SHORT BRIEFINGS ON LONG TERM THINKING – EPISODE 28

Meet the companies disrupting the world's biggest killer

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MB Hello and welcome to *Short Briefings on Long Term Thinking*. Thanks for joining us. I'm Malcolm Borthwick, managing editor at Baillie Gifford.

These are exciting times for cardiac medicine. Technology is transforming the treatment, diagnosis and prevention of heart attacks, strokes and other blood circulation problems. That's just as well because the challenge is huge.

These are the leading killers of our age. By the time you finish listening to this podcast about eight people in the UK will have died of these ailments. That's a rate of one person every three minutes. To discuss why the figure is set to fall and some of the firms making that possible, I'm joined by Rose Nguyen, an Investment Manager in the Health Innovation Fund.

Before we start the conversation, some important information. Please remember that, as with all investments, your capital is at risk and your income is not guaranteed.

Rose, great to have you with us on *Short Briefings on Long Term Thinking*. Thanks for joining us.

RN Thank you, Malcolm, for having me and thank you everyone who is tuning into this podcast.

MB Let's start with why cardiovascular diseases are so hard to cure.

RB Heart disease is a very common disease, as you mentioned. It's the number one killer globally but it's also a very complex disease. Heart disease is an umbrella term that includes many different conditions that affect the heart and the blood vessels. The most common condition is a build-up of plaques and fatty deposits inside of the arteries and the blood vessels, and this will restrict blood flow and can lead to heart attacks, strokes, organ failures and so on.

Unlike many other diseases, rare diseases that are caused by single gene mutations, heart diseases have been very difficult to cure and eradicate because of the complexity of its biology. It is the result of the interaction of many genes in our body and on so many other environmental factors like lifestyles, diet, smoking habits and so on. So, how the disease manifests itself and how it progresses differs vastly from one person to another.

That's why it has been very difficult to treat with the types of medicines that we have today, which are mostly generic medicines that are one-size-fits-all and they don't take into account the differences between the individuals. If medicines don't work then the other option that we have is surgeries, but surgeries have been typically very invasive and risky up until recent years. So, that is the scale of the challenge that we face but I believe that, with the pace of innovation that we are seeing in the field, there are reasons to be optimistic about the future.

MB And tell me why you're optimistic about the future?

RN The reasons why I am optimistic about the future is because there is this great convergence happening among many different fields of sciences and technologies and they are all coming together to transform life sciences and potentially transform how we diagnose, treat and prevent heart diseases in the future.

Over the past five to ten years, we have seen massive advances in some areas of technologies like genes sequencing, material sciences, biomedical engineering, imaging and so on. Maybe just take gene sequencing as an example. The first human genome cost $3 billion and 13 years to complete back in 2000 but now we can routinely sequence a whole human genome for under $700 in under an hour. That massive decline in cost and time over the years has been made possible due to advances in chemistry, optics, software, data analytics and so on. And I think gene sequencing is probably the one technology that has really revolutionised life sciences.

Thanks to gene sequencing, now we understand much more about the biology of heart diseases, the genes that are involved in contributing to higher likelihood of getting heart attacks in humans. Such insight can help us develop much more precise medicines to cater for the individuals. To give you an example of some of the insight that we have derived from genetics, scientists have performed many population genome studies over the years and they have discovered many risk genes that contribute to higher risk of getting heart diseases.

One of them is called PCSK9. This is a gene that regulates the amount of cholesterol in the blood stream but some individuals who are unlucky to inherit two copies of mutated PCSK9 gene can develop heart attacks in their childhood and if you inherit one copy of this mutated gene, you can develop heart attacks in your 40s or 50s. So, these are an incredible insights, really important knowledge, that have just been unravelled recently thanks to new tools like gene sequencing.

MB Let's explore the three broad areas of progress in more detail, treatment, diagnosis and prevention. Where would you like to start?

RN Let's start with diagnosis because I actually think this is one of the biggest challenges that we face in our battle against heart diseases. The challenge here is that heart disease is very difficult to diagnose. It is often mistaken as signs of old age, with symptoms like shortness of breath, fatigue, chest pain and so on. So, it's often even ignored by the patients themselves.

Then, the second part is, even when you go to get your health check-up, the current method for diagnosing heart diseases is not very accurate at all. One of the most common tests at the moment to diagnose heart disease is a stress test. You basically put a patient on a treadmill to make them do some exercises and then you can see how their heart performs under stress and see if there's any area of the heart that is deprived of blood. But a stress test is highly inaccurate. About 20-30 per cent of patients who are sent home actually have undetected heart disease, heart problems.

There's a very innovative US company aiming to transform this paradigm of diagnosis by using a combination of advanced imaging and AI algorithms. It uses CT scans which capture the image of a patient's heart and then it uses AI to reconstruct a 3D computer model of the heart and calculate exactly the blood volume that flows through each artery.

So, this helps the doctors diagnose patients much more accurately and they can also pinpoint exactly which artery has some blockage within the heart. This technology has already been approved in many countries, including the UK and the US. It has been studied in more than 10,000 people. So, very hopeful that technologies like this can potentially transform the way we diagnose heart diseases and leave no one behind.

MB That's fascinating and it's a common theme in *Short Briefings* actually about how companies are using AI to crunch data and make progress. Another company that we're very excited about at Baillie Gifford is Shockwave Medical and we spoke to the company's CEO to ask him what problem his company is trying to solve.

[Doug Godshall:] *Hi. This is Doug Godshall, the CEO of Shockwave Medical. At Shockwave, we're in the business of improving outcomes in patients suffering from severe cardiovascular calcification and at Shockwave we introduced this revolutionary new technology that delivers shockwaves, little sound waves in a catheter, just next to the arteries, inside the artery actually. Those sound waves crack the calcium and, once the calcium is cracked, the vessel opens up very benignly, without trauma and blood flow is restored to the heart muscle or to the legs or the feet or wherever the blood is flowing to.*

MB And Shockwave has a fascinating backstory, doesn't it Rose.

RN Yes. It has a very unique but also a very humble beginning, actually. The story was that the company was founded in 2009 by three co-founders, one engineer, one businessman and one physician. And they had this crazy idea, which was disregarded by many people at the time, which was to use lithotripsy, which is the technology that is used to break kidney stones. The idea was to use lithotripsy but somehow modify it so that it can break calcium inside the blood arteries and the

blood vessels.

Now, if you have ever seen the machine that breaks kidney stones, you will probably understand why many people laughed at this idea in the past because the machine is huge, it's very bulky. So, their challenge was to figure out a way to make this machine somehow fit into a catheter that can go inside our artery and then break the calcium inside the artery wall.

But they managed to achieve just that, but without any funding in the beginning, they had to produce their prototype machines inside a garage. And do you know how they proved the technology with the proof of concept? They collected eggshells from their own chicken farms, and they used the technology, and they could show that it breaks the outer shell of the egg without damaging the membranes inside the hard shell. So, that is their proof of concept and the rest is history.

MB I love those early stories about them buying ultrasound equipment on eBay and various other things as well. Fascinating. And you've been to see them, as well, in California.

RN Yes. I went to visit their headquarters in 2019, in San Francisco, and I had a great meeting with their CEO, Doug Godshall. He also demonstrated the technology to me and I was very impressed by how simple it is to use and yet how effective it is. I also talked to many physicians and cardiologist in the field as part of our due diligence work and their feedback was overwhelmingly positive. They have never seen a technology like this.

It's very rare in medical technology to have this combination of novelty, safety, effectiveness and ease of use. Usually, it takes a long time to train doctors on a new medical technology but with Shockwave's approach it takes less than one patient for them to get very familiar and up to date with the technology. So, yes, we invested in the company back in 2019 after visiting them and after my round of work.

MB So, let's go back to Doug for the last word on Shockwave. We also asked him "what would the world look like if his company was successful?"

[Doug Godshall:] *We would envision that all the patients who have calcification, which is a growing problem, would have access to our therapy, they would not have to go to surgery. Patients who have calcified valves in the heart could be treated with our lithotripsy system and they wouldn't have to have their valves replaced or wouldn't have to have their valve replaced as quickly. So, better outcomes, lower costs, fewer implants required for the patients suffering from these diseases and that should all accrue to the benefit of both patient but also the healthcare system by reducing complications, reducing complexity.*

MB It conjures up images of what the Nobel Prize-winning physicist, Richard Feynman, talked about in the late 50s in terms of swallowing the surgeon.

RN Companies like Shockwave, they still require some degrees of invasiveness to put

external catheters into the body but the future could be surgeries that are totally non-invasive. The idea may sound science fiction but there are actually research teams already working on that concept of developing nanorobots that can march through our bloodstream and break up calcium inside our blood arteries, guided by MRI imaging. So, you could imagine one day in the future you could actually swallow these nanoparticles, these nanorobots, that can basically do the surgeries inside of our body for us.

MB We've talked about treatment and diagnosis. Let's move on to the third part, which is prevention. Tell me about a company that you're excited about in this area, Rose.

RN With prevention, we all know that lifestyles and diet are one of the most effective ways to reduce your risk of getting heart diseases and heart attacks. So, leading a healthy lifestyle is the number one defence against heart diseases and there are companies like Beyond Meat and Peloton and so on that are encouraging people to do that in a more effective way. However, for the individuals who are unlucky to inherit some serious risk genes, lifestyles alone may not be enough, so we might need some medical intervention to help prevent heart attacks in those individuals.

There is a really interesting company called Verve Therapeutics in the US. It is developing a gene editing treatment to edit out the very serious risk genes, like PCSK9 that I mentioned earlier, to lower the chance of heart attacks in humans. This approach is revolutionary, and this is the first time that a gene editing treatment is being tested in humans.

The data that the company has shown in non-human primates is very impressive. They are able to show that after taking out the PCSK9 gene the non-human primates are perfectly healthy and the level of bad cholesterol in their bloodstream has been reduced by more than 70 per cent, and the impact of that is persistent for up to two years now. I am very impressed by such results and hopefully those results will translate into humans as well.

MB Are there any ethical considerations with gene editing?

RN This is a question that is asked by a lot of people and specifically in this case, where you permanently turn off a gene in a human body. It's fair that some people may feel uncomfortable about that.

However, again, through human genome studies we actually have discovered that there are many people around the world who are born without the PCSK9 gene and they are perfectly healthy, and they actually have a much lower chance of heart attacks compared to the average population. There are already drugs approved on the market that also target the same gene. So, as far as we know, with all of the data that we have, editing out this gene seems to be perfectly safe for humans.

Now, you may ask why does nature give us a gene that does not serve any purpose? I asked this question to the management team of Verve Therapeutics actually and they said that one hypothesis that the scientists have is that this gene might have played some roles in the past, in the very early days of human evolution when food resource was scarce. It might have played a role during periods of starvation but

now we have the exact opposite problem of excess food and not enough energy burn.

So, it could be that this gene, even if we allow nature to take its course, this gene might be edited out by nature after many years. So, what Verve is doing is basically speeding up the natural course of evolution in a way.

MB And what companies are you researching right now?

RN I just finished a report on a company called STAAR Surgical. It's also really cool. Instead of laser eye surgery for people with shortsightedness problems it developed this lens that you can insert on top of your natural lens in the eye, and it will correct for shortsightedness, farsightedness and so on. Compared to laser eye surgery this has much better outcomes, especially for people who have very serious shortsightedness problems like above minus six. It also has fewer side effects, no dry eye syndrome and things like that.

I didn't know about this company until very recently but I was chatting with my parents, my family back in Vietnam and they were saying, oh, your brother is considering an eye treatment because he has quite bad eyesight, like minus nine. So, I was asking them, oh, is he doing laser surgery? And my parents were like, no, no, no. Nowadays, there's a much more innovative, much better treatment and it turns out to be the one offered by STAAR.

And so I thought if my parents know about this before me, it is probably quite a strong signal that this is reaching some sort of critical tipping point in terms of its adoption curve. So, I did the research and I got quite excited about it.

MB Is your brother in Vietnam?

RN Yes. He's in Vietnam and he knows about it because his colleague got the treatment. So, now it's got to a point where word of mouth becomes a way to educate people.

MB Tell me a little bit about your own journey, Rose, because you're clearly enthusiastic about the topic. How did you become interested in health innovation?

RN I joined Baillie Gifford as part of the training programme for graduates and so I've been rotating through several teams before coming to Health Innovation. But even when I was in my previous teams, I have always been drawn to healthcare companies, and I think part of the reason might be because I was brought up in a family with two parents who are pharmacists, so our dinner conversations always touch on health topics and medicines and so on.

So, it is something that is very close to my heart, but I would say that the critical moment that makes me decide to join Health Innovation was when I did a research project in my previous team looking into the history and the future of medicine. Through this research project I realised the pace of innovation in healthcare and life sciences is accelerating at a very rapid rate, and things that seemed like science fiction ideas a couple of years ago are now turning into reality. So, as an investor,

I think there is no better hunting ground for great investment ideas than healthcare. So, that's why I decided to join Health Innovation.

MB And that's a great way to end the podcast, Rose. Thanks so much for joining us on *Short Briefings on Long Term Thinking*.

RN Thank you, Malcolm.

MB And thanks to you, the listeners, for investing your time in *Short Briefings on Long Term Thinking*. You can find our podcast at bailliegifford.com/podcasts or subscribe at Apple Podcasts, Spotify or on TuneIn.

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