually started more positively than we expected (Figure 3). During September, the Trust's net asset value declined 2.4% to 174.15p, under-performing the MSCI World Healthcare Index by 277bps. We estimate that the continued weakening of sterling contributed 426bp to the evolution of the NAV, which is in line with our estimate for the FX benefit to the MSCI World Healthcare Index.



Source: Bellevue Asset Management, 30.09.2022

The Healthcare IT and Healthcare Technology sectors both contributed positively to the evolution of our NAV over the month; all other sub-sectors were negative with Focused Therapeutics and Diagnostics the biggest laggards.

The evolution of the portfolio is summarised in Figure 4 below and we would make the following comments: we increased our exposure to Dental as the sub-sector weakened further. Although our overall exposure to Diagnostics fell on share price weakness, we added to our holdings. Diversified Therapeutics holdings were unchanged and Focused Therapeutics holdings decreased. We added to our Healthcare Technology and Healthcare IT holdings and reduced exposure to Managed Care. Med-Tech was essentially unchanged and we added materially to both Services and Tools.

	Subsectors end Aug 22	Subsectors end Sep 22	Change
Dental	0.9%	1.0%	Increased
Diagnostics	10.9%	10.4%	Decreased
Diversified Therapeutics	6.9%	6.3%	Decreased
Focused Therapeutics	25.8%	25.4%	Decreased
Healthcare IT	5.4%	5.9%	Increased
Healthcare Technology	3.3%	4.0%	Increased
Managed Care	9.2%	9.1%	Decreased
Med-Tech	18.1%	18.1%	Unchanged
Services	14.9%	15.1%	Increased
Tools	4.7%	4.8%	Increased
	100.0%	**100.0%**	

Source: Bellevue Asset Management, 30.09.2022

The investment portfolio remains unchanged, with the same 29 holdings. There was no share issuance during September because the Trust's shares remained at a discount to NAV that averaged 5.5% across the month, compared to a discount of 4.0% during August.

The net acquisitions to our holdings and the decline in NAV led to the leverage ratio increasing from 4.9% at the end of August to 6.2% at the end of September (note – the August figure takes account of the pending dividend payment that investors received in early September; this actually left the Trust's accounts before the end of August).

Manager's Musings

For those of you who have made it this far into the monthly missive, we feel a bit of levity and positivity is required. So, let us leave behind market meandering and our maladroit macro-economic observations and delve into some blue-sky optimism.

We start with a question: what are the most important clinical programmes ongoing in the world today, in terms of the potential future impact on alleviating humanity's burden of morbidity and suffering.

We have listed our views on a few of the more interesting ones below that cover the three key areas of either detecting, preventing or managing a potentially serious medical condition in a way that could impact many lives and also save society tens of billions of dollars in avoided medical costs and improved quality years of life for those impacted.

Hopefully, these summaries will serve as a reminder to us all how amazing and constructive science can be and also demonstrate once more that, when people work together, they can achieve the most incredible things.

There is so much in the world right now to worry about, let's take a little time to out appreciate the objective truth that today is still the best time for the average human being to have been alive, apart from tomorrow, which will be better again.

The synthetic pancreas

There are some nine million people in the world living with Type 1 diabetes, a third of whom are in lower income countries. All these patients must inject insulin for the rest of their lives.

Whilst pumps controlled by algorithms and continuous glucose monitoring technology have greatly improved control for those fortunate enough to be able to afford them, it is still a reality that high blood sugar damages peripheral nerves and vasculature and increases the long-term risks of macro cardiovascular and neuro-degenerative diseases.

Low blood sugar episodes can range from merely very unpleasant to fatal. The lifetime costs of managing a Type 1 diabetes patient in the US have been estimated at ~$1 million.

Whilst it would be lovely to imagine this disease being confined to history, its underlying cause remains elusive. Some foreign agent appears to induce an immune reaction that creates auto-antibodies which also attack the islet cells of the pancreas.

A number of common viruses have been implicated but not definitively and there is no clarity as to why some people manage to cope with infections of these viruses without any long-term complications, whereas others succumb to diabetes.

This has led to various attempts at building a synthetic pancreas, either technologically (impossible to make small enough to be implantable) or using cadaverous islet cell transplants (not enough donor tissue, a theme we will return to). However, cell engineering has progressed to the point where it is possible to generate synthetic islet cells.

Fortunately, the body's islet cell mass is tiny (around 1cm3 of tissue, not all of which are insulin-secreting cells) and can thus be enveloped into a container that allows tissue fluid in and out but does not allow immune cells to 'see' the synthetic cells and attack them.

There are a couple of companies working on this type of approach, but the most advanced programme is Vertex Pharmaceutical's VX-880 programme, where the first few patients are seeing good results with unencapsulated cells and concomitant transplant rejection drugs. The encapsulated cell trials without the immune-suppressive drugs have yet to commence.

Given the costs of managing the disease and the patient benefit of potentially being able to go back to leading a 'normal' life after receiving one of these cellular implants, the commercial opportunity here is significant, as are the potential benefits to society. The programme is not yet advanced anywhere near enough to be a justification for owing Vertex in its own right, but this bio-engineering project offers some interesting upside optionality that could, in time, transform millions of lives. Vertex Pharmaceuticals is included in the BBH portfolio.

The GSK malaria vaccine programme

Regular readers will know that we are seldom fans of 'big pharma' and often cite GSK as the apotheosis of the persistent mediocrity that defines the breed. Just as a broken clock can be right twice per day, then so even the most mediocre can rise to be exceptional.

GSK's vaccine Mosquirix (a.k.a. RTS,S) has been in development since 1987, but only received a recommendation from the World Health Organisation in 2021, some 34 years later; such are the complexities of developing a vaccine against a pathogen with multiple life cycle stages and also intended for delivery in remote locations that complicate delivery and storage.

The phase 3 trial followed some 15,500 children for more than four years. Whilst a lot of the funding has come from various foundations and NGOs, the company has nonetheless devoted time, money and resources to this programme for decades and continues to support manufacturing and donations of finished vaccine doses (it is a four-dose vaccination).

A number of pilot programmes are underway across sub-Saharan Africa and long-term follow up studies from earlier cohorts suggest the vaccine has a durable impact on the incidence of severe malaria going out to about 10 years. GSK's programme will continue to follow these cohorts for several more years to come. It is planned that that vaccine manufacturing know-how will ultimately be shared with other local companies in a manner similar to the Oxford (AZN) COVID vaccine.

The economic and health burden of malaria cannot be overstated. Half the world's population live in areas where people are at risk of catching Malaria and an estimated 250 million people are laid low by serious cases of infection, leaving them unable to work, attend school or care for their families.

More than 95% of these serious cases are in sub-Saharan Africa. The disease kills more than 600,000 people every year and 80% of these are in children under the age of five. The socio-economic burden of the disease is very hard to measure, but is estimated by the CDC at $12 billion per annum.

All of GSK's work has shown the RTS,S vaccine is both safe and effective in young children. If the vaccine can reduce severe illness and death in these crucial early years, it will hopefully leave people stronger and healthier to cope with the risks of infection later in life (as yet we do not have enough data on this latter point, but the trend is a positive one so far). Humanity has enjoyed some tremendous success with preventative vaccination programmes: smallpox, polio, measles, mumps, rubella and most recently SARS-CoV-2.

Within a few years, Mosquirix will have joined this list and the world will be a better place for many children yet to be born. We can confidently say that GSK will never be in the BBH portfolio, but we are not so narrow minded as to not doff our cap to a tremendous piece of philanthropic medical research.

Bio-engineering of organs for transplant

We previously described how there are not enough harvestable islet cells to offer cadaverous insulin implants. However, exogenous insulin is there as a readily available life-long alternative. There is a more serious general shortage of organs for transplant, owing to the majority of people dying in old age (with

organ failure being a common aspect of eventual death) and the need for a high degree of immunological matching between donor and recipient.

In the US alone, there are about 40,000 organ transplants every year and around 106,000 on the waiting list at any given time. Around 20 people on the list die each day without receiving their potentially life-saving transplant and less than half of those who go on to the waiting list can realistically expect to eventually receive an organ in time.

One potential solution to this challenge is to genetically engineer animal strains to be less immunogenic (i.e. more compatible with human tissue) and then farm animals as a source of organs. This is referred to as xenotransplantation and the first whole organ xenotransplants (from engineered pigs) into a live patient were undertaken in early 2022.

Both hearts and kidneys have been transplanted. These pigs are bio-engineered, having received a number of genetic modifications to reduce the risk of acute (i.e. immediate) rejection. Further genetic modifications to improve bio-compatibility are likely over the coming years. This pioneering research is being led by the University of Maryland Medical Center in Baltimore, USA.

The other alternative is to "grow" new human organs to order. Whilst this does not immediately resolve the issue of rejection, we are much more familiar with managing human donor rejection from decades of traditional transplant surgeries and, in time, we may also be able to develop human stem cell lines that are less inherently immunogenic so that people could receive an 'off the shelf' organ.

Immunogenicity aside, the main challenge with replacing a functioning organ with anything synthetic ("bio-engineered") is one of structure. Even if you had a supply of the relevant stem cells to grow an organ, it is not as simple as putting a few cells in a dish and then waiting for a fully formed heart to emerge a few months later.

The cells need a scaffold to form the correct structure: the "extra-cellular matrix". This is an incredibly complex and delicate three dimensional structure, whose constituents vary with each organ system but is chiefly composed of three types of protein that readers will be familiar with: collagen, elastin and keratin.

Bio-engineering "Blade Runner" style remains a science-fiction fantasy. We currently lack the technological know-how to 3D print a whole-organ ECM to order, although this may be possible one day and there is some work ongoing to produce specialised sheets of ECM material using 3D-printing to repair damaged tissue in the heart or the lung. The Biomedical Engineering department at Carnegie Mellon University in the United States is doing some interesting work in this area.

Whilst it is a delicate structure, the ECM is much more robust one than the cells which it contains and it is thus possible to denude the matrix of cells to leave the matrix structure intact. Theoretically then, we could harvest organ ECMs from cadavers. The harvested ECM is not immunogenic and thus can be recycled as a scaffold to grow a new organ.

There will be a far greater supply of viable ECMs from organ donors than whole organs, so this is an exciting prospective step in improving the supply of donor organs. A micro-cap US biotechnology company called Miromatrix is active in this area.

The nature of the matrix itself seems to impart information to progenitor cells such that they "know" what part of an organ they are supposed to become and you see specialisation and migration of the progenitor cells over the matrix to eventually form the complex organ that is desired. However, the business of growing a functioning heart, lung or kidney is still complex and we are many years away from having the first viable synthetic organs for transplant.

Coming back to xenotransplants; simple structures for wound repair (including synthetic ECM materials derived from pigs) have been used for various surgeries for some years now (e.g. prosthetic cornea ECMs known as a keratoprosthesis).

Early stage cancer screening using liquid biopsy of cell-free tumour DNA

In contrast to the bio-engineering examples cited previously, liquid biopsy is a technology that we know "works" and is technically feasible today. The key questions for society are related to its deployment. Used appropriately, this could be a game changer for society. Used inappropriately, it could be an expensive folly that sows more misery than good.

Any early stage diagnostic is trying to balance two opposing, but equally important parameters: sensitivity and specificity. The first dictates how likely the test is to pick up a positive result. When you are on a fishing expedition for early stage (i.e. asymptomatic disease), a high degree of sensitivity is required; you want to catch as many real cases as possible.

On the other hand, one needs a test with a high degree of specificity to reduce the risk of false positives. Anyone who has ever been referred to an oncologist themselves, or had this happen to someone they care about, knows the excruciating wait for confirmatory tests to clarify whether or not someone has cancer and what their prognosis is. Time literally stands still.

There are two broad diagnostic panels for the detection of multiple types of early stage cancer ("MCED test") that are close to widespread commercialisation: Galleri from GRAIL (a subsidiary of Illumina) and Exact Sciences, whose MCED is called CancerSEEK. Galleri is designed to detect a wider range of tumour types (50) than CancerSEEK. Both tests have demonstrated their detective power for early stage tumours that would not otherwise be detected.

The Trust is a shareholder in Exact Sciences, but the optionality of exposure to its MCED is not a key plank of our investment thesis, rather one that is discounted to zero in the current valuation. You will also find many analysts commenting that GRAIL is considered to be a drag on the valuation of Illumina (i.e. the shares would re-rate higher if this business was spun off). Why are investors not so excited by this potential revolution in cancer detection and treatment?

There are two key challenges. The first is obviously cost and the second is the reality of false positive results. We can illustrate these points with some data. In GRAIL's PATHFINDER trial, 6,621 outwardly healthy people aged 50+ were screened with its Galleri test, yielding 92 positive signals (1.4%). Subsequent investigations (scans and other tests including physical biopsy samples) confirmed cancer in 35 of these patients within three months (i.e. 38% of the initial positives were confirmed as true positives), which suggests that 57 (i.e. 62%) were false positives.

Since the PATHFINDER data was initially published, the algorithms have been refined and today only 59 of those 92 would still be considered to be a positive sample. Nonetheless, that means at best there are nearly as many false positive results (41%) as true positives. These are lab-based tests so they can continue to evolve and it is likely that the false positive result can be further reduced. However, our research tells us that there will be quite a lot of physician resistance to recommending these tests if false positive results remain at such levels.

If we extrapolate the data available today to the population level and imagine that, for every 100,000 over 50s screened for early cancer, 900 would test positive. Of those, 531 would go on to receive a confirmatory diagnosis and 369 would be deemed to be negative. At $950 per test and let's call it $3,000 for all of the secondary tests and scans, we would have spent $95,000 on the primary screening and $2.7m on the follow-up, equal to $2.8m in total or $5,200 per true positive result.

We would also have scared the bejesus out of 369 healthy people (it may well also be the case that the passage of time will show that some of those false positives become true positives, but more data is needed to clarify this point).

Exact Sciences initial screening study with CancerSEEK was called DETECT-A. In that study, 9,911 healthy women aged 65-75 were screened. 490 of these were initially deemed positive and these were re-tested. 134 were positive the second time around and 127 of these were then sent for imaging, leading to 26 imaging-confirmed (i.e. per protocol) cancers.

One can safely assume that the re-test need not be a notifiable event, but the same thing applies here that 127 women were sent for further studies and only 26 of these (21%) were ultimately true positives. Moreover, 22 of those 101 women ultimately determined not to have cancer went on to have much more invasive testing than simple imaging.

There were also 67 cases of cancer in the 9,421 women who tested negative initially (0.7%) after one year of follow-up, so one could argue that the test missed more cancers than it caught for whatever costs were involved.

In the total 'per protocol' sample, there were 96 confirmed cancer cases (0.97%) and the early stage test detected only 27% of these. Again, we would stress this data is more than two years old and the CancerSEEK test has continued to evolve, making the actual numbers of true and false positives of limited relevance now.

However, it does serve to highlight that whatever diagnostic pathways are used with these tests will require further refinement and also careful patient selection. There is simply no merit in using these sorts of tests in a younger population for example.

We remain very excited about the long-term potential for MCED tests to transform cancer care, but we are still far away from this becoming a routine diagnostic procedure like a PSA test, mammogram or pap smear.

Even assuming that we can reach a false positive versus detection threshold that society deems acceptable, the costs of widespread screening will be high and the whole medical system will need adapt because our current oncological approach is hugely geared to later-stage cancers that are not amenable to surgical resection or radio-ablation.

That leads us to the most exciting element of the early CancerSEEK data: of those 26 positive confirmed cases, 15 were found to be loco-regional and nine were amenable to curative surgery. So 9/26 or 34% of those who were found to have cancer they didn't yet know about were "cured" because the tumour was found so early. That is an outcome that oncologists dream about and is the reason why we need to persist with the development and evaluation of these testing approaches.

The future is bright

All of the caveats being made, the examples cited above enable us to imagine a world that is very different to the one we inhabit today, where literally tens of millions of people could benefit from life-changing novel interventions to either detect, prevent or manage serious medical conditions.

We are not fantasists, but pragmatists. We only invest in things that are supported by real data. Many of the ideas described above are either very early stage or still generating the necessary data. We may have exposure to some of these, but none are core elements of an investment thesis to which we ascribe a positive net present value, but rather side projects.

However, we consider ourselves long-term investors and we continue to monitor the frontiers of medical progress to wait for those compelling opportunities to enter (e.g. our four-year wait to get involved in gene therapy, ultimately with Sarepta).

Being able to evaluate and follow these exciting medical developments is one of the most interesting and uplifting elements of being a healthcare portfolio manager and certainly helps one to retain a positive frame of mind amidst an otherwise dispiriting geo-political and economic discourse.

We always appreciate the opportunity to interact with our investors directly and you can submit questions regarding the Trust at any time via:

shareholder_questions@bellevuehealthcaretrust.com

As ever, we will endeavour to respond in a timely fashion and we thank you for your continued support during these volatile months.

Paul Major and Brett Darke

Objective

The fund's investment objective is to achieve capital growth of at least 10% p.a., net of fees, over a rolling three-year period. Capital is at risk and there is no guarantee that the positive return will be achieved over that specific, or any, time period.

Risk Return Profile

This product should form part of an investor's overall portfolio. It will be managed with a view to the holding period being not less than three years given the volatility and investment returns that are not correlated to the wider healthcare sector and so may not be suitable for investors unwilling to tolerate higher levels of volatility or uncorrelated returns.

The risk indicator assumes you keep the product for 5 years. The actual risk can vary significantly if you cash in at an early stage and you may get back less.

The summary risk indicator is a guide to the level of risk of this product compared to other products. It shows how likely it is that the product will lose money because of movements in the markets or because the fund is not able to pay you.

This fund is classified as 6 out of 7, which is a medium-high risk class. This rates the potential losses from future performance at a medium-high level, and poor market conditions will likely impact the capacity to pay you.

The portfolio is likely to have exposure to stocks with their primary listing in the US, with significant exposure to the US dollar. The value of such assets may be affected favourably or unfavourably by fluctuations in currency rates.

This fund does not include any protection from future market performance so you could lose some or all of your investment.

If the fund is not able to pay you what is owed, you could lose your entire investment.

Target market

The fund is available for retail and professional investors in the UK who understand and accept its Risk Return Profile.

Chances

- Healthcare has a strong, fundamental demographic-driven growth outlook.
- The fund has a global and unconstrained investment remit.
- It is a concentrated high conviction portfolio.
- The fund offers a combination of high quality healthcare exposure and a 3.5% dividend yield.
- Bellevue Healthcare Trust has an experienced management team and strong board of directors.

Inherent risks

- The fund invests in equities. Equities are subject to strong price fluctuations and so are also exposed to the risk of price losses.
- Healthcare equities can be subject to sudden substantial price movements owning to market, sector or company factors.
- The fund invests in foreign currencies, which means a corresponding degree of currency risk against the reference currency.
- The price investors pay or receive, like other listed shares, is determined by supply and demand and may be at a discount or premium to the underlying net asset value of the Company.
- The fund may take a leverage, which may lead to even higher price movements compared to the underlying market.

Management Team

Paul Major
Portfolio Manager
since inception of the fund

Brett Darke
Portfolio Manager
of the fund since 2017

Awards

Sustainability Profile – ESG

Exclusions:	[X] Compliance UNGC, HR, ILO	[X] Controversial weapons
	[X] Norms-based exclusions	
ESG Risk Analysis:	[X] ESG Integration	
Stewardship:	[X] Engagement	[X] Proxy Voting

CO2 intensity (t CO2/mn USD sales):	25.8 t (low)	MSCI ESG coverage: 100%
MSCI ESG Rating (AAA - CCC):	AA	MSCI ESG coverage: 100%

Based on portfolio data as per 30.09.2022 (quarterly updates) – ESG data base on MSCI ESG Research and are for information purposes only; compliance with global norms according to the principles of UN Global Compact (UNGC), UN Guiding Principles for Business and Human Rights (HR) and standards of International Labor Organisation (ILO); no involvement in controversial weapons; norms-based exclusions based on annual revenue thresholds; ESG Integration: Sustainability risks are considered while performing stock research and portfolio construction; Best-in-class: systematic exclusion of "ESG laggards"; MSCI ESG Rating ranges from "leaders" (AAA-AA), "average" (A, BBB, BB) to "laggards" (B, CCC). Note: in certain cases the ESG rating methodology may lead to a systematic discrimination of companies or industries, the manager may have good reasons to invest in supposed "laggards". The CO2 intensity expresses MSCI ESG Research's estimate of GHG emissions measured in tons of CO2 per USD 1 million sales; for further information c.f. www.bellevue.ch/sustainability-at-portfolio-level

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