PERSPECTIVES

FEBRUARY 2015

21st CENTURY THEMES

Innovation driving long-term returns in healthcare

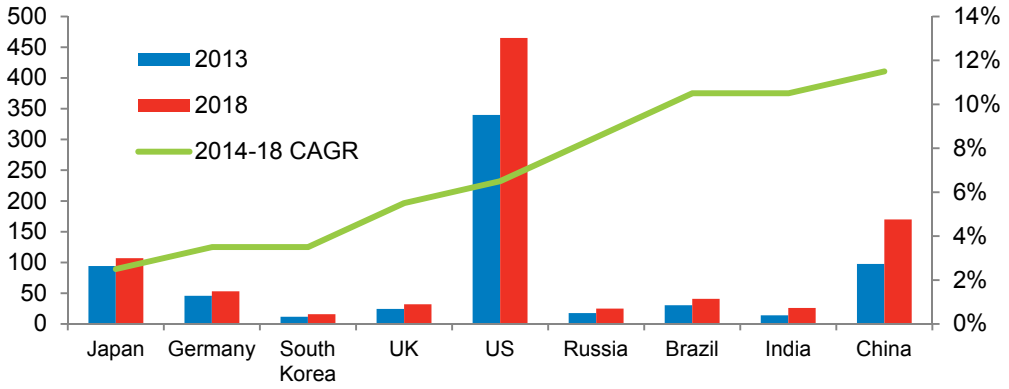
Ageing populations; strengthening emerging market demand; and increasing levels of chronic illness are key structural drivers supporting healthcare investment. We are also in an exciting period of medical innovation that will create lucrative new markets and further support healthcare earnings. Indeed, we may well be at the start of a long cycle of new therapies in areas such as gene therapy, immunotherapy and 3D printing. Rewards for research-driven investors who can identify the best opportunities in this innovation pipeline should be considerable.

STRUCTURAL DRIVERS

We know population ageing is fast becoming a global phenomenon. The number of people over 60 is expected to reach 2 billion by 2050, compared with 606 million in 2000. This has significant healthcare implications, given that nearly half of all lifetime care expenditure occurs from 65, with a third occurring from 85.[1] And while life expectancy is increasing, so too is the rate of chronic illness globally. Globally, healthcare spending is likely to grow strongly and in the developing world is expected to surge (chart 1).

While these factors present a positive structural environment for the healthcare industry, perhaps the most exciting developments are happening within the laboratory, thanks to the incremental development of a range of novel therapies.

Chart 1. Growth in spending on medicine (USD billions)



Source: IMS Market Prognosis, September 2014

THE HUMAN GENOME: THEN AND NOW

The late 1990s saw great optimism about the emerging field of genomics, which reached fever pitch in 2000 when it was announced that the human genome had been sequenced (the sequencing project was formally completed in 2003). Genomes are the complete set of instructions needed to make every cell, tissue and organ in the human body (genomes are made up of DNA and genes, though genes constitute just 2-3% of genomes). Genome sequencing determines the order of DNA (written using just four letters: A, C, T, and G) for entire organisms.[2]

Biotech stocks soared during 1999-2000 as investors anticipated windfalls off the back of genomic research, with hopes that it could lead to new treatments for a whole host of diseases. However, rampant investor optimism was much too premature, and largely failed to account for the complexities and costs in this new field of research, and for the long development times for drugs, with R&D periods typically averaging 10-15 years.[3] In addition, the broad market collapse of 2000 hit higher-risk/reward sectors such as biotech particularly hard.

AT A GLANCE

- We are at the start of a long pipeline of new treatments coming to healthcare markets.
- Companies are at last starting to deliver drugs based on human genome research.
- Immunotherapy, gene therapy and RNA interference are some of the most fertile areas of innovation.
- Medical devices are the number one area of use for 3D printing.
- Due to the binary nature of returns in the biotech space, careful research is essential for making successful investments.

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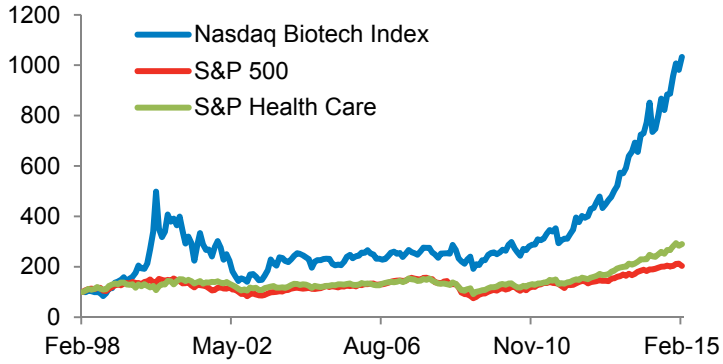
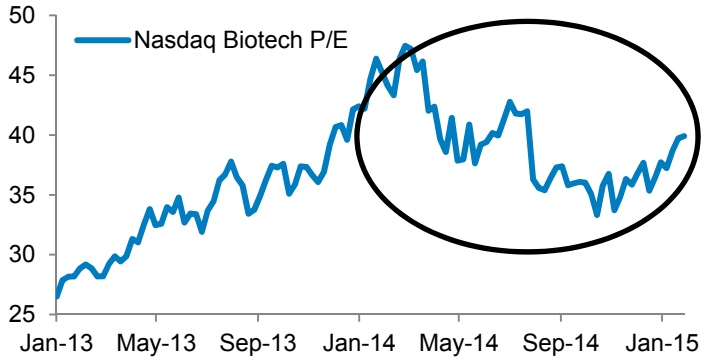
Fast forward to today, and healthcare – and biotech in particular – are once again posting impressive returns (chart 2). Critically, biotech outperformance over the last year has been driven by solid earnings growth rather than sentiment-driven multiple expansion (chart 3). The aggregate market cap of the biotech space has not kept pace with earnings growth, while much of the positive earnings surprises in healthcare over the last three years have been driven by biotech. [4] Investors were pained by the collapse in biotech from 2000-03. So was the initial optimism around genome benefits justified, but just too early?

Chart 2. Biotech outperformance (indices rebased to 100)



Source: Datastream, 29.01.2015

Chart 3. Earnings growth has stabilised the sector's P/E



Source: Datastream, 02.02.2015

FALLING R&D COSTS ARE DRIVING INNOVATION

Mapping the human genome was a great achievement, yet it had little immediate clinical impact, largely owing to the high costs of experimentation: the Human Genome Project took 13 years and cost US$3bn. However, subsequent years have seen a dramatic fall in costs. It costs just $1,000 per genome using **Illumina**'s HiSeq X Ten System, with the company expecting costs of just $200-300 on a 5+ year horizon. What had been impossible until recently is now not only possible but affordable, which has big implications for the effectiveness of R&D. Dr Craig Venter, a key figure in the Human Genome Project (whose own genome was among the first sequenced) is heading a new start-up, Human Longevity Inc., which aims to sequence one million genomes by 2020.[5]

This more cost-effective environment for innovation combined with what many industry executives perceive as an increasingly permissive US regulatory environment – the Food & Drug Administration approved 41 new drugs in 2014, the most since 1996 [6] –means that there are good reasons for thinking that today's environment should be conducive for certain genomic prospects.

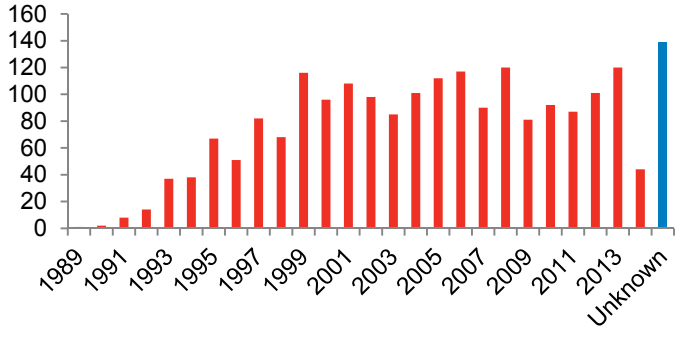
"Genomics is where the computer industry was in the 1970s – at the beginning of a technological revolution. The 70s was the right time to be investing in a diversified portfolio of breakthrough computer technologies. Those who did so despite claims that it was too risky were rewarded early."

Hilary Natoff
Portfolio Manager

GENE THERAPY

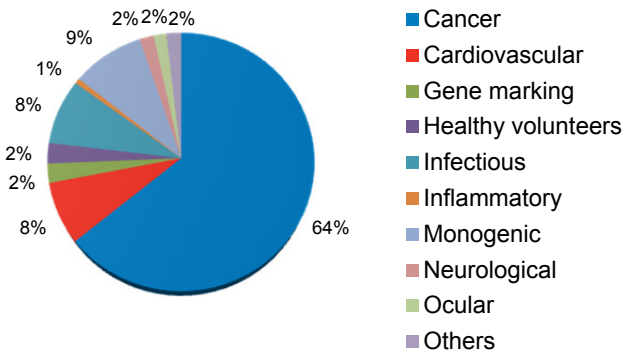
Gene therapy is about curing disease by replacing the missing or defective gene causing a particular disorder. The 'corrected' gene is delivered to the patient's DNA through a virus; the most efficient delivery vehicle actually being HIV, with the viral genome deleted so that the virus cannot transmit HIV or infect new cells. Though approved clinical trials have been on-going for over two decades on a variety of diseases and indicators (charts 4 and 5) progress has been slow but incremental. In 2012, the EU approved the first ever gene therapy drug: uniQure's Glybera, designed to treat lipoprotein lipase deficiency – a rare metabolic disease.

Chart 4. No. of gene therapy trials approved worldwide



Source: Journal of Gene Medicine, John Wiley & Sons Ltd, 2014. 'Unknown' refers to trials in countries where regulatory agencies did not disclose the year.

Chart 5. Indicators/diseases addressed in trials



Source: Journal of Gene Medicine, John Wiley & Sons Ltd, 2014

STOCK HIGHLIGHTS

- **uniQure**: given its first mover advantage, uniQure is well placed for further gene therapy development, which could include Parkinson's and haemophilia treatments.
- **Avalanche Biotech** is developing gene therapies to treat people with sight-threatening ophthalmic diseases, such as age-related macular degeneration. Trial results for drug AVA-101 are expected in the summer.
- **Bayer**: the high-risk nature of R&D in gene therapy tends to mean heavier involvement on the part of small biotech firms relative to established pharma companies. But Bayer is showing interest, and is collaborating with Dimension Therapeutics to produce a gene therapy treatment for haemophilia A.
- **Illumina**: though it's not a drugs producer, Illumina has been the prime beneficiary of the collapse in genome sequencing costs, and has established itself as the market leader in sequencing equipment.
- **BioMarin** develops drugs to address rare genetic disorders, which allows for a lower FDA-approval barrier. Its new drug Vimizim – which received FDA approval last year – is used for treating Morquio syndrome, a metabolic disease which inhibits the body's ability to process sugar.

IMMUNOTHERAPY

This field of research is perhaps the most exciting, well-developed innovation opportunity in healthcare now. In particular, immuno-oncology has gone from being relatively unknown just a few years ago to being a major area of research in pharmaceuticals and biotech. It attempts to use the body's immune system to fight disease. In the context of cancer, this means either 'turning on' mechanisms within a person's immune system to fight tumour cells, or by turning off the mechanism in tumour cells which impede a natural immune response.[7]

As of last summer, pharmaceutical firms had cumulatively initiated nearly 80 immune-based clinical studies, with Citigroup analysts predicting that immuno-oncology drugs could be generating $35bn in annual sales over the medium term, and will constitute 60% of cancer treatments by 2023 (from 3% today). This would make immunotherapy drugs the biggest market in medicine.[8] Important company developments in this field include:

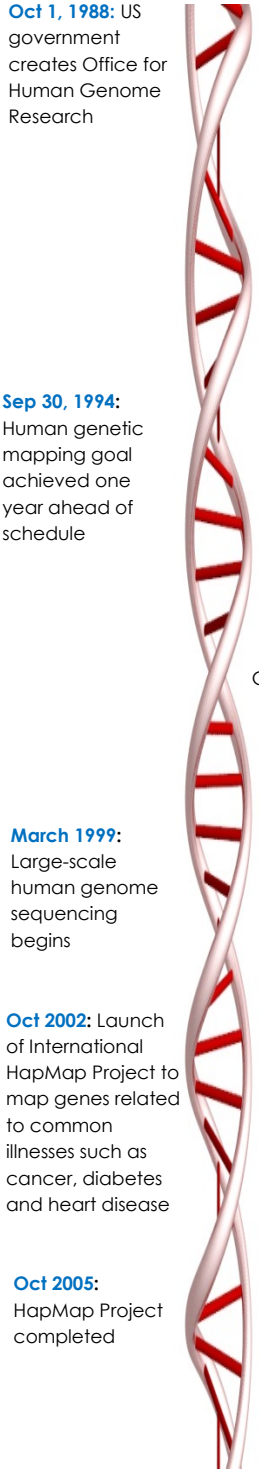
- **Roche** is perhaps the leader in the field of oncology. On 6 February 2014 Genentech – a member of the Roche Group – received FDA approval for expedited development of its anti-PD-L1 immunotherapy drug MPDL3280A, which could be used to treat lung and bladder cancer. Anti-PD-L1 drugs work by blocking a tumour's ability to evade the immune system's defences.
- **Bristol-Myers Squibb (BMY)** has transformed itself in recent years from a regular, branded drug company into one focused on immunotherapy research and development. It has enjoyed recent success with its Yervoy and Nivolumab treatments for melanoma, and via a partnership with **Innate Pharma** has the licence to another promising drug, lirilumab (more info below).
- **AstraZeneca** has an anti-PD-L1 in development (MEDI4736), which in combination with Tremelimumab – a CTLA-4 antibody with proven efficacy at treating melanoma at BMY trials – looks promising, and is expected to be completed in January 2017.[9]
- **Innate Pharma** is a pure-play immunotherapy smallcap. It is developing lirilumab, a drug with good prospects for treating Acute myeloid leukaemia (AML) – cancer of the white blood cells – and which has potential for treating solid tumours.[10]

RNA INTERFERENCE

RNA interference (RNAi) refers to a variety of different technologies that use RNA – nucleic acids that play a major role in protein synthesis – to selectively 'silence' a defective gene or pathway of genes. This amounts to an 'upstream' attack on disease in comparison with immunotherapy and gene therapy, which attempt intervention once diseased enzymes have appeared. In 2011 RNAi received a big boost with the launch of 'Kynamro' an RNAi treatment produced by **Isis** for treating cardiovascular disease; and a drug from Alnylam ('Patisiran') for treating amyloidosis – a group of rare but serious conditions caused by deposits of abnormal protein, called amyloid, in tissues and organs throughout the body.

Companies are developing drugs for treating a variety of conditions – including cancer, cardiovascular, liver, metabolic, renal, hematologic, viral, skin and ocular diseases. Due to risk aversion and the uncertainties of the technology, big pharma companies have been

Chart 6. Human genome research timeline



Source: National Human Genome Research Institute

reticent about investing heavily in this sector, with many selling RNAi assets at very low costs.[11] Biotech companies are thus likely to capture the majority of value in this sector.

- **Alnylam** is the market leader in this space, and aims to have three marketed products and 10 clinical-stage candidates by 2020. The firm has a partnership with Genyme (a **Sanofi** subsidiary), under which the latter has the rights to marketing outside North America and Europe for all of Alnylam's orphan genetic disorder pipeline drugs.[12]
- **Isis** is the leader in 'antisense' technology – one of the three categories of RNAi (the others being siRNA and microRNA). It has numerous clinical and preclinical development programmes, partnered and un-partnered) in the areas of orphan disease, cardiovascular disease, metabolic disease, cancer and inflammation.[13] On 10 February it announced that it had earned a $5m milestone payment from partner **Biogen Idec**, as part of a partnership agreement to develop drugs for treating neurological disorders.

3D PRINTING

"3D printing is now being used to make customised implants, and the Holy Grail, in 20 years, is that we may see 3D printing of actual human organs"

Hilary Natoff
Portfolio Manager

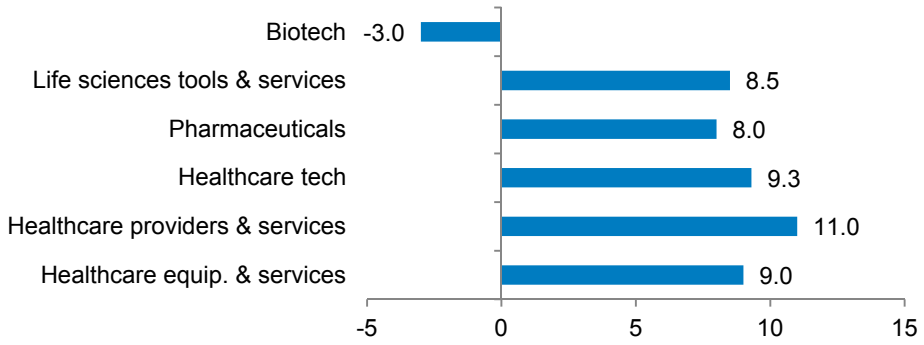
Printing bodily organs sounds like something from a sci-fi novel, but additive manufacturing technology has an increasingly important role to play in medicine. Surgeons are using 3D printing to create exact replicas of patients' organs, which they can then practise procedures on – dramatically minimising the risk of complications during actual procedures and reducing the time taken to complete operations.

Medical devices are the number one area of use for 3D printing – for example, hip and spinal implants, braces (Invisalign) and hearing aids. Organovo is a company that uses cell-based assays for 3D printing bio-therapeutics derived from living organisms. They created the first commercial 3D bio-printer in 2010, and have succeeded in printing functional blood vessels and cardiac tissue using cells obtained from a chicken. Printers for medical devices currently cost in the range of $250-500,000, and are being used for low volume, high value treatments. But as with all new technologies, costs are coming down rapidly, and it's not inconceivable that medical 3D printers could soon become commonplace.

CONCLUSION

Investment returns in the R&D and biotech areas tend to be binary – either very lucrative or damaging to capital invested, due to the sharp differentiation between winners and losers. This is borne out by analysis of cash flow return on investment averages across the sector, with biotech delivering on average a negative return (chart 7) despite many instances of outstanding returns too. This emphasises the point that careful research will be crucial if investors are to reap the benefits of the current innovation wave in healthcare.

Chart 7. Cash flow return on investment averages for different healthcare sectors



Source: Credit Suisse, HOLT Global Industry CFROI Performance Handbook, February 2013. No. of stocks observed: healthcare equip. & services: 3,165; providers & services: 2,891; healthcare tech: 275; biotech: 2,655, pharma: 3,812; life sciences: 782

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