Oncology: Advancing cancer treatment in the age of precision medicine
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Introduction: A new era of cancer care

The last 15 years have brought amazing progress in the battle against cancer. Less than 50 years ago, our approach to cancer treatment was all brute force – using all-purpose compounds, such as alkylating agents, to attack every kind of tumor, knowing that they would also take their toll on healthy tissue.

Then we moved into the ’90s when a few compounds in development were aimed at specific molecular targets for particular cancers. Targeting specific tumor types limited the range of application of these treatments, but it reduced off-tumor effects, which decreased the side effects. It was the beginning of a personalized medicine approach to cancer care.

Then we learned how to leverage genomic alterations, with treatments like gefitinib, which combats NSCLC sparked by mutations in the epidermal growth factor receptor (EGFR) gene, and crizotinib, which provides impressive outcomes in NSCLC patients with the EML4-ALK fusion. That created an opportunity to develop this agent for a specific sub-population of patients with NSCLC.

Despite the initial excitement over the efficacy of these targeted treatments, in many cases resistance emerged and patients relapsed. It became clear that while these agents take out one target in the cancer cell, they will not necessarily cure a population of patients.
Welcome to the age of precision

In 2013 Nature published the Cancer Genome Atlas, which set the stage for a new era of precision-based care. This information and future genomic analyses will aid oncologists as they select the patients most likely to respond to a specific treatment, with the overall goal to develop a medication that attacks the right targets, in the right disease, in the right patient, at the right dose to obtain the desired outcome.

With the complexity of genomic alterations in tumor cells coming to light, the future of cancer investigation and care will emerge and evolve in four key ways:

- Intervention trials will test combinations of rationally selected agents targeted for specific niche populations of patients with a specific array of genomic alterations in a particular tumor context.
- Real-world observational trials and registries are expected to be able to collect patient-level clinical and genomic data on well-characterized cohorts of patients.
- The public domain will include readily available, patient-level data linked to genomic data.
- Data aggregators and analytic tools will efficiently and rapidly sort through these patient-level data sets to improve the design of new agent development programs and clinical decision-making.

This future state of maximally leveraging genomic information allows for truly personalized precision cancer care. In short, genomics-based techniques will greatly influence the oncology ecosystem from the very beginning of drug discovery through treatment.

“The Art & Science of Evidence – Oncology” is one in a series of compendiums featuring blogs and bylined articles from Quintiles’ experts. This collection explores innovative accomplishments, new opportunities and ongoing challenges in oncology and immunotherapy research for the coming years.
Immunotherapy is one of the most promising avenues of research in the battle against cancer. This treatment path uses small molecules and biologics to harness a patient’s own immune system to fight the tumor – a novel approach that is poised to revolutionize cancer treatment.

This promise has been a long time coming. Scientists in the cancer research world have been working on immunotherapy treatments for decades, since the first observations were made about how important the immune system is in modulating and potentially killing cancer. These early realizations where made nearly a century ago, and we are only now beginning to harness the immune system in cancer therapies. Although there is no conclusive evidence that immunotherapy will be a “magic bullet” for all cancer indications and a significant number of patients, there is strong reason to believe it will be a dynamic treatment option going forward.

**Exciting innovations**

Many important discoveries have already been made that provide insight into how the immune system works and how it attacks cancer. For example, recent drug approvals take advantage of checkpoint inhibitors as a novel approach to immunotherapy. Instead of stimulating the immune system directly, checkpoint inhibitors block the built-in brakes that tumors apply to the immune system, allowing the system to continue to attack the cancer. This has been an unprecedented advance in the treatment for patients. We’ve found that generally 20 – 40 percent of patients will respond to this single intervention even when other treatments have failed before\(^2\). Durable responses are even more noteworthy given the resistance to targeted therapies that is so often seen in oncology. Most exciting will be the results obtained in the many combination trials currently underway.
It has yet to be determined how these new immunotherapies will displace or complement existing therapies such as IL-2 treatment in metastatic melanoma. Approved in 1998, IL-2 has shown very good responses in a small group of otherwise very healthy metastatic melanoma patients. The therapy continues to be recommended with close safety monitoring by some but may be replaced with newer therapies or clinical trials for qualifying patients. In non–small cell lung cancer, combinations with existing targeted or chemo therapies may address the patients that lack the defining molecular characteristics for targeted agents such as crizotinib.

And there are many other products in development that span a spectrum of mechanisms and modalities, including checkpoint regulators, immunomodulators, vaccines and cell-based therapies such as CAR T-cell approaches.

**Challenges ahead**

Although these approaches offer encouraging new opportunities, a more complete understanding of the cellular and molecular components of the tumor-immune system interaction, including the formation of neo-antigens or new targets for the anti-tumor immune response, will be necessary for the development of rational and efficacious immunotherapies in the future.

Although there is no conclusive evidence that immunotherapy will be a “magic bullet” for all cancer indications and a significant number of patients, there is strong reason to believe it will be a dynamic treatment option going forward.

We have yet to identify how the various immunotherapy treatments can be targeted to patient groups to achieve the greatest real-world benefits for patients. Basic research and clinical results suggest that certain treatments such as radiotherapy may induce new targets for the anti-tumor immune response. This may be in addition to the existing repertoire of the anti-tumor response determined, in part, by the tumor’s genetic alterations. We have yet to see whether immunotherapies in oncology will lead us to a precision medicine approach or broad applicability across indications and patient groups.
The current competitive landscape for immunotherapies is highly complex based on ongoing trials identified on clinicaltrials.gov and other sources. At present, competition is particularly strong in the areas of solid tumors, melanoma and non-small cell lung cancer. It remains to be seen whether classical tumor-type classifications will ultimately give way to molecular pathway-based classifications, or whether a new clinical development paradigm of mega-Phase I studies followed by rapid registration will become established.

Going forward, a central principle that we must remember is that the immune system does not operate separately from other biological systems in the patient, including the inflammatory system. Therefore, we may not be able to define optimal immunotherapy strategies without also considering patient comorbidities and other factors. To avoid wasted time and money, an informed approach is needed for the immunotherapy platform from the outset of development. The rapidly emerging research results describing immunotherapy targets, drug combinations and responsive patient characteristics should lead to better informed studies and more successful trial outcomes.

To avoid wasted time and money, an informed approach is needed for the immunotherapy platform from the outset of development.
Thanks to the commitment by leading cancer researchers, along with innovative partnerships between pharma, academia and the government to share knowledge and work collaboratively, we have made significant strides in developing new technologies and treatments for this disease. And many of the most innovative accomplishments involve immunotherapy.

Immunotherapy, which harnesses the power of the immune system to attack cancerous cells, has played an integral role in oncology research for more than a century, but in the last few years we’ve seen many extraordinary discoveries that are transforming our approach to cancer care and dramatically improving the number of patients receiving treatment and duration of their survival.

**Why immunotherapy works**

The immune system is an ideal anti-cancer agent because it controls an array of diverse immune cells that have a high degree of specificity and the ability to distinguish minute chemical alterations. It also has a long memory, which means once a body develops immunity to a specific cancer, that immunity can last for up to several decades after effective antigen priming. Immunotherapy can also be delivered in various therapeutic formats.

One of the most exciting formats is checkpoint inhibitors, which work by releasing the natural brakes on the immune system so it can attack cancer tumors on its own. This is a game-changing development that promises to have a huge impact on patient outcomes, because checkpoint inhibitors cause the immune system to target the tumor in real time, rather than waiting for lab tests to hunt down vulnerabilities in the tumor, which can change over time and delay treatment.
From a research perspective, immune checkpoint inhibitors are leading the way in clinical discovery and enthusiasm, given the exciting data yielded to date. As further research continues to elucidate the biology behind the anti-tumor immune response that is released by these checkpoint inhibitors, they are beginning to clarify why certain patients and indications may be more amenable to this class of agents, all of which helps us hone our ability to deliver precision medicine and improve outcomes for cancer patient worldwide. And while checkpoint inhibitors alone are good, there is much more work needed. Combining them with other immune therapies or more traditional methods such as surgery, radiation therapy, chemotherapy and new therapies targeted at a specific mechanism is likely to be beneficial.

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Opportunities to accelerate development

Such dramatic innovations are likely to continue in the oncology, thanks in part to new collaborations developed to support work in this space. For example, The National Immunotherapy Coalition (NIC) was recently established to bring expert and industry leaders together to drive the next generation of immunotherapy in cancer research. It will also form the basis of The Cancer MoonShot 2020 an unprecedented collaboration of multinational pharmaceutical, biotechnology companies, academic centers and community oncologists will make possible access to more than 60 novel and approved agents under exploration, and will enable rapid testing of novel immunotherapy combination protocols3. The NIC expects to design, initiate and complete randomized clinical trials in cancer patients with cancer at all stages of disease in up to 20 tumor types in as many as 20,000 patients by the year 2020.

Similarly, three research centers in the UK are collaborating to advance academic discoveries into commercially viable immuno-oncology cellular therapy4. The venture, which includes Cancer Research Technology, Cancer Research UK’s
commercialization arm; Cell Therapy Catapult, an organization working to move cell and gene therapy from academia to industry; and the University of Birmingham, is grounded on a new-generation chimeric antigen receptor T cell (CAR-T), directed toward a new and highly specific marker of CLEC14a tumor angiogenesis. The therapy acts as a vasculature disruptive agent that compromises the tumors' oxygen supply, inhibiting growth. The approach is expected to enter into clinical trials as soon as preclinical development is finished.

Regulatory agencies, including the U.S. Food and Drug Administration and European Medicines Agency, are also showing significant interest in the potential of immunotherapy, further validating the impact of this treatment path.

Such advances are generating incredible excitement in the field of oncology, and giving hope to millions of cancer patients who no longer need to think of their diagnosis as a death sentence. But this is just the first wave for immunotherapy development and we have so much more to discover. While the initial promise of immunotherapy rests largely in its aptitude for broad application in various patient populations, the algorithm for effective use in oncology is excruciatingly nuanced, and reduces the reality of broader success at this time. The real hope now is to understand why immunotherapy can work, and when it cannot.

To do that we need to continue supporting cross-industry collaborations among leaders from the biopharma community, academia, regulators and private sector investors, who have the resources and passion to drive these discoveries forward; then creating environments in which they can share ideas and brainstorm solutions. Such collaborations are the best hope for driving this research forward, and accelerating delivery of much-needed, new cancer therapies to patients.
There has always been a desire among oncology physicians and their patients to more precisely match treatments to the specific demands of each tumor. Over time that desire has moved closer to reality thanks to the use of biomarkers in the classification and development of treatments for different types of cancer.

A biomarker is a biological molecule found in blood, tissue or body fluids that can be used to identify the presence of an abnormal process or disease. For example, a biomarker may be secreted by a certain type of tumor, or it could be a physical response by the body’s immune system to the presence of a tumor. By identifying biomarkers, researchers and physicians can determine whether a specific treatment is appropriate for a specific tumor type and track their ongoing presence or absence as a measure of how well the body responds to a treatment. Biomarkers can also help indicate drug efficacy, toxicity or resistance, and they may be useful in pharmacodynamics-based therapeutic drug monitoring as surrogate and non-surrogate endpoints.

These are all developments that regulatory agencies, including the U.S. Food and Drug Administration and European Medicines Agency, are significantly interested in because they provide information that can help vastly improve the way we treat cancer.

Oncology’s matchmaker:
How biomarkers in immunotherapy bring precision medicine to the fight against cancer

Eric Groves, MD, PhD
**Better results, better matching**

Biomarkers offer two types of information that can support clinical study objectives and endpoints: predictive, identifying patients who are susceptible to a particular drug effect, which may involve benefit or harm; and pharmacodynamic, revealing target engagement and the magnitude of biological response post therapeutic intervention. These results can be used to support drug development and patient care to improve outcomes and reduce the risk that patients will be subjected to ineffective or inappropriate treatments, which may cause harm or discomfort while delaying their ability to secure more effective treatment options.

In patient care, biomarkers may be diagnostic, indicating the presence or absence of pathogenic processes, or prognostic, providing information on the likely future clinical course in the absence of a therapeutic intervention. Used in companion diagnostics, biomarkers help predict responses to therapy. They may also be used in multiplex or multi-analytic diagnostic panels, in next generation-sequencing (NGS) genomic panels, or in whole exon sequencing (WES) or whole genome sequencing (WGS).

The complexity of the immune system and tumor biology also results in a wealth of biomarkers and potential targeted indications and patient populations. New diagnostic tools, such as more powerful standardized flow cytometry and NGS, can better profile immune response and utilize the immune repertoire for patient selection in clinical trials.

**Pitfalls slow progress**

The promise of biomarkers as a vital tool to fight cancer is without question, but physicians and researchers must figure out how to identify which biomarkers are relevant, how to use them effectively, and how to figure out what role they will play in the future of immunotherapy treatments.
them to benefit patients. Yet there are also many obstacles in the way. Physicians and researchers now must figure out how to identify which biomarkers are relevant, how to use them effectively, and how to figure out what role they will play in the future of immunotherapy treatments. Here are just a few of the challenges that stand in their way:

**More data means more complexity.** Recent advances that allow for broad spectrum biomarker measures are already enabling researchers to simultaneously identify multiple flaws and abnormalities that aren’t otherwise obvious. This is a great step forward in the ability to accumulate more data more quickly, but it also adds an extra layer of complexity as researchers and physicians are left to determine which abnormality or flaw is relevant and warrants targeted treatment.

**The industry at large must work together to advance immunotherapy, investing in more research focused on biomarker technology and assays, and collaborating to identify the best ways to get the most information out of every trial.**

**Every patient (and tumor) is different.** Physicians and researchers must address the fact that each patient has a unique genetic make-up and response rate, which will impact the successful use of biomarkers in their treatment. According to research available today, targeted small molecule therapy can yield high response rates, but it is often prone to resistance. Treatment of patients with immune checkpoint inhibitors can also differ from use of conventional therapies in the need to identify unconventional responses, and to understand and manage immune-related adverse events. And current assays for patient selection may not always have adequate specificity and sensitivity. That can force researchers to raise the threshold to meet specificity goals, which may result in excluding some potential responders.
We don’t know what we don’t know. Another major risk in the development of products in this area is failure to anticipate unique properties of the response to the immunomodulator. For example, the mechanism-of-action (MOA) model may be unrepresentative, leading to targeting of unresponsive subpopulations; patient selection assays may be weak; and combinations of immunomodulators may lead to unexpected autoimmune syndromes, and may interfere with desired immunomodulatory effects in ways not seen in animal models.

Small populations make verification difficult. If researchers cannot secure a large enough group of patients in the target subpopulation, due to requirements for a novel screening or limited number of potential candidates, it can be difficult to accumulate enough data to validate results. Monitoring of pharmacodynamic (PD) responses can also pose challenges related to sample handling, lack of availability of clear surrogates of desired bioactivity, or the fact that relevant samples may only be obtainable from repeated tumor biopsies.

More work needs to be done. As the science behind the development of immunotherapy advances, these issues will only become more complex, requiring the industry at large to work together to advance the field. That means investing in more research focused on biomarker technology and assays, and collaborating to identify the best ways to get the most information out of every trial.

It is still early days, and the best approach is a collaborative one. If we work together as an industry and are willing to share our successes and failures, we will drive this research forward faster and more effectively than if we work alone. As the old saying goes, “a rising tide lifts all boats.” If we can raise the tide on biomarker research for immunotherapy, biopharma, payers and patients will all benefit.
Physicians and scientists have recognized for many years that not every patient responds to a given drug in the same way. Some patients may derive very good therapeutic benefit from a given drug, and others may not. Similarly, some patients may show severe adverse drug reactions while others experience no side effects.

With the tremendous increases in our knowledge of molecular biology, genetics and genomics in recent years, we are now much better placed to understand the biological reasons for differences in patients’ responses to the same drug, and this is particularly true in the field of oncology.

Imagine a hypothetical scenario in which 10 different genetic variants are involved in the development of cancer. It is possible that a drug already on the market may help patients possessing just one of those variants. The question then becomes: how do we identify patients who should receive the drug? By taking a tumor biopsy from a patient and looking for the presence or absence of the appropriate genetic biomarker, we may determine which patients should be given the drug, and which ones should not. As real examples, consider crizotinib and vemurafenib, which were approved by the United States Food and Drug Administration (FDA) in 2011 in combination with FDA-approved companion diagnostic tests. Crizotinib is indicated for the treatment of locally advanced or metastatic non–small cell lung carcinoma that is anaplastic lymphoma kinase (ALK)–positive as detected by the associated FDA-approved predictive biomarker test. Vemurafenib, indicated for melanoma, is approved for patients with a certain abnormal variant of the BRAF gene, BRAFV600E, as identified by the associated FDA-approved test. These examples illustrate how cancer genomics has moved into clinical practice.
Now let’s look at this issue from a different but equally important perspective. Imagine a scenario in which a biopharmaceutical company is developing a new oncology drug, and is conducting clinical trials to evaluate whether the drug can provide therapeutic benefit to certain individuals. All previous research had led the company to believe that this drug may provide therapeutic benefit to individuals whose tumor possesses a certain genetic variant. Just as we did in the previous scenario, imagine that there are 10 different variants, and the company believes that the drug will help only individuals with variant A. The most efficient way to determine whether the drug is indeed safe and efficacious is to include only patients with variant A in the clinical trial. If the clinical trial were open to all comers, and only a small and unknown proportion of participants possessed variant A, then even if the drug is highly effective for those with variant A, the aggregated clinical trial results are likely to suggest that the drug is not effective. Moreover, individuals with variants B thru J are unlikely to benefit and may be harmed if treated with the drug. For these reasons, the trial design should exclude patients with variants B through J.

The question therefore becomes this: when recruiting patients to participate in a clinical trial, how do we ensure that appropriate patients are selected efficiently, even if a relatively rare genetic inclusion criterion must be met? The answer is to pre-profile a large number of patients and create a registry of genetic information such that patients who are genetically appropriate are selected to participate in the trial.

Pre-profiling, which prospectively stratifies patients through genetic screening, provides two significant advantages in the treatment of cancer. First, it provides value to patients and their physicians via access to rapid, broad-based genomic testing of their cancer to see which marketed drugs may provide them with the most therapeutic benefit. Second, it provides the best means of identifying patients who are appropriate for clinical trials involving drugs that are likely to be effective treatments for their cancer.
After attending the annual American Society of Hematology (ASH) conference recently, I have been thinking a lot about the advances we have made in hematopoietic cell transplants (HCT), and the challenges we continue to face. The advent of HCT in the mid-1970s gave oncologists and hematologists a powerful weapon against leukemia, lymphomas and immune system diseases. But this treatment comes with a dangerous and sometimes deadly complication – acute graft versus host disease (aGVHD).

aGVHD is a frequent result of HCT, especially when using allogeneic cells – those that come from a relative or other donor – which account for roughly 65% of all graft sources. Since 1980, more than 125,000 allogenic transplants have taken place.

As its name implies, aGVHD is the result of graft cells identifying the host’s body as a foreign object, which causes it to attack the patient’s organs. In acute cases, this occurs before day 100 post-transplant and the damage is mainly targeted against the liver, gut and skin which can cause rash, nausea and vomiting, diarrhea, jaundice and other symptoms.

Despite more than five decades of research into methods to prevent aGVHD, this complication continues to be a significant cause of illness and death among transplanted patients. Each year more than 8,000 patients undergo HCT and the majority will suffer some manifestations of graft versus host disease, particularly if the donor’s human leukocyte antigen (HLA) is not a perfect match.
The standard treatment for aGVHD includes high dose of corticosteroids as first line of treatment, which can have long-term side-effects; and immunosuppressants that make the cells less reactive, which weakens the body’s immune system, making the patient more vulnerable to infections. Resolution of inflammation and facilitation of rapid immune reconstitution in those with only a limited response to corticosteroids is a research arena that remains rife with opportunity and urgent clinical need.

**We need more research**

There is still no cure on the horizon; however, several advancements have led to novel aGVHD detection, prophylaxis and treatment methods in the past five years. Currently, researchers are investigating new modalities, including small molecules that target different checkpoints in the aGVHD cascade, cytokine/growth factor milieu-based therapies, cell-based therapies, alteration of host microbia, infusion of T-regs or other suppressor populations, as well as new approaches to modify the graft. Several clinical trials are also available for the treatment of steroid-refractory aGVHD that include a combination of basiliximab plus infliximab (combined targeting of the IL-2 receptor and TNFα, NCT01485055); tocilizumab (targeting the IL-6 receptor, NCT01475162, NCT01757197), α1 antitrypsin (NCT01523821, NCT01700036); and brentuximab vedotin (NCT01596218). This is an area of research that has been core to my work, and over the past five years many novel approaches to early diagnosis, prevention and treatment of aGVHD have moved forward. Many of the researchers responsible for these efforts will be present at the ASH conference to discuss the latest efforts to treat and cure malignant & non-malignant hematology diseases. While none of the presentations specifically touches on aGVHD, it will be an underlying issue on everyone’s mind. Whether these experts are exploring new gene therapies to potentially avoid transfusions leading to aGVHD, or conducting research into preventing this disease, we are all keenly focused on the impact aGVHD has on patients, and the direct need to focus more research efforts into overcoming its impact worldwide.
China’s recent surge in higher income families, its growing aging population and steady growth in biopharmaceutical sales suggest significant market potential in the future. The current landscape for biopharmaceutical development in China is certainly emerging, but challenges remain.

It creates opportunities for local biopharmaceutical companies to establish dominance in the global marketplace if they can overcome several hurdles such as early phase development, regulatory oversight, biomarker driven studies and clinical trial data quality.

This has been a difficult journey. In the past, Chinese biopharma companies have suffered under the perception that they are better at following than innovating, which has limited their impact on global research and their ability to bring new treatments to market. Yet that is beginning to change. Over the past ten years, the Chinese government, academic organizations and biopharmaceutical companies have been working to transition the nation from a consumer of generic drugs into a developer of innovative therapies, specifically as it pertains to cancer treatments.

The Chinese government has taken steps to strengthen intellectual property rights and made regulations more amenable to biopharma innovation as it targets the discovery of 100 new drugs by 2020\textsuperscript{14}. And the progress they have made is impressive. The number of clinical trials performed in the country has risen steadily, especially for oncology drug development. We’ve also seen more recent examples of treatments being developed and independently brought to market successfully by Chinese companies. Zhejiang Beta Pharma developed icotinib, an epidermal growth factor receptor tyrosine-kinase inhibitor\textsuperscript{15}. It proves that not only can local
firms meet global quality standards in the process of drug development, they also deliver products with better tolerability and similar effectiveness at a lower cost. Gastric cancer candidate, the vascular endothelial growth factor receptor (VEGFR) inhibitor apatinib, was developed by Chinese researchers. Jiangsu Hengrui Medicine Co., Ltd. advanced the drug into Phase III development and finally approved for marketing in China, suggesting its anti-angiogenic approach has potential in heavily pre-treated patients with metastatic gastric cancer\textsuperscript{16}.

These oncology projects, coupled with advances in manufacturing and research in the country, demonstrate that Chinese organizations are more than able to deliver leading edge cancer research that meets both the local and global needs of patients.

**Meet local needs locally**

Such growth in the local biopharma marketplace is not just important to decrease treatment expenditures. It is vital to the millions of Chinese patients with China-specific type cancers who are not always best served by treatments designed for western countries.

Many global pharmaceutical companies fail to take into account the unique characteristics and medical needs of patients in Asia. It means the treatments that come to global market are sometimes not as effective for Chinese patients as they are for those in other countries. For example, patients with gastric cancer in China and the West having different epidemiology, etiology, tumor location and other defining factors, making a treatment developed for overseas markets not entirely satisfying.

China is already the third largest pharmaceutical market in the world\textsuperscript{17}, but it will not settle for treatments that were created to solve other people’s problems. Increased investment in innovative drug development and continued regulatory reforms are bolstering the industry and making it possible for Chinese biopharma companies to better meet the needs of its massive population.
Cancer science has evolved fast over the past decade. Better knowledge of basic cancer biology based on increased understanding of cell signaling and mechanism of disease, and greater access to genomics and other “-omics” data has led to the rapid development of precision medicine and the growth of immuno-therapeutics.

New drugs with their new targets and new mechanisms of action, and their greater specificity, safety and efficacy, combined with earlier and more accurate diagnoses, have led to improvements in patient’s outcomes and survival. This has benefits not only for the patients and their families, but to society as a whole.

These innovative therapies add extra layers of complexity to diagnosing and treating cancer. For example, in lung cancer in the 1990s, classification was relatively simple. Over two-thirds of lung cancers were described as adenocarcinomas, and the remaining third were large cell or squamous cell lung cancers, and the treatment choices were limited and often empirically based on physician experience and patient responses. Just a quarter of a century later, around three-fifths of lung cancers can be defined by eight or more different mutations, and treatment choices are driven by cancer genetics and tumor cell receptors.

**Access problems at the point of delivery**
Treating patients with immunotherapeutics or other drugs targeted to their specific mutations improves an individual’s outcomes, but comes with additional testing requirements and higher-cost drugs compared with standard chemotherapeutics.
Other issues increasing the burden on the UK’s already finite resources include:

- Increasing levels of cancer
- An aging population, with rising numbers of age- and lifestyle-related cancers
- Cancer survivors who are living longer, and so require support for longer periods
- Better informed patients
- People who are more willing to talk about “the big C,” and so are more likely to visit doctors
- An increasingly vocal and well-informed patient population
- Lack of access to diagnosis or treatment
- Primary care physicians reticent to refer patients, or simply not recognising cancer symptoms early enough
- Lack of access to drugs not endorsed by health technology assessment (HTA) bodies such as NICE
- Tightening budgets
- Expert cancer centres already at capacity
- Lack of reporting systems or integrated testing pathways, and insufficient communication between departments in hospitals and clinics, so delays in test results, or wrong test results requested

All of these can delay or prevent access to treatment for patients who become anxious, and where immediate initiation of the right treatment is crucial.

**Finding a route to access**

There are a number of possibilities for improving access to cancer treatment, and improving the patient experience. By working more closely with HTA bodies prior to approval, biopharma companies could increase the chance of recommendation
and reimbursement. Once drugs are on the market, greater consideration needs to be given to outcome-based, risk-sharing schemes and other variable pricing approaches that could also help individual patients gain access to drugs.

Improving clinical pathways could also make a significant difference, by ensuring that the best possible use is made of all resources. Take the story of one of the UK’s largest centralized gynaecological cancer clinics as an example: patients had to travel lengthy distances and wait for long periods to see clinicians who were under severe time pressures, for appointments that often overran. This left both patients and physicians unsatisfied.

Creating new treatment and referral pathways tailored to different cancer types and alternative patient follow-up approaches, including clinics led by clinical nurse specialists rather than doctors, and nurse-led telephone follow up, cut waiting and travel times. It made better use of the clinic’s healthcare professionals and other resources, increased patient satisfaction ratings, and reduced the overall number of patient follow-up appointments.

By creating robust diagnostic and clinical pathways, and ensuring that reporting and recording systems are integrated, patients should be able to access the best care that the NHS can provide.
Oncology is a growing area, with new breakthroughs being made and innovative cancer therapeutics reaching the market. However, there are still barriers to market access, which could be overcome by the use of local data. In 2009, there were around two million cancer survivors in the UK. As the UK population grows and ages, and as the survival rate for cancer improves, these numbers are expected to grow at around a million per decade, rising to around 5.3 million in 2040. This growth rate is expected to be higher in older patients and in the longest survivors, but overall is likely to slow down. Amongst cancer survivors, around one in four are living with the after effects of cancer treatment, including poor health and disability, and these all have a long-term impact on both the social and the healthcare economy.

The challenge. The increasing number of cancer patients and survivors, and their increasing lifespans, means that patients will remain on treatments for longer, and may need long-term support to deal with potential adverse effects, particularly as they age. An increasing level of expenditure is putting already stretched healthcare systems under increasing amounts of financial pressure. This is further accentuated by the availability of innovative therapeutics and technologies that are safer and more effective than existing treatments, but may be higher cost or require hospital stays or more input from clinical staff, for example intravenous administration. The outcome of this is a competition for increasingly scarce resources, and so healthcare providers and health technology assessment bodies are forced to decide which medicines will deliver the best long-term value for different types of...
cancer. This may vary from region to region, and has sometimes been described as “postcode prescribing.”

**Designing better care pathways.** A potential solution to this conundrum is to look at the most cost-effective way to use existing and innovative treatments. This includes discussions on where is the right place to treat patients, including an increasing move towards community and home care treatment. This opens up questions about monitoring and maintaining psychological support for patients, their families and careers, adherence to treatment regimens, and the impact on toxicity. Healthcare providers need to ensure that the care pathway is designed to be sustainable and to meet all of these needs.

**The solution: Localized data**

Finding the best way to use drugs, designing better care pathways and supporting the provision of additional funding for treatments requires additional data, for example from the real world use of drugs. This may be gathered as part of a clinical trial, through an accelerated approval process that requires companies to continue to collect data, or once a drug has reached the domestic market. This local data provides information on patients’ compliance in everyday use, as well as the treatment’s impact on length of life, and perhaps more importantly, on quality of life. Anonymized real world data can be collected from patients’ electronic medical records (EMRs), including patient profile information, compliance and outcomes.

While accessing and analyzing this data does place an increased burden on the pharmaceutical industry, it can improve access to treatments, therefore leading to better patient outcomes.

**Amongst cancer survivors, around one in four are living with the after effects of cancer treatment, including poor health and disability, and these all have a long-term impact on both the social and the healthcare economy.**
When we talk about all of the recent success in the oncology sector, successful clinical trials usually get most of the headlines. And rightfully so. This research has been carefully crafted to test the safety, efficacy and performance of groundbreaking drugs, bringing life changing solutions to millions of cancer patients around the world.

But clinical trials aren’t the only place where innovations in oncology research are taking place. Just as important are the oncology patient registries and non-interventional studies designed to complement trials by gathering real world data about patients outside of the trial environment.

**Trial vs registry**

Clinical trials are designed to test drugs on a very specific population of patients who tend to meet strict inclusion/exclusion criteria, which often includes requirements that they not suffer from co-morbidities or take medications for other diseases. These criteria are important because they create an environment where researchers can collect accurate data about treatment and outcomes, without fear that other medications or conditions will cloud their results.

But because of these criteria, participants in oncology clinical trials tend to be much “healthier” than the broader population of cancer patients treated in the real world – those who may have multiple conditions, such as hypertension, diabetes, pulmonary disease or other health issues and may be taking other medications. The clinical trial data may not explore how the new treatment may interacts with other medications and may use intermediate endpoints – that is where registries and non-interventional studies come in.
In non-interventional (or observational) studies, researchers track patients’ use of prescribed treatments in real world conditions, without interfering in any of their treatment decisions. Participating patients take the drugs prescribed by their doctors, and are in no way influenced by the observational study. This environment offers a wealth of valuable data for researchers to explore things like drug utilization, potential off-label use, and potential side effects that may not have been picked up during the trials, and understand how the new treatment works in different subgroups of patients. Additionally, in some countries the effect of the new therapy on quality of life may be explored.

Patient registries use observational methods to gather real world information about patients with a specific cancer diagnosis or treatment. Registries can be used as a vehicle to answer multiple research questions.

Along with creating a venue to recruit new patients for future clinical trials, patient registries give researchers a valuable real world environment to study treatment experiences, patient outcomes, and in some cases overall quality of life as it relates to their disease.

Patient registries and non-observational studies can also be used to monitor outcomes and study best practices in care or treatment, either for a specific duration or over a long period of time. This is important as many new oncology treatments are targeted at specific biomarkers that may allow patients to live longer, and researchers need to know whether the treatment patients received for their cancer will have any long-term implications. This data is often sought by regulators, who are increasingly interested in real world research as part of post-approval pharmacovigilance, as well as by payers to support coverage decisions. Physicians and patients are also interested to learn what the best treatment is for specific patients. Data can also be used to develop hypotheses and answer key research questions to support current and future studies. For example, if a drug extends a patient’s lifespan but they spend that extra time bedridden, is it worth it?

Plan early and keep it simple

But building and maintaining oncology registries and observational studies isn’t easy, especially when there is growing competition among competing research groups for patients to enroll in these registries. To be successful, you need to start planning for these studies earlier on in the product life cycle, and ideally before the
end of the Phase III studies. This will give you the best chance of building a useful study to generate valid evidence to support multiple stakeholder needs. It will also require upfront thinking to plan the best strategy for identifying where to target recruitment efforts for the target population given the crowded marketplace for treatments of many of our cancers.

Once clinics and patients have agreed to take part, the most important thing you can do is to keep things simple and aligned with routine clinical practice. It can be very tempting to want to collect endless data about patients’ lives and their medical history, but if there is too much information to be collected it’s more likely they will drop out. Health care providers are busy, and we must not forget that the patients have cancer, which means if something is too burdensome and taking too much of their time, they will quickly give up on a voluntary observational study.

To avoid overwhelming your clinics and study participants, identify what data you absolutely need to meet your research objectives, then stick to it. Limit questionnaires to fifteen minutes, use technology to streamline the collection process and to reduce data entry errors, and – most importantly – make sure every question adds value.

You also want to be sure you understand exactly where key pieces of data will come from based on the patient care pathway. In many cases, oncology patients get their treatments from infusion centers, which means that details about the new treatment may not be available in regular pharmacy databases. Your study design needs to account for all of these variables if you want the study to be accurate and accepted by physicians and regulators.

Despite the challenges, registries and real world studies are a vital and valuable part of oncology research. All stakeholders today are interested in this real world data, and the sooner you start planning and implementing these complementary studies the more comprehensive and valuable that data will be.
The pursuit of value-based pricing for pharmaceutical drugs makes sense in theory – drugs that deliver greater patient value should reward a higher price point. Proving the incremental value of a treatment relative to its competitors is a complicated challenge that the industry is only beginning to figure out. Myriad valuation techniques are currently used by various healthcare system stakeholders to appraise drugs, yet no gold standard framework exists.

A team of experts at Quintiles established an initiative to develop an integrated, systematic and evidence-based approach to appraising a drug’s relative performance. We created a multi-attribute valuation methodology that would take into account efficacy, safety and economic factors to determine the relative value of pharmaceuticals. Given the plethora of publications on cancer drug valuation schemes, we decided to pilot this framework on a cohort of oncologic therapies. We performed regression analysis to determine the relationship between incremental drug effectiveness and the Quintiles Drug Value Score. We also reviewed the existing value-based assessment frameworks for cancer drugs to assess the strengths and limitations of each framework.

We reviewed published clinical trial results archived in PubMed from 2005-2013 and Health Technology Assessments (HTAs) captured in Quintiles’ HTA Accelerator database to measure key value attributes – including overall survival, progression-free survival and adverse events – of four oncology drugs. The cost per month of each drug was calculated based on dosing and published wholesale acquisition...
costs. Drugs were then compared vis-à-vis value score vs. cost per month to understand the value-cost relationship.

**A rationale for value based pricing**

Our analysis shows a positive relationship between clinical benefits generated and cost of drug. Notably, there is a distinct correlation between pricing and survival rates: the framework showed an increase of approximately $221/month (p < .05) for each month of overall survival improvement.

This research represents an important next step in rationalizing value-based pricing in oncology treatments. Our evidence-based appraisal framework offers a pragmatic approach to pricing drugs in a value-based environment. The framework also provides pharmaceutical companies a mechanism to assess future-state external valuations of target-product profiles as well as an evidence development strategy for demonstrating value-based pricing of their drugs.

We shared the details of these results in a poster at the 18th Annual European Congress of the International Society for Pharmacoeconomics and Outcomes Research in 2015 and we are excited to see where these results take us. Further research is needed to compare the results of this multi-attribute analysis and scoring framework with frameworks being developed by other organizations.

Notwithstanding its limitations, we expect this framework to be a valuable tool for biopharma companies to better position their treatments with payers and policy-makers. We are looking forward helping our customer use this tool to more quantitatively define their value propositions and demonstrate the competitive advantage of their drugs. By proving their external value of their medications, pharma can capture more intrinsic value of their innovation.

**Our analysis shows a positive relationship between clinical benefits generated and cost of drug. Notably, there is a distinct correlation between pricing and survival rates.**
References


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Director of Epidemiology and Outcomes Research

Jaclyn Bosco, PhD, MPH, is Director of Epidemiology and Outcomes Research and works with customers to develop strategies for using patient registries and other observational study methods for real-world evidence generation to support the safety and effectiveness of drugs, biologics and biosimilars and devices.

Dr. Bosco has more 10 years of practical experience leading non-interventional and observational research studies, and has conducted studies across the globe including North America, Europe and Asia-Pacific regions. She is experienced in helping customers refine their research questions based on various stakeholder needs, identifying the best approach for capturing data on a global scale as well applying local approaches to address market-specific needs, and designing and executing medical chart review studies, patient registries, pregnancy registries, and observational comparative effectiveness and safety research studies.

Dr. Bosco received her PhD in Epidemiology and MPH in Epidemiology and Biostatistics from the Boston University School of Public Health (BUSPH) and completed her research fellowship with Dana Farber Cancer Institute/Harvard Medical School. She is an Adjunct Assistant Professor of Epidemiology at BUSPH, and is currently a member of the International Society for Pharmacoepidemiology (ISPE) Education Committee and Biologics-SIG, International Society for Pharmacoconomics and Outcomes Research (ISPOR), the Society for Epidemiologic Research (SER), and American Association of Cancer Research (AACR) Molecular Epidemiology Working Group and Behavioural Sciences in Cancer Research Working Group.
John J. Doyle, DrPH, MPH
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John Doyle leads the Values & Outcomes efforts – working with Life Science companies to navigate the transformational changes in the health care marketplace from a population health perspective.

As the global health care system migrates from volume to value and outcomes-based medicine, Dr. Doyle’s team of strategists partners with clients to diagnose, strategize, and illuminate a product’s benefit-risk and economic profile tailored to a myriad of market stakeholders to drive healthcare system performance in an increasingly evidence-based environment. Functional areas of expertise include pricing and reimbursement, health economic and outcomes research (HEOR), and medical affairs.

Over the last two decades, Dr. Doyle has authored more than 100 abstracts and original research articles in a variety of therapeutic areas, with special concentration in oncology. He has lectured for academic and commercial audiences in the U.S., Canada, Europe, Latin America and Asia.

Dr. Doyle received a Bachelor of Science degree in Applied Economics with a concentration in the Life Sciences from Cornell University. He received a Master of Public Health degree and a Doctor of Public Health degree in Epidemiology from the Mailman School of Public Health at Columbia University, where he maintains an adjunct faculty position.

Eric Groves, MD, PhD
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Board certified in oncology and internal medicine, Dr. Groves has more than 20 years’ experience in drug development as corporate officer/senior manager, clinician and researcher. Prior to joining Quintiles in August 2007, Dr. Groves was at Ligand Pharmaceuticals Inc., starting in August 1999 as Vice President, Project Management and corporate officer. From 1994 until joining Ligand, Dr. Groves held a number of positions at Sanofi Pharmaceuticals, most recently as Vice President, Project Direction, where he was responsible for the worldwide strategy of and project direction for late-stage Sanofi oncology projects. From May 1991 through October 1994, Dr. Groves served as Senior Project Director for the research division of Sterling Winthrop Corporation, and served as acting Vice President, Discovery and Clinical Research, Immunoconjugate Division. He was Director of Clinical Research and Development at CETUS Corporation from 1989 through 1991.
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Dr. Mosher is a Senior Oncology Medical Director in the Medical Strategy & Science, Therapeutic Science & Strategy Unit for North America. Dr. Mosher is Board Certified in Hematology with more than 18 years of clinical experience in Hematology/Oncology (benign hematology, solid tumors, hematologic malignancies and bone marrow transplant) and 10 years research experience (focused mainly in oncology, neurology, immunology and early phase trials).

Dr. Mosher received her Medical Degree from San Martin de Porres University in Lima, Peru and completed a Hematology/Oncology Fellowship at San Marcos University in Lima, Peru. Prior to joining Quintiles, Dr. Mosher was a Medical Director, Hematology/Oncology – Medical Affairs at PRA Health Sciences and a Medical Director – Medical Affairs for a biotech company developing dendritic cell cancer vaccines.

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Terry L. Murdock is vice president and head of the Oncology Center of Excellence at Quintiles. He focuses on developing insights and innovations that help improve the probability of success of Quintiles’ oncology customer development projects and programs. As part of a team, he provides customers with alternative and innovative design aimed to improve the efficiency of development of oncology assets.

Terry has 20 years of work experience as a successful senior executive in the medical research industry, specializing in oncology, multiple sclerosis and other autoimmune diseases. He is experienced at establishing operational excellence within culturally diverse environments with a track record executing operational, clinical and commercial plans. Prior to joining Quintiles, Terry held senior positions focused on clinical drug development at Ergomed, Genzyme/Sanofi, ILEX Oncology and US Oncology.

Terry earned his M.S. in biology and a B.S. in science in microbiology from the University of Texas at Arlington. He is a registered microbiologist for the American Society of Clinical Pathology and a registered medical technologist for American Medical Technologists.
Paul Sutton
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Paul Sutton is the Director of Outcomes and Value, Commercial UK, where he leads the design and implementation of health informatics, data analytics, service pathway evaluation and modelling, and patient outcome audit service: to help pharmaceutical clients (and their NHS stakeholders) understand, realise and demonstrate real-world outcomes and value for their brands at a local health economy level in the UK market.

Prior to Quintiles, Paul held key positions with Bupa Home Healthcare, developing value-added services for Pharma; and with Bupa Health Dialog as a senior management consultant to NHS clients. Paul worked in the NHS for 12 years, culminating in senior commissioning roles in NHS Manchester. Paul received his Bachelor of Arts and Master of Arts degrees from Oxford University.

Brad Smith, PhD
Vice President, Advisory Services

Dr. Smith leads the transnational medicine advisory services within Quintiles. In this position, he leads biomarker and companion diagnostic strategy and planning interactions throughout the organization including clinical, laboratory, consulting and commercial projects.

Dr. Smith has more than 20 years of experience in biological research in academia, biotechnology and clinical services including five years of experience in planning and design of clinical development plans and protocols for drug development. Prior to Quintiles, Smith spent 10 years at Cell Signaling Technology responsible for technical and corporate development of biomarker and diagnostic businesses. He is the author of multiple basic research, translational medicine and clinical publications and patents.

Dr. Smith’s scientific background includes research positions at Stanford University and University of California, San Francisco focused on cellular signaling mechanisms of disease. He holds a Doctoral degree from Stanford University and Master’s and Bachelor’s degrees from University of California, Santa Cruz.
Dean Summerfield, D.Phil.
Senior Vice President, Advisory Services

Dean Summerfield leads advisory services for Integrated Healthcare Services (IHS) at Quintiles and is Managing Director for the European Advisory Services group. He is responsible for the full breadth of practices including Research and Development Strategy; Commercial Strategy; Commercial Effectiveness; Market Access; Regulatory and Quality.

Summerfield has nearly 20 years of experience in providing advisory solutions to life sciences clients and a proven track record of enabling companies to improve their probability of success and maximize commercial value through fact-based strategies and enabling their implementation. He has worked with a wide range of pharmaceutical and medical device companies in engagements from long-term strategy to day-to-day operations spanning across clinical and commercialization. Summerfield holds a D.Phil., M.A. and B.A. in Chemistry from the University of Oxford.
Helena Zhang, MD
Chief Medical Officer and Head of Center of Clinical Excellence, Greater China, Quintiles

Dr. Helena Zhang is Senior Director and Chief Medical Officer for Quintiles in the Greater China region. In this role she serves as Quintiles China lead medical expert and provides leadership in the ethical conduct of studies. Dr. Zhang joined Quintiles China in 2007 and had been instrumental in enhancing strategic partnerships with top hospitals, Key Opinion Leaders and medical associations in China. These strategic relationships with sites and KOLs in various therapeutic areas and medical associations helped established Quintiles’ leadership position in China’s sites and investigation network. Dr. Zhang is also a board director for clinical research and drug safety with the Chinese Society of Clinical Oncology (CSCO).

Dr. Zhang joined the biopharmaceutical industry in 1994 where she spent six years with two leading medical device companies in China. Following which, Dr. Zhang was involved in pre-clinical development at Indiana University Medical School in the U.S. where she authored six papers for international journals and congresses. She then joined Paraxel and subsequently Quintiles upon her return to China in 2006.

Dr. Zhang is a medical doctor by training from Shanghai Jiaotong University Medical School, China, she also holds a Master’s Degree in Business Administration from Cardiff Business School, Cardiff University, UK.