

# The diagnostics sector

The other side of the healthcare coin

Healthcare equipment & services

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The practice of medicine can be roughly divided into two specialties: the diagnosis of disease and the treatment of disease. Historically, healthcare investing has been focused on treatment, with pharmaceutical and biotech companies commanding the majority of attention. However, diagnosis remains a significant opportunity for the informed investor. Diagnostic products are pervasive in the healthcare system and as varied as the diseases the humans encounter. This report provides an overview of both the diversity and the commonalities in this market.

## Beyond sensitivity and specificity

Sensitivity and specificity are the statistics that are most commonly invoked when describing a diagnostic test. They are the rates of true positives and true negatives respectively and are frequently cited because in theory they do not depend on the prevalence of the disease being examined. However, in practice these values are highly contingent on the circumstances under which they are looked at. Moreover, they only tell half of the story, and the value of a test is inseparable from how it fits into the real world environment of a disease. Therefore, it is important to understand how these data were gathered and how these circumstances reflect the environment in which the disease is encountered.

## A multifaceted regulatory framework

In the US, most diagnostics are regulated as medical devices. As part of this, they are stratified based on their level of risk, with three independent approval pathways for standalone tests: premarket approval (PMA) for high risk tests, De Novo request for low risk tests, and 510(k) for tests with a previously approved predicate (which is the vast majority of applications). Review times are generally six months to a year. Tests attached to a single laboratory can also be regulated as laboratory developed tests (LDTs). In Europe, the process is both more lenient and more complicated with marketing approval primarily through the CE marking system, but with numerous state-level controls and different regulations for devices and in vitro diagnostics. Also, the majority of in vitro diagnostics do not get CE marking before entering the market. The EU is in the middle of a multi-year harmonization process to require all new tests to receive a CE mark and oversight.

## Levels of diagnostic clinical studies

In the early stages, companies may employ retrospective studies to examine the parameters of their tests. Although these studies are useful, low-cost methods of validating a test, they lack the rigor of prospective studies and are susceptible to 'overfitting', where the data perfectly fits an individual trial but cannot be replicated. Therefore, prospective trials are the gold standard for evaluating clinical validity. However, there is a standard beyond validity, where the value of test is evaluated. Clinical utility is the measure of how the diagnostic changes clinical practice. These trials are not always required for regulatory approval but can be essential for inclusion into medical recommendations and for reimbursement.

### Companies in this report

BioPorto Diagnostics\*  
Check-Cap  
Epigenomics  
Invitae  
Orasure  
Quotient  
Telix\*  
TruScreen  
VolitionRx\*

\*Clients of Edison Investment Research

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## Contents

The diagnostics sector.....	3
Diagnostic statistics.....	3
Sensitivity and specificity.....	4
Positive and negative predictive value.....	5
Regulatory framework.....	6
United States.....	6
Europe.....	8
Clinical studies of diagnostics.....	9
Retrospective versus prospective studies.....	9
Clinical validity versus clinical utility.....	10
A selection of diagnostic market segments.....	10
Prenatal testing.....	11
Circulating tumor DNA and liquid biopsy.....	11
Colorectal cancer.....	11
Consumer genomics.....	12
Clinical microbiology screening.....	12
Company profiles.....	
BioPorto Diagnostics.....	14
Check-Cap.....	15
Epigenomics.....	16
Invitae.....	17
OraSure.....	18
Quotient.....	19
Telix Pharmaceuticals.....	20
TruScreen.....	21
VolitionRx.....	22

## The diagnostics sector

Diagnostics are healthcare products or services designed to help identify medical disorders or provide data to a physician for assessment. Products can be divided in three categories:

- Diagnostic devices: mechanical, electric, optical, or other devices used by a physician to assess a disease state. These can range from something as simple as a reflex hammer, to a colonoscope or an MRI machine.
- In vitro diagnostics (IVDs): tests that perform chemistry on human tissues or samples to identify a disease or medical state. These include diagnostics used at home (such as a pregnancy test), at the point of care (such as a rapid HIV test), or in a laboratory setting (such as DNA sequencing).
- Imaging agents: chemicals introduced to the human body to help identify structures or substances using radiographic equipment. These can be substances specific to the identification of an individual disease (such as probes for the detection of beta-amyloid for the diagnosis of Alzheimer’s disease) or agents useful in a range of scenarios (such as MRI contrast agents). These products are by far the minority of the market.

In addition to these broad categories, there is a framework of support services and capital equipment. For instance, the IVD market relies on a network of labs both at the point of care to obtain tissue samples as well as processing labs where the tests are run. The latter are enabled by high throughput equipment such as ELISA machines and DNA sequencing, which represent their own established markets.

Although there is significant diversity, there is a set of common organizing principles across the sector. For instance, all diagnostics that provide a binary readout share a set of statistics used in their clinical evaluation. Additionally, the vast majority of clinical diagnostics share a common regulatory framework in the US and EU (with the exception of imaging agents). It is therefore important to outline the factors that are useful for the evaluation of these products both across the sector and in individual instances.

## Diagnostic statistics

There are a set of statistics that are important for understanding the performance of a clinical diagnostic. The purpose of clinical studies is frequently to determine these statistics and they are the criteria by which tests are evaluated by regulatory authorities.

At its core, a diagnostic is valuable when the test result strongly correlates with the true presence or absence of the medical condition it is probing. It is important that it provides a positive test result in those patients that truly have the condition and a negative test result in those that do not. In statistical parlance, we want all patients positive for a condition (P) to be represented by a true positive (TP) and likewise those that are condition negative (N) should have true negative (TN) test results.

Exhibit 1: Diagnostic statistical parameters			
	Has condition (P)	Does not have condition (N)	
Test positive	True positive (TP)	False positive (FP)	Positive predictive value, PPV (TP/(TP +FP))
Test negative	False negative (FN)	True negative (TN)	Negative predictive value, NPV (TN/(TN+FN))
	Sensitivity (TP/P)	Specificity (TN/N)	

Source: Edison Investment Research

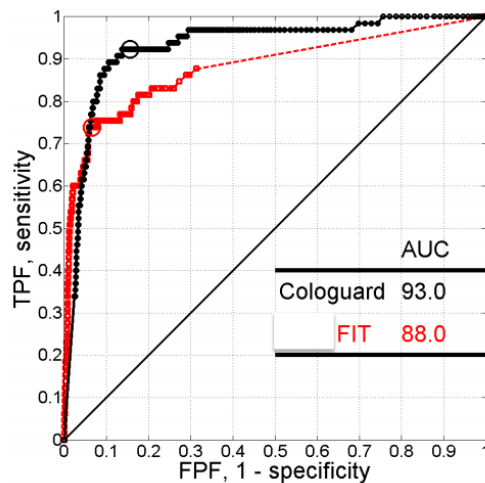
## Sensitivity and specificity

The most basic measure of a test's ability to identify a condition is its sensitivity, also known as the true positive rate (TP/P). This is the fraction of patients in the study that had disease and received a positive test result. This statistic is conversely related to the false negative rate (FN/P), or those patients that were missed by the diagnostic and received a negative test result although they had the disease. For instance, if a test has a sensitivity of 99% we can infer that there is a 1% false negative rate.

However, the sensitivity alone is not sufficient to evaluate the utility of a test. The specificity, also known as the true negative rate (TN/N), must also be considered. Similarly the specificity of a diagnostic is conversely related to its false positive rate (FP/N), that is, a test with a specificity of 90% has a false positive rate of 10%.

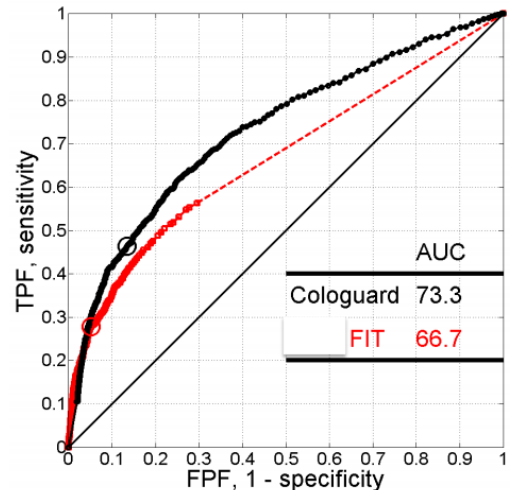
There is a balance drawn between sensitivity and specificity when designing a test. For instance, many tests return a value for a parameter such as the concentration of a biomarker or a biophysical measurement, and when this value is above a pre-specified threshold the test is treated as a positive. For instance the protein troponin increases in the blood in response to heart damage, and if it is higher than a particular threshold, it can be considered a positive test for myocardial infarction. However, where this threshold is drawn is a subject of debate, and will affect the sensitivity and specificity in a reciprocal fashion: a low threshold will capture more positive patients (higher sensitivity) but at the cost of increased false positives (lower specificity), and vice versa for a high threshold. This relationship is most clearly captured in the receiver operating characteristic (ROC) curve. The ROC curve captures the relationship between sensitivity and specificity as the parameters of the test are varied. The area under the curve (AUC) measurement of this plot is a measure of the diagnostic value of the test that is agnostic to the parameters of the test.

**Exhibit 2: ROC curve of Cologuard vs FIT for colorectal cancer**



Source: FDA Summary of Safety and Effectiveness for Cologuard. Note: FIT=fecal immunochemical test

**Exhibit 3: ROC curve of Cologuard vs FIT for colorectal adenomas**



Source: FDA Summary of Safety and Effectiveness for Cologuard. Note: FIT=fecal immunochemical test

In theory the sensitivity and specificity (as well as the ROC) of a diagnostic are intrinsic properties of the test. These values do not depend on the prevalence of the disease being examined, so in theory the performance of the test in a trial should be transferable to the clinic even if a greater or fewer number of patients with the condition are seen. However, there are some caveats to this generalization. Although these values are not sensitive to the prevalence of the condition, they are can be highly sensitive to the characteristics of the patients being examined. For instance, the sensitivity of a test is highly dependent on the severity of disease. It is naturally easier to identify a stage four cancer patient than a stage one patient. Similarly, the specificity of a test can be affected

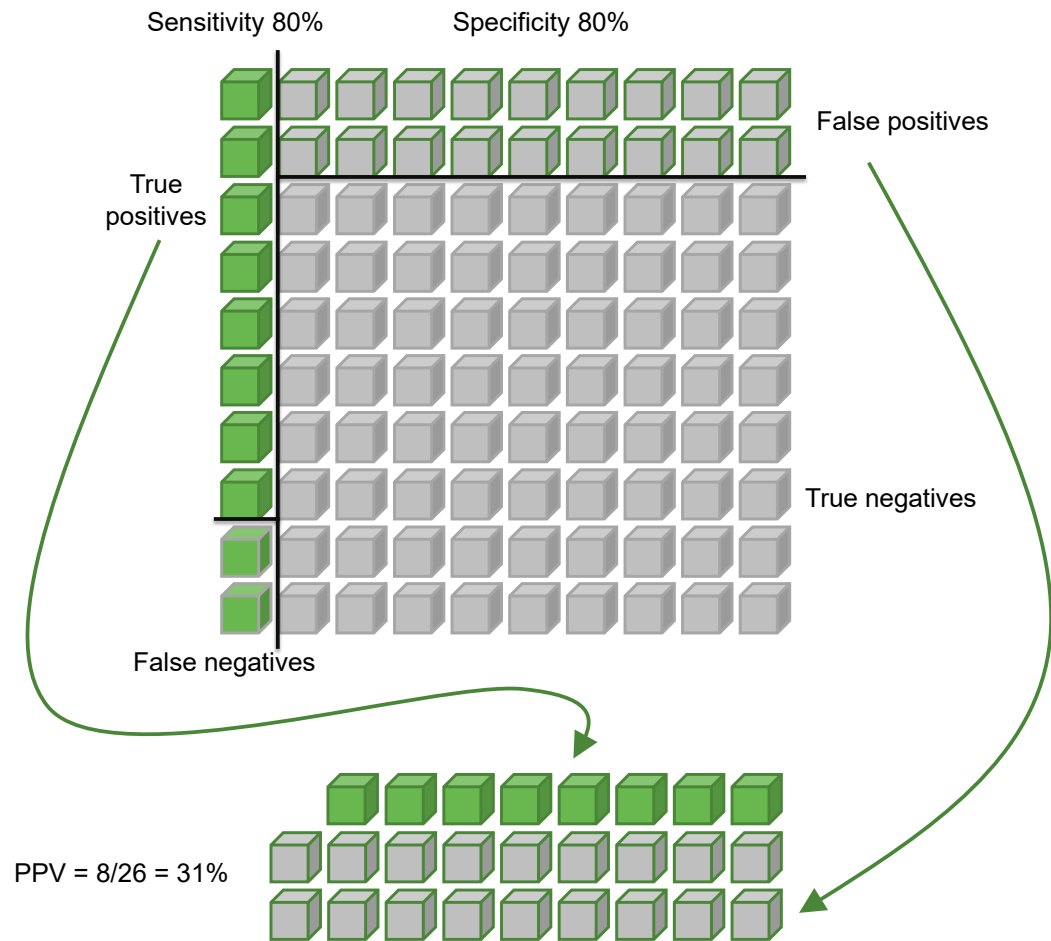
by other confounding conditions present in the disease-negative population. This is particularly important for the clinical utility of a test because the patients being tested frequently have other conditions that could contribute to false positives. For instance, a patient presenting to the doctor with gut pain should perhaps be tested for colon cancer, but they may instead have a different disorder such as colitis, and a good test should be able to tell the difference. A test for colon cancer may have a much better-looking specificity if it is only compared to healthy individuals and not patients with other gut disorders. It is therefore important when evaluating a diagnostic to understand the conditions under which it was tested and to guarantee these match the population it will encounter in practice.

## **Positive and negative predictive value**

The positive predictive value (PPV) of a diagnostic is the rate at which a positive test result reflects a true positive, and the opposite for the negative predictive value (NPV). These statistics are typically not presented in the description of a test (such as in clinical trial results) because these values (unlike sensitivity and specificity) depend on the prevalence of the condition being tested, and therefore the PPV or NPV seen in a clinical trial may not be representative of what will be seen in the general population. However, these statistics can dramatically change how a diagnostic affects the delivery of care and are a matter of significant concern for regulators when evaluating how a test will affect clinical practice.

One factor that arises in situations where a disease of low prevalence is being tested is that even with high sensitivity and specificity, a minority of patients testing positive actually have the disease (the PPV is low). This is commonly described as a case of the base-rate fallacy (Exhibit 4). The evaluation of a diagnostic must therefore include an assessment of the risk associated with an incorrect diagnosis. If, for instance, patients undergo risky surgery following a positive test result, a low PPV would be unacceptable, as it may have a net negative impact on health.

**Exhibit 4: Illustration of the base rate fallacy**



Source: Edison Investment Research. Note: In this example, there are 100 people being tested for a disease. The prevalence is 10%, so 10 people have the disease (green boxes). The test has 80% sensitivity so of these people with disease, eight are identified (true positives, green boxes with green borders). The test also has 80% specificity, so of the 90 without disease, 72 test negative (true negatives, grey boxes with grey borders). This leaves 18 false positives (grey boxes with green borders). The total number of positive tests (true positives and false positives) is 26, eight of which actually have the disease, so the PPV is 31%.

The NPV tends to be important when a test is used to 'rule-out' certain common conditions. In many instances it is more important that a test catches every instance of patient with a condition at the cost of over-diagnosis. An example would be a test for concussion or brain injury. It would be important in this case to minimize the number of patients with a brain injury that are discharged from the hospital at all costs (ie maximize the NPV). Patients that test positive can be subsequently followed up with further testing, such as an MRI, which carries negligible risk. Such rule-out tests can also be useful to reduce healthcare spending. An inexpensive test with a high NPV can rule out patients before they undergo unnecessary and expensive further testing and interventions. This is the logic behind using the fecal immunochemical test as a first-line screen for colorectal cancer (CRC). Although the test has a relatively low sensitivity of 74% (at 96% specificity), the NPV of the fit test is over 99% and it can help patients avoid unnecessary colonoscopy.

## Regulatory framework

### United States

There are multiple frameworks under which diagnostic tests can seek regulatory approval in the US. Standalone tests are regulated as medical devices in the US, which means they are assigned a

class based on their risk to health. For other medical devices the class is assigned on the basis of the risk of injury to the patient from using the device, but for diagnostics, the class is generally assigned on the basis of the strength of the diagnostic claims being made and the potential harm of misdiagnosis.

<b>Exhibit 5: Diagnostic medical device classes</b>			
<b>Class</b>	<b>Risk</b>	<b>Examples</b>	<b>Regulatory controls</b>
Class I	low	Aberrometers, visual acuity charts, gout tests	General controls: protections against adulteration and misbranding, reporting of recalls
Class II	moderate	Home pregnancy tests, hearing tests, rapid flu tests	General controls and special controls: must meet established performance standards, special labelling requirements, postmarket surveillance
Class III	high	Cancer tests, blood gas analyzers, hepatitis B tests, glucose sensors	General controls and PMA: must go through an agency review process that evaluates the safety and efficacy of the product

Source: FDA

A developer of a diagnostic test may need to seek an investigational device exemption (IDE) to perform clinical trials to support marketing approval. An IDE is similar to the investigational new drug (IND) application used for pharmaceuticals. The IDE application includes the plan for the clinical study so an institutional review board at the FDA can evaluate if it adheres to good clinical practice. Additional details include information on informed consent and any monitoring that will be put in place. An IDE is generally required if performing the study poses significant risk. For instance, the clinical trial of a cancer diagnostic that informs a patient's treatment in the study would require an IDE in place. However, for diagnostics, there are a number of different ways clinical studies can be structured such that an IDE is not needed. For instance, if the results of the test are not released to physicians on the study, they cannot make interventions that would impart risk to the patient. If administration of the test itself does not carry a risk, then an IDE may be avoidable in this circumstance

New class III medical devices must undergo the PMA process in which the safety and efficacy of the device is evaluated by a board at the FDA. This is analogous to the new drug application (NDA) process for pharmaceuticals. The PMA application must be supported by a body of clinical and preclinical data, and therefore diagnostics that are approved through this route must undergo clinical trials. The FDA has 180 days to review a PMA, although in practice it generally takes longer, but less than a year.

Novel class I and II devices undergo a less rigorous review process called the De Novo request, in which they must provide a discussion of risks associated with the device and controls to limit those risks. These applications may include clinical or laboratory data to provide additional assurances with regards to risk. The statutory review time for a De Novo request is 150 days.

However, most devices are not approved through the PMA or De Novo pathway, but through the so-called 510(k) route. A 510(k) application is for devices that are 'substantially equivalent' to a predicate device. There are two ways of satisfying substantial equivalence:

- The device has the same intended use and the same technological characteristics.
- The device has the same intended use and the technical characteristics do not raise questions of safety and effectiveness and the sponsor has provided sufficient information in the application to support it is at least as safe and effective as the predicate diagnostic.

New diagnostics can use the latter criteria to support approval without the need for a PMA if they can improve on an existing test. In this case, clinical studies may be needed to demonstrate the test is safe and effective. It is worth noting that the criteria for substantial equivalence is substantially more lenient in this case than for the analogous processes for therapeutics: ANDAs for generic drugs and 505(b)2s for reformulations. Both the ANDA and 505(b)2 require the chemical entity being used to be identical to the predicate and, in the case of an ANDA, in vivo performance must be identical. A 505(b)2 always requires new efficacy clinical trials as well. The 510(k) is different in

that it is not only designed for new versions of pre-existing tests but for new tests that address the same intended use. 510(k) review times are approximately six months.

In vitro diagnostics are subject to an additional layer of regulation as part of the clinical laboratory improvement amendments (CLIA) law. CLIA is the law regulating clinical laboratories and the tests that can be performed at them. The FDA assigns a level of complexity to the test under review: waived, moderate or high. Tests with moderate or high complexity may only be performed in a registered CLIA lab, whereas waived tests do not share this requirement. The CLIA labs themselves are monitored by the Center for Medicare and Medicaid Services (CMS) and state agencies.

However, the CLIA lab system can be used as method of marketing a test without FDA approval. LDTs are any analysis performed by a CLIA lab that is not associated with an FDA-approved product. These include all variety of routine workups such as the measurement of electrolytes or enzymes from blood, as well as more complex analysis the laboratory chooses to do. The regulation of LDTs was established to encompass this general laboratory work, but some companies have developed products that are LDTs performed at a single CLIA facility. Oncotype DX marketed by Genomic Health (GHDX) is an example.

The regulation of LDTs is fundamentally different than stand-alone tests. It is administered by CMS, which ensures that the tests provide 'accurate results'. This is a different criteria than FDA-regulated diagnostics designed to provide an accurate diagnosis. For instance, an LDT that measures a biomarker must only provide an accurate concentration of that biomarker. The test need not demonstrate efficacy in diagnosis. However, any company providing an LDT must be able to support any claims with evidence. The FDA has routinely identified such overreaches in its continuing efforts to increase oversight over LDTs.

A final complexity to the system regulating diagnostics in the US is that imaging agents are regulated as drugs. Officially they are referred to as 'medical imaging drugs' and they require all the regulatory steps common to pharmaceuticals: IND, NDA, BLA, etc.

## Europe

In Europe, diagnostic equipment is regulated as medical devices and in vitro diagnostics are regulated as a separate product class, but both are administered through the Conformité Européenne (CE) marking system. A CE mark is an indication that products of certain classes meet the health and safety requirements set forth for that class, and is applied to a wide range of products including those outside of healthcare. CE marks are granted by 'Notified Bodies' or independent bodies that are nominated for review of these products by member states. The CE marking process is substantially less burdensome than the approval process in the US. Although it is generally easier for a product to enter the market in Europe and the system affords more flexibility, devices and IVDs are regulated by a larger number of agencies on both the EU and member state level. However, in 2017 the EU initiated a modernization and harmonization process through the passage of the new so-called Medical Device Regulation (MDR) and In Vitro Diagnostic Regulation (IVDR). Member states have until 2020 to become compliant with the MDR and until 2022 for the IVDR. This will have a larger impact on IVDs because historically, most IVDs have been able to avoid CE marking in Europe, with only one in five obtaining the designation.

Similar to the US, devices are categorized according to level of risk and similarly stratified into classes I, IIa, IIb and III. Low risk (class I) devices can be 'self-certified', meaning that the manufacturer states it is in compliance with marking guidelines. Moderate and high risk (class IIa, IIb and III) require clinical trials, unless a predicate device can be cited, which generally allows the device to avoid clinical review.

IVDs are classified by risk, but include an assessment of their public health risk. Tests for high-risk infectious disease for instance receive the highest risk class (class D), whereas cancer tests and



other diagnostics without a public health impact have a lower classification (class C). A new aspect of the IVDR is that clinical data and assessment are a requirement for classes B through D. The relevant regulatory bodies must evaluate data on the scientific validity, analytic performance and clinical performance of a diagnostic, and these data should be provided in the CE marking technical material.

Similar to the US, in Europe imaging agents are regulated as drugs. Specifically they are regulated under the same umbrella as radiopharmaceuticals (regardless of whether they emit radiation).

Exhibit 6: Diagnostic device and IVD classifications in the EU		
Class	Risk	Description
<b>Devices</b>		
Class I	Low	Unlikely to pose a risk to health
Class IIa	Low-medium	Has the potential to injure
Class IIb	High-medium	Support life
Class III	High	Generally limited to implantable devices
<b>IVD</b>		
Class A	Low personal risk, low public health risk	General laboratory products, histological stains, culture media
Class B	Moderate personal risk, low public health risk	Pregnancy tests, cholesterol tests, glucose tests
Class C	High personal risk, low public health risk	Companion diagnostics, cancer staging tests, lower risk sexually transmitted diseases
Class D	High personal risk, high public health risk	HIV tests, HCV tests, other infectious diseases, tissues tests for transplantation

Source: MDR, IVDR

## Clinical studies of diagnostics

Unlike for therapeutics, which have a highly structured clinical development pathway with Phase I, II and III studies typically, diagnostics share far fewer organizing principles. As outlined in the previous section, the level of clinical data needed for approval can vary significantly based on circumstance. However, there are some details regarding the design of clinical studies that are important to understand in this market when evaluating a diagnostic.

### Retrospective versus prospective studies

In many cases, especially for IVDs, it is possible to run retrospective clinical studies. A retrospective study is on previously collected samples from patients that are tested and compared to their medical records. Such studies are a low cost because they only require the company developing the test to acquire a set of tissue samples with associated medical records and do not require the costs associated setting up clinical trial centers, enrolling physicians etc. This type of study can be especially useful in the early stages of diagnostic development to test validity in a low-impact setting.

Moreover, when a test is first developed, many of the parameters regarding its operation may not be known and a retrospective study can be the fastest way to identify these values. For instance, when investigating a new biomarker, the threshold that should be considered a positive test may be unknown. This is why caution should be taken when evaluating clinical trial results reported from retrospective studies. Because these parameters are not known in advance (defined post hoc), they can be chosen to optimize the results from the individual study. Subsequent studies must therefore be performed using the same parameters to ensure the results can be replicated. The risk that the parameters of a test are optimized for an individual study increases with the number of parameters set. This is the so-called problem of 'overfitting'. With a sufficient number of parameters, every data point in a dataset can be perfectly modelled, inflating the reported statistics. However, this is unlikely to ever be replicated in a subsequent study without refitting these parameters again.

A prospective study, by comparison, is when patients are assessed using the investigational diagnostic when they present at the clinic and subsequently followed up to confirm their disease

status. Virtually all clinical studies used to support the approval of therapeutics are prospective, and generally medical device applications that require clinical data also include prospective data. The data gathered in prospective studies more closely reflects that seen in the real world because the company cannot control the patients being enrolled (outside of their inclusion/exclusion criteria). This will ensure the data gathered includes real world complicating factors, such as patients with variable histories and statuses.

## Clinical validity versus clinical utility

The clinical validity of a test is whether it can reliably identify a patient with a particular disease. The entirety of our discussion to this point has focused on this measure of a diagnostic's value. Trials examining the clinical validity of a test focus on determining reliable sensitivity and specificity statistics.

However, a different discussion of the value of a diagnostic is for its clinical utility. Clinical utility is whether a test can effectively change clinical practice to improve outcomes. There are many scenarios in which a test can be clinically valid but lack clinical utility. For instance, a test could accurately identify a disease, but this does not alter a doctor's course of action. Alternatively, a test could work, but the interventions taken by a doctor carry significant risk.

A real-world example of the discrepancy between clinical validity and clinical utility is in using the prostate-specific antigen (PSA) test. The PSA test is widely used for detecting prostate cancer. A pooled analysis found a sensitivity of 32% for low-grade cancer and 68% for high-grade cancer at a specificity of 85%.<sup>1</sup> However, the PSA test is not recommended by a number of national bodies setting clinical guidelines, including the US Preventive Services Task Force (USPSTF), which specifically recommends that it not be used in patients over 70 years old. In its recommendation, the USPSTF cited that PSA screening prevented 1.3 prostate cancer deaths per 1,000 men over approximately 13 years and there was no measurable reduction in all-cause mortality.<sup>2</sup> The benefit from testing was limited by the long course of the disease, the likelihood of other causes of death during that period and the risks associated with over-diagnosis and treatment.

For practical purposes, most diagnostics do not demonstrate clinical utility to support approval. In many cases, the utility of a diagnosis is already established. For instance, given the established utility of detecting HIV, new tests will not need to re-establish this, especially if they outperform their predecessors. In many other cases, the clinical utility is presumed by regulators. However, these studies can be very useful for bodies like the USPSTF that determine treatment guidelines, as outlined above. Additionally, inclusion in clinical guidelines is often a predicate for reimbursement, so these studies can be essential to the long-term market viability of a product.

## A selection of diagnostic market segments

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The diagnostic market is highly variable, with many independent market niches. These niches vary depending on the diseases and conditions quantified and often rely on widely disparate technology. Here we provide brief outlines of a selection of market segments of particular interest given the ongoing development of these markets.

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<sup>1</sup> Wolf AMD (2010) American Cancer Society guideline for the early detection of prostate cancer: update 2010. *CA Cancer J Clin* 60, 70-98.

<sup>2</sup> US Preventive Services Task Force (2018) Screening for Prostate Cancer; US Preventive Services Task Force Recommendation Statement. *J Am Med Assoc* 319, 1901-1913.

## Prenatal testing

There are a range of different prenatal tests available to assess both the parent and fetus. It is now routine in the US for one or both parents to be screened for markers of genetic disease before birth. There are a large number of companies offering these services, typically through CLIA labs. Historically, chromosomal abnormalities in the fetus were typically assessed using an amniocentesis, although there have been significant advances in the development of non-invasive prenatal testing (NIPT). In NIPT, the mother's blood is drawn and small quantities of fetal DNA are isolated and used for assessment. Two companies involved in NIPT testing are Natera and LabCorp. The global NIPT market has been estimated to reach \$3.6bn in 2019.<sup>3</sup>

Additionally, there are a range of tests attached to fertility services. An evolving market is that for preimplantation genetic screening and preimplantation genetic diagnosis. These are services aimed at screening embryos used in IVF for chromosomal abnormalities or genetic disease respectively. This should allow parents with a high-risk backgrounds to increase the potential for healthy birth. Hypothetically, this technology could enable screening for other, non-health-related traits such as sex. The market is still in its infancy, but there are over 200,000 IVF cycles per year that could be affected.<sup>4</sup>

## Circulating tumor DNA and liquid biopsy

Circulating tumor DNA (ctDNA) and liquid biopsy are experimental technologies being developed for the detection of cancer. CtDNA was born out of NIPT testing and is essentially the same technology: instead of trace fetal DNA being detected in the blood of a mother, trace tumor DNA is detected in a patient. The DNA of cancer cells is altered from that of the patients and when these cells die, they release DNA into the blood stream. With a liquid biopsy, instead of DNA, whole cancer cells (circulating tumor cells, CTCs) are isolated from a patient's blood. The technological hurdle is identifying and isolating the very small number of cancer cells in the blood. Both of these technologies could hypothetically be used to screen patients for the presence of cancer or be used to monitor patients with a prior cancer diagnosis. In theory the data collected from the DNA or cells could then also be used to identify the correct treatment regimen for the tumor based on the specific genetic markers present.

There are a large number of ctDNA and liquid biopsy technologies, all developing slightly different methods for DNA and cell isolation. These range from small private and microcap companies to multibillion dollar venture capital financed companies such as Grail, to projects at biotech's biggest players such as Janssen, which developed the CellSearch CTC test approved in 2004 (although it was subsequently sold to Menarini-Silicon Biosystems). JP Morgan optimistically estimated the combined liquid biopsy/ctDNA market would reach \$22bn by 2020 (in a 2015 report), although most subsequent estimates have been substantially below this figure. For instance, data from BIS Research (via Statista) estimates \$0.72bn in sales in 2016 and \$4.43bn in 2025.

## Colorectal cancer

Colorectal cancer (CRC) diagnostics require a special mention given the unique need in this space and the high degree of development toward meeting these unmet needs. CRC is one of the most common cancers, with approximately 1.36 million cases per year worldwide.<sup>5</sup> Prognosis is highly dependent on the stage at which the cancer is detected, highlighting the need for improved CRC screening program participation. According to the American Cancer Society the five-year survival

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<sup>3</sup> Allyse M, et al. (2015) Non-invasive prenatal testing: a review of international implementation and challenges. *Int J Women's Health* 7, 113-126.

<sup>4</sup> CDC 2015 Assisted Reproductive technology National Summary Report

<sup>5</sup> International Agency for Research on Cancer

rate for patients who have their cancer detected in the localized stage is 90%, compared to just 14% when there are distant metastases.<sup>6</sup>

Colonoscopy is the gold standard for CRC detection with 95% sensitivity and specificity, and it is recommended that patients receive the procedure every 10 years. However, the procedure is invasive and not devoid of risk. Both the pain associated with the procedure and the laxative prep can limit compliance. An alternative is yearly testing with the fecal immunochemical test (FIT), which is non-invasive, but has a low sensitivity (74%) and requires the handling of feces. Exact Sciences launched its fecal test Cologuard in 2015, which combines the immunochemical test from FIT with a set of DNA-based biomarkers. Cologuard outperforms FIT, albeit at high cost (\$649 list price). The product had sales of \$118m in Q318, although it is not yet profitable. There is significant effort to develop a blood-based test, which could be administered in the doctor's office, thereby being part of regular check-ups and increasing compliance.

**Exhibit 7: CRC screening test data comparison**

	Company	Type	Cost	CRC sensitivity	AP sensitivity	Specificity
Colonoscopy	Various	Invasive	\$1,200	95%	95%	95%
Sigmoidoscopy	Various	Invasive	\$600	50%	50%	92%
FIT	Various	Fecal	\$23	74%	24%	96%
gFOBT	Various	Fecal	\$5	40-70%	12-24%	93-98%
Cologuard	Exact Sciences	Fecal	\$649	92%	42%	87%
Epi proColon	Epigenomics	Blood	\$339	68-72%	22%	81%
Nu.Q™	VolitionRx	Blood	\$100 or less	74-91%	31%*	90%
Colox	Novigenix	Blood	\$300	78%	52%	92%

Source: FDA, Exact Sciences, World Gastroenterology Organization, Agency for Healthcare Research and Quality, Imperiale et al., Multitarget Stool DNA Testing for Colorectal-Cancer Screening, *N. Eng. J. Med.* 370, 1287-1297, CMS. Notes: AP=adenomatous polyps. \*Improved to 62% with a specificity of 90% with alternate panel, although CRC accuracy on this panel undisclosed.

## Consumer genomics

With the steadily lowering costs of genetic sequencing, it is now feasible for individuals to reasonably afford to sequence their own DNA. There have been a number of companies that have arisen offering this service, with the most prominent being 23andMe and Ancestry.com. These tests are purely elective and typically provide insight into a person's genealogy and an insight into certain genetic risk factors. The latter has been a point of contention with the FDA regarding the extent to which these tests constitute the diagnosis of a disease. The FDA previously banned 23andMe from providing genetic health assessments, but the latter has subsequently received 510(k) or de novo approval for a range of different test for genetic disease and risk factors. However, due to these barriers, there is a side market for service that interpret genomic data obtained in these tests. These include both formal analysis from a genetic counsellor or geneticist, as well as automated systems of questionable regulatory compliance. Estimates of sales of consumer genomics tests are generally small (\$140m for 2018 in Statista from Credence Research).

## Clinical microbiology screening

All medical facilities rely to some extent on the services of microbiology screening services. Microbiology involves detecting and identifying infectious organisms such as bacteria. This is essential for the diagnosis of the disease as well as identifying the correct antimicrobial to use in the event of an infection. The process of identifying a microorganism is typically done by hand by a trained microbiologist. A patient's tissue sample is plated on one of a number of different media and subsequently screened after a period of growth. A typical hospital-based microbiologist will screen hundreds of such samples per day. Historically, species were determined using a combination of culture conditions, staining and visual inspection, and this practice is still widespread. In recent times this can be supplemented with mass spectroscopy and DNA sequencing.

<sup>6</sup> American Cancer Society (2017) *Colorectal Cancer Facts & Figures 2017-2019*

There are significant efforts to streamline this workflow both to improve throughput as well as result turnaround times. Culturing a microbiological sample can take significant time when the prognosis for an infected patient is deteriorating. There are two main developments to this end. The first is to develop more highly automated systems to improve culture workflow and sample preparation, although these fundamentally do not change the identification process. Other companies are developing novel all-in-one systems, typically targeted at individual or small panels of pathogens to provide rapid diagnoses in short periods. For instance, T2 Biosystems has a system to identify bacterial and fungal infections from blood in a few hours without the need for separate culturing. Curetis's device similarly can identify common pneumonia and tissue infections in hours. The above systems are FDA approved, with the main hurdle being integration into hospital algorithms and achieving capital equipment placements.

## **Company profiles**

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The following pages provide individual profiles from a selection of diagnostic companies. These companies were chosen to represent the range of development stages and the diversity of technological approaches. We present how these companies' decisions are made to address the various market segments they intend to target.

# BioPorto Diagnostics

## Innovation in the detection of kidney injury

BioPorto is developing The NGAL test for the detection of acute kidney injury (AKI). The biomarker NGAL is elevated in response to kidney injury more quickly and more reliably than the standard-of-care, serum creatinine (SCr). The company already markets The NGAL test and other NGAL-based products for research purposes, and the biomarker is well understood and has been the subject of inquiry for 15 years. The company has two ongoing programs for adult and pediatric AKI, both of which should have approval decisions in 2019.

### The limitations of serum creatinine

AKI is almost exclusively diagnosed by monitoring levels of SCr, which has major limitations. In particular, changes in SCr only occur after significant damage has occurred, and may take 24 hours or more. There is therefore limited capacity to intervene to improve outcomes. Even in this case, SCr is not a particularly good marker for AKI: 51% sensitivity and 61% specificity to detect severe tubular injury (as determined by histology).

### Two ongoing NGAL programs

BioPorto is seeking approval of The NGAL test as a 'rule-out' test for AKI. Its most recent study, which was submitted to the FDA in 2018, had 17 sites and over 500 patients (results undisclosed). However, the agency requested additional information to support the rule-out claim and the company now expects a final decision in mid-2019. In a previous study, BioPorto found a 70–79% sensitivity and 73–77% specificity for stage 2–3 AKI, which is roughly consistent with other studies of the marker. The company is also engaged in a retrospective study of pediatric patient samples that it believes can support a separate application for pediatric AKI. In this case, the samples have already been tested using the company's NGAL ELISA kit, so the results are roughly known. Results from this study are expected in H119.

### There is a widespread need for innovation in AKI

AKI is a common complication to a wide range of medical disorders and treatments, from sepsis to surgery. It is therefore routine to test for AKI in the hospital setting, in particular the intensive care unit and the emergency room, if a risk has been identified. Around 2% of hospital in-patients and 40% of intensive care unit patients have AKI. The company has pre-existing distribution agreements with Roche and Siemens, through which we expect the product to be launched.

#### Historical financials

Year end	Revenue (DKKm)	PBT (DKKm)	EPS (DKK)	DPS (DKK)	P/E (x)	Yield (%)
12/14	18.7	(15.1)	(0.11)	0.0	N/A	N/A
12/15	20.4	(13.0)	(0.09)	0.0	N/A	N/A
12/16	20.7	(24.7)	(0.17)	0.0	N/A	N/A
12/17	25.2	(36.9)	(0.22)	0.0	N/A	N/A

Source: Company reports. Note: PBT and EPS as reported

#### Healthcare equipment & services

**Price\*** **DKK3.96**

**Market cap** **DKK616m**

DKK6.38/US\$

\*Priced at 25 January 2019

#### Share price graph



#### Share details

Code	BIOPOR
Listing	NASDAQ Copenhagen
Shares in issue	155.5m
Net cash end Q318 (pre November raise DKK39.5m net)	DKK13.5m

#### Business description

BioPorto is a diagnostic company focused on the development and marketing of antibodies and other products for research and diagnostics. This includes a portfolio of products marketed for research use and The NGAL Test, which the company has submitted to the FDA for the prediction of acute kidney injury.

#### Bull

- A faster, more reliable test.
- Existing relationships with major distributors.
- Short timeline to approval decision.

#### Bear

- Prior FDA hang-ups.
- Need to shift longstanding clinical practice.
- Distributor model is lower margin.

#### Analyst

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**BioPorto Diagnostics is a research client of Edison Investment Research Limited**

# Check-Cap

## Colon mapping pill device

Check-Cap is developing an ingestible capsule that provides a 3D scan of the colon for the detection of colorectal cancer and polyps. It uses a combination of low-dose x-ray imaging techniques to provide a map of the colon that can be subsequently reviewed by a physician. It does not require the burdensome laxative prep of a colonoscopy and the company is positioning it as an alternative for moderate risk populations.

### Colon imaging obtained at home

At its core, the C-Scan device is a miniaturised x-ray emitter that radially scans during its progress through the colon. The doses of x-rays used in the procedure are very small compared to those encountered during typical radiographic procedures. The device uses a combination of Compton backscattering and x-ray fluorescence to provide a detailed physical map of the colon. These data are transmitted to a battery-powered receiver unit that is adhered to the patient's back. The long-term goal is for this unit and the whole procedure to be administered at home and the data transmitted to a reviewing physician. The company estimates that a physician should be able to perform a diagnosis in 30 minutes or fewer, given the high quality of the data provided (similar to that of an x-ray or CT scan).

### Result improving with device refinement

The C-Scan device is undergoing a continuous improvement development cycle, with new features integrated on a rolling basis. These include both improvements to the device itself, integrating features such as motion tracking and updates to the scanning algorithm. An earlier clinical study to support CE marking showed a sensitivity/specificity of 44/89% for precancerous polyps. However, the most up-to-date version of the device showed results of 76/80% in a recent interim clinical readout (n=31). To date, the device has been tested in over 250 instances, with no safety concerns.

### Targeting launch in EU/Israel in 2019

The system has received CE marking in Europe and has been approved for marketing in Israel. The company is setting up manufacturing to support a commercial launch of the product in both regions in mid- to late 2019. The company expects the final results from the ongoing post-CE mark study to further support marketing claims for the launch. During this period, it also hopes to initiate studies of the device in the US. Investigational device exemption approval should be around the end of 2018 to support the launch of a US pilot study in 2019.

#### Historical financials

Year end	Revenue (\$m)	PBT (\$m)	EPS (\$)	DPS (\$)	P/E (x)	Yield (%)
12/14	0.0	(0.6)	(14.16)	0.0	N/A	N/A
12/15	0.0	(12.3)	(12.67)	0.0	N/A	N/A
12/16	0.0	(8.8)	(7.31)	0.0	N/A	N/A
12/17	0.0	(9.8)	(6.72)	0.0	N/A	N/A

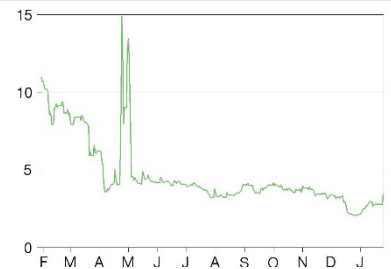
Source: Company reports

#### Healthcare equipment & services

**Price\*** **\$3.41**  
**Market cap** **\$18m**

\*Priced at 25 January 2019

#### Share price graph



#### Share details

Code	CHEK
Listing	NASDAQ
Shares in issue	5.3m
Net cash at Q318	\$17.6m

#### Business description

Check-Cap is a medical device company developing the C-Scan device for the detection of colorectal cancer and pre-cancerous polyps. The device consists of an ingestible scanning capsule and a data collection unit mounted to a patient's back. The product is CE marked and commercially approved in Israel.

#### Bull

- Innovative technology that provides a 3D map of colon.
- Avoids laxative prep of colonoscopy.
- Near-term commercialization expected.

#### Bear

- Device underperforms colonoscopy.
- US studies not yet initiated.
- Limited cash.

#### Analyst

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# Epigenomics

**Healthcare equipment & services**

## An approved molecular test for CRC

Epigenomics developed and markets the blood-based colorectal cancer (CRC) screening test, Epi proColon. The product measures the methylation of the Septin 9 biomarker in the blood, which increases in response to CRC. It was approved by the FDA in 2016 on the basis that a blood-based test could improve compliance over fecal tests in non-compliant populations. Sales for the first nine months of 2018 were €1.3m.

### Significant need for more CRC testing options

Despite a concerted effort, there are still major gaps in testing for CRC. The gold standard for detection of CRC is colonoscopy, which is highly effective (95% sensitivity/95% specificity) but expensive (approximately \$1,200) and invasive. The inexpensive (<\$30) fecal immunochemical test (FIT) is typically used as a first-line screening (74/96%), but requires handling feces and has a low compliance. Cologuard from Exact Sciences is also a fecal test, albeit with significantly improved statistics over FIT (92/87%), as well as significantly higher cost (\$650). The goal with Epi proColon (72/81%) is to provide a test that can be administered via a blood draw at a doctor's office and have significantly higher compliance over FIT and colonoscopy, which have adherence rates of 65% or lower.

### Biggest hurdle: Reimbursement

The sales ramp of Epi proColon has been slow, which is largely attributable to the hurdles the company has encountered with reimbursement. This resistance has been met in both the US with insurers and the state-sponsored screening programmes in Europe, which both opt for FIT testing given the significantly lower cost. The company is pursuing a legislative approach to achieving reimbursement, and the Centers of Medicare & Medicaid Services (CMS) was urged to reimburse for blood-based CRC tests in a recent appropriations report issued by Congress. The CMS also recently announced a provisional reimbursement rate of \$192/test.

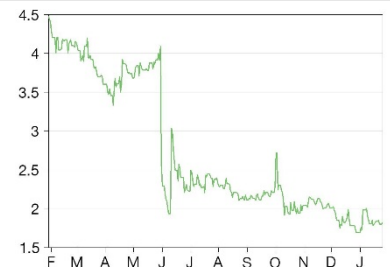
### Future directions: Lung and liver

The company is also developing blood-based tests for the detection of lung and liver cancer, using similar technology. The company received a CE mark for Epi proLung in late 2017 and the product is available in Europe, although it intends to optimise the product further. In addition, the company recently publicised results from a study using Septin 9 to detect liver cancer, which showed 91% sensitivity and 87% specificity, with is significantly better than the most common used biomarker now AFP (41–65%/80–94%). The liver test was recently CE marked and the company intends to start a clinical study in in 2019.

**Price\*** €1.82  
**Market cap** €66m

\*Priced at 25 January 2019

#### Share price graph



#### Share details

Code	ECX
Listing	XETRA
Shares in issue	36.0m
Net cash at Q318	€7.2m

#### Business description

Epigenomics is a developer of molecular diagnostics for the detection of cancer. It markets Epi proColon, a blood-based diagnostic for colorectal cancer, which is approved in the US and Europe. It is also developing a test using similar technology for the detection of cancer in the liver and lung.

#### Bull

- Test is approved and marketed in the US and Europe.
- No other approved blood-based CRC tests.
- Technology is adaptable to other cancers.

#### Bear

- Achieving reimbursement has been difficult.
- Product must compete with established technology.
- Additional capital likely to be needed before profitability.

#### Analyst

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#### Historical financials

Year end	Revenue (€m)	PBT (€m)	EPS (€)	DPS (€)	P/E (x)	Yield (%)
12/14	1.5	(8.9)	(0.65)	0.0	N/A	N/A
12/15	2.1	(9.2)	(0.52)	0.0	N/A	N/A
12/16	4.2	(12.3)	(0.55)	0.0	N/A	N/A
12/17	1.9	(10.4)	(0.44)	0.0	N/A	N/A

Source: Company reports



# Invitae

## Aiming to address all your genetic needs

Invitae is a genomics company aiming to laterally integrate the multiple disparate genetic testing markets. There is a range of different circumstances in which an individual undergoes diagnostic genomics, from prenatal screening to cancer diagnosis. However, despite different markets, the sequencing task is fundamentally the same. The company's goal is to provide a comprehensive sequencing solution across these markets, driving margins through volume.

### A one-stop genetic shop

The genetic testing market has developed exceptionally quickly, with a range of companies providing specialised solutions to individual genetic testing problems. Because of this, there are no fewer than 70 active companies filling these various individual niches. Invitae initially developed testing panels for hereditary markers for cancer, cardiology, neurology and rare diseases, but has subsequently expanded via acquisition into reproductive and maternal health. The physical process of obtaining sequences in each of these instances is fundamentally the same, and efficiency should improve with increased volume. However, the company has also invested in solutions to aid in the analysis aspect of the business at scale.

### Validation with biotech partnerships

The company has over 30 programs across the pharmaceutical industry generally to identify and test for genetic diseases that Invitae is targeting or marketing products for. For instance, it has a collaboration with Alnylam to test for hereditary ATTR amyloidosis with the goal of furthering Onpattro sales. Invitae has two additional collaborations with Alnylam to test for primary hyperoxaluria and acute hepatic porphyrias as well as collaborations with Biogen to test for SMA and Biomarin to perform testing in childhood epilepsy. In each case, the biopharma provides the financing for the arrangement so the test is provided at no cost.

### Moving toward genetic information management

Given the increase need for genetic services across the lifetime of patients, the company sees the market evolving from one in which an individual marker is interrogated for an individual disorder to one where a patient's entire genetic profile is obtained at an early stage, which is subsequently referenced throughout the individual's life. The company's lateral integration therefore fits into a broader strategy of being a manager of a patient's genetic profile. This has the potential to provide improved care by providing early insight into risks.

#### Historical financials

Year end	Revenue (\$m)	PBT (\$m)	EPS (\$)	DPS (p)	P/E (x)	Yield (%)
12/14	1.6	(47.5)	(56.14)	0.0	N/A	N/A
12/15	8.4	(89.8)	(3.18)	0.0	N/A	N/A
12/16	24.8	(100.3)	(3.02)	0.0	N/A	N/A
12/17	65.2	(125.2)	(2.65)	0.0	N/A	N/A

Source: Company reports

#### Healthcare equipment & services

**Price\*** **\$14.79**

**Market cap** **\$1,104m**

\*Priced at 25 January 2019

#### Share price graph



#### Share details

Code	NVTA
Listing	NYSE
Shares in issue	74.62m
Net cash at Q318 (prior to November equity/debt offering of \$5m net)	\$75.6m

#### Business description

Invitae is a genetic services company that provides testing for a range of heritable disorders such as cancer, cardiovascular, neurological and rare diseases. It also provides a suite of tests for reproductive and maternal health, and has a series of ongoing partnerships in biotech and pharma.

#### Bull

- Increasing market share in a growing market.
- Opportunity for consolidation in fragmented market.
- High-profile partnerships.

#### Bear

- Competitive market.
- Loss making despite revenue.
- Genetic information strategic goal has a long timeline.

#### Analyst

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# OraSure

**Healthcare equipment & services**

## An established oral testing business

OraSure has two main lines of business. First, its infectious disease division develops rapid point-of-care lateral flow devices, many using oral samples. The majority of revenue from this segment is for infectious disease tests and OraSure markets rapid HIV and HCV tests among others. Second, through two wholly-owned subsidiaries, DNA Genotek and CoreBiome, OraSure offers end-to-end services for the genomics and microbiome industry comprising study design, sample processing, sequencing and analysis.

### Strong growth of HIV OraQuick driven by ex-US

The company's longest-standing business has been the development of lateral flow rapid-testing devices for reliably detecting infectious diseases such as HIV, using saliva or blood, and HCV, using blood. The infectious disease division had combined global sales of \$42.5m for the first nine months of 2018. These tests, built on the OraQuick platform, are positioned as ideal for situations where routine blood testing is not viable, such as in the field, at home or in low infrastructure environments. The company's HIV test is the best-selling (\$32m) and fastest-growing (28% y-o-y) product from the OraQuick brand, with growth driven by adoption in the developing world, particularly Africa, which is supported by the Gates foundation.

### Leveraging the growth of genomics

The company reported revenue of \$56.3m from the sales of its genomics collection devices in the first nine months of 2018, primarily associated with the Oragene product. Oragene is the only FDA-cleared collection device containing a preservative that allows a person's saliva sample to be stabilized and transported at ambient temperatures to a sequencing facility for extraction and analysis. The development of a non-invasive (ie not blood based) solution for DNA collection that is supply-chain amenable is one of the developments that enables the rise of consumer genomics businesses. This commercial genomics segment remains the largest market for the product, amounting to \$48m in the first nine months of 2018.

### Microbiome in early stages

Following the rise of the consumer genomics industry, OraSure has identified other emerging markets that rely on standardized sampling, and microbiomics fits into that niche. There is growing evidence of the importance of the human microbiome in health, although the microbiome-testing market remains in its infancy. The company has developed products to collect and stabilize microbiome samples. Sales were \$4.8m over the first nine months of 2018, but growing at 102%.

#### Historic financials

Year end	Revenue (\$m)	PBT (\$m)	EPS (\$)	DPS (\$)	P/E (x)	Yield (%)
12/14	106.5	(4.3)	(0.08)	0.00	N/A	N/A
12/15	119.7	8.8	0.14	0.00	88.8	N/A
12/16	128.2	20.3	0.35	0.00	35.5	N/A
12/17	167.1	41.0	0.51	0.00	24.4	N/A

Source: Company reports

**Price\*** **\$12.43**
**Market cap** **\$761m**

\*Priced at 25 January 2019

#### Share price graph



#### Share details

Code	OSUR
Listing	NASDAQ
Shares in issue	61.25m
Net cash* at Q318	\$192.1m

\*Includes short-term investments

#### Business description

OraSure is a developer of rapid point-of-care diagnostics for infectious disease and DNA/RNA collection devices. Its main products are the OraQuick lateral flow tests for HIV and HCV and the Oragene collection device used across the consumer genomics industry.

#### Bull

- Profitable and growing.
- Multiple established product lines.
- History of successful product development.

#### Bear

- Domestic infectious disease testing slowing.
- New technology threat in collection business.
- Microbiome testing in early stages.

#### Analyst

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# Quotient

## Bringing innovation to transfusion testing

Quotient has leveraged its knowledge of this market to develop the MosaiQ platform, a high-throughput screening device that uses microarray technology to perform blood typing and disease screening on thousands of samples per day. The product was recently submitted for its first CE mark for a blood group antigen panel and Quotient hopes to place the first units in Europe in 2019. It also intends to complete further US and EU field studies in 2019 to support expanded testing capacity for launch in 2020.

### The MosaiQ system: High throughput and versatile

All blood entering the transfusion supply chain must be tested for its blood type and for a series of diseases such as HIV and hepatitis. Historically, Quotient has sold reagents for this business that are used in testing platforms developed by other companies. The market for these platforms is dominated by a small number of large players such as Beckman Coulter, Abbott and Bio-Rad. However, Quotient recently developed its own proprietary platform with the goals of unifying all the required tests on a single low cost platform. The MosaiQ system uses microarray cartridges that both limit the amount of fluid handling needed to test a blood sample and provide efficiency and the modularity to adapt the system to new panels of tests.

### Initial launch in 2019, expanding in 2020

The company expects to launch the MosaiQ system in Europe in 2019, which will include the capital equipment platform as well an initial blood typing microarray. This initial panel was submitted for CE mark approval in September 2018 and includes a basic panel of the most relevant blood group antigens. The panel achieved high concordance with standards for both antigens and antibodies (99%+ and 97.3%). The company hopes to expand the number of antigens tested and submit for approval in both the US and Europe by the end of 2019. Concurrently, it will be seeking approval for an initial disease array for launch later in 2019.

### Expansion potential into other areas of blood testing

The potential of the MosaiQ system is realized in the capacity to develop new microarray panels that can then be integrated seamlessly into the existing blood testing workflow. There is therefore significant potential for Quotient to move into other areas of blood testing such as molecular disease testing (for congenital diseases) and patient screening (as opposed to the transfusion screening). The company is currently undergoing preclinical development in both these areas, which could represent significant increases in its addressable market.

#### Historical financials

Year end	Revenue (\$m)	PBT (\$m)	EPS (\$)	DPS (\$)	P/E (x)	Yield (%)
12/14	17.7	(50.1)	(4.00)	0.00	N/A	N/A
12/15	18.0	(33.9)	(1.73)	0.00	N/A	N/A
12/16	20.1	(85.1)	(3.02)	0.00	N/A	N/A
12/17	23.9	(83.0)	(2.02)	0.00	N/A	N/A

Source: Company reports

## Healthcare equipment & services

**Price\*** **\$8.24**

**Market cap** **\$447m**

\*Priced at 25 January 2019

#### Share price graph



#### Share details

Code	QTNT
Listing	NASDAQ
Shares in issue	54.3m
Net debt at Q318	\$53.5m

#### Business description

Quotient is a transfusion diagnostics company that has historically sold reagents for the transfusion business, but recently developed the MosaiQ system, a high-throughput blood typing and serological screening platform utilizing microarray technology.

#### Bull

- Platform provides increased versatility and throughput.
- Existing connections in the transfusion business.
- High capacity for further expansion of tests offered.

#### Bear

- Competition from large established players.
- Timelines for capital equipment replacement can be long.
- High debt load.

#### Analyst

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# Telix Pharmaceuticals

## Targeted radiation to image and treat cancer

Telix has assembled a portfolio of promising molecularly targeted radiation (MTR) therapeutic and imaging products for three different cancers. Each product has been validated by clinical studies or compassionate use in patients, thus reducing development risk. Preparations for a confirmatory Phase III study for kidney cancer imaging agent TLX250-CDx and for multiple Phase I/II studies of other agents are underway. It has begun commercialising an investigational prostate cancer imaging kit in the US, and is developing plans for a short pivotal study to allow full approval.

### A portfolio of advanced products

Telix's MTR products comprise a radioactive isotope attached to either an antibody or small molecule that targets delivery to kidney, prostate or brain cancers (TLX250, TLX591/illumet and TLX101, respectively). Telix has enhanced a number of the acquired products, and has revised and updated the development strategies to account for market developments. Modifications to individual products include changing to a different radionuclide that generates sharper images or tweaking the targeting antibody to improve pharmacodynamics and ease of manufacture.

### TLX250-CDx: Identifying dangerous kidney cancers

TLX250-CDx has previously demonstrated high sensitivity and specificity for imaging clear cell renal cell carcinoma, the most common and aggressive form of kidney cancer, in a Phase III study. The product has been enhanced by switching to the <sup>89</sup>Zr radionuclide that improves signal to noise ratio and produces clearer images. The confirmatory ZIRCON Phase III study has received regulatory and ethical approval to commence recruitment at the first trial site in Australia, with the first sites in Europe expected to come on line before the end of the year.

### Commercialisation of PSMA imaging agent underway

Telix continues to make impressive progress developing its portfolio of products. Commercialisation of illumet (TLX591-CDx) as an investigational product for imaging prostate tumours is underway in the US, with Cardinal Health appointed as a sales and distribution agent and scale-up manufacture of the kit in the US initiated. It is developing plans for a Phase III study based on blinded re-reads of existing scans, which could potentially allow a US filing in 2019. Following the acquisition of ANMI in November, it is pursuing worldwide development of illumet.

### Well funded to achieve milestones

Development of some portfolio products stalled under previous ownership due to lack of funds or other roadblocks. Telix is well funded to progress key projects to milestones. Management has extensive experience developing radio-therapeutics.

#### Historical financials

Year end	Revenue (A\$m)	PBT* (A\$m)	EPS (c)	DPS (c)	P/E (x)	Yield (%)
12/17	0.4	(6.4)	(5.0)	0.0	N/A	N/A

Source: Telix Pharmaceuticals

#### Healthcare equipment & services

**Price\*** **A\$0.74**  
**Market cap** **A\$157m**

\*Priced at 25 January 2019

#### Share price graph



#### Share details

Code	TLX
Listing	ASX
Shares in issue	212.3m
Net cash at 30 September 2018	A\$37.3m

#### Business description

Telix Pharmaceuticals is a Melbourne-headquartered global biopharmaceutical company focused on the development of diagnostic and therapeutic products based on targeted radiopharmaceuticals or molecularly targeted radiation.

#### Bull

- Commercialisation of illumet investigational agent for prostate cancer imaging underway in the US.
- TLX250-CDx demonstrated high sensitivity and specificity in a previous kidney cancer Phase III.
- Well-funded to reach development milestones.

#### Bear

- Competing PSMA diagnostic imaging agents in development.
- FDA may request a prospective illumet Phase III, which could delay filing by one or two years.
- Value creation dependent on successful R&D progress.

#### Analysts

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**Telix Pharmaceuticals is a research client of Edison Investment Research Limited**

# TruScreen

## Fast and objective cervical cancer screening

TruScreen is focused on the effective commercialisation of its second-generation TruScreen2 optoelectronic cervical cancer screening device, which has already been launched in key target markets. The device provides objective and real-time cervical cancer screening assessments and requires only limited training for the operator, which makes it well-suited for developing countries.

### Fast and objective cervical cancer screening

TruScreen2 is a rapid, easy-to-use screening tool that provides real-time objective detection of precancerous and cancerous cervical cells. Direct comparison studies have consistently shown the first-generation TruScreen1 device has a higher sensitivity (70–79%) than the widely used Pap test (36–73%) for detecting high-grade precancerous changes, the key goal of cervical cancer screening programmes. Interim analysis from a clinical assessment of TruScreen2 reported improved sensitivity. Specificity of both TruScreen devices is acceptable.

### Well-suited to low healthcare-resource countries

We see the main commercial opportunity for TruScreen as underserved, often rural and regional, populations in developing countries. The minimal training required and instantaneous result with TruScreen are important advantages in regions that often do not have established laboratory infrastructure or processes for recalling patients to report test results several days later.

### Approvals and distributors in place to drive growth

The second-generation TruScreen2 device gained CE Mark approval in April 2016 and CFDA approval in China in December 2017. Distributors have been appointed in 24 countries. Sales in FY18 were modest, in part due to the delayed approval in China, but sales grew by 523% in H1 FY19 to NZ\$1.4m. In September, TruScreen received an initial order from the National Aids Council of Zimbabwe to supply NZ\$0.5m of TruScreen systems for a pilot programme providing cervical cancer screening to HIV-positive women. Africa represents a major market opportunity.

### Gaining traction in key China market

China is the primary market for TruScreen, with growing demand and a number of initiatives underway. TruScreen's devices have been selected as the primary screening tool for up to 50 planned clinics, with the first eight now installed. A large-scale evaluation with the Centre for Disease Control in at least 12,000 women across eight provinces is expected to be completed by the end of FY19. Separately, a major programme in Xinjiang Province will see TruScreen installed in 190 hospitals.

#### Historical financials

Year end	Revenue (NZ\$m)	PBT* (NZ\$m)	EPS (c)	DPS (c)	P/E (x)	Yield (%)
03/16	1.6	(1.3)	(0.8)	0.0	N/A	N/A
03/17	1.4	(3.5)	(2.1)	0.0	N/A	N/A
03/18	2.2	(4.2)	(2.1)	0.0	N/A	N/A

Source: TruScreen accounts

The diagnostics sector | 29 January 2019

#### Healthcare equipment & services

**Price\*** NZ\$0.19  
**Market cap** NZ\$41m

\*Priced at 25 January 2019

#### Share price graph



#### Share details

Code	TRU
Listing	NZAX
Shares in issue	216.9m
Net cash at 31 October 2018	NZ2.3m

#### Business description

TruScreen's real-time cervical cancer technology measures electrical and optical signals from cervical tissue and uses a sophisticated proprietary algorithm framework to distinguish between normal and abnormal tissue, to identify precancerous changes, or cervical intraepithelial neoplasia.

#### Bull

- Regulatory approvals, distributor relationships in place and initial sales achieved.
- Instant result readout and better sensitivity than Pap test.
- Growing traction in key China market.

#### Bear

- Increased utilisation of HPV testing may affect adoption by government screening programmes.
- Sales are below break-even level.
- TruScreen test specificity is below the ideal level.

#### Analyst

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# VolitionRx

## Blood-based cancer screening

VolitionRx is developing the Nu.Q™, cell-free nucleosome-based blood test for a series of different cancers. The test detects the fragments of chromosomes that are released after cancer cell death and uses the modifications present on these structures to rule out other diseases. This provides a non-invasive method of detecting cancer and because the technology is based on the routine ELISA test, it is easily integrated into existing protocols at a low cost. VolitionRx has a broad R&D program and expects to announce major milestones in coming months, culminating with CE marking and launch of both colorectal cancer (CRC) triage and frontline screening tests in Europe, potentially in 2019.

### Lead program is CRC screening

The company is in clinical trials to support the marketing of the test for colorectal cancer in Europe, Asia and the US. The program in Europe includes development of a frontline CRC screening test and a triage test to be administered after a positive fecal test. Key upcoming readouts potentially in 2019 include results of the updated Nu.Q™ CRC triage test and CE marking, and the final panel for the Nu.Q™ CRC frontline screening test based on 4,300 samples, which will be validated in a 12,000+ sample study and a CE mark obtained.

### Start of commercial phase with research use sales

In May 2018, VolitionRx announced a global sales and distribution agreement with Active Motif that is distributing kits based on VolitionRx's technology for research use. While VolitionRx focuses on cancer, the Nu.Q™ assays can be used in other conditions. This is not likely to lead VolitionRx to break even; however, the benefits of such business include a high-margin royalty stream, increasing awareness of the nucleosomics technology within the research community and obtaining insights into various other applications for Nu.Q™ assays.

### Additional indications

Newer application areas in the R&D pipeline include prostate cancer, with positive first data published in August 2018; a follow-up trial is planned for 2019. First results from the endometriosis trial are due in the coming months after the blood sample collection was completed in August. Endometriosis is a slowly progressing, difficult to diagnose and potentially serious condition in women, where a non-invasive test could be an advantage presuming sufficient accuracy. In addition, VolitionRx is exploring its technology's potential in the animal health market.

#### Historical financials

Year end	Revenue (\$m)	PBT* (\$m)	EPS* (\$)	DPS (\$)	P/E (x)	Yield (%)
12/14	0.0	(8.4)	(0.62)	0.0	N/A	N/A
12/15	0.0	(9.7)	(0.54)	0.0	N/A	N/A
12/16	0.0	(12.5)	(0.54)	0.0	N/A	N/A
12/17	0.0	(15.1)	(0.57)	0.0	N/A	N/A

Source: Company reports

#### Healthcare equipment & services

**Price\*** **\$2.33**  
**Market cap** **\$82m**

\*Priced at 25 January 2019

#### Share price graph



#### Share details

Code	VRNX
Listing	NYSE American
Shares in issue	35.3m
Net cash at end Q318	\$14.2m

#### Business description

VolitionRx is a life sciences company developing novel, simple-to-use, blood-based tests to diagnose a broad range of cancers and other conditions by identifying and measuring nucleosomes in the blood stream. The primary focus is to develop the Nu.Q™ family of blood-based diagnostics tests for colorectal cancer.

#### Bull

- A blood-based test has clear advantages over existing colorectal cancer screening methods (fecal tests, colonoscopy).
- Potential for additional applications.
- Partnership with Active Motif could help to increase awareness of the technology.

#### Bear

- Test is still in development phase (not clinical phase), so some development risk remains.
- Significant cash flows only expected once tests are launched in Europe 2019 and later in the US.
- Competitors Epigenomics and Exact Sciences encountering barriers to adoption of their tests, although Volition's test is differentiated.

#### Analysts

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