Medtech: Going steady

BY ELIZABETH CAIRNS | JULY 2022

Evaluate Medtech

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Introduction

After a couple of years of Covid-fuelled growth, the medtech industry is starting to settle back to something we could call – if we could bear to – the "new normal". That is, back to steady levels of growth and investment across most areas of the market. Evaluate's consensus forecasts now extend to 2028, and in this ebook we take a first glance at what that year might hold. We also consider the current landscape, and take a deep dive into one of the more innovative areas, liquid biopsy.

What will 2028 look like? We'll explore in more depth in the first section, but we see the industry growing at 5% a year. Naturally, when you look under the hood there is some variation across the different areas, with the highest growth – 10% CAGR – coming from the rather niche area of nutritionals (IV vitamins). Among more mainstream segments, we see 7% CAGR for diabetic care and orthopaedics and lower levels for the larger areas such as diagnostics and drug delivery (3% and 2% CAGR, respectively). Looking at the biggest players in the market, the top slot will still be held by Medtronic in 2028 as it continues its consistent levels of growth. Other players – find out who further down – may still be growing but are being outpaced by the competition and find themselves significantly lower than in our previous forecasts.

What else is happening? Digital health continues to divide the crowd when it comes to investment, and we see some interesting differences in speed to market across the various segments that we dig into here. What's not happening, on the other hand, is deal-making. Last year venture-backed companies waited longer than average for a takeout, and longer than ever for an IPO. And so far in 2022 there have been just a handful of IPOs, so the challenges of the wider healthcare market are very much apparent in medtech.

That's the context so let's dive in.

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Part 1: A look to the future

Up-and-down test sales and a bigger Medtronic: medtech in 2028

BY ELIZABETH CAIRNS, 20 JUNE 2022

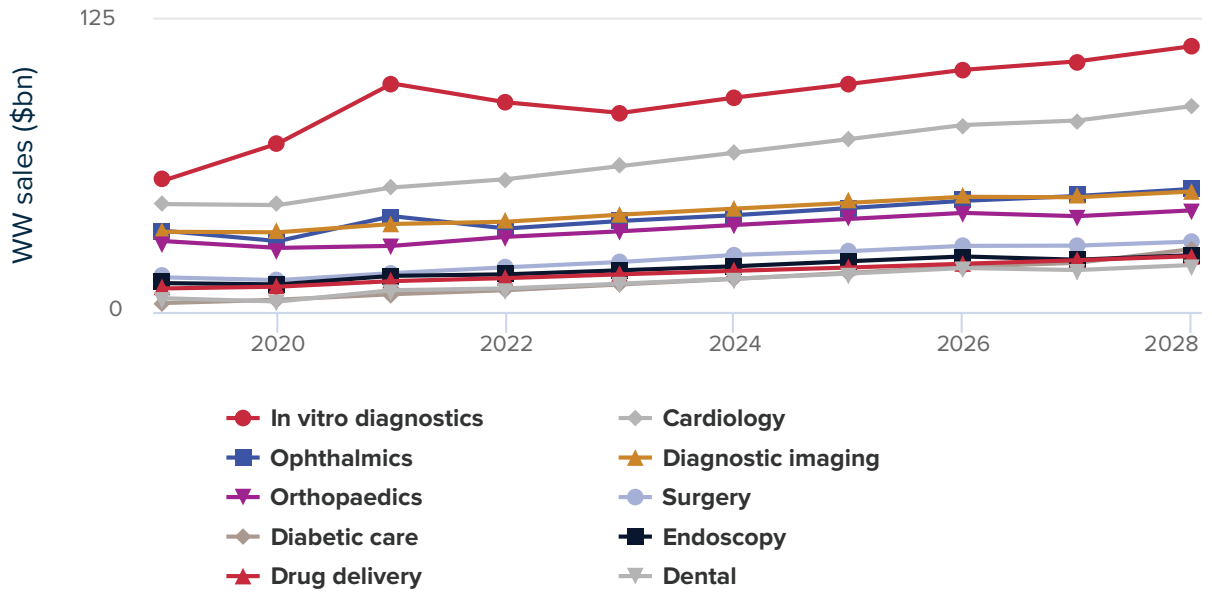
Medtronic, Siemens and Stryker are all expected to seize greater market share, while Roche slides down the rankings.

The medtech industry as a whole will soon be worth three quarters of a trillion dollars. New consensus forecast data from Evaluate Medtech, reaching to 2028, foresee an industry growing at 5% a year, with in vitro diagnostic technology making up the largest segment.

As for the leading company, Medtronic is expected to remain at the top of the heap out to 2028 and marginally increase its share of the market, in spite of recent supply chain troubles. Roche's sales, meanwhile, are set to grow so slowly that it will drop from the fifth largest company by medtech sales to the ninth.

The top 10 biggest areas in medtech

2019-2028



Source: Evaluate Medtech

As the graph above shows, diagnostics makers enjoyed extraordinary success across 2020 and 2021 – and no prizes for guessing why. As the pandemic has eased, however, the sellside believes that sales of Covid assays will fall, and this is by far the biggest factor behind the forecast decline in test sales to 2023.

After that sales start to rise again, breaching the $100bn mark in 2025 and hitting $115bn in 2028.

Several areas experienced the opposite pattern over the pandemic, with makers of surgical, orthopaedic, ophthalmic and dental technologies suffering particularly badly in 2020. These segments are forecast to pick up from this year, however, and grow steadily thereafter.

JOCKEYING FOR POSITION

As for the biggest companies six years hence, Medtronic retains its top spot when judged by sales of medical devices. Last year Abbott, fuelled by sales of its Covid diagnostics, overtook Johnson & Johnson to snag the number two post; the top four companies will stay locked in these positions until 2028, according to consensus.

Naturally these forecasts cannot take account of any major takeovers or other business development moves that might occur in the future. Medtronic's management, for example, has hinted that the company might divest some of its slower-growing units, and while the M&A scene is pretty moribund at the moment companies will start buying again. This data should give a reasonably good idea of expectations for organic growth, however.

On this measure Stryker is a riser, moving up two places from its current place in the rankings, reaching the top five in 2028. As with many orthopaedic groups its sales slumped in 2020, but it has staged a remarkable recovery and is seen growing at a respectable 7% annually to 2028.

Top 10 medtech companies in 2028					
	WW medtech sales ($bn)			Market share	
Company	**2021**	**2028e**	**CAGR**	**2021**	**2028**
Medtronic	31.7	44.1	+5%	5.8%	5.9%
Abbott Laboratories	29.9	39.0	+4%	5.5%	5.2%
Johnson & Johnson	27.1	36.2	+4%	5.0%	4.8%
Siemens Healthineers	21.3	32.5	+6%	3.9%	4.4%
Stryker	17.1	26.6	+7%	3.1%	3.6%
Becton Dickinson	18.9	23.1	+3%	3.5%	3.1%
Essilor Luxottica	15.2	23.0	+6%	2.8%	3.1%
Philips	16.3	21.9	+4%	3.0%	2.9%
Roche	19.4	21.2	+1%	3.6%	2.8%
Boston Scientific	11.9	18.5	+7%	2.2%	2.5%

Source: Evaluate Medtech

Roche, on the other hand, is forecast to slip four places. Its sales are growing overall, but at a slower pace than rivals, and its diabetes and molecular diagnostics sales are actually forecast to fall. The former consists mainly of relatively basic blood sugar monitoring systems that require users to prick their fingers and test a small drop of blood, a technology that is fast losing ground to more advanced systems such as continuous glucose monitors.

But it is molecular diagnostics that will really do for the Swiss group, in the sellside's view. Sales of this unit soared to $5.3bn in 2021 but will fall beneath $4bn next year on cratering Covid test demand. The effects of the pandemic continue to make themselves felt.

Medtech research spending set to slow in 2022

ELIZABETH CAIRNS, 4 JULY 2022

And some diagnostics groups are forecast to actually cut R&D outlay this year as the pandemic eases.

In 2020 the novel coronavirus prompted the largest medtech companies to boost their spending on R&D significantly, with the top 10 groups investing more than $15bn between them in bringing new technologies to market. And from then to 2021, the increase was even sharper, with this figure reaching $17.4bn.

When these big medtechs report their financial results for the current year, however, the sellside sees their R&D expenditure increasing much more slowly. After that, moderate growth will see the top 10 cohort spend just shy of $23bn on in-house development in 2028.

These forecasts, compiled by Evaluate Medtech from sellside reports and recently extended out to 2028, see Medtronic as the biggest spender on research in six years' time, with an R&D bill of $3.4bn. In terms of spending as a proportion of sales, however, Philips is forecast to lead – but this is arguably more to do with falling sales than increased spending.

While the rate of growth in a medtech's R&D outlay can fluctuate, it is rare for companies – divestments aside – to make actual cuts to their research spending. But four of the top 10 companies are forecast to do just that in the coming few years.

From 2021 to 2022, the sellside believes that Becton Dickinson, Philips and Roche will downgrade their research spending, by 7%, 4% and 0.4%, respectively. In all three cases this is a retrenchment from the splurges of 2020 and 2021 as they raced to develop technologies to aid the fight against the coronavirus – diagnostics from BD and Roche, and ventilators from Philips.

In 2023, Abbott is forecast to make the same move.

Following that, analysts expect a return to the steady, even growth that had been the usual pattern in pre-pandemic years – excluding large strategic moves such as mergers and divestments, that is.

CALM AFTER THE STORM

A look at proportional spending – what fraction of a company's medical device sales they re-invest in medtech research – shows a similarly turbulent few years, with a calmer period beyond 2023. For many of the companies, the change in proportional spending is less to do with managerial decisions to allocate cash to R&D than it is with marked variation in revenues.

Abbott, its coffers swelled by Covid test revenues, spent just 7.4% of its gross income on research in 2021, versus 9.4% in 2019. The same pattern may be seen with Roche's proportional spending, and for the same reason.

Philips embodies the opposite situation. It upped its R&D spending by a huge 28% in 2020 as it refocused to become a pure-play medtech company, and did its damnedest to get new ventilators to hospital wards. But damned, in fact, it was: faulty ventilators have been repeatedly recalled over the past year or so and the group's revenues have stalled.

Its overall sales grew by just 1% from 2020 to 2021, and are forecast to do the same to 2022. This means that in 2021 it spent a whopping 13.3% of its sales on R&D. This proportion is forecast to shrink in the years to come, though will remain higher than other big medtechs. The question for investors is when the fruits of this investment might appear.

Part 2: 2022 – the story so far

To back, or back away from, digital health?

BY ELIZABETH CAIRNS, 15 JUNE 2022

Some medtech venture investors are taken with the promise of digital technologies, while others find them easy to resist.

Accelerated by the Covid pandemic, when telehealth and disease management apps came into their own, digital health is sparking great interest from venture funders. Some, like HLM Ventures, specialise in digital health, attracted by the speed of development and lower regulatory risk versus conventional devices.

But not all VCs have been won over to the digital world. France's Truffle Capital eschews this space entirely, solely backing developers of implanted medical devices. Intriguingly, though these two investors have taken opposing stances, their understanding of the advantages and disadvantages of the digital world align perfectly.

That digital health is increasingly appealing to VCs is undeniable; the biggest round in medtech so far this year went to the virtual care specialist Biofourmis, and Mindmaze and Viz AI both pulled in nine-figure rounds, for their digital therapeutics and AI-based diagnostic tech respectively.

Digital health vs "classic" medtech - 2022's biggest VC rounds				
Date	**Company**	**Investment ($m)**	**Round**	**Technology**
Digital health				
Apr 26	Biofourmis	300	D	Virtual care and disease management software, including for heart failure
Feb 17	Mindmaze	105	Undisclosed	Digital therapeutics, including a video game for stroke rehabilitation
Apr 7	Viz AI	100	D	AI-enabled diagnosis and triage of stroke, aortic disease, pulmonary embolism and cerebral aneurysms
May 2	Hello Heart	70	D	Heart health management app
Mar 24	Osso VR	66	C	Virtual reality for training surgeons
Traditional medtech				
Jan 27	Enable Injections	215	C	Wearable subcutaneous drug delivery technology
Mar 30	Billiontoone	125	C	Molecular diagnostics, including non-invasive prenatal testing
Feb 17	Nalu Medical	104	Undisclosed	Neurostimulation for neuropathic pain
Mar 1	Visby Medical	100	E	Infectious disease testing
Jan 10	Memed Diagnostics	93	C	Crispr-based molecular diagnostics

Source: Evaluate Medtech, company communications.

HLM has not invested in these groups specifically, but it does play in these segments. It was an early investor in Teladoc, leading that group's series B round in 2013. Teladoc's stock soared during the pandemic and it bought Livongo in the summer of 2020 (Teladoc bets $18.5bn that Covid-19 will change the world for good, August 6, 2020).

"Pre-pandemic, the usage of telehealth was still very low," Steve Tolle, general partner at HLM, tells Evaluate Vantage. "A lot of people had access to it in theory, because their employers had it as part of their benefits, but very few people used it."

Now that "the horse is out of the barn" on telehealth, one of the pressures on HLM, as an investor in digital health, has eased: the commercial path for virtual care providers is now clearer. On the minus side, the market is vastly more crowded.

"In the digital health world, there's less risk from regulation because there is very little regulatory oversight. The biggest risk is competition and scale, and adoption," Mr Tolle says.

QUICK VS THOROUGH

Antoine Pau, a partner at Truffle Capital, agrees – despite Truffle's policy of avoiding investing in digital health. "We like therapeutic devices. You can measure a life-saving clinical outcome with clear endpoints. [These devices] will ultimately command higher prices, higher reimbursement and faster market access."

Naturally, developing a medical implant is a longer and more expensive business than launching an unregulated app or other software. Truffle's portfolio includes Carmat, the maker of the Aeson artificial heart which finally put itself on a commercial footing last year, after a long and tortuous journey.

Mr Pau admits that Aeson is "probably one of the most complex devices ever developed". But he says the time and expense is justified since Aeson's complexity provides a very high barrier to entry for potential competitors, enabling Truffle to recoup its investment.

He also downplays the regulatory risk for traditional

devices, pointing out that breakthrough device designation can smooth the path to market.

And, partly because their developers might not seek formal approval, digital health products have a harder time obtaining reimbursement and achieving widespread market access. A developer of a more familiar medical implant will know exactly how to demonstrate its worth compared with the standard of care, and if the clinical data does back the new device, doctors and payers will be much more easily persuaded of its value, Mr Pau says.

BIGGER AND LATER

Historically, both HLM and Truffle started investing in companies at an early stage – HLM in series A or B rounds and Truffle even earlier, essentially helping found the companies it backs. But both are now going later.

HLM is now active in series C rounds too, investing anywhere from $2m to $50m. Citing market dynamics, Mr Tolle says that these days, backing a series C-stage, revenue-generating digital health company with a path to an exit makes sense.

"You're not going to have a massive stake in a company, you're not going to have 10 or 15%, you're going to have 2%. But it's an investment that's more likely to have a positive return in an unpredictable market," he says.

Truffle, meanwhile, is raising a new fund that will invest in pre-commercial to early commercial medtechs, providing significant investments to see companies at this stage of development through until profitability.

"It will be covering a very strong need, especially in Europe, for funds that are experienced in medtech but have the capacity to invest more, such as writing €30-50m cheques in those companies that are having difficulty raising substantial funding at this stage," Mr Pau says.

The fact that HLM's investments are, on average, smaller than Truffle's indicates the relative cheapness of developing digital health products compared with more traditional medical devices. If that is an advantage, it is one that must be balanced with the risks when assessing the promise and pitfalls of digital health.

Diagnostics beat implants in the race to market

BY ELIZABETH CAIRNS, 23 MAY 2022

Roche had the most innovative approvals over the last five years – but took second place in terms of speed.

Diagnostics companies have a sizeable advantage over developers of other forms of medical devices in that their products achieve approval in a much shorter time frame. An analysis of the number and speed of FDA approvals of innovative medical technologies over the last five years puts the test makers Roche and Qiagen way out in front; makers of complicated hospital equipment and heart implants, like Asahi Kasei and Abbott, lag behind.

But a look at the development strategies used by these companies – whether they tend to develop their products in house or obtain them via company acquisitions – gives a less clear-cut picture. In some cases internal R&D was rewarded with swift approvals, whereas some of the groups benefited from prioritising M&A.

The analysis below considers the companies that received at least five FDA first-time premarket approvals, humanitarian device exemptions or de novo 510(k) clearances between the start of 2017 and the end of last year. These regulatory paths are used for medical technologies unlike anything already on the market – products that represent true advances.

Roche leads the way in terms of the number of these

approvals, with 21 – all for in vitro diagnostics. All were either tests to aid cancer treatment – including liquid biopsies – or for infectious disease. These being relatively simple, non-invasive products, they are easily evaluated for approvability, and Roche's products were greenlit in a mean of just 8.3 months.

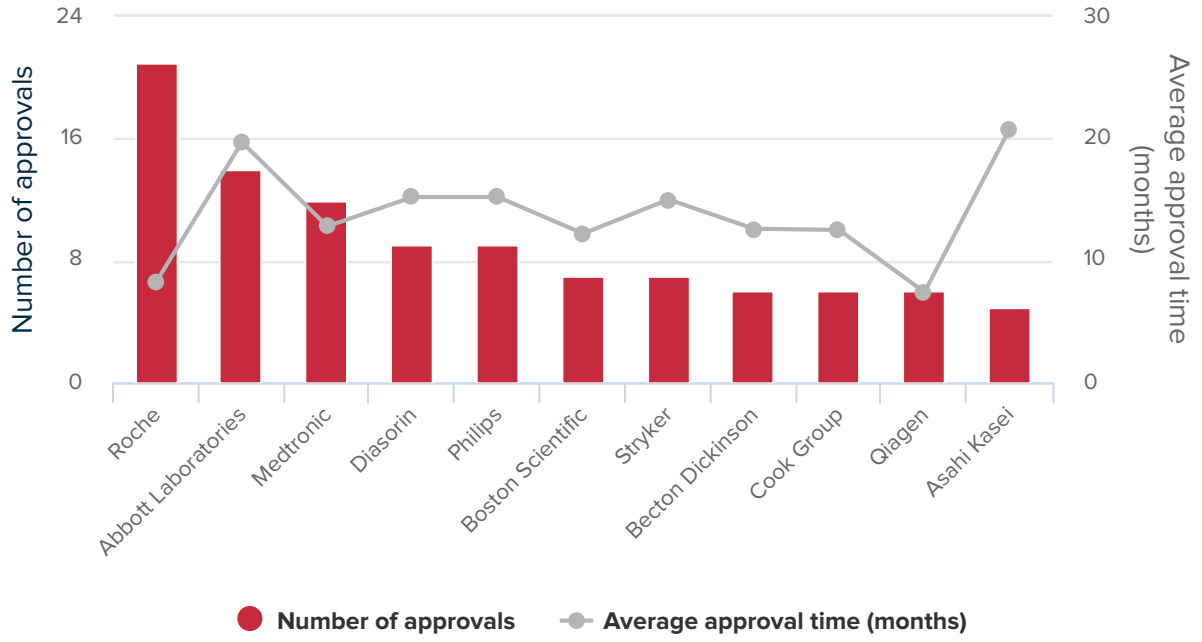
THE WINNER

But another company was faster still. Qiagen's tests, mostly designed for tumour profiling but also including a test to predict the risk of preterm birth, were approved in an average of 7.4 months.

It should be noted that, though both Qiagen and Roche were heavily involved in Covid test development, the figures for these companies do not incorporate any Covid tests; these reached market via the emergency authorisation pathway and do not appear in this analysis.

Innovative device approvals by company

2017-2021



Source: Evaluate Medtech

Of course, diagnostics makers can bypass the FDA if they wish, marketing their tests via Clia waiver rather than seeking formal approval. Most diagnostics groups make use of the Clia pathway, so arguably this analysis does not give a complete picture of how quickly these companies' products go on sale.

All the tests for which Qiagen did receive FDA approval over the past five years, and all but one of Roche's, were developed organically from internal R&D efforts. The other pure-play diagnostics company in the cohort, Diasorin, also worked entirely in-house.

Among more traditional medtech companies strategies diverge – and so do the results.

Of the 10 companies in this cohort, Becton Dickinson

is by far the keenest on buying in innovation. Many of its approved products came via the acquisition of CR Bard in 2017, including the Covera and Venovo stents. The purchase of Lutonix supplied the drug-coated angioplasty balloon of the same name.

The approach seems to be working. The devices it bought were evaluated and approved by the FDA an average of six months faster than the products BD developed in house.

Innovative device approvals 2017-21 by company strategy			
Company	**% developed in-house**	**Ave approval time in-house (months)**	**Ave approval time bought in (months)**
Becton Dickinson	17%	17.7	11.6
Philips	78%	17.5	7.3
Asahi Kasei	80%	7.4	18.5
Medtronic	83%	12.3	15.3
Abbott Laboratories	86%	11.8	67.6*
Boston Scientific	86%	12.9	8.4
Stryker	86%	15.3	13.0
Roche	95%	8.0	6.0
Cook Group	100%	12.5	-
Diasorin	100%	15.2	-
Qiagen	100%	7.4	-
Average		12.5	19

*Abbott time is skewed by one outlier: the Amplatzer Post-Infarct Muscular VSD Occluder took nearly 10 years to be approved.

Source: Evaluate Medtech.

To be considered bought in, a device's regulatory submission must have been made by a company that was subsequently bought by the recipient of the approval.

In fact, for most of these groups, the products that came via acquisitions completed FDA review more swiftly than those developed internally. With dealmaking seemingly largely off the table this year, medtechs could soon find themselves waiting longer for their approvals.

For medtechs seeking deals, it's hurry up and wait

BY ELIZABETH CAIRNS, 6 MAY 2022

Last year venture-backed companies waited longer than average for a takeout, and longer than ever for an IPO.

Considering the pandemic was very much still rampaging, last year was surprisingly good for the medtech industry in terms of venture funding, flotations and M&A values. But a new Evaluate Vantage analysis points to one way in which the environment got worse.

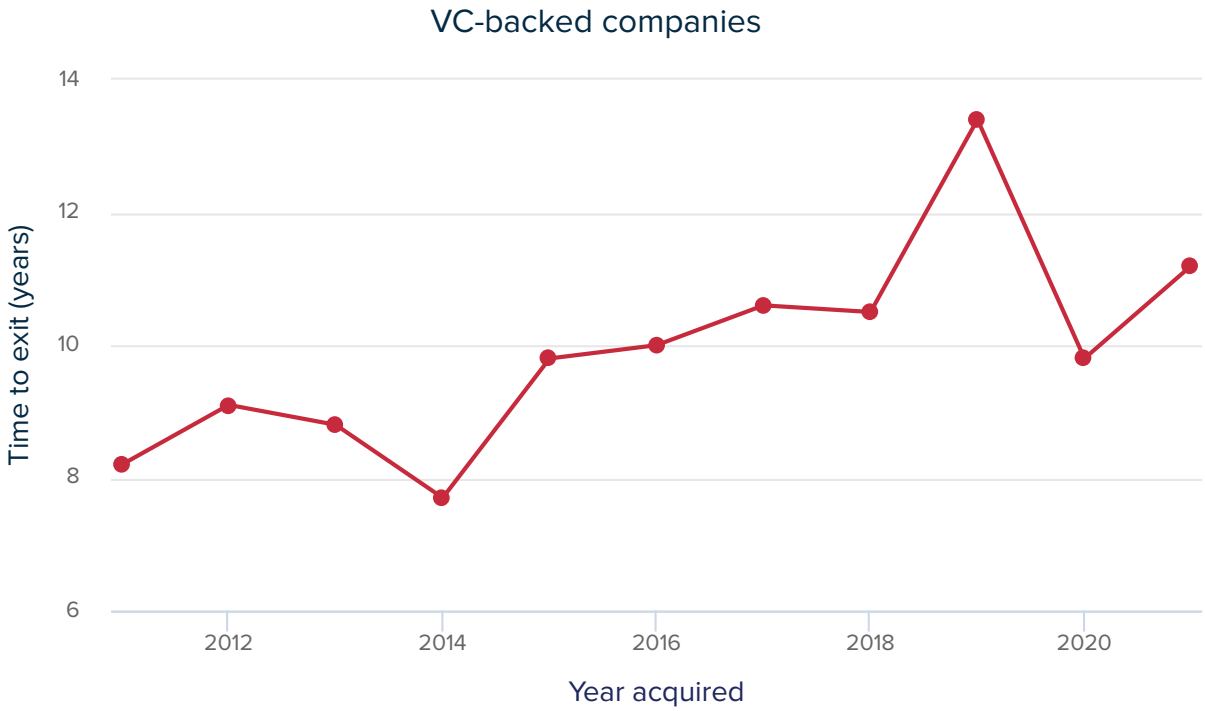
With huge sums being disbursed by venture investors, medtechs have had little reason to seek liquidity via a listing or to give in to bids from potential buyers. Consequently the average time between a private company's founding and its 2021 exit, via either an IPO or an acquisition, was longer than any time since 2014, at 12 years.

The analyses below consider only those companies that are primarily or totally funded by VCs. Thus Ortho Clinical Diagnostics, for example, whose January IPO was the largest of 2021, is not included since it has never received venture cash.

BUYERS PLUMP FOR OLDER TARGETS

The startling drop in the time to acquisition of private medtechs seen in 2020 was thrown into reverse last year. The companies bought in 2020 were acquired an average of 9.8 years after their establishment. For those bought in 2021, the figure was well above a decade, at 11.3 years.

Medtechs' time to exit via M&A



Source: Evaluate

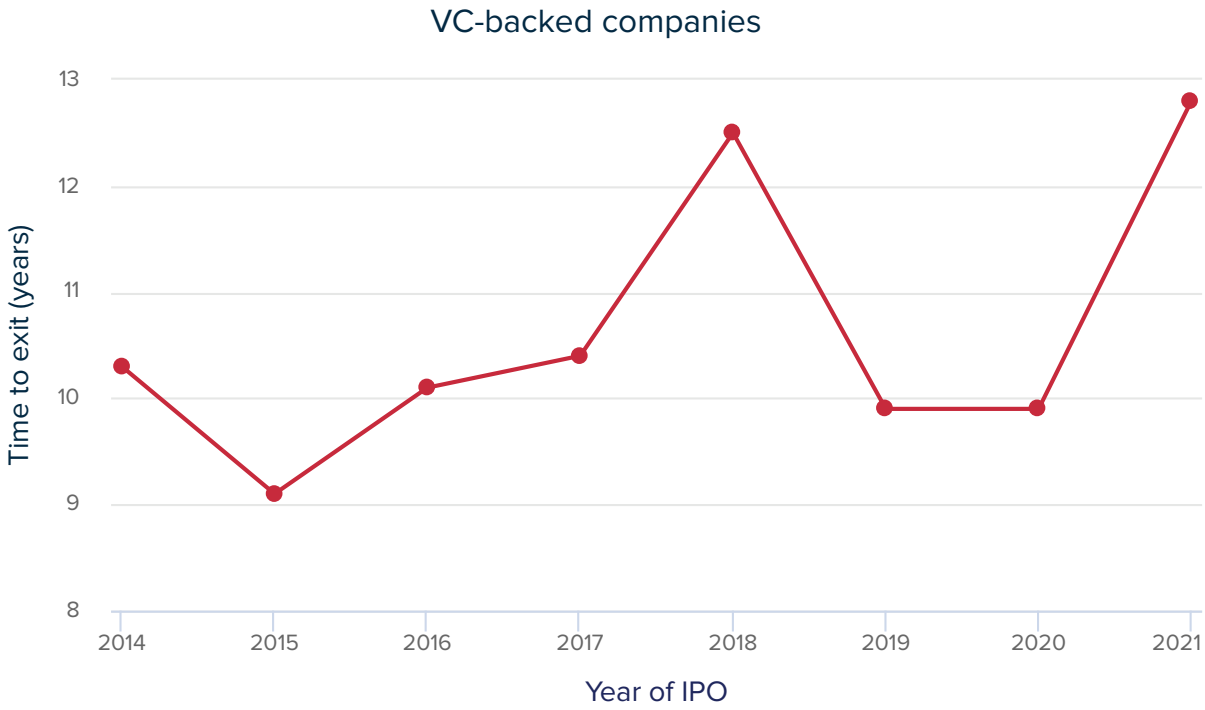
The lengthening time for venture-backed companies to be acquired is a clear consequence of VCs' own preference for investing in older groups whose devices are approved and even reimbursed, since they make for safer bets than clinical-stage start-ups. As Vantage's analysis of VC trends over the past decade has shown, the number of investments has fallen steadily as the cash is concentrated in larger rounds for later-stage companies.

Defying this trend was Thrive Earlier Detection, the liquid biopsy developer snapped up by Exact Sciences just over a year after coming out of stealth mode. Evidently a presence in a hot area is a major attraction.

CARPE DIEM

And if the wait for an acquisition lengthened in 2021, the interval between founding and IPO widened still further. The VC-funded groups that went public in 2021 did so in an average of 12.8 years – hanging on nearly two years longer than those that listed in 2020.

Medtechs' time to exit via IPO



Source: Evaluate

It might be that the welcoming IPO environment that persisted throughout much of 2021 finally lured companies that had been private for some time onto the public exchanges. Perhaps they felt that if they didn't make the leap while the markets were receptive, they would have to remain private for an inconveniently long time. If that was the reasoning, it seems to have been correct: the window slammed shut towards the end of last year, and so far in 2022 there have been just three medtech IPOs.

Venture capitalists backing these groups are themselves tremendously well funded, so they will be able to view the longer road to an exit with some equanimity. Even so, a return to a shorter exit interval across this year would not be unwelcome.

Part 3: The future of liquid biopsy

Liquid biopsy developers take aim at colorectal cancer

BY ELIZABETH CAIRNS, 10 FEB 2022

Natera and Guardant are about to shake things up with indication-specific blood tests, but Exact is keeping faith with Cologuard – for now.

The first pan-cancer blood tests were approved by the FDA in 2020. Now several liquid biopsy companies are turning their attention to new settings specifically in colorectal cancer – screening and detecting cancer recurrence – and testing for this tumour type could soon change drastically.

Recent data from Natera have shown for the first time that its Signatera blood test can predict which post-surgical colorectal cancer patients will benefit from adjuvant chemotherapy. And Guardant Health will soon present data from a vast pivotal trial of its colorectal screen, Lunar-2, potentially threatening the current leader in non-invasive screening, Exact Sciences.

Natera has long been one of the leaders in so-called minimal residual disease detection – using circulating tumour DNA (ctDNA) to pick up malignant re-growth following surgical removal of tumours, a

market SVB Leerink analysts put at $20bn. Now data from the Galaxy sub-study of the Circulate-Japan trial, which emerged at the Asco-GI meeting last month, have taken things a step further.

SO WHAT?

Signatera and tests like it have been shown to effectively differentiate whose cancer will or will not recur, according to Alexey Aleshin, the company's vice-president. "But the lingering question for the last few years has been, so what? Can we actually intervene based on ctDNA positivity or negativity and alter outcomes?," he adds.

The Galaxy data show that the answer is yes, he says. Of patients with stage III cancer with a positive Signatera result, those who did not receive adjuvant chemotherapy had a greater than eightfold increase risk of recurrence versus those who did – a significant difference. This is the first definitive link that post-surgical treatment guided by Signatera can improve outcomes.

Signatera could also track which patients are benefiting from the chemo. Chemo-treated patients who cleared their ctDNA – going from having a positive Signatera result to a negative – did significantly better than those who remained positive, with a six-month disease-free survival of 100% and 58% respectively.

Indeed, the patients who went from positive to negative did as well as patients who were ctDNA-negative to begin with.

Mr Aleshin says the group expects these data to increase interest in the test, though he declines to say exactly what it might mean for sales.

BLOOD AND GUTS

Also in colorectal cancer, but in the screening setting rather than recurrence, a battle is looming. The pivotal Eclipse trial of Guardant's Lunar-2 liquid biopsy, a vast undertaking in 13,000 patients, will report this summer.

The gold standard for colorectal cancer screening is colonoscopy, but compliance with this invasive and unpleasant procedure is low. The main non-invasive screen is Exact Sciences' faecal test Cologuard, which has been tremendously successful since its launch in 2014. If Lunar-2 reaches market on the strength of the Eclipse readout – and a filing is pencilled in for the second half of this year – it could cut into Cologuard's sales, particularly if people decide they prefer giving a blood sample to a faecal sample.

Of course, Exact has its own liquid biopsy, a pan-cancer test obtained via its acquisition of Thrive Earlier Detection in 2020. It would be logical to assume that Exact would be putting Cologuard aside and throwing its efforts behind the blood test to try to compete with Guardant and the other liquid biopsy developers. It would also be wrong.

Instead the group is trumpeting Cologuard 2.0, a second-generation faecal test designed to have better efficacy. Data from a small trial, also presented at Asco-GI, showed the test to have sensitivity of 95% for colorectal cancer, 83% for high-grade dysplasia and 57% for all advanced precancerous lesions, all at a pre-set specificity of 92%.

Paul Limburg, Exact's chief medical officer, believes Cologuard 2.0 has an advantage over Lunar-2, however, in that as well as picking up early malignancies it can also detect precancerous lesions.

"Biologically, precancerous lesions may not have the same potential to shed biomarkers into the bloodstream," he says. Detecting them using a stool-based test is biologically and technically feasible, he says, but a liquid biopsy would not be able to match this.

The next step for Exact is Blue-C, the pivotal trial of Cologuard 2.0. Dr Limburg says this will have to exceed what the first-gen test showed in its pivotal trial, which was 92% sensitivity and 87% specificity. Blue-C will report in 2024.

But a parallel trial suggests that Exact is keeping

its options open when it comes to blood tests for colorectal cancer. Patients enrolled in Blue-C may also provide a blood sample. “Those specimens will be used to further explore blood-based biomarkers, compare performance to other existing assays – with the development of a blood based assay in mind,” Dr Limburg says.

This is unlikely to form the basis of an approval application for a liquid biopsy to screen for colorectal cancer, however, so a blood test to rival Lunar-2 is not imminent. Exact will be dependent on first-generation Cologuard for some time yet.

Freenome aims to take on the big beasts

BY ELIZABETH CAIRNS, 25 MAY 2022

Forthcoming data in colorectal cancer screening could put the company's liquid biopsy on the market – but it looks like Guardant might get there first.

The private liquid biopsy developer Freenome has eschewed the multi-cancer path to focus instead on a very specific setting for its first blood test: screening for colorectal cancer.

But the readout of its vast trial in this setting has been delayed from this year to next, and in the meantime Guardant Health, an established liquid biopsy player, will report data from a very similar study of a rival test. Freenome is banking on its novel approach, looking at RNA and proteins as well as DNA, winning out in the clinic. It might be a harder task to win out in the market.

"Most companies start off building a diagnostic test with the technology first and then try to use the technology to have multiple indications. We flip that on its head," Jimmy Lin, Freenome's chief scientific officer, tells Evaluate Vantage.

Freenome is targeting colorectal cancer first because of the overwhelming evidence that if the disease is caught and treated early there is a major improvement in outcomes. Consequently there are

also clinical guidelines recommending screening, and a clear path to reimbursement.

The company's unnamed test is in the 25,000-strong study Preempt-CRC, with a plan to file for premarket approval on the results. Preempt-CRC had been expected to report this year, but the company tells Vantage that the data will now come in 2023.

SCREEN TEST

The current ruler of the non-invasive colorectal cancer screening niche is Exact Sciences, with its stool test Cologuard (see above). The argument made by liquid biopsy developers is that blood testing is more acceptable to patients than faecal tests, and would be widely preferred if accuracy was as good.

But the real fly in Freenome's ointment is not Exact but Guardant. That group is aiming to add another cancer blood test to its tumour agnostic Guardant360 assay, approved in 2020. The pivotal Eclipse trial of Guardant's colorectal screen Lunar-2 is to report this summer, so the best case could see this test approved by the end of this year.

Mr Lin is unruffled. "Guardant's technology is solely focused on next-generation sequencing of nucleotides," he says. "Our technology includes nucleotides as well as protein data."

This "multiomics" approach gives a more holistic picture of a patient's cancer, he says, and also allows detection of adenoma – a pre-cancerous condition that allows the cancer to be headed off before it even develops. "That's where we're really going to be shining," he says.

The proof of this assertion will come with the Preempt-CRC data. But some seem to be convinced already.

Freenome is phenomenally well funded, having raised over $800m in venture cash from no fewer than 34 separate investors, including Google, Novartis and Roche. And earlier this year Roche made a separate investment of $290m, putting Freenome firmly in unicorn territory.

Roche, of course, has its own liquid biopsy, the pan-cancer FoundationOne Liquid CDx. Perhaps it is marking Freenome for a future acquisition, the idea being that it would be able to compete directly against Guardant in not one but two settings.

Mr Lin swerves this question. He hints that, as with Novartis, Roche's interest might be more to do with the application of Freenome's tech to aid in either drug discovery or choosing patients for clinical trials. He adds that there is a collaborative aspect to the Roche-Freenome relationship, with the sharing of technology and expertise in both directions.

MULTIOMICS FOR MULTI-CANCER

And, even within cancer diagnosis, Freenome's platform could be applicable beyond colorectal. In February the group began enrolling into a trial called Vallania to explore the use of multiomics to detect multiple cancers. The plan is to test the same blood sample using the current colorectal diagnostic and an as-yet to be developed test for other cancers.

Vallania is designed to find out what these tumour types might be; lung and pancreatic cancers are first on the list. Theoretically, it might be possible for Freenome to come up with a pan-cancer test almost by default.

This would involve "taking a real deliberate stepwise approach", Mr Lin says, adding cancers one by one, or a few at a time. But if Freenome does manage to develop a multi-tumour test it would enter a market with two players already in situ. As with colorectal screening, the technology will need to distinguish itself in terms of performance if Freenome is to make its mark.

Selected liquid biopsies				
Company	**Liquid biopsy**	**Tumour type**	**Intended use**	**Status**
Guardant Health	Guardant360	Pan-cancer	Helps assign targeted therapy	Approved in US Aug 7, 2020, price approx $6,800
	Lunar-2	Colorectal	Screening	Pivotal Eclipse trial to report mid-2022
	Lunar-2	Lung	Screening	Pivotal Shield trial to report 2024
	Reveal	Colorectal	Postsurgical, detects disease recurrence	Launched as LDT Feb 16, 2021
Roche	FoundationOne Liquid CDx	Pan-cancer	Helps assign targeted therapy	Approved in US Aug 27, 2020, price $5,800
Grail (Illumina)	Galleri	Pan-cancer	Screening and identification of tumour origin	Launched as LDT Jun 4, 2021, price $949; approval poss 2023
	Unnamed assay	Pan-cancer	Postsurgical, detects disease recurrence	In development
Exact Sciences	Multicancer early detection (MCED)	Pan-cancer	Screening	FDA breakthrough device status; pivotal trial to start 2022
	Unnamed assay	Colorectal	Postsurgical, detects disease recurrence	Correct-MRD II trial to report 2028
Natera	Signatera	Pan-cancer	Postsurgical, detects disease recurrence	Launched as LDT Aug 21, 2017; Natera will seek individual FDA approvals as CDx
	Signatera	Colorectal, melanoma, lung	Tracks response to immunotherapy	Bespoke trial to report 2025
Freenome	Unnamed assay	Colorectal	Screening	Preempt CRC trial to report 2023
	Unnamed assay	Lung, pancreatic	Screening	Vallania trial to report 2024
Invitae	Stratafide	Pan-cancer	Helps assign targeted therapy	FDA breakthrough device status
	Unnamed assay	Colorectal, bladder, lung	Postsurgical, detects disease recurrence	Maria trial to report 2026

LDT = lab-developed test.

Source: Evaluate Medtech & company websites.

Screen time for Guardant

BY ELIZABETH CAIRNS, 3 MAY 2022

Guardant Health, first to market with a pan-cancer liquid biopsy, is also the first to launch a blood test to screen for colorectal cancer.

The Shield assay, formerly called Lunar-2, went on sale yesterday in the US as a homebrew test to detect colorectal cancer in average-risk people aged 45 and older. Sales are unlikely to be stratospheric at first: the vast Eclipse trial, designed to support FDA approval of the test in this setting, has not yet reported – the data might come at Asco next month. Approval for Shield, should it be granted, ought to allow sales-boosting reimbursement and guideline changes, though guidelines are unlikely to be updated before 2026, according to Stifel analysts.

At that point Shield would amount to a major threat to Exact Sciences' Cologuard stool test, currently the leading non-invasive colorectal screen. In advance of the Eclipse readout, Guardant released new data from a smaller study indicating that Shield's sensitivity and specificity for detecting cancer were 91% and 92% respectively – competitive with Cologuard and the clinical-stage second-gen version of that test. Guardant is also investigating Shield as a screen for lung, pancreatic and bladder cancers, but for now all the attention remains on Eclipse.

Guardant's liquid biopsies

Company	Liquid biopsy	Intended use	Tumour type	Status
Guardant Health	Guardant360	Helps assign targeted therapy	Pan-cancer	Approved in US Aug 7, 2020, price approx $6,800
	Reveal	Postsurgical, detects disease recurrence	Colorectal	Launched as LDT Feb 16, 2021
	Shield	Screening	Colorectal	Launched as LDT May 2, 2022, price TBD; pivotal Eclipse trial to report mid-2022
			Lung	Pivotal Shield trial to report 2024
			Pancreatic	In development
			Bladder	In development

LDT = lab-developed test.

Source: Evaluate Medtech & company website.

A new kind of liquid biopsy

BY ELIZABETH CAIRNS, 25 MAY 2022

Several liquid biopsies are available in the US, but until today they all worked by detecting DNA shed by solid tumours into the blood. Now they are joined by a different approach: Angle's Parsortix system sieves entire cancer cells out of a blood sample so that researchers can analyse them for clues to the best treatment decisions. The device today received de novo clearance for use in patients with breast cancer – the third blood test to be FDA-regulated, and the first for this specific indication. Angle says this is the first de novo clearance for a new instrument in oncology "for many years". Five years ago Angle said the Parsortix instrument costs around £40,000 ($52,000), with the single-use cassettes needed to analyse samples going for around £100 – but this was in Europe, and for research rather than clinical use. How the system will be priced in the US is not yet clear, though Angle said that per test, Parsortix would be "substantially cheaper" than the average cost of a breast cancer tissue biopsy – $16,000 in the US. Payers will take a keen interest in how the Parsortix price compares with the other liquid biopsies on the market.

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