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• CAPITAL PARTNERS •

December 2019: A drug approval, a question answered, and a blood test for cancer

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Dear investors and well wishers,

The fund returned 7.5% in November with strong contributions from Carvana and Amarin. If you'd like to see our latest investment presentation please get in touch.

We recorded a podcast with Eti Amegor, available from iTunes [here](#), or your browser [here](#).

Perhaps surprisingly, quite a people are listening in, so if you want us to answer any questions or address any particular investments please shoot me an email.

For a quick recap on Amarin, this is the US biotech marketing pure EPA, a component of fish oil.

An 18,000 person [study](#) in Japan showed pure EPA reduced the risk of heart attacks by 19% over 4.6 years, which seems to have been largely ignored until Amarin released [results](#) of their own, showing in an >8,000 person study that EPA reduced the risk of heart attacks by about 25% over 4.9 years.

These benefits are a similar order of magnitude to statins, the most successful of which generated over \$100 billion of sales. So this is an exciting opportunity – and data to be aware of if you're concerned about your own heart health.*

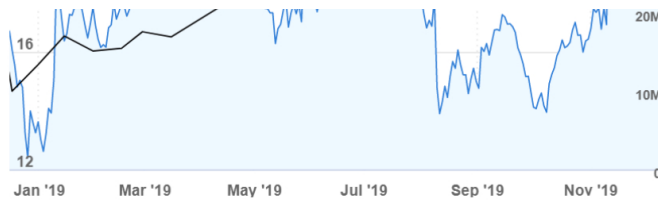
We found this quite convincing, but as seems to happen in a number of our stocks, the internet disagreed, and Amarin became a cult short. The angry opinions and threats flying around twitter were sharply magnified when the FDA decided to hold an advisory committee, which some took to indicate regulatory scepticism.

Fortunately, the medical profession seems to have come to the same conclusion we did, and sales of Vascepa have already accelerated to a \$448m/year run rate, over 100% year-on-year.

Even better, the FDA's assembled advisory committee offered unanimous support, and last Friday the stock was placed in a trading halt and the FDA approved the expanded label.

The question now is whether Amarin will be bought out by a major pharmaceutical company, which would be net value accretive for everyone, or turn this into a blockbuster drug on their own.





Black line indicates short interest – we were buying heavily in the latest dip around \$16. Short interest peaked around 16% and is currently 13%.

Thorny fund management questions

There are a number of difficult portfolio management questions that we spend a lot of time thinking about.

These include how to manage FX, whether to park surplus cash in government bonds, whether to short, and when to sell. Some of these have quite coherent answers, so I've given our answer to one of those below.

#1: Should we own megatech companies like Microsoft, Google, Amazon and Apple?

Our answer is no.

These constitute some of the best risk/reward opportunities in the market right now, with net cash and solid growth, while trading at reasonable multiples. We're optimistic over the multi-decade outlook for business computing, search, e-commerce, social advertising and cloud computing. In the past we have made quite profitable investments in some of these companies.

	Enterprise value US\$b	2020 EV/EBITDA	Net cash US\$b	Growth 2019-2020
Google	810	12	117	18%
Facebook	525	12	52	22%
Amazon	863	17	23	18%
Microsoft	1,098	18	55	12%
Apple	1,105	14	98	6%
Average	880	14	69	15%

There's every chance they maintain 15% growth, and with a little multiple expansion, could return >20% over the mid-term.

But this is not our business. You're better off buying these yourself, and if so inclined, should probably buy the index.

The companies above, Microsoft, Apple, Amazon, Google and Facebook, make up 46% of the Nasdaq 100.

Discerning between Google at 12x EBITDA and 18% growth, vs Facebook at 12x EBITDA and 22% growth, is a poor use of time, as the factors driving the performance of one over the other all lie in the future.

The index offers quite concentrated exposure to those long-term thematic.

More importantly, the index gives you the *other* 54%, which most likely includes the next five megatech companies.

What's less well understood is that there's often a net benefit to market indices as the fortunes of sectors wax and wane.

For example, when oil prices drop 50%, as has happened multiple times over the past few years, fuel costs are cut for everyone else. This flows straight through to pretax profits with a corresponding impact on index value.

For a more relevant example, at some point in the next 10 years, a new tech model for advertising may arise, which would capture market value from Google and Facebook. That rise will be captured by the index, but might lead to extended period of underperformance for an investor concentrated in Google and Facebook.

It may seem strange for me to be advocating an index, but we see our fund as a helpful adjunct to a portfolio predominantly invested in these kinds of investments. Our portfolio companies are generally growing much faster and (we certainly believe) are creating more value on a capital-return basis.

Diagnostics: A blood test for cancer

A blood test for cancer is something of a holy grail in oncology, as it would allow cancers to be found and treated before symptoms show up, without surgery or harmful radiation.

A universal cancer test would involve the entire population being tested on a regular basis, so the commercial opportunity here is spectacular too.

Scientists have known since the 1940s that cancer cells shed tiny bits of DNA into the bloodstream (circulating tumor DNA). These fragments can be as small as 200 base pairs, and extraordinarily dilute, at less than 0.01% of the free DNA in blood.

Finding these proverbial needles is a non-trivial challenge, but it's all very possible with existing technology.

Guardant Health, our new portfolio company, is attacking this problem obliquely with a staged three part plan – something we always love to see.

Step 1: Sequence current cancer patients – already a \$200m/year business

The first part involves testing those with advanced cancers (and hence high levels of circulating tumor DNA).

Typically genetic testing a cancer involves cutting out tumor tissue and sending it to a lab. This is slow, painful, expensive and awkward: think prostate biopsies and colonoscopies.

The first line of treatment is often be started before the genetic data arrives, 3-4 weeks after biopsy.

A few years ago Guardant developed a blood test for circulating tumor DNA with a turnaround of 6 days, and there's now a convincing body of literature highlighting the test's improved speed and accuracy.

In the most common form of lung cancer (85%) Guardant's simple blood test outperformed tissue sampling in both speed and accuracy ([paper](#)), and using *both* Guardant's test and tissue sampling increased detection by 48%.

Guardant also sells tests to the next generation of biotech companies, who typically target those with particular genetic variations of advanced cancers.

This all adds up to a roaring trade: Guardant generated \$200 million of 70% gross margin revenue, growing at 180% year-on-year.

Guardant has completed over 100,000 tests, and as only a small part of each blood sample is used, Guardant holds an increasingly valuable bank of samples and data.

Step 2: Test for recurrence

The next step is to test past patients for recurrence, using the same circulating tumor DNA sequencing technology. This is an easier problem than universal screening, as the type and genetic signature is already known, but harder as the DNA is more dilute.

Circulating tumor DNA has a half-life of about 2 hours, so Guardant's test offers the possibility to track the progress of a cancer as often as required, without the issues associated with repeated surgery or radiation imaging.

In particularly well researched cancers, the specific mutations that lead to resistance are well known, and their presence can be tested in real time.

Guardant has shown they can often predict relapse well before anything shows up in an X-ray, allowing those patients to immediately restart treatment, while sparing those who don't need it.

Step 3: A universal cancer test for asymptomatic individuals

The steps above have allowed Guardant to build market-leading expertise as they build towards their long-term goal.

There are three ways to test ctDNA:

1. Test the genetic code of cell-free DNA in the blood
2. Test for changes to DNA that happen (typically methyl groups that bind to DNA and switch genes on and off.)
3. The fragmentation patterns of DNA, as when tumor cells break down, the DNA fragments in specific ways

There are well-funded competitors in the space, but Guardant is currently unique in testing all three ways.

U.S. Patient Population	Advanced-Stage Cancer ~700 K	Early Cancer, Survivors ~15 million	Asymptomatic, Hi-Risk 35+ million
Information	Therapy Selection GUARDANT360 GEMNI	Recurrence Monitoring LUNAR Assay	Screening & Early Detection LUNAR Assay
Intervention	Targeted & Immunology therapies 50+ biopharma companies	Neoadjuvant, Adjuvant, or Curative	Curative or Preventative
U.S. Market Size	~\$6B	~\$15B	\$30B+

False positives comprise a key challenge in developing population-wide screening.

A test with 99% specificity sounds good – but if you test 100,000 people that's 1,000 false positives. In this context, those people would be subject to highly invasive regimens of unnecessary surgery and radiation, as doctors would be obliged to explore all avenues looking for a disease that's not there.

A multi-pronged approach is the best way to minimize these issues.

To summarize, Guardant has a clear roadmap for:

1. Blood tests to overtake tissue biopsies when testing advanced cancer patients
2. Regular blood tests monitoring recurrence in cancer survivors
3. Testing healthy, asymptomatic people for circulating tumor DNA that indicates cancer.

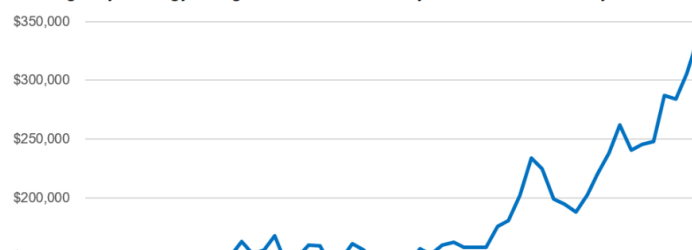
The current market price could be justified by (1) alone. We've gone quite deep on this one, so if you want to know more, please get in touch.

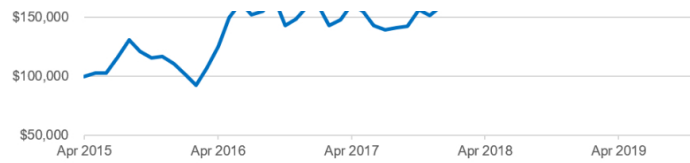
Summary

Our main strategy has now grossed 20% over the last 6 years and 5 months.



Our long only strategy has grossed about 28% a year over the last 4.5 years:





We're acutely aware that many investors joined us in July-October last year before the market sell-off, so there's plenty of work still to do.

With another reporting season under our belt, the fundamentals underlying our long term investments are progressing nicely.

These are in companies we've written about at length, including Afterpay, Carvana, Pinduoduo, Amarin, Pointsbet, diagnostics and US software.

After a long period of investment over the past year or so, we're hoping to reap the rewards of these investments over the next few years, and with a bit of luck, our recent good fortune in the life sciences will continue too.

Best wishes
Michael

*to be clear, there is still no evidence that fish oil works - this only applies to pure EPA. Fish oil includes a mix of EPA and DHA, and it looks like DHA negates the benefits of EPA. Exactly how and why is still unclear.

Our fund is available to wholesale clients, and the online form can be accessed using the button below.

Invest

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