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COMPASS Report

CANCER – Strategy for affordable care

Over- and underuse of clinical interventions have led to an increase in avoidable costs

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INDUSTRY NOTE

Cancer - Strategy for affordable care

KEY TAKEAWAY

The cancer burden is growing globally. Each year >18 million people are diagnosed, nearly 10 million die and the estimated economic cost exceeds $1 trillion. From early diagnosis to late-stage disease, cancer care often involves inappropriate or unnecessary interventions that drive costs but provide limited clinical benefit. Coupled with an increased understanding of cancer biology and rapid technological advances, this has been driving momentum for precision medicine, leading to patient and societal benefits. The use of biomarkers and sophisticated diagnostics is facilitating early intervention through robot-enabled minimally invasive surgery and locally delivered radiotherapy. Immuno-oncology has revolutionised cancer care, with the focus now on identifying combinations that further improve long-term outcomes. Liquid biopsies and companion diagnostics are increasingly being used to personalise therapy.

Health economics increasingly driving reimbursement decisions
The ability to deliver affordable care is at a turning point, as increasing care costs are driving cancer expenditure to unsustainable levels. The need to balance finite healthcare budgets against steadily growing demand is driving a rise in health technology assessments ("HTAs") to inform reimbursement and coverage decisions. These are based on a detailed analysis of the economic impact. Hence, health economics is becoming as important in assessing the commercial viability and value of new products as the conventional analysis of clinical efficacy and safety.

Early diagnosis key to improving outcomes, but over-diagnosis remains a challenge
The benefits of early detection and diagnosis of cancer in decreasing the incidence of metastases and increasing survival are well established. However, many available imaging and biomarker-based diagnostics are not sufficiently specific, often leading to over-diagnosis and unnecessary interventions. The focus is on the development of minimally invasive liquid biopsies that can provide primary screens and / or confirmatory tests, such as those based on epigenetic markers.

Robotic surgery poised for a shake-up, driven by innovative, affordable solutions
Robotic surgery is currently restricted to urology and gynaecology, due mainly to high capital costs and underutilisation. We anticipate a dramatic change with the introduction of innovative, lower-cost systems from multiple players seeking to disrupt the market dominated by Intuitive Surgical's da Vinci system. Coupled with the earlier diagnosis of smaller, operable tumours, this should propel robotic techniques to standard of care in surgical intervention in oncology.

Radiotherapy: from palliative to curative care
New modalities such as proton beam therapy are capable of localised dose delivery to cancer cells, thus sparing healthy tissue and reducing the incidence of secondary tumours. We believe that the cost debate surrounding particle therapy should be rendered obsolete by a growing body of clinical evidence and new capitation models.

Late-stage therapy moving towards combinations with checkpoint inhibitors
Immuno-oncology is revolutionising cancer care. The dramatic effects of immune checkpoint inhibitors ("ICIs") in many solid cancers and CAR-T cell therapies in some blood cancers have demonstrated the significant potential of harnessing the patient's own immune system to successfully fight cancer. The quest for combinations and the resulting fragmentation of the market should provide opportunities for large pharma and emerging biotech alike.

Companion and complementary Dx help identify those likely to benefit
The growing range of blood- and urine-based companion and complementary diagnostics is facilitating the personalisation of medicine by guiding appropriate treatment selection, as well as enabling the monitoring of continued susceptibility to therapy, the emergence of resistance and disease progression.

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Executive Summary

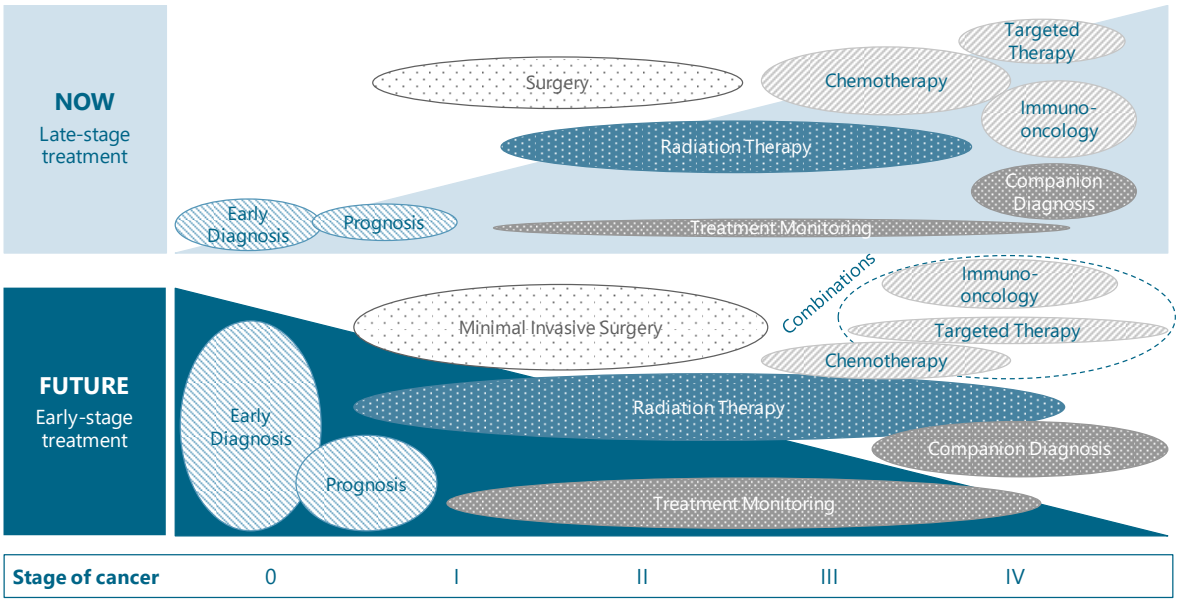
The analysis of healthcare investment opportunities needs to increasingly consider health economics

This report is a roadmap to investable technologies in oncology. The burden of cancer is growing, and the disease is becoming a major economic expenditure for all developed countries. While the analysis of healthcare investment opportunities has historically focussed on patient groups and clinical data, we believe that it is no longer complete without also considering health economics. We analyse the drivers and industrial solutions to the cancer cost curve and clinically relevant health technologies to fight cancer. We look at health economics and illustrate the frameworks within which Health Technology Assessment ("HTA") bodies operate to recommend new technologies to public reimbursement lists. We believe that only solutions with clinically relevant improvement and acceptable economic benefit will prevail and provide attractive investment ideas. We highlight attractive sub-sectors such as robotic surgery, radiotherapy, early screening, immuno-oncology and companion diagnostics. We discuss where we see investment opportunities fitting our expectations and valuation framework.

Move to precision medicine shifts spending to early-stage Tx

CHART 1 illustrates our key takeaways: we expect the move towards precision medicine to shift cancer spending from late- to early-stage treatment, leading to individual patient and wider societal benefits. Better screening and precision medicine should combine cost containment with clinical success and hence higher clinical efficiency.

CHART 1: Cancer treatment modalities



Source: goetzpartners Research

Indirect costs and economic loss outstrip direct costs

The reduction of indirect costs or economic loss due to new healthcare technologies needs to be considered when debating the direct costs of cancer

The ability to deliver affordable cancer care is at a turning point. A mixture of regional differences (growing and aging populations), emerging new technologies (instruments, devices and modern drug therapies) and increasing care costs are driving cancer costs to unsustainable levels. In addition to direct costs, there are significant additional (indirect) costs due to premature death, morbidity and unpaid care, which are estimated at over $1 trillion per year. There is little data to understand the impact on this from new drug therapies and other technologies, although survival rates have increased, and many cancers are curable with modern medicine.

Cancer care: better interventions, earlier

While rapid developments in the understanding of cancer promise to radically improve the survival of patients with late-stage disease, we believe that the growing availability of more accurate diagnostics will produce a sustained shift towards earlier diagnosis and targeted personalised cancer care. The identification of specific epigenetic markers has led to the development of new diagnostic technologies for large-scale screening as well as confirmation and prognosis, thus enabling detection whilst limiting over-diagnosis and unnecessary interventions.

Over-diagnosis is currently a major impediment to early diagnosis, but real progress is being made with more accurate molecular markers

Adoption of robotic surgery will be driven by innovation by new entrants

Success of early diagnosis hindered by insufficient specificity

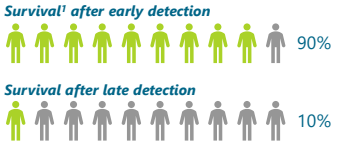
The benefits of early detection and diagnosis of cancer in decreasing the incidence of metastases and increasing survival are well established (CHART 2). However, there are relatively few cancers, such as cervical and colon cancer, where routine screening even among high-risk populations is practicable. While there have been substantial advances in imaging technology, specificity remains insufficient, and many techniques are too cumbersome or invasive for large-scale implementation. Image-based screening such as mammography for breast cancer does not reliably identify early-stage disease and is marred by over-diagnosis. Although sensitive for primary screening, blood tests such as PSA (prostate) yield many false positives, leading to unnecessary, expensive, and frequently harmful interventions. The focus is on the development of minimally invasive liquid biopsies that can provide primary screens and / or confirmatory tests, allowing for early detection whilst avoiding unnecessary intervention.

Earlier and more accurate diagnosis should facilitate targeted intervention and the precise delivery of radiotherapy

More accurate techniques should facilitate the shift to early intervention

Earlier and more accurate diagnosis should allow for earlier intervention, facilitated by the growing availability of minimally invasive surgery ("MIS") and the ability to provide highly targeted radiotherapy ("RT"). The adoption of MIS is likely to be driven by the increasing availability of surgical robotics. We are already seeing this trend in the US through the growing use of Intuitive Surgical's established da Vinci system (CHART 3), with a similar trend set to follow in Europe and Asia as a host of new entrants provide access to more affordable systems. In addition to surgery, the development of targeted RT and especially proton beam therapy ("PBT") should allow increasing numbers of early-stage cancers to be treated with RT while reducing damage to surrounding healthy tissues.

CHART 2: Impact of early diagnosis



[1] 5-year survival
Source: OECD, goetzpartners Research

Penetration of robot-assisted surgery relatively modest, particularly ex-US…

Although conventional open surgery still dominates the treatment of most cancers, increasing early diagnosis of smaller, non-metastatic cancers plus greater choice and availability of robotic systems should see a steady increase in the use of robot-assisted surgery ("RAS"). The advantages of minimally invasive surgery ("MIS") are well established; however, the technical skill required for e.g. laparoscopy is very high and thus not easily taught. While these problems can be significantly reduced using RAS, with the technology now dominant in procedures including prostatectomy and hysterectomy in the US, the cost of the available systems and their running expenses have restricted adoption for other procedures and in more economically constrained healthcare systems outside the US.

CHART 3: da Vinci Xi system

Source: Intuitive Surgical

… but adoption expected to increase

Many key patents that have allowed the market leader Intuitive Surgical to maintain a near monopoly in the US. Their expiry has been encouraging a variety of ambitious new players to enter the field. The innovation and ambition to lower system costs is expected to boost adoption of robotic surgery in general surgery as well as outside the US. Given the advantages to both patients and health providers, we expect robotic surgery to become dominant across general surgery, including surgical oncology. While we expect Intuitive Surgical to maintain its dominance in the US, owing to its extensive installed base, we see considerable opportunity for new entrants offering both innovation and more cost-effective solutions in other markets, particularly in Europe and Asia. A number of larger players including Verb Surgical (J&J / Google joint venture) and Medtronic have systems in development, and there are also a number of privately held surgical robotic pure players that we believe investors should keep on their radar as their products move towards the market and the companies consider public listings.

Rapid innovation in particle therapy providing cost-effective curative care

Radiotherapy: dramatic change from palliative to curative care

The radiotherapy ("RT") industry has been transformed by the introduction of volumetric modulated arc therapy ("VMAT") and intensity-modulated radiation therapy ("IMRT") – software innovations that allow for greater accuracy and treatment efficacy. In turn, these innovations have contributed to the accelerated adoption of RT. While Elekta had several setbacks in recent years, Varian and IBA enjoyed stellar performances, underlining the strong demand for these modern innovations in RT. More than 63% of all diagnosed cancer patients in the US receive some form of RT in standard treatment plans, but this figure drops to 35% in Europe and even less in other regions.

Currently available RT modalities include photons, protons and heavy ions

Affordable RT on the horizon

The debate on cancer economics has largely focused on expensive cancer drugs, while radiation technologies, which have undergone significant developments over the last 5 - 10 years, remain to be evaluated. Considering all costs across the life cycle of this resource, it is broadly speaking more cost-effective than surgery and chemotherapy. However, national budgets are in a paradoxical situation where delivering affordable RT in the mid-term is compromised by both under-capacity and underinvestment in conventional radiotherapy and over-penetration of newer technologies with far greater instalment costs. We review RT and its future potential for all currently available modalities and highlight that research efforts with respect to particle therapy have grown exponentially, with some recent findings opening new frontiers and arguments for its use.

Fragmentation of the combination therapy market create significant opportunities for a broad range of big pharma and innovative biotech companies

Late-stage therapy moving towards combinations with immune checkpoint inhibitors

Current treatment of late-stage cancer is still largely dominated by chemotherapy and radiotherapy. Although there has been a proliferation of potent targeted therapies that specifically target cancer cells in individual patients, these are frequently restricted to relatively small patient subpopulations and can be prone to the development of resistance. Progress with immune checkpoint inhibitors ("ICIs") across solid cancers and dramatic effects of CAR T-cell therapies in some blood cancers have demonstrated the significant potential of harnessing the patient's own immune system to successfully treat cancer. Treatment with ICIs has yielded dramatic improvements in overall survival, with responses lasting ten years or more. However, less than half of patients typically respond. Virtually all large oncology players have an ICI on the market or in development with the focus also spreading to the development of ICIs in combination with other drugs. There are currently over 700 ongoing combination trials involving other immunomodulators and a whole swathe of other cancer therapies, including chemotherapy, radiotherapy, targeted therapies, oncolytic viruses, cancer vaccines and antibody-directed therapies.

Increasing fragmentation creates opportunities for multiple players

While it is impossible to say at this stage which of these combinations will yield the most efficacy, we believe it is likely that the therapeutic landscape will be populated with a broad range of ICI combinations. The market leaders Merck & Co. and BMS are well placed to retain a substantial market share, but fragmentation of the market through the proliferation of combinations may allow other large oncology players with ICI programmes, such as AstraZeneca, Merck KGaA, Pfizer and Roche to also be significant participants. The quest for combinations and fragmentation of the market should provide significant upside for a broad range of smaller biotech companies. We see upside for companies developing targeted cancer therapies whose efficacy could be enhanced by unleashing the immune system. Recent deal activity reflects increasing interest for local immune-modulators, oncolytic viruses and cancer vaccines. Several small European oncology companies, including Affimed, Medigene, Targovax and 4SC look to benefit.

Molecular diagnostics moving mainstream for diagnosis and monitoring

Molecular diagnostics are playing an increasingly important role in the personalisation of cancer therapy. There are currently over 30 companion diagnostics linked to the use of specifically targeted cancer therapies, and biomarkers were used in nearly 40% of oncology trials in 2018, up from 25% in 2010 (IQVIA). A growing repertoire of additional genetic markers are increasingly used to guide treatment and determine individual prognosis. Such tests can enable patients to receive the most effective treatments for their specific cancer or to avoid the discomfort and expense of unnecessary or ineffective interventions. This targeted approach is particularly important for immuno-oncology drugs, which help focus the immune response to the cancer tissue (CHART 4).

CHART 4: The future of drug therapies

Source: goetzpartners Research

Liquid biopsies moving mainstream, allowing disease, Tx monitoring at the point of care

Although most tests have been developed for the analysis of solid biopsies taken from cancer tissue, advances in DNA detection technology and particularly the increasing availability of next generation sequencing are driving a rapid increase in diagnostic tests for tumour analysis of samples taken from blood or other biofluids such as urine. These liquid biopsies may not only allow the earlier selection of the appropriate targeted therapy, but also the monitoring of the cancer disease status and potentially provide a vital early indication of the development of resistance to specific therapies.

Multiparametric analysis drives complexity

These tests are becoming increasingly complex, as they monitor multiple parameters such as drug susceptibility, immune status and treatment efficacy. Although development of companion diagnostics has largely been performed through collaboration between large pharma and larger diagnostic players, there are increasing numbers of smaller, service-based companies that provide a range of proprietary and / or widely available tumour profiling and prognostic tests. The movement towards liquid biopsies should also allow for more repeated longitudinal testing, opening opportunities for point-of-care platforms developed by smaller innovators.

Companion and complementary diagnostics focus treatment on those likely to benefit

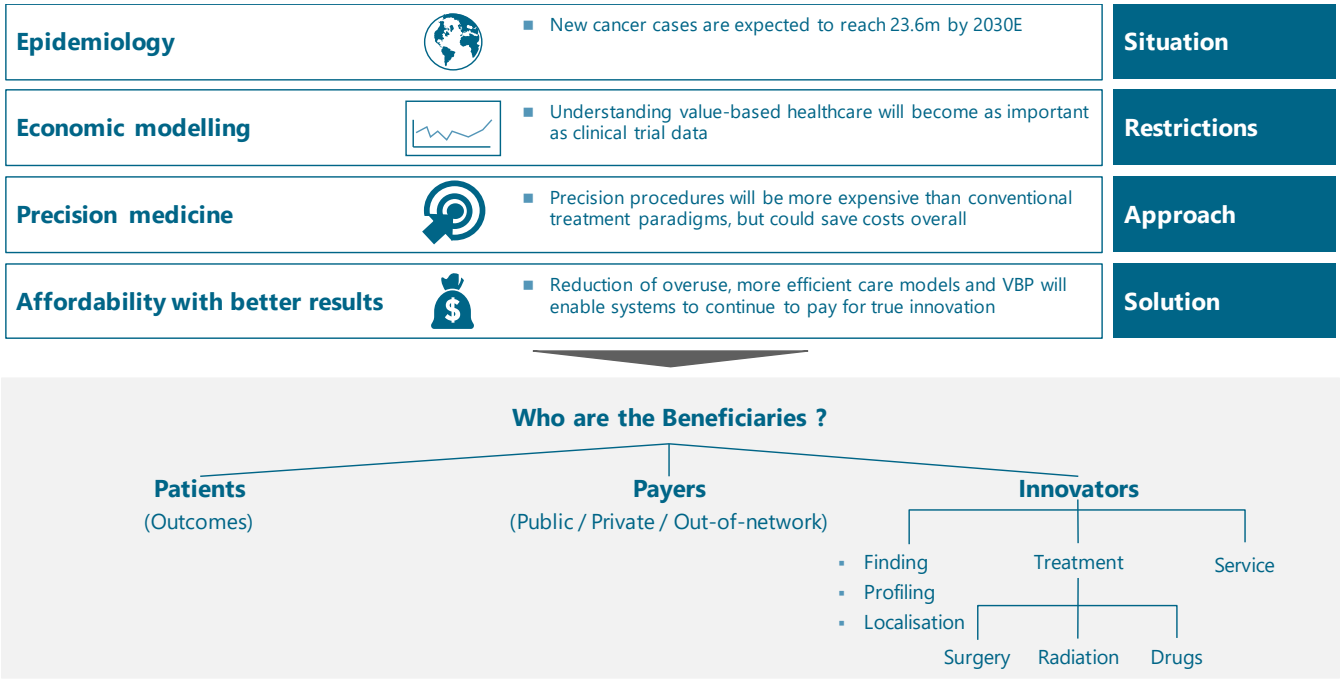
The targeting of therapies to specific patients will be facilitated by the growing range of blood-based companion and complementary diagnostics. These will be used both to optimise the choice of primary therapy and for disease monitoring, allowing therapy to be adapted to emerging clones to prevent treatment resistance.

Healthcare economics gaining importance

HTAs are being increasingly used to inform reimbursement and coverage decisions

In our view, a thorough understanding of economic models and HTAs will be as important in assessing the commercial value of new products and hence healthcare investment opportunities overall as the conventional analysis of clinical trials. This is due to the increasing use of HTAs to inform reimbursement and coverage decisions by insurers and national health systems to balance finite healthcare budgets against steadily growing demand. As a result, reimbursement lists are becoming more stringent. We have organised our analysis into four main areas (CHART 5) to provide a roadmap for oncology investors.

CHART 5: Situation overview



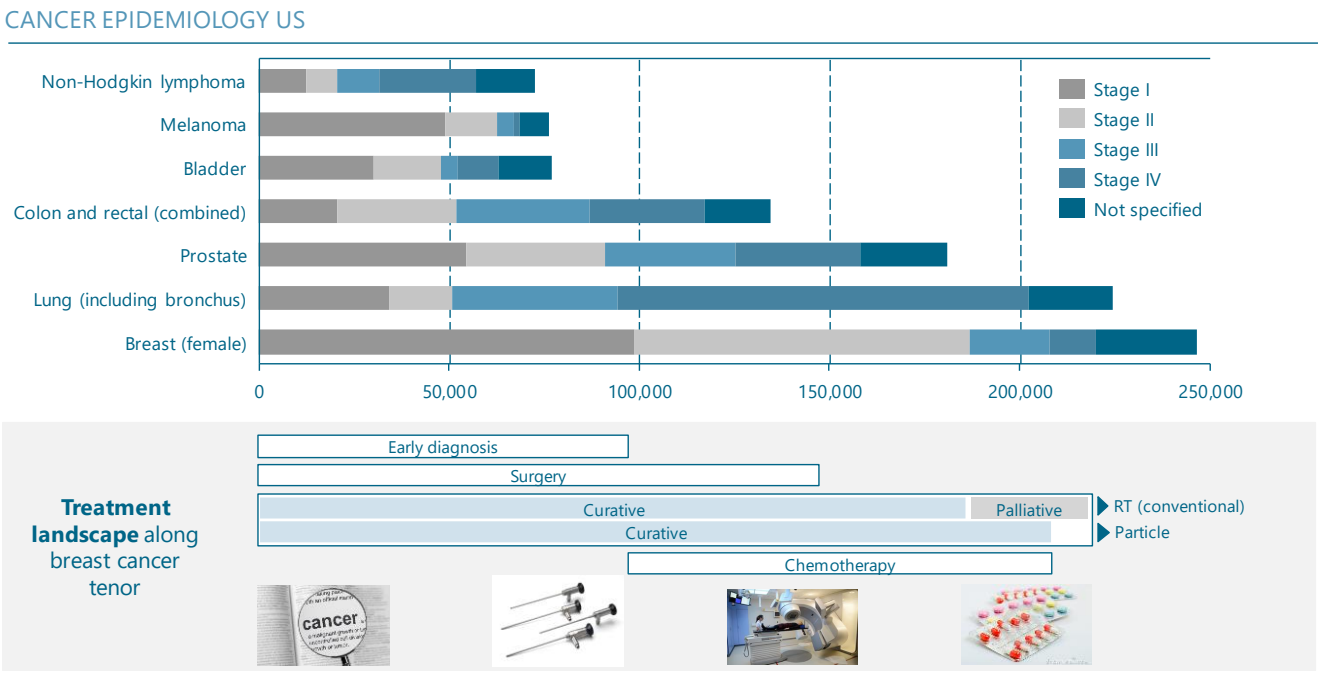
Abbreviations: VBP, value-based pricing
Source: goetzpartners Research

1. **Epidemiology** studies the incidence (new cases) and prevalence (total cases) of a disease across populations. Within the context of cancer treatment, this discipline aims to identify the driving forces behind both the increasing prevalence and prevention of cancer.
2. **Economic modelling** helps quantify the cost of the healthcare burden. We discuss how HTA bodies and payers are expected to manage increasing costs and expect the number of health technologies to be reduced in the future as a result. Statistical significance in randomised clinical trials ("RCTs") alone will therefore no longer be enough to drive adoption, in our view. As a result, multiple emerging technologies may be excluded from reimbursement lists.
3. Advances in science and engineering should drive clinical practice towards **precision and personalised medicine**, reflecting a strong segmentation of technology use. We anticipate smaller patient groups to be treated with new technologies and combinations of new technologies specific to patients' profiles and disease stages.
4. We believe that the adoption of precision medicine in clinical practice, e.g. targeted therapies, particle therapy and the use of companion diagnostics will ultimately result in a **higher return for payers and improved outcomes for patients**. Furthermore, we hypothesise that the use of precision medicine will eventually reduce costs, partially through a reduction in economic losses related to shorter recovery times, which confer an increase in the economic productivity of patients.

Epidemiology suggests 23.6m new cancer cases in 2030E

Cancer is a major public health issue (CHART 6, CHART 7). In 2012, over 14.1m new cases were recorded. At the end of 2012, there were approximately 32.5m people living with cancer who had been diagnosed in the previous five years. An estimated 169.3m years of healthy life were lost globally because of cancer in 2008. The growing global economic toll is expected to balloon in coming decades. If recent trends in major cancers continue, the burden of cancer will increase to 23.6m new cases each year by 2030E, according to the WHO. This represents an increase of 68% compared with 2012 – 66% in low and medium Human Development Index ("HDI") countries and 56% in high and very high HDI countries.

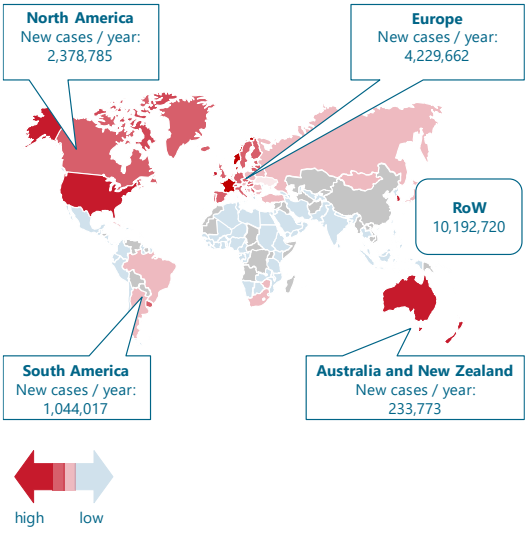
CHART 6: Prevalence of the seven most common cancer types



Source: Cancer Research UK, The 10 Most Commonly Diagnosed Cancers, World, 2012 Estimates, American Cancer Society: Cancer Facts and Figures 2016. Atlanta, Ga: American Cancer Society, 2016

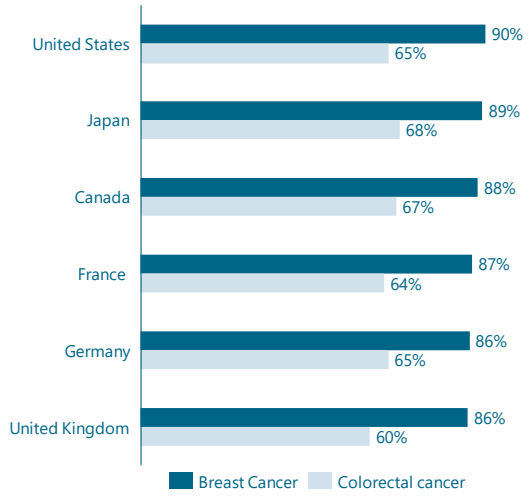
Approximately 44% of cancer cases and 53% of cancer deaths occur in countries at a low or medium level on the Human Development Index ("HDI"). As low HDI countries become more developed through rapid societal and economic changes, they are likely to become "westernised", bringing cancer survival rates in line with higher HDI countries (CHART 8).

CHART 7: Prevalence and epidemiology of cancer



Source: WHO, Global Cancer Observatory, 2018

CHART 8: 5-year survival rate: breast and colorectal cancer



Source: OECD Health Data 2014, Age standardised rate

Treatment costs and economic considerations

In this section, we elaborate on the growing socioeconomic burden of cancer, as well as current and future challenges for payers in developed countries. The growing annual fiscal burden from healthcare spending on new and existing technologies to treat cancer is well publicised and discussed in many reports. However, we feel that little has been done to understand the other side of the equation: the magnitude of economic losses due to cancer. We feel that this topic deserves more attention to better assess and predict future measures of governments' abilities to overcome the widening funding gap.

Drug costs represent less than 11% of total costs, but may help prevent more than 11% of economic losses

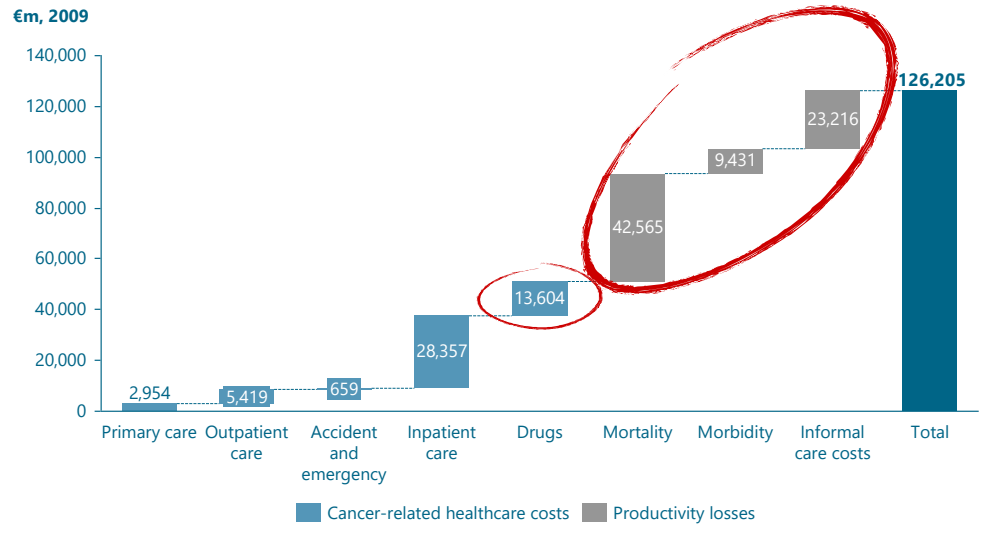
Economic losses due to cancer represent c.60% of total costs of cancer to societies

Economic loss, e.g. due to mortality, morbidity and informal care costs, represent c.60% of the total burden, while drugs represent <11%. How much has been saved in terms of economic loss due to healthcare technology? Where would the inflection point be when incremental spending begins to cause societal damage? In turn, this inflection point would potentially determine the element of self-funding required. We think this would be a better way to understand the cost burden and future implications as opposed to the short-sighted and blunt argument of technology spend vs. GDP.

Rising global cancer prevalence and productivity loss create a growing economic toll

According to World Cancer Day, the total annual economic cost of cancer is estimated at over $1 trillion – more than any other disease in the world. In a study published a few years back, the American Institute of Cancer Research ("ACR") estimated that cardiovascular disease costs c.$750bn followed by diabetes with an annual cost of c.$200bn. Another study published in the Lancet in 2014 calculated the average cost for one extra year of life. The authors found that this figure rose from $54,100 in 1995 to $139,100 in 2005 and $207,000 in 2013. According to the Agency for Healthcare Research and Quality ("AHRQ"), half of all cancer costs in the US were related to hospital outpatient and doctor office visits, with only 11% of the total costs derived from prescription drugs.

CHART 9: Cost of cancer in EU member states, 2009



Source: goetzpartners Research, The Lancet Oncology Commission (2013)

The big four cancers could be tackled with prevention and diagnostic screening programmes

The total cost of cancer to the EU was €126bn in 2009, with direct healthcare spend accounting for €51bn (40%, CHART 9). Across the EU, the healthcare cost of cancer amounted to €102 per capita but varied substantially from €16 (Bulgaria) to €184 (Luxembourg) across individual member countries. Productivity losses because of early death amounted to c.€42.6bn, lost working days to c.€9.43bn and informal care costs to c.€23.2bn. Lung cancer had the highest economic cost (€18.8bn, 15% of overall cancer costs), followed by breast cancer (€15.0bn, 12%), colorectal cancer (€13.1bn, 10%), and prostate cancer (€8.43bn, 7%). These four cancer types have a higher chance of being treated successfully than others which are less well understood. This "westernisation" effect is a result of reductions in infection-related cancers, outweighed by an increasing burden of cancers associated with dietary and hormonal risk factors.

HTA bodies will determine drug adoption in the future in addition to drug approval authorities

Drug approval authorities such as the FDA and the EMA focus mainly on RCTs instead of economic considerations. However, HTA bodies such as The National Institute for Health and Care Excellence ("NICE") (UK) and the Institute for Quality and Efficiency in Healthcare ("IQWiG") (Germany) will, in our view, become ever more influential in the drug approval process across all jurisdictions in developed countries. These bodies carry out HTAs to help inform reimbursement and coverage decisions for novel treatments. We clarify how HTA bodies work and how we see them shaping the drug and medical device industries.

Imperfect care models and overuse through both physician (US) and patient-induced demand (EU) create inefficiencies and unnecessary cost factors

In- and outpatient care represent some 28% of the total cost burden. Our panel at the 2nd goetzpartners COMPASS event (29th June 2017) concluded that this cost block represents significant savings potential. We have identified inefficiencies in the care models and overuse of services driven by demand from physicians and providers, especially in the US. The moral hazard of full insurance and no co-pay for cancer care in Europe also creates patient-induced overuse of services.

Evaluating the cost effectiveness of new treatments

The rising direct costs of cancer care have led to a focus on more affordable care models. Value-based pricing ("VBP") of new technologies or approval based on incremental cost-effectiveness in relation to average national income are promising methods for setting limits on the cost of new treatments. Cost effectiveness is typically evaluated using an incremental cost-effectiveness ratio ("ICER") that compares the cost and effect of a new treatment to a control group of a pivotal RCT or a less efficacious and less costly alternative. Overall, the ICER represents the average incremental cost associated with one additional unit of the measured effect. For cancer, the ICER is often expressed as an incremental cost per life year, or quality adjusted life years ("QALY") gained. The calculation is as follows:

$$ICER = (Cost_{new} - Cost_{old}) / (Effectiveness_{new} - Effectiveness_{old})$$

Cost-effectiveness is overlooked in comparison to statistical significance

The FDA approves therapies based on statistics but often with limited clinical relevance

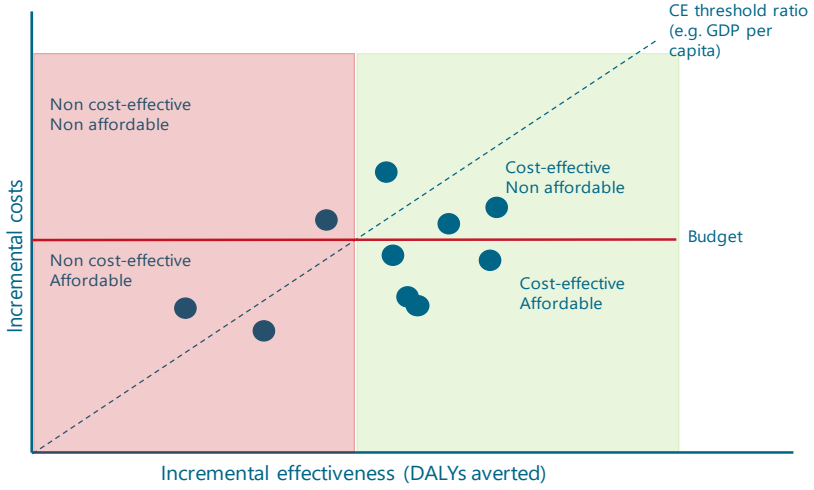
RCTs aim to establish statistically significant differences between the experimental and control arms, with less attention paid to clinical relevance of the treatment effects. One prominent example was a combination of erlotinib and gemcitabine for which investigators reported a statistically significant increase in median overall survival of 0.33 months versus gemcitabine alone as a first-line treatment for pancreatic cancer. The FDA subsequently approved the therapy despite the limited clinical benefit and an estimated incremental cost per life year gained of almost $500,000. Even if a therapy brings an acceptable ICER or QALY, the adverse events or toxicity could have adverse effects on these metrics.

Value-based care may be more transformative than scientific breakthroughs

The oncology industry needs to follow a significantly more integrated approach to make new treatments more economically viable

Pricing and reimbursement will without doubt become one of the most challenging topics healthcare companies face under this new paradigm. The rapidly escalating cost trajectory of the past decade has been partly driven by pricing new therapies based on the costs of existing therapies, rather than rational economic models (CHART 10). The alarming pace of drug price growth appears to be moderating, but the upward trajectory continues at a speed that is not sustainable.

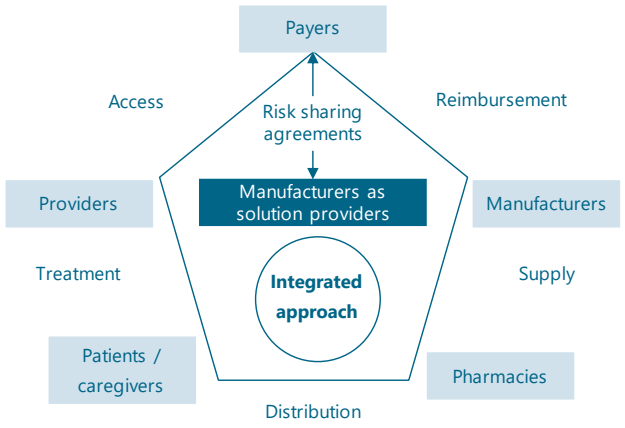
CHART 10: Cost-effectiveness vs. affordability is a key consideration in deciding on interventions



Abbreviations: DALY, disability-adjusted life year
Source: goetzpartners Research

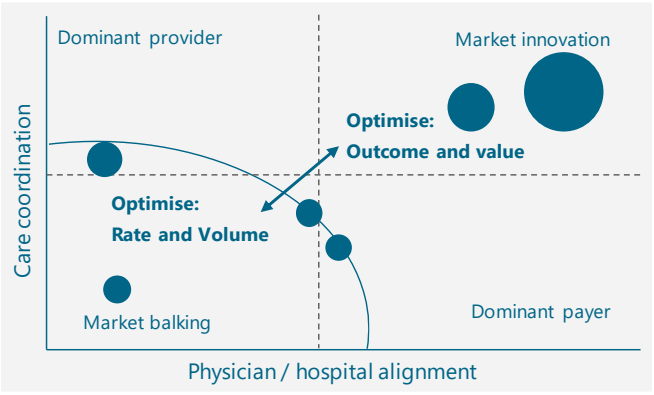
The discipline of health economics underpins the work of publicly funded HTA agencies such as NICE in the UK, IQWiG in Germany, the Swedish Council on Health Technology Assessment ("SBU") in Sweden and the Pharmaceutical Benefits Advisory Committee ("PBAC") in Australia. Health economics is also closely linked to the objectives of the more recently established Patient-Centered Outcomes Research Institute ("PCORI") in the US. PCORI will initially focus on comparative effectiveness. This could potentially lead to a wider application of cost-effectiveness-based criteria for determining treatment entitlements in the US.

CHART 11: Outcome-based risk model to improve treatment regimes



Source: goetzpartners Research

CHART 12: Value-based payment models vary by market



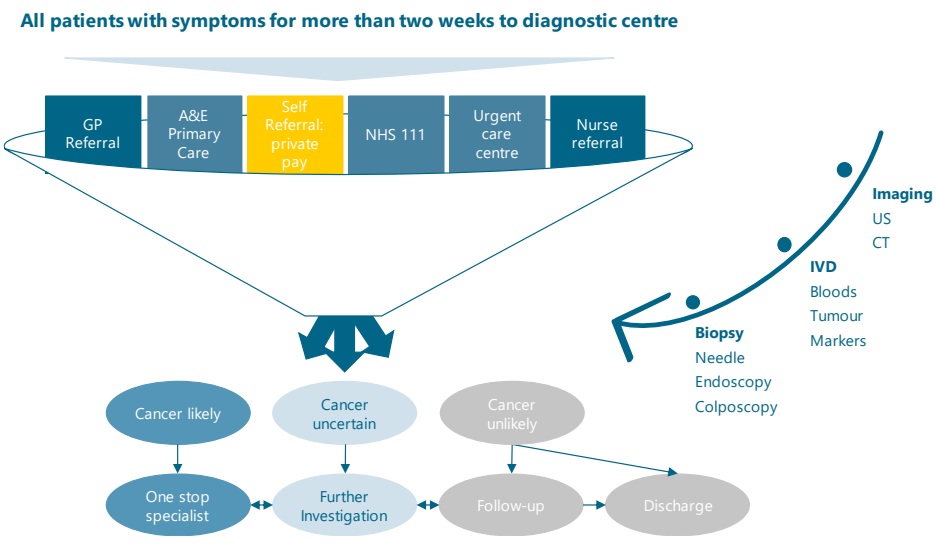
Bubble size = savings opportunity

Source: goetzpartners Research

Value-based pricing more applicable to "real world" scenarios outside of RCTs

Insurers who have the muscle to negotiate risk-sharing agreements with drug companies will likely look to the ICER draft analysis of "reasonable" costs for cancer drugs. VBP models will become increasingly relevant as real-life settings do not always corroborate results from RCTs. Current value assessment and appraisal approaches for medical technologies – which use economic evaluation or adopt comparative clinical benefit assessments to inform coverage decisions and improve efficiency in resource allocation – have been subject to criticism for many reasons. Most HTA systems base their decision-making process on cost per outcome metrics of economic evaluations such as the cost per QALY. CHART 13 shows a potential paradigm for cancer funding which improves on the currently flawed care structure. This model should lead to better and more efficient management of resources. Following a first contact, patients enter a diagnostic "funnel" and are then directed to the correct silo / centre / channel.

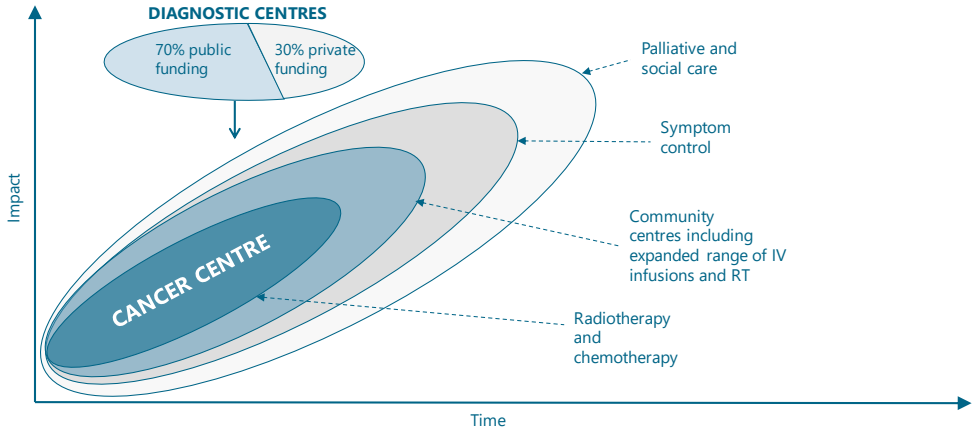
CHART 13: Future model for cancer management and funding



Abbreviations: IVD, in vitro diagnostics; US, ultra-sound; CT, computed tomography
Source: goetzpartners Research, Karol Sikora's slide goetzpartners COMPASS event 2016

CHART 14 highlights the need for diagnostic testing and subsequent cancer management to be co-ordinated in a multi-disciplinary cancer centre in order to prevent the overuse of therapies.

CHART 14: The future networks of cancer



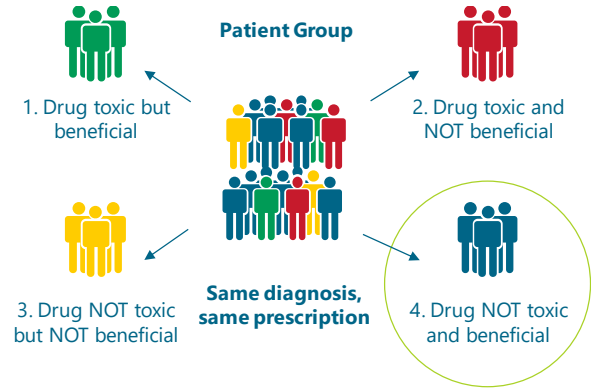
Source: goetzpartners Research

Precision medicine increases treatment effectiveness

Precision medicine:
Evidence-based medicine that incorporates genetic and biologic information to individualise treatment and guide prevention strategies

We believe that the more we understand about tumour biology and related patient segmentation, the more precisely health technologies can be applied in individual patients, types of cancers and stages of disease. While the extent of individual treatment might increase, we believe that the overall costs could be well controlled. Under this paradigm, treatment regimens are more efficient and effective, thus potentially lowering the direct costs of care by reducing overuse and reducing indirect costs such as the economic loss associated with disease.

CHART 15: Precision medicine enables drug targeting based on patient-specific genetic alterations

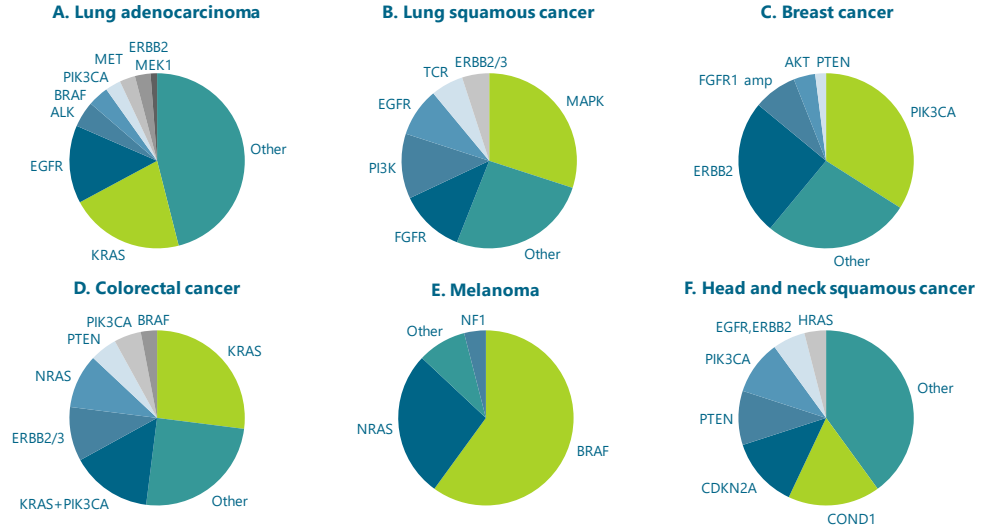


Drugs against genetically-defined targets have shown significantly superior response rates of 70-80% in cancer indications vs. the typical 15-20% with chemotherapy

Source: Chakma Journal of Young Investigators. Vol 16, 2009

CHART 16 overleaf illustrates the complexity and heterogeneity of tumour profiles. This enables the subsequent identification of an appropriate therapy on an individual patient basis.

CHART 16: Genomic alterations in common solid tumours



Source: Roychowdhury *et al.* 2011, *Science Translational Medicine*; Garraway 2013, *Clinical Oncology*

Early diagnosis key to improving outcomes

The benefits of early detection and diagnosis of cancer are well established. By enabling earlier, more effective, less complex, and more affordable treatment, early diagnosis leads to a decrease in the incidence of metastases and a concomitant increase in survival, whilst reducing overall costs.

Focus on the development of molecular diagnostics that provide a reliable diagnosis and avoid unnecessary intervention

However, there are relatively few cancers, such as cervical and colon cancer, where routine screening even amongst high-risk populations is currently practicable. While there have been substantial advances in imaging technology, there is still insufficient specificity and some modalities are too cumbersome or invasive to implement on a large scale. Image-based screening, such as mammography for breast cancer, does not reliably identify early-stage disease and is dogged by over-diagnosis. Although sensitive for primary screening, blood tests such as PSA in the prostate yield many false positives, leading to unnecessary, expensive, and frequently harmful interventions. The focus is therefore on the development of accurate, minimally invasive liquid biopsies that can provide primary screens and / or confirmatory tests, thus allowing for early detection whilst avoiding unnecessary intervention.

Epigenetics providing real progress in both tumour detection and profiling

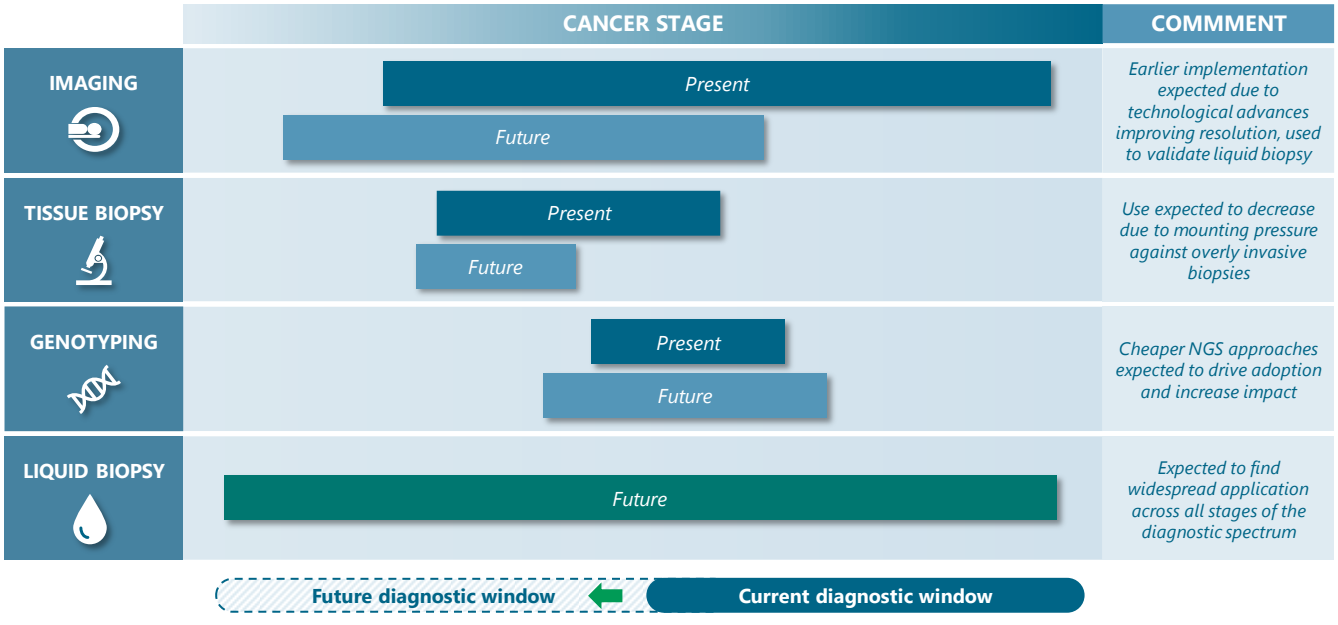
While companies such as Illumina spin-out Grail have major plans for mass screening, significant commercial progress is already being made in the development of liquid biopsies based on the detection of cancer-specific genetic – particularly epigenetic – markers released into the blood and urine in a handful of cancers including prostate and colon. Markers for many other cancers still need to be developed. Given the ethical and regulatory risks, early diagnosis remains the domain of risk-taking smaller companies such as MDxHealth, Epigenomics, Exact Sciences and Inivata, with few larger companies yet to fully commit.

The benefits associated with improved ease-of-use of liquid-based testing are two-fold: (1) methods such as urine or venous blood sampling are more convenient for the patient compared with more traditional screening methods such as physical examination or imaging; (2) increased convenience drives screening adherence. This is especially important for cancers such as colorectal, where only one in seven people eligible in the EU undergo regular screening with currently available methods.

The analysis of breath may become an increasingly important diagnostic tool

A novel approach under development is breath biopsy, where a diagnostic test analyses the chemicals in human breath to detect changes indicative of cancer. The leader in this field is UK company Owlstone Medical, which is currently conducting large-scale trials in partnership with AstraZeneca and GSK to identify novel biomarkers for asthma and COPD for personalised medicine applications.

CHART 17: Expected shift in the diagnostic landscape



Source: goetzpartners Research

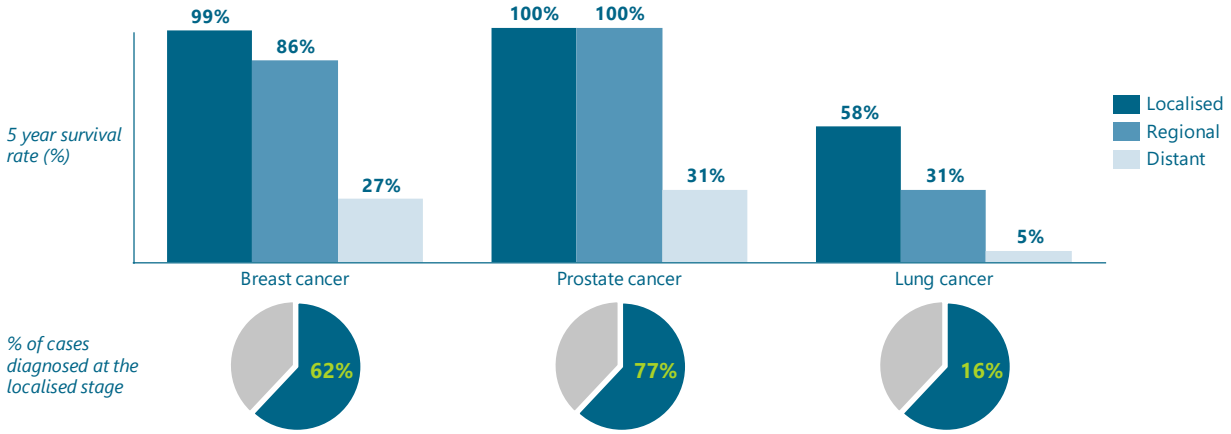
Higher survival for cancers that can be diagnosed early

Advantages of early diagnosis for treatment:

- *Easier resection due to smaller tumour size*
- *Less heterogenous cancer*
- *Immune system still intact*
- *Body more resilient to aggressive treatment*

Some cancers are more prone to being diagnosed early than others: 62% and 77% of patients diagnosed with breast and prostate cancer, respectively, are diagnosed at a stage when the cancer is still highly localised, while the same applies to only 16% of lung cancer cases (CHART 18). This has a direct impact on survival rates: 90% of patients diagnosed with breast cancer will now survive longer than 5 years, compared with only 19% for lung cancer. These figures have remained relatively stable for decades. The fact that lung cancer detected at the earliest stage (Stage I) can be cured with surgery or radiation more than 80% of the time emphasises the strong case for early detection in improving lung cancer. While the disease is disproportionately deadlier than other cancers, early detection is just as relevant in improving survival for other cancers, especially considering expected improvements in treatment modalities that will likely amplify this benefit in the near future.

CHART 18: Breast, prostate and lung cancer 5-year survival by stage at diagnosis

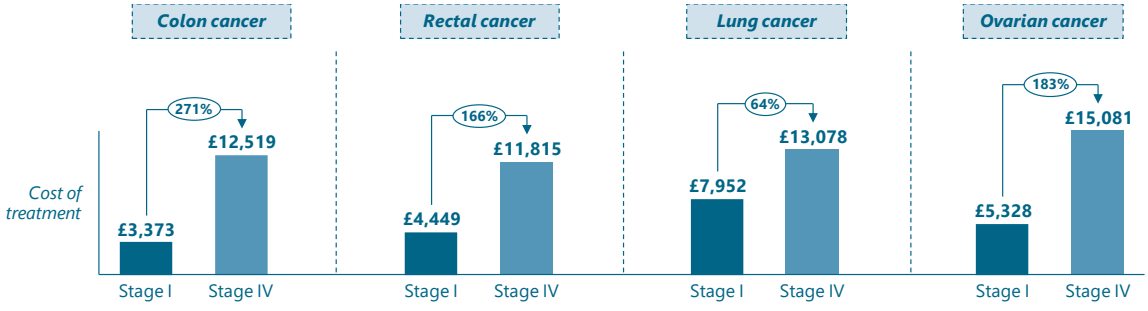


Localised: confined to primary site. Regional: spread to regional lymph nodes. Distant: cancer has metastasised
Source: National Cancer Institute (SEER)

Limiting the economic burden

In addition to improving patient outcomes, early diagnosis can also provide significant cost savings by avoiding the high treatment costs associated with life-threatening metastatic disease. CHART 19 outlines the stage-specific costs of treatment for several cancers in the UK. Overall, treatment for Stage III and Stage IV cancers costs the NHS more than twice the amount spent on treatment for Stage I and Stage II cancers. More accessible diseases, such as colon cancer, can be treated at a relatively low cost if detected early, but treatments costs tend to rise sharply as the disease progresses. However, for less accessible diseases such as lung cancer, which involves the complex resection of localised disease, the cost differential between early- and late-stage treatment appears to be relatively low compared to other cancers which implies lower potential cost-savings from earlier diagnosis on an individual patient basis. Nevertheless, on a population-wide basis, this trend is expected to reverse due to the high prevalence of lung cancer (excluding high recurrence rates for lung cancer).

CHART 19: Treatment costs are significantly lower at earlier stages of disease

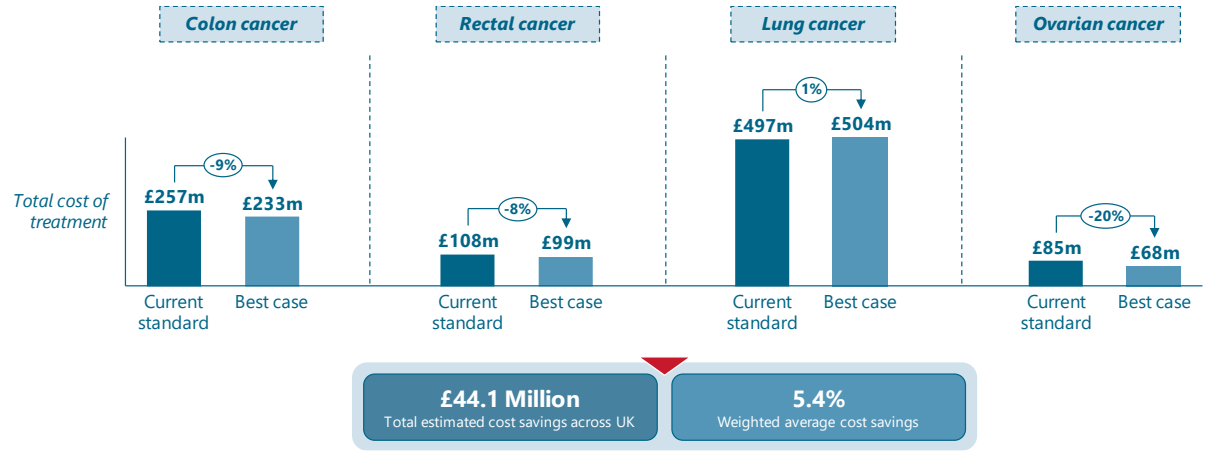


Source: Cancer Research UK, 2014

Cost-analysis indicates potential for substantial savings due to earlier detection

Across England, there are large geographical variations in the proportion of patients diagnosed with cancer at each stage. Below, we present an analysis of the potential cost-savings associated with a hypothetical shift from average UK diagnostic rates to the rates of the best institutions in England (a realistic best-case scenario applied across the country). Looking at colon, rectal, ovarian and lung cancer, the analysis, which is based on a previous cost analysis prepared for Cancer Research UK, suggests significant cost-savings of c.£44m (CHART 20), driven by only a small redistribution of average diagnostic stages as exemplified by the best Clinical Commissioning Groups ("CCGs") in England.

CHART 20: Case study | Estimated cost savings if early diagnosis rates achieved in leading institutions are applied across the UK



Source: Incisive Health, Cancer Research UK

Indirect cost-savings arising from lost productivity and side-effects/complications associated with systemic treatment represent additional upside

Additional upside expected from indirect cost savings and improved diagnostic rates

We emphasise that the above analysis is only driven by a small improvement in diagnostic rates to mirror those already achieved by leading institutions in England. However, we assume that new and effective early diagnostics will trigger a much more significant shift in diagnostic rates in the near term, therefore generating further savings. We highlight that these statistics only incorporate the direct costs of treatment. We therefore expect much higher cost-savings from early detection when accounting for indirect costs such as lost productivity and side effects, which are unevenly distributed towards later stages of disease. Furthermore, accurate profiling of a cancer to avoid over-diagnosis should minimise intervention in patients with non-life-threatening cancer, thus also significantly reducing the frequent costs arising from unnecessary intervention and therapy.

The case of lung cancer: a call for improved clinical effectiveness

As shown in CHART 20, detecting and treating lung cancer at an early stage but where it is no longer curable can be associated with higher overall costs than diagnosing it late. This is due to a patient receiving multiple lines of therapy with predominantly palliative rather than curative intent. This case highlights the limitations of early detection in the absence of effective treatment options.

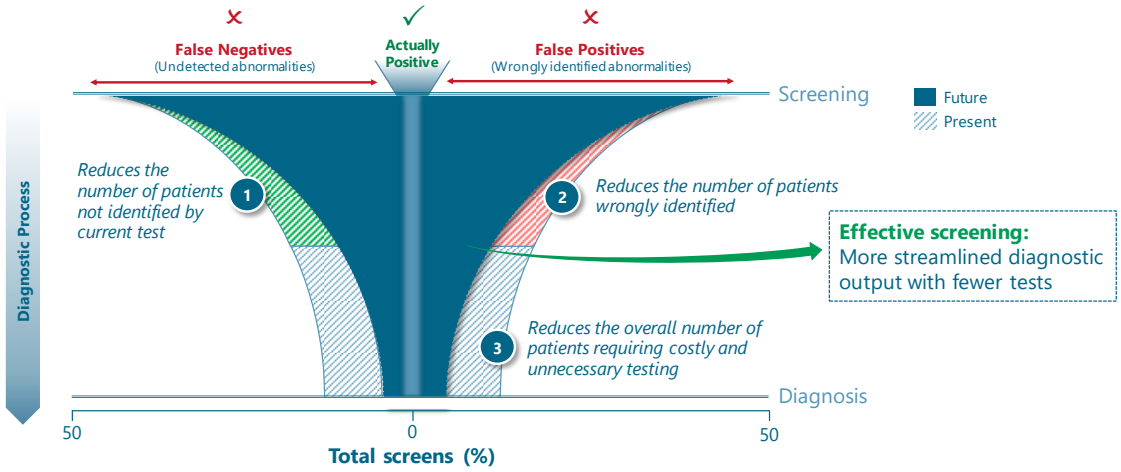
Technological gap

Current diagnostic modalities (1) lack sensitivity to efficiently detect smaller lesions, (2) require long turnaround times, and (3) are expensive

Reducing the frequency of unnecessary, costly and invasive screening

Given the clear benefits of early diagnosis, but the limitations of many current diagnostic methods, there is an obvious need for further development of non- or minimally invasive tests (e.g. blood or urine) that can not only detect cancer early, but also avoid over-diagnosis by providing an accurate indication of whether the cancer is aggressive and requires intervention or not. As highlighted in CHART 21, in an ideal situation the primary screen would be sufficient to detect aggressive disease and determine if an individual should receive invasive intervention. Under the current paradigm, the patient – whether at high risk (e.g. from lifestyle or primary screen) or outwardly healthy – must go through a series of steps to confirm the presence of disease first, and then through further steps to determine whether the disease is life-threatening and eligible for aggressive treatment. The key role of early diagnosis is to simplify the whole process by condensing time-consuming, consecutive steps into a centralised, one-step process. This could save time and further increase clinical cost-effectiveness by providing an early indication of the legitimacy of using invasive interventions on a patient basis.

CHART 21: Optimised non-invasive screening programmes provide a more effective and streamlined diagnostic process



Source: goetzpartners Research

Current screening options leave substantial room for improvement in most cancers

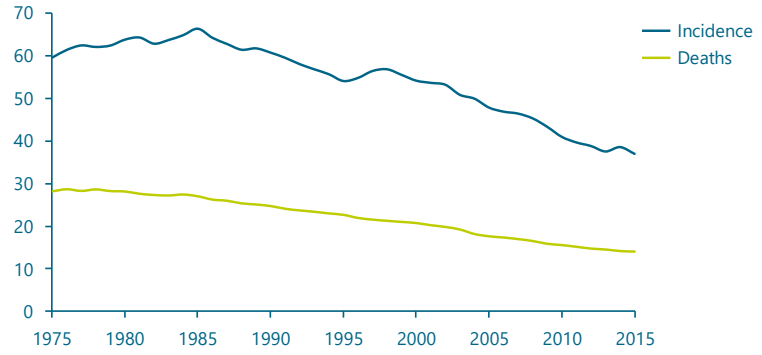
The impact of early cancer detection and diagnosis on increasing chances of successful treatment and survival are well documented. However, there are currently few cancers where early screening is either practicable or precise enough to be effective. Due to a current lack of specific and easily measurable markers, diagnosis still largely relies on imaging and subsequent invasive biopsy of high-risk populations or patients with appropriate symptoms.

Early screening applicability: the cases of cervical and colon cancers

Except for cervical and colon cancer, few cancers are currently suitable to early-stage screening

Cervical and to a lesser extent colon cancer are two cancers which have historically been subjected to the implementation of routine screens. Both cancers are characterised by 'relatively' easy access via colposcopy (cervical cancer) and colonoscopy (colon cancer), which enables simple examination and removal of early cancerous or pre-cancerous tissue. Although over-diagnosis is not infrequent, the necessary interventions are relatively straightforward, reducing the financial and clinical impact of over-diagnosis. Frequent screening for these two types of cancer has been shown to have a significant impact on the respective incidence and death rates, as highlighted for colon cancer in CHART 22.

CHART 22: Declining incidence of colorectal cancer per 100,000 in the US



Source: US Centres for Disease Control and Preventions ("CDC")

CT imaging for lung cancer leads to increased over-diagnosis and over-treatment

Early screening in lung cancer saves lives, but at a cost

The benefits of screening in cancers such as lung, where easy access is not possible, are not clear cut. While screening of asymptomatic patients may save lives, there are questions as to whether the resulting highly invasive interventions in many patients – particularly those who either do not have the disease or do not require treatment – is really worth it. While the low-dose CT scanning recommended for former or current heavy 30 pack year (equivalent to 1 pack per day for 30 years) smokers in the US results in a 16% - 20% reduction in lung cancer deaths in those screened, around 96% of positive patients ultimately never show any sign of cancer development, as the nodules identified are frequently benign or growing too slowly to pose a mortal risk. Unlike in the cervix or colon, confirmatory or early interventions in the lung are highly invasive, exposing patients to risky and expensive interventions.

Mammography has little impact on metastatic disease

The need for a better alternative to mammography

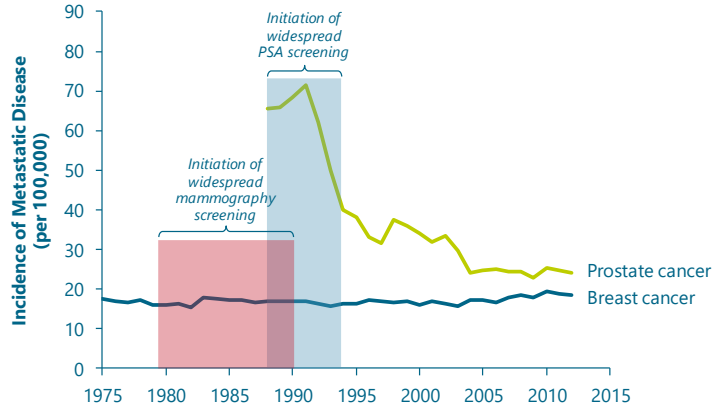
Similarly, while there have been significant reductions in mortality from breast cancer, mammographic screening may do more harm than good. A study performed in the UK ("The benefits and harms of breast cancer screening: an independent review", *Lancet*, 2012) concluded that up to 4,000 women in the UK were subjected to treatment that they did not really need. Increased survival has instead been suggested to be more related to improved treatments (Bleyer & Welch, 2012) than improved screening accuracy. Evidence suggests that breast cancer screening may have relatively little impact on the incidence of metastatic disease, due to imaging frequently identifying the disease too late. Mammography screening leads to diagnosis of more cancers, but these tend to be smaller (Welch, Prorok, O'Malley & Kramer, 2016). If more evolved variants of mammography do exist, such as 3-D mammography (higher screening efficiency and reliability) or magnetic resonance imaging ("MRI") (92% screening efficiency, which is three times as high as traditional mammography), these alternatives remain insufficient and imperfect. 3-D mammography is twice as radioactive. MRI yields many false positives which may increase cost and patient anxiety.

Prostate screening reduces metastases, but over-diagnosis leads to unnecessary large-scale intervention

The limitations of the PSA-test

In contrast to imaging, the development of sensitive blood-based screens has been shown to have a dramatic effect on the incidence of metastatic disease. In prostate cancer, the widespread implementation of PSA screening led to a substantial decrease in the incidence of metastatic disease in the US in the 1990s (CHART 23). However, governmental transparency regarding the risks of over-diagnosis associated with PSA tests has led to a decrease in the number of PSA screenings.

CHART 23: Impact of PSA screening on metastatic disease incidence



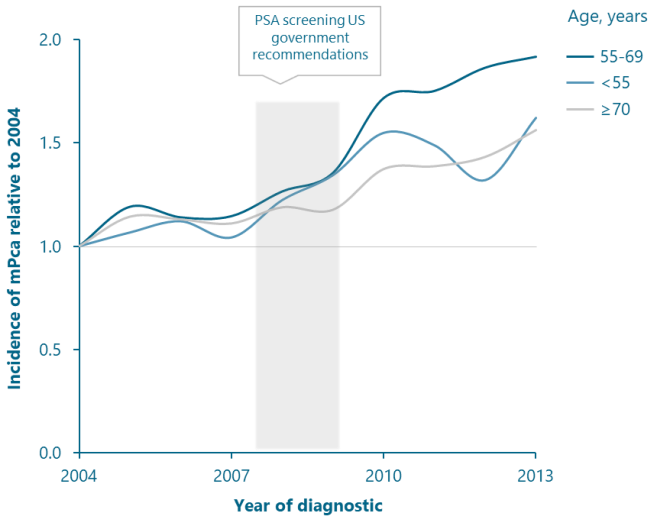
Source: Adapted from New England Journal of Medicine: *Trends in Metastatic Breast and Prostate Cancer — Lessons in Cancer Dynamics*

A 2015 study designed to assess changes of PSA testing following US Preventive Services Task Force ("USPSTF") PSA screening recommendations, which disclose the main risks of PSA tests showed a significant decline in PSA testing from 2008 to 2013 subsequent to 2008 regulatory disclosures, with a concomitant increase in the diagnosed incidence of prostate cancer (CHART 24).

Need for a more efficient diagnostic process

To reverse this trend and move back towards less PSA testing, substantial efforts should be deployed to find a better and less intrusive alternative to traditional biopsy and other heavy surgical procedures. Liquid biopsy is a highly promising alternative, due to minimal intrusiveness, superior convenience and low costs. Large-scale implementation of prostate liquid biopsies is likely to have a material impact on the incidence of metastatic prostate cancers for two main reasons: (1) diagnostic capabilities would be augmented due to better access to genetic samples (blood or urine), increasing the probability of detecting potentially aggressive cancers early; (2) men who were initially reluctant to take a PSA test for fear of the risk of intrusive interventions would have no disincentive for routine screening if even positive results lead to non-intrusive diagnostic methods. Alternatively, research efforts should be made to replace PSA with a more precise and less dissuasive screening method.

CHART 24: Increasing incidence of metastatic prostate cancer



Source: Weiner, Matulewicz, Eggener & Schaeffer, 2016; Li, Berkowitz & Hall, 2015

Progress and future outlook

The three components of early detection and their benefits over physical biopsies

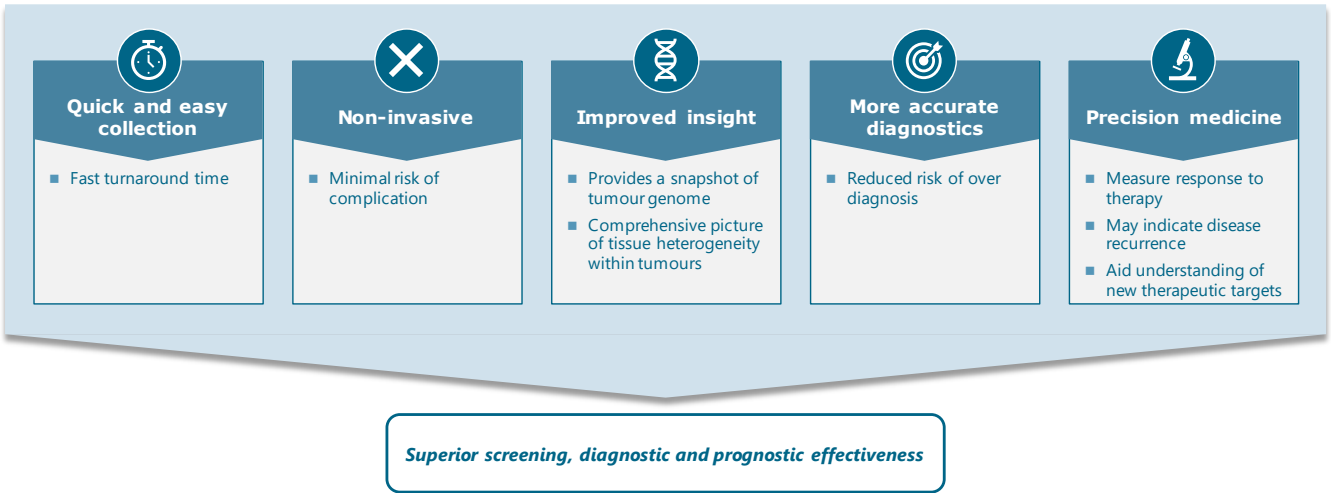
In order to add material value, early diagnosis should provide three types of information through minimally invasive procedures to help guide optimal treatments:

1. Determine unequivocally whether the patient has cancer;
2. Provide the specific location of the tumour;
3. Insights on histological type and disease severity.

The potential of liquid biopsies

Accurate liquid-based testing has the potential to transform cancer diagnosis to the point where simple tests could be used across an asymptomatic population to reliably detect molecular abnormalities that are associated with disease. In other words, in addition to being used as a diagnostic tool – usually applicable to high-risk / symptomatic populations – it could also be used as a screening tool deployed on a very large scale to detect early anomalies. Due to the systemic approach, small traces of molecules circulating in the blood can be identified to create a comprehensive molecular tumour profile. This cannot currently be recreated using random tissue samples, due to tumour heterogeneity.

CHART 25: Benefits of liquid biopsy over traditional biopsy



Source: goetzpartners Research

Two different approaches: CTCs and ctDNA

The most commonly used approach analyses circulating tumour cells ("CTCs") that detach themselves from a primary tumour and circulate in the bloodstream around the body. This circulation of detached cells forms the basis of the formation of metastasis during later cancer stages, but evidence for primary tumours can be detected in the blood quite early on. This makes it a useful tool for diagnosis, prognosis and assessment of a tumour's treatment sensitivity based on its molecular profile. Advances in DNA sequencing have brought about the analysis of cell-free circulating tumour DNA ("ctDNA") as an indicator for tumour burden. The cell-free ctDNA may be secreted by viable tumour cells or released following tumour cell death. It is technically easier to isolate, more stable than whole cells, and a good indicator for tumour heterogeneity.

Using confirmatory tests to increase diagnostic accuracy for prostate cancer

Although no test has yet been developed to replace PSA, there has been significant progress in the development of tests that can confirm a diagnosis as well as provide an indication of the aggressiveness of the disease. Several tests have been developed to help rule in or rule out the presence of cancer in men with elevated PSA (CHART 26). These tests focus on the detection of genetic markers released by the cancer into the blood or urine.

CHART 26: Selected marketed confirmatory molecular tests for prostate cancer

Test name	Developer	Target
PHI	Beckman Coulter	Protein, PSA species (blood)
ExoDx Prostate	Exosome Diagnostics (Bio-Techne)	Exosomal miRNA (urine)
Progensa PCA3	Hologic	mRNA (urine)
ConfirmMDx	MDxHealth	Methylated DNA (tissue)
SelectMDx	MDxHealth	3 mRNAs (urine)
4Kscore	Opko	Kallikriens, PSA species, HK-2 (blood)

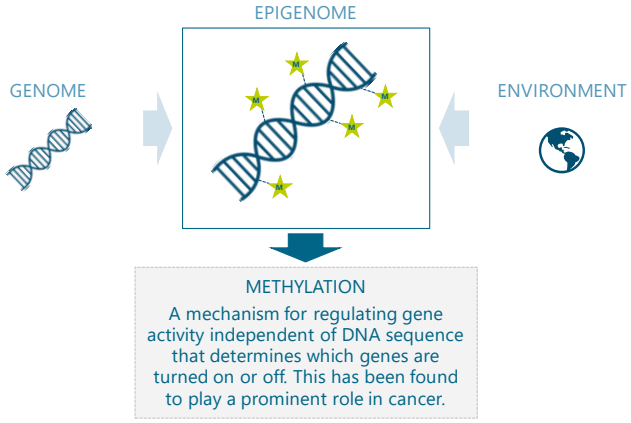
Source: goetzpartners Research

Measuring epigenetic changes to detect tumours and their location

Rather than analysing variations in the structure of DNA directly, epigenetic testing targets chemical markers attached to DNA that are indicative of cancer

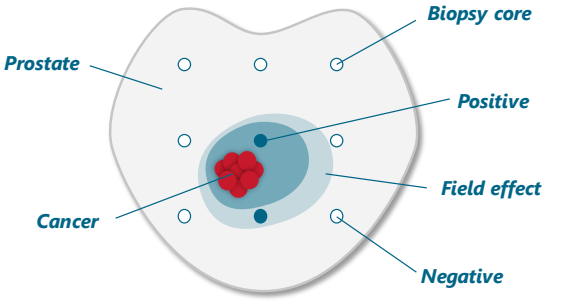
Two of the most compelling tests have resulted from progress in our understanding of epigenetics and its role in cancer. The transformation of healthy cells into cancerous cells arises because of the aberrant expression of genes that control cell growth and function. While this can result from gene mutation, which changes the underlying sequence of DNA encoding the gene, it can also result from epigenetic changes involving alterations in gene expression without modifying the underlying sequence. The most widely studied form of epigenetic control is through methylation (CHART 27), which can be detected in DNA released into the blood or urine or in some cases in a field of pre-cancerous tissue surrounding the tumour. This 'field effect' can be useful in detecting tumours that would otherwise be missed by biopsy and standard cytology (CHART 28).

CHART 27: The fundamentals of epigenetics



Source: goetzpartners Research

CHART 28: Utilising the epigenetic field effect for tumour localisation



Source: goetzpartners Research

Epigenetics can provide information on aggressiveness of prostate cancer

Epigenetic testing supports tumour characterisation and treatment choice

Epigenetics is also able to provide information on the nature of the disease. A large proportion of prostate cancer is indolent, posing little threat to the patient and requiring no intervention aside from regular observation. The two prostate tests SelectMDx and Confirm MDx developed by Belgian company MDxHealth provide both an accurate indication of the presence of prostate cancer and a measure of whether the disease is aggressive and requires further intervention. Similarly, molecular tests have been developed for the confirmation of bladder cancer. Of the patients with blood in their urine and at risk of bladder cancer that are currently referred for cystoscopy, less than 10% have cancer, equating to c.81,190 new cases of bladder cancer in the US in 2018. A variety of urine tests have been developed to better identify the low number of patients who are positive (CHART 29).

CHART 29: Selected FDA-approved primary molecular screens for bladder cancer

Test name	Developer	Target
UroVysion	Abbott	DNA (urine)
NMP22 BladderChek	MatriTech (Abbott)	Nuclear matrix protein 22 (urine)
AssureMDx	MDxHealth	Methylated DNA (urine)
Cxbladder	Pacific Edge	mRNA (urine)

Source: goetzpartners Research

Increasing development of confirmatory tests to verify LDCT scan

As the leading cause of cancer deaths, lung cancer represents a large unmet medical need, especially since most patients are diagnosed late. Low-Dose CT ("LDCT") testing used for screening of high-risk populations has poorly specificity, frequently causing unnecessary biopsies. Veracyte has developed a test for lung cancer called Percepta that allows the risk of lung cancer to be assessed in high-risk heavy smokers after a questionable LDCT scan. However, the test requires a bronchoscopy and has a relatively low specificity of c.50%. Oncimmune's EarlyCDT-Lung test based on autoantibodies provides a 2 - 3 times improvement in the identification of cancer in smaller nodules identified by LDCT screening.

CHART 30: Post-LDCT lung cancer confirmation and early biomarker tests

Test name	Developer	Target
Post-LDCT lung cancer confirmation tests		
Biodesix Lung Reflex	Biodesix	DNA (blood)
EarlyCDT-Lung	Oncimmune	Autoantibodies (blood)
Percepta	Veracyte	mRNA (bronchial scrapes)
Early biomarkers tests		
N/a	Hummingbird Dx	miRNA (blood)
Nu.Q	VolitionRX	Nucleosomes (blood)

Source: goetzpartners Research

How early is too early?
Being able to measure early molecular changes may increase the frequency of false positives associated with detection of spontaneous mutations that do not require intervention

Reliable pre-screens for lung cancer could reduce reliance on non-specific LDCT

A range of companies have programmes focussed on the development of early diagnostics for lung cancer. Many of these are developing tests as a pre-screen prior to the recommended non-specific LDCT scans for 30 pack year smokers. Tests from Epigenomics and VolitionRX are focused on the detection of epigenetic and other DNA markers released by the cancer cells into the blood. Early diagnosis has predominantly targeted the detection of markers released by cancer cells, given the growing recognition of how tumour cells interact and communicate with the immune system. However, attention is also turning to monitoring the immune system for indications of the presence of cancer cells. Hummingbird Diagnostics is developing blood-based microRNA signatures that measure levels of immune cell-derived microRNA in whole blood. Its lead programme is for the diagnosis of cancer in heavy smokers.

First minimally invasive screens for colon cancer based on epigenetics

Modest advances in colon cancer screening

Non- or minimally invasive tests suitable for large-scale screening of healthy individuals remain rare. However, two that have been developed for the detection of colon cancer also rely on the detection of epigenetic markers. The first, Cologuard from Exact Science, detects modified cancer-derived DNA in stool. The second, Epi proColon from Epigenomics, allows modified DNA markers to be detected in blood. Both tests appear to have similar sensitivity and specificity, but as a blood test Epi proColon would appear to have the advantage in terms of convenience. There are also a range of protein-based screens. Some of these focus on the detection of autoantibodies. While some of these tests appear to be relatively specific, their sensitivity is generally too low.

CHART 31: FDA-approved primary molecular screens for colon cancer

Test name	Developer	Target
Epi proColon	Epigenomics	Septin-9 methylated DNA (blood)
DNA Colodguard	Exact Sciences	Hb, methylated DNA, KRAS, ACTB (stool)

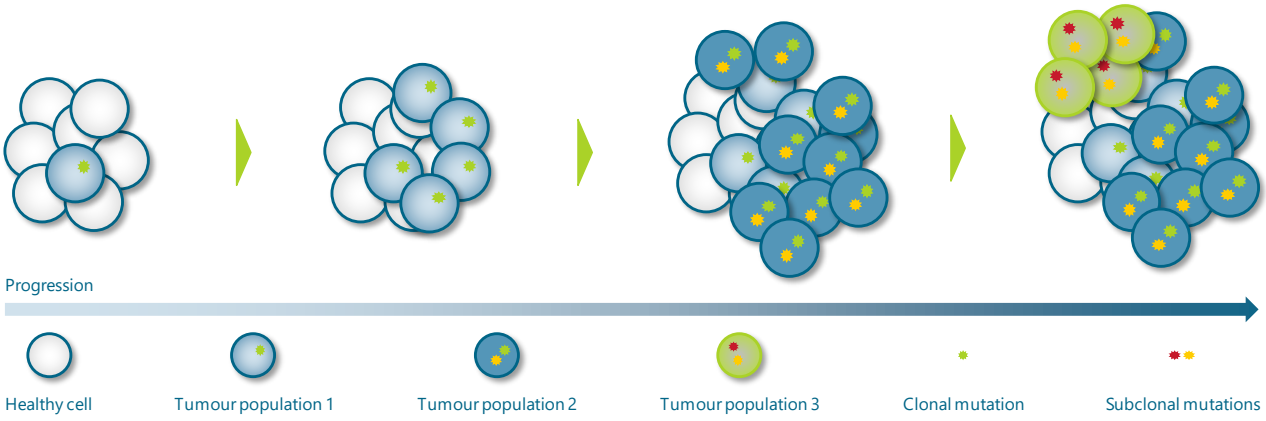
Source: goetzpartners Research

The case for precision medicine

Liquid-based biopsies can help detect tumour markers in heterogenous tumours…

The case of liquid biopsies for precision medicine is clear - classifying disease based on the underlying genetic and biological characteristics facilitates treatment selection and may predict response to a specific treatment, allowing bespoke and targeted therapeutic intervention for those likely to respond while sparing expense and side effects for those unlikely to respond. Precision medicine in oncology is currently still largely dependent on the analysis of tissue biopsies taken from the tumour. Such biopsies are difficult to collect and potentially harmful to the patient. Most tumours are highly heterogeneous collections of cells, including a variety of cancer cells and normal cells, as highlighted in CHART 32. Using needle biopsies, it is nearly impossible to collect a full complement of tumour cells. As a result, cells carrying important tumour markers may be absent from the biopsy core despite being present in the tumour. Liquid-based testing may represent a more reliable way to detect these markers. The nature of the testing should also increase the potential monitoring frequency compared with regular biopsies.

CHART 32: Heterogeneity of tumour cell collections



Source: goetzpartners Research (adapted from PC Nowell (1976) – The clonal evolution of tumour cell population)

Adoption of liquid biopsy will allow early detection as well as easier longitudinal disease and treatment monitoring

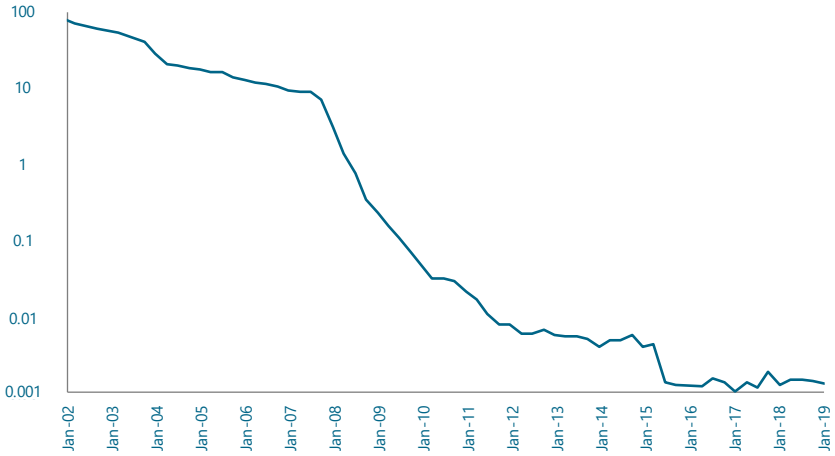
…and monitor patient-specific response

Effective liquid biopsies should allow monitoring of the appearance of tumour resistance markers as well as the appearance or disappearance of specific drug-targeted driver mutations, which underlie the frequently transient response to targeted therapies. Improvements in the collection and analysis of DNA and RNA means that cancers can be monitored in liquid biopsies from blood or even urine through the analysis of ctDNA. Tests have already been developed for the detection of common cancer-linked markers to guide therapy. These should enable detection and longitudinal monitoring of the tumour's genetic profile and drug susceptibility, as well as characterisation of drug susceptibility profiles of smaller / earlier tumours. The information obtained can be used to select the right targeted therapy as early as possible to further improve outcomes, including survival.

From genotyping to genomic sequencing

Tumour genotyping allows for the identification of genetic abnormalities that drive particular tumours. Genotyping uses microarrays (plates coated with known DNA sequences associated with cancer) to detect these regions in a sample, providing small packets of data for pre-established sequences associated with cancers. Genomic sequencing on the other hand is the identification of the DNA sequence of an entire genome, providing more data with more meaning and context even in regions not currently prone to harbouring cancer-specific mutations. Despite rapid improvements in both cost and speed of sequencing an entire genome over the last decades (CHART 33), sequencing remains expensive for routine application. Big data tools applied to genome sequencing should improve cancer diagnosis and guide pathologists towards the optimal choice of therapy.

CHART 33: Cost of genome sequencing ($m)



Source: National Human Genome Research Institute

High costs of late-stage therapy should encourage adoption

Below we highlight the key divers for the adoption of early diagnostics.

CHART 34: Drivers for the adoption of early diagnostics

Clinical	• Potential to reduce metastatic disease and mortality • Need for less-invasive tests to improve patient experience • Incentive to reduce unnecessary intervention due to over-diagnosis
Economic	• Need to alleviate the economic burden of late-stage therapy • Global shift towards value-based payment models • Increasing number of early detection companies entering the market
Scientific	• Proliferation of specific disease and prognostic biomarkers • Increasing number of cutting-edge genome sequencing technologies
Other	• Rising awareness of early diagnosis benefits • Growing influence of healthcare lobbies

Source: goetzpartners Research

Increased understanding in tumour biology and technological progress

We expect rapid developments in the understanding of cancer biomarkers combined with technological progress in detecting increasingly low levels of molecular markers (including DNA, RNA and proteins) that are frequently released into body fluids such as blood and urine to drive the development of effective early diagnosis tests. Developments in DNA detection and sequencing technology should facilitate the detection of such markers at increasingly low concentrations, and some of them might be used as early cancer markers. With our improved understanding of the role of the immune system in the development of cancers, there is also increasing interest in identifying immune cell markers that could be developed as early cancer diagnostics.

Non-invasive approaches enhance patient experience, thus improving compliance

Abundance of screening and molecular profiling technologies

The proliferation and increasing accessibility of non-invasive approaches to molecular profiling should facilitate large-scale diagnosis and in turn reduce the incidence of metastatic disease. The adoption of non-invasive approaches should be further propelled by the clinical simplicity of these procedures, which do not require a high level of training to be carried out. Finally, improved patient experience and hence adherence is likely to change the way cancer diagnosis is perceived overall, as the most dissuasive and unpleasant aspects of the process are eliminated by the adoption of non-invasive approaches.

Global shift toward value-based payment model

Significant efforts are being made to promote the adoption of value-based payment models, also referred as alternative payment models ("APM"). These economic models add more flexibility for the reimbursement of innovative medical products and technologies, by assessing them based on their cost-effectiveness rather than their upfront cost (the latter are often prohibitive if taken in isolation). This paradigm shift can be expected to facilitate the adoption of cutting-edge screening and diagnostic solutions by lowering financial and regulatory barriers.

Challenges include improving sensitivity

The factors hindering adoption of early diagnostic tools and the challenges facing active players are highlighted in CHART 35 below.

CHART 35: Improving the sensitivity of liquid biopsy tests will be key in reducing unnecessary intervention

Clinical	• Identification of biomarkers suitable for non- or minimally invasive analysis • Development of markers for both cancer detection and risk profiling • Need for extended large-scale longitudinal studies
Economic	• Need for more flexible payment structures • Building a strong economic rationale for healthcare commissioners • Competitive pressure of major providers of expensive late-stage drugs
Scientific	• Need for more sensitive and precise liquid biopsy technology • Need for more powerful and flexible data analysis techniques
Other	• High fragmentation of the global healthcare landscape • Numerous ethical questions surrounding early diagnosis • Substantial regulatory barriers

Source: goetzpartners Reasearch

Proper validation of early screens is a mammoth task

Need to improve accuracy and clinical validation of new tests

The clear challenge is identifying and validating appropriate blood or urine biomarkers for early diagnosis which not only detect disease, but also assess severity. This should help to avoid the over-diagnosis associated with the use of PSA or mammography. Validation of early-stage diagnosis in the general population would require the screening of large numbers of individuals. Such trials would be expensive, by their nature requiring elaborate longitudinal analysis and follow-up work of largely healthy populations over long time periods. Furthermore, the regulatory hurdles facing any early diagnostic screen are likely to be high given the consequences of over- or misdiagnosis. We would anticipate that the development of these tests would initially be limited to high-risk populations such as smokers in the case of lung cancer, and / or where there is an existing primary test or screen (e.g. PSA for prostate and mammography for breast cancer).

Heterogenous healthcare landscape

Due to major discrepancies between healthcare systems globally, regulatory and social barriers are likely to be significant. We could therefore expect a heterogeneous development of the early diagnosis market. In 2015, approximately 35% of low-income countries reported that pathology services were generally available in the public sector compared to more than 95% of high-income countries (Guide to Early Cancer Diagnosis, WHO, 2018). Therefore, market development is constrained by the fact that many countries - especially low-income - do not provide access to public pathology frameworks, without which the adoption of diagnosis solutions is not even foreseeable. The development of the early diagnosis market will also strongly depend on the flexibility of reimbursement policies, which have substantial power in promoting or restraining scientific progress and commercial deployment.

The implementation of the most efficient, value-enhancing and sustainable solutions should maximise value for all stakeholders

Benefits of early diagnosis need to be promoted to drive uptake

To overcome the fragmentation of the global healthcare landscape and relieve regulatory barriers, significant political power must be exerted to promote the benefits of early diagnosis both from a clinical and economic perspective, which in turn should facilitate the global adoption and implementation of early detection in the short to medium term. If we can acknowledge the efforts of a few lobbying initiatives (American Cancer Society, National Cancer Intelligence Network, National Awareness and Early Diagnosis Initiative), there is still room to improve global awareness of early diagnosis virtues. Alternatively, the increasing recognition of value-based payment models or alternative payment models should drive further improvement in this area by shifting the focus of current healthcare systems towards the implementation of the most efficient, value-enhancing and sustainable clinical solutions.

Development paths and status

Given the large-scale application of screens in a healthy population, regulatory standards are high, and tests require extensive validation

The development of early screens is associated with significant regulatory hurdles

While the goal of early diagnosis would be to provide a screening test for outwardly healthy individuals, the scale of the studies necessary for discovery and validation, combined with the regulatory and ethical hurdles associated with such screening tests have put a brake on development. Many companies are focussed on the detection and analysis of ctDNA to identify specific mutations relevant to profiling the tumour and to guide therapy in patients previously diagnosed with cancer. These are currently more relevant to the development of companion and complementary diagnostics covered in later chapters. The clinical significance of the detection of these same mutations in healthy populations has yet to be proven. Companies such as Pathway Genomics who have claimed a link between the detection of these mutations in blood and early diagnosis have received warning letters from the FDA.

Illumina spin-out Grail raised $1.5bn to develop early screens

Large players, with few exceptions, have hesitated to enter early diagnosis

Given the outstanding ethical and regulatory problems surrounding early diagnosis, large diagnostic players appear to have hesitated to embark on significant early diagnostic programmes. The notable exception has been Illumina, which founded a daughter company, Grail, to utilise Illumina's next generation sequencing technology to detect and characterise ctDNA fragments to develop early cancer diagnostic screens. Grail has raised c.$1.5bn in equity to fund the costly development of early screens. Grail's STRIVE study, a prospective, observational, longitudinal cohort study, is testament to the capital-intensive validation process behind the development of early diagnostics. The company recently announced the successful enrolment of 100,000 patients to validate a blood test for the early detection of multiple cancer types. Participants will be followed for up to five years to capture clinical progress.

Maximising diagnostic accuracy by combining different screening approaches

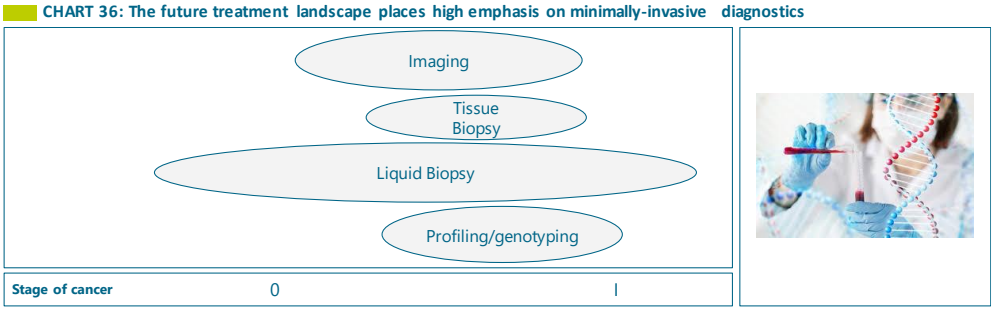
With precision medicine expected to play an increasing role in the future cancer treatment paradigm, we feel that the need to discriminate between aggressive, potentially metastatic cancer and slowly growing indolent forms may accelerate the development of large-scale cancer screens. This may involve a combination of screening for circulating tumour markers with other approaches such as monitoring of the immune system's reaction as provided by Hummingbird's miRNA signature-detecting pipeline. These combinations could provide a more sensitive and accurate alternative to current methods.

Minimally invasive methods will promote early detection

Screening and confirmation are expected to increasingly rely on liquid biopsies

In the near term we anticipate the launch of additional confirmatory tests in cancers with recognised pre-screens or risk factors. The development of routine molecular cancer screens that can detect cancer but at the same time avoid over-diagnosis appears to be some time away. Given the enormous benefits of early diagnosis both in terms of saving lives and reducing the proportion of cancer patients requiring expensive and frequently unpleasant late-stage therapy, the move towards early diagnosis is inevitable and strongly depends on the development and implementation of the appropriate technology, which should be facilitated by an innovation-conducive regulatory landscape. While imaging will remain a significant component to enable localisation and removal of the cancerous cells, early diagnosis will be largely dependent on the further development of accurate non- or minimally invasive liquid biopsies. In the long term we expect the emergence of a myriad of diverse early detection tools that will be combined strategically to maximise clinical efficiency.

CHART 36: The future treatment landscape places high emphasis on minimally-invasive diagnostics



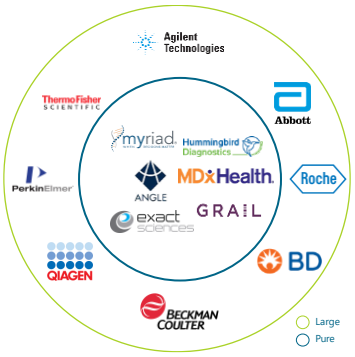
Source: goetzpartners Research

Industry overview and key players

Early screening is a c.$200bn potential market opportunity

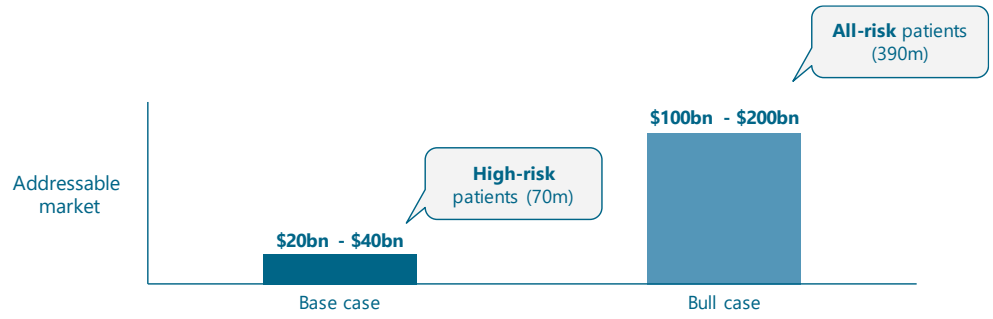
Although the current market for early molecular screening is relatively small, with the largest single product Cologuard from Exact Sciences generating around $266m, the potential market is substantial. Assuming an average cost per test of $500 - $1,000 performed bi-annually, Grail estimates that screening of high-risk patients, such as heavy smokers, could generate $20bn - $40bn p.a. rising to $100bn - $200bn if screening of healthy all-comers was achieved.

CHART 37: Key players



Source: goetzpartners Research

CHART 38: Early diagnosis market potential



Source: Grail

Few major players fully engaged in the race

The liquid biopsy landscape is becoming increasingly crowded

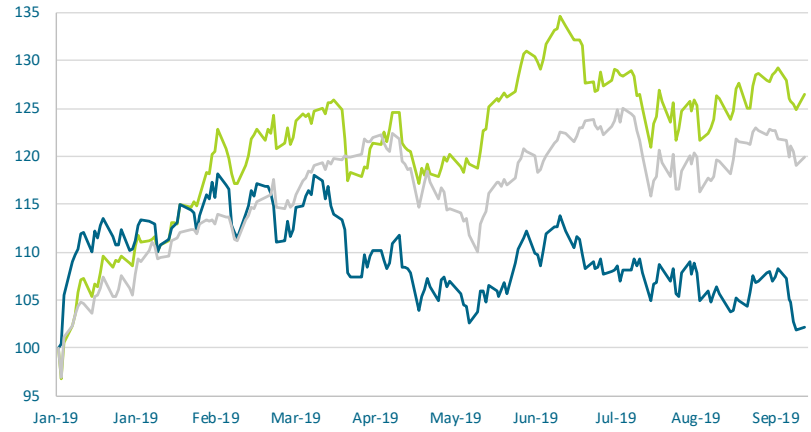
Although we would expect the larger diagnostic players to become involved as the market develops, we anticipate that smaller companies will lead the development of early diagnosis in the short and medium term. In our view, the major focus will remain on the development of liquid / blood-based diagnostics that can confirm or complement the use for existing screens such as PSA, mammography or LDCT scanning in high-risk patients. The promising clinical results demonstrated by liquid biopsy players such as Guardant Health (Lunar-2 assay *programme*), OncoCyte (DetermaVu™), or Personal Genome Diagnostics (Plasma Select™ – R 64) reinforce the overall credibility of liquid-based diagnostic solutions as a more efficient alternative to traditional biopsy. Furthermore, due to the sizeable market potential, more companies are entering the sector to take advantage of growing investor interest, which has delivered considerable outperformance (CHART 40).

CHART 39: Selected liquid-based early diagnostic tests for the cancer space

Company	Product or aim	Test stage
Grail	Screen for multiple cancers	Research
Integrated Diagnostics	XpresysLung 2 – decision-making tool for CT lung nodule	Commercial
Oncimmune	EarlyCDT-Lung – decision-making tool for CT lung nodule	Commercial
Epigenomics	Epi proColon – screen for colon cancer	Commercial
Epigenomics	Epi proLung – screen for lung cancer	Commercial
Epigenomics	Liver test for patients with cirrhosis	Research
Laboratory for Advanced Medicine	IvyGene – confirmation tests for 4 cancers	Commercial
John Hopkins Group	CancerSEEK – screen for 8 cancers	Research
Freenome	Screen for various cancers	Research
Genesys Biolabs	Paula's Test – screen for lung cancer	Commercial
Chronix Biomedical	Screen for lung cancer	Research

Source: Pharma Intelligence

CHART 40: Liquid biopsy index market performance YTD



The GenomeWeb Index is an index of 30 major publicly traded molecular diagnostic / liquid biopsy companies
Source: goetzpartners Research

CHART 41: Private liquid biopsy players

Company	HQ	Application
AccuraGen.	US	Unspecified
Beckman Coulter	IE	Unspecified
BioIVT	US	Unspecified
Capio	SE	Various cancers
Caris Life Sciences	US	Unspecified
Cellmax	US	Colorectal cancer
Chronix Biomedical	US	Unspecified
CirculoGene Theranostic	US	Unspecified
Clinical Genomics	AU	Colorectal cancer
Epic Science	US	Prostate cancer
GRAIL	US	Various cancers
Inivata	GB	Lung cancer
MiRXES Pte	SG	Gastric, breast cancer
OncoGenesis	US	Cervical cancer
OncoHealth Corp.	US	Cervical cancer
Personal Genome Dx	US	Unspecified
RareCyte	US	Unspecified
Roche Diagnostics	DE	Various cancers
VisionGate	US	Lung cancer

Source: FactSet

CHART 42: Public liquid biopsy players

Company	Mkt Cap ($m)	Revenue ($m)	HQ	Application
Roche Holding	204,059	58,085	CH	Lung cancer, solid tumours
Abbott Laboratories	147,878	30,578	US	Bladder cancer
Hologic	13,496	3,218	US	Prostate cancer
QIAGEN	7,483	1,502	NL	Companion diagnostics test for AstraZeneca's Iressa
Bio-Techne Corporation	7,414	714	US	Prostate, lung, solid tumours
Guardant Health	5,934	91	US	Lung, breast, colorectal cancer
Genomic Health	2,529	394	US	Breast, prostate, colon cancer
Natera	2,300	258	US	Companion diagnostic for AstraZeneca's Lynparza
Myriad Genetics	2,115	851	US	Ovarian, breast, skin cancer
PlexBio Co.	1,382	2.7	TW	Colorectal cancaer
OPKO Health	1,287	990	US	Prostate cancer
Veracyte	1,163	92	US	Lung, thyroid cancer
Biocartis Group	350	33	BE	Colorectal, lung cancer
Castle Biosciences	309	23	US	Skin cancer
Lineage Cell Therapeutics	147	1.4	US	Lung cancer
ANGLE	142	0.9	GB	Unspecified
Pacific Edge	110	2.6	NZ	Bladder cancer
OncoCyte Corp.	109	-	US	Lung cancer
Biolidics	61	0.9	SG	Unspecified
MDxHealth	61	28	BE	Prostate, bladder cancer
Oncimmune Holdings	57	0.3	GB	Lung cancer
Vermillion	51	3.1	US	Ovarian cancer
Epigenomics	49	1.8	DE	Colorectal, lung, liver cancer
StageZero Life Sciences	19	0.2	CA	Colorectal, lung, prostate, breast cancer
Biocept	19	3.3	US	Gastric, breast, lung, other cancers
Trovagene	9	0.4	US	Lung cancer

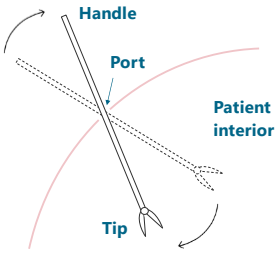
Source: FactSet, as of 01/10/19

Surgery remains the mainstay of early treatment

Robotics expected to provide mass access to minimally invasive surgery

Although conventional open surgery remains dominant in the treatment of most cancers, we anticipate a steady increase in the use of robot-assisted surgery ("RAS"), due to the increasing availability and greater choice of robotic systems at significantly reduced costs, coupled with the increasingly early diagnosis of non-metastatic cancers. Given a variety of advantages compared with open surgery, manual laparoscopy has found widespread adoption across most invasive surgical specialties. The reduction of the incision size minimises scarring, blood loss and risk of infection, leading to a shorter recovery period and hence significant health-economic improvements. However, while the advantages of manual laparoscopy are well established, two major shortcomings limit practicality: a lack of surgeons that are adequately skilled to reliably perform these difficult procedures, and the poor ergonomic conditions under which the procedures are commonly performed. This causes fatigue and discomfort which can adversely affect surgical outcomes. RAS devices have been designed to overcome these deficits with multiple proven benefits (CHART 44).

CHART 43: Fulcrum effect



Source: goetzpartners Research

CHART 44: Advantages and drawbacks of robotic surgery over manual laparoscopy

Advantages	Disadvantages
Eliminates fulcrum effect (CHART 43)	Lack of tactile feedback
Improved ergonomics	High capital costs
Depth perception	Bulky instruments and lengthy installation
Reduction of physiological tremor	System maintenance
Scaling of hand movements	Lack of direct access to the patient
Seven degrees of freedom of the instruments	Unproven efficacy
Reduced surgeon fatigue	Chance of breakdown
Shallower learning curve	Surgeon is located outside of the sterile field
Potential for telesurgery	

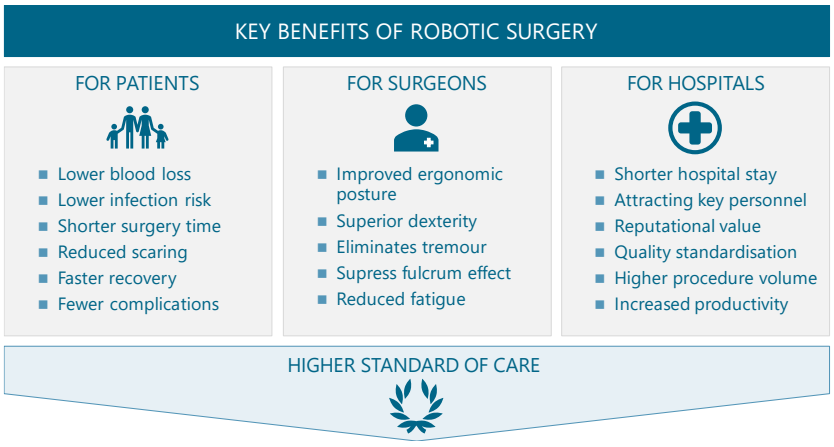
Source: goetzpartners Research, NBCI, SAGES

While robotic techniques dominate specialities such as urology and gynaecology in the US, the cost of the available systems and their running expenses have restricted adoption either for other procedures or in more economically constrained, payor driven healthcare systems outside the US.

Robotics enable increase dexterity, reduce skill-based errors

Most importantly, robotic systems eliminate the fulcrum effect, which describes the fact that during manual laparoscopy, the instrument's distal ends move in opposite direction to the surgeon's hand, making handling non-intuitive and difficult to learn (CHART 43). Furthermore, robotic instruments can be controlled more precisely, offer augmented dexterity to the extent of full 360° rotation, remove hand tremor and are more akin to using open surgical tools. In light of these and many other advantages for patients and healthcare providers (CHART 45), we anticipate that robotic surgery will become dominant across general surgery, including surgical oncology.

CHART 45: The benefits of robotic surgery for stakeholders



Source: goetzpartners Research

Constrained healthcare budgets and smaller hospitals have struggled to justify the significant capital outlay for currently marketed robotic systems

Adoption constrained by high capital costs and poor utility

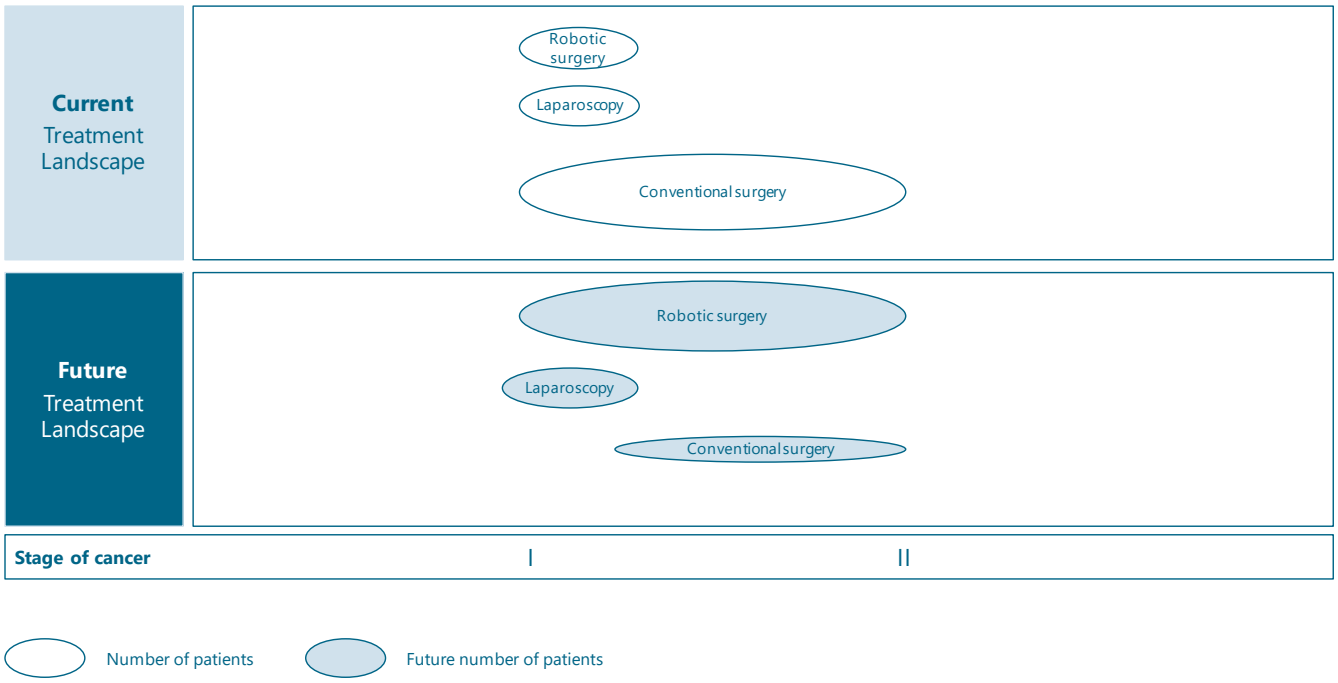
A critical factor limiting the global adoption of robotic surgery is the high capital and maintenance cost associated with robotic systems. Apart from the US market, global penetration has been relatively modest, especially in regions where hospital financing capacity and reimbursement flexibility in the healthcare sector are more restricted. Having held a near monopoly in robotic surgery for the last 20 years, Intuitive Surgical has leveraged the absence of legitimate competition combined with increasing clinical demand for robotic surgery to maintain a high-price strategy. While some competitors such as TransEnterix have attempted to set foot in the market, ISRG has capitalised on the proven technical efficiency of the da Vinci robotic platform to remain market leader.

Historically a monopoly, new entrants will drive down system costs and drive innovation, opening up significant opportunities for both large and small new players, particularly in Europe and Asia

Expiration of Intuitive Surgical's intellectual property opens market to new players

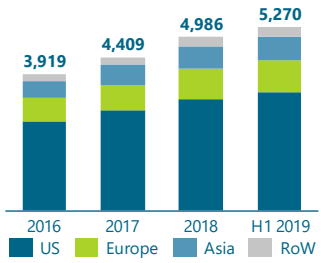
The expiry of many key patents that have, until now, enabled Intuitive Surgical's market dominance, has encouraged a variety of large and small players to enter the field. The resulting innovation and ambition to drive down system costs is expected to substantially boost adoption of robotic surgery in general surgery as well as outside the US. Based on an extensive installed base of more than 3,400 systems in the US and c.5,300 worldwide, we expect Intuitive Surgical to maintain its dominance in the US. Nevertheless, we see considerable opportunity for new entrants offering both innovative and more cost-effective solutions in other markets, particularly in Europe and Asia. While several larger players including Verb Surgical (J&J and Google's Verily joint venture) and Medtronic have systems in development, there are many privately held surgical robotic pure plays that investors should also have on their radar as their products move towards the market and the companies consider public listings.

CHART 46: Robotic surgery is currently underutilised, but potential exists to standardise treatment with the introduction of enabling tools



Source: goetzpartners Research

CHART 47: da Vinci installed base

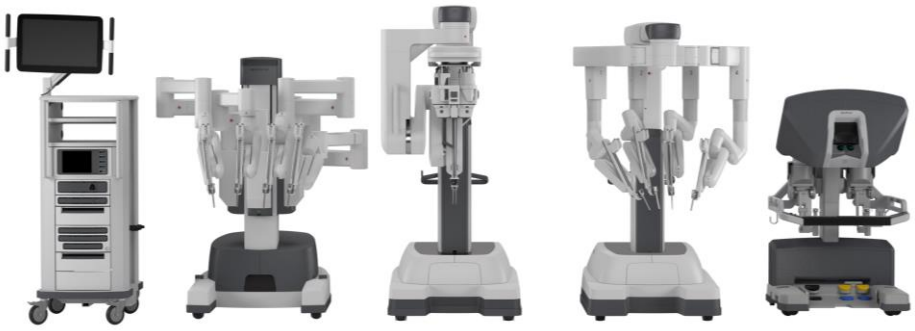


Source: Intuitive Surgical

RAS is currently confined to a few areas

Surgical intervention in cancer is still dominated by conventional open surgery. There has been a growth in minimally invasive laparoscopic (keyhole) surgery. However, the surgical skill required and the difficulty in teaching it have restricted its adoption. Although these problems can largely be overcome using RAS, the high cost and a lack of innovation have restricted the use of the technology much beyond a few core procedures. Robot techniques dominate urology and gynaecology procedures in the US, with over 80% of prostatectomies and hysterectomies performed using the da Vinci platform (CHART 48). As of the end of H1/2019, Intuitive Surgical had 5,270 systems worldwide (CHART 47).

CHART 48: da Vinci 4th generation platform



Source: Intuitive Surgical, goetzpartners Research

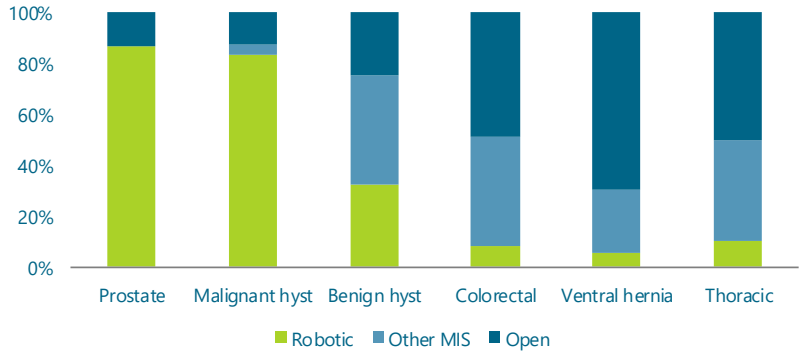
Intuitive Surgical patents has blocked new market entrants

Robotic surgery is dominant in US urology and gynecology, and present in c.90% of surgical hospitals

While there has been significant adoption of minimally invasive surgery ("MIS") for colorectal, ventral hernia and thoracic surgery, the adoption of robotic surgery beyond urology and gynaecology and outside of the US has been relatively poor, (CHART 49), despite availability of the technology for nearly twenty years. The dominant IP position of Intuitive Surgical has restricted market entrants and innovation in these specialties. The high capital and running costs have restricted adoption of the technology in more cash constrained markets outside the US both in Europe and Asia.

There is a significant demand for robotic systems in general surgery and markets ex-US

CHART 49: Robotic surgery penetration, 2015



Source: Intuitive Surgical

New players aim to lower costs

Book price for the da Vinci systems is typically $1.5m - $2m, recurring costs for accessories and instruments range from $700 - $3,500 per procedure, and service fees total c.$150k per year

The significant gap in the market left by Intuitive Surgical has encouraged several others to enter the space. These new entrants are typically well funded and originate from several industry sectors such as medical device manufacturers, technology companies and smaller start up entrants. Thus, we see these entrants as providing legitimate competition for Intuitive Surgical as a result of innovative technologies and a dramatic decrease in both the per surgery and upfront cost. Several players with systems in development such as CMR and Medtronic have a stated aim of reducing the per surgery cost of RAS to be equal to that of manual laparoscopy. This is expected to both increase adoption and drive higher utilisation of robotic systems. Modularity is also a key feature of new systems in development. This provides hospitals with flexibility when acquiring systems and also drives utilisation by allowing for more efficient use of operating rooms.

Single port vs. multiport systems

Robotic systems for soft tissue surgery typically come in one of two configurations: multi and single port. Multiport systems utilise a number of small incisions through which the robotic instruments pass, whereas single port systems, such as the da Vinci SP use a single, larger incision. By using a single incision, single port systems are designed to conform to an ever more literal interpretation of minimally invasive surgery. However, these systems have only recently started to enter the market and hence long-term clinical evidence on infection rates and efficacy vs. multiport is yet to be established.

CHART 50: Approval status for marketed and developmental robotic surgery systems

	System	FDA	CE mark
Multiport systems			
avateramedical	avatera	×	× (2019E)
CMR Surgical	Versius	×	✓
Distal Motion	Dexter	×	×(2020E)
Intuitive Surgical	da Vinci Xi	✓	✓
Intuitive Surgical	da Vinci X	✓	✓
Meere Company	REVO-I	×	×
Medtronic	Hugo	× (2022E)	×(2021E)
TransEnterix	Senhance	✓	✓
Verb Surgical	Unknown	× (2020E)	×
Intuitive Surgical	da Vinci SP	✓	×
Medrobotics	FLEX	✓	✓
Titan Medical	SPORT	× (YE2020E)	×

Source: goetzpartners Research

Decreasing costs and improved utilisation will drive adoption

There is a need for systems that provide a significant technological improvement to make the surgical robot an indispensable tool as opposed to a niche technology

The clinical advantages of minimally invasive surgery are well documented. The large incisions associated with traditional open surgery can leave the patient exposed to many risks, including blood loss, post-operative infection, and scarring. Whilst manual laparoscopy is often faster in terms of OR time and post-operative recovery, the efficacy of robotic techniques is yet to be proven in practice. Thus, the major outstanding question for the current paradigm of robotic surgery is whether the advantages outweigh the capital cost.

Large medtech unable to pass on opportunity

We see significant competition to Intuitive Surgical from multinationals and well-funded independent ventures

Although initially critical of the potential for robotically assisted procedures, perhaps due to their significant vested interest in conventional laparoscopic tools, both J&J and Medtronic have announced their intention to enter the market through new proprietary systems currently in late-stage development. As opposed to generating costly in-house technologies and IP, strategy has focused on adopting robotic surgery programs through bolt on acquisitions, de-risking development. Both companies have deep pockets for R&D activities, and synergies with subsidiary companies Covidien and Ethicon will provide potential to leverage product loyalty.

High M&A deal flow highlights demand from large corporates

A recent surge in M&A activities within surgical robotics has led to an overall increase in valuations across the sector. Strategic acquisitions have been particularly prevalent with J&J most recently acquiring Auris Health for $3.4bn, Medtronic acquiring Israeli company Mazor Robotics at and enterprise value of $1.7bn and Siemen's Healthineers acquiring Corindus Vascular Robotics for c.$1.1bn (expected to complete in Q4 2019). We have summarised selected M&A deals in CHART 51 below.

Cost reduction to facilitate penetration

Retail price for the da Vinci systems is typically $1.5m - $2m, recurring costs for accessories and instruments range from $700 - $3,500 per procedure and service fees total c.$150k per year. With companies such as Medtronic and CMR expected introduce systems that lower the per procedure cost to be in line with manual laparoscopy, we expect a significant increase in the number of hospitals procuring robotic systems in underserviced regions such as Europe and Asia. Lower costs and hence more systems per hospital will also facilitate the adoption of robotic techniques in a wider range of specialties as systems will no longer be monopolised by urology and gynaecology departments.

CHART 51: M&A in the robotics space

Date	Target	Acquirer	Rationale	EV ($m)	Implied EV/Sales
Aug-19	Corindus Vascular Robotics	Siemens Healthineers	Expand Siemens's advanced therapies portfolio through the addition of Conrindus's CorPath vascular robotic system	1,100	102.0x
Feb-19	Auris Health	Johnson & Johnson	Acquire Auris' surgical robotics platform, potentially as a hedge against J&J's Verb Surgical partnership with Verily (Alphabet)	3,400	N/A
Nov-18	Invuity	Stryker Corporation	Add Invuity's enhanced visualisation instruments to orthopaedic portfolio	190	4.8x
Sep-18	Mazor Robotics	Medtronic	Allow Medtronic to gain a foothold in the orthopaedic surgical robotics market	1,700	26.2x
Jul-16	Medtech	Zimmer Biomet	Acquire the ROSA Brain and ROSA Spine systems, complementing Zimmer Biomet's orthopaedic device portfolio	132	13.2x
Apr-16	Hansen Medical	Auris Health	Merger consolidate Auris' technology platform, providing flexible catheter manipulation technology from the Magellan intravascular system	80	5.0x
Oct-15	Blue Belt Technologies	Smith & Nephew	Add Blue Belt's CT free Navio navigation system for arthroscopy	275	14.5x
Sep-13	Mako Surgical	Stryker Corporation	Acquire the Mako partial knee, total knee and total hip surgical platforms for orthopaedic procedures to feed synergies with Stryker's orthopaedic device portfolio	1,650	16.0x
Median					**14.5x**
Mean					25.9x

Source: Mergermarket, press releases, goetzpartners Research

c.60% of operations are open procedures

Procedure growth and expansion in new areas supported by technology progress

The gap in penetration between the US and Europe is driven by the varying revenue models. The US system is driven by patient demand whereas a payor driven model persists in Europe. A combination of fast-paced technological progress and extended clinical coverage of robotic surgery is likely to yield substantial growth in robotic procedure volume, primarily fuelled by (1) further penetration in procedures where the clinical relevance and economic viability of robotic surgery has become more evident; (2) extension to other procedures / specialties where robotic surgery is progressively gaining traction; and (3) the emergence of enabling technologies supported by clinical evidence which will in turn fuel demand in underpenetrated payor-driven regions. Given the arguments around the cost of cancer care, long-term efficacy data and economic viability will form a crucial role in the health economic argument for robotic surgery.

CHART 52: Reduced cost will be a significant driver for the widespread adoption of robotic techniques in surgery

Clinical	• MIS is associated with lower infection rates and shorter hospital recovery time • Robotic surgery facilitates MIS uptake due to lower skill-based barriers to entry • MIS promoted by earlier diagnosis
Economic	• Increased availability of lower cost robotic technology • Elimination of the cost gap between robotic and manual laparoscopic procedures • Shorter OR time and hospital stay improve hospital economics • Reduced economic burden as a result of quicker recovery and lower infection
Scientific	• Intuitive Surgical patent expiration facilitates new entrants joining the market • Innovation drives the development of enabling tools due to higher competition • Drive towards integrated solutions for the OR as a whole

Abbreviations: MIS, minimally invasive surgery
Source: goetzpartners Research

Further benefits of robotic surgery hinge on additional enabling technologies

We see the introduction of new technologies as a key future driver of the surgical robotics market, especially into new experimental disciplines where positive clinical evidence is yet to be established. Technological improvements such as a systems integration approach, software consolidation and data amalgamation will make the surgical robot an indispensable tool in the modern operating room ("OR"), resulting in faster adoption. The conventional radiotherapy market underwent a similar transition whereby linear accelerators enjoyed accelerated demand driven by new additional technologies (e.g. treatment planning software, VMAT), which allowed for greater accuracy and treatment efficacy. In the context of oncology surgery, improved surgical tools (e.g. guided surgery) are particularly relevant, as the complete removal of cancerous tissue whilst sparing healthy tissue is critical to successful outcomes.

Demand for integrated OR solutions

There is a need for systems that provide a significant technological improvement to make the surgical robot an indispensable tool as opposed to a niche technology. Such systems will be more intelligently designed to improve hospital workflows, improve the tools available to surgeons (easier surgery facilitates less time per operation = higher volume), and optimise surgical outcomes for patients. ORs are becoming increasingly complex with limited data sharing across systems from different providers creating information silos. The surgical robot can become a key pillar in the modern, integrated OR by amalgamating data channels to add proven additional value which in turn should drive uptake.

Capital costs remain the largest barrier to entry… for now

The economic benefits of minimally invasive surgery have been well documented. The major barriers to adoption have been the capital cost of the system and running costs with respect to consumables, but these are expected to reduce significantly as new players enter the market over the next two to three years. While Intuitive Surgical's installed base will remain a significant hurdle to new entrants in the US, we believe that lower costs combined with increased innovation should be a major driver for the adoption of robotic surgery, particularly in oncology, in Europe and Asia. The key challenges for widespread adoption of robotic techniques are summarised in CHART 53 below.

CHART 53: Challenges

Clinical	• Limited uptake beyond core specialties • Resistance from surgeons to adopt new technologies/techniques • Clinical benefits unproven and not yet quantified • High risk oncology procedures may see slower penetration
Economic	• High upfront capital costs in addition to high per procedure cost • Additional infrastructure required to sterilise instruments between surgeries • Budget-constrained healthcare systems in Europe and Asia
Scientific	• Innovation stifled by cost constraints • Instrument degradation during reprocessing • Closed system architecture promotes information islands within the OR

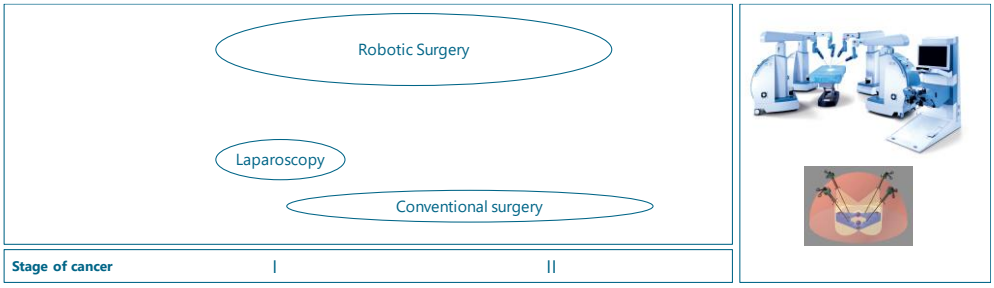
Source: goetzpartners Research

Future treatment landscape and use in precision medicine

Innovation should see robotic surgery adopted as standard of care across surgery

The ability of RAS to extend the advantages of laparoscopy should drive its adoption as the standard of care (costs permitting) in all but a few specialist situations. Although some surgeons may initially resist adoption, the increased safety and efficiency of robotic surgery means that the main barrier to adoption is cost. The need to remove smaller cancers due to earlier diagnosis will require more precise surgery in order to minimise collateral damage to the surrounding organs and tissue. This can be achieved through the use of robotic systems, which should help drive its widespread adoption in oncology.

CHART 54: Future treatment landscape



Source: goetzpartners Research

Significant market opportunity

$4bn current market only represents 2% of the potential opportunity worldwide

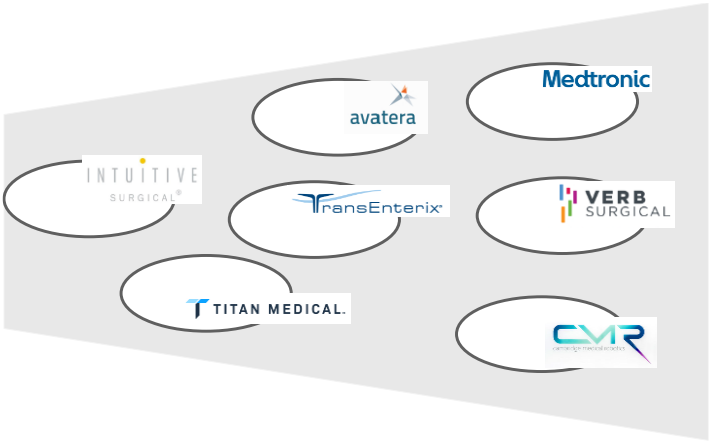
The potential for robotic surgery is substantial. Valued at around $4bn and projected to reach $13bn by 2025E, thus far the technology has only been widely adopted in urology and gynaecology in the US, accounting for around 2% of the total potential procedures worldwide. With an installed base covering 70% of the larger hospitals in the US, Intuitive Surgical is well established in this substantial market. The company has already attempted to protect against new entrants with the introduction of the cheaper X model. Europe and Asia are still largely up for grabs. It is only the availability of technology at the right price point that is holding the market back. Hence, there are significant opportunities for new entrants who can provide innovative, cost-effective solutions.

Winners and losers are hard to call

New players will look to take market share not only from Intuitive Surgical but also manual laparoscopy and open surgery

Multi-national players such as Medtronic, J&J and Verb Surgical are favourites to take a substantial share of this developing markets. Backed by influential key opinion leaders, some of the smaller start-ups have already established a lead in development and may become attractive acquisition targets for other players looking to gain a foothold in this market. Winners and losers are difficult to call given the lack of detail on the underlying technologies and limited clinical experience with competing systems.

CHART 55: Selected robotic surgery players



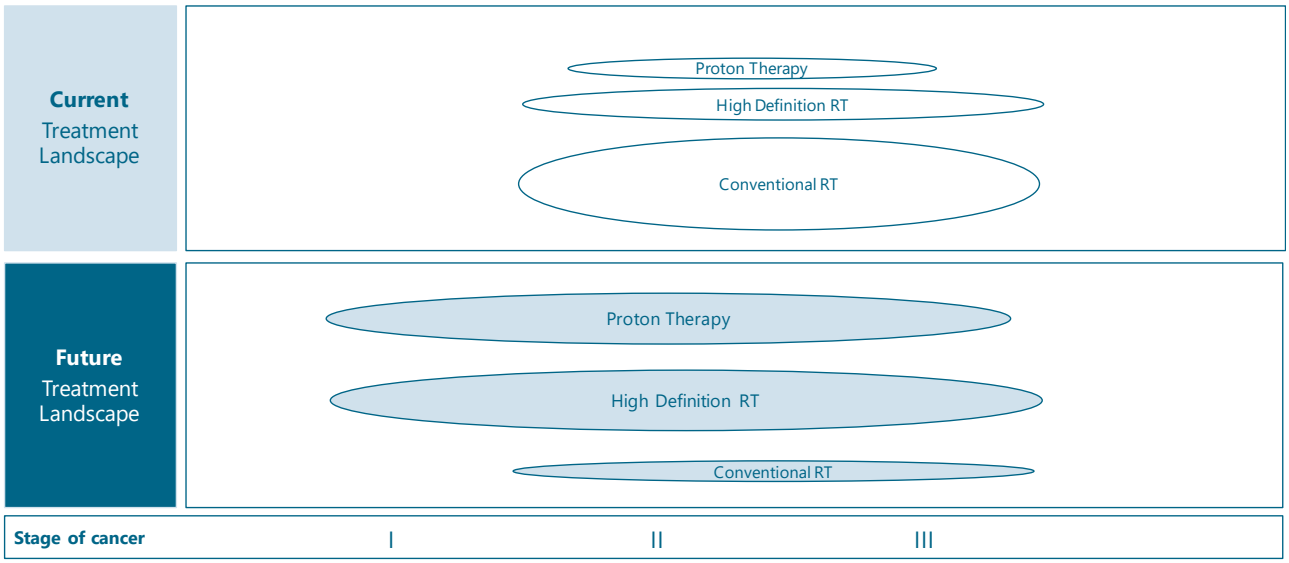
Source: goetzpartners Research, Company logos from Company websites

RadioTx dominated by conventional technologies

VMAT was the last significant innovation implemented into RT systems

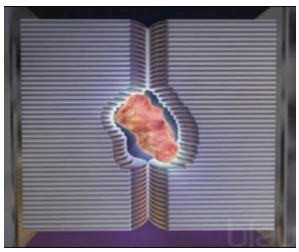
The last decade has brought several new technologies into clinical practice that target tumours with greater precision. In this section, we briefly explain the technology underlying both photon and particle-based RT and the limitations associated with such techniques. The evolution of RT techniques since 1990 has changed the way it is used for cancer patients. The most recent innovation which has resulted in significant capability advances was volumetric modulated arc therapy ("VMAT"), an advanced form of intensity modulated radiation therapy ("IMRT") that delivers a precisely sculpted 3D dose distribution with a 360-degree rotation of the gantry in a single or multi-arc treatment. This is achieved in a much shorter time period, reducing treatment time from 8 - 10min to less than 2 minutes.

CHART 56: Proton therapy and high definition radiotherapy will play an important role in the future treatment landscape



Source: goetzpartners Research

CHART 57: Multi leaf collimator

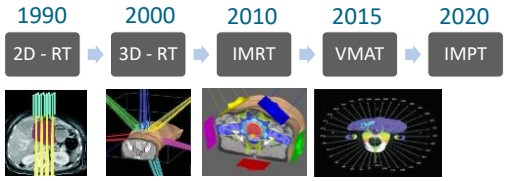


Source: Blausen Medical

The multi-leaf collimator ("MLC"), a photon-based technique, allows for the rapid shaping of the beam to conform to the shape of the tumour and improve healthy tissue sparing, but toxicity is still significant (CHART 57). Below we list trends in this space:

- **Particle therapy over photon-based RT**: Particle therapy enables more precise targeting based on the physical properties of particles, as explained in more detail in the next section;
- **Improvement of RT techniques such as adaptive radiotherapy ("ART")**: New techniques to adapt treatment plans to anatomical variations and tumour progress (growth / shrinking) has and should continue to make state-of-the-art instruments using photons and particles more efficient / precise;
- **Software improvement of modern treatment planning systems ("TPS")**: Better software improves the planning and delivery of the beam during the treatment regimen;
- **Imaging techniques**: Imaging before and especially during treatment still has significant development potential. The integration of imaging techniques with better resolution of soft tissue should help to improve delivery.

CHART 58: The evolution of beam modality technologies for conventional radiotherapy

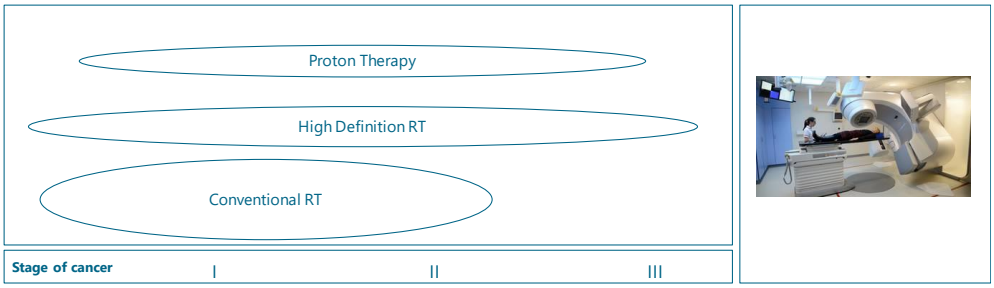


Source: ESTRO 2016, Turin; goetzpartners Research

LINACs remain the most widely used technology

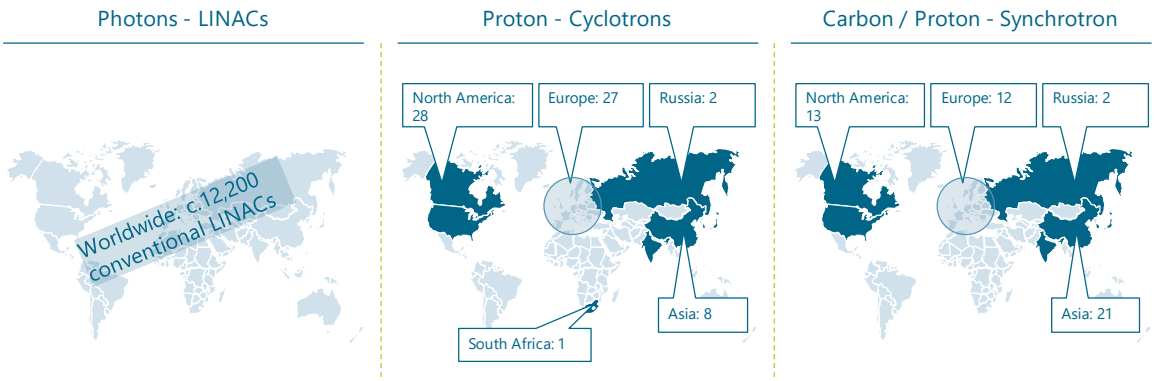
Linear accelerators currently dominate the RT field, with growth outside of the US in particular expected to be driven by underuse. Innovation of LINAC hardware has stagnated following the introduction of IMRT with the software market in the US growing significantly faster than that for hardware. Software such as treatment planning systems ("TPS") and oncology information systems ("OIS") is more profitable, and independent developers such as RaySearch and Neusoft are gaining market share.

CHART 59: Current treatment landscape for radiotherapy



Source: goetzpartners Research

CHART 60: Status quo of photon and particle facilities



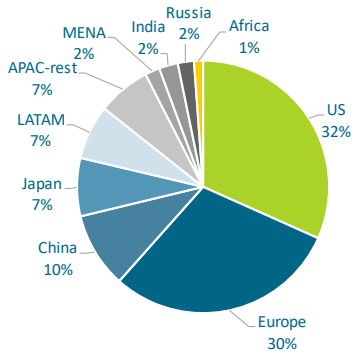
Source: Directory of Radiotherapy Centres, Particle Therapy Co-operative Group, goetzpartners Research

CHART 61: Number of LINACs per region

Region	Installed LINACs
United States	3,712
Europe	3,506
China	1,132
Japan	872
LATAM	817
APAC-rest	798
MENA	222
India	283
Russia	243
Africa	135

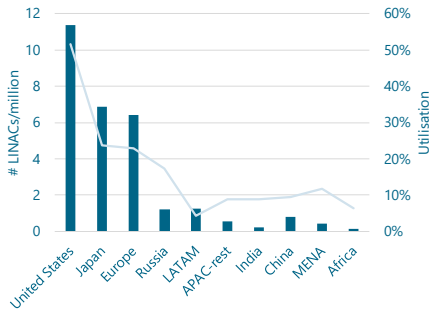
Source: Directory of Radiotherapy Centres, goetzpartners Research

CHART 62: LINAC % distribution by region



Source: Directory of Radiotherapy Centres, goetzpartners Research

CHART 63: # LINACs and utilisation as % of diagnosed cancers

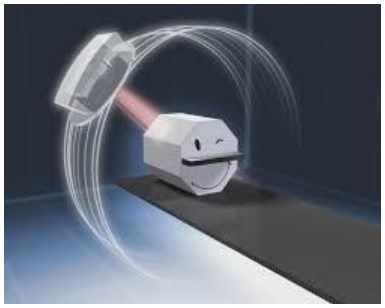


Source: Directory of Radiotherapy Centres, goetzpartners Research

Photon-based technology and its limitations

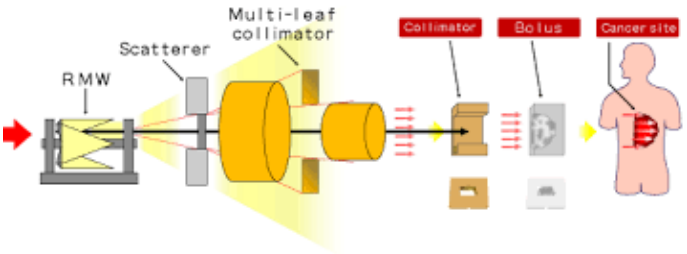
Photons are the most commonly used type of RT treatment for prostate, lung and breast cancer. Since photons have neither mass nor charge, they travel easily through target materials. There is an initial increase of energy as they interact with the electrons in the target material, which enhances the radiation effect. As a result of this, their peak dose is reached within a few centimetres from the entrance surface – the so-called "dose accumulation effect". The radiation decreases as the photons travel through and exit the body.

CHART 64: VMAT is an advanced form of IMRT



Source: goetzpartners Research, ESTRO 2016

CHART 65: IMRT schematic



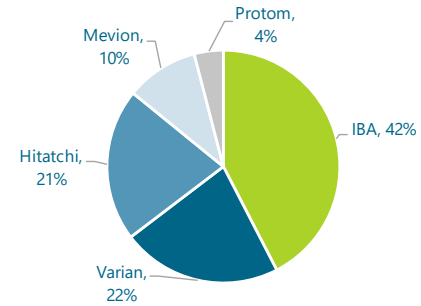
Source: goetzpartners Research, ESTRO 2016

3D plans initially had a significant dose deposition in the entry and exit fields. With multiple field plans, rapid arc or helical techniques, these doses tend to be significantly smaller, although the delivery of a deadly dose to cancer cells often requires low to moderate doses to surrounding organs. The possible side effects include gastrointestinal ("GI") and genitourinary ("GU") problems and potentially a slightly higher risk for secondary malignancies. Therefore, photon therapy does not seem appropriate to treat organs located deep within the body.

Most patients treated with particle therapy have received protons

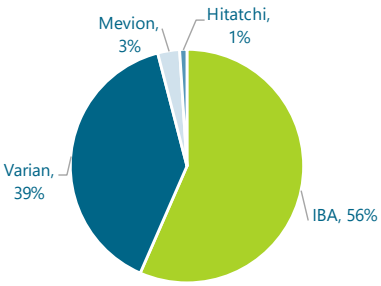
As of 2018, more than 210,000 patients had received therapy with heavy particles, with proton beam therapy ("PBT") accounting for over 190,000 worldwide. Protons are considered low linear energy transfer ("LET") radiation, comparable to photons. Heavy particles include carbon ions, oxygen as well as neutrons. Varian and IBA are at the forefront of industrialising the particle accelerator technology and have launched off-the-shelf products. Software is a driving force of innovation in conventional RT technology, where older RT machines could achieve equal or better results with a good TPS product when compared with the results from a last generation hardware and second tier TPS software.

CHART 66: North America – PT Installed rooms



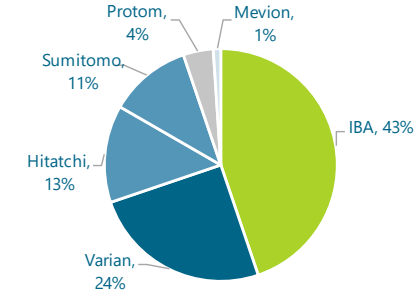
Source: IBA, goetzpartners research

CHART 67: Europe – PT installed rooms



Source: IBA, goetzpartners research

CHART 68: Asia ex. Japan – PT installed rooms

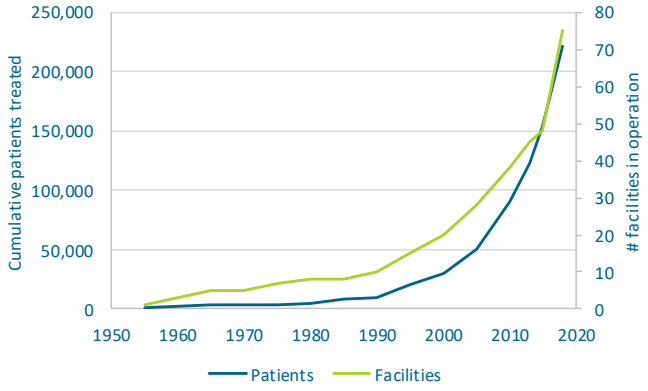


Source: IBA, goetzpartners research

Carbon ion therapy is still in its infancy

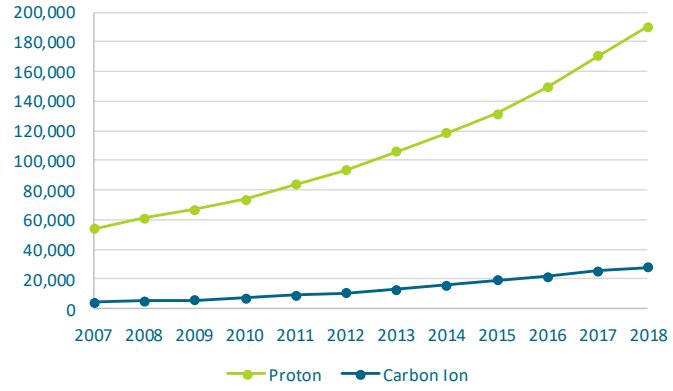
Particles applicable for use in radiation oncology can be charged (protons, carbon ions) or neutral (neutrons). The term "heavy particle therapy" is generally used to distinguish it from conventional X-Ray RT, which uses massless photons. The use of heavy particles other than protons is limited to only seven operating carbon ion facilities worldwide. Treatment with carbon ions can be considered experimental; hence, reliable evidence is only just emerging, and no conclusions can yet be drawn about its effectiveness or toxicity.

CHART 69: Particle facilities in operation worldwide



Source: Particle Therapy Co-Operative Group, goetzpartners Research

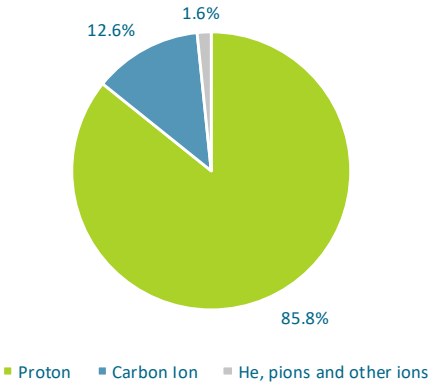
CHART 70: Patients treated with protons and carbon ions worldwide since 2007



Source: Particle Therapy Co-Operative Group, goetzpartners Research

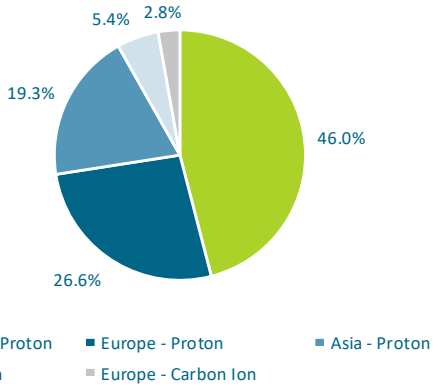
CHART 69 and CHART 70 above show the steep adoption of particle therapy. The underlying factor behind the strong increase in adoption was the addition of better imaging and software products bundled with particle systems. To avoid toxicity to healthy tissues, a key requirement for systems it that the particle beam is precisely controlled. One could make the argument that price hasn't played a big role as particle technology coupled with higher beam precision offers compelling benefits for patients.

CHART 71: Patients treated with particle therapy 1954 - 2018



Source: Particle Therapy Co-Operative Group, goetzpartners Research

CHART 72: Patients treated by particle type – 2018, n=21,683



Source: Particle Therapy Co-Operative Group, goetzpartners Research

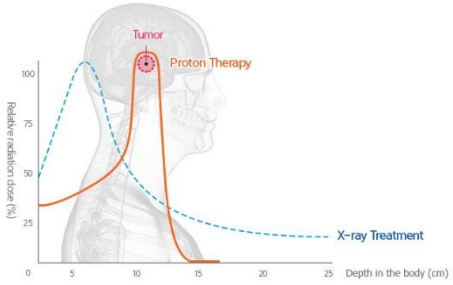
Particle therapy delivers a more effective radiation dose vs. photon beams

Ionising radiation, be it x-ray based (photons), neutrons, ions, protons, alpha particles or heavy nuclei, have a relative biological effectiveness ("RBE") when arriving at the tissue. The RBE is the ratio of biological effectiveness of one type of ionising radiation relative to another, given the same amount of absorbed energy (CHART 74). It is defined as the ratio of doses of photons and charged particles inducing the same biological effect. Knowledge of the depth-dependent RBE values are crucial for the assessment of the potential clinical advantages of ion beams compared to protons, for which in general a constant RBE of 1.1 is assumed for clinical applications. In addition to depth, the RBE also depends on parameters such as ion charge and energy, dose level and the intrinsic radio-sensitivity of the target tissue. Systematic experimental investigation of these dependencies is thus of fundamental importance for the clinical application of ion beams.

Photons ineffective against certain radio-resistant tumours

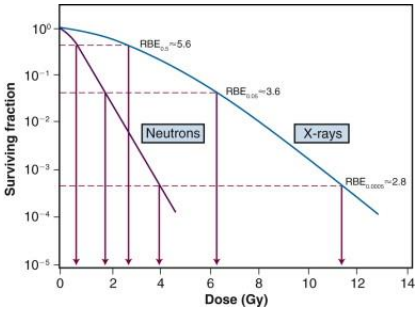
There are many tumour types that are radio-resistant and where photons are non-effective. This means that when cells are radiated, DNA repair mechanisms suffice to fix the damage caused. The heavier the particles and the higher the RBE, the higher the likelihood that enough DNA double strands break beyond repair. To date, clinical evidence for the superiority of intensity modulated PBT over IMRT is low. Available evidence points to fewer side effects with similar tumour control. Future studies could demonstrate a significant advantage not only with regards to precise dose delivery (Bragg peak, CHART 73), but also through better tumour control through the higher RBE (overcoming radio resistance). While we think that PBT has a long way to go, proton players may introduce industrial products for other heavy ions in the next decade.

CHART 73: Bragg peak and energy distribution



Source: Samsung Hospital

CHART 74: Illustration of RBE for x-rays and neutrons



Source: Zeman 2016, *Clinical Radiation Oncology*

CHART 75: RBE for different irradiation methods

Radiation	Energy w_R (formerly q)
X-rays, gamma rays, beta particles	1.0
Neutrons (< 1MeV)	2.5
Neutrons (1 – 50MeV)	5.0
Neutrons (> 50MeV)	2.5
Protons, charged pions	2.0
Alpha particles, nuclear fission products, heavy nuclei	20.0

Source: goetzpartners Research

PBT can lower the risk of treatment related side effects and provide a valuable tool for dose escalation or re-irradiation. Widespread implementation is currently hindered by the cost of the technology and limited approval from healthcare payers. Per treatment fraction, proton therapy is more expensive than standard photon therapy. However, if costs associated with treating side effects, sequential mortality and new hypo fractionation schemes are factored in, proton therapy can be shown to be cost-effective for the management of several tumour types. The current debate around costs tends to overlook the existing evidence from clinical and cost-effectiveness data.

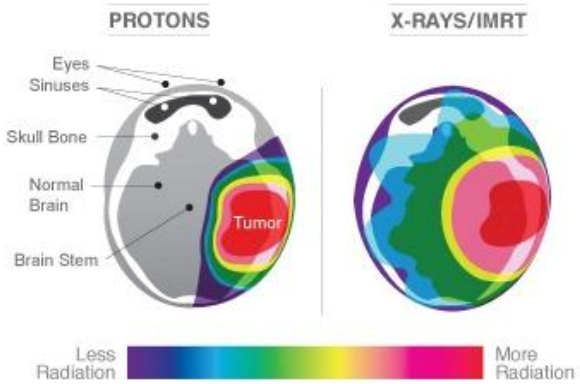
Precise dose delivery of proton beam enables sparing of healthy tissue

More focused beam with less damage of healthy tissue

The main rationale for the use of PBT despite its high cost arises as a result of the beneficial physical properties of the particle beam. A proton beam can be better focused than a photon, thus sparing more healthy tissue. CHART 76 below compares the dose distribution of photon beam (left) and proton beam (right) techniques. In the high dose region near the tumour, the proton beam plan is more conformal to the tumour shape than the proton plan. In the low dose region, there is improved sparing of the normal structures (heart, lung, oesophagus, and spinal cord). For many tumours, calculating an exact dose distribution is essential. For example, when treating breast tumours, critical heart structures and their location in relation to the tumour must be considered. Radiating prostate cancer can cause incontinence and infertility. The treatment of brain tumours requires extra care, particularly in children who are more sensitive to radiation in general.

Implementation of proton therapy is currently hindered by the cost

CHART 76: Comparative dosimetry for photon (left) versus proton (right)

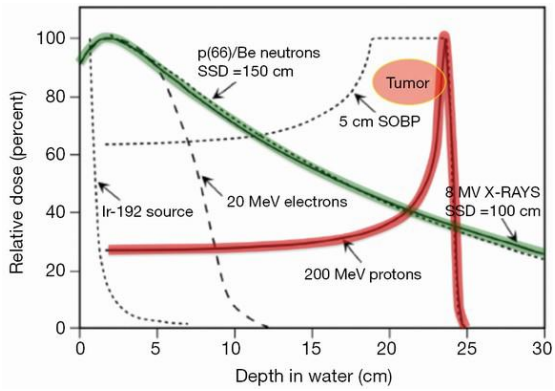


Source: ProCure Training and Development Centre, 2015

Charged heavy particles give up most of their energy immediately before coming to rest

The underlying reason driving the advantages of PBT is the way in which the dose is distributed within the tissue. The physical properties of particles and photons in tissue are illustrated by the Bragg peak, which shows that there is a very small entry dose for protons, with a high-energy disposal at the target and no residual protons passing through the tumour and into the distal tissue (red, CHART 77). In contrast, photons have both an entry and exit beam and continuously lose energy after entering tissue, resulting in a high dose delivered to tissue proximal to the tumour (green, CHART 77).

CHART 77: Dose distribution (photon/proton) – Bragg peak



Source: Huan Giap, Scripps Proton Therapy Centre, San Diego, goetzpartners Research

Proton therapy has shown improved cancer control and decreased toxicity vs. RT

Conformal RT techniques for prostate cancer are expected to reduce urinary and rectal toxicity and improve disease control through facilitation of dose escalation. The increased costs associated with these techniques have led payers and insurers to demand clinical data demonstrating improved disease control and less toxicity. Several comparative-effectiveness studies of conventional radiation therapy, 3-dimensional conformal radiation therapy ("3DCRT"), intensity-modulated RT ("IMRT") and PBT have now been reported. In a randomised study comparing high to low proton boost, Zeitman *et al.* showed a significant increase in PSA-free survival in the high vs. low-dose arm. Since equally high doses can be applied with photons, a randomised trial comparing high dose regimes for photons and protons is warranted.

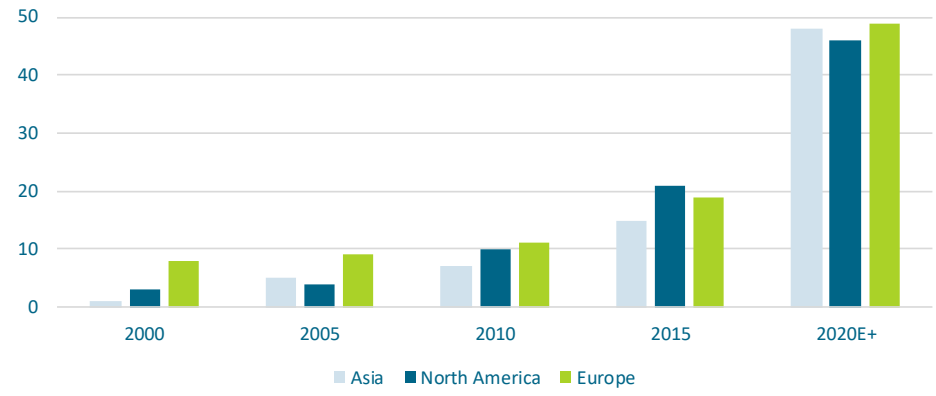
Secondary cancer is one of the main arguments to increase the use of proton technology

Historically, conventional photon therapy (x-ray based) was only used for palliative care (pain relief). This changed with the introduction of IMRT, VMAT and TPS – technologies which have been successfully applied to cure certain tumour types. This has increased the need to limit radiation dose to prevent the formation of secondary cancers (tumour formation years after successful treatment). Consequently, proton therapy has become increasingly clinically relevant as it minimises dose spilling.

Specialist centres to drive rapid growth of proton therapy

Proton therapy is actively and repeatedly discussed within the framework of particle therapy for the treatment of prostate cancer ("PC"). The argument in favour of treating prostate cancer with protons is financial, as small volumes are treated and treatment times are low, resulting in a hypothetical high patient throughput. The world's largest proton centre, Loma Linda in California, focuses almost exclusively on PC treatment and therefore represents an interesting example for commercial success with particle therapy. Similar proton therapy centres are likely to be set up in the foreseeable future, with the number of centres in operation worldwide expected to grow from 97 as of September 2019 to over 135 by 2021E (CHART 78).

CHART 78: Proton therapy centres by geography



Source: Particle Therapy Co-Operative Group, goetzpartners Research

Price trends of drugs put PT costs into perspective. Episode-based models or capitation models could trigger a higher adoption rate of PT in a more holistic treatment approach

Episode-based or capitation models could trigger higher adoption…

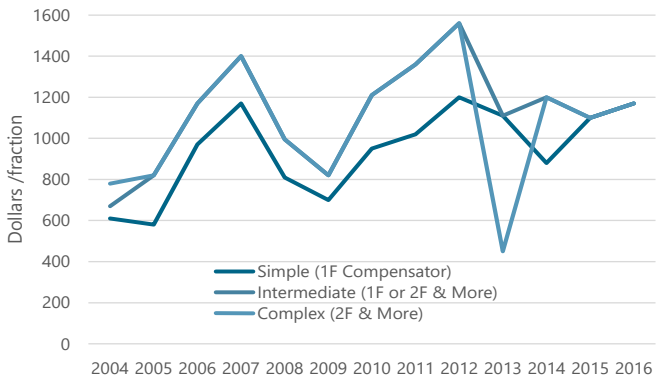
The price trends described in CHART 125 put PBT costs into perspective, in our view. Investors focus on expected price decreases for proton machines and we feel that clinical evidence and improving beam delivery could render the cost debate obsolete. The introduction of expensive cancer treatments has prompted policy makers to explore alternative payment approaches that might rein in costs. We believe there will be more frameworks for "episode-based" payments during cancer treatment, which would cover the costs of drugs and RT for a predefined treatment period. This has the potential to reduce costs and improve patient outcomes. If bundling or episode-based treatment is successful, the concept could be expanded to encompass longer treatment periods across oncology care components.

The drug industry could lose lobbying power with the introduction of capitation models and bundling

… and reduce the use of expensive drugs

The incentives for bundled payment metrics to encourage cost reduction may be too large. In some cases, differences between potential payment levels and care costs are so large that they could encourage physicians to make decisions driven by financial considerations instead of the needs of individual patients. Capitation models could encourage a higher adoption of proton therapy as they would spread the costs over many patients, thus lowering the overall cancer treatment cost. Similar effects were observed for the rationalisation of drug use for dialysis in the US, where the government bundled drugs into overall reimbursed treatment costs and EPO use was reduced by 30% - 40%.

CHART 79: Medicare reimbursement rate evolution (dollars per fraction)



Source: goetzpartners Research estimates

Reimbursement potential of $7.5m per room for proton therapy

We looked up prostate cancer treatment procedures and their costs in the US as an example to put PBT costs in context. CHART 80 below gives an overview of the costs for the clinical treatment course. The average annualised drug cost of $150,000 equates to c.$40m for 250 patients / year. A proton room costs between $18m and $30m (declining) and can treat about 250 patients / year (6,250 radiations p.a. equals 25 radiations per patient). If we assume an investment horizon of 10 years (depreciation period) and a cost of $20m for a PBT room, the average cost per years is $8,000 / patient per year. This would be comparable to the current US reimbursement rate of $1,200 per fraction with 25 fractions per patient, which results in a total cost of $30,000 / patient / year. 6,250 fractions / machine per year would result in annual reimbursement income of $7.5m per year. Including the service charges 7% ($4.2m over three years), the purchase of a PBT system would almost break even after year three.

CHART 80: Prostate cancer treatment costs in the US, 2015

Treatment	Description	Mean cost
Radical prostatectomy	Complete removal of the prostate gland is performed with the use of one of three surgical approaches: radical retropubic prostatectomy, laparoscopic radical prostatectomy or robot-assisted prostatectomy. The latter two are less invasive.	$16,762
Brachytherapy	Brachytherapy with the use of low-dose-rate isotopes involves permanent implantation of seeds that emit a low dose of radiation over a period of several months. Some patients also receive a boost of external-beam radiation therapy or androgen-deprivation therapy.	$17,076
IMRT	Advanced form of three-dimensional radiation therapy. Involves use of a computer-driven machine that revolves around the patient as it delivers radiation. Radiation beams are aimed at the prostate from multiple angles. Intensity can be adjusted to maximise the dose targeted at cancerous tissue and minimize the dose to surrounding healthy tissue.	$31,574
Androgen-deprivation therapy	Hormone treatment that reduces the effects of testosterone, thereby slowing the growth of prostate cancer. Medications are administrated orally or injected to reduce or block circulating androgens.	$2,112
Active surveillance	Active plan to postpone intervention. Typically involves monitoring with office visits every 6 months, prostate-specific antigen testing, digital rectal examination and prostate biopsy.	$4,228
Cryosurgery	Liquid nitrogen or liquid carbon dioxide is used to freeze tissue in order to destroy abnormal cells.	
Stereotactic body radiation therapy	Type of external-beam radiation therapy. Involves the use of special equipment to position a patient and precisely deliver radiation to tumours in the body (except the brain). The total dose of radiation is divided into smaller doses given over a period of several days. Helps spare normal tissue.	
External-beam radiation therapy as a three-dimensional conformal treatment	Also called three-dimensional radiation therapy and three-dimensional conformal radiation therapy. Procedure uses a computer to create a three-dimensional picture of the tumour, allowing doctors to give the highest possible dose of radiation to the tumour, while sparing as much of the normal tissue as possible.	$20,588

Note: The mean cost for each treatment is provided in 2015 USD. Reliable cost-estimate data are not available for cryosurgery and stereotactic body radiation therapy because these procedures are much less common than the other procedures listed.
Source: NEJM, 2015

The average cost of cancer surgery in the US ranges from $14,161 (robot assisted) for a prostatectomy to $56,587 for a pancreatectomy. The average costs of chemotherapy (includes both modern combined with standard chemo in most cases) is c.$102,395 / year. Following on from the table above, the more important and crucial question is the extent to which particle therapy (proton, carbon, helium etc.) can penetrate the RT market.

CHART 81: Comparison for US cancer treatment costs

Cost	Modern therapy Immune therapy (+)	Standard therapy Chemotherapy (*)	Modern therapy Proton therapy	Standard therapy IMRT RT
Material cost (1)	$90,000	$1,200	$8,000	$2,800
Service cost (2)	-	-	$5,600	$980
Treatment (3)	$2,800	$2,800	$2,800	$2,800
Hospital stay	$10,000	$10,000	$7,500	$7,500
Total cost	$102,800	$14,000	$23,900	$14,800
Reimbursement	$113,080	$15,400	$40,000	$35,761

(*) standard chemotherapy are cytostatics like 5-FU, leucovorin
Note: (1) PBT machine $20m depreciated over 10 years, 25 fractions per patient and 250 patients per year; for RT we calculated $3,5m per machine and same patient/fractionation assumptions for drugs we assumed 3 rounds/year and standard chemo $400/round and modern drug costs $30,000 per round. (2) Service costs are 7% of purchase price/#of patients per year; (3) treatment assumes staff 1 oncologists and three support staff members per machine (physicists, nurses, Radiologists etc. (+) modern drug therapy includes biologics like Avastin, Herceptin etc.
Source: goetzpartners Research

Clinical studies and early evidence for new advantages of PBT over RT

There are several published reviews comparing IMRT with particle therapy. While there is still not much evidence from direct head-to-head trials, there are several published *meta analyses* published showing the superiority of particle therapy. In dosimetric studies of a small patient group, Vargas *et al*. showed a reduced mean rectal (59%) and bladder (35%) dose for PBT compared to IMRT. Early outcomes from single arm, prospective trials confirmed these results. Nihei *et al.* described the incidence of late grade ≥2 rectal and bladder toxicity at 2 years to be 2.0% and 4.1%, respectively.

Proton therapy associated with lower toxicity

Similarly, another study found positive early outcomes with image-guided proton therapy, suggesting high efficacy and minimal toxicity with 1.9% grade 3 GU symptoms and <0.5% grade 3 GI toxicities. Generally, the dose to healthy tissues was substantially lower with PBT, in the range <50% of the target prescription. A retrospective analysis of the Medicare database compared early toxicity in 421 men using PBT with 842 matched controls treated with IMRT. A statistically significant decrease in GU toxicity was observed for PBT at 6 months. Other studies have also found IMRT to be favourable over PBT with regard to toxicity. An analysis from the Medicare Surveillance, Epidemiology, and End Results ("SEER") database in the US identified 684 men treated with PBT between 2002 and 2007 and compared these with a cohort treated with IMRT.

High-risk patients benefit but overall survival improvement not yet established

A few major studies have been conducted to assess the impact on overall survival of PBT. One dose-escalation study was carried out at The Proton Centre in Boston. Zietman *et al.* randomised 393 patients with PSA <5 ng/ml to a low-dose arm (50.4 Gy photon therapy + 19.8 GyE proton boost) and a high-dose arm (50.4 Gy photon + 28.8 GyE proton boost). The analysis revealed a significant difference in biochemical recurrence-free survival in favour of the high-dose arm. Subgroup analysis of low and high-risk patients (depending on the Gleason score) showed a significant advantage for the high-dose group in both cases. An impact on OS was not observed, but there was also no increase in either acute or late toxicities in either arm compared to the incidence of comparable photon studies.

A Phase III trial comparing PBT to IMRT for low or intermediate risk prostate cancer (PARTIQol) started in 2012 and is expected to complete in 2021E

Finally, the American Society for Radiation Oncology ("ASTRO") conducted an evidence-based review of the use of PBT in different tumour types which resulted in its recommendation for use in treating several tumours including CNS and paediatric malignancies. For select other tumours such as prostate cancer, ASTRO recommends treatment only within the context of clinical trials. Whiles PBT showed efficacy, there was no evidence suggesting its superiority over photon-based approaches.

A high publication rate confirms continued high interest in PBT and its characteristics. Reading such publications gives the impression that the authors often take a similar stance to ASTRO, which concludes the abstract of its evidence-based review with the words: "More robust prospective clinical trials are needed to determine the appropriate clinical setting for PBT". There is much discussion and disagreement concerning toxicities, cost–effectiveness, and the potential for better outcomes. Several trials are underway, among them a multi-institutional randomised Phase III study (A Phase III Randomised Clinical Trial of Proton Therapy Versus IMRT for low or intermediate risk PC; clinicaltrials.gov ID NCT01617161) comparing PBT to IMRT. It is now in its eight year and, together with others, should shed some light onto the discussion of PC and RT with photons and particles, potentially allowing for individualised RT ("iRT") concepts.

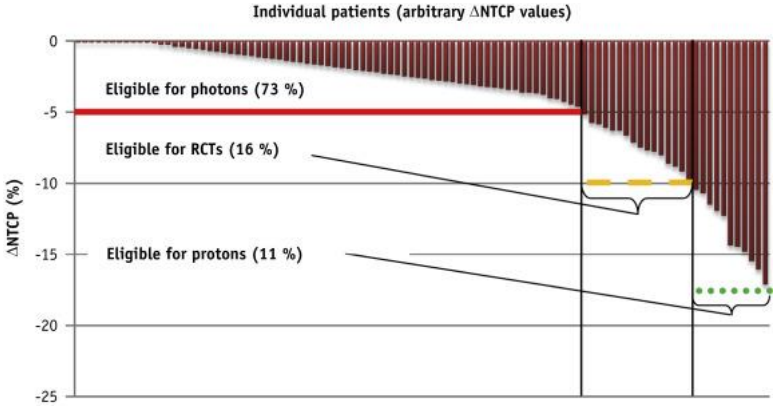
New approach in Holland, which is based on normal tissue complication probability ("NTCP") models has been adopted to select patients for PT vs. RT

There is an ongoing discussion regarding the lack of evidence for proton treatment for multiple potential indications. Even for the most widely accepted condition, paediatric tumours, it is unclear if superiority of protons over photons has been sufficiently demonstrated. Dutch scientific and healthcare governance bodies have recently issued landmark reports regarding the generation of relevant evidence for new technologies in healthcare including PBT. An approach based on normal tissue complication probability ("NTCP") models has been adopted to select patients who are most likely to experience fewer (serious) adverse events achievable by state-of-the-art proton treatment. While the above model appears to be critical of a wider utilisation of PT in cases, it is a firm step towards a much wider adoption of PT than the *status quo*. The NTCP model suggests that 11% of diagnosed cancers are eligible for PT.

Proton therapy's high precision is a major driver for adoption

The increasing cost of drug therapies and inappropriate use of late-stage treatments are a serious challenge. RT is growing in importance, driven by improving precision to treat tumours by minimising the toxicity to the tumour-surrounding tissue. While the US has already embraced the use of RT with a utilisation rate of >50% for the treatment of diagnosed cancers, Europe and other regions have significantly lower adoption rates. The industry is likely to benefit from regions catching up with ASTRO and ESTRO recommendations (between 40% and 55%).

CHART 82: Waterfall plot of ΔNTCP (protons minus photons) – eligibility plot for appropriate RT technologies per tissue



Source: Widder *et al. 2016, International Journal of Radiation Oncology • Biology • Physics, ASTRO*

CHART 83: Proton therapy drivers

Clinical	• Growing base of clinical data • High utilisation of radiotherapy to treat cancer due to high precision in targeting tumours
Economic	• Proton therapy may have high treatment costs but has fewer side effects and can therefore be as cost effective as conventional radiotherapy
Scientific	• Improvements to treatment planning and imaging software will allow for increasingly targeted treatment • High rate of scientific publication
Other	• Underuse of radiotherapy in emerging markets presents significant upside potential

Sourcfe: goetzpartners Research

We believe that over time, PT will overcome the limitations of conventional LINACs and enjoy more widespread adoption. Key challenges that need to be overcome include high installation costs, although these have already fallen materially in the last 5 - 10 years and the sheer size of these systems (e.g. cyclotrons). These and other barriers to adoption are summarised in CHART 84.

CHART 84: Challenges to adoption for proton therapy

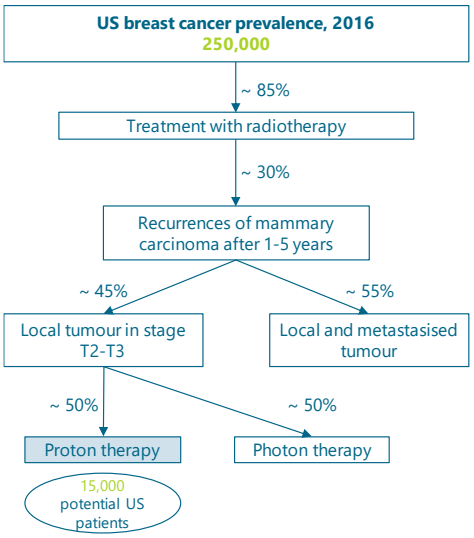
Clinical	• As an emerging therapy, data availability for proton therapy is considerably less than for conventional radiotherapy
Economic	• High system upfront cost of proton centres limits uptake • Significant infrastructure investment (e.g. shielding) and high installation costs for conventional cyclotrons and synchrotrons • Proton therapy has been demonstrated to be cost-effective in some indications
Scientific	• Current systems are large and require extensive infrastructure thereby limiting suitability for many radiotherapy centres, especially when situated in cities
Other	• Drug therapies could render radiotherapy obsolete

Source: goetzpartners Research

Precision medicine justifies use of particle therapy

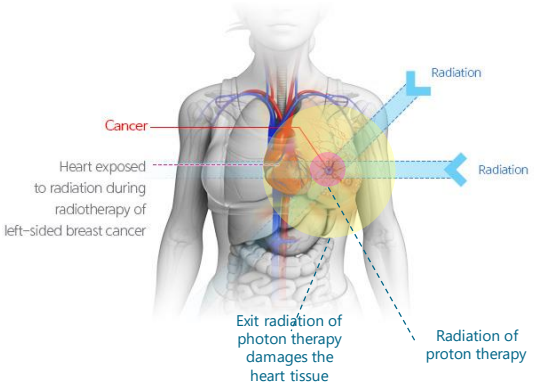
The principal argument for using particle therapy over conventional RT is the sparing of healthy surrounding tissue, which helps to avoid secondary tumours. The second argument is the prevention of direct effects from radiation overdose to the surrounding tissue. Below we describe and quantify the potential market opportunity, which extends beyond paediatric tumours.

CHART 85: Radiotherapy for breast cancer



Source: American Cancer Society: Cancer Facts and Figures 2016

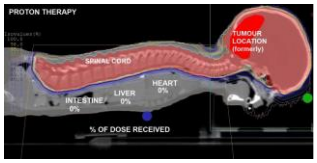
CHART 86: Beam dynamics: proton vs. photon therapy



- Patients with left sided breast cancer receiving conventional radiation therapy (photon therapy) have heart exposed to radiation
- Targeted proton therapy enables dose delivery w/o an exit dose

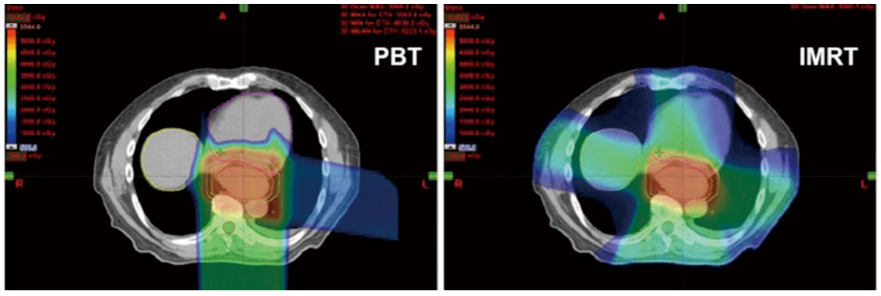
Source: Samsung Hospital

CHART 87: Development path for radiotherapy

Development Path	Next Steps	Long-term Development Aims
	▪ Multimedia imaging ▪ Precise functional anatomy ▪ Robotic set-up ▪ Optimised conformal planning ▪ Proton therapy ▪ Biological optimisation ▪ Designer fractionation	▪ Local therapy ▪ Single fraction ▪ Radiosurgery ▪ Bulk reduction prior to CT
▪ Increasing establishment of proton beam therapy centres ▪ More targeted treatment using RT with enhanced imaging and software tools		

Source: goetzpartners Research

CHART 88: Improved targeting = less damage to surrounding tissue

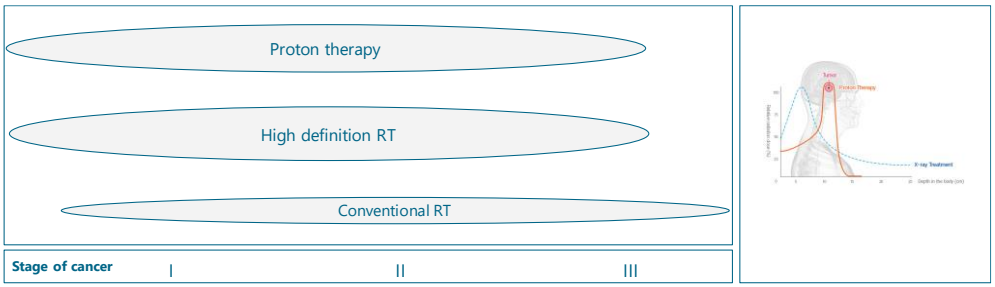


Source: Badyan *et al.* 2018, *Journal of Gastrointestinal Oncology*

To meet demand, increases in the number and utilisation of RT systems are required

The RT capacity in Europe varies significantly. The question of over and under capacity and the over and underuse of this methodology is still not sufficiently answered. The average number of RT machines per million of population in EU states varies from 1.3, 2.8 and 2.0 in Romania, Poland and Bulgaria respectively, to 6.5, 7.6, 8.2 and 9.7 in France, The Netherlands, Sweden, and Denmark. In the former countries, there is significant unmet RT need with a requirement to modernise capital infrastructure.

CHART 89: Future treatment landscape for radiotherapy



Source: goetzpartners Research

The quest to improve the therapy ratio (maximising tumour dose while reducing dose to surrounding tissue) has resulted in the development of innovative radiation technologies such as IMRT, stereotactic RT and particle therapy such as proton and carbon therapy. Whilst they offer the potential to reduce long-term toxicity through improvement in dose deposition and accurate target localisation, there is a paucity of randomised evidence of their benefit in achieving clinically relevant improved outcomes. To inform the discussion, ESTRO has launched the Health Economics in Radiation Oncology ("HERO") project to develop a knowledge base and a model for health economic evaluation of radiation treatments at the European level.

Radiotherapy is not at the forefront of public interest, despite proven effectiveness

Of all the new technologies, the case of RT demonstrates the paradox of public policy towards affordable cancer care: a failure to deliver basic service needs, yet willingness to 'over-spend' on technologies that have not been demonstrated to be cost-effective. However, stimulating debate in this area remains a challenge, as it appears that the public identifies more with concerns regarding drug access than RT. This is despite data that estimates the impact of chemotherapy on 5-year survival for all cancers to be 2% compared to 16% overall for RT.

Late-stage treatment moving towards ICI combos

The current treatment of late-stage cancer is still largely dominated by chemotherapy and RT. Although there has been a proliferation of potent targeted therapies that specifically target cancer cells in individual patients, these are frequently restricted to relatively narrow patient subpopulations and can be prone to the development of resistance. Recent progress with immune checkpoint inhibitors ("ICIs") in a variety of mainly solid cancers and the dramatic effects of CAR-T cell therapies in some blood cancers have demonstrated the significant potential of harnessing the patient's own immune system to successfully treat cancer.

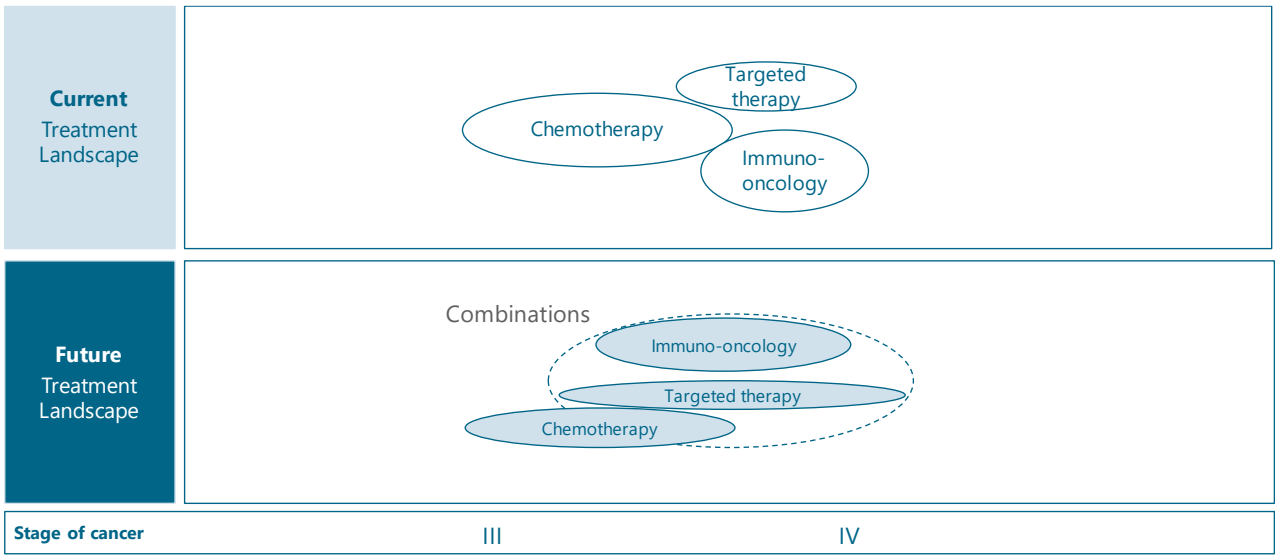
Increasing focus on combinations

Treatment outcomes with ICIs have been remarkable and – unlike most other late-stage therapies – sustained over time but are currently limited to a minority of patients. Nevertheless, ICIs have been establishing themselves as first-line therapies for advanced lung, skin and renal cancers over the past 2 - 3 years, particularly in the US. Most major oncology players have an ICI on the market or in development. The focus is on the development of ICIs in combination with other drugs. There are currently over 800 combination trials in progress involving other immunomodulators and a whole swathe of other cancer therapies, including chemo- and radiotherapies, targeted therapies, oncolytic viruses, cancer vaccines and antibody-directed therapies. While it is impossible to predict which combinations will yield the most efficacy, given the variability in response of different cancers at different clinical stages, we believe it is likely that the therapeutic landscape will be populated with a broad range of different ICI combinations.

Fragmentation of the ICI market provides opportunities for many players

The market leaders Merck & Co. and BMS are well placed to take a substantial market share. However, fragmentation of the market through a proliferation of combinations may allow other large oncology players with marketed or developmental ICIs such as Roche, AstraZeneca, Merck KGaA / Pfizer and Sanofi to be significant players. The quest for combinations and fragmentation of the market should also benefit a broad range of smaller biotech companies. We see upside for companies developing specifically targeted cancer therapies whose action could be amplified by unleashing the immune system. We are already detecting signs of deal flow not only surrounding local cancer-specific immune modulators, but also oncolytic viruses, as well as interest around cancer vaccines. Smaller European oncology companies including Medigene, Targovax, 4SC and Affimed look well positioned to benefit.

CHART 90: Treatment landscapes for late-stage therapies



Source: goetzpartners Research

Current treatment landscape dominated by chemotherapy

CHART 91: Chemotherapy remains the primary option despite its toxicity

Source: goetzpartners Research

While we have seen dramatic progress in immune-based therapies, chemotherapy remains the primary option for most patients in most cancers (CHART 91). However, although effective in targeting the viability of rapidly dividing cancer cells, chemotherapeutic agents are highly toxic and sometimes intolerable or fatal side effects that limit their clinical utility.

Developmental efforts have focused on targeted therapies…

Hence, drug developers have focussed on the development of therapies that more specifically target the biological pathways that support cancer cell growth and survival and avoid the collateral damage of conventional chemotherapeutics. A broad range of such targeted therapies have been developed with around 50 different drugs belonging to 30 different classes. Most of these target hormones, growth factors and associated cellular signalling pathways that promote cancer cell growth. They include drugs such as tamoxifen that target hormones like oestrogen and testosterone in breast, prostate, ovarian and womb cancers.

EGF pathway a major area of focus

The most abundant group targets the epidermal growth factor ("EGF") pathway. It comprises many small molecules and antibodies, that target EGF receptors or the downstream intracellular signalling pathways that mediate EGF action in cancer cells. Such drugs would include Merck KGaA's mAb Erbitux (cetuximab) and many small molecules (CHART 92) that target the protein kinases, signalling enzymes inside the cell which translate the EGF signal into cancer cell growth and survival. This last group is often associated with specific "driver" mutations that have occurred in the cancer cell and are linked to the aberrant activation of the uncontrolled growth that underpins tumour expansion. The prevalence of these mutations varies. The targeting of the right drug to the right tumour or patient is frequently dependent on the identification of the specific mutation and / or marker in the patient using companion diagnostics. Use of a companion diagnostic to limit the use of a drug to the appropriate patients can more than double the median objective response rates ("ORR") from 23% for oncology drugs without to over 55% for those with a companion diagnostic.

CHART 92: Small molecule kinase inhibitors

Molecule	Trade name
afatinib	Giotrif
axitinib	Inlyta
bosuntinib	Bosulif
crizotinib	Xalkori
dasatinib	Sprycell
erlotinib	Tarceva
gefitinib	Iressa
imatinib	Glivec
lapatinib	Tvverb
nilotinib	Tasigna
pazopanib	Votrient
regorafenib	Stivarga
sorafenib	Nexavar
sunitinib	Sutent

Source: goetzpartners Research

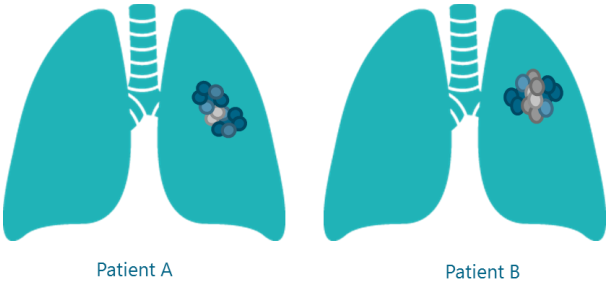
Tumour microenvironment another popular target

Targeted drugs also include those that impact cancers by influencing the microenvironment surrounding the tumour. These includes drugs such as Roche's Avastin (bevacizumab) that effectively starve the growth of the cancer by preventing the development of a tumour blood supply through blockage of the vascular endothelia growth factor ("VEGF"), and interferons that change the local immune response or inflammatory environment.

Targeted therapies work in small patient subsets and are prone to resistance

Many drugs in these classes have been shown to be effective and approved. However, there is considerable heterogeneity among cells in the tumour both between patients and within the cancer itself (CHART 93). The variation in the mutations in signalling pathways from patient to patient means that each targeted therapy is often only effective in a small subset of patients (frequently <10%), leading to a growing fragmentation in therapy. These drugs are also prone to the development of resistance. While the drug may slow or destroy a large number or even the majority of the cancer cells, the heterogeneity of cells within any one cancer means that treatment-insensitive cells within the tumour take the opportunity to proliferate and fill the space (CHART 93). As a result, targeted therapies can extend survival only by a few months or perhaps years, but not cure the disease.

CHART 93: Cancer heterogeneity impedes effectiveness of drug therapies



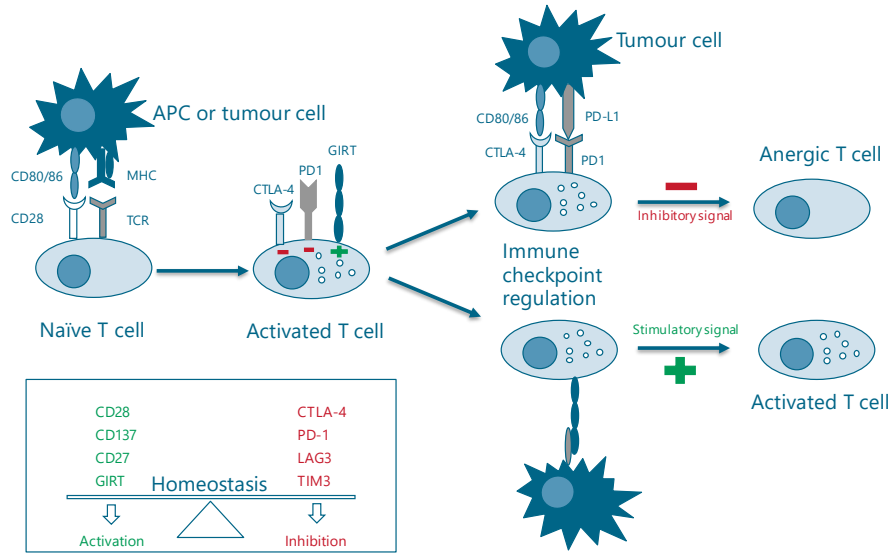
Source: goetzpartners Research

Immune checkpoint inhibitors unlock the power of the immune system to attack tumour cells by "taking off the breaks" on cytotoxic T cells

Cancer cells exploit immune checkpoints to prevent being killed

It has long been thought that successful long-term control of cancer might lie in harnessing the patient's own immune system. However, while cancer immunotherapies such as the cancer vaccine Provenge were approved, attempts to harness the immune system have been hampered by the ability of cancer cells to evade immune attack. It was only following the unravelling of immune regulation that real progress was made. The immune response which has evolved to destroy both external pathogens and cancer cells is regulated by a complex balance of inhibitory and stimulatory factors in place to keep the immune system in check, limit collateral damage to healthy tissue and prevent autoimmune disease. Cancer cells that carry on their surface receptors for inhibitory factors can switch off the immune response mediated by T cells. Blocking the function of immune checkpoints such as CTLA-4 and PD-1 on T cells with selective ICIs can block this inhibition, allowing the immune system to attack the cancer.

CHART 94: The immune system is regulated by a complex balance of inhibitory and stimulatory factors



Source: Merck & Co, goetzpartners Research

The majority of big oncology players have checkpoint inhibitors on the market or in development

Profound effects of ICIs have led to their adoption as standard of care

The impact of the first generation of approved ICIs, Yervoy (ipilimumab), Opdivo (nivolumab), Keytruda (pembrolizumab) and Tecentriq (atezolizumab) has been striking in many solid tumours beyond the initial indications of melanoma and lung cancer. In patients that respond, the effects of the drugs extend far beyond that usually seen with other chemo- or targeted therapies. ICIs have been approved for the treatment of a range of cancers where they are steadily being adopted as standard of care ("SoC"). Although Merck & Co. and BMS lead the field, most large pharma companies with a serious interest in oncology have their own ICI either already approved or in late-stage development (CHART 95).

CHART 95: Marketed immune checkpoint inhibitors

Product	Generic	Company	Target	1st FDA approval	Indications	2018 sales ($m)
Keytruda	pembrolizumab	Merck & Co	PD-1	Sep-2014	Cervical cancer, Endometrial cancer, Esophageal carcinoma, GC, cHL, HCC, HNSCC, MCC, melanoma, NSCLC, RCC, SCLC, UC	7,171
Opdivo	nivolumab	BMS	PD-1	Dec-2014	CRC, HCC, cHL, HNSCC, melanoma, NSCLC, RCC, SCLC, UC	6,735
Yervoy	ipilimumab	BMS	CTLA-4	Mar-2011	CRC, melanoma, RCC	1,330
Tecentriq	atezolizumab	Roche	PD-L1	May-2016	Bladder cancer, Breast cancer, NSCLC, SCLC	789
Imfinzi	durvalumab	AstraZeneca	PD-L1	May-2017	NSCLC, UC	633
Bavencio	avelumab	Merck KGaA / Pfizer	PD-L1	Mar-17	MCC, RCC, UC	81
Libtayo	cemiplimab	Sanofi	PD-1	Sep-18	CSCC	15

Abbreviations: cHL, classical Hodgkin's lymphoma; CRC, colorectal cancer; CSCC, cutaneous squamous cell carcinoma; GC, gastric cancer; HCC, hepatocellular carcinoma; HNSCC, head and neck squamous cell cancer; MCC, Merkel cell carcinoma, NSCLC, non-small cell lung cancer; RCC, renal cell carcinoma; SCLC, small cell lung cancer; UC, urothelial cancer

Source: goetzpartners Research, FDA, Company press releases

Limited differentiation between competing ICIs

Overall, there seems to be limited differentiation between the different PD-1 / PD-L1 inhibitors. There have been differences in trial outcomes, but we suspect that this may have more to do with clinical trial design than fundamental differences in the mAbs themselves. The class does seem to be more potent than the CTLA-4 inhibitor Yervoy, as demonstrated in multiple head-to-head trials. Hence, industry has been focusing more on PD-1 / PD-L1 inhibitors for combination therapy.

Dramatic response in some cancers, but virtually none in others

Strength of response depends on type of cancer

There are differences between responses of different cancers to ICIs (CHART 96). At one end of the range cancers such as Hodgkin Lymphoma and melanoma respond well, while the response to pancreatic cancer is weak and in NSCLC only modest.

CHART 96: Cancer-to-cancer variation in ICI response

	No response	Weak response	Good response
Response in tumour type	Non-MMR def. CRC (<5%)	NSCLC (15-20%)	HL (65-80%)
	Pancreatic	SCLC (15-25%)	PDL-1 +ve UC (45%)
	P53 / RAS tumours	RCC (15-30%)	Melanoma (30%)
		HNSCC (20%)	B/T cell NHL (30%)

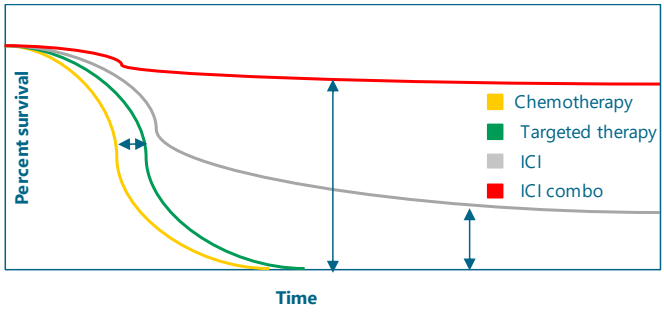
Abbreviations: CRC, colorectal cancer; HL, Hodgkin's lymphoma; HNSCC, head and neck squamous cell carcinoma; NHL, non-HL; NSCLC, non-small cell lung cancer; RCC, renal cell carcinoma; SCLC, small cell lung cancer; UC, urothelial carcioma
Source: goetzpartners Research

The key driver is lifting the tail of the survival curve

ICIs lift the tail of the survival curve. The key challenge is to expand this benefit to more patients across late-stage cancers

The clear clinical driver in oncology now is to extend the sustained long-term survival benefits seen with immuno-oncology in a minority of patients into most patients across cancers. While chemotherapy and targeted drugs have been able to shift the survival curve slightly to the right (CHART 97), the advent of ICIs has significantly lifted the tail of the survival curve with a minority of patients surviving for many years after treatment. The challenge now is to lift the tail extending survival for more patients across late-stage cancers. In the same way as vaccination provides safe and cost-effective long-term protection against infection, activating the immune system against cancers could provide a safe and economically viable means of controlling cancer. While the initial intervention might require the use of expensive therapies, long-term maintenance may only require the occasional booster. CHART 98 provides an overview of the key factors driving the use of ICIs.

CHART 97: Survival impact of cancer treatments



Source: goetzpartners Research

"Breakthrough Designation" by FDA can substantially reduce development times

Breakthrough Therapy Designation knocks years off the development timetable

From a regulatory standpoint, the FDA is increasingly providing drug development *programmes* with 'Breakthrough Designation'. This enables drug developers to expand existing Phase I / II clinical trials into pivotal trials based on outstanding early efficacy data. Although this does not necessarily increase the probability of approval, it can substantially abbreviate the clinical trial process, potentially knocking years off the development timetable. Indeed, some drugs with Breakthrough Therapy Designations have been approved after being tested only in Phase I, Phase II or Phase I / II trials.

CHART 98: Drivers

Clinical	• Significantly improved overall survival in ICI treated patients, shifting survival from months to years in >20% of patients • Strong rationale for combinations to extend ICI benefits • Effective targeting of immune therapy could reduce toxicity
Economic	• Sustained impact of ICIs via immune system may reduce need for repeated use of expensive drugs
Scientific	• Accelerated FDA approval of ICIs due to breakthrough designation and fast track development programmes reducing development time • Clinical endpoints adapted for immunotherapy • Many drugs for combination therapies are already approved or have extensive safety data
Other	• Development of diagnostics to identify likely ICI response • Rapid point of care profiling through liquid biopsies • Increasing understanding of the nature and regulation of the immune response

Source: goetzpartners Research

Over 1,000 combination trials ongoing

The remarkable benefits of ICIs have focussed attention on the potential of harnessing the immune system to fight cancer. This success, together with an increased understanding of the relationship between cancer and the immune system, is driving the investigation of new combination therapies that can extend these benefits to more patients in more cancers. There are currently over 1,000 clinical trials that involve I-O combination therapies. While some involve wholly novel approaches, many are using already approved or late-stage drugs. Although frequently not the primary target, the immune system is thought to play a role in the anti-cancer action of many existing drugs, including chemotherapeutics and targeted therapies, creating opportunities for synergies.

Multiple challenges remain

The development of the next generation of cancer therapies faces considerable challenges (CHART 99). The success of the first-generation of ICIs means that they will frequently become the standard of care, raising the hurdle for any follow-on therapies and forcing new products to be trialled in combination. Dominated by large pharma and with over 1,000 combination trials ongoing, competition to recruit clinical trial subjects will remain fierce in the major cancers, particularly for smaller R&D companies. Rapid developments in the field may result in rapid clinical changes in clinical practice and standard of care, which could make trial design and preparation of data for the regulators difficult (CHART 100). This may be compounded by the continued fragmentation of treatment regimens generated through the proliferation of a range of potential combination therapies as well as the need to personalise therapy to maintain specificity.

CHART 99: Challenges

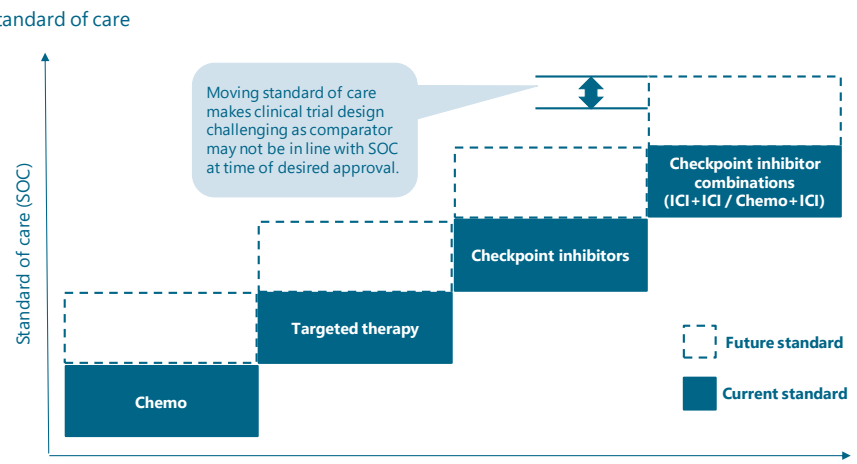
Clinical	• Need to develop multiple combinations for different cancers and stages • Need to asses long-term impact of on patient immune system • Large clinical trials required in the face of high competition from multiple drugs • Extensive combination studies will lead to fragmentation of treatment regimes
Economic	• Stacking of payments from combinations • Longer survival could mean larger and longer-term costs • Efficacy will drive demand for potentially costly therapies
Scientific	• Increasing complexity of regulatory approval for combinations • Widespread adoption of drugs as standard of care may stifle innovation
Other	• Development of dynamic immune markers for treatment monitoring

Source: goetzpartners Research

There is also an urgent need for the development of effective biomarkers. While diagnostics for current ICI are available, they are not well standardised and require a tissue biopsy, which can frequently miss the relevant cancer cells. The development of reliable liquid biopsies that are predictive of both a positive response as well as the serious and sometimes fatal adverse reactions which sometimes occur with these drugs remains a considerable challenge.

The development of combination therapies may also create significant economic challenges. The combination of what are already expensive cancer therapies has the potential to lead to unsustainable drug pricing. While we believe that expensive immunotherapies will ultimately only have to be used intermittently or perhaps even just at the start, drug developers must work hard during the clinical studies to gather data to justify later reimbursement.

CHART 100: Improving standard of care makes effective trial design difficult



Source: goetzpartners Research

Precision medicine justified based on higher response rates

Precision medicines are already a well-developed theme in the treatment of late-stage cancer with the attempt to move away from the more widely used toxic chemotherapeutic agents. As outlined above, these drugs can range from hormones and growth factors to drugs that are specifically targeted at pathways or receptors which are specific to the cancer cells. As detailed in the next chapter, this latter group of drugs are frequently associated with the use of companion or complementary diagnostics to identify patients in which the drugs are likely to be effective or potentially harmful.

Biomarkers help select responsive patients

The use of targeted therapies has often been shown to be highly effective in responsive patients. However, for the most part the patients responsive to any single targeted therapy constitute a very small proportion (often less than 10%) of the total patient population in any one cancer indication. Although carried by over 20% of the cancer population, drugs targeted at KRAS mutations have remained elusive and its presence is currently used to guide against the use of drugs such as Erbitux and Vectibix in colorectal cancer or Tarceva or Iressa in lung cancer (CHART 101). Thus, while biomarkers can guide effective therapy, on the current basis this approach would require at least ten different targeted therapies per cancer. This stratification of patients by drug response clearly has implications for treatment management and cost.

Effective targeting important to minimise side effects

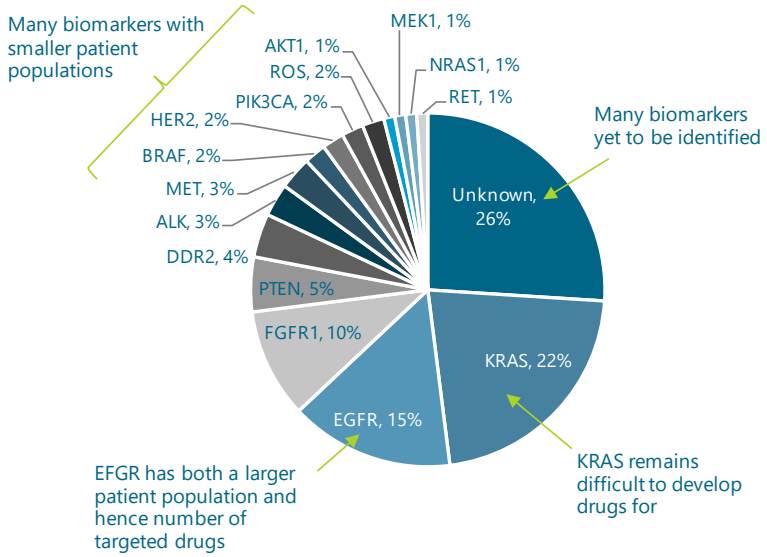
The ability to target therapies at the cancer will become more critical when they are used in combination. Given the heterogeneity of many solid cancers, the impact of targeted therapies may be limited when used alone. Combination with ICIs might amplify these effects by drawing in the immune system to attack the cancer more broadly, but side effects in non-cancerous cells may also be amplified by activation of the immune system. This must be minimised by more effective cancer targeting.

Urgent need for improved markers of immune status for companion and complementary diagnostics

Diagnostics tests that can predict response to ICIs remain to be developed

A variety of diagnostic tests have been developed using PD-L1 as a potential marker for patients who may be responsive to treatment with ICIs. However, unlike most other cancer markers which are mutated genes specific to cancer cells, PD-L1 is a wild-type marker whose expression within the tumour reflects a tumour's immune status. It is a dynamic marker that reflects the status of the cancer at a single point in time. The levels of PD-L1 have been shown to be affected by immune-modulators such as interferon as well as immune challenges with cancer-derived antigens. It is generally considered to be a poorly standardised diagnostic and may have questionable value when used in combination with other drugs that could change underlying PD-L1 expression. Tests have been developed to detect so-called micro-satellite instability ("MSI"), a predictor of the immunogenicity of cancers that may provide guidance regarding the potential responsiveness of cancers to ICIs as monotherapies.

CHART 101: Spectrum of mutations in lung adenocarcinomas



Source: Covance

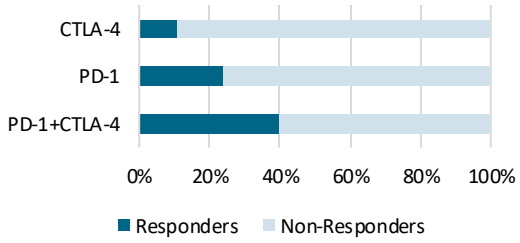
Development path and status

With ICIs increasingly adopted as standard of care, attention is now focussed on how the benefits of these drugs can be delivered to more patients in more cancers. With virtually every pharma company with an interest in oncology developing their own, there is a growing array of ICIs on the market and in the pipeline. What we believe will really differentiate these products will be the identification of effective therapeutic combinations.

Early approaches have focused on combining two ICIs…

The focus is on ICI combinations with therapies that increase the immune response against the tumour either by promoting localised tumour inflammation or by targeting one or more of the other immune regulatory factors that would otherwise suppress the anti-cancer immune attack. The first approach centred on combining ICIs with each other, e.g. the PD-1 antagonist nivolumab with the CTLA-4 antagonist ipilimumab. This has shown some success with the approval of nivolumab / ipilimumab combinations in metastatic melanoma, renal cell carcinoma and colorectal cancer, but is associated with increasing toxicity. AstraZeneca has also indicated that it will continue to look at the potential of its recently approved PD-L1 antibody durvalumab with its own CTLA-4 antagonist tremelimumab.

CHART 102: Tumour response rate increased in ICI combination therapy



Source: Prescribing information

...which increases overall toxicity

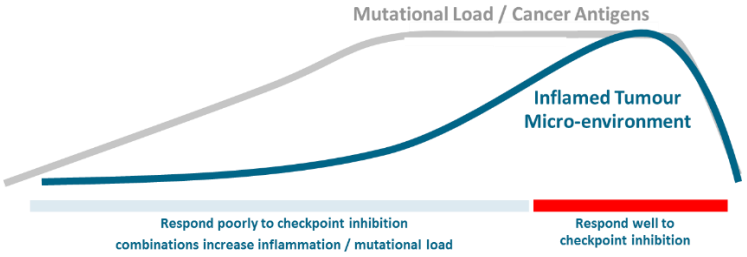
The immune-related adverse events ("irAEs") which result from the use of ICIs drugs are generally transient. While severe irAEs can normally be dealt with using immuno-suppression, available data suggests that some ICI combinations might be prone to adverse reactions. Combinations of the PD-1 and CTLA-4 targeted drugs nivolumab and ipilimumab show greater incidence of irAEs than either agent alone. Some concerns were also raised regarding the safety of combinations involving BRAF agents and ICIs following the occurrence of substantial liver toxicity in a prospective trial combining ipilimumab with vemurafenib. However, as such effects were not observed with dabrafenib and ipilimumab, this does not appear to be a class effect.

Tumour microenvironment takes center stage: hot tumours respond better to ICIs

Tumour must be inflamed ("hot") to respond to ICIs

Although ICI / ICI combinations have shown some promise, the major challenge is to extend the benefits of immunotherapy to patients and cancers that have so far been unresponsive to checkpoint inhibition alone. In this regard, much attention is focussed on the tumour microenvironment. As well as the mutational load that increases the cancer immunogenicity, evidence suggests that response to the current ICIs is limited to those patients and cancers where the tumour microenvironment is already immunologically inflamed ("hot") and thus heavily populated with the immune cells (particularly T cells) that mediate the immune attack (CHART 103).

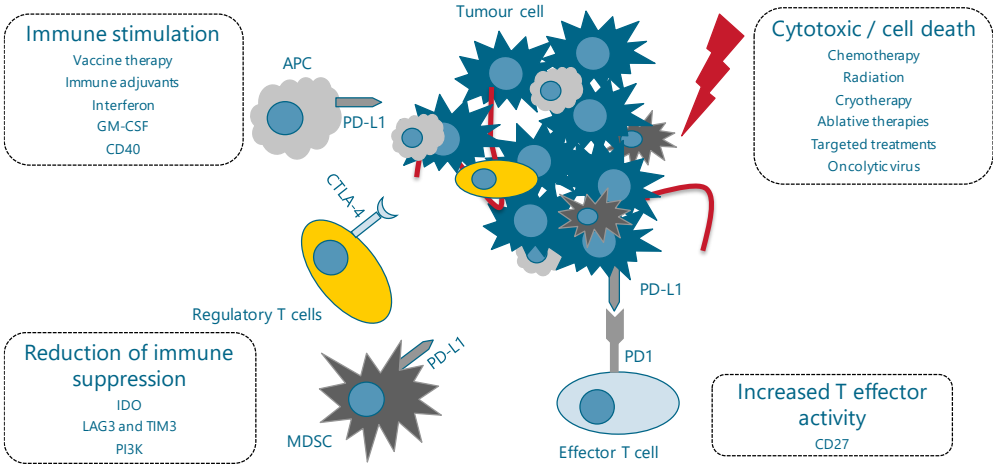
CHART 103: Tumour micro-environment and the ICI response



Source: Adapted from Harris *et al.*, 2016

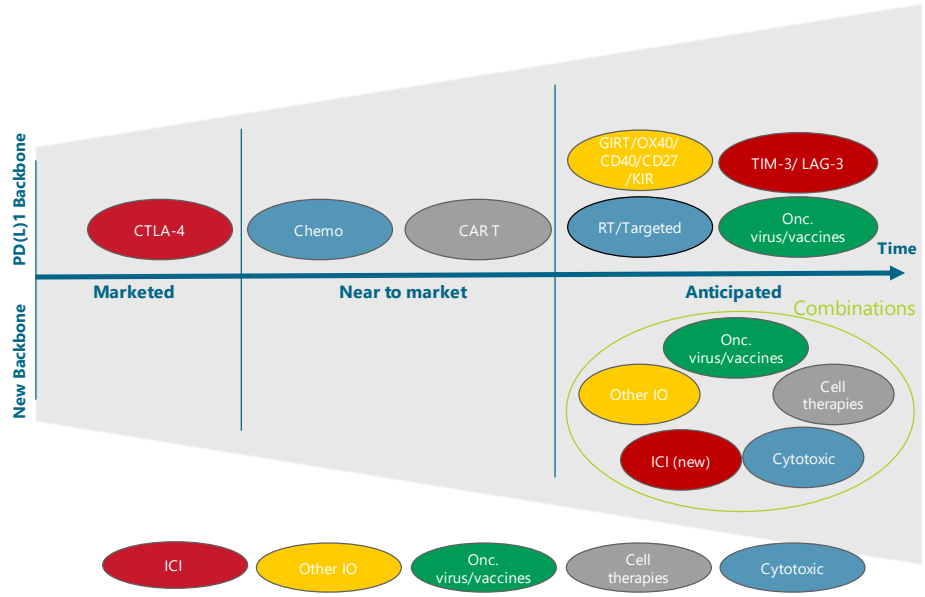
It is this localised tumour inflammation that many combinations in development are seeking to promote. Reviewed in Harris, Brown & Yap (2016), potential combinations comprise established cytotoxic approaches, including chemo-, targeted and RT, as well as a broad range of novel immuno-stimulants, such as cancer vaccines, checkpoint modulators and inhibitors of immune expression (CHART 104). There is an extensive pipeline of checkpoint combinations following on the tail of the first CTLA-4 / PD-1 combinations (CHART 105). These include existing chemo, targeted therapies as well as a range of new therapies targeting the tumour microenvironment or other aspects of immune regulation.

CHART 104: Potential classes of checkpoint inhibitor combinations



Source: Adapted from Harris et al., 2016

CHART 105: Growing diversity of immunotherapy combinations



Source: goetzpartners Research; cytotoxic therapies = chemotherapy, radiation therapy, targeted therapies

Combination with chemotherapy a favoured approach

Most of the currently approved PD-1 / PD-L1 agents are currently in Phase III trials with chemotherapeutic agents. The latter are thought to stimulate the immune system either through the exposure to the immune system of cancer antigens when the cancer cells die or by suppressing the levels of certain (T reg) cells that would otherwise suppress the immune response. While there may be some synergy in the shorter term, the poor tolerability of chemotherapeutics and their side effects may limit the utility of such combinations in the long term. Trials with ipilimumab and dacarbazine showed increased levels of adverse events such as liver toxicity vs. either product alone.

Focus on targeted therapy to avoid immune responses in healthy tissues

At least 36 Phase II / III trials combining ICIs with targeted therapies

The big focus is on the development of ICI combinations with highly targeted drugs where the ICIs can unleash the immune system on the cancer but avoid amplifying unwanted drug-related immune reactions in other healthy tissues. Such therapies include the targeted EGFR pathway inhibitors and antagonists, highly targeted RT, drugs that specifically increase the immunogenicity of the tumour microenvironment, cancer targeted viruses and vaccines, and a range of other cancer immunotherapies. We are aware of at least 36 clinical programmes combining ICIs with targeted therapies with at least ten in Phase II or III. These include several late-stage trials including small molecule tyrosine kinase inhibitors (e.g. dabrafenib) and mAbs targeting VEGF (e.g. bevacizumab).

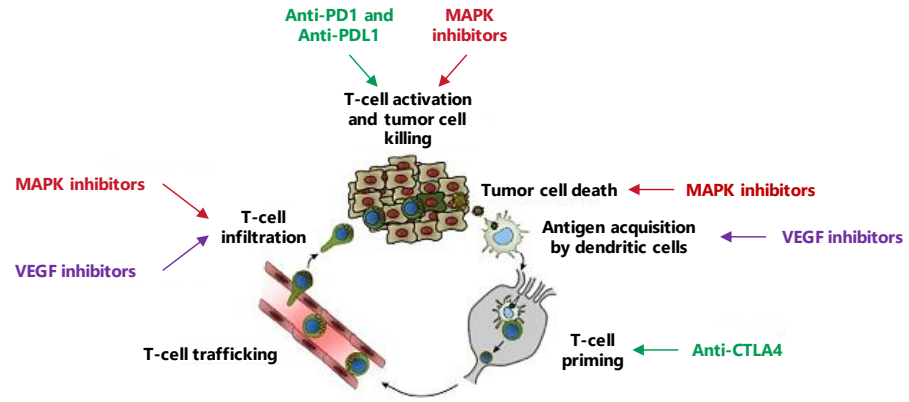
CHART 106: Selected ICI / targeted therapy combinations

I-O targets	Targeted therapy	MoA of combination	Stage	Comments
atezolizumab	bevacizumab	PD-L1 + anti-VEGF	II/III	RCC
	vemurafenib	PD-L1 + BRAF inhibitor	I	Melanoma
	erlotinib or alectinib	PD-L1 + EGFR / ALK inhibitor	I	NSCLC
nivolumab	bevacizumab	PD1 + anti-VEGF	II	RCC
	ipilimumab	PD-1 + RTK inhibitor	III	RCC
	capmatinib	PD-1 + c-Met	III	NSCLC (MET+)
pembrolizumab	dabrafenib + trametinib	PD-1 + BRAF + MEK inhibitor	I/II	Melanoma
durvalumab	dabrafenib + trametinib	PD-L1 + BRAF + MEK inhibitor	I/II	Melanoma
ipilimumab	vemurafenib	PD-1 + BRAF inhibitor	II / II / I	Melanoma / lymphoma / solid tumours
ipilimumab + nivolumab	dabrafenib + trametinib	CTLA-4 + PD-1 + BRAF + MEK inhibitor	III	Melanoma (BRAF MUT); suspended
avelumab	axitinib	PD-L1 + VEGFR / cKIT / PDGFR inhibitor	Marketed	RCC

Source: Morrisey *et al. 2016,* Company pipeline and press releases

As well as directly or indirectly killing tumour cells, many of these targeted drugs also have stimulatory effects on the immune system (CHART 107).

CHART 107: Immunological impact of targeted therapies



Source: Hughes *et al., 2016*

Radiotherapy can stimulate immune attack of cancer through the release of cancer-specific proteins from dead or dying irradiated cells leading to the death of tumour cells distant from the irradiated area

ICI / RT combo a promising approach, owing to synergistic effects

While ICI combinations may amplify and perhaps sustain the impact of targeted therapies on responsive patients, there will clearly be no additional benefits for non-responding patients, who must therefore be treated with other ICI combinations that specifically target the cancer cells. We believe that combination of ICIs with RT could be of interest. Several studies have suggested that combinations of RT with CTLA-4 inhibitors ipilimumab and tremelimumab have synergistic effects. Cell death induced by RT is thought to lead to an immunogenic response and data suggests that this can lead to an immune response towards cancer cells at a distance from the primary site. BMS has many clinical studies combining PD-1 / L1 inhibitors with RT in a large range of different cancers (reviewed in Kang *et al.* 2016 *Journal for Immune Therapy of Cancer*). Most are in Phase I or II and anti-PD-1 nivolumab has progressed to Phase III. The combination of immunotherapy and RT looks particularly interesting, especially as the ability to target RT to the tumour improves with the development of high-definition delivery and the growing availability of highly targeted proton beam therapy.

Oncolytic viruses are looking promising...

There is a growing list of immunotherapeutic approaches that are already approved or in development as monotherapies (CHART 108). These include the oncolytic virus vaccine Imlygic (talimogen laherparepvec, T-Vec), the bispecific antibody therapy BiTE, the SLAM7 inhibitor Empliciti targeting NK cells and many products in the pipeline that may have synergy when combined with ICIs. Oncolytic viruses that specifically target cancer cells look particularly promise. They are natural or modified live viruses that only replicate in cancer cells. In doing so, the vaccine not only causes the infected cancer cells to lyse and die, but also induces an anti-cancer immune response against both infected and non-infected cancer cells. In some cases, it further attacks the tumour blood vessels and restricts blood supply. The ability of oncolytic viruses both to promote inflammation in the tumour micro-environment and increase the abundance of new antigens makes them prime candidates for combination with ICIs.

...with several combinations being tested...

Several ICI combination studies are already underway. T-Vec has already been shown to substantially boost the response rate to the CLTA-4 inhibitor ipilimumab. PsiOxus has entered agreements with both Merck and BMS to investigate the potential of its oncolytic virus enadenotucirev with pembrolizumab and nivolumab, respectively. Cavatak has shown encouraging results in melanoma with both ipilimumab and pembrolizumab. Following encouraging results in the treatment of cervical intraepithelial neoplasia ("CIN"), Transgene has entered an agreement with Pfizer and Merck KGaA to develop its MVA-based oncolytic vector TG4001 for the treatment of HPV-linked head and neck cancer. This is effectively a triple combination with TG4001 also engineered to carry the gene for the IL-2 immunostimulatory peptide. Targovax has engineered an adenovirus that specifically infects and kills cancer cells. The virus ONCOS102 also carries the immunostimulant GMCSF.

CHART 108: Immunotherapy overview

Checkpoint inhibitors	Immunomodulation and stimulation	Oncolytic viruses and cellular vaccines
Description: Overcome mechanism to hide tumour cells from immune system **Marketed agents:** PD-1 / L1: Opdivo, Keytruda, Tecentriq, Bavencio, Imfinzi, Libtayo CTLA-4: Yervoy **Pipeline:** LAG3: BMS986016, eftilagimod alpha TIM-3	**Description:** Change tumour microenvironment **Pipeline:** CSF1R **Description:** Co-stimulatory agents: **Pipeline** CD137 / 41BB, OX40, CD27	**Description:** Boost immune system anti-tumour response **Marketed:** Vaccine: Provenge Oncolytic virus: Imlygic **Pipeline:** Vaccines: CRS-207, TG4010 Oncolytic virus: enadenotucirev, TG4001

Cellular immunotherapies	NK-targeting approaches	Bispecific antibodies
Description: Modification of patient's own immune cells to target cancer cells **Pipeline:** Dendritic cell therapies	**Description:** Targeting of NK cells rather than T cells **Marketed:** Empliciti **Pipeline:** KIR (lirilumab, monalizumab)	**Description:** Fusion protein targeting two specific binding regions e.g. T cell / NK cell and tumour cell **Marketed:** Blincyto **Pipeline:** AFM13, XmAb20717, XmAb14045, IMCgp100

Molecular targets/technologies in *italic*
Source: goetzpartners Research

Engineered oncolytic viruses could allow for the local targeted delivery of a range of immune modulators and anti-cancer biologics

...in over 40 trials

As of September 2019, there were more than 40 oncolytic viruses at various stages of development. It is thought that oncolytic viruses could be engineered to deliver genes encoding a full range of immunostimulants and regulators including checkpoint inhibitors directly to the tumour in one virus. This may avoid some systemic side-effects as well as perhaps reduce the financial burden of applying multiple drugs. Transgene and Targovax currently have research programmes following this approach.

CHART 109: Selected approved and developmental oncolytic viruses

Drug	Mechanism of action	Admin	Developer	Stage	Further comments
Imlygic (T-VEC)	HSV with GM-CSF transgene	IT	Amgen (BioVex)	Marketed	First approved oncolytic virus. In several trials as monotherapy or in combination
Enadenotucirev	Chimeric Ad5, no transgene	IV	PsiOxus	I	In development for ovarian cancer (+ paclitaxel) and carcinomas (+ nivolumab)
TG4001	Vaccinia virus Ankara with HPV16 E1 transgene	IT	Transgene	II	Monotherapy for HPV +ve cancers. In development in combination with ICI for head and neck cancer
ONCOS-102	Chimeric Ad5 / 3 with GM-CSF transgene	IT, IP	Targovax	I/II	In trials for a variety of cancers incl. melanoma with ICI
LOAD703	Chimeric Ad5 / 35 with TMZ-CD40L and 4-1BBL transgenes	IT	Lokon Pharma	I/II	Trials ongoing in pancreatic cancer and solid tumours
CG0070	Adenovirus backbone with a GM-CSF transgene	IV	Cold Genesys	II	Phase II trials in bladder cancer as mono and combo therapies with ICIs (Keytruda) ongoing
TELOMELYSIN (OBP-301)	Type 5 adenovirus with hTERT promoter	IT	Oncolys BioPharma	II	Phase II ongoing in combination with ICIs for gastric and head and neck cancers
PEXA-VEC	Vaccinia virus with GM-CSF and beta-galactosidase transgenes	IT focus	Transgene	III	Phase III PHOCUS trial in liver cancer halted in August 2019 following interim analysis
CAVATAK	Non-gene modified Coxsackievirus	IT, IV	Merck & Co (Viralytics)	II	Phase I and II trials ongoing in melanoma, prostate, lung and bladder cancer
DNX-2401	Chimeric Ad5 / 3, no transgene	IT, IV	DNAtrix	II	Phase I trials in glioma as a monotherapy ongoing. Phase II trial in combination with Keytruda for glioblastoma ongoing
Pelareorep	Non-gene modified reovirus	IV	Oncolytics Biotech	II	In development as a combination with ICIs in a range of solid tumours
RP1	HSV with GM-CSF, GALV and ipilimumab transgenes	IT	Replimune	I/II	Phase II combination trials with Opdivo ongoing in melanoma and bladder cancer
Voyager-V1	VSV virus with NIS and human interferon beta transgenes	IV	Vyriad	I	Phase I trials in colorectal cancer, MM, AML and endometrial cancer ongoing

Source: goetzpartners Research

ICIs are breathing life back into cancer vaccines…

ICIs could breathe life back into cancer vaccines designed to direct immune attack towards cancer cells. While several vaccines have shown promise, most have yet to achieve the required efficacy to warrant approval. Several approaches have been used to generate vaccines capable of generating an effective immune response against cancer cells, including peptides, viral vectors, DNA, mRNA and bacteria. Few have been able to overcome tumours' ability to evade immune attack. To date, the only cancer vaccine to receive approval in the US was the dendritic cell ("DC") vaccine Provenge (sipuleucel). DC vaccines are produced by removing these antigen-presenting cells ("APC") from the patient, priming them with the appropriate cancer antigen and then returning them to the patient, where they trigger an anti-tumour immune response. Although Provenge failed due to unsustainable costs associated with the personalised manufacture, a DC vaccine approach has been adopted by Medigene, which the company believes can overcome many of the shortcomings of Provenge.

…and have the potential to enhance their potency

There are several cancer vaccines in development. However, after repeated failures, the prospects of these vaccines working as monotherapies look poor, and real efficacy may only be achieved with combinations that stimulate or unlock the immune system. A vaccine which delivers the cancer antigen MUC1 with the immune T cell stimulant IL-2 TG-4010 developed by Transgene appears to extend the lives of patients with late-stage NSCLC. The action of cancer vaccines could also be potentially be boosted by combination with ICIs to release immune suppression. Transgene recently completed enrolment of a Phase II study supported by BMS, combining TG4010 with nivolumab. Targovax is developing mutant RAS neoantigen vaccines that are present in over 20% - 30% of all cancers. The approach has shown some promise in pancreatic cancer, but the trials were not placebo controlled.

CHART 110: Selected cancer vaccines in development

Drug name	Developer	Drug type	Stage	Further comments
Provenge	Dendreon / Valeant	DC vaccine	Market	Withdrawn in the EU
TG4010	Transgene	Viral vaccine	II	In combination with nivolumab
ADXS-PSA	Advaxis	Bacterial vaccine	I/II	In combination with pembrolizumab
MDG1011	Medigene	DC vaccine	I/II	Tailored to treatment of pts with low tumour burden
TG01	Targovax	KRAS peptide	I/II	In trials for pancreatic and other cancers

Source: Company pipeline and press releases

Preclinical data generated thus far provides support

Preclinical data suggests that ICIs could enhance cancer vaccine efficacy and improve immune cell infiltration receptors (Kleponis, Skelton & Zheng, 2015), although there is currently limited human data (Karaki *et al.* 2016). While the vaccine GVAX was found to be tolerable in combination with ipilimumab, it failed in a combination trial of two vaccines GVAX+CRS-207 (ECLIPSE trial, Aruro, press release, 2016). In prostate cancer, where PD-1 and PD-L1 therapy has so far been ineffective, multiple trials combining cancer vaccines with ICIs are ongoing. These include combinations of pembrolizumab with pTVG-HP plasmid DNA vaccine (in mCRPC patients [NCT02499835]), and with ADXS31-142 (a listeria monocyto-genes/PSA [Lm-LLO-PSA] vaccine [ADXS-PSA]) in pre-treated mCRPC patients (NCT02325557).

Cellular immunotherapies such as CAR-T can have dramatic benefits in blood cancers, but can cause potentially life-threatening side effects

CAR-T cell therapies have produced remarkable responses in blood cancers

Cellular immunotherapies such as CAR-T have generated considerable excitement in the treatment of blood cancers. They are based on the genetic modification of a patient's T cells, which are removed through leukapheresis and modified such that they bind to cancer cells. Studies in relapsed / refractory ("r/r") lymphoblastic leukaemia have seen response rates of 60% - 90%, often sustained over several years. Novartis's Kymriah was approved for r/r acute lymphoblastic leukaemia ("ALL") based on a complete response rate of 83%.

CRS is generally not life-threatening if dealt with promptly. However, it has all the symptoms associated with a serious infection, such as acute fever, is extremely unpleasant and requires expertise to control

A death was reported in Kite Pharma's pivotal trial for Yescarta (axicaptagene). The prescribing information therefore contains a black box warning and the drug is only available through a risk evaluation and mitigation strategy ("REMS")

Safety concerns and personalised manufacturing issues the key challenges

However, these remarkable effects are offset by substantial safety, technical, regulatory and logistical challenges. The approach depends on engineering antibodies and / or receptors that recognise markers on the surface of the cancer cells. It is critical that such or similar markers are not found elsewhere on healthy cells that would otherwise also be attacked. T cell therapy has been associated with cytokine release syndrome ("CRS") and has resulted in cerebral oedema, leading to death in some patients. In addition to the safety concerns, the need to extract cells from the patient, modify and return these significantly complicates both the regulatory and manufacturing process. Given the impressive response rates in blood cancers, companies such as Autolus in the UK are seeking to target the engineered T cells at cancer cells in a more precise manner and provide the means to switch the process off should severe side effects occur. Finally, access is an issue as only a few cancer centres have achieved accreditation to manufacture CAR-T cells.

CHART 111: Marketed CAR-T cell therapies

Product	Drug	Company	1st FDA approval	Price ($)	2018 sales ($m)
Kymriah	tisagenlecleucel	Novartis	Aug-2017	475,000	76
Yescarta	axicabtagene ciloleucel	Gilead (Kite)	Oct-2017	373,000	264

Source: goetzpartners Research

Pipeline includes NK cell-targeting therapies

Many immunotherapies in development are T cell based, however, there are also new developments in therapies targeting NK cells. In November 2015, BMS / AbbVie's Empliciti (elotuzumab) was approved as the first immune stimulatory mAb for the treatment of multiple myeloma. Empliciti activates NK cells by targeting the signalling lymphocyte activation molecule family 7 ("SLAM7"). Lirilumab is a checkpoint inhibitor developed by Innate Pharma in collaboration with BMS that blocks the interaction between KIR2DL-1, -2, -3 and its effectors. This action is thought to facilitate the activation of NK cells. In February 2017, the mAb failed to meet the primary endpoint of the EffiKIR trial in elderly patients with acute myeloid leukaemia, raising doubts over the viability of this mechanism of action in monotherapy. Further agents targeting NK rather than T cells include monalizumab (co-developed by Innate Pharma and AstraZeneca) as well as certain bispecific antibodies (Rezvani *et al.* 2015).

CHART 112: Selected approved and developmental natural killer cell based therapies

Target	Agent	Company	Mechanism of action	Stage	Comments
SLAM7	Emplicity	BMS	mAb exerting efficacy via NK-cell mediated antibody-dependent cellular toxicity ("ADCC")	Market	Approved for multiple myeloma
KIR	Lirilumab	Innate / BMS	Immunomodulator, acts predominantly on NK cells	Phase IIa	
NKG2A	Monalizumab	Innate / AstraZeneca	Humanized IgG4	Phase II	Developed in combination with durvalumab (solid tumours) & cetuximab (head & neck)

Source: goetzpartners Research

Next generation checkpoint inhibitors in development

LAG-3 an increasingly popular target

Therapeutic antibodies have also been developed against a range of other T cell receptor proteins that act like ICIs to unleash the immune system to attack cancer cells. The most advanced of these targets is lymphocyte activation gene 3 ("LAG-3"). BMS has several studies running with its anti-LAG-3 mAb BMS-986016 (relatlimab) in combination with its CTLA-4 and PD-1 inhibitors ipilimumab and nivolumab. These include late-stage trials in renal cell carcinoma, gastric cancer, metastatic colon cancer and NSCLC. Although clinical trials indicate an increased incidence of serious adverse events leading to treatment discontinuation, preclinical data suggests that combination of PD-1 and LAG-3 inhibitors is far more potent than either agent alone. Australian biotech Immutep is entirely focused on LAG-3 and has four LAG-3 targeted assets with four distinct modes of action in development. Its lead candidate eftilagimod alpha, a soluble LAG-3 protein that activates dendritic cells through binding to MHC class II, has shown encouraging results in melanoma and is currently being tested in a registrational Phase IIb trial in metastatic breast cancer, for which data is expected in Q1/2020E.

CHART 113: LAG-3 inhibitors in development

Compound	Company	Mechanism of action	Stage	Indications
Relatlimab	BMS	Anti-LAG-3 mAb	II / III	Melanoma, NSCLC, CRC, GC, RCC and other solid tumours
Eftilagimod alpha	Immutep	Soluble LAG-3 Ig fusion protein	IIb	BC, NSCLC, SNHCC, melanoma
MK4280	Merck & Co.	Anti-LAG-3 mAb	II	NSCLC, other solid and haematological tumours
LAG525	Novartis / Immutep	Anti-LAG-3 mAb	II	Multiple advanced solid tumours
BI 754111	Boehringer Ingelheim	Anti-LAG-3 mAb	I	NSCLC, H&N, melanoma, glioblastoma, other solid tumours
MGD013	Macrogenics	Bispecific mAb (PD-1 x LAG-3)	I	Advanced solid neoplasms
TSR-033	GSK / Tesaro	Anti-LAG-3 mAb	I	Advanced solid tumours
FS-118	F-Star	Bispecific mAb (LAG-3 x PD-L1)	I	Advanced solid tumours
Sym022	Symphogen	Anti-LAG-3 mAb	I	Advanced solid malignancies or lymphomas
INCAGN02385	Incyte / Agenus	Anti-LAG-3 mAb	I	Advanced malignancies
Xmab22841	Xencor	Bispecific mAb (LAG-3 x CTLA-4)	I	Advanced solid tumours
REGN3767	Sanofi / Regeneron	Anti-LAG-3 mAb	I	Advanced solid malignancies or lymphomas

Source: goetzpartners Research

Double-headed bispecific antibodies bring immune cells into contact with tumour cells

First bispecific is already on the market

Other antibody approaches include bispecifics with two different binding domains capable of binding two different targets simultaneously. BiTEs can bring T cells into contact with cancer cells by binding to separate receptors on both cells. Blincyto developed by Micromet (acquired by Amgen), was approved by the FDA for Philadelphia chromosome-negative r / r ALL, albeit with a black box warning for CRS. Bispecific antibodies are also being developed as "two-in-one combinations", such as Xencor's preclinical XmAb20717, which binds to both PD-1 and CTLA-4.

Alternative approach combines a mAb with a TCR

A variation on the bispecific approach is to combine an antibody with a T cell receptor ("TCR"). Immunocore has engineered immune mobilising monoclonal TCRs against cancer ("ImmTACs"), which have a specific cancer cell binding T cell receptor and a T cell activating antibody fragment. Currently in a pivotal trial as a monotherapy and in Phase I / II in combination with durvalumab and tremelimumab, the molecule is designed to attract and activate T cells within the cancer.

CHART 114: Selected approved and developmental bispecific molecules

Drug name	Developer	Drug type	Stage	Further comments
Blincyto	Amgen	BiTE	Marketed	FDA approved since 2014
IMCgp100	Immunocore	ImmTAC	Pivotal trial	
AFM13	Affimed	TandAb	II	Combination with pembrolizumab for refractory Hodgkin lymphoma
IMCgp100	Immunocore / AstraZeneca	ImmTAC/ICI	I/II	Duravalumab / tremelimumab combo in development with AstraZeneca
XmAb20717	Xencor	bispecific mAb	I	Potential "two-in-one" checkpoint inhibitor
XmAb14045	Xencor	bispecific mAb	I	Strategic collaboration for bispecific mAb programmes

Source: Company pipeline and press releases

Antibody-drug conjugates use specific antibodies to target toxins to cancer cells

ADCs direct powerful toxins to tumour cells

Antibody-drug conjugates ("ADCs") combine the specificity of mAbs with cytotoxic drugs by linking them together. The antibody directs the toxin to the cancer cell by binding to a cancer-specific marker on the cell surface. Several ADCs have been approved. Kadcyla (trastuzumab emtansine) developed by Roche directs the toxin emtansine to HER-2 positive breast cancer cells that have resisted other therapies. Seattle Genetics's Adcetris (brentuximab vedotin) was approved by the FDA in 2011. Mylotarg (gemtuzumab ozogamicin) marketed by Wyeth (now Pfizer) was withdrawn from the market due to concerns over safety and lack of efficacy. The approach is frequently limited by the toxicity of the toxin-laden mAb or tumour cells with low levels of marker on their surface. The toxins carried by the antibodies must therefore be active at very low concentrations in active and dormant cells. Working with the potent mushroom toxin amantine, Heidelberg Pharma has an ADC that it believes meets these criteria. Lead asset HDP-101 is currently in late preclinical development for multiple myeloma.

CHART 115: Selected ADC molecules

Drug name	Developer	Structure	Stage	Further comments
Adcetris	Seattle Genetics	anti-CD30 auristatin conjugate	Marketed	FDA approved 2011
Kadcyla	Roche	anti-Her2 emtansine conjugate	Marketed	FDA approval in 2013
HDP-101	Heidelberg Pharma	anti-BCMA amantine conjugate	Preclinical	
Mylotarg	Wyeth / Pfizer	anti-CD33 calicheamicin conjugate	Withdrawn	First FDA approved ADC (2000). Withdrawn in 2010 due to safety and efficacy concerns

Source: Company pipeline and press releases; Perez *et al.* 2013

Early days for other next-gen combinations

Further next generation molecules are in development with some early-stage data available but lacking later stage data. While some of the molecules are investigated as monotherapies, the focus overall is on combinations.

CHART 116: Selected next generation immunotherapy molecules in development

Drug name	Developer	Drug type	Stage	Further comments
Pexidartimib	Plexxikon	CSF1R	III	Multiple targets including CSF1R
Utomilumab	Pfizer	CD137 / 41BB	III	In multi arm trial in combination with avelumab and other
Cabiralizumab	BMS	CSF1R	II	
Emactuzumab	Roche	CSF1R	I/II	
Urelumab	BMS	CD137 / 41BB	I/II	In combination trials with rituximab and other
PF-04518600	Pfizer / Roche	OX40	I/II	In combination with 4-1BB agonist and PD-L1 inhibitor
Varilumab	Celldex / BMS	CD27	I/II	In combination with PD-L1
MK-4166	Merck	GIRT	I	

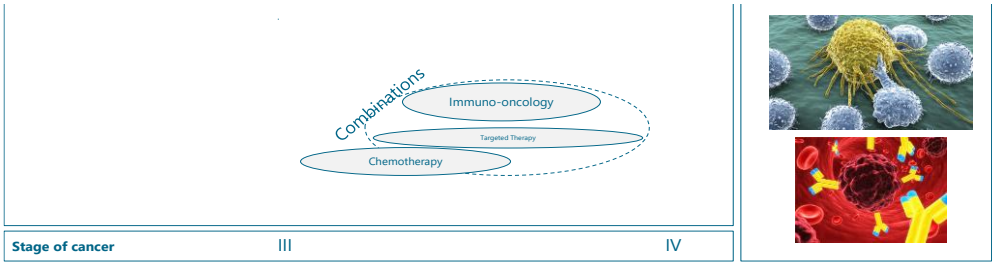
Source: goetzpartners Research; Company webpages, clinical trials.gov

Future treatment landscape centred around ICI combos

Future landscape to be dominated by a diverse range of immunotherapy combinations as a function of cancer and disease stage

All evidence suggests that there will be a continued focus on the development of combination therapies centred around a backbone of ICIs. Increasing adoption of PD-1 / PD-L1 antagonists as standard of care is likely to see them at the centre of many treatment combinations across cancer indications. Due to the high number of ongoing clinical trials in this field as well as the absence of late-stage data in many settings, it is impossible to predict which combinations may dominate in the long term. Given the inherent heterogeneity and complexity of cancers and the variety of promising candidates in combination, we suspect that oncologists will adopt a patchwork approach to cancer therapy with a variety of ICI combinations addressing the needs of different patients in different cancers at different stages of disease. The focus is expected to remain on combinations of immunotherapeutic agents such as ICIs with new and existing "driver" targeted therapies, as well as other targeted immunobiologics. These might include engineered oncolytic viruses, vaccines and targeted cell-based therapies.

CHART 117: Future treatment landscape



Source: goetzpartners Research

Complementary and companion diagnostics will aid patient selection

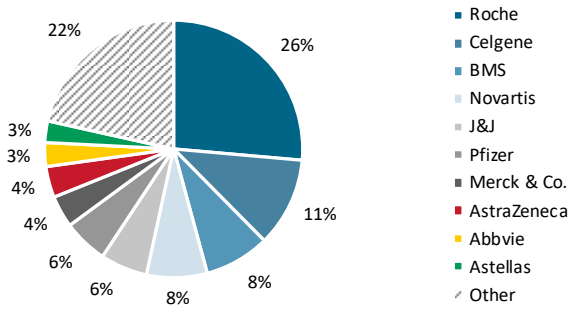
Choice of combination will largely be driven by patient screening and monitoring using companion and complementary diagnostics

The ability to choose specific therapies for individual patients is likely to be driven by the development of complementary and companion diagnostics, especially liquid biopsies. As detailed in the next chapter, there has been significant progress in the development of liquid biopsies based on the detection of ctDNA. Such diagnostics have already been developed for the detection of the specific tumour mutations that govern the susceptibility of cells within the tumour to specific tumours. The ability to monitor blood for these markers should negate the need for tissue biopsies, thus easing tumour profiling and potentially allowing such profiling to be performed at earlier stages, allowing targeted therapies to be used earlier in disease progression.

$150bn market dominated by a few large players

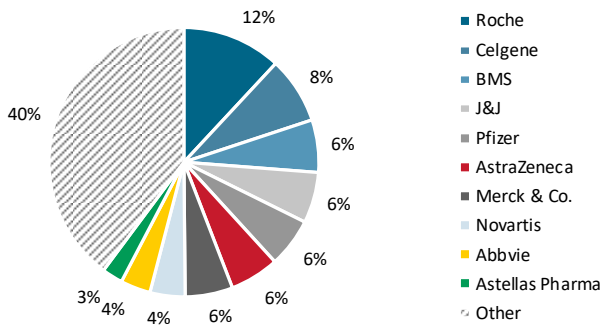
According to IQVIA, the global oncology therapeutic market was worth c.$150bn in 2018 and is expected to exceed $200bn by 2023E, with much of this growth driven by immuno-oncology, particularly ICIs. While Roche is expected to remain the largest player, its market share is likely to be eroded significantly by patent expiries and competition from biosimilars.

CHART 118: Oncology market share 2017A



Source: Evaluate Pharma 2019; goetzpartners Research

CHART 119: Oncology market share 2024E

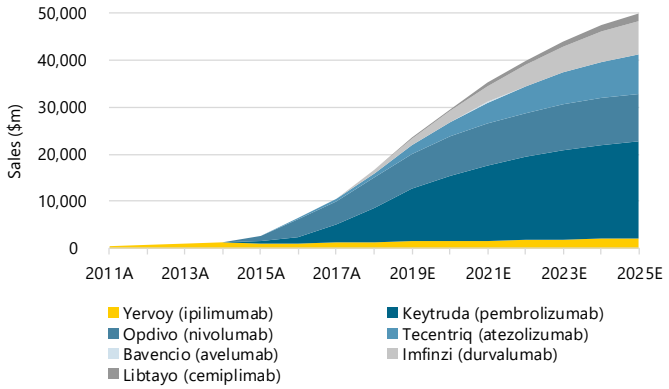


Source: Evaluate Pharma 2018; goetzpartners Research

Checkpoint inhibitors have created a $16.7bn market since 2011

Checkpoint inhibitors led by Merck's Keytruda and BMS's Opdivo generated $16.8bn in 2018 sales (CHART 120), led by BMS and Merck & Co., which held a combined market share of >90% (CHART 121). We expect the ICI market to expand to >$50bn in 2025E, based on approved drugs alone (CHART 120).

CHART 120: ICI sales, 2011A – 2025E



Source: Company financial results

CHART 121: Market shares of leading ICI companies, 2018A

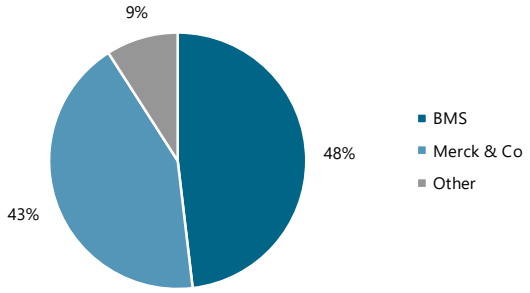
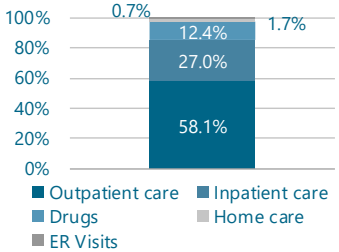


CHART 122: Cost of cancer breakdown in the US, 2015

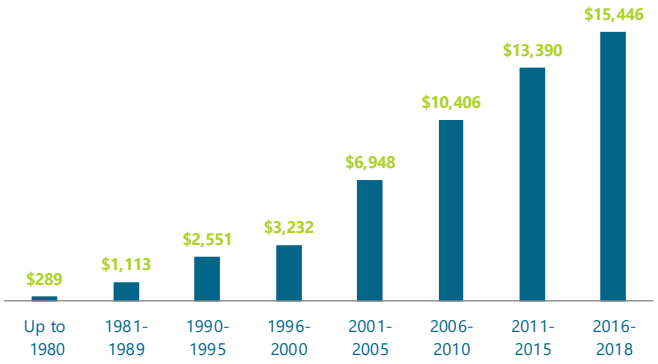


Source: Agency for Healthcare Research and Quality ("AHRQ")

Prices for new cancer drugs have experienced galloping growth

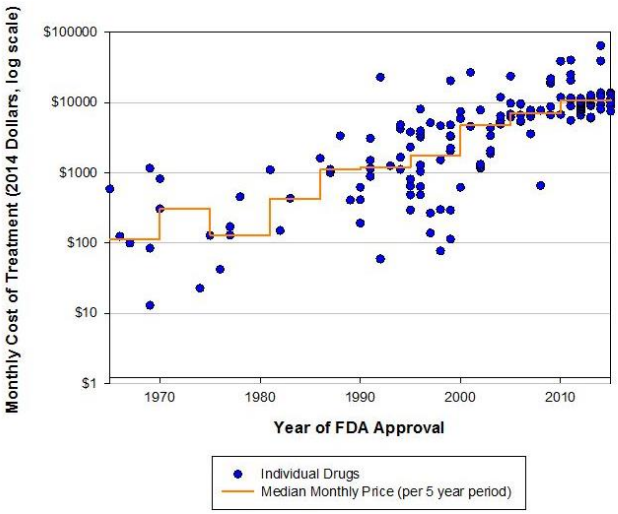
Despite accounting for a relatively small fraction of total cancer-related expenses (CHART 122), the cost of cancer drugs has been a sensitive debate for some time and intensified in recent years following the launch of multiple drugs costing in excess of $100,000 per year. In 2018, the mean cost of new brands was c.$150,000, in line with the anti PD-1 / L-1 checkpoint inhibitors Keytruda and Opdivo, while Novartis's CAR-T cell therapy Kymriah (tisagenlecleucel) is the most expensive cancer drug on the market with a price tag of c.$475,000. The National Bureau of Economic Research stated that prices for cancer drugs increased by 10% ever year between 1995 and 2013, equivalent to c.$8,500 per year after adjusting for inflation and survival benefits. CHART 123 and CHART 124 below plots the monthly treatment costs of cancer drugs at the time of FDA approval.

CHART 123: Median monthly costs of cancer drugs at time of FDA approval



Source: Memorial Sloan-Kettering Cancer Centre

CHART 124: Median monthly costs of cancer drugs at time of FDA approval (log scale)



Source: Memorial Sloan-Kettering Cancer Centre

CHART 125 below shows drug price vs. life years gained. There is a 95% confidence interval for each additional life year. In financial terms, the effect is $75,000 per year gained. The additional component is "the willingness to pay for a quality-adjusted life-year", which is often difficult to satisfy given the modest survival benefits and harsh side effects.

CHART 125: Drug prices vs. life years gained

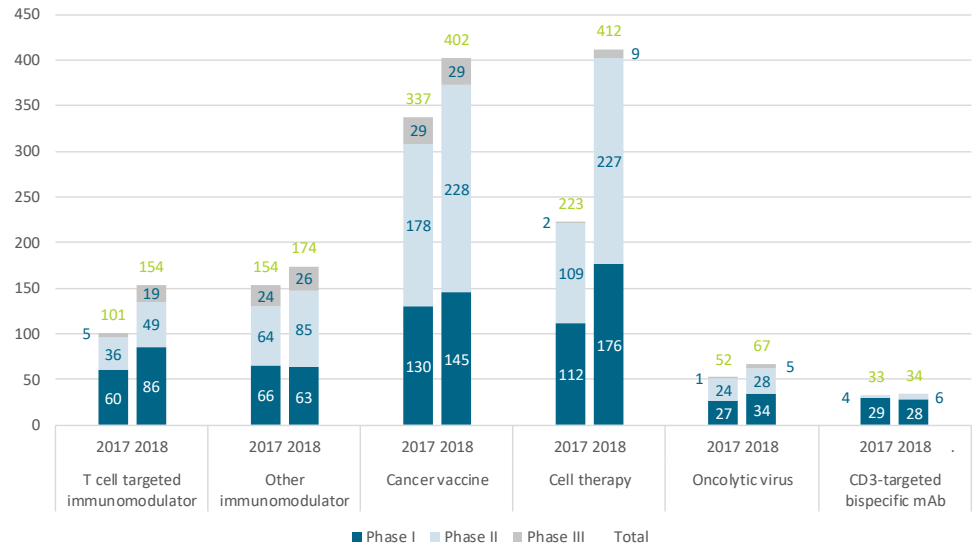
Source: Journal of Economic Perspectives

BMS and Merck & Co. likely to be the beneficiaries of growth in the cancer therapy market, driven by I-O and ICIs

Merck & Co. and BMS lead in terms of ongoing I-O trials

ICIs form the backbone of new IO combination therapies and are increasingly adopted as the standard of care. Hence, almost all the major pharma companies have ICI programmes. With apparently little to differentiate them as monotherapies, the development of effective combinations is likely to provide the most significant differentiating factor. Merck & Co. and BMS are currently running over 50% of the IO clinical trials (CHART 126) and Merck has taken the lead in terms of ongoing combination trials.

CHART 126: Immuno-oncology therapy pipeline, 2017 vs. 2018

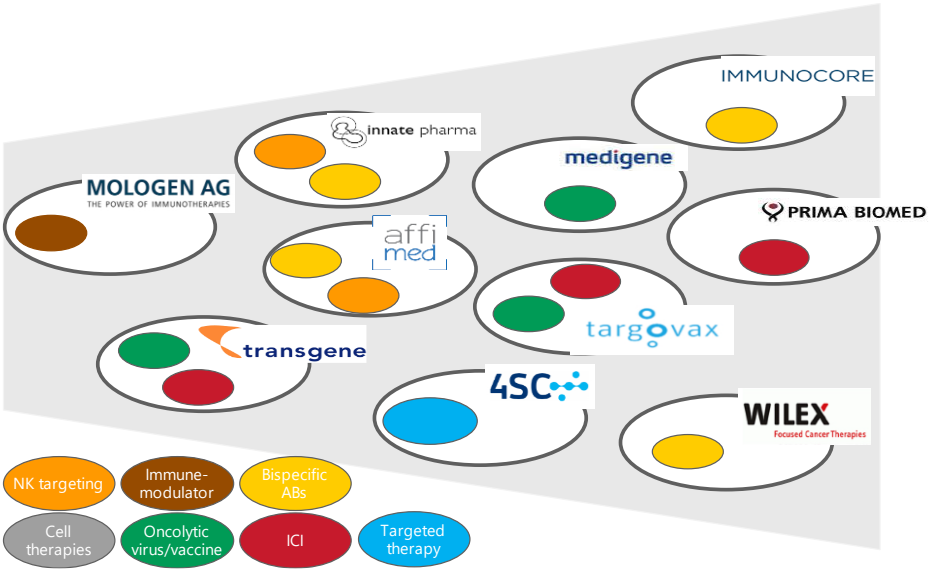


Source: Cancer Research Institute, goetzpartners Research

Smaller biotechs could offer significant upside

The potential variety of combinations may create significant opportunities for a broad range of small companies, where many of the more innovative combination candidates lie. With many of these still valued at historic lows, the prospect of deal flow and possible market entry could offer significant upside for investors looking to benefit from the immuno-oncology revolution. Leading European players are featured below (CHART 127).

CHART 127: Key European biotech companies with cancer therapies in development



Source: goetzpartners Research, Company logos from Company websites

Consolidation has been ramping up

There have been many multi-billion-dollar M&A deals in the immuno-oncology space driven by large pharma's quest to acquire promising technologies developed externally (CHART 128).

CHART 128: Select M&A transactions in the immuno-oncology space

Date	Target	Country	Description	Acquirer	EV ($m)	Rationale
Jul-19	Array BioPharma	US	Discovery, development and commercialisation of small molecule drugs	Pfizer	11,400	Strengthen leadership in oncology, add breakthrough combination of BRAF / MEK inhibitors for a potential first-in-class therapies
Jul-19	Mavupharma	US	Novel approaches to target STING pathway for treatment of cancer	AbbVie	n.a.	Further I-O portfolio and assist in the development of transformative medicines
May-19	Nuevolution AB	US	Develops drugs for oncology and chronic inflammatory diseases	Amgen	167	Enhance offerings to serve its customers better
Jan-19	Loxo Oncology	US	Develops and commercialises medicines for patients with cancer	Eli Lilly	8,000	Broaden the scope of oncology portfolio through the addition of a marketed therapy and a pipeline of medicines for cancer patients
Dec-18	Tesaro	UK	Develops drugs and therapies for cancer treatment	GSK	4,296	Strengthen pharmaceutical business and build pipeline and commercial capability in oncology
Dec-18	Potenza Therapeutics	JP	Discovers and creates innovative therapeutics to treat cancer	Astellas	164	Novel assets have the potential to make a pronounced difference for patients in need
Sep-18	Tusk Therapeutics	UK	Discovers and develops therapeutic antibodies	Roche	761	Develop novel antibodies
May-18	Armo Biosciences	US	Late-stage I-O company with multiple assets in the clinic, incl. lead I-O asset pegilodecakin	Eli Lilly	1,600	Access pegilodecakin, which has shown clinical benefit as single agent and in combination with chemo and CIs across several tumour types
May-18	BeneVir Biopharm	US	Specialised in the development of oncolytic viruses for immunotherapy	Janssen (J&J)	1,040	Complements own I-O research
Feb-18	Viralytics	AU	Oncolytic virus technology	Merck & Co.	394	Viralytics's approach of engaging innate immune system complements own I-O strategy
Jan-18	Cascadian Therapeutics	US	Cancer-focused biotech. Lead asset in clinical development for mBC	Seattle Genetics	614	Enhance late-stage pipeline with potentially best-in-class, orally available tyrosine kinase inhibitor ("TKI") that is highly selective for HER2
Jan-18	Juno Therapeutics	US	Pioneer in the development of CAR T and TCR therapies evaluating multiple targets and cancer indications	Celgene	9,000	Leverage a novel scientific platform and scalable manufacturing capabilities to complement Celgene's leadership in haematology and oncology
Dec-17	Ignyta	US	I-O company focused on cancers with specific rare mutations	Roche	1,700	Entrectinib gives Roche the opportunity to expand its portfolio of oncology medicines
Dec-17	Cell Design Labs	US	Pre-clinical stage company with expertise in custom cell engineering	Gilead	567	Addition of synNotch and Throttle technology could lead to the treatment of a broader range of haematological malignancies and solid tumours
Aug-17	Kite Pharma	US	Leader in the field of cell therapy	Gilead	11,900	Establish Gilead as a leader in cellular therapy
Aug-17	IFM Therapeutics	US	Works with innate immunity and its role in regulating the immune system	BMS	300	Strengthen oncology pipeline focus on innate immunity by accessing STING and NLRP3 agonists
Jun-17	Altor BioScience	US	Focus on immunotherapeutic agents for cancer, viral infections and autoimmune diseases	NantCell	290	n.a.
Jan-17	Dendreon	US	Develops personalised immuno-therapeutics for cancer. First company to launch a cancer vaccine (Provenge)	Sanpower Group	820	Promote Provenge outside of the US, starting with China and Southeast Asia
Feb-15	Flexus Biosciences	US	Discover agents for the reversal of tumour immunosuppression	BMS	1,250	Accelerate ability to explore numerous immunotherapeutic approaches across tumour types through the addition of an IDO inhibitor

Abbreviations: IL-8, interleukin-8; IO, immuno-oncology; mBC, metastatic breast cancer
Source: Mergermarket, company press releases, goetzpartners Research

Companion Dx help personalise treatment

Molecular diagnostics are playing an increasingly important role in the personalisation of cancer therapy. There are currently over 30 companion diagnostics ("CDx") linked to the use of specifically targeted cancer therapies, and biomarkers were used in 39% of oncology trials in 2018, up from 25% in 2010 (IQVIA). A growing repertoire of additional genetic markers are increasingly used to guide treatment and determine individual prognosis. Such tests can help ensure patients receive the most effective treatments for their specific cancer and avoid the discomfort and expense of unnecessary or ineffective interventions.

Shift from solid to liquid biopsies

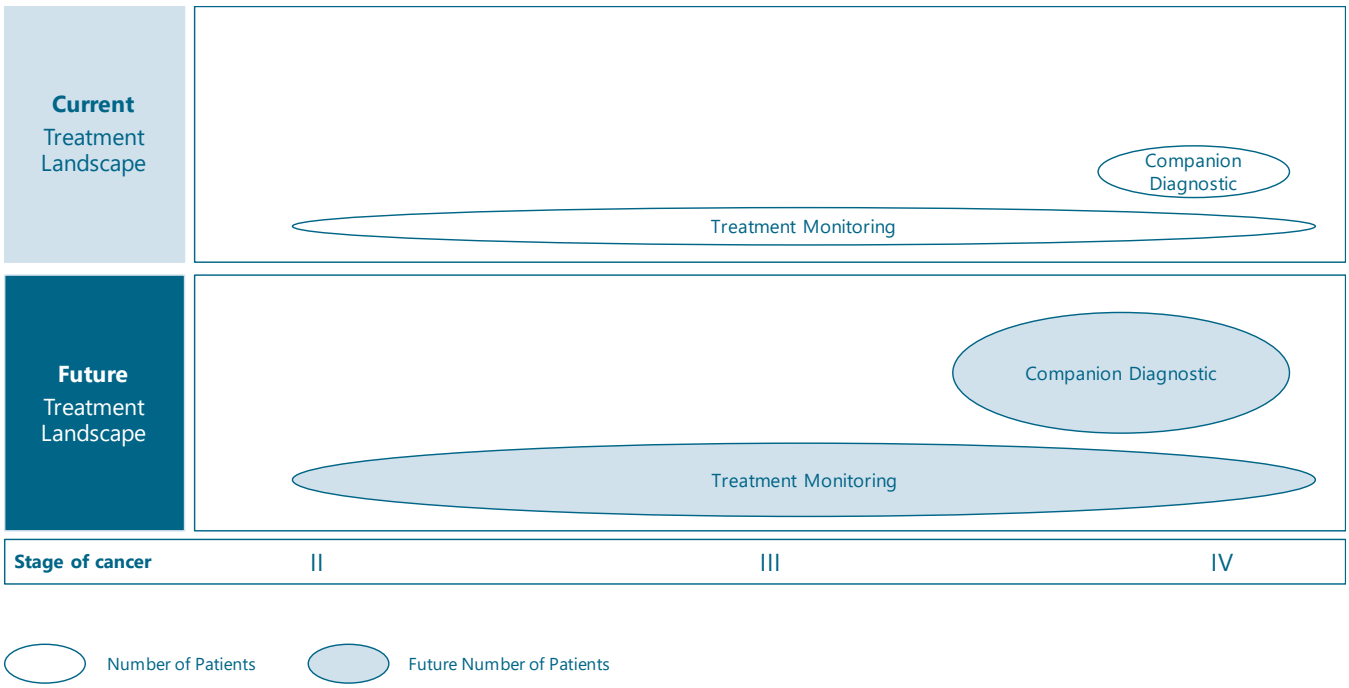
Tests likely to become increasingly complex, but development of automated platforms should allow for increasingly rapid point-of-care disease profiling and monitoring

Although most tests have been developed for the analysis of solid biopsies taken from cancer tissue, advances in DNA detection technology and particularly the increasing availability of next generation sequencing are seeing a rapid increase in diagnostic tests for tumour analysis of samples taken from blood or other biofluids such as urine. These liquid biopsies may not only allow for earlier selection of the appropriate targeted therapy, but also the monitoring of the cancer disease status and potentially provide a vital early indication of the development of resistance to specific therapies. These tests are likely to become increasingly complex, as they are developed to monitor multiple parameters to include drug susceptibility, immune status, and treatment efficacy.

Emerging companies drive much of the innovation

Although the development of CDx has largely been performed through collaboration between large pharma and the larger diagnostic players, there are increasing numbers of smaller service-based companies that provide a range of proprietary and / or widely available tumour profiling and prognostic tests. The shift towards liquid biopsies should also allow more repeated longitudinal testing, opening opportunities for point-of-care platforms developed by smaller innovators. Overall, we would expect increasing opportunities in liquid-based companion and disease / treatment monitoring diagnostics.

CHART 129: Identification of treatment success beyond imaging



Source: goetzpartners Research

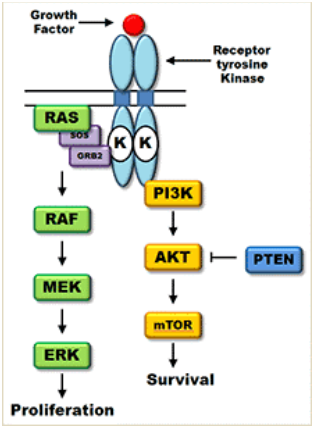
CDx have been a focus in oncology since the 1970s

According to the FDA, a CDx is defined as a diagnostic device that provides information that is essential for the safe and effective use of a corresponding therapeutic product. CDx have been a focus in oncology since the development of tamoxifen in the mid-1970s to the approval of the Tecentriq (CHART 130).

CHART 130: Companion diagnostics from tamoxifen to Tecentriq

Source: Jorgensen & Hersom, 2016

CHART 131: Map kinase pathway drives cancer growth and survival



Source: www.mycancergenome.com

CDx can detect driver mutations that can be targeted with specific drugs

Many CDx are based on biomarkers that link a drug to a specific genotypic marker that defines the sensitivity or otherwise of the cancer cell to a particular drug. Sequencing efforts have identified about 140 genes known to be drivers of the oncogenic phenotype. These are closely linked to disease mechanisms that support oncogenesis and determine cell fate and survival, and genome maintenance. These driver genes frequently encode the receptors and / or intracellular enzymes that form part of a growth cascade that ultimately leads to cancer cell proliferation or survival. It is frequent mutations in these pathways that lead to the uncontrolled growth that promotes cancer. The prevalence of driver mutations vary widely from patient to patient, with the result that many targeted drugs are only effective in a small proportion (5% - 15%) of patients. The use of the CDx allows these small numbers of responding patients to be picked out for treatment with a highly targeted therapy.

Large and growing number of approved CDx

There are currently over 30 FDA-approved CDx linked to the use of close to 20 oncology drugs. Most have been developed by collaboration between pharma and diagnostics companies (CHART 132). Many of the more established and broadly used drugs have more than one CDx associated with their use. Most of these drugs are small molecules targeting enzymes in the signalling cascade, and there are also a few mAbs targeting receptors on the surface of the cancer cell. These include Herceptin, which targets the HER2 receptor and has ten approved CDx associated with its use, as well as Erbitux, an EGF receptor targeting agent. Two CDx have also been developed to guide the use of anti-PD-1 Keytruda. Many tests rely on the collection and analysis of tissue using solid tumour biopsies. One approved CDx for AstraZeneca's Tagrisso relies on the analysis of tumour DNA released into the blood. These liquid biopsies are a key focus for CDx development moving forward.

CHART 132: Oncology drugs with FDA approved companion diagnostics

Drug	Developer	Target	Number of approved tests
Herceptin (trastuzumab)	Foundation Medicine (Roche), Ventana, Abbott, Dako (Agilent), Biogenex, Life Technologies, Leica Biosystems	HER2	11
Erbitux (cetuximab)	Foundation Medicine (Roche), Roche, Qiagen, Dako (Agilent)	EGFR, KRAS	4
Vectibix (panitumumab)	Foundation Medicine (Roche), Illumina, Roche, Qiagen, Dako (Agilent)	EGFR, KRAS	
Xalkori (crizotinib)	Foundation Medicine (Roche), Ventana, Life Technologies, Abbott	ALK	
Iressa (gefitinib)	Qiagen, Roche, Foundation Medicine (Roche), Life Technologies	EGFR	3
Kadcyla (ado-trastuzumab emtansine)	Foundation Medicine (Roche), Dako (Agilent)	HER2	
Mekinist (trametinib)	Foundation Medicine (Roche), Life Technologies, bioMerieux	BRAF	
Perjeta (pertuzumab)	Foundation Medicine (Roche), Dako (Agilent)	HER2	
Rubraca (rucaparib)	Myriad Genetic, Foundation Medicine (Roche)	BRCA	
Tafinlar (dabrafenib)	Foundation Medicine (Roche), Life Technologies, bioMerieux	BRAF	
Alecensa (alectinib)	Foundation Medicine (Roche), Ventana	ALK	2
Cotellic (cobimetinib)	Foundation Medicine (Roche), Roche	BRAF	
Gilotrif (afatinib)	Qiagen, Foundation Medicine (Roche)	EGFR	
Gleevec (imatinib mesylate)	ARUP, Dako (Agilent)	BCR-ABL	
Lynparza (olaparib)	Myriad Genetic, Foundation Medicine (Roche)	BRCA	
Tagrisso (osimertinib)	Roche, Foundation Medicine (Roche)	EGFR	
Tarceva (erlotinib)	Roche, Foundation Medicine (Roche)	EGFR	
Zelboraf (vemurafenib)	Roche, Foundation Medicine (Roche)	BRAF	
Zykadia (ceritinib)	Foundation Medicine (Roche), Ventana	ALK	
Balversa (erdafitinib)	Qiagen	FGFR	1
Braftovi (encorafenib)	bioMerieux	BRAF	
Idhifa (enasidenib)	Abbott	IDH2	
Keytruda (pembrolizumab)	Dako (Agilent)	PD-L1	
Piqray (alpelisib)	Qiagen	PIK3CA	
Rydapt (midostaurin)	Invivoscribe	FLT3	
Talzenna (talazoparib)	Myriad Genetic	BRCA	
Tasigna (nilotinib)	MolecularMD Corporation	BCR-ABL	
Tecentriq (atezolizumab)	Ventana Medical Systems	PD-L1	
Tibsovo (ivosidenib)	Abbott	IDH1	
Venclexta (venetoclax)	Abbott	Bcl-2	
Vizimpro (dacomitinib)	Qiagen	EGFR	
Xospata (gilterinib)	Invivoscribe	FLT3	

*ado-trastuzumab emtansine
Source: FDA, goetzpartners Research

Accuracy of diagnostics for ICIs brought into question

CDx have also been approved for use with Keytruda (pembrolizumab). The assay uses a histological test for PD-1 expression within the tumour. However, the ability of these diagnostics to predict checkpoint response has been drawn into question, due to the inherent complexity and dynamic nature of the immune response. The level of expression of the PD-L1 receptor may vary considerably from tumour to tumour and the correlation between this expression and response is not cut and dried.

Complementary Dx can be used to guide therapy, but are not a prerequisite for drug use

The FDA first approved complementary diagnostics for Tecentriq (atezolizumab) and Opdivo (nivolumab). These are defined as "*Tests that identify a biomarker-defined subset of patients that respond particularly well to a drug and aid risk / benefit assessments for individual patients but are not pre-requisites for receiving the drug.*" The FDA also approved Myriad Genetics' BRACAnalysis CDx as a complementary diagnostic to help identify ovarian cancer patients most likely to benefit from GSK's / Tesaro's recently approved PARP inhibitor Zejula (niraparib).

CDx are increasingly performed by specialised service laboratories as part of increasingly complex patient and tumour profiling used to personalise therapy

Test also available as both IVDs and LDTs

Although the FDA approves both companion and complementary tests as in vitro diagnostics ("IVD") Class III products that are normally required to show a high level of analytical and clinical performance, these tests are also available as laboratory developed tests ("LDTs"). LDTs are covered by the Clinical Laboratory Improvement Amendments ("CLIA") regulations, which allow laboratories approved by Centres for Medicare & Medicaid Services ("CMS") to develop and perform their own tests. Several oncology reference laboratories provide in-house versions of the FDA-approved diagnostic tests together with a range or their own analyses which are aimed at helping physicians to profile patients and their tumours to help identify the optimum therapy for each individual patient.

CHART 133: Selected oncology test providers

Company	Selected tests	Cancers	Analysis
Biodesix	GeneStrat Genomic testing Veristrat Proteomic Testing	Lung cancer, unspecified other cancers	Genomic and proteomic analysis
Caris Life Sciences	Molecular Intelligence	Breast cancer, colon cancer, lung cancer, ovarian cancer	Multiple analysis
Castle Biosciences	DecisionDX-Melanoma	Cutaneous melanoma	Genomic analysis
Roche (Foundation Medicine)	FoundationOne FoundationOne Heme	Solid tumours Hematologic malignancies and sarcoma	Genomic analysis
Genoptix	Lung Molecular Profile Lymphoid Molecular Profile Melanoma Molecular Profile Myeloid Molecular Profile Prosigna® Breast Cancer	Lung, lymphoid, melanoma, myeloid, breast cancer	Genomic analysis
Guardant Health	Guardant360	Solid tumours	Genomic liquid biopsy
NeoGenomics Laboratories	NeoType tumour profiles	Hematologic and solid tumours	
Pathway Genomics	CancerIntercept Monitor CancerIntercept Detect	Various cancers	Genomic liquid biopsy
Sysmex Inostics	Range of mutational diagnostic services and IVD kit	Various cancers	Genomic tissue and liquid biopsy using OncoBEAM

Source: goetzpartners Research

Prognostic Dx used to predict cancer recurrence and guide level of subsequent Tx…

Several diagnostics have been developed to help physicians choose the most appropriate therapeutic class for individual patients. These prognostic diagnostics have been developed for cancers including breast and prostate. In breast cancer, Oncotype DX, Endotype DX and Mammoprint measure the expression of a range of genes in breast cancer tissue. Together with a variety of other factors, the expression of these genes in certain patients allows physicians to predict both the likely re-occurrence of the cancer after surgery and whether they are likely to benefit most from standard hormonal therapy alone or a mixture of hormonal and more aggressive chemotherapy. Similarly, in prostate cancer, the Oncotype DX and Prolaris tests help physicians judge whether the patient is more likely to have the indolent or the aggressive form of prostate cancer (the latter requires immediate intervention).

CHART 134: Selected prognostic tests

Test	Cancer	Developer
Oncotype DX	Breast	Genomic Health
MammaPrint	Breast	Agendia
Prosignia	Breast	Nanostring
EndoPredict	Breast	Myriad
Oncotype DX	Prostate	Genomic Health
Prolaris	Prostate	Myriad

Source: goetzpartners Research

Acceptance by clinical community still patchy

Such tests are not without controversy. They do not necessarily deliver the same results in every patient and cannot be relied on on a stand-alone basis. However, they are increasingly accepted as useful tools for determining risk and guiding therapy if taken together with a variety of other tumour parameters. There are currently only a handful of biomarkers that allow disease monitoring in cancer. These include CA-125 for ovarian cancer, AFP for liver cancer, CEA for colorectal cancer and lactate dehydrogenase for melanoma. These tests have varying levels of acceptance amongst the clinical community. For most cancers, regular monitoring with CT scanning and MRI are the only options.

Higher response rates the most compelling driver

Screening patients CDx can more than double median response rates

The obvious clinical driver for the development of CDx is to direct appropriate therapies to those patients most likely to respond (CHART 135).

CHART 135: Drivers for the use of companion diagnostics

Clinical	• High need to identify likely responders • Need to identify patients more likely to experience side effects
Economic	• Identification and subsequent treatment of patients likely to respond reduces unnecessary therapy costs • Regular monitoring allows termination of treatment when patients no longer benefit
Scientific	• A high number of targeted therapies and immunotherapies are already approved, some in combination with biomarkers • First liquid biopsy test for caner gained FDA approval in June 2016 (cobas FGFR, Roche), paving the way for additional approvals
Other	• Cancers are highly complex and biomarkers need to determine the best course of treatment • Targeted therapies are considerably more efficacious in relevant in patients expressing relevant biomarkers

Source: goetzpartners Research

Analysis of the targeted drugs approved over the last 15 years reveals that the ORR for drugs with CDx ranged from 41% - 80% compared to 7% - 45% for those where no companion diagnostic is available (CHART 136). This equates to a more than doubling of the median ORR from 23% to 55%.

CHART 136: Responses to targeted therapies with and without CDx

Drug	Indication	Biomarker (s)	Response rate (%)
DRUGS WITH CDX			
Pertuzumab (Perjeta)	Breast cancer	HER2	80.2
Crizotinib (Xalkori)	NSCLC	*ALK*	65.0
Erlotinib (Tarceva)	NSCLC	*EGFR*	65.0
Osimertinib (Tagrisso)	NSCLC	*EGFR T790M*	59.0
Cetuximab (Erbitux)	Colorectal cancer	EGFR/*KRAS*	57.0
Imatinib mesylate (Gleevec)	GIST	CD117	53.9
Dabrafenib (Tafinlar)	Melanoma	*BRAF*	52.0
Vemurafenib (Zelboraf)	Melanoma	*BRAF*	48.4
Ado-trastuzumab emtansine (Kadcyla)	Breast cancer	HER2	43.6
Pembrolizumab (Keytruda)	NSCLC	PD-L1	41.0
DRUGS WITHOUT CDX			
Bevacizumab (Avastin)	Colorectal cancer	–	45.0
Ixabepilone (Ixempra)	Breast cancer	–	34.7
Paclitaxel protein-bound particles (Abraxane)	NSCLC	–	33.0
Pemetrexed (Alimta)	NSCLC	–	27.1
Pembrolizumab (Keytruda)	Melanoma	–	24.0
Capecitabine (Xeloda)	Colorectal cancer	–	21.0
Ziv-aflibercept (Zaltrap)	Colorectal cancer	–	19.8
Eribulin Mesylate (Halaven)	Breast cancer	–	11.0
Ipilimumab (Yervoy)	Melanoma	–	10.9
Sunitinib malate (Sutent)	GIST	–	6.8

The indications in the table are for advanced and / or metastatic disease. All drugs listed obtained FDA approval after 2000.
Abbreviations: GIST, gastrointestinal stromal tumours; NSCLC, non-small cell lung cancer
Source: Jorgensen & Hersom, 2016

Development of minimally invasive liquid biopsies facilitates the development of rapid multi-parameter disease profiling and monitoring

The use of CDx should not only maximise survival benefits, but also facilitate patient selection allowing for smaller, more targeted pivotal clinical trials as well as easing the drug's course through the regulatory process. Similar drivers, although to a lesser extent, apply to the development of complementary and prognostic diagnostics. There is also a significant need for markers to monitor disease after treatment to allow for rapid intervention before the returning cancer becomes symptomatic or visible by imaging. Equally, monitoring helps to identify any change in drug susceptibility (e.g. driver mutation profile) so that the drug regime can be adjusted appropriately. This also brings economic benefits in the form of lower costs for clinical trials and less inappropriate use of expensive drugs.

The discovery and use of relevant diagnostic biomarkers are driven by the increasing ability to rapidly detect and analyse low levels of DNA and other biomolecules through rapid progress in technologies including next generation sequencing. These innovations will drive the development of liquid biopsies (mostly from blood), measuring multiple molecular parameters without the need to access frequently scarce tissue. The ability to measure multiple parameters from blood enables the development of diagnostic panels that combine companion and complementary diagnostic tests with the prognostic tests that guide the broader therapeutic approach to further personalise patient care. Developments in immunotherapy and the understanding of the role of immunity in cancer progression will drive an increasing need for biomarkers capable of predicting and guiding the response to checkpoint inhibitors and a whole new range of other immunotherapies and their combinations.

Substantial scientific, technical and other challenges

The scientific and technical challenges of identifying relevant biomarkers and developing companion and related diagnostics remain substantial, as summarised in CHART 137 below.

CHART 137: Challenges to the adoption of companion diagnostics

Clinical	• Lack of standardisation for a test can limit use outside of centres with high levels of oncology expertise • Depending on indication, there may be limited treatment options, making it difficult to exclude patients based on biomarker expression
Economic	• Biomarkers can reduce patient population size, thus limiting the market opportunity for cancer drugs
Scientific	• The majority if ICIs to date have been approved on their own in the absence of a biomarker • Regulatory agencies are still unfamiliar with liquid biopsies and criteria for market clearance may yet still evolve
Other	• PD-L1 diagnostics have proven unreliable due to the dynamic expression of this biomarker • Requirements to combine biomarkers adds complexity

Source: goetzpartners Research

A small proportion of patients have cancers that carry markers for specific therapies

For example, many of the targets only occur in a very small proportion of patients (sometimes < 5%). As illustrated for lung cancer in CHART 101, this requires knowledge of multiple markers and a large proportion of patients have yet to be assigned a marker at all. Some patients test positive for more than one driver mutation, meaning that physicians must base their choice on additional factors. Although the advent of next generation genetic sequencing technologies has facilitated biomarker identification and analysis, the validation of the clinical utility of such markers will remain a challenge, due to the inherent heterogeneity of cancer. Many CDx developed to date are associated with driver mutations written into the genetic code of the cancer cells. Although markers such as microsatellite instability ("MSI") and tumour mutational burden ("TMB") appear to predict the likely immunogenicity, the immune system response and its interaction with the tumour is a dynamic process dependent on a range of factors. It may prove difficult to develop useful reliable predictive biomarkers in what is a highly dynamic process.

Economic hurdles to diagnostic development remain

The economic hurdles facing companion diagnostic development remain significant. CDx are frequently developed through collaboration between pharma and diagnostics companies. While pharmaceutical companies are increasingly bearing the cost of companion diagnostic development, the relative market value of the drug compared to the diagnostic means that the upside remains in drug development. There is little incentive for drug companies to fund the development of clinically valuable broader complementary diagnostic tests that may promote the use of drugs from other companies in the same class. Instead, they are motivated to focus on CDx that promote the use of their drugs alone.

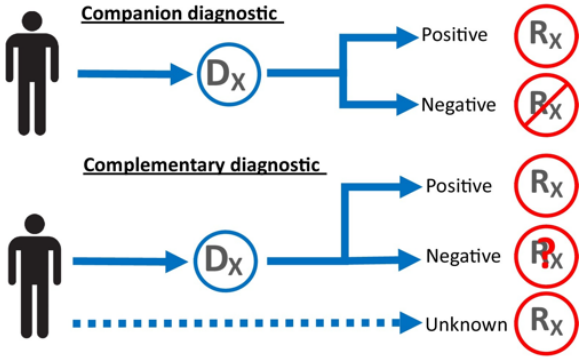
The regulator can be unpredictable

The potential regulatory risks for diagnostic players developing CDx was well illustrated by the experience of Myriad Genetics. Myriad developed a CDx for Tesaro's Zejula only to find that the FDA ultimately approved the drug for use in patients beyond the scope of CDx and thus diagnostics would not be required for its use. Equally, the market opportunity for CDx can be limited by competition from copy-cat LDTs. The lack of incentives for diagnostics companies to risk capital and human resources on innovation calls for regulatory change.

Clear role for CDx in precision medicine

CDx are designed to identify patients likely to be responsive to a specific drug. The case for complementary diagnostics is less clear cut (CHART 138). A positive test indicates that a patient is more likely to respond, while a negative result does not necessarily rule out a potential response to treatment.

CHART 138: Companion vs. complementary diagnostics

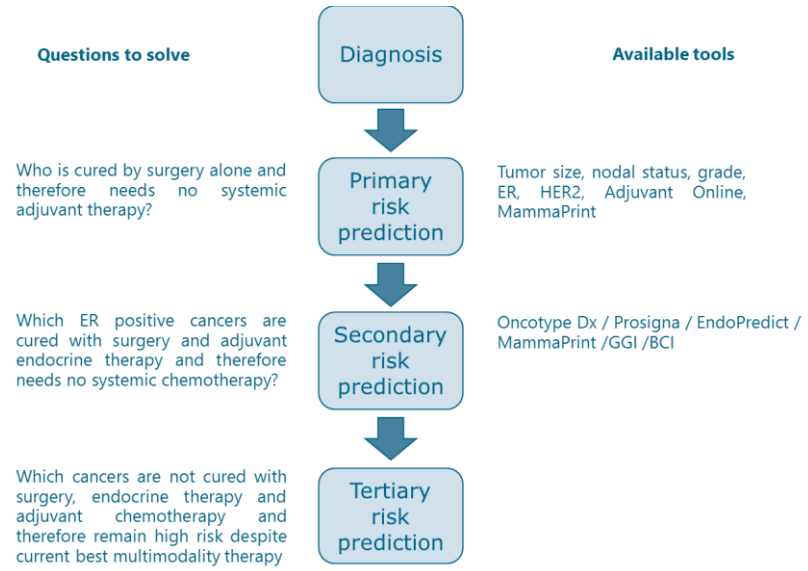


Source: Jørgensen, 2016

Breast cancer illustrates benefits of prognostic screens unrelated to specific drugs

The development of liquid diagnostics involving ctDNA should facilitate minimally invasive profiling of the tumour (CHART 141), allowing for the early selection of targeted therapy, plus regular longitudinal monitoring for drug susceptibility, the development of drug resistance, and disease progression. The use of diagnostic testing of known cancers is also well illustrated by the availability of prognostic screens in breast cancer, which enable the physician to select the course of therapy most appropriate to the patient but are not linked to the efficacy of any specific drug.

CHART 139: Precision medicine in breast cancer

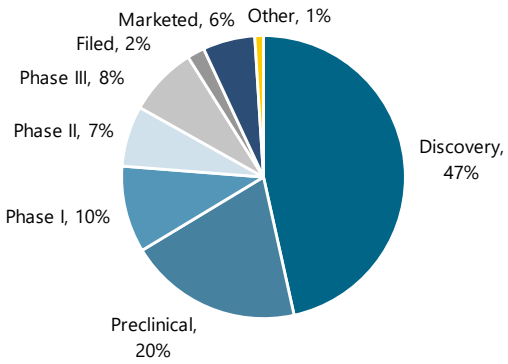


Source: goetzpartners Research

Development path and status

There continues to be a plethora of deals between large pharma and diagnostics companies and laboratories to develop CDx. While the majority of these deals are focussed on the discovery phase (CHART 140) with limited information released into the public domain, there has been a marked shift away from diagnostics based on tissue biopsies to the analysis of tumour-related markers, particularly DNA, found in blood and other biofluids.

CHART 140: Nature of companion diagnostic deals, 2015



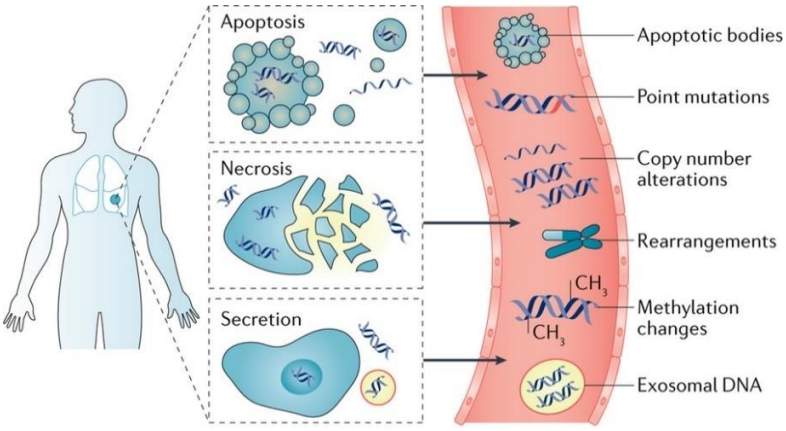
Source: Patel *et al.*, 2015

Growing focus on liquid biopsies for long term disease profiling, treatment and resistance monitoring

Focus on circulating tumour DNA for liquid biopsies

The major focus is on the detection and analysis of DNA released by the tumour into the blood and other fluids (Figure 153). ctDNA provides valuable information including that on the presence of driver mutations that can help guide treatment options. The analysis of other mutations and methylation patterns is being used to develop liquid biopsies capable of monitoring tumour drug susceptibility and resistance, thus enabling them to be adjusted as the disease progresses or is put into remission. It has been suggested that monitoring the development of EGFR resistance via the T790 mutation and then initiating appropriate treatment holidays could improve outcomes in some patients.

CHART 141: Liquid biopsies are based on circulating tumour DNA



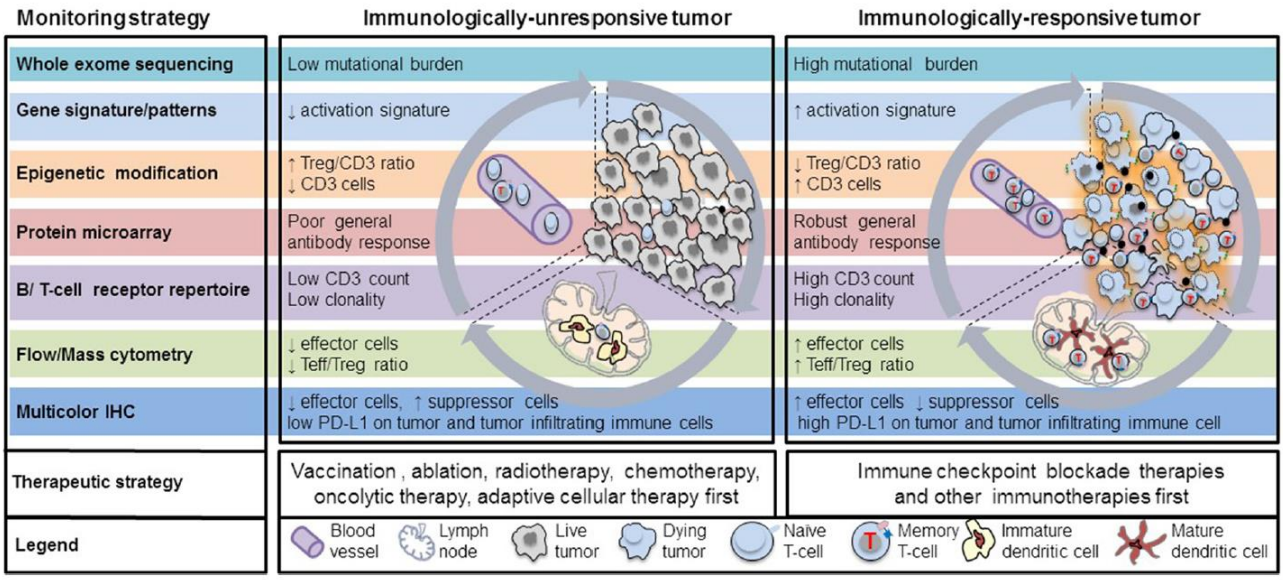
Source: Wan *et al.*, 2017

Liquid-based multi-parameter tests could open the door to immune profiling and targeted immunotherapies

Increased use of multi-parameter assays

Until recently, CDx have focussed largely on single molecular parameters. In the case of solid tumours, the samples undergoing analysis were generally drawn from tissue removed by biopsy. The development of liquid biopsies should facilitate the increased use of multi-parameter assays. New technologies including NGS, multiplex PCR and direct detection, coupled with the inherent complexity of cancer and particularly the growth of immuno-oncology, have been driving a shift towards multi-parameter molecular assays performed in samples taken from blood. Nanostring, for example, has developed a fluorescent direct detection platform that can detect large numbers of specific genetic sequences as well as proteins simultaneously from a single sample. These multi-parameter assays aim to provide predictions of the overall prognosis, providing a "cancer immunogram".

CHART 142: Novel immune monitoring assays to identify new biomarkers



Source: Yuian *et al.*, 2016

Variety of parameters could allow monitoring of tumour immunity and immune system

The immune response to any cancer is dependent on a whole variety of factors, which only a multi-parameter test could monitor. Although the monitoring of PD-1 / PD-L1 expression will probably continue to require tissue biopsy or the development of very sensitive assays based on CTCs, there are a variety of other parameters that could allow the monitoring of tumour immunity and the immune system. This could include markers such as for MSI in the ctDNA, whole blood microRNA signatures that are thought to reflect the activity of the immune system, and other complex DNA expression patterns detectable through NGS.

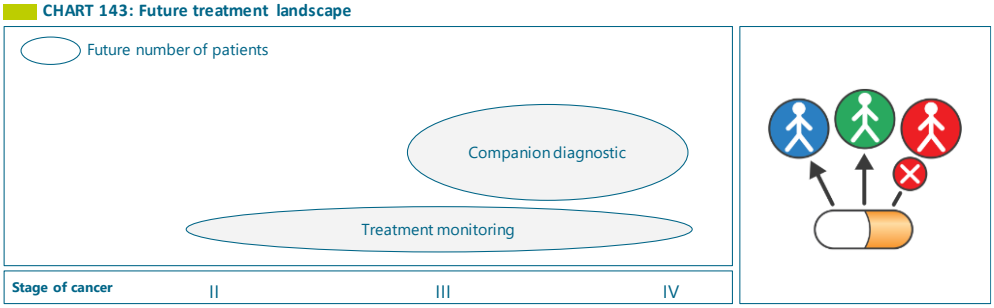
Point-of-care MDx platforms being developed to reduce turnaround time

Oncology-related diagnostics are mostly performed remotely by testing laboratories. However, there are a variety of point-of-care molecular diagnostics platforms available or under development, such as that from Biocartis. These are being prepared to provide rapid turnaround on site analysis, particularly in the areas of companion / complementary diagnosis and drug resistance monitoring.

Use of Dx expected to increase significantly

We anticipate a significant increase in the use and availability of companion, complementary and treatment monitoring diagnostics. This will be driven by the discovery of new biomarkers via next generation sequencing as well as the increasing ability to detect markers in body fluids, allowing easier and more routine sample collection. The diagnostics are likely to become increasingly complex with the use of sophisticated multiplex signatures. Given the increasing focus on the immune system, we would expect an increasing number of these diagnostics to focus on monitoring immune activity.

CHART 143: Future treatment landscape



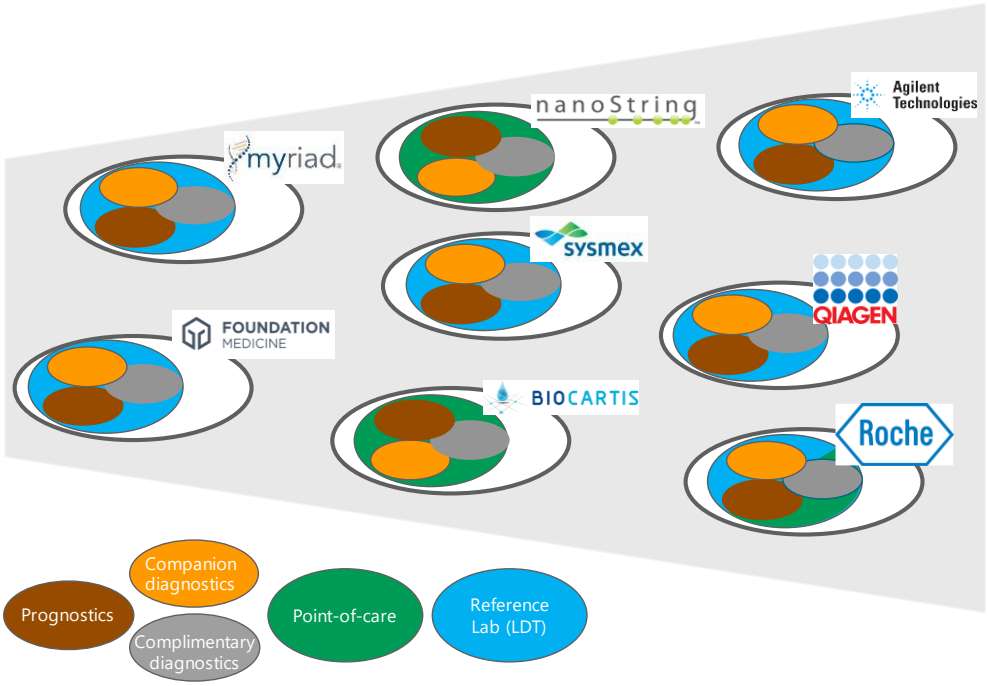
Source: goetzpartners Research

Industry outlook and key players

Large diagnostics companies likely to remain major players with increasing role for reference lab service providers and innovative point-of-care diagnostic platforms

Major test developers including Roche Diagnostics, Abbott Laboratories, Agilent Technologies, Qiagen, Thermo Fisher Scientific and Myriad Genetics are expected to continue to be major developers of CDx. While the increasing complexity of the analysis and the heterogeneity of the tests may see an increasing role for service providers able to provide both testing and analytical services, there should be an increasing role for point-of-care diagnostic platforms in routine treatment monitoring or in territories where central laboratory testing is limited.

CHART 144: Selected companion diagnostics players



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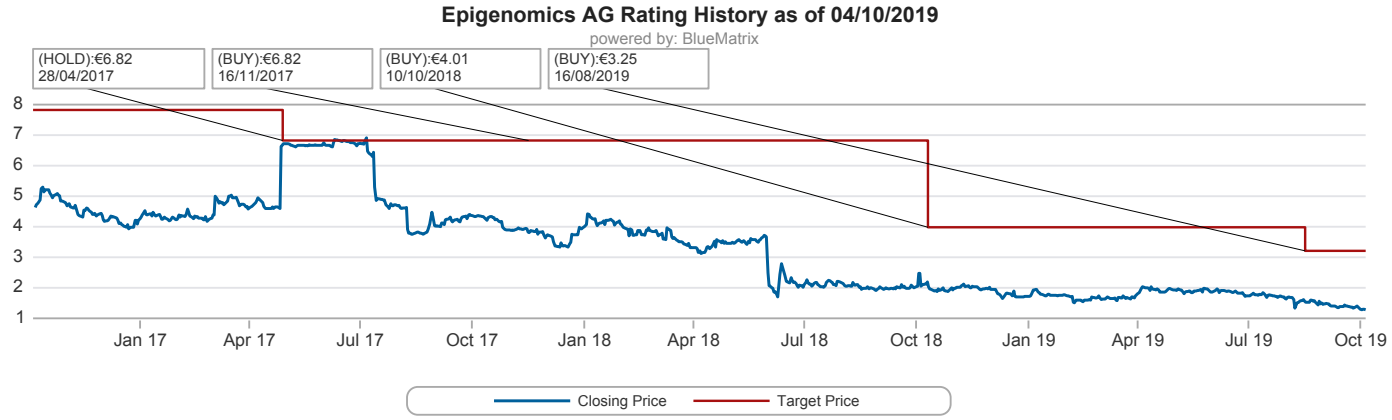

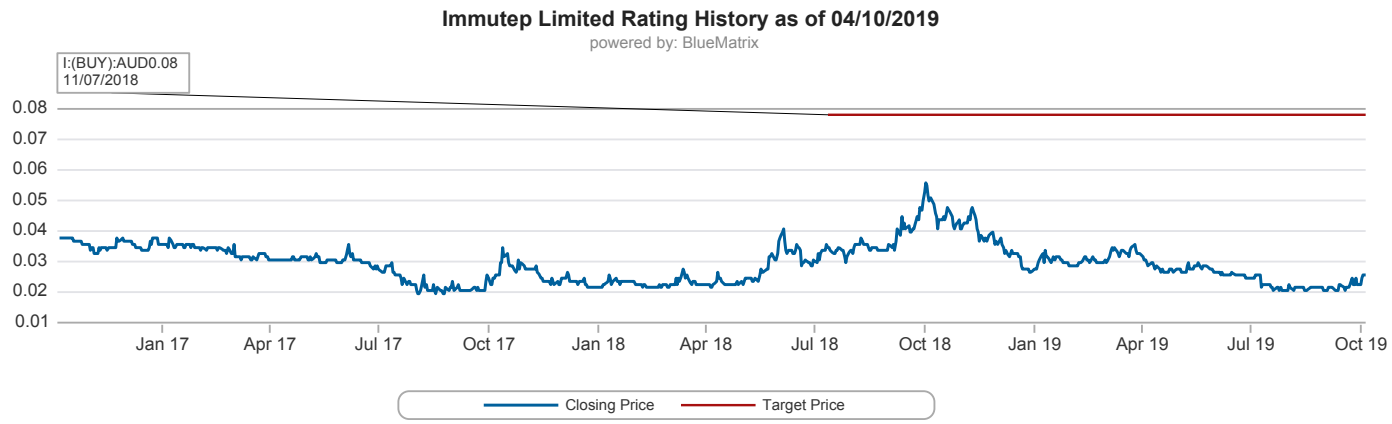

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