Bellevue Healthcare Trust

JULY 2022

Factsheet

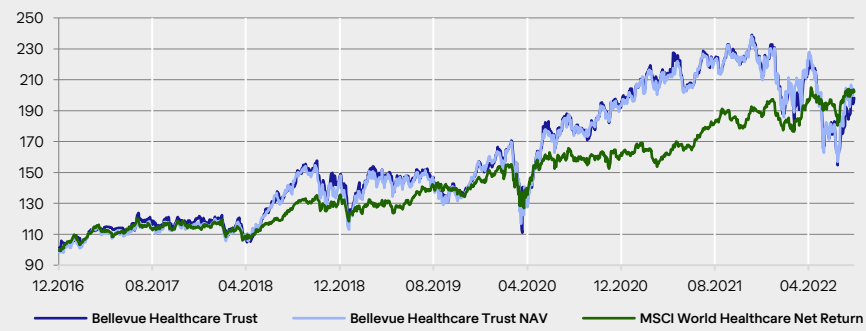
London Stock Exchange (LSE)

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	13.2%	-10.6%	10.7%	35.4%	39.3%	68.0%	98.3%
NAV	10.3%	-8.0%	13.7%	40.3%	47.7%	76.1%	102.8%
BM	2.4%	11.6%	25.4%	42.1%	60.0%	77.3%	102.0%

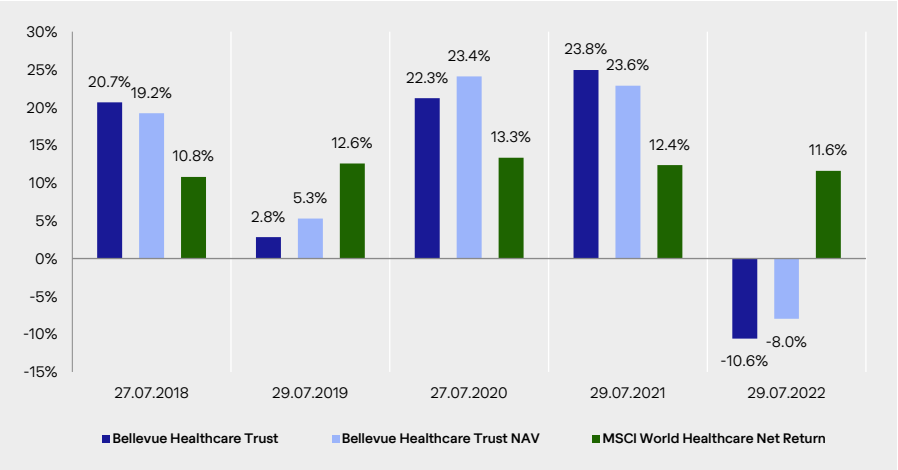
Annualized

1 Y	3 Y	5 Y	ITD
-10.6%	10.6%	10.9%	12.9%
-8.0%	11.9%	12.0%	13.3%
11.6%	12.4%	12.1%	13.2%

Annual performance

	2017	2018	2019	2020	2021	YTD
Share	14.8%	5.8%	23.1%	30.1%	12.5%	-12.1%
NAV	11.3%	7.1%	29.7%	24.5%	14.5%	-10.1%
BM	8.3%	8.1%	21.2%	9.1%	20.8%	2.4%

Rolling 12-month-performance



Fund facts

Share price	GBp 166.40
Net Asset Value (NAV)	GBp 170.01
Market Capitalisation	GBp 997.3 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	586'624'189
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	0.56
Correlation	0.32
Volatility	30.7%
Tracking Error	19.86
Active Share	95.33
Sharpe Ratio	0.5
Information Ratio	0.03
Jensen's Alpha	7.27

Source: Bellevue Asset Management, 31.07.2022;
Calculation over 3 years.

Source: Bellevue Asset Management, 31.07.2022; all figures in GBp %, total return / BVI-methodolog; the performance has been calculated for the period 29 June to 29 July 2022

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

Sarepta Therapeutics	7.4%
Jazz Pharmaceuticals	6.9%
Option Care Health	6.7%
Insmed	5.7%
Axonics	5.4%
UnitedHealth Group	5.3%
Apellis Pharmaceuticals	4.8%
CareDx	4.4%
Amedisys	4.4%
Charles River Labs	4.3%
Total top 10 positions	55.3%

Sector breakdown

Focused Therapeutics	25.7%
Med-Tech	16.8%
Services	15.4%
Diagnostics	11.1%
Managed Care	8.8%
Diversified Therapeutics	6.9%
Tools	5.2%
Healthcare IT	4.9%
Health Tech	4.1%
Dental	1.0%

Geographic breakdown

United States	94.8%
China	2.6%
Canada	1.6%
Switzerland	1.0%

Market cap breakdown

Mega-Cap	14.1%
Large-Cap	9.1%
Mid-Cap	54.8%
Small-Cap	22.1%

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

Source: Bellevue Asset Management, 31.07.2022;
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.

Welcome to our July jocundity. The schools are out and the sun is shining. Thank goodness it's holiday season, because nothing works: there aren't enough staff at the airports (and it can take an age to renew your passport), ambulances and GP appointments vie with unicorns for rarity, there isn't enough water for the garden and the price of everything rises literally before our eyes. At least the rolling blackouts haven't yet started.

Where will it end? Worry not, for the Truss/Sunak brains trust will shortly carry us into the sunny uplands. Decades of chronic under-investment and poor planning will fall away in mere weeks and before you know it, we'll be saved. If not, "no idea Keir" or whatshisface from the other lot whose name we cannot recall will suddenly have some policies. It's all good; Thomas Hobson be damned.

For those desperate for good news, the stock market has recently began to offer some cheer. Perhaps we are finding a bottom. Sentiment certainly seems to have reached that point where few investors are expecting positive news. However, we continue to see opportunity and that is an exciting distraction from the chaos of everyday reality in basket-case UK.

Monthly review

The wider market

After several months of negative performance, the MSCI World Index delivered a positive return of 7.9% in dollars (+7.9% in sterling), only the second positive month so far in 2022 (March being the other). Is this a directional change, or merely a pause on a continued downward trend (a "head fake" as our American cousins would call it)? This has been a keenly debated topic and it has been interesting to see some of Wall Street's most notable equity strategists disagreeing on how the runes have fallen.

The picture is undoubtedly a complex one. In no particular order, one must consider where we are in the rate tightening cycle, where we are in the economic cycle (will there be a recession and attendant rise in unemployment?), how much worse the geo-political outlook will get (and concomitant impact on energy supplies and supply chain disruption, including food (why do some people still believe Putin won't turn all the gas off when it suits?) and of course how much of any of the above is already priced into markets.

On this latter point, we remain firmly of the view that, for the broader market at least, Wall Street earnings estimates do not adequately capture the downside risks from the above and therefore need to fall further (the "P" always falls first, the "E" comes later). That having been said, the initial reporting season for the broader market has not been as bad as we feared, with underlying demand trends in many sectors holding up well with a significant proportion of the movement in estimates/guidance from US companies being attributed to the strength of the dollar (a tailwind for European companies and a headwind for those based in the US) rather than an underlying slowdown in activity. European reporting has been more in line with our expectation and the divergence between the broad economic outlook for the United States and continental Europe grows starker by the day.

In some ways, right now feels like the eye of a storm: things appear superficially calm and some pressures (raw materials, microchips, container rates, oil price) are trading as if the worst is behind us (or as if demand is falling – take your pick). However, common sense suggests this more benign environment is unlikely to be the case for the wider economy over the medium-term.

Let us use General Motors Q2 update as an example: its truck plants are finally back to running at full capacity and it has secured all of the raw materials for its battery needs through 2025; enough to build ~1m electric vehicles. Production is up 30% versus one year ago with low levels of finished inventory. Moreover, customers seem happy to place orders and wait many months for a new vehicle and then pay thousands of dollars more when it arrives.

On the other hand, unfinished inventory continues to be a burden as supply chain disruptions still seep into the system. Many profitable optional extras are not available due to the prioritising of some components to high end, higher margin vehicles. Although raw material prices are flattening off, GM still forecasts production and logistics costs will halve FY22 profits versus what they would have been one year ago on the same level of revenues.

Moreover, people might decide to order fewer new vehicles in the future as economic pressures finally bite. With delivery times being so long, some of those "firm orders" may evaporate.

Walking away from a few thousand dollar deposit is hard, but not as hard as finding the money to finance a new vehicle that costs more than you expected and needs to be financed at a much higher interest rate (in 2021, 92% of new cars in the UK were bought on finance versus outright, most deals are at fixed rates). Thus, whilst the company is clearly doing a very good job in managing its current production operations, it has no more visibility into the potential evaporation of demand than anyone else. Nonetheless, GM finished the month up 14%.

As the saying goes – economic catastrophes unfold very slowly at first and then suddenly very quickly. These are tricky times indeed…

We list the sector performances in Figure 1 below and, at face value, it betrays a definite tilt toward optimism around discretionary spending, with Tech & Semis, Autos and Retailers leading and classical defensives like Telecoms lagging. Despite the more positive sentiment narrative, it is also interesting to see Household & Personal Products lagging as the 'trading down' thesis continues to play out.

Why have we listed Technology ahead of Autos and Retailers? As is often the case, the extreme performance of Autos was in large part due to Tesla and Rivian; the sector would have returned +8.2% absent these two tech proxies, leaving it in the middle of the table. A similar pattern would apply if we were to remove the Amazon leviathan from the retailer data; that sector would have returned +10.1%. Both are widely recognised as "Tech" proxies and thus it makes sense to suggest that a pro-technology theme was the prevailing one during July.

Sector	Monthly perf (USD)
Automobiles & Components	20.3%
Retailing	17.8%
Technology Hardware & Equipment	16.5%
Semiconductors & Semiconductor	15.9%
Commercial & Professional Services	11.0%
Consumer Services	10.2%
Software & Services	10.0%
Capital Goods	9.8%
Consumer Durables & Apparel	9.7%
Diversified Financials	9.4%
Transportation	9.2%
Real Estate	7.8%
Food & Staples Retailing	7.4%
Energy	6.6%
Healthcare Equipment & Services	5.9%
Utilities	4.7%
Banks	4.4%
Materials	3.9%
Food, Beverage & Tobacco	3.2%
Pharmaceuticals, Biotechnology	1.8%
Media & Entertainment	1.7%
Household & Personal Products	1.3%
Insurance	-0.2%
Telecommunications Serivces	-2.0%

Source: Bellevue Asset Management, 31.07.2022

On a final note, it was interesting to see the July instalment of BofA's widely respected Fund Manager Survey point to some of the most bearish positioning feedback seen in 20 years, with investors in "full capitulation mode" regarding the global growth outlook. July may not mark the beginning of a meaningful market upswing, but there is little other way to go when sentiment hits rock bottom.

Healthcare

A less defensive, more pro-consumer sentiment is less supportive for the healthcare sector and so it lagged the broader Index. The MSCI World Healthcare Index ended the month up 3.3% in sterling terms (+3.2% in dollars). The preceding paragraphs have once again focused on the uncertainties around consumer discretionary spending and perhaps the risks that people 'trade down' on staples (more Aldi and Primark, less Waitrose and Joules; keep the current car for another year or two).

One could rightly argue healthcare stands apart from all of this, as the majority of spend sits in the non-discretionary bucket; you don't choose to be unwell, nor can you do much about the timing. As ever though, the picture is more complex. Around 70% of healthcare expenditure goes to the management of chronic (i.e. long-term) health conditions and around 85% of expenditures arise outside of the emergency room setting. In other words, the interactions and interventions are planned in advance; plans can be changed and interventions deferred (by the patient or otherwise, cf. NHS waiting lists).

We have seen this play out ever since the first wave of the pandemic, with the elderly in particular choosing to stay away from their doctor. Even to this day, we are 'missing' thousands of COVID-era cancer cases because of the failure to pick up the signs in routine medical appointments that never took place. It is fanciful to believe underlying incidence has changed. Hospitals will not admit you if you have COVID and many 'worried well' will not go in for a routine appointment or minor procedure due to their fear of contracting the virus once they are admitted to the hospital.

We must therefore consider a number of external factors such as COVID waves (especially in China) when we think about future utilisation trends. Here in the UK, these may not be directly linked to the wider economic outlook, but nonetheless they must be understood.

In the US, the picture is more nuanced. If you are a beneficiary of an employer-sponsored health insurance plan and you fear that you may become unemployed due to a coming recession, there is actually an incentive to bring forward treatment and get it done whilst someone else is paying the bills and you are only on the hook for the initial deductible co-payment.

This trend is known as a "deductible flush" and could give a false impression with respect to the post-COVID pace of recovery in elective procedure volumes. So far, there is no sign of such a 'flush' and several other indicators do not suggest that Americans are unduly concerned about a recessionary outlook, although this could change rapidly in the coming months (US new home sales are finally stalling and the turn came faster and more aggressively than anyone expected).

And where are we with those underlying healthcare utilisation trends? It is still early in the reporting season and it is important when considering Med-Tech companies to distinguish between procedural trends and capital equipment trends, for the latter is a lagging consequence of weakness in the former.

The US procedure volume picture remains somewhat murky, with insurers United Health and Elevance (formerly Anthem) reporting better-than-expected medical cost ratios on lower overall non-COVID volumes, although both saw some pickup in ambulatory care/outpatient facility volumes. This was supported by J&J, who reported strong procedure volume trends for its US, European and LatAm Med-Tech business, as did Stryker and Intuitive Surgical, although both those companies' positive procedural volume trends were offset by weaker capital equipment purchasing activity by hospital customers. In an entirely unsurprising development, Smith & Nephew underperformed its US ortho/med-tech peers through Q2. We tried to recall a time when this business performed well and quickly came to the conclusion that it has been a basket case for as long as we can remember…

As regards the hospital groups that have reported (UHS, HCA, Tenet and CYH), they described more mixed results that tend toward optimism on a continued path of recovery to pre-pandemic activity levels rather than tangible data that such a trend is well established, and a continued battle on the labour cost/staffing front (impacting both admissions capacity and margins). With these trends in mind, hospitals are conserving cash and hence capital equipment spending is softer.

It is still easy for hospital management teams to 'blame' COVID whilst we continue to see waves of Omicron descendants sweep through the population. Nonetheless, it does feel like we have experienced some sort of reset, whereby procedure volumes are not going to catch up to pre-COVID predicted levels for 2023 for example.

Why might this be? There was undoubtedly a long-standing baseline of unnecessary procedures driven by the perverse incentives of a fee-for-service model. Perhaps the lower frequency of appointments precludes such hard selling of marginally beneficial procedures to patients. Perhaps it is a long overdue consequence of the gathering shift toward value-based care models that should discourage over treatment. Time will tell, but we are very happy to have minimal direct exposure to facilities during this interregnum.

Healthcare's performance dispersion by sub-sector is illustrated in Figure 2 and we would make a couple of observations: Hospitals (Facilities) entered the month trading at multi-year relative valuation multiple lows in EV/EBITDA terms and in this context, it is unsurprising to see a bit of a bounce on the somewhat positive messaging. Going into July Dental, Diagnostics and Healthcare Technology had been the worst-performing healthcare sub-sectors this year (declining 55%, 36% and 35% respectively) so again one should not be too surprised to see a bit of a recovery on more constructive overall market sentiment.

	Weighting	Perf (USD)	Perf (GBP)
Facilities	0.8%	19.8%	19.9%
Dental	0.4%	15.7%	15.7%
Healthcare IT	0.7%	14.8%	14.9%
Tools	8.3%	12.2%	12.3%
Diagnostics	1.5%	11.8%	11.8%
Healthcare Technology	0.6%	11.4%	11.4%
Services	2.4%	8.0%	8.2%
Med-Tech	12.3%	6.2%	6.3%
Distributors	1.4%	0.0%	5.6%
Generics	0.4%	5.5%	5.6%
Other HC	1.5%	5.6%	5.3%
Managed Care	11.6%	4.8%	4.9%
Focused Therapeutics	7.5%	2.6%	2.7%
Conglomerate	12.6%	-0.5%	-0.4%
Diversified Therapeutics	38.1%	-0.7%	-0.7%
Index perf		**3.2%**	**3.3%**

Source: Bloomberg/MSCI and Bellevue Asset Management (UK) Ltd. Weightings as of 30.06.2022. Performance to 31.07.2022.

Geo-politics aside, whether or not this positive investor sentiment to the wider market continues will come down to whether or not companies are willing and able to navigate their way through a different and more challenging environment on the economic and monetary policy side.

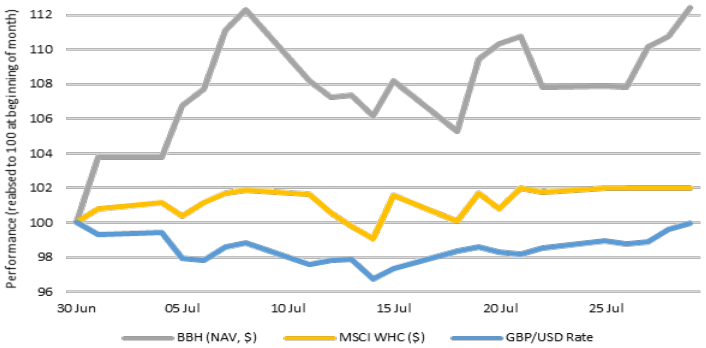
Thankfully, for most of healthcare, the broader economic conditions are secondary to the demand outlook. If you have good products that improve patient outcomes, lower costs and allow caregivers to make better decisions on behalf of their patients, then you will be rewarded with revenues.

The Trust

Those familiar with our portfolio will know that we have long-been significantly overweight Diagnostics, Healthcare Technology and Healthcare IT and thus it should come as no surprise that the portfolio materially outperformed the MSCI World Healthcare Index during July. Adjusting for the ex-dividend impact, the Trust's net asset value rose 10.7% to 170.01p. For the first time in several months, foreign exchange did not have a meaningful impact on our own performance or that of the wider market. We estimate the FX impact was only +10bp, in line with that seen for the MSCI World Healthcare Index.

The more constructive dynamic that emerged in the latter part of June where company-specific positive news flow was rewarded by the market seemed to remain intact through July. Whilst we have made some progress in clawing back some relative underperformance, we remain very firmly of the view that there is still a very long way to go and that many of our holdings are materially under-valued on a sub-sector relative, market relative and historical relative basis.

The positive performance alluded to above was broad based, and there were no unexpected surprises or announcements (M&A etc.) during the month. All sub-sectors other than Diversified Therapeutics contributed to the positive performance, which was led by Services, Focused Therapeutics and Med-Tech. The evolution of the NAV during the period is illustrated in Figure 3:



Source: Bellevue Asset Management, 31.07.2022

The investment portfolio again remains unchanged, with the same 29 holdings. There was no issuance during the month because the shares have fallen back onto a discount to NAV that averaged 4.4% across July. Our four UK-listed healthcare investment trust peers who also publish daily net asset values also all traded at a discount to NAV over the month.

Thanks to the positive portfolio performance and the setting aside of some cash to cover the forthcoming dividend, the leverage ratio decreased from 12.1% at the end of June to 9.6% at the end of July. The evolution of the portfolio is summarised in Figure 4 below. During July, we added to five positions and reduced nine, with the remainder unchanged.

The reduction in our Dental holdings was due to active re-allocation. The increases in Diagnostics and Healthcare IT and the decrease in Managed Care were driven entirely by positive relative performance. Services saw a net decrease in exposure offset by positive relative performance. Both Diversified and Focused Therapeutics saw a reduction in our overall holdings, whereas we added to our overall holdings in Tools, Healthcare Technology and Med-Tech.

	Subsectors end June 22	Subsectors end July 22	Change
Dental	1.0%	0.9%	Decreased
Diagnostics	10.7%	11.1%	Increased
Diversified Therapeutics	8.1%	6.9%	Decreased
Focused Therapeutics	26.4%	25.8%	Decreased
Healthcare IT	4.7%	4.9%	Increased
Healthcare Technology	3.6%	4.1%	Increased
Managed Care	9.5%	8.8%	Decreased
Med-Tech	16.2%	16.8%	Increased
Services	14.7%	15.4%	Increased
Tools	5.2%	5.2%	Unchanged
	100.0%	**100.0%**	

Source: Bellevue Asset Management, 31.07.2022

Manager's Musings

Oncological obtrusion part 2

Our missives are intended to be thought provoking and (hopefully) interesting to read. It is thus welcome when they generate some debate with our readers. All ideas progress through challenge; there is no such thing as a "safe space" for ideas and we welcome all discussions on the topics we raise, and the Trust in general, even if you disagree with our views and the decisions that we take based upon them.

Given how emotive cancer is as a subject, and how much money has been invested in tackling it, one should not be surprised that suggesting there are other, better things to invest in might draw some disagreement. Few can argue with our core tenet that classical chemotherapy sucks – it surely stands in perfect opposition to Hippocrates suggestion from his Epidemics essays: "first do no harm". The credo of chemo seems more like "do as much harm as possible without killing the patient"; a crude weapon of mass destruction with scant regard for collateral damage.

If the R&D outcomes of recent years have not lived up to the hype, and failed to banish this particular approach from the armamentarium, surely that does not mean there is nothing to hope for? We pointedly did not say this, we merely argued that the field was too crowded and too uncertain to make the risk reward favourable from an investment standpoint. "But what about personalised cancer vaccines?" some of you asked, noting that topic drew nary a mention.

This is a fair point and we are actually somewhat enthusiastic about this field of study. We would again emphasise (apropos last month's missive), that a 'field of study' is a worthy area of research that should receive grant funding; this is not the same as a sound basis for a positive investment case.

Indeed, we would argue that our optimistic view on this as an area of research supports the previous argument not to invest widely into oncology R&D (including those companies conducting such cancer vaccine research). We shall endeavour to explain why in the following paragraphs (which presume a degree of familiarity with the content of last month's factsheet).

Back to basics

Let us first describe (in very simplistic terms) the principles and history of therapeutic cancer vaccines before moving into the modern era and the prospects for the next generation of products to actually work. We must draw a distinction between therapeutic vaccines and those against cancer-inducing ('oncogenic') pathogens (e.g. vaccination against the HPV virus).

Almost all the healthy cells in your body display their protein contents on their surface via MHC proteins (red blood cells are an exception). Simplistically, one can think of this as an 'inventory' of the cell's contents. These MHC receptors interact with the immune system (T-cells and antibodies) and alert it to the presence of foreign tissue (likely an infectious agent) so that the infected cells can be destroyed.

This process is going on continually and is known as immuno-surveillance. It is much more complex in reality than the simple summary described here and it also requires several cytokine molecules to be present to generate an effective immune response. As such, the local environment around a cancer cell (commonly referred to as the 'tumour micro-environment') plays a role, and this ties into the immune cloaking effects described in last month's missive that allow some tumours to escape the immune system's attention. We will come back to this point later.

As described last month, cancer arises when cells begin to divide in an uncontrolled manner. At the molecular level, one or more gene mutations result in the over-production (over expression) of a normal signal or receptor that induces uncontrolled proliferation by drowning out other signals, or some other protein product is produced in a mutated form that prevents regulatory processes from controlling division. In either case, a cell will be over-expressing a protein or it will be expressing a protein that is mutated (often both are true; cancer typically involves the processes going wrong in multiple ways as there are numerous checks and balances in the regulatory systems).

What this means in practical terms is that the 'inventory' presented to the immune system on those MHC receptors will look abnormal and the immune system can identify these cells as containing foreign material and destroy them, or detect that they are over-active and counter these signals in a process known as equilibrium. This is how the immune system is able to keep a lid on uncontrolled cellular proliferation most of the time.

In terms of the combination of mutations that drive uncontrolled cellular proliferation, everybody's cancer will be unique to them. However, certain tissue types show common over-expression of certain receptors or proteins and, in this way, we can link certain cancers to certain patterns of over-expression. This is the basis of many of the early stage cancer detection ('next generation sequencing') tests that are now on the market. In addition to their value as a diagnostic sign-post, it is easy to understand how these proteins that are commonly over-expressed could become a basis for therapeutic intervention.

Back to the future

With the basic science covered, let us come back to vaccination as a cancer treatment. Thus far there have been four distinct approaches to anti-tumour vaccination:

1. Induction of an immune response through vaccination using an antigen linked to an over-expressed protein or a common functionally mutated protein.
2. Treatment with modified dendritic cells forced to express a common tumour antigen and thus initiate a sustained immune response.
3. Treatment with an oncolytic virus that will preferentially replicate in tumour cells using a virus already likely to induce a meaningful response.
4. Creation of a bespoke vaccination through identification of epitopes unique to a person's tumour burden via the proteomic sequencing of a biopsy sample.

The first approach is the one that is most similar to traditional vaccination against an infectious agent and has been widely evaluated, thus far to little avail. Two projects made it into later-stage larger trials: Tecemotide (aka Stimuvax, BLP-25) was a synthetic antigen that mimicked a glycoprotein called MUC-1 that is widely over-expressed in a number of different cancers and was evaluated in several clinical trials from 2001 to around 2014. Whilst none of the trials were successful, they generated positive signals that encouraged the developers to continue plugging away. Eventually though, they gave up.

Melanoma-associated antigen 3 (MAGE-A3) is another antigen associated with several types of cancer and is also a negative prognostic indicator (i.e. cancers that over-express MAGE-A3 are more difficult to treat). Around the same time as Tecemotide was being evaluated, GlaxoSmithKline developed a vaccine consisting of recombinant MAGE-A3 protein (GSK-2132231) and an already proven adjuvant (a compound added to vaccines to increase the intensity of immune response) and tested it in two large-scale phase 3 trials for both melanoma and lung cancer. Neither showed any activity and the programme was ended.

We have used these two examples because they were the ones that progressed into large-scale (1000+ patient) studies. However, we are aware of a further 14 tumour-specific antigens where vaccine trials have taken place since the mid-1990s. The bottom line here is that there is no classical single antigen therapeutic cancer vaccine on the market.

Why didn't they work? Was the antigen itself too weak to illicit an immune response, or is the immune response that is generated too weak on its own to overcome the tumours cloaking propensities? Could the solution be to use multiple antigens in the hope that you get a polyclonal response to the tumour?, or combine with a checkpoint inhibitor to enhance immune presentation by the tumour cells. We will return to these questions in due course.

The second approach offers an alternative solution to the induction of a powerful response. Sipuleucel-T (marketed as Provenge by Dendreon, which is now privately owned) is a therapeutic cancer vaccine (of sorts) that was approved by the FDA for the treatment of asymptomatic or minimally symptomatic metastatic castration-resistant prostate cancer (mCRPC) in 2010.

The therapy involves the collection and isolation of immune cells called dendritic cells. These cells are antigen presenting cells and their function is to process antigen material (the stuff presented on those MHC proteins mentioned previously) and act as an intermediary to other types of immune cells to co-ordinate a broad response against that antigen.

The harvested dendritic cells are then exposed in vitro to an antigen called prostatic acid phosphatase (PAP), which is commonly expressed on prostate cancer cells. The cells are then matured with cytokines and re-infused into the patient, where they induce a sustained immune response. Why is this a "vaccine"? The therapy induces an immune response against the cancer cells and is thus technically a vaccine (the WHO definition of a vaccine is "something that trains your body to create antibodies").

Provenge did not live up to initial commercial hopes and Dendreon went bankrupt in 2014; its assets were later acquired and the company has changed hands several times since. The main drawback initially was the time it took to harvest, process and mature the cells, although this is now down to about three days.

Although the treatment modestly extends survival, it is not curative. As the company has been private since 2015, it is difficult to ascertain commercial sales, but revenues were self-reported to be around $300m in 2017, well below the last audited figure in 2014 and the company has not launched any further products based on the same approach and looks to have pivoted to being a cell therapy contract manufacturing company.

The third approach is the use of an oncolytic virus. Talimogene laherparepvec (aka T-VEC, marketed by Amgen since 2015 as Imlygic for the treatment of melanoma) is a modified herpes simplex virus and the approach echoes Coley's toxin (cf. last month's musings), whereby an immunogenic pathogen is injected directly into a tumour to induce an immune response.

Where this 130 year-old idea has been updated is that the modified virus is lacking a key part of its genome so that it will not reproduce in a healthy cell as it cannot successfully 'hijack' the replication machinery of the cell (cells have evolved innate responses to viral attack and these must be overcome if the virus is to reproduce). In contrast, most melanoma cells contain mutations that make them vulnerable to such viral attack and thus the T-VEC will reproduce in them and thus attract the immune system's attention.

This approach is well suited to melanoma as the skin tumours are easily accessible for direct injection. However, melanoma is a very well served market already and so the drug has met with limited commercial success (revenues are not disclosed by Amgen but look to be somewhere in the $50-100m per annum range after seven years on the market). Amgen has no other oncolytic virus products in its R&D pipeline.

In conclusion then, there have been many attempts to develop therapeutic cancer vaccine products over the past 30 years but these have ended in either utter failure or been a commercial flop due to a combination of limited efficacy, high complexity or cost. The idea is sound in principle, but clearly more challenging in reality than one might imagine.

That having been said, the reasons for failure from the first approach can only really fall into two buckets, since we know well that the epitopes being targeted are valid: the failure to induce a strong enough immune response or the tumour micro-environment supporting the response leading to an attack on the tumour.

"Great Scott!"

The next generation of prospective therapeutic cancer vaccines cover the first and fourth approaches. Technology has moved on and we better understand now why the immune system cannot always 'see' a tumour, even when we know the targeted epitope is being over-expressed and further we know that this issue can be addressed in some patients via the use of a checkpoint inhibitor drug targeting that PD-1/PD-L1 pathway.

Let us deal with the first approach. As noted previously, single antigen vaccines as monotherapy have not proven to be effective, but that does not mean that the idea is without merit. We know that a polyclonal (more than one antibody) immune response is better than a monoclonal one, and that the best way to illicit a polyclonal response is to vaccinate with multiple antigens, to promote the immune response if possible and to maximise visibility via utilisation of a checkpoint inhibitor.

The German mRNA vaccine company BioNTECH is exploiting both these ideas in a programme called FixVac, which thus far has initiated trials with five cancer-specific vaccines. Each vaccine consists of four mRNA sequences, each coding for a non-mutated (i.e. over-expressed) antigen associated with a specific tumour type and each sequence is encapsulated in a liposome that is designed to integrate it into dendritic cells, which are critical with 'training' and maintaining an immune response (cf. Provenge mentioned previously).

The first of these, BNT-111 (melanoma) and BNT-113 (HPV+ve squamous head and neck) are currently in phase 2 trials. BNT-112 (prostate), BNT-115 (ovarian) and BNT-116 (non-small cell lung cancer) are in phase 1. In each case, the vaccine is co-administered with Regeneron's PD-1 inhibitor cemiplimab. BNT-111 has received Fast Track designation from the FDA following promising early results from the phase 1 where a mix of partial responses and stable disease were seen, including one complete response. Various secondary assessments of immunological activity suggested a strong response against the targeted antigens was achieved. Final results from the BNT-111 phase 2 study will be available in 2024/25, but we would expect to see interim results before then. Meanwhile, we view the phase 1 results as interesting rather than compelling.

The fourth approach has been made more practical by the huge improvements in gene sequencing technology and the now relatively low cost of producing custom sequences of genetic material. Without wishing to diminish the scientific complexity of the process itself, it is not really very complicated or expensive anymore to get a full genetic workup on a tumour biopsy (various commercial labs can do this to order, or a hospital or academic research team could buy the equipment to do it themselves if they were well funded), identify unique epitopes via comparison to various public databases such as OpexVax and then create vaccines (adjuvanted-protein or mRNA-based) from this data to create a truly unique and personalised approach to cancer treatment.

Positive studies using this approach have been reported by teams at Dana Faber Cancer Institute (for aggressive brain tumours) and the Broad Institute (Melanoma). These results include some complete responses, akin to functional cures.

Both BioNTECH and US-based Moderna, the other major player in mRNA vaccines are looking at this approach with their iNeST (autogene cevumeran) and MRNA-4157 programmes respectively. In each case, a tumour biopsy will be compared to healthy cells from a blood sample to identify unique cancer-specific epitopes and a cocktail for 20-odd custom mRNA sequences will be created as a vaccine. Moderna's construct is co-administered with Merck's PD-1 drug pembrolizumab. Early results from the Moderna programme look very interesting, with some complete responses without detectable disease and results from a 150-patient phase 2 study could be available at the end of this year and we are genuinely excited to see what the results look like.

"Nobody calls me chicken"

Let us come back to the original question – why aren't we keen on investing in cancer if we think there is a possibility that personalised cancer vaccines, when used in combination with a checkpoint inhibitor, may potentially be curative for some patients?

Firstly, let us imagine this stuff does work really well. Happy days all around, unless of course you make your money from selling some other type of very expensive cancer treatment. If you think a revolution is around the corner, the best thing to do is leave town for a bit. That way you may keep your head. Everyone else can stick around and eat cake, that's fine with us.

Secondly, let us put down the Kool-Aid for a moment and take some deep breaths. We have been here before, more than once; optimism is one of humanity's greatest traits. However, we are talking about positive results in a few patients. The results are amazing for them, no doubt. But let us see how far this goes in terms of cancer types and patient types with a bit more data before we start betting the farm.

Thirdly, we must consider the IP situation here. From what we can tell, Moderna and BioNTECH are planning to do exactly the same thing. Others have done it before with off the shelf kit. How easy is it to build a protected franchise in this stuff? Can others follow? If you wish to commercialise such a product at scale, you need to convince regulators, doctors and patients that you can deliver the product to them in an acceptable timeframe (cf. Dendreon). In this respect, you may be better with some artisan product from a cancer lab at a major hospital than with big pharma. Based on what the research-led initiatives have said, this is going to be expensive and the economies of scale are not that huge, given it's a bespoke product for each patient.

Finally, let us assume that we can get comfortable with points 2&3. There is then the question of whether or not the assets in question represent a good investment opportunity. In the case of BioNTECH and Moderna, this question is currently clouded by the wider COVID vaccine situation.

Interesting times indeed and we are very much looking forward to seeing how things unfold... from the sidelines.

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):	26.5 (low)	MSCI ESG coverage: 100%
MSCI ESG Rating (AAA - CCC):	A	MSCI ESG coverage: 100%

Based on portfolio data as per 30.06.2022 (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