NDF RESEARCH

Providing independent research coverage of ASX-listed Life Science companies

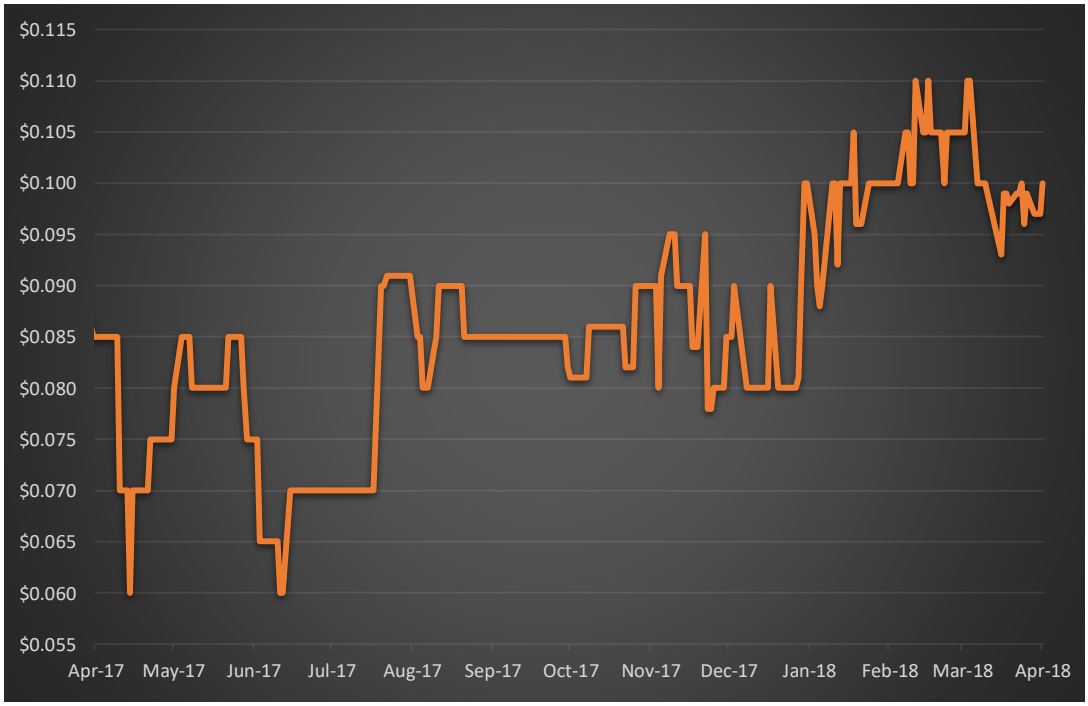
Invitrocue (ASX: IVQ)

Initiation of Coverage – Friday 20 April 2018

The next step in predicting cancer treatment outcomes

Invitrocue is a Singapore-based company that was founded in 2012 to commercialise two technologies for 3D cell culture, HepatoCue and 3D CelluSponge. These technologies are used to develop *in vitro* liver models to improve toxicology testing. Invitrocue also offers a clinical service called Onco-PDO, a tool for selecting the right drugs from an *in vitro* model of a patient's tumour. Invitrocue is leveraging on its expertise and know-how in 3D cell culture to grow patient-derived cancer cells in its scaffolds and other platforms to test them against a range of cancer therapies. With Onco-PDO, the way is open for low-cost personalised cancer medicine, where the market opportunity lies in the billions. We value Invitrocue at 7.3 cents base case and 24.4 cents per share optimistic case. Our target price of 16 cents per share sits at the midpoint of our valuation range. We see Invitrocue being re-rated by further data showing the power of Onco-PDO, and the commencement of clinical studies to validate Onco-PDO ahead of regulatory approval.

Rating	Risk	Current price	Target price
Buy	Speculative	$0.10	$0.16



Stock details

Daily Turnover: ~A7,000
Market Cap: A$48.5m
Shares Issued: 485.5m
52-Week High: $0.11
52-Week Low: $0.06

Analyst: Stuart Roberts
stuart@ndfresearch.com
+61 447 247 909

Please note: This report has been commissioned by Invitrocue and NDF Research will receive payment for its preparation. Please refer below for risks related to Invitrocue as well our General Advice Warning, disclaimer and full disclosures. Also, please be aware that the investment opinion in this report is current as at the date of publication but that the circumstances of the company may change over time, which may in turn affect our investment opinion.

About NDF Research

NDF is an independent equity research firm based in Sydney, Australia. It focuses on Life Science companies that are publicly traded on the Australian Securities Exchange (ASX), most of which are headquartered in Australia and New Zealand. ASX hosts one of the world's premier equity markets for biotech and medical device companies and is home to world-beating companies such as CSL and ResMed and emerging pioneers such as Mesoblast and Impedimed.

NDF's Founder and Senior Analyst, Stuart Roberts, has been involved in Life Sciences since 2002 as a sell-side analyst as well as an executive of two ASX-listed immuno-oncology drug developers.

NDF believes that ASX-listed companies have been largely overlooked in the global Life Sciences boom that began in late 2008, partly because of insufficient quality research. NDF's goal is to provide such research and introduce investors around the world to potential future billion-dollar companies from 'Down Under'.

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Ferry at the end of a rainbow on Sydney Harbour, August 2014

In this report

Introducing Invitrocue, ASX: IVQ

Invitrocue is a Singapore-based bioanalytics company with global operations in Australia, Asia and Europe, whose products and services help predict the effect of drugs in human tissue before they are used in people. The company was founded in 2012 as a spin-out from A*STAR, the Singapore government's prestigious Agency for Science, Technology and Research, to commercialise '3D cell culture' technology developed by Professor Hanry Yu and colleagues at A*STAR's Institute of Bioengineering and Nanotechnology. In 2018 Invitrocue has two major businesses – a liver model business and a cancer model business. The liver models are primarily used by pharma companies to analyse the *in vitro* toxicity of drug compounds, while the cancer models are used by physicians to develop a drug regimen suitable for individual patients.

What is Invitrocue's field of 3D cell culture and why is the company's technology potentially valuable? Traditionally, when clinicians and research scientists want to study human tissue, they first culture the relevant cells in a lab plate. This results in a so-called '2D cell culture' where the cells spread out in two dimensions. While valuable, 2D cell culture has drawbacks in that cells generally interact with each other in three dimensions, meaning that 2D cell culture models do not accurately reflects all aspects of tissue as it naturally occurs. Hanry Yu and colleagues have created two distinct '3D cell culture' systems that can overcome many of the traditional drawbacks of 2D systems. For its 3D liver model, Invitrocue's technology is valuable because it provides a better model to study the potential toxicity profile of drugs. For its 3D cancer models, which it calls Onco-PDOs, the value lies in the ability to run biological simulations that help determine what drugs or drug combinations actually work for individual cancer patients.

Why are Invitrocue's liver models important? One of the more important functions performed by the liver is filtration of the blood to remove toxins. Consequently, before a drug can enter clinical studies ahead of gaining marketing authorisation or regulatory approval, its developers need to assure that it will not be hepatoxic, that is, damaging to the liver. Invitrocue's 3D liver model provides an early way of being able to predict a drug's hepatoxicity profile. For the company, the model provided an initial product with which to start up, and continues to be a core business.

Why are Invitrocue's cancer models important? The striking thing about cancer is its heterogeneity. The baffling variety of gene mutants involved in any one cancer means that every tumour is slightly different. This means, in turn, that different drugs and drug combinations will work for different patients. The ability of Invitrocue's Onco-PDO cancer platform to replicate a patient's own cancer in the laboratory for the purpose of running various drug dosing simulations models and predicting treatment response, opens up a low-cost way of providing such 'personalised medicine'. Invitrocue screened its first commercial customer in Singapore in April 2018.

INVITROCUE'S ONCO-PDO BUSINESS ALLOWS CANCER TREATMENT PREDICTION

What is the business model for Invitrocue? Invitrocue charges for the reagents and other consumables used in creating its models as well as fees for analysing the data which the models generate. We believe the global market opportunity for the 3D liver model is worth at least US$500m while for Onco-PDO the opportunity is a multi-billion dollar one.

If Invitrocue is so good, why is it capitalised at only A$48.5m/US$37.8m? Invitrocue is relatively new as a public company, having only listed on ASX in early 2016[1]. We think the story has yet to be widely publicised to investors, in part because the company is based in Singapore whereas its investor based is mostly in Australia. We also think that as knowledge spreads of the bioanalytic power of Invitrocue's models, and as revenue for the business grows, Invitrocue stock will be well-placed to re-rate. We believe that Invitrocue can serve as a 'poster child' for Singapore's vibrant biotechnology sector, which is one of the most productive in the world[2] but is not represented by many publicly traded companies.

Ten reasons to look at Invitrocue

1) **Onco-PDO is a powerful tool for personalised medicine in cancer.** With recently-published data suggesting that patient-derived organoids can be as effective as patient-derived xenografts in selecting drugs specific for a tumour, we believe that Invitrocue is well placed to become a world leader in the field of personalised medicine in cancer through Onco-PDO.
2) **Personalised medicine in cancer is a large market opportunity**. With ~US$120bn spent annual on drugs to treat cancer, we believe there is at least aUS$2bn market opportunity awaiting any tool that can help tailor the right drugs to the right patients.
3) **Clinical data is coming for Onco-PDO**. Invitrocue has published two milestones scientific papers in the prestigious journals *Nature Medicine*[3] and *Nature Communications*[4] using more than 200 laboratory and clinical data points. More clinical partnerships are being set up globally in all key cancer indications and markets, including Australia, Singapore, Hong Kong, Japan, Germany and the UK. More recently, the company published another two peer-reviewed papers describing its ability to build *in vitro* lung cancer and liver cancer organoids.
4) **Commercial readiness.** The company is in the process of setting up a global network of Onco-PDO joint laboratories with key leading scientific and clinical thought leaders. This approach will not only fast track its clinical validation but builds a ready channel for commercialisation. Invitrocue has received its first commercial patients in 2018.
5) **The regulatory hurdles are low for Onco-PDO**. Since Onco-PDO is, in effect, a biological decision support system to guide the on-label use of approved drugs, there is no immediate need to seek regulatory approval before marketing the product. This makes it relatively easy for Invitrocue to grow early revenue, Obviously, once the product transitions to a kit-based form, a mere 510(k) approval in the US market would be all that is required, and achievement of this clearance plus a CE Mark can then take the business to the next level.

INVITROCUE HAS STARTED TO RECEIVE ITS FIRST COMMERCIAL PATIENTS IN 2018

[1] Via a backdoor listing into a shell that was previously called Bunuru Corporation, ASX BUN. Bunuru announced the acquisition of Invitrocue in June 2015.
[2] The Singapore government has also chosen to invest heavily in Life Sciences infrastructure such as the Biopolis science park and various new research centres. It has also used the tax system to encourage Big Pharma to move to the City-State. The government funds basic research heavily through A*STAR.
[3] Nat Med. 2017 Oct;23(10):1167-1175. Epub 2017 Sep 18.
[4] Nat Commun. 2017 Sep 5;8(1):435.

6) **Invitrocue is rapidly expanding the reach of Onco-PDO,** with 2018 a year in which the team is expected to attract key opinion leaders to advocate for its use in various cancers. We expect that it can be introduced in Europe and North America by around 2020.
7) **HepatoCue provides better tools for evaluating liver tox**. The ability to better understand the hepatotoxicity profile of a drug is worth >US$500m, a market which Invitrocue is well placed to go after with HepatoCue.
8) **The rise of liver disease is increasing the value of HepatoCue as a diagnostic tool**. With Hepatitis B and NASH, among other conditions, representing a heavy disease burden, Invitrocue's 3D liver models may potentially be used to screen for novel drug compounds in what is an important and potentially lucrative area of unmet medical need.
9) **Invitrocue is growing sales**. The revenue base, while small (ie only S$0.8m in calendar 2017), is growing quickly, reflecting the relative ease with which Invitrocue can gain early commercial users from its foundation technologies.
10) **Invitrocue has a solid management team**. CEO Dr Steven Fang previously built Cordlife, a successful Singapore-based cord blood bank. Backing Fang is a quality board that includes founder Professor Hanry Yu.
11) **Invitrocue has upside on our numbers.** We value Invitrocue at 7.3 cents base case and 24.4 cents per share optimistic case. Our target price of 16 cents per share sits at the midpoint of our valuation range.

Invitrocue is a player in the multi-billion-dollar field of cell culture

Cell culture is a fundamental building blocks of today's pharmaceutical and biotechnology industries. When a biotech company or an academic lab is working on a new drug or vaccine, early in the process it will need to engage in cell 'culture', which is the growing of particular cell type in an artificial environment[5]. In cell culture, cells extracted from a human or other organism are proliferated in a vessel such as a dish, plate or flask using a 'culture medium' to supply the necessary nutrients and a 'substrate' to which the cell needs to be connected in some way before it can grow. Often the substrate is the surface of the vessel itself. Without cell culture there could be no modern biotech industry, since it is fundamental to the way many drugs and vaccines are produced[6], while for drug and vaccine research the tools of cell culture are critical - as well as allowing the normal physiology and biochemistry of cells to be studied, cells need to be cultured in order to be able to see if a drug or vaccine candidate is working as expected, or if it will have toxic side effects. When scientists use the term *in vitro*, Latin for 'in glass',

INVITROCUE HAS BEEN BUILT ON INNOVATIVE CELL CULTURE TECHNOLOGIES

[5] The word 'culture' stems from the Latin verb *colere*, 'to cultivate'. For background on the English word see *The Meaning of "Culture"* by Joshua Rothman, The New Yorker, 26 December 2004.
[6] Particularly biotech drugs, where the drug is expressed in, say, CHO cells (Appl Microbiol Biotechnol. 2012 Feb;93(3):917-30. Epub 2011 Dec 9), or in *E. Coli* (J Microbiol Biotechnol. 2015 Jul;25(7):953-62).

they mean a study on cells obtained from culture, which they generally perform before moving to *in vivo* studies in animals. We estimate that cell culture is a >US$20bn market globally[7].

Traditionally cell culture was '2D cell culture', that is, the cells were grown in a two-dimensional 'monolayer' on a flat polystyrene or glass dish, or inside the wells of a culture plate, to which the cells adhered. 2D cell culture is quick, simple, and well understood, having been performed routinely for the best part of a century[8]. So long as the environmental conditions are the same in each dish, 2D cell culture can in many cases provide valuable clues about what one compound is doing to cells as opposed to another compound. The trouble with 2D cell culture is that it doesn't reflect what happens *in vivo*, where cells grow in a complex three-dimensional microenvironment, interacting with each other and with the surrounding 'extracellular matrix' (ECM), and where blood vessels continuously supply nutrients to the cells and take away their waste products. This means that 2D cultured cells can be considerably different from what such cells would be like if cultured in 3D[9], leading to poor predictability of the performance of a drug *in vivo*[10]. That awareness has increased the demand in recent years for 3D cell culture systems, which is where Invitrocue believes it can be a world leader.

'3D cell culture' is rapidly emerging as a research tool. In 3D cell culture, which first emerged in the 1980s[11], cells are grown in ways that mimic the actual three-dimensional conditions to be found in the body. One common theme in 3D cell culture is the 'scaffold' made from a porous biocompatible material that allows cells to sit in an ECM-style three-dimensional architecture while being cultured[12]. Another common theme is the 'bioreactor', that is, a vessel that can precisely controls the environmental conditions required for cell culture, including temperature, pH, nutrient supply, and waste metabolite removal[13]. 3D cell culture is still emerging as a cell culture paradigm and is therefore a relatively small part of the cell culture market worth perhaps US$4bn, but it is growing quickly, probably at 20% p.a.

Invitrocue wants to be a player in the 3D cell culture market. Invitrocue was formed in 2012 to commercialise its 3D liver models and a 3D cell culture system that are the brainchild of Professor Hanry Yu of the National University of Singapore (NUS)[14]. As well as his Chair at NUS, Yu also maintains a laboratory at the Institute of Bioengineering and Nanotechnology (IBN), one of 18 research institutes maintained by A*STAR, the Singapore government's Agency for Science, Technology and Research. It was the Yu Group at IBN that created HepatoCue and 3D CelluSponge in roughly the five years to 2011. In each case, the Yu Group at IBN had been seeking ways to develop better culture hepatocytes, that is, liver cells, allowing more accurate *in vitro* models of the liver that could be highly useful in toxicology testing. With Onco-PDO, the way is now opening to develop the potential of *in vitro* cancer models, highly useful in devising personalised cancer treatments.

INVITROCUE WANTS TO BE A PLAYER IN THE 3D CELL CULTURE MARKET

[7] See *Cell culture markets proliferating* by Cindy Neeley, Thermo Fisher Scientific, 24 February 2015.
[8] The idea of tissue culture dates from 1885, when the German zoologist Wilhelm Roux (1850-1924) was able to maintain embryonic chick cells in a saline solution. In 1907 the American Ross Harrison (1870-1959) was able to culture neurons in tissue culture, while in the early 1920s the Frenchman Alexis Carrel (1873-1944), a Nobel laureate, pioneered 2D cell culture as we know it today.
[9] Int J Biochem Cell Biol. 2004 Aug;36(8):1447-61.
[10] J Biotechnol. 2006 Apr 10;122(3):372-81. Epub 2006 Jan 30.
[11] For an early example see Proc Natl Acad Sci U S A. 1992 Oct 1;89(19):9064-8.
[12] Methods Mol Biol. 2011;695:17-39.
[13] Biotechnol Bioeng. 2008 Apr 1;99(5):1250-60.
[14] Where he is Professor of Physiology. NUS is a Top 20 University globally, at No. 15 on the QS World University Rankings for 2018.

Invitrocue is being built on two major 3D cell culture systems

HepatoCue is a 3D cell culture system for liver cells. Invitrocue's initial technology, which originated from the Yu Group around 2006, represented one of the first genuine 3D solutions for culture of hepatocytes, hence the name 'HepatoCue'. Hepatocytes are difficult to culture in a 2D format because the bunching together of the cells on the culture plate tends to cause their 'de-differentiation' into cells that are not liver-specific[15]. Part of the '3D' solution to this problem had been known for a long time: If hepatocytes were glued to the substrate with a sugar called galactose, for which there is a natural receptor on the hepatocytes[16], these cells would proceed to form spheroids, that is, sphere-like constructs. Being three-dimensional, these spheroids could maintain high levels of cellular functionality[17]. The downside to this approach was twofold: Firstly, the spheroids would frequently detach from the substrate. Secondly, the envelope of these spheroids was so tight that not enough oxygen and nutrients could get inside to help maintain the constituent cells[18]. Around 2006 Hanry Yu and his colleagues at IBN solved these problems simply by adhering the spheroids to the substrate with two glues rather than one – galactose plus a peptide called RGD. The latter glue was, as its name suggests, made up of the three-amino acids arginine (R), glycine (G) and aspartate (D), and had a long history of use as an adhesive peptide in the biomaterials field[19]. When the galactose-plus-RGD combination was used with PET (ie polyethylene terephthalate, the well-known plastic) as the substrate, the result was a monolayer of well-nourished 3D hepatocyte spheroids that stayed glued to the substrate. A*STAR filed for patent protection over this platform[20] and the work was published shortly thereafter in the journal *Biomaterials*[21]. Five years later, in 2011, the Yu lab was able to show that changing the ratio of RGD to galactose in the glue would allow 'tethered spheroids' that didn't have to stay glued to the PET substrate – and therefore were more truly three-dimensional – but were of such size as to allow nutrients to penetrate[22]. What the Yu lab had created was a 3D cell culture system for liver cells that would work seamlessly with the traditional and low-cost 2D multi-well screening platforms used the world over and would therefore be highly scalable as a testing platform. The only downside as far as being a tool to evaluate liver toxicity was that HepatoCue could only be used for acute testing, since the spheroids would break down after a week or so.

HEPATOCUE ALLOWS *IN VITRO* LIVER MODELS TO BE CREATED

3D CelluSponge is a highly effective scaffold for 3D cell culture. We noted above that one of the major themes of contemporary research into 3D cell culture systems is scaffolds that can mimic the ECM. The thinking is that a porous structure, whether made of natural or synthetic material, can allow seeded cells to produce a new functional matrix, so long as the starting cells can adhere to the scaffold and so long as the pores are large enough

[15] Curr Drug Metab. 2006 Aug;7(6):629-60.
[16] J Biomater Sci Polym Ed. 1992;3(6):499-508.
[17] Biochem Biophys Res Commun. 1992 Apr 15;184(1):225-30.
[18] Biotechnol Bioeng. 2004 Jun 20;86(6):672-80.
[19] Biomaterials. 2011 Jun;32(18):4205-10.
[20] See WO/2007/136354, *Bioactive surface for hepatocyte-based applications*, priority date 24 May 2006.
[21] Biomaterials. 2006 Nov;27(33):5669-80. Epub 2006 Aug 10. In 2007 the Yu lab showed some of the superiority of this system to 2D monolayer and 3D spheroids in Tissue Eng. 2007 Jul;13(7):1455-68.
[22] Biomaterials. 2012 Mar;33(7):2165-76. Epub 2011 Dec 19. In effect the HepatoCue system was 'tunable' – if just monolayer was needed, RGD was adequate as the conjugate, while for spheroids galactose would do the trick. Changing the mix of the two conjugates changed the morphology of the desired cells.

allow the right diffusion of nutrients, metabolites and soluble factors into the scaffold[23]. Around 2008 the Yu Group at IBN, which has a strong interest in tissue engineering, invented a scaffold for such an application made from hydroxypropyl cellulose[24], a biocompatible polymer polysaccharide commonly used in the pharmaceutical industry[25]. They found that that it was possible to take this material and turn it into a hydrogel scaffold with pores large enough to grow new tissue by modifying it with allyl isothiocyanate, a sulphur-containing chemical known for bringing the 'heat' to wasabi, horseradish and mustard. The Yu Group published the engineering process for their cellulosic hydrogel scaffold, which they called 3D CelluSponge, in the journal *Biomaterials* in 2010[26]. The Yu Group believed that their new scaffold had merit because it was cellulosic and because it was a hydrogel. Cellulose doesn't break down easily[27] and cellulose-based materials are easy to source[28], while hydrogels, that is, polymer networks with high water content, have long been regarded as ideal scaffolds for tissue engineering because of their ability to simulate soft tissue[29]. That said, all sorts of polymeric scaffold candidates are described in the tissue engineering literature[30], which begged the question as to what was so good about the Yu Group's new scaffold that it merited forming a company around it? That question had been partly answered a few months before the *Biomaterials* paper by another paper in *Regenerative Medicine* from a group at Singapore's Nanyang Technological University. The Nanyang group had used 3D CelluSponge, coated with collagen, to culture mesenchymal stem cells, the stem cells in all our bodies that originate in bone marrow and give rise to a variety of cell types. The Nanyang group were able to show that those cells, inside 3D CelluSponge, could successfully differentiate into neural cells[31]. What this showed was that the kind of cellulosic hydrogel the Yu Group had created had replicated the complex three-dimension environment needed to engineer new nerve tissue. Then in 2011 the Yu Group at IBN showed that the 3D CelluSponge, when coated with galactose, could grow long-lasting hepatocyte spheroids[32]. Not only did Yu et. al. now have a validated liver model for sub-acute toxicity testing – the gap left by the relative instability of HepatoCue spheroids – but the mesenchymal stem cell work suggested a broad potential application for the platform.

HepatoCue and 3D CelluSponge allowed Invitrocue to start up as a provider of liver modelling services. Invitrocue's initial thinking was that liver models would provide sizeable growth opportunities for the new A*STAR spinout. The world's pharma industry spends US$150bn on R&D[33], and one of the factors that can support new drug candidates emerging from this spend is an understanding of potential liver toxicity. When a drug will cost more than US$2bn to develop[34], any low-cost tool to improve R&D effectiveness can prevent large downstream losses. The market for liver toxicology has been estimated at US$1.3bn[35], and Invitrocue has enjoyed modest revenues in its start-up years from supplying its models.

LIVER MODELING SERVICES HELPED GET INVITROCUE STARTED

[23] Biotechnol Adv. 2017 Mar - Apr;35(2):240-250. Epub 2017 Jan 14.
[24] See *Forming porous scaffold from cellulose derivatives*, WO/2009/078819, priority date 18 December 2007.
[25] One product noted for its use of HPC is eye drops such as Lacrisert from Bausch + Lomb.
[26] Biomaterials. 2010 Nov;31(32):8141-52. Epub 2010 Aug 5.
[27] Since the β(1–4) glycosidic bonds in the polysaccharide can only be broken down by cellulase.
[28] See *Nisso opens expanded HPC plant on back of pharma demand* by Dan Stanton, In-Pharma Technologist, 10 May 2015.
[29] Biomaterials. 2002 Nov;23(22):4307-14.
[30] For a recent review see J Biomed Mater Res B Appl Biomater. 2017 Feb;105(2):431-459. Epub 2015 Oct 23.
[31] Regen Med. 2010 Mar;5(2):245-53.
[32] Biomaterials. 2011 Oct;32(29):6982-94.
[33] Source: IFPMA facts and figures report 2017.
[34] See J Health Econ. 2016 May;47:20-33. Epub 2016 Feb 12.
[35] Source: Organovo Investor Presentation, November 2015, slide 10.

3D CelluSponge has opened up a huge opportunity in personalised cancer medicine. We noted above that Invitrocue's scientists had identified a broad potential application for the 3D CelluSponge platform. The one that has emerged with the biggest potential upside for shareholders is as a tool for personalised cancer medicine, for which the commercial and clinical upside is immense.

Onco-PDO - Invitrocue enters the field of personalised cancer medicine

3D CelluSponge can grow cancer 'organoids' that mimic real tumours. When 3D CelluSponge was invented in 2011, the Yu Group at IBN were able to show that this technology could culture, into spheroids, a breast cancer cell line called MCF-7[36]. Over the next five years the Yu Group experimented with a variety of standard tumour cell lines, and then cells taken from patients, and showed that the 3D CelluSponge technology could be reliably used to grow homogeneous three-dimensional 'organoids' representing a wide range of cancer types, including lung, renal, colorectal, breast and liver cancer. What the Yu Group had invented was a way of picking which drugs would work for which patient: Take a sample of the patient's cancer, use 3D CelluSponge to grow that sample into sufficient numbers of so-called Patient-Derived Organoids (PDOs) – no mean feat given the small amount of starting material[37] – and test through high-throughput screening a range of cancer drugs and drug combinations against the PDOs *in vitro*. The drug combination with the highest kill rate on this 'cancer avatar' could then be used on the patient. Invitrocue called this product 'Onco-PDO' and started talking about it publicly around May 2016[38].

Personalised medicine - why Invitrocue's Patient-Derived Organoids can potentially be very valuable. For most chemotherapy or radiotherapy treatment approaches to cancer, only a certain number of patients will respond to the treatment, even as the treatments become more 'personalised', that is, specific for only a certain subset of patients. Take an old example: only around 15-20% of all breast cancer is positive for an oncogene (ie cancer-causing gene) called HER2[39]. Herceptin, a monoclonal antibody drug which directly targets the product of this oncogene, gained FDA approval in September 1998 as one of the first personalised cancer medicines[40]. In the pivotal study that preceded this approval, just under half the patients in the study registered a response to the drug when combined with chemotherapy[41]. Yet the favourable clinical outcomes in HER2-positive breast cancer and later in gastric cancer for patients that *did* respond drove peak sales of US$6.85 for Roche in 2014 before the first 'biosimilars' came on the market. Personalised or 'precision' medicine, which could predict in advance which

CANCER MEDICINE IS INCREASINGLY BECOMING PERSONALISED

[36] Tissue Eng Part C Methods. 2011 Nov;17(11):1097-107. Epub 2011 Sep 1.
[37] A fine needle biopsy is generally only good for 0.5 to 1 million cells (see Diagn Pathol. 2007 Aug 23;2:31), which is relatively little if one needs multiple spheroids, especially since the first fraction of the cells would be needed for histological and genomic analysis, before the remaining cells could be used to create PDOs.
[38] See the Invitrocue market release dated 12 May 2016 and headlined *'Invitrocue expands 3D cell-based platform for oncology'*.
[39] See, for example, Clin Med Res. 2009 Jun;7(1-2):4-13, in which a 7-year retrospective study of 1,134 invasive breast cancer cases found 17.7% of subjects analysed were HER-2 positive.
[40] Another early personalised cancer medicine was Gleevec for Chronic Myelogenous Leukemia, FDA approved in May 2001. It was a huge commercial success for Novartis, enjoying peak sales in 2014 of US$4.7bn.
[41] Versus 32% for chemotherapy alone – see Ann Oncol. 2001;12 Suppl 1:S57-62.

HER2-positive patients would respond to this expensive drug[42], or another, lower-cost drug combination, would save healthcare systems billions and potentially benefit patients who would be non-responders to Herceptin.

Why Invitrocue decided to make a business out of Patient-Derived Organoids – the case of Patient HN137, September 2017. Various academic groups around the world have experimented in recent years with spheroidal patient-derived tumour models[43]. What motivated Invitrocue to champion routine clinical use of patient-derived tumour models, and turn Onco-PDO into a business, was the experience of the first patients, and, in particular, one known in the literature as 'Patient HN137'. Invitrocue had established a joint laboratory with A*STAR's Genome Institute of Singapore (GIS) which, under the leadership of Dr. Ramanuj DasGupta, who is now Chief Scientific Officer of Invitrocue[44], was working on combining Onco-PDO with Next Generation Sequencing, Artificial Intelligence and data mining in the search for new biomarkers that could guide treatment. The initial focus of the joint lab was on head and neck cancer, colorectal cancer, liver cancer; and triple-negative breast cancer – all cancers prevalent in Southeast Asia[45]. When the DasGupta lab made Onco-PDOs from head and neck squamous cell carcinoma patients, they first showed that these models could predict treatment outcomes as effectively as patient-derived xenografts, an old but costly and time-consuming approach in which mouse models of the individual tumour are painstakingly created. Patient HN137 had stage IV (ie advanced) oral squamous cell carcinoma that was resistant to cisplatin. The Onco-PDOs of the primary tumour and of the tumour metastasis at the lymph node both suggested that the tumour would be susceptible to a drug called Iressa, best known as a therapy for Non-Small Cell Lung Cancer (NSCLC), generic name gefitinib[46]. This drug was known to work in perhaps a third of all recurrent or metastatic head and neck cancer patients[47]. The decision to administer Iressa to HN137 was able to be taken quickly - the suggested treatment approach was generated with the help of the Onco-PDOs in just 72 hours and the patient was being treated within six days[48]. On Iressa, HN137 experienced a significant regression within six weeks of treatment, and while the tumour again progressed after six months on this drug, the GIS investigators were also able to use the PDOs to identify a biomarker that would show HN137's tumour becoming gefitinib-resistant. The GIS team published their work in the journal *Nature Communications* in September 2017[49]. Around the same time a team led by Dr Gopal Iyer[50] at the National Cancer Centre Singapore (part of Singapore's largest public hospital group) identified another biomarker that predicted the initial treatment success with Iressa experienced by HN137 – a mutation in a piece of 'long noncoding RNA' associated with EGFR, which is the target of Iressa[51]. This finding was published in *Nature Medicine*[52].

ONCO-PDO HELPED PICK THE RIGHT DRUG FOR PATIENT HN137

Evidence that Onco-PDO works – Replication of the genome and transcriptome of patient-derived xenografts, January 2018. As we noted above, traditionally the best way to test whether a drug would work

[42] In the US it cost ~US$3,200 per month in 1998 – source: Memorial Sloan Kettering Cancer Center.
[43] For a review see Pharmacol Ther. 2016 Jul;163:94-108. Epub 2016 Apr 8.
[44] See the Invitrocue market release dated 23 November 2016 and headlined '*Invitrocue appoints Dasgupta Ramanuj, PhD as Senior Scientific Director*'
[45] See the A*STAR press release dated 24 July 2017 and headlined '*Public-private partnership between Singapore-based start-up Invitrocue and A*STAR's Genome Institute of Singapore*'.
[46] FDA approved for Non-Small Cell Lung Cancer in 2003 – see www.iressa.com.
[47] Br J Cancer. 2006 Mar 13;94(5):631-6.
[48] See Invitrocue's 23 August 2017 Investor Presentation, slides 9 to 11.
[49] Nat Commun. 2017 Sep 5;8(1):435. Note, the 'Methods' section of the paper describes 'Derivation of PDC [ie patient-derived primary culture] cell lines and cell culture' in a generic way without describing the use of 3D CelluSponge. Invitrocue did not therefore disclose to the ASX the 5 September 2017 publication of this paper, having fulfilled its Continuous Disclosure obligations through a 23 August 2017 Investor Presentation.
[50] His full name is Narayanan Gopalakrishna Iyer.
[51] EGFR is the Epidermal Growth Factor Receptor (EGFR), known to overexpress in Non-Small Cell Lung Cancer as well as other cancers.
[52] Nat Med. 2017 Oct;23(10):1167-1175. Epub 2017 Sep 18.

against a human cancer was to create a PDX, that is, a 'patient-derived xenograft', in which a patient's tumour was implanted into an immunodeficient mouse and the various drug combinations tried out against those mice. The trouble with PDXs is that even though they have been around since the late 1980s[53], and have been known to accurately predict treatment response for patients, they are hideously expensive – anywhere from US$10,000-15,000[54], up to US$30,000-40,000[55] – to prepare for a single patient. In early January 2018, in a *Biomaterials* paper, the Yu Group at IBN were able to show that, for primary liver cancer, Onco-PDOs could replicate the genome and transcriptome of 14 PDXs, strongly suggesting that Invitrocue's system could become a new standard in personalised cancer medicine[56]. For one thing, it can take three months to generate the PDXs required, whereas Invitrocue believes that the maximum time to complete manufacture of Onco-PDOs will be two weeks for selected cancer types. For another, only two or three drugs can be used on each PDX mouse created. Onco-PDOs operate under no such constraint. An Onco-PDO approach can also enable any number of in-laboratory simulations by simply growing more Onco-PDOs, subject to the quality of cancer tissues received.

Evidence that Onco-PDO looks like the real thing, March 2018. In May 2016, when Invitrocue first unveiled its Onco-PDO work, it announced a collaboration with a research group at the Second Affiliated Hospital of China's Soochow University[57] where that group would use Invitrocue's approach to develop PDOs for NSCLC and test them for their treatment prediction ability. In March 2018 the Soochow group published a paper in the online journal PLOS One showing that their NSCLC PDOs retained the phenotypic cellular characteristics of the original tumour even after massive 120 days in culture[58]. We expect further published work from the Soochow group on the effectiveness of their Onco-PDOs in drug testing.

Further clinical data is likely coming for Onco-PDO. In February 2017 Invitrocue announced that it would be collaborating with the Singapore National Cancer Centre (part of Singapore's largest public hospital group) and separately the Garvan Institute in Sydney on further validation of Onco-PDOs as a decision support tool for cancer treatment. Ethics approval for the Garvan study, to be undertaken in collaboration with the nearby St Vincent's Hospital, was obtained in August 2017. Three other similar collaborations are being planned globally to further fast track the clinical and commercial roll out of Onco-PDOs.

INVITROCUE IS WORKING WITH VARIOUS CLINICAL GROUPS ON ONCO-PDO

The path to market for Onco-PDO. Since Onco-PDO is only a biological decision-support system for oncologists prescribing approved cancer drugs, Invitrocue was able from 2017 to earn revenue from early lab-based users of the technology without having to gain regulatory approvals. The company announced in April 2018 that it had screened its first commercial customer in Singapore, a patient with colorectal cancer. We understand that Invitrocue intends to charge the equivalent of A$2,000 to A$5,000 per test depending on whether the test is for cancer drug resistance, fpr treatment options post-relapse or for sensitivity to agents that have yet to be tried for the patient. Onco-PDO is now in use in Singapore, Hong Kong, China and Australia. The ongoing regulatory burden is relatively light - once the product transitions to a kit-based form, a mere 510(k) approval in the US market

[53] The first significant PDXs with patient-predictive value were created by Heinz-Herbert Fiebig at the University of Freiburg in Germany – see Behring Inst Mitt. 1984 May;(74):343-52.
[54] See *Exome sequencing, avatar mouse models show promise for personalized cancer Rx; new trial started* by Julia Karow, genomeweb, 7 May 2014
[55] See *My mighty mouse* by Megan Scudellari, The Scientist, 1 April 2015.
[56] Biomaterials. 2018 Mar;159:229-240. Epub 2018 Jan 4
[57] Soochow University is located in Suzhou, a city in the eastern Chinese province of Jiangsu. The Medical Schools of universities in China have one or more hospitals affiliated with them. Soochow has two.
[58] PLoS One. 2018 Mar 15;13(3):e0194016.

would be all that is required, and achievement of this clearance plus a CE Mark can then take the business to the next level. We expect five main developments for Onco-PDO from here:

- Further clinical work to validate the approach across a wide range of cancers – potentially this would use data gathered by Invitrocue's collaborators GIS and the National Cancer Centre in Singapore and the Garvan Institute in Sydney;
- The signing up of new collaborators in markets that Invitrocue wishes to enter – witness, for example, a recent grant which will help fund validation work in the UK and Europe[59];
- Securing of Key Opinion Leaders in various key jurisdictions around the world;
- Development and formal clinical testing of the Onco-PDO kit, followed by the requisite regulatory approvals;
- Marketing of the kit-based Onco-PDO products as they are formally launched.

Welcome to the boom in personalised cancer medicine

Onco-PDO will sell into a receptive market for personalised cancer medicine. The development of Onco-PDO is timely for Invitrocue because personalised cancer medicine, while it had been talked about for years, began in our view to 'mainstream' around 2012. That was the year that Foundation Medicine[60] launched its FoundationOne product, the world's first fully informative cancer genomic profile that was 'pan cancer'. By 2012 many new cancer drugs in development were highly targeted, as evidenced by Boehringer Ingelheim's lung cancer drug Gilotrif[61], FDA approved in 2013, which was designed to target, not just the aforementioned EGFR oncogene, but specific mutations within EGFR[62]. Also, by 2012 the liquid biopsy, where cancer DNA was sourced from blood rather than from tissue – markedly increasing the available material for analysis – was gaining traction[63], and other non-invasive diagnostics based on DNA were also emerging, as typified by Cologuard, a stool DNA screening test for colorectal cancer. Exact Sciences[64] gained FDA approval for that product in August 2014. The first liquid biopsy, a Roche EGFR mutation test, gained FDA approval in 2016[65]. All these developments have made oncologists much

WE BELIEVE PERSONALISED CANCER MEDICINE HAS BEEN GOING 'MAINSTREAM' SINCE ABOUT 2012

[59] See the Invitrocue press release dated 26 February 2018 and headlined *'Invitrocue secures grant from Northern Ireland to commercialise Onco-PDO'*.
[60] Cambridge, Ma., Nasdaq: FMI, www.foundationmedicine.com.
[61] Generic name afatinib, see www.gilotrif.com.
[62] The original EGFR-targeting drug was AstraZeneca's Iressa, FDA approved in 2003. This was the drug which worked for Patient HN137 in Singapore. A competing EGFR drug called Tarceva (erlotinib), from Roche and a US drug developer called OSI Pharmaceuticals (now Astellas), gained FDA approval the following year. In each case the indication was simply for patients who had failed previous rounds of chemotherapy. Fast forward close to nine years, to mid-2013, and when Boehringer Ingelheim introduced Gilotrif (afatinib), this drug was indicated strictly for metastatic NSCLC patients, where there was, not just EGFR overexpression, but EGFR with the two most common mutations within the receptor, called the 'exon 19 deletion' and the 'L858R mutation'. What had happened was that science had gained much greater insight into the large number of mutations that could show up in EGFR, allowing drugs to be tailored accordingly. This tailoring has taken a big step forward in the last twelve months, with AstraZeneca being granted regular approval by the FDA in March 2017 for Tagrisso (osimertinib), which targets the T790M mutation in EGFR associated with acquired resistance to the previous drugs, and Gilotrif having its indication broadened in January of this year to encompass three more EGFR mutations called S768I, L861Q, and G719X. What enabled these drugs to be commercially successful was partly the sheer size of the lung cancer patient population, but, more importantly, the knowledge that drug better targeting drugs to the mutations would improve survival outcomes.
[63] Either from Circulating Tumour Cells (CTCs) or circulating tumour DNA – see Front Med. 2017 Dec;11(4):522-527. Epub 2017 Jul 25.
[64] Madison, Wi., Nasdaq: EXAS, www.exactsciences.com.
[65] The test was a companion diagnostic for the Roche drug Tarceva.

more willing than in the past to explore personalised treatment options for their patients. Throw in the fact that global cancer drug spending crossed the US$100bn mark in 2014[66], and it's fair to say that interest in treatment prediction modalities has been increasing with payors as well, as evidenced most recently in a decision by the Centers for Medicare & Medicaid Services, which administers America's Medicare insurance program, to start covering FDA-approved cancer gene tests[67]. We believe that Onco-PDO will attract favourable payor interest over time, as a potentially lower cost option. In a market we estimate to be worth ~US$2bn p.a. today, there will be plenty of upside for Invitrocue.

The fact is, every patient's tumour is different, so every treatment should be, too. If you want one reason why the War on Cancer has yet to be won, consider the sheer diversity of cancer to be found, not between, say, non-small cell lung cancer and bladder cancer – and there are over 200 different organs that can give rise to cancer – but between just patients with, ostensibly, cancer of the same organ. Indeed, it's worse than that. Within each patient the cancer can differ not just inter-tumourally (between the primary tumour and metastatic sites) but intra-tumourally (within a single tumour mass). The general term for this is 'tumour heterogeneity' and while it has been known about since the 1980s[68], the advent of cancer genomics, using the tools of Next Generation Sequencing, in which the DNA of tumours can be quickly sequenced and analysed for mutations[69], has revealed the huge amount of diversity in any one cancer[70]. Consider just one example: A Norwegian group examined radical prostatectomy specimens and looked at each tumour-containing block in each specimen for mutations in a single tumour-suppressor gene called PTEN, known to be important in prostate cancer[71]. They found 75% intra-tumour heterogeneity in just this one gene![72]. Tumour heterogeneity is one obvious reason why cancers tend to develop resistance to treatment – the drugs selected may hit one or more variant of the cancer in a patient but miss others[73]. That in turn would explain why tumour heterogeneity is known as an independent predictor of cancer survivorship[74]. Tumour heterogeneity may even have foiled some of the more personalised drugs available today[75]. Sounds daunting, doesn't it? Invitrocue's leadership would answer 'not necessarily'. Tumour heterogeneity may be a serious issue in terms of understanding cancer, but it need not necessarily be a barrier to more effective treatment options than those currently available. When the entire picture of the cancer can be

ONCO-PDO CAN BE A POWERFUL WEAPON AGAINST TUMOUR HETEROGENEITY

[66] See *The cancer drug market just hit $100 billion and could jump 50% in four years* by Matthew Herper, Forbes, 5 May 2015. The source of this estimate, IMS, believes the figure could be US$150bn by 2020.
[67] With *Medicare support, genetic cancer testing goes mainstream* by Megan Molteni, Wired, 20 March 2018.
[68] One landmark paper in the field was one from Gloria Heppner, now at Wayne State University in Detroit that was published in the journal Cancer Research in 1984 (see Cancer Res. 1984 Jun;44(6):2259-65). The first clues on tumour heterogeneity emerged in the early 1950s – see Acta Chir. Scand. Suppl. 1952;172:7–190.
[69] Onco Targets Ther. 2016 Dec 2;9:7355-7365.
[70] For a good review see F1000Res. 2016 Feb 29;5. pii: F1000 Faculty Rev-238.
[71] PTEN, short for 'Phosphatase and Tensin homolog', is significant because mutated PTEN shows up in a broad variety of cancers, including glioblastoma as well as endometrial, breast, thyroid and prostate cancers. PTEN, when it doesn't work properly, contributes to the cancer activity of the PI3K/AKT signalling pathway.
[72] Br J Cancer. 2017 Jul 25;117(3):367-375. Epub 2017 Jun 15.
[73] Biochim Biophys Acta. 2010 Jan;1805(1):105-17. Epub 2009 Nov 18.
[74] Eur Radiol. 2012 Apr;22(4):796-802. Epub 2011 Nov 17.
[75] Take colorectal cancer as a classic example of this. When an oncogene called K-RAS is 'wildtype' (ie 'normal') in this cancer, it can be susceptible to two monoclonal antibody drugs called Erbitux and Vectibix. The trouble is, of course, that some patients with ostensibly wildtype K-RAS may in fact have some mutant-KRAS as well - when one group of investigators looked at the RAS genes in patient biopsies, they found intra-tumoural heterogeneity for RAS mutation in 33% of cases and inter-tumoural heterogeneity in 36% (Int J Mol Sci. 2016 Dec; 17(12): 2015). What that would mean in practice is that tumour samples taken from the wrong part of the tumour could indicate that the patient has wildtype K-RAS when in fact mutant K-RAS, which would not respond to the drugs, is the predominant version in this cancer.

accurately modelled, high-throughput screening tools can be used to run multiple combinations of existing drugs against the model. Invitrocue's Onco-PDO provides one such modelling tool[76].

Company	Location	Code	Market cap (USDm)	Web
Exact Sciences	Madison, Wi.	Nasdaq: EXAS	5,660	www.exactsciences.com
Foundation Medicine	Cambridge, Ma.	Nasdaq: FMI	2,680	www.foundationmedicine.com
Myriad Genetics	Salt Lake City, Ut.	Nasdaq: MYGN	2,030	www.myriad.com
Genomic Health	Redwood City, Ca.	Nasdaq: GHDX	1,140	www.genomichealth.com
NeoGenomics	Fort Myers, Fl.	Nasdaq: NEO	742	www.neogenomics.com

Genomics are what most people think about when they think 'personalised cancer medicine', mainly because of the high speed and low cost with which huge blocks of DNA can be sequenced today[77], and the variety of techniques that have been developed to get at tumour DNA[78]. This in turn has meant that mutations within the genetics of a tumour can be easily identified, providing numerous biomarkers of interest[79]. Aiding the mainstreaming of genomics in personalised cancer medicine is the availability of high-resolution tools which to compare the newly sequenced patient data, such as the Cancer Genome Atlas[80], a National Institutes of Health database of genomic information from more than 15,000 human tumours representing multiple types of cancer. And at the patient end, there is increasing acceptance of cancer genetic testing, as evidenced by the rise in the revenue of NeoGenomics[81] from US$60m in 2012 to US$259m in 2017. All these factors have helped three notable cancer genomics companies that have emerged in recent years to become billion-dollar companies:

CANCER GENOMICS HAS CRESATED SOME BILLION DOLLAR COMPANIES

- **Foundation Medicine**. This company's FoundationOne test can detect mutations in more than 300 cancer-related genes and suggest implementable clinical action[82].
- **Myriad Genetics**. This company, which was originally built on its ownership of the famous BRCA1 and BRCA2 oncogenes[83], has since added numerous other tests, some of them with considerable predictive ability such as EndoPredict for identifying distant metastases in ER+/HER2- breast cancer patients[84].

[76] For a recent review paper on the use of 3D cell culture in personalised cancer medicine, in which Hanry Yu is one of the authors, see SLAS Technol. 2017 Jun;22(3):245-253. Epub 2017 Mar 9.
[77] There has been much talk in recent years of a 'US$1,000 genome' in a single day (as against the US$2.7bn in FY1991 dollars of the first human genome, which took almost 15 years to complete in 2000). While US$1,000 genomes are not commonplace yet, we are getting close (see Eur J Health Econ. 2017 Jun;18(5):623-633 Epub 2016 Jul 5).
[78] Including multiregion sequencing, single-cell sequencing, analysis of autopsy samples, and longitudinal analysis of liquid biopsy samples - see Nat Rev Clin Oncol. 2018 Feb;15(2):81-94. Epub 2017 Nov 8.
[79] Generally in the personalised cancer medicine field the term 'biomarker' is used to refer to DNA indicative of cancer. RNA, proteins, or metabolites can also be assayed for indications that the cancer would respond to treatment, but these can be less specific to a particular cancer – see Genomics Proteomics Bioinformatics. 2017 Aug;15(4):220-235. Epub 2017 Aug 13.
[80] Contemp Oncol (Pozn). 2015;19(1A):A68-77.
[81] Fort Myers, Fl., Nasdaq: NEO, www.neogenomics.com.
[82] Oncologist. 2016 Aug 26. [Epub ahead of print]
[83] The American actress Angelina Jolie drew significant public attention to the BRCA1 gene in May 2013 when she had a preventative double mastectomy after finding that she was BRCA1-positive. BRCA1 and BRCA2, known to indicate a heightened breast cancer risk, were discovered in 1994 and 1995 respectively by Myriad Genetics. These genes code for tumour suppressor genes that are important in DNA Damage Response pathways. Myriad's patents were eventually invalidated by the US Supreme Court in a case called Association for Molecular Pathology v. Myriad Genetics that was decided in 2013.
[84] Br J Cancer. 2013 Dec 10;109(12):2959-64. Epub 2013 Oct 24.

- **Genomic Health**. This company's Oncotype DX range of multi-gene classifiers are now available for use in breast, colon and prostate cancer. In breast cancer Oncotype DX helps select the patients for whom chemotherapy would be effective[85].

3D cell culture models have advantages over the genomic models. We argue that there are basically only two kinds of cancer 'models' with which to tailor a personalised cancer treatment regimen – genomic models or 3D cell culture models like Invitrocue's. We also think that the 3D cell culture approach has competitive advantage because it can be less complex, and more 'holistic':

- **Less complex.** As we saw above in the case of tumour heterogeneity in PTEN, genomic analysis has a habit of throwing up huge masses of data in terms of point mutations, copy number changes and so on that is difficult to reduce to practice[86], whereas with 3D cell culture models there are a relatively small number of tumour models – recall that for HN137 there was one from the primary tumour and one from the lymph node metastasis - so the ability to yield clinically actionable data is a lot higher.
- **More holistic**. With 3D cell culture the oncologist is looking at overall tumour function rather than individual tumour gene function. The trouble with DNA biomarkers is the complexity of the signalling networks that drive tumour growth. A biomarker that at one time may indicate responsiveness to treatment could change over time, due to the known propensity of cancer cells to adapt their signalling circuitry to chronic drug treatment[87]. More importantly, there are very few clinically actionable DNA biomarkers out there.

We believe that oncologists will increasingly use both approaches. In 2017 Foundation Medicine enjoyed US$152.9m in revenue, up 31% on 2016, with over 67,000 clinical tests performed during the year. It's fair to say, therefore, that the genome-based approach to treatment prediction has gained a firm following amongst clinicians. Such tests, however, are still expensive and not always reimbursed (yet). We believe that the 3D cell culture approach will attract a following as a lower cost option that is easier to implement and doesn't require expensive equipment. That is Invitrocue's opportunity.

WE BELIEVE CELL CULTURE MODELS CAN BE A LOWER-COST TREATMENT PREDICTION MODALITY THAN GENOMICS

We estimate the diagnostic part of personalised cancer medicine is worth US$2bn p.a. globally. Diagnostic testing tends to take up a very small percentage of overall healthcare spending in advanced industrial countries. One 2016 study established that, in Germany and the US, *in vitro* diagnostics - diagnostic tests suitable for central laboratories rather than point of care tests – accounted for only 1-2% of total healthcare expenditure but guided fully two-thirds of clinical decision making[88]. We used this estimate as a proxy for the amount which the system would be willing to spend on tool that would guide drug treatment. On our estimate of US$119bn for the global market for cancer drugs as it stood in 2017[89], being roughly a third of total cancer healthcare costs[90], a 1.7% spend on treatment decision support systems would translate to a US$2bn opportunity without even accounting for the efficiency gains of better treatment decision support.

[85] Eur J Surg Oncol. 2017 May;43(5):931-937. Epub 2017 Jan 9.
[86] For some perspective here see *Big science: The cancer genome challenge* by Heidi Ledford, Nature, 14 April 2010.
[87] Genes Dev. 2012 Apr 1;26(7):641-50.
[88] PLoS One. 2016 Mar 4;11(3):e0149856.
[89] See the IQVIA Institute's Global Oncology Trends 2017 report dated 31 May 2017.
[90] Cancer typically consumes 6-7% of healthcare budgets (Annals of Oncology 18 (Supplement 3): iii8–iii22, 2007) and the typical healthcare budget across the globe is 6% of GDP (source: data from CIA World Factbook)

Valuing Invitrocue

We value Invitrocue at 7.3 cents per share base case and 24.4 cents per share optimistic case, using a DCF-based approach. We value the company only for Onco-PDO and assumed that the company did not partner the technology in order to grow usage quickly but retained 100%. Our main assumptions were:

- **WACC:** ~13.2%, appropriate in our view for a 'High' risk rating[91];
- **Probability of clinical success.** We noted above that the regulatory hurdles for commercialising Onco-PDO are fairly low. However, to account for the potential for any regulatory requirements that may slow CE Mark and 510(k) approval from the FDA for the kit-based form of the product, we weighted our DCF by 90%;
- **Time horizon**. We used a 15-year time horizon in our DCFs followed by a terminal value;
- **Clinical costs.** We assume no further research-focused clinical work needs to be undertaken in order to commercialise Onco-PDOs in all key markets;
- **Capex.** We assume that Invitrocue needs to spend 1-2% of revenue on capex related to its various service labs for Onco-PDO;
- **Peak sales.** We assumed peak sales for Onco-PDO of ~US$45m (base case) to US$90m (optimistic case). That this is reasonable is suggested by the current commercial experience of Foundation Medicine and similar companies which we noted above.
- **Margins**. We assume 50-66% gross margins for Onco-PDO from 2018/2019, alongside SG&A expenses equal to 10-20% of sales. We assume both COGS and SG&A decline by 0.1%-0.2% of revenue annually.
- **Currency:** While Invitrocue reports its numbers in Singapore dollars, we translated for valuation purposes a US$ revenue stream back into AUD$ at a long-run exchange rate for the AUDUSD of 0.7.
- **Tax:** We assumed a 17% tax rate as per the tax regime in Singapore.
- **Corporate overhead.** We assumed the equivalent of A$250,000 per month in corporate overhead going forward.
- **Further capital.** Since its backdoor listing in early 2016 Invitrocue has raised A$6.5m in four transactions at an average 8.9 cents per share. We assume one further capital raising of A$6m at 8 cents per share.

[91] For a relevant discount rate, we use WACCs of between ~11% and ~15% depending on the risk for Life Science companies. This is derived from a RFR of 2.7%; a MRP of 7.5%-11.5% (7.5% for 'medium risk' companies, 9.5% for 'high risk' companies and 11.5% for 'speculative' companies); and an ungeared beta of 1.1. We regard Life Science companies with existing businesses, or who have enough capital to reach the market with their products, as 'Medium' risk. Companies that have small revenue streams from marketed products but that are still potentially in need of capital are 'High' risk. Everything else is 'Speculative'.

	Base	Optim.
Patient-derived organoids (A$m)	48.7	156.6
Total programme value	48.7	156.6
Value of tax losses	4.2	4.2
Corporate overhead	-18.9	-18.9
Cash now (A$m)	1.5	1.5
Cash to be raised (A$m)	6.0	6.0
Option exercises (A$m)	4.3	4.3
Total value (A$m)	45.8	153.8
Total diluted shares (million)	630.1	630.1
Value per share	$0.073	$0.244
Valuation midpoint	$0.159	
Share price now (A$ per share)	$0.100	
Upside to midpoint	58.5%	

Re-rating Invitrocue

We see three main factors helping to re-rate Invitrocue to our target price:

- Further clinical data, published as well as topline, on the utility of Onco-PDOs;
- Further collaborations with hospitals and diagnostic testing laboratories related to the introduction of Onco-PDOs in new markets;
- Completion of development of the first kit-based Onco-PDO products.

Invitrocue's solid management team

CEO Dr **Steven Fang** started Invitrocue after a previous success building a cord blood banking company called CordLife, which was co-founded by Fang in 2001 and which is now a public company in Singapore[92]. Earlier in his career Fang had held management positions at Becton Dickinson, Baxter Healthcare and Sterling Pharmaceuticals. We think Fang's varied experience in CordLife as well as his current involvement in Clearbridge Accelerator, a Singapore technology commercialisation and incubation firm, bodes well for success with the Onco-PDO technology now coming to the forefront at Invitrocue.

STEVEN FANG PREVIOUSLY BUILT CORDLIFE

CSO Professor **Hanry Yu** brings to Invitrocue considerable insight, from his background in cell biology and his current academic work at IBN and at National University of Singapore, to the challenges and potential capabilities of Onco-PDOs.

[92] SGX: P8A, www.cordlife.com.

Martin Bach, VP, Operations, who joined Invitrocue in 2015, brings operational experience in healthcare and medical device companies gained through a number of start-up companies.

The Invitrocue board, which includes Fang and Yu, has a range of skills vital for an early stage Life Sciences company. Ms **Jamie Khoo** and **Chow Yee Koh** brings corporate skills, while **Ms Ee Ting Ng** mainly has a scientific research background. Dr **Andreas Lindner** brings a background in medical start-ups.

Invitrocue's **scientific and medical advisors** have considerable medical insight into the challenge of developing Onco-PDOs and the company's other technologies. Professor **Shervanthi Homer-Vanniasinkam,** a UK-based authority on vascular surgery, brings knowledge of *in vitro* modelling[93] while Professor **Chng Wee Joo**, who directs Singapore's National University Cancer Institute, brings knowledge on the genetics of blood cancers as they relate to treatment outcomes[94].

Appendix I – An Invitrocue glossary

510(k) – Regulatory approval for a medical device in the US where the device has been found to be functionally equivalent to a device (called the 'predicate device') that was on the market before 1976.

3D cell culture – Cell culture in which cells are able to grow and interact with their surroundings in all three dimensions.

3D CelluSponge – An Invitrocue product in which cellulosic sponges are used to grow spheroids of uniform size.

A*STAR – The Agency for Science, Technology and Research, a Singapore government body which funds basic scientific research. Invitrocue's technology was funded by A*STAR.

Biopsy – Removal of a sample of tissue from the body, generally for diagnostic purposes.

Cellulose – A polysaccharide assembled from glucose monomers. Cellulose is the main constituent of plant walls. Invitrocue's 3D cell culture scaffolds are made out of cellulose.

Galactose – A sugar with the formula $C_6H_{12}O_6$. Invitrocue uses galactose to turn its cellulosic sponges into scaffolds for 3D cell culture.

HepatoCue – An Invitrocue product in which 'tethered spheroid' hepatocytes are created using RGD and galactose as anchors to the substrate.

Hepatocyte – A liver cell.

Hepatotoxic – Damaging to liver cells.

Hydrogel – A crosslinked polymer network that can absorb large amounts of water.

In vitro – Latin for 'in glass', referring to data obtained through testing in a test tube.

[93] See, for example, J Surg Res. 2012 Nov;178(1):e35-41. Epub 2012 Mar 22.
[94] See, for example, Blood. 2007 Apr 15;109(8):3177-88. Epub 2006 Dec 21.

In vivo – Latin for 'in life', referring to data obtained through testing in live organisms including animal models and humans.

Liver – An organ in the abdominal cavity that has a number of responsibilities. It plays an important role in metabolism, not least through its production of bile; it stores glycogen, a carbohydrate the body converts to glucose for energy purposes when required; and it helps detoxify certain poisons.

Macroporous – Having large holes.

Monolayer – A cell culture that is anchorage-dependent in that cells can only grow when attached to the surface of the culture vessel.

Monomer – A simple compound whose molecules can join together to form oligomers or polymers.

Next Generation Sequencing – Methods for sequencing DNA that build on the original methods devised by Novel laureate Fred Sanger, but that are able to operate much faster and cheaper.

Non-Small Cell Lung Cancer (NSCLC) – The main form of lung cancer, comprising about 80-85% of all lung cancer. 'Small Cell' Lung Cancer (SCLC) is so called because of the physical appearance of the cancer cells in this condition. Non-Small Cell Lung Cancer cells don't have this appearance. NSCLC is easier to surgically remove while small cell lung cancer responds better to chemotherapy and radiation.

Oncogene – A gene known to be cancer-causing.

Onco-PDO – Short for Oncology Patient-Derived Organoid, Invitrocue's technology to scaffold patient-derived cancer cells so that they can be grown in culture.

Organoid – Three-dimensional clusters of cells grown *in vitro* from stem cells that mimic a particular organ in the body.

PDX – Short for Patient-Derived Xenograft, an animal model of cancer in which a human tumour is taken from a patient and grafted onto a mouse without a functioning immune system, so that the tumour will stay in place.

Peptide – Two or more amino acids linked by chemical bonds.

Personalised medicine – Medical treatment customised for each individual patient.

Phenotype – An organism's expressed physical traits, as opposed to its 'genotype', which is the genes that the organism inherits. The distinction underlies the fact that each gene in an organism's gene set may or may not express itself physically.

Pluripotent – A stem cell capable of turning into almost all cell types. Embryonic stem cells are pluripotent.

Polymer – A large molecule composed of repeating structural units called monomers, connected by chemical bonds.

RGD – A peptide often use in biomaterials because it has cell adhesion properties.

Scaffold – A structure to assist the proper culture of cells.

Spheroids – Sphere-shaped aggregates of specific cell types.

Stem cells – Cells that can differentiate into many different cell types when subjected to the right biochemical signals.

Appendix II – Invitrocue's core intellectual property

Invitrocue's intellectual property for HepatoCue and 3D CelluSponge is covered by two disclosed patent families[95]:

Bioactive surface for hepatocyte-based applications, WO/2007/136354, priority date 24 May 2006, invented by Yanan Du, Rongbin Han and Hanry Yu.

- This patent application covers Invitrocue's HepatoCue product.

Forming porous scaffold from cellulose derivatives, WO/2009/078819, priority date 18 December 2007, invented by Zhilian Yue, Feng Wen, Hanry Yu

- This patent application covers Invitrocue's 3D CelluSponge product.

Appendix III – Capital structure summary

		% of fully diluted	Note
Ordinary shares, ASX Code IVQ (million)	485.5	87.5%	
Unlisted options (million)	69.7	12.5%	Average exercise price 6.2 cents, average expiry date 06-Mar-2029
Fully diluted shares	555.1		

Current market cap:	A$48.5 million (US$37.8million)
Current share price	$0.100
Twelve month range	$0.059 - $0.125
Average turnover per day (last three months)	154,900.0

[95] Invitrocue has also licensed from A*STAR two patent families: WO/2011/123068 (*A method and system for determining a stage of fibrosis in a liver*, priority date 31 March 2010, invented by Hanry Yu, Dean Tai, Yuting He and Shuoyu Xu) and WO/2014/109708 (*A method and system for assessing fibrosis in a tissue*, priority date 8 January 2013, invented by Hanry Yu and Shuoyu Xu). These relate to technologies allowing the computational biology of liver fibrosis, potentially valuable given the large market opportunity in NAFLD (Nonalcoholic Fatty Liver Disease) and NASH (Nonalcoholic Steatohepatitis). It is estimated that around 30% of US adults have NAFLD with the potential to lead to fibrosis and cirrhosis of the liver. NASH impacts around 2-3% of the general population of most Western countries.

Appendix IV – Major shareholders

Invitrocue currently has four substantial shareholders:

- Steven Fang (23.8%);
- Wong Bei Keen, a Singapore-based businesswoman (17.0%);
- Hanry Yu (10.2%);
- Clearbridge Accelerator, a Singapore venture capital company that has co-funding support from the Singapore government (7.8%)

Appendix V – Papers relevant to Invitrocue

Du et. al. (2006), *3D hepatocyte monolayer on hybrid RGD/galactose substratum.* Biomaterials. 2006 Nov;27(33):5669-80. Epub 2006 Aug 10.

- This paper describes the original development of HepatoCue.

Du et. al. (2007), *Identification and characterization of a novel prespheroid 3-dimensional hepatocyte monolayer on galactosylated substratum.* Tissue Eng. 2007 Jul;13(7):1455-68.

- This paper describes demonstrates the functional properties of hepatocyte spheroids assembled using HepatoCue.

Gu et. al. (2010), *Control of* in vitro *neural differentiation of mesenchymal stem cells in 3D macroporous, cellulosic hydrogels.* Regen Med. 2010 Mar;5(2):245-53

- This paper describes the use of 3D CelluSponge in growing neural tissue from mesenchymal stem cells.

Yue et. al. (2010), *Preparation of three-dimensional interconnected macroporous cellulosic hydrogels for soft tissue engineering.* Biomaterials. 2010 Nov;31(32):8141-52. Epub 2010 Aug 5.

- This paper describes the engineering from hydroxypropylcellulose of the hydrogel material for the 3D CelluSponge series.

Zhang et. al. (2011), *A robust high-throughput sandwich cell-based drug screening platform.* Biomaterials. 2011 Feb;32(4):1229-41. Epub 2010 Oct 23.

- This paper covers a sandwiched hepatocytes model developed by the Yu laboratory in which galactose is used to engineer the membrane.

Nugraha et. al (2011), *Galactosylated cellulosic sponge for multi-well drug safety testing.* Biomaterials. 2011 Oct;32(29):6982-94. Epub 2011 Jul 8.

- This paper describes how galactose-conjugated 3D Cellusponge is able to produce hepatocyte spheroids of uniform size that retain proper hepatocyte functionality.

Ananthanarayanan et. al (2011), *Purpose-driven biomaterials research in liver-tissue engineering.* Trends Biotechnol. 2011 Mar;29(3):110-8. Epub 2010 Dec 2.

- This review paper looks at the state of the art in 2011 in liver modelling.

Xia et. al (2012), *Tethered spheroids as an* in vitro *hepatocyte model for drug safety screening.* Biomaterials. 2012 Mar;33(7):2165-76. Epub 2011 Dec 19.

- This paper introduced Invitrocue's 'tethered spheroid' model, providing proof of concept that the HepatoCue system, based on ratios of RGD and galactose in the hepatocyte tethering, can work as a superior *in vitro* liver model.

Ananthanarayanan et. al (2014), *Scalable spheroid model of human hepatocytes for Hepatitis C infection and replication.* Mol Pharm. 2014 Jul 7;11(7):2106-14. Epub 2014 May 6.

- This paper shows the use of galactose-conjugated 3D Cellusponge in modelling Hepatitis C infection, with a 9-fold increase in viral entry over conventional monolayer culture.

Wang et. al (2015), *HepaRG culture in tethered spheroids as an in vitro three-dimensional model for drug safety screening.* J Appl Toxicol. 2015 Aug;35(8):909-17. Epub 2014 Dec 15.

- This paper shows that a cell line called HepaRG[96] can work well with the HepatoCue system.

Xia et. al (2016), *Cytochrome P450 induction response in tethered spheroids as a three-dimensional human hepatocyte in vitro model.* J Appl Toxicol. 2016 Feb;36(2):320-9. Epub 2015 Jul 21.

- This paper shows that HepatoCue is a better indicator of liver toxicity, in terms of production of Cytochrome P450, than collagen sandwich cultures.

Tong et. al (2016), *Constrained spheroids for prolonged hepatocyte culture.* Biomaterials. 2016 Feb;80:106-120. Epub 2015 Dec 3.

- This paper reports an optimised version of the sandwich hepatocyte model described above in Zhang et. al. (2011) above, using a membrane made out Parylene modified with polyethylene glycol and galactose.

Tasnim et. al (2016), *Functionally enhanced human stem cell derived hepatocytes in galactosylated cellulosic sponges for hepatotoxicity testing*. Mol Pharm. 2016 Jun 6;13(6):1947-57. Epub 2016 May 24.

- This paper demonstrates that hepatocyte-like cells derived from pluripotent stem cells were superior to primary human hepatocytes in terms of their hepatocyte functionality when cultured in Invitrocue's 3-D cellulosic scaffold system.

[96] Methods Mol Biol. 2010;640:261-72.

Fong et. al. (2016), *Heralding a new paradigm in 3D tumor modeling*. Biomaterials. 2016 Nov;108:197-213. Epub 2016 Sep 2 (full text available for free online).

- This review paper discusses the future of 3D tumour modelling, including Patient-Derived Organoids.

Chia et. al. (2017), *Phenotype-driven precision oncology as a guide for clinical decisions one patient at a time.* Nat Commun. 2017 Sep 5;8(1):435.

- This paper presents the first case reports of treatment decisions guided using Onco-PDOs.

Tan et. al. (2017), *Long noncoding RNA EGFR-AS1 mediates epidermal growth factor receptor addiction and modulates treatment response in squamous cell carcinoma.* Nat Med. 2017 Oct;23(10):1167-1175. Epub 2017 Sep 18.

- This paper identifies the biomarker which would have predicted the treatment success of the case studies reported in Chia et. al. (2017).

Fong et. al. (2018), *Generation of matched patient-derived xenograft in vitro-in vivo models using 3D macroporous hydrogels for the study of liver cancer.* Biomaterials. 2018 Mar;159:229-240. Epub 2018 Jan 4.

- This paper shows that Invitrocue's Onco-PDO system can replicate the genetics of patient-derived xenografts in primary liver cancer.

Zhang et. al. (2018), *Establishment of patient-derived tumor spheroids for non-small cell lung cancer.* PLoS One. 2018 Mar 15;13(3):e0194016.

- This paper describes the establishment of patient-derived tumour spheroids for NSCLC.

Appendix VI – Companies to watch

Company	Location	Code	Market cap (USDm)	Web
MDxHealth	Herstal, Belgium	Euronext Brussels: MI	314	www.mdxhealth.com
Immunovia	Lund, Sweden	Nasdaq OMX Stockh	273	www.immunovia.com
NanoString Technologies	Seattle, Wa.	Nasdaq: NSTG	243	www.nanostring.com
Veracyte	South San Francisco, Ca.	Nasdaq: VCYT	198	www.veracyte.com
Celcuity	Minneapolis, Mn.	Nasdaq: CELC	171	www.celcuity.com
Cellink	Göteborg, Sweden	Nasdaq OMX Stockh	128	www.cellink.com
Epigenomics	Berlin, Germany	Xetra: ECX	117	www.epigenomics.com
OncoCyte	Alameda, Ca.	NYSE MKT: OCX	101	www.oncocyte.com
HTG Molecular Diagnostics	Tucson, Az	Nasdaq: HTGM	96	www.htgmolecular.com
ANGLE plc	Guildford, UK	LSE: AGL	81	www.angleplc.com
VolitionRx	Namur, Belgium	NYSE MKT: VNRX	66	www.volitionrx.com
InvitroCue			38	

ANGLE plc. This company's Parsortix technology allows viable Circulating Tumour Cells to be sourced from blood samples. Having whole cells means that analysis can be made of DNA, RNA and proteins, which is a big step forward from only having circulating tumour DNA to analyse. Parsortix is CE Marked as a tool for sourcing CTCs, and ANGLE is seeking FDA approval for its use in the diagnosis of metastatic breast cancer, as an alternative to tissue biopsy.

Celcuity. This company's CELx platform uses takes culture cells from patient tumours and analyses them for the activity of various aberrant signalling pathways indicative of cancer. This helps ensure that patients receive the right targeted therapies where those therapies involve such pathways. The company's first test from this platform was the CELx Breast Test measuring HER2 signalling activity, which can help select the right patients for anti-HER2 therapy[97].

Cellink. This company's technology allows 3D printing of organs and tissue, which are sold to academic labs around the world. Cellink announced in January 2018 that it would be collaborating with a privately held French company called CTIBiotech[98] on 3D printing of fully functional human tumours.

Epigenomics. This company's technology allows liquid biopsy of cancer through detection of DNA methylation biomarkers. The company has diagnostics on the market for colon and lung cancer.

MDxHealth. This company's ConfirmMDx product is a test for the DNA methylation status of three prostate cancer genes which can detect cancer from its 'epigenetic' profile, even if the original biopsy did not directly sample cancerous tissue. The product reduces the need for repeat biopsies where the standard PSA test is still high[99]. MDXHealth is also working on epigenetic biomarkers for other cancers such as bladder and kidney cancer.

HTG Molecular Diagnostics. This company develops technologies based on Next Generation Sequencing for rapid molecular profiling. Its HTG EdgeSeq system can obtain thousands of RNA samples for analysis from a single assay in under three days.

Immunovia. This company's IMMray technology is an antibody microarray platform that can detect cancer from a blood test by surveying the various immunoregulatory proteins that would be associated with it. The company's first commercial test is PanCan-d for the early detection of pancreatic cancer[100]. Immunovia is working on tests for other cancers and for autoimmune disease.

NanoString Technologies. This company's nCounter Analysis System allows rapid and low-cost analysis of genes, proteins and other diagnostic targets of interest. The company has used its technology to develop Prosigna, a prognostic indicator for distant recurrence of breast cancer[101].

OncoCyte. This company's technology uses gene expression patterns associated with embryonic stem cell development to search for cancer genes in cancer tissues obtained from blood or urine. A confirmatory lung cancer diagnostic has reached the commercial launch stage.

[97] Oncotarget. 2016 Nov 29;7(48):78577-78590.
[98] Lyon, France, privately held, www.ctibiotech.com
[99] Am Health Drug Benefits. 2014 May;7(3):129-34.
[100] Mol Oncol. 2016 Oct;10(8):1305-16. Epub 2016 Jul 12.
[101] J Breast Cancer. 2017 Sep;20(3):286-296. Epub 2017 Sep 22.

Veracyte. This company's Gene Expression Classifier algorithms analyse the genomic profile of tissue looking for gene combinations indicative of cancer. The company has Gene Expression Classifier diagnostics for thyroid and lung cancer as well as a rare lung disorder called idiopathic pulmonary fibrosis. The product can analyse DNA from 'brushing' specimens without the need to sample lesions directly[102].

VolitionRx. This company's technology allows the DNA signature of cancer to be detected in circulating nucleosomes, that is, DNA wrapped around a protein core called a histone. A suite of diagnostics called 'Nu.Q' are being launched, starting with a colorectal cancer diagnostic[103].

Risks related to Invitrocue

Risks specific to Invitrocue. We see five major risks for Invitrocue as a company and as a listed stock:

- **Market acceptance**. There is the risk that Onco-PDO will fail to attract a strong following from oncologists.
- **Funding risk**. More capital will likely be needed to continue clinical and commercial development of Onco-PDO as well as Invitrocue's other projects in the bioanalytics field.
- **Regulatory risk**. There is the risk that Invitrocue may be required to develop more data on the clinical effectiveness of Invitrocue before it is permitted to offer Onco-PDO services in major markets.
- **Distribution risk.** There is the risk that Invitrocue will fail to find commercial partners allowing it to build a global reach with its current suite of services.
- **Technology risk.** There is the risk that newer technologies with a superior cost profile in the personalised oncology space can emerge before Invitrocue has fully realised the commercial potential of Onco-PDO.

Risks related to pre-revenue Life Science companies in general.

- The stocks of biotechnology and medical device companies without revenue streams from product sales or ongoing service revenue should always be regarded as speculative in character.
- Since most biotechnology and medical device companies listed on the Australian Securities Exchange fit this description, the term 'speculative' can reasonably be applied to the entire sector.
- The fact that the intellectual property base of most biotechnology and medical device lies in science not generally regarded as accessible to the layman adds further to the riskiness with which the sector ought to be regarded.

Caveat emptor. Investors are advised to be cognisant of the abovementioned specific and general risks before buying any the stock of any biotechnology or medical device stock mentioned on this report, including Invitrocue.

[102] BMC Cancer. 2016 Feb 26;16:161.
[103] Clin Epigenetics. 2017 May 15;9:53.

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