PharmaVentures
the deal experts

Diagnostics

More important than ever, but there's still a way to go

September 2021

Diagnostics

More important than ever, but there's still a way to go

Just the other week, it was announced that Illumina had acquired GRAIL (subject to approval from the regulators), a company it formed in 2016 and spun out. Illumina retained a 12% stake in the business and has decided the time is now right to bring it back into the fold. History repeats itself in that the deal took place (as with most diagnostics) at a point at which the technology was in market, or at least market ready. The GRAIL, Galleri diagnostic test, is available as a CLIA waived test to detect 50 different cancers before symptoms appear. The test is yet to be FDA approved or reimbursed and currently costs just under $1000, but this milestone achievement, off the back of more than $2B in investment and a research effort that covered more than 100,000 people, was sufficient to make Illumina want to pay around $8B to reacquire the business.

Is this the first sign that diagnostics are poised to take a much more prominent and potentially game changing role in directing a personalised medicine approach and leading the utility of tailored therapeutic regimens that clinicians and payers can both get behind, or just the next step in providing more things that doctors can test for and base their decision on? If we take a look at the direction diagnostics technologies are taking and those on the horizon, we can get some insight into what benefits might be achieved and who for.

The underlying principle in diagnostics is that obtaining some data relating to a disease or condition that is actionable in a potentially positive way is beneficial for the patient and helps the clinician make the best treatment decisions. It has followed that measuring more things that we think are disease related and having more data to evaluate should lead to better understanding and better decisions, with the ultimate beneficiary being the patient.

Diagnosing and treating infectious diseases is perhaps the purest and simplest diagnostic/treatment axis. Identify the infective agent, give the drug that kills it, patient is cured. It becomes problematic when bacteria become resistant to the drugs, and viruses emerge to which we have no immediate effective treatment (HIV historically, and more recently COVID-19). Other diseases where the biology is less well understood, cancer, neurological and autoimmune diseases are good examples and are much more complex and difficult to deal with. Identifying the disease may be quite readily achievable but deciding what

Diagnostics

More important than ever, but there's still a way to go

to do for the best in terms of treatment is far more difficult, and simply measuring more biomarkers that may have more or less relevance for an individual patient's treatment can just make the clinician's job harder rather than easier. So, the all-encompassing term "diagnostics" covers a wide area and, in reality, there are two arms; diagnosis/monitoring of the disease and treatment selection. There is, of course, the whole other related discipline of preventative medicine, where we need accurate determination of things that are likely to happen to an individual before they occur. We still come back to the common link in all scenarios, of having to have something we can action as a result of the knowledge gained that will improve the outcome for the individual.

The subject area is too large to cover in this article, so let's focus on one of the most active areas, oncology.

Diagnostic testing for oncology started to become routine and useful with the discovery and development of protein biomarkers such as CEA, AFP, CA15-3, PSA etc., whose presence or elevation in blood or tissue was indicative of different cancers. Their sensitivity and specificity was not spectacular but they still provided a useful aid to the clinician in diagnosis and treatment monitoring. Many are still in use today. The mainstay of diagnostics in oncology for many years now has been single gene testing using PCR technologies, where the detection of specific genes and mutations of clinical relevance has been standardised across multiple platforms and providers. In NSCLC, where there is much activity in both therapeutics and diagnostics, it has been routine since the early 2000s to test for EGFR exon 19 deletions or exon 21 L858R mutations, and although when they were first known about there was no associated treatment, the first generation TKIs erlotinib and gefitinib were approved in the 2010's and since then 2nd and third generation TKIs have been approved, with Osimertinib specifically targeting T790m mutations and has extended progression free survival times to almost 19 months compared to 10 months for gen 1 molecules. Treatments for other molecular subsets of lung cancer are also being developed based upon the understanding of major driver pathways, such as EGFR, PI3K/AKT/mTOR, RAS–MAPK, and NTRK/ROS1. Many drugs targeting these pathways have been developed and shown clinical benefits such that around 30% of patients can receive an improved treatment based upon the diagnostic determination of the mutation characteristics of their tumour. Whilst this is of significant patient benefit, we still know that patients become resistant to TKIs and will relapse; multiple pathways are involved, and how to target these and when is still unclear. Combination therapies are being trialled and there is much activity in combining TKIs, chemotherapies and radiotherapy with checkpoint inhibitors.

Checkpoint inhibitors are revolutionising cancer treatment, and yet the accompanying diagnostics are still quite crude. PD-L1 testing has not, to date, proven itself to be a reliable indicator of response in most cases. Tumour mutational burden (TMB) has also been investigated as a predictive marker for checkpoint inhibitor use but work to date has shown variability in its applicability, and although the FDA approved pembrolizumab, in solid tumors with a tumor mutational burden (TMB) ≥ 10 mutations/megabase based on the FoundationOne CDx assay, there are still concerns over the thresholds used to predict therapy response across a range of solid tumours with some instances where high TMB does not predict response.

Where do we go from single gene detection and TMB for better tests and improved outcomes?

One obvious place to go would be to implement NGS as a routine methodology to determine mutational status and better tailor treatments. Whole genome sequencing (WGS) can now be achieved rapidly in a single lab for around $1000. This may look like it is now within the realm of commercial mass testing viability. However, it is still relatively expensive, and does not yet reliably detect low level mutations in mixtures of tumour and normal cells. Furthermore, the number of mutations

detected is potentially overwhelming, with anywhere from around 1,000 to 15,000 mutations per patient, most of which are either irrelevant, of unknown importance or, even if known about and associated with NSCLC, may not guide any available therapeutic approach.

Whole exosome sequencing (WES) provides an alternative to WGS and is used currently as an interrogation tool in cancer. Unlike WGS it is limited to 5% or less of the genome that lies in the exons of genes. Whilst quicker and cheaper than WGS, the level of analysis possible means that low frequency clinically relevant mutations can be missed.

RNA-Seq methods permit sequencing of mRNA and small RNAs as well as RNA transcripts themselves. It can also pick up gene fusions and noncoding RNAs (ncRNAs) and microRNAs which have been implicated in cancer pathogenesis and may have diagnostic and/or prognostic value. Some of these are novel, and proving their importance and prevalence in cancer can take significant amounts of time and resource as major pharma and diagnostics companies rely heavily on well-known annotated databases to validate presence and prevalence of mutations. However, this is clearly some way from routine clinical use and commercial application.

Perhaps molecular analysis is not the whole answer, so what else is there?

Whilst more sophisticated methods of molecular analysis are generating ever more data to analyse, it may not provide us with the most useful answers in diagnosis and therapy selection. There is undoubtedly a combination of genetic and environmental components involved in diseases and responses to therapy, so what else is being measured beyond genomics in an attempt to improve patient outcomes? Liquid biopsy technologies are something of a half-way house between tumour mutational analysis and blood-based protein detection. Sensitivity is a key requirement and many PCR based methods are unable to detect infrequent copy numbers in a sample against background noise.

Improvements have been achieved by several companies implementing blocker sequences to limit amplification of wild type DNA, and the South Korean company Genecast has developed a novel polymerase system that only amplifies mutant DNA to improve sensitivity.

Aside from liquid biopsy, there are a few other analytical technologies which may prove to be useful in combination with genetic testing in diagnosis, prognosis and treatment selection. One such technology has been developed by the Dutch biotech Pamgene who has been applying its kinome analysis platform for many years to help pharma companies identify and validate kinases and phosphatases involved in specific pathways for drug discovery. The company realised that patients generate specific kinome profiles which can indicate how an individual patient is likely to respond to a particular therapy. They have developed the IOpener™ platform, combining kinase profiling with sophisticated algorithms, which has already achieved much better indication of response to checkpoint inhibitors in a range of cancers and, combining their approach with IHC detection of PD-L1 and other genetic markers, may provide even better predictive capability. Another similar approach is being developed by Kinomica using their KScan™ LC-MS/MS approach, incorporating machine learning to elucidate kinase activity in patients. The company has successfully applied the technology to increase the number of patients who are likely to respond to the Novartis drug midostaurin.

Isn't this an ideal area for AI to be applied?

The two companies above are both applying sophisticated algorithms and /or machine learning to make sense of the data being generated by their respective platforms. We have also seen the potential for data generation on a massive scale by NGS and related technologies. NGS will, like many technologies that have preceded them, become quicker and cheaper to use. So, is AI being applied and how will it bring benefits? One of the issues faced by having greater numbers of ever improving

Diagnostics

More important than ever, but there's still a way to go

diagnostics is that more information isn't necessarily better and too much information can impair a clinician in making the best decisions for a patient. It has been reported that Physicians spend a lot of time studying the "Impression and Plan" zone of the notes (67% of total reading time), while "Laboratory Results" was screened for only 9 seconds! Diagnostics laboratories have been earlier adopters of computer aided systems since the 1980's. with use of Computerized Clinical Decision Support Systems (CCDSS) from within Laboratory Information Systems (LIS). However, these are more "expert rules" systems based around traditional "if/then" type scenarios rather than Machine Learning or Deep Learning AI systems. It is not an insurmountable step from one to the other, but it will take time, as the consequences of an error in an AI algorithm can have significant impact for multiple patients compared to one false negative in a traditional diagnostic test.

AI has been implemented in pattern recognition in cardiovascular applications to aid clinicians as well as breast, ophthalmic, respiratory and dermatology radiographs and image analysis. Results are at least as good as the best expert opinions. Other settings where it is believed early wins for AI could be seen are in test selection to identify which tests actually deliver changes in patient care. Use of AI demonstrated that reduction of up to 44% of test orders could be achieved and the orders were made up to 4 hours sooner than if they were done by a clinician. Interpretation of results may be another area where gains can be achieved. One model system was able to predict sepsis onset 6 hours sooner. In oncology, it is believed AI will help identify new biomarkers from the wealth of omics data that is being generated but there is clearly some way to go before AI modalities are routinely in use in clinical oncology settings.

Recent Deal Activity in Diagnostics

A look at deal activity can give an indication of the near-term horizons of diagnostics technology, as assets are generally licensed at or near to market. There are always exceptions; Geneweave, for example, on which Roche placed an initial bet of $190M for the antibiotic resistance technology company in 2015 when it was thought to be close to commercialisation but still does not seem to have emerged fully.

Table 1 shows diagnostics deals over 2020/2021 with total deal values of over $100M.

Table 1
Diagnostics deals over 2020/2021 with total deal values of over $100M.

Deal Title	Total Deal Value (USD M)	Indication	Deal participant summaries
Thermo Fisher Scientific to acquire Qiagen	11595.00	Infection	Diversified diagnostics, reagents and instrumentation suppliers. Deal failed – insufficient shareholder support.
Illumina acquires GRAIL	8000.00	Cancer	Illumina, Inc. provides sequencing and array-based solutions for genetic and genomic analysis. GRAIL develops Galleri, a screening test for asymptomatic individuals over 50 years of age; and DAC, a diagnostic aid for cancer test to accelerate diagnostic resolution for patients for whom there is a clinical suspicion of cancer.
Exact acquires Thrive Earlier Detection	2150.00	Cancer	Exact Sciences Corporation provides cancer screening and diagnostic test products. Thrive develops CancerSEEK, a liquid biopsy test that interrogates genomic mutations in tumour DNA and protein markers in plasma
Roche to acquire GenMark Diagnostics	1800.00	Infection	Roche Diagnostics develops diagnostic products for a wide range of indications. GenMark Diagnostics, Inc. designs and manufactures multiplex molecular diagnostic solutions.
DiaSorin to acquire Luminex	1800.00	Not Applicable	DiaSorin S.p.A. develops, manufactures, and distributes immunodiagnostic and molecular diagnostics testing kits across multiple indications. Luminex Corporation develops, manufactures, and sells proprietary biological testing technologies and products for the diagnostics, pharmaceutical, and research industries.
Invitae acquires ArcherDX	1400.00	Cancer	Invitae Corporation offers genetic tests in multiple clinical areas. ArcherDX, Inc. develops research use only and personalized cancer monitoring products for therapy optimization and cancer monitoring.
Hologic acquires Mobidiag	808.00	Not Applicable	Hologic, Inc. develops, manufactures, and supplies diagnostics products, medical imaging systems, and surgical products for women's health.

Diagnostics

More important than ever, but there's still a way to go

Deal Title	Total Deal Value (USD M)	Indication	Deal participant summaries
IQVIA acquires remaining Quest Diagnostic's minority share in Q2 Solutions	760.00	Diversified	Hologic, Inc. develops, manufactures, and supplies diagnostics products, medical imaging systems, and surgical products for women's health. Mobidiag Oy, develops and provides molecular diagnostic assays for the diagnosis of pathogenic microbes causing severe infections.
Agilent acquires Resolution Bioscience	695.00	Cancer	Agilent's Diagnostics and Genomics segment provides arrays for genomic analysis, immunohistochemistry, in situ hybridization, and hematoxylin and eosin staining and special staining instruments, consumables, and software for quality control analysis.
Veracyte acquires Decipher Biosciences	600.00	Cancer	Veracyte, Inc. operates as a genomic diagnostics company primarily offering solutions in lung cancer. Decipher Biosciences, Inc., develops and sells genomic testing products in prostate cancer.
PerkinElmer acquires Oxford Immunotec	591.00	Infection	PerkinElmer, Inc. provides products, services, and solutions to the diagnostics, life sciences, and applied services markets worldwide. Oxford Immunotec offers ELISPOT assays for T cell measurement which is used for diagnosing infection with Tuberculosis.
Thermo Fisher Scientific acquires Mesa Biotech	550.00	Infection	Thermo Fisher is a global diagnostics, reagents and instrumentation manufacturer and supplier. Mesa Biotech, Inc. designs, develops, manufactures, and commercializes molecular diagnostic tests. It offers a PCR-based rapid point-of-care testing platform for detecting infectious diseases, including SARS-CoV-2, Influenza A and B, respiratory syncytial virus, and Strep A.
Exact Sciences acquires Base Genomics	416.50	Cancer	Exact Sciences Corporation provides cancer screening and diagnostic test products. Base Genomics Limited develops a DNA methylation technology. named TAPS that simultaneously generates genetic and epigenetic information. It has application in early cancer detection, patient monitoring, longitudinal epigenetic studies, companion diagnostics, biomarker discovery, non-invasive prenatal testing and infectious diseases, including COVID-19.
NeoGenomics to acquire Inivata	390.00	Cancer	NeoGenomics, Inc. operates a network of cancer-focused testing laboratories in the United States, Europe, and Asia. Inivata Is a clinical cancer genomics focused on developing applications for circulating tumor DNA (ctDNA) analysis to improve cancer testing and treatment.
Bio-Techne acquires Asuragen	320.00	Cancer	Bio-Techne's Diagnostics and Genomics segment provides diagnostic products, for regulated diagnostics market, exosome-based molecular diagnostic assays, advanced tissue-based in-situ hybridization assays for spatial genomic and tissue biopsy analysis, and genetic and oncology kits for research and clinical applications; and nucleic acid analysis products for use in diagnostic or research applications, as well as instruments and process control products. Asuragen offers reagent kits for complex testing in genetics and oncology applications. The company also develops and commercializes companion diagnostics for investigational allele-selective therapeutic programs targeting Huntington's disease.
Veracyte acquires HalioDx	313.38	Cancer	Veracyte, Inc. operates as a genomic diagnostics company primarily offering solutions in lung cancer. HalioDx SAS designs and develops in-vitro diagnostic products in the immuno-oncology field.
Hologic acquires Biotheranostics	232.50	Cancer	Hologic, Inc. develops, manufactures, and supplies diagnostics products, medical imaging systems, and surgical products for women's health. BioTheranostics, Inc, discovers, develops, and commercializes proprietary molecular-based diagnostic, prognostic, and predictive tests that provide physicians with information to guide them in cancer treatment.
Hologic acquires Diagenode	159.00	Infection	Hologic, Inc. develops, manufactures, and supplies diagnostics products, medical imaging systems, and surgical products for women's health. Diagenode S.A. develops and manufactures instruments and reagents systems for life science research and molecular diagnostics markets.
PerkinElmer to acquire IDS	155.00	Unknown	PerkinElmer, Inc. provides products, services, and solutions to the diagnostics, life sciences, and applied services markets worldwide. IDS develops, manufactures, and markets immunoassays and analyser technologies in endocrinology specialty testing and complementary fields.
Quest Diagnostics acquires Blueprint Genetics	110.00	Other/ Miscellaneous	Quest Diagnostics Incorporated provides diagnostic testing, information, and services across a range of indications. Blueprint Genetics Oy provides clinical genetics testing followed by blueprint and customized next-generation sequencing services.

Diagnostics

More important than ever, but there's still a way to go

Figure 1 shows the total $ amounts for diagnostics deals by therapeutic area. As we can see, the vast majority of money is being spent on cancer diagnostics, with a significant amount also spent on infection. This is not surprising, given the current COVID-19 pandemic.

Total $ amounts for diagnostics deals by therapeutic area

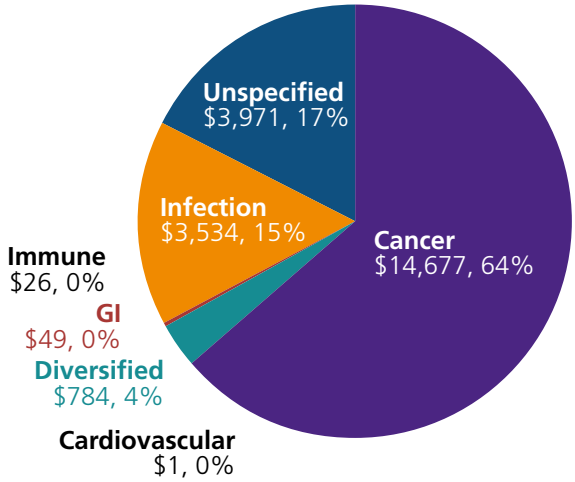

Figure 1

Figure 2 shows the deals and their total deal values across the same time period. We can see the majority of the deals are below $1B with a small number of larger deals and one mega-deal of $8B (Illumina's acquisition of GRAIL).

Total deal values

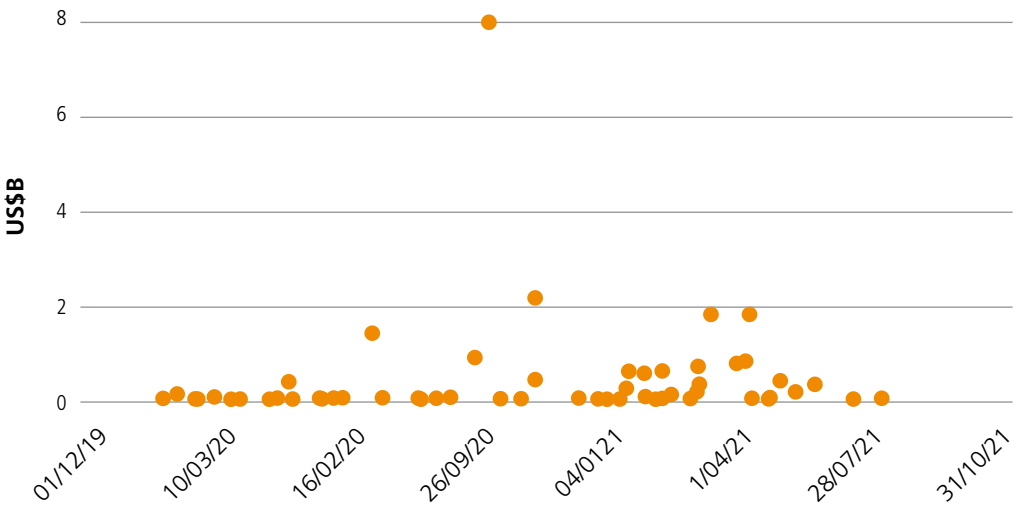

Figure 2

Diagnostics

More important than ever, but there's still a way to go

Concluding Remarks

Diagnostics are clearly improving and enabling better clinical decisions to be made, especially in oncology where mutation detection is enabling much more personalised approaches to treatment. There is still a long way to go, but combinations of diagnostics tests and technologies (beyond genomics) is giving a more detailed picture on which to base treatment decisions and we are in an age where it is not just about diagnosing the disease but also selecting the most appropriate treatment and personalising it. The impact of AI has yet to be really seen and it is likely to give even greater improvements for patients and clinicians.

Beyond oncology we have also seen improvements, and the response of the diagnostics sector to the COVID-19 pandemic showed how quickly new diagnostics can be brought into routine use in critical circumstances where there was an immediate public health need to try to limit the spread of the infection whilst vaccines and treatments were developed. Diagnostics will continue to have a key role here.

The deal space is active and still characterised by trading of in market or near market assets. Transactions are dominated by oncology applications.

Ultimately. we would want to see diagnostic technologies playing a leading role in personalised preventative medicine. Predicting problems and appropriate treatments before they arise, and should any arise, determining the most effective treatment. There is a school of thought that says we have enough therapies already developed that, if coupled with the right diagnostic tools, could enable selection of drug combinations to tackle almost any condition. To reach this nirvana will require a whole new way of developing and regulating drugs for use across multiple conditions, rather than the current one disease, one drug, one clinical trial model. There have been many false dawns for diagnostics where a more pivotal role was anticipated. That day is still to come but it is quite a way off.

References

Enabling Precision Oncology Through Precision Diagnostics. Noah A. Brown 2020

Rise of the Machines: The Inevitable Evolution of Medicine and Medical Laboratories Intertwining with Artificial Intelligence—A Narrative Review. Janne Cadamuro. 2021

Medtech Dive, medtechdive.com August 2020

Cancer diagnostics based on plasma protein biomarkers: hard times but great expectations. Ulf Landegren, Maria Hammond. October 2020

Tumor Mutational Burden as a Predictor of Immunotherapy Response: Is More Always Better? John H. Strickler et al. 2020

TTMB IS NOT ESTABLISHED AS A MARKER FOR PEMBROLIZUMAB EFFICACY IN NSCLC. Roy S Herbst et al. ESMO 2019.

The role of PD-L1 expression as a predictive biomarker: an analysis of all US Food and Drug Administration (FDA) approvals of immune checkpoint inhibitors. Andrew A. Davis1,2 and Vaibhav G. Patel 3. 2019

The emerging treatment landscape of targeted therapy in non-small-cell lung cancer. Min Yuan et al 2019.

Do Early-Generation TKIs Still Have a Place in EGFR exon 19 or exon 21 L858R-Mutated NSCLC? Katarina Zimmer. 2021

PharmaVentures
the deal experts

PharmaVentures is a premier transaction advisory firm and a leading international company in partnering, M&A deals and strategic alliances. For the past 29 years, PharmaVentures has acted as an advisor on over 900 deal-related projects covering licensing, mergers, acquisitions, divestments, and joint venture activities for companies worldwide.

PharmaVentures' deep bank of specialist experience, deal analytics and network of contacts among innovators and large pharma makes it uniquely placed to support business in all aspects of deal making and strategic planning. PharmaVentures is well known for its deep insight into deal structures and its success for generating partnering interest.

PharmaVentures' services include:

- **M&A**
  Divestments, mergers, acquisitions, and strategic transactions)
- **Licensing**
  In and out licensing
- **Fundraising**
- **Strategy**
  Commercialisation, deal strategy, due diligence, market entry
- **Valuation and Positioning**
  Licensing, M&A, fundraising, and expert testimonies

PharmaVentures is based in Oxford, UK, and employs over 20 professionals and has associates in Europe and Asia-Pacific.

PharmaVentures Capital Ltd is a wholly owned subsidiary of PharmaVentures Ltd. All regulated activities are delivered through PharmaVentures Capital Ltd, which is authorised and regulated by the Financial Conduct Authority (741356).

For more details click here.

Licensing and partnering can be transformative to a company, just by making informed changes to your strategy.

Talk to PharmaVentures. We can help you partner for success.
Please call **+44 (0) 1865 332700** or email: **enquiries@pharmaventures.com**

PharmaVentures Ltd
Triumph House, Parkway Court, John Smith Drive
Oxford Business Park, Oxford OX4 2JY

+44 (0) 1865 332700
Email: enquiries@pharmaventures.com
www.pharmaventures.com