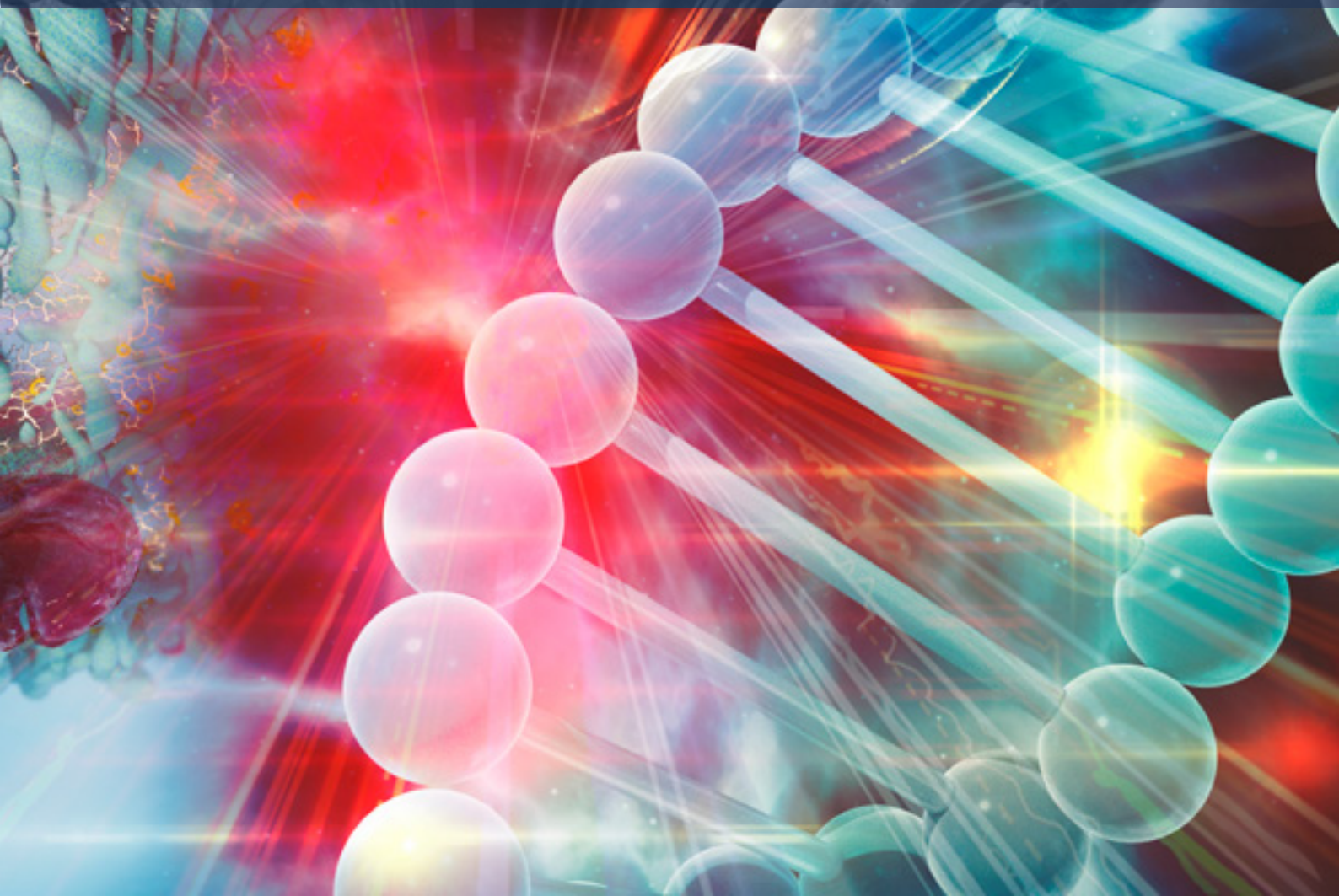
Cambridge Consultants

ENGINEERING THE FUTURE OF INNOVATIONS IN ONCOLOGY

AUGUST 2020



About the author

Harshal is part of Cambridge Consultants' global medical division based out of Boston. He has more than 13 years of experience in medical device development, product lifecycle strategy and innovation management. He has significant domain expertise in the oncology patient journey, the economics of cancer care and innovations in oncology as a therapeutic area. He has a Bachelor of Mechanical Engineering from Nirma Institute of Technology in India, and an MBA from Syracuse University, New York. He recently completed a post graduate program in cancer biology and therapeutics development from Harvard Medical School.

CONTENTS

1 INTRODUCTION

Oncology as a therapeutic area continues to receive massive amounts of R&D investment. More and more established pharma/biotechs are entering the field or strengthening their commitment to oncology, while venture and private equity capital continues to flow into oncology-focused startups. Drug discovery gets the maximum investment flow, owing to the primary goal of industry and academia to find a cure for cancer. But a host of emerging areas – including new cutting-edge technologies, innovative product platforms and process improvement methodologies and data driven tools – are attracting an equal share of investment.

There are several driving factors behind this direction of innovation, but the first and foremost is the massive cost burden of cancer care globally. While complete cure for cancer may remain a long-term goal, the healthcare system is reacting to the ground reality of increasing patient population and resulting cost of care at a system level. A new class of drugs, based on the rapidly improving clinical and molecular level understanding of key cancer types, has improved the overall survival rates and quality of life for patients of many cancer types. Data-driven technology superpowers, with their strategy to enter a healthcare sector that is increasingly trying to introduce a value-based reimbursement framework, saw clear opportunity to leverage their massive computing, analytics, and execution capabilities in the new market segment. Combined with numerous other industry and economic factors, the cancer care pathway is poised to see major changes in coming years. These unavoidable changes across the value chain of cancer care will necessitate careful strategic planning by all the players involved if they are to stay relevant in this rapidly evolving therapeutic area.

This whitepaper aims to highlight some of the most crucial changes this therapeutic area is experiencing. It offers a framework for biopharma companies to strategize innovation that would enable integration of relevant emerging technologies into their product and services and stay on the leading edge of the curve.

While we have touched upon several aspects of the oncology care pathway, we have specifically excluded the field of surgical oncology to maintain the focus of the whitepaper on biopharma.

2 MACRO FACTORS FUELING CHANGES IN THE ONCOLOGY THERAPEUTIC AREA

Before we dive into the innovation framework, it is important for us to understand the factors driving the market-wide changes in this therapeutic area. These macro factors are most impactful in pushing innovation in a certain direction with increased pace than others. While we won't touch upon very high-level macroeconomic and geo-political issues that indirectly affect the entire healthcare segment, it is important to understand that the starting point of some of the relevant market forces have roots in these global shifts. While they are unavoidable, they are equally unpredictable and susceptible to change in either direction.

2.1 TWO NUMBERS WITH COMPOUNDING EFFECTS

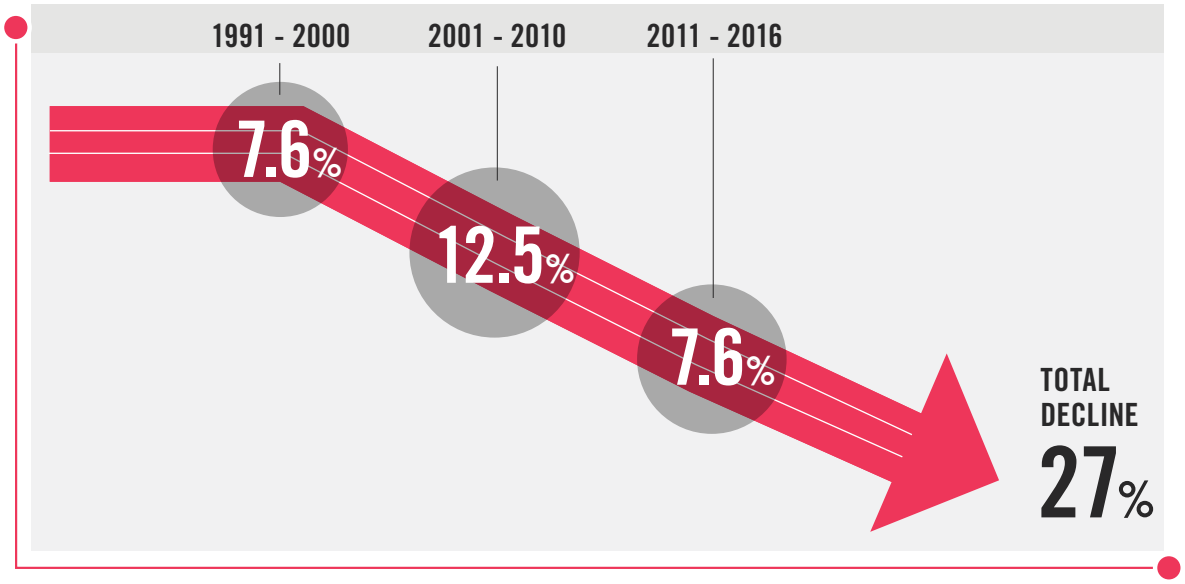
We all have a general understanding that the prevalence of cancer is on the rise. While the rate of new cases per 100,000 is expected to remain largely consistent[1], over the last decade the number of annual new cases has increased from 1.5 million to 1.9 million in the US. The growth in new cases is quite consistent across all the developed countries and is expected to climb at a steady rate for the foreseeable future owing to the growing population and shifting median age towards a higher number (aging population) globally.

An even more important figure is the progression free survival (PFS). It indicates the duration during or after treatment that the patient lives with the disease, without the condition worsening, or the disease progressing further. PFS is up by 60% since 2004. Combining that with new incidences gives the massive figure of more than 70 million in the healthcare system receiving care on a continued or prolonged basis.

The overall survival rate of 64.7% in the US improved by 24% in last 10 years[2]. This increases spending, as some patients end up requiring above average level of healthcare throughout their lives, such as precautionary or supplementary monitoring to improve quality of life, amongst other services.

All in all, it points towards an unsustainable healthcare bill for any setup – private or nationalized system globally.

PERCENT CHANGE BY DECADE IN US DEATH RATE FROM CANCER



SOURCE: ACS Journal - Cancer Statistics, 2016

2.2 INDUSTRYWIDE PIPELINE TRANSFORMATIONS

In 2020 the US healthcare system is expected to spend about $150bn on oncology drugs alone[3]. Sensing this opportunity early, a number of established biopharma companies heavily invested in the therapeutic area. Some even transformed themselves into oncology-focused companies by building an internal R&D pipeline or with the help of active M&A and licensing activities. As is the case with any free market innovation economy, this has created a fiercely competitive field when it comes to cancer drugs.

Add to that the tremendous amount of academic research which, if successful, leads to the creation of a startup. Many of those remain committed to commercializing their drugs instead of getting acquired – at least until the full potential of their drug platform or invention is realized. Ultimately, this makes inorganic growth even costlier and justifying ROI becomes a daunting task for established biopharma.

However, digging deeper into the annual reports, quarterly calls and executive briefings of all the leading oncology players suggests that their investment appetite is increasing for both internal as well as external R&D. The primary reason is that there are still enough unmet needs in oncology care to ensure handsome rewards for drugs that provide meaningful outcomes and improvements for patients. It only means that the competition to acquire the most promising drug candidates will continue to be fierce. The drive to establish superiority of the treatments using all possible available tools and technologies will continue to gain momentum.

ESTABLISHED ONCOLOGY BIOPHARMA

Bristol-Myers Squibb · AMGEN · Roche · Lilly · NOVARTIS · MERCK · AstraZeneca · janssen

EXECUTIVE LEVEL COMMITMENT ON RENEWED / NEW FOCUS ON ONCOLOGY

abbvie · BAYER · Boehringer Ingelheim · Takeda · Eisai · IPSEN Innovation for patient care · Daiichi-Sankyo

SIGNIFICANT ONCOLOGY FOCUSED M&A LICENSING ACTIVITY

SANOFI · gsk · Pfizer · astellas · Sumitomo Dainippon Pharma · teva · GILEAD

ESTABLISHED STARTUPS

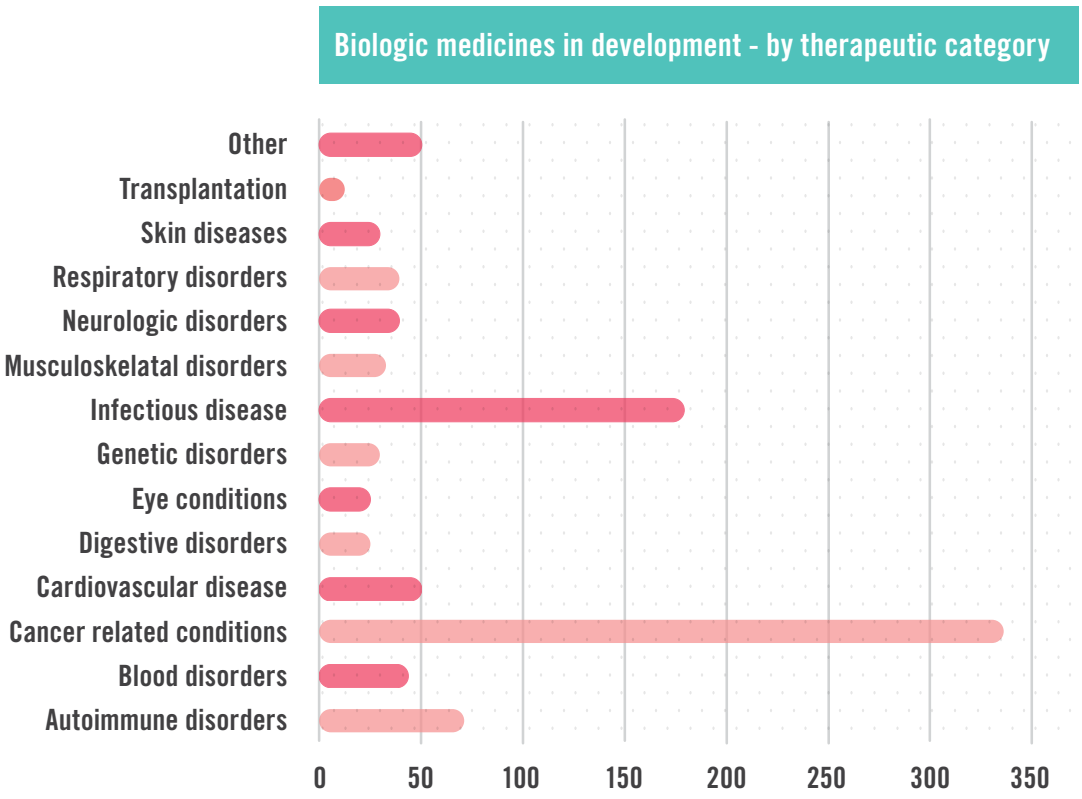
CLOVIS ONCOLOGY · LOXO ONCOLOGY · CRISPR THERAPEUTICS · AnaptysBio · RubiusTherapeutics

2.3 SURVIVAL OF THE FITTEST DRUG

A PhRMA report shows that there are more than 300 biologics under development for cancer and related conditions. For comparison, that figure is more than the total number of drugs for next six therapeutic areas combined.

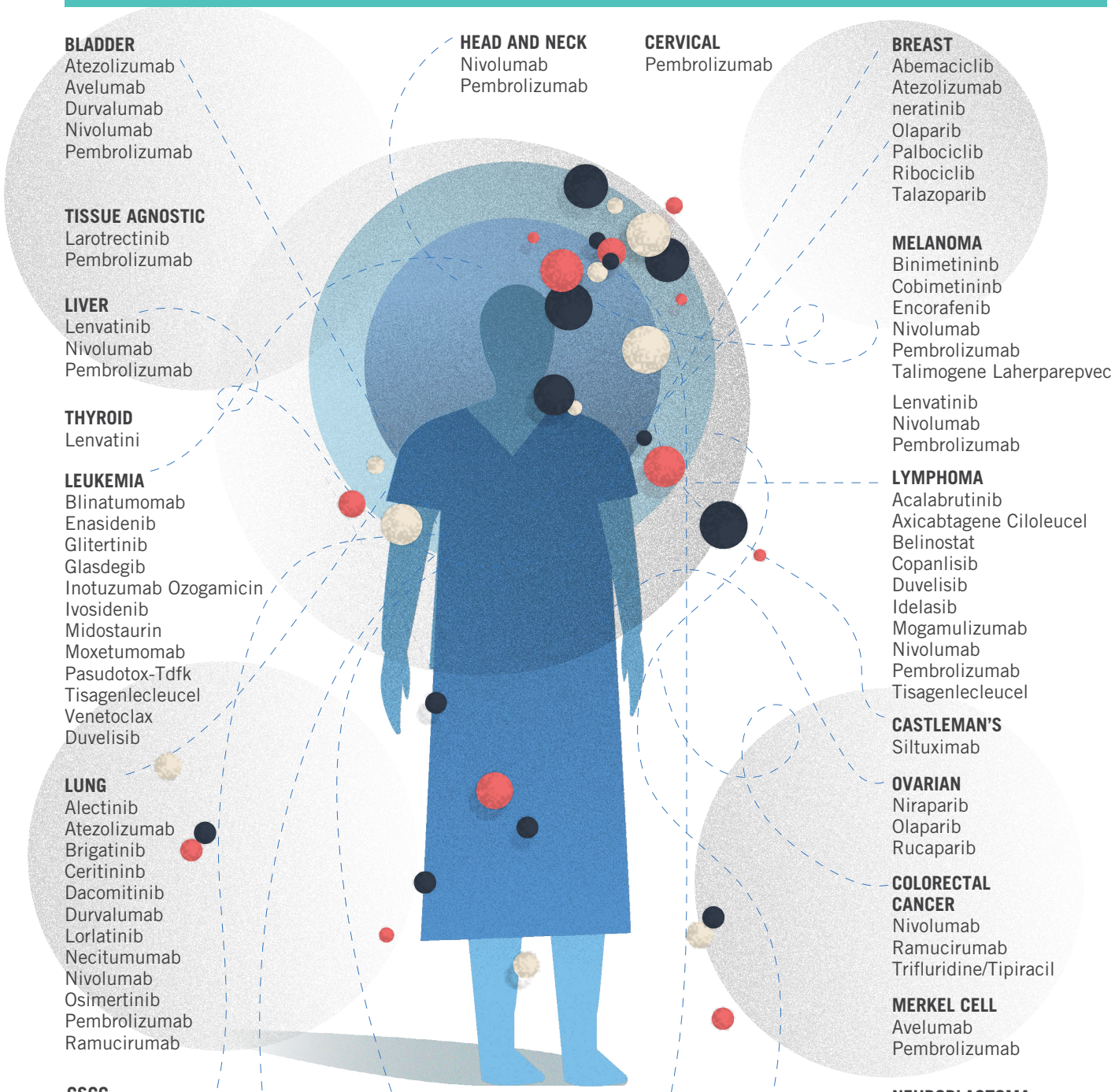
Between 2014 and 2018, the US FDA approved more than 35 new drugs for almost every type of cancer. While therapeutic efficacy will be the single biggest factor governing the success of any drug, it is increasingly evident that finding a 'universal magic bullet' is quite unlikely in the world of cancer care. Even the most successful drug has to support a solid health economics and outcomes case based on real-world evidence[4]. With the ever-increasing cost of cancer care, the healthcare system is going to increasingly expect new therapies to demonstrate significant and meaningful improvement in outcomes. The motivation will shift towards value-based reimbursement as opposed to reimbursement based on traditional superiority established during clinical trials, based on pure PFS end points.

This will compel industry to plan an R&D strategy that leverages latest technologies and data driven analytical tools to establish the real-world evidence of their therapies. This has potential to change the way industry conducts clinical research and the way NMEs and NBEs are selected for further clinical development. The decision framework for R&D has to involve broader perspectives on improving outcomes during clinical trials as well as in commercial setup with the help of technology and data tools. In our world the drug R&D and the ecosystem design to treat the patient using that drug must start at the same time and be an integral part of the decision framework from concept to commercialization.



SOURCE: PhRMA Biologics Under Development Report, 2018

New active substance approval in oncology by tumor type, 2014 - 2018



SOURCE: IQVIA, Apr 2019

2.4 INNOVATION FROM EVERY DIRECTION

Established biopharma companies deployed a very successful model of business development, licensing and M&A to fill gaps in their discovery pipeline. However, a rather simplistic model of inorganic growth in oncology assets is increasingly proving a costly affair due to the higher premiums those mature/late stage assets command.

More importantly, there is an increasing amount of work being done on new types of drug discovery tools, drug testing tools, molecule and antibody synthesizing technologies and technologies that enable manipulation at cellular and genomic level to produce a new class of cancer targeting medications.

These innovations are receiving funding from non-traditional setups such as universities, taxpayer-funded government agencies, NGOs and even patient advocacy groups. From the legal and IP point of view, acquiring these technologies on an exclusive basis may not be possible. This means that leveraging these licensed technologies in a timely manner and building an internal IP based on those 'open innovation' technologies that gives competitive edge is vital to the innovation strategy for biopharma. CRISPR and PRIME editing technologies are relevant examples, but there are many more innovations in diagnostics, medical imaging and drug discovery that are in this bucket.

Biopharma that is usually more accustomed to outright acquisition or exclusive development/marketing rights may have to adapt to this new way of partnering. Collaborating with agencies and organizations will play a crucial role in funding research in core science and other underfunded disease specific treatments.

"Collaborating with agencies and organizations will play a crucial role in funding research in core science."

3 CHALLENGES FOR ONCOLOGY-FOCUSED BIOPHARMA

The macro factors highlighted earlier are invariably creating challenges for oncology-focused biopharma that need grassroot level changes in operational and innovation strategy. As is the case with any industry, biopharma continues to evolve with the new challenges it faces due to macro/economic factors. However, some of the issues in the oncology area might be fundamentally challenging to the way industry is structured and operates. Here is our take on the most important ones with that are directly relevant to oncology.

3.1 NEED FOR EARLY PATIENT ENGAGEMENT

Due to the relatively unpredictable or unknown disease-causing factors for most types of cancers, typically it has been difficult to achieve direct engagement. This is in contrast, for example, to how diabetes-focused companies have engaged with their patients or 'future patients' based on leading indicators such as obesity or hypertension.

However, it is evident that understanding patient lifestyle, specific risk profile and the daily life hazards they are exposed to is increasingly important for use as one of the inputs into the drug discovery, drug testing and clinical trial process. With the new era of affordable genomic sequencing, it is possible with many cancers to flag high risk patients for developing mutation-specific drugs. However, engaging in a meaningful way with members of the general population who are high risk but not yet cancer patients is not something that oncology-focused biopharma or oncology organizations within a large biopharma are accustomed to. It can be detrimental when strategizing the focus of clinical research and even clinical trial recruitment.

3.2 PRIORITIZATION AND AGILITY IN THE DRUG DISCOVERY AND TESTING PROCESS

The increasing level of understanding about different types and sub-types of cancers at molecular level is fueling the idea that some should be treated as rare or unique. The breakdown of types and sub-types is cascading at many levels and all of them, in all possible ways, are quite different diseases. Ultimately, biopharma is faced with a prioritization challenge on how to test as many drugs as possible for as many cancer types as possible. Even with the massive R&D funding in oncology, prioritization in drug discovery and testing is more challenging than before.

3.3 DESIGNING AND PLANNING FOR THERAPY DELIVERY IN DIFFERENT SETUPS

Typically, cancer drugs are formulated for administration in a hospital or clinic by a trained medical professional. However, errors in clinical environments are not uncommon. New drugs with complex preparation and validation requirements – such as reconstituting multiple liquid and solid forms, and mixing cocktail therapies based on exact biomarkers – may introduce challenges from a workflow point of view. It certainly introduces more room for errors. Such challenges may change when we think about hospitals in developing countries as opposed to developed ones. Overcrowding, lack of protocols and lack of trained support staff can all contribute to different challenges when designing drugs that are impossible to supply as simple formulations.

When it comes to drug administration at home, a very different set of challenges emerges. With increasing cost pressure, it may be unavoidable to move some of the safer drugs that require frequent doses for a long duration, or for the rest of the patient's life, to self/home administration. Making the process foolproof and reporting the subsequent patient-reported or auto-collected outcomes back to the care delivery team in a seamless manner is essential. Designing the drug formulation, delivery system and monitoring/reporting infrastructure can present challenges from usability, human factors, data management and partnering viewpoints that biopharma hasn't traditionally faced.

3.4 ADAPTING TO NEW PARTNERSHIP MODELS AND NEW TYPES OF PARTNERS

Technology giants and computing powerhouses have shown increasing interest in contributing their core strengths towards innovations in cancer research and care delivery. Considering how big an opportunity this might offer for such companies with data-driven business models, they are increasingly expected to be a strong and integrated player across the value chain in cancer care. Biopharma companies should leverage their core strengths, however. Partnering between two IP sensitive industries and the industries that traditionally prefer to be in the driving seat in their respective domains may not be an easy balance to strike.

This is not limited to consumer products, wearables or IT companies, but extends to the subsidiaries, investments, and platform solutions that come under their umbrella. Directly and indirectly their role may extend into drug discovery, medical imaging, automation and high-speed manufacturing. Finding the right operating model and a clear vision of the relationship hand-off between these partners, biopharma and patients is a new turf indeed.

"Closer relationships with CMOs and other partners including specialized equipment vendors and software providers become essential."

3.5 MANAGING THE MANUFACTURING LEARNING CURVE OF MODERN THERAPEUTICS

For some years now pharma companies have been managing the learning curve of manufacturing biologics, sometimes using their own facilities and sometimes in partnership with CMOs. This move to protein-based drugs required therapy developers to gain an understanding of new manufacturing, quality control and analytics processes. With the advent of immune-oncology these skills are even more important, and with further refinements towards patient-specific and tumor-specific therapies, manufacturing small batches at high quality and low cost becomes essential. It is challenging for a pharmaceutical company that has a proud history in large scale manufacture of small molecules to adapt to this new paradigm. Consequently, closer relationships with CMOs and other specialist partners including specialized equipment vendors and software providers become essential.

A further extension of this trend has occurred with the advent of cell and gene therapies. These are extremely complicated therapeutic modalities which require many different biological steps in their production process. It appears unlikely that any single pharmaceutical company will have the capabilities, experience and understanding to produce these therapies entirely in-house. The rise of specialist providers of components such as viral vectors and culture media means that the supply chain and procurement logistics for pharma companies producing these new therapies are extremely complex. Again, there is a strong trend towards personalization of these therapies which results in challenges around manufacturing of batch sizes potentially limited to a single dose for a single patient. The quality control and process reliability implications are daunting.

An additional challenge is that for these advanced therapies, the manufacturing process can be very manual and rely on highly skilled operators in expensive clean room environments to produce the drug product. This has already been seen as unsustainable and resulting in a cost of goods which hinders patient access and profitability. There is a real drive towards closing and automating these manufacturing processes , which in turn requires the development of specialized instruments and equipment and new process workflows. Established bioprocessing equipment providers have been slow to react to this challenge and there are very few acceptable hardware platforms available for manufacture of these products. Pharma companies are having to adopt the mantle of becoming manufacturing process equipment developers in order to be able to satisfy the requirements of their production process.

4 PARTNERSHIP-DRIVEN INNOVATION FRAMEWORK IN ONCOLOGY

The proposed innovation framework is aimed at helping oncology-focused biopharma companies to integrate next generation engineering and technological aspects in their R&D and commercialization strategy.

The framework can also help them identify gaps in their existing capability and infrastructure in order to prepare a transformation plan that is future ready.

The scope of the proposed innovation framework excludes the clinical decision on what cancer types to target, what specific mutations and inhibitors to work on, and specific modalities of drug and drug discovery processes to adopt.

Our aim, by presenting this framework, is to highlight all the technological and engineering levers that the drug discovery process and the drug specific commercialization plan must integrate in order to maintain the edge in an increasingly competitive and demanding therapeutic area. An area, indeed, that is facing pressure to deliver better outcomes at a faster pace.

4.1 HIGH-THROUGHPUT R&D

In pre-clinical setups, most companies have adapted to newer screening processes, including automated high-frequency screening, to identify positive hits on activators or inhibitors. In order to optimize the R&D throughput even further, computing power and microfabrication technologies can be used for rapid antibody design, custom gene synthesis (DNA printing), DNA editing tools, and simulated in-vitro platforms such as organ-on-a-chip technologies.

All these cutting-edge technologies are maturing at a rapid pace, as demonstrated by the new block of technology-driven companies such as Twist Bioscience, Evonetix, Emulate Bio and Synthego. The integration of drug discovery and design tools are increasingly democratized by these startups. As a result, adopting them is probably considerably cheaper and easier than adopting a first gene sequencing platform in the 1980s.

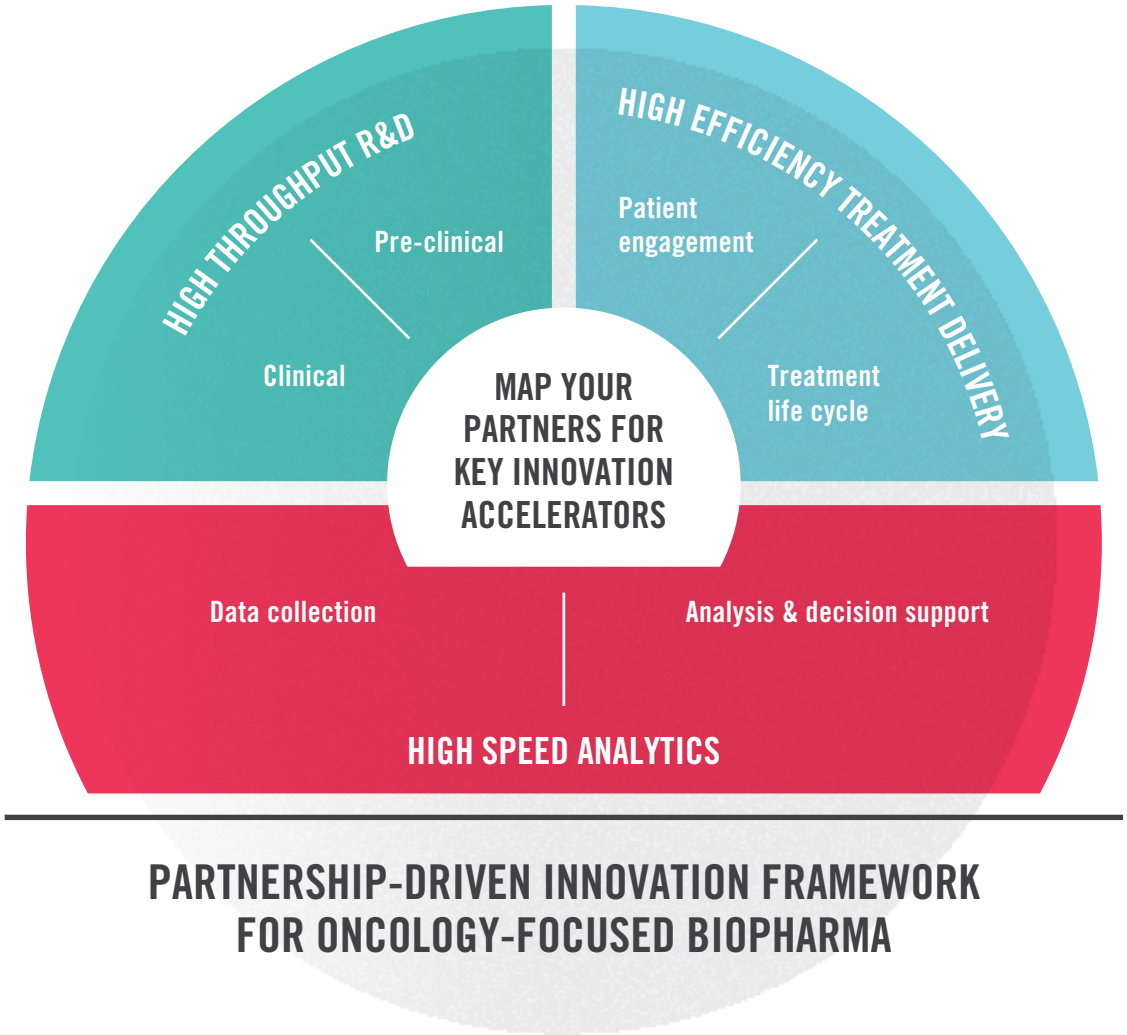
HIGH THROUGHPUT R&D	HIGH EFFICIENCY TREATMENT DELIVERY
PRE-CLINICAL ▪ Rapid drug discovery and design tools (Computational Design, Full stack DNA printing, CRISPR,..) ▪ In-vitro Drug Testing (Organ-on-Chip, AI driven tissue/ organ level simulation and modelling)	**PATIENT ENGAGEMENT** ▪ Patient risk profile data ▪ Biomarkers and CDx ▪ Monitoring and QoL improvement tools
CLINICAL ▪ CTMS for adaptive platform trials ▪ Closed loop connectivity with patient wearables and sensors integration	**TREATMENT LIFE CYCLE** ▪ Minimally invasive drug delivery for difficult to access organs/tumors ▪ At home therapy administration and closed loop monitoring ▪ Long-term drug delivery (smart implants)
HIGH SPEED ANALYTICS ▪ Pre and post diagnosis patient specific data analytics ▪ Seamless integration of analytics and decision modelling with internal processes	

In a clinical setup, the most challenging part is to shift from traditional, randomized clinical trials (RCTs) to adaptive platform trials. Widely touted as the future of clinical trials for cancer drugs, this is a regularly discussed and debated issue in the industry. It was, for example, a topic of the 2017 Harvard Case Study.

The first key benefit of an adaptive platform trial is the ability to share the control arm of the patient pool to test multiple drugs. Secondly, it offers the ability to test multiple therapeutics for efficacy at once in a single indication or a single therapeutic across multiple indications or multiple patient subtypes. The third and most critical and equally sensitive benefit is the ability to change significant trial design features based on pre-specified outcome scenarios at frequent interim analysis points – a methodology that is in sharp contrast to the traditional RCTs.

If planned and executed successfully, adaptive platform trials can test multiple drugs at once, individually or in combination for the same indication, or one drug for multiple indications. This can potentially shorten to less than a third the lab-to-launch time for a portfolio of drugs or a drug for a portfolio of indications.

However, this requires much more granular and meticulous data collection and infrastructure to analyze the data in more complex ways than the simple end points of RCTs. It also requires infrastructure to manage such complex operation. Consequently, a closed loop connected trial management system with a partner who can provide analytics and computing horsepower becomes necessary. This goes beyond a CTM system and includes seamlessly integrated data collection devices at the clinic, at the patient's home and in the form of wearables with relevant sensors.



PARTNERSHIP-DRIVEN INNOVATION FRAMEWORK FOR ONCOLOGY-FOCUSED BIOPHARMA

4.2 HIGH-EFFICIENCY TREATMENT DELIVERY

A typical drug launch plan takes into account epidemiologic data and diagnosis rates as part of the commercialization strategy. A typical lifecycle plan for an oncology drug is primarily focused on getting it to market as quickly as possible and making it available in the form that is easiest to manufacture. For biologics, that usually means vials or at best a pre-filled syringe.

The primary goal should still be getting the drug to market in the quickest way and navigating through the path of least resistance. Our innovation framework calls for an integrated lifecycle plan that, in parallel, starts to work on the strategy for after the initial launch. In essence, the second step in this lifecycle management becomes the primary game plan for the drug. It would include a number of elements, starting with early patient screening, CDx and monitoring Dx partnerships. It would also include innovation in treatment delivery options in the hospital setup as well as beyond the hospital phase when the therapies are necessary on a long-term basis or for the rest of the patient's life.

The underlying assumption here is that biopharma companies can no longer afford to be just a provider of therapies. They will increasingly take on the role of innovation catalyst throughout the value chain in order to ensure the success of their drugs.

A couple of the more innovative biopharma players have already started to display such an integrated approach in their drug development and commercialization processes. Adapting with this kind of agility is essential for high efficiency treatment delivery.

4.3 HIGH-SPEED ANALYTICS

The increased need to demonstrate the value of novel therapies is a lever that has an important role in the innovation framework. While the industry needs the technology and computing superpowers to help through various stages of care delivery, the opportunity is equally high for players to enter the largely untapped and complex market. They can provide their scale and skills in data capturing, monitoring, analytics and overall patient-facing digitization to leverage their understanding of the consumer mindset.

This innovation lever will require some level of investment in organization wide infrastructure and platform technologies. At best, ROI can only be measured at a portfolio of drugs level. There is a possible role for such partners in providing understanding of patient behavior, screening and lifestyle modification opportunities in high risk populations, data capturing platforms and technologies during clinical trials and in a commercial setup. Furthermore, their ability to provide analytics at a level that is far beyond the core competency of traditional biopharma company makes their value critical in the innovation process.

"The primary goal should still be getting the drug to market in the quickest way and navigating through the path of least resistance."

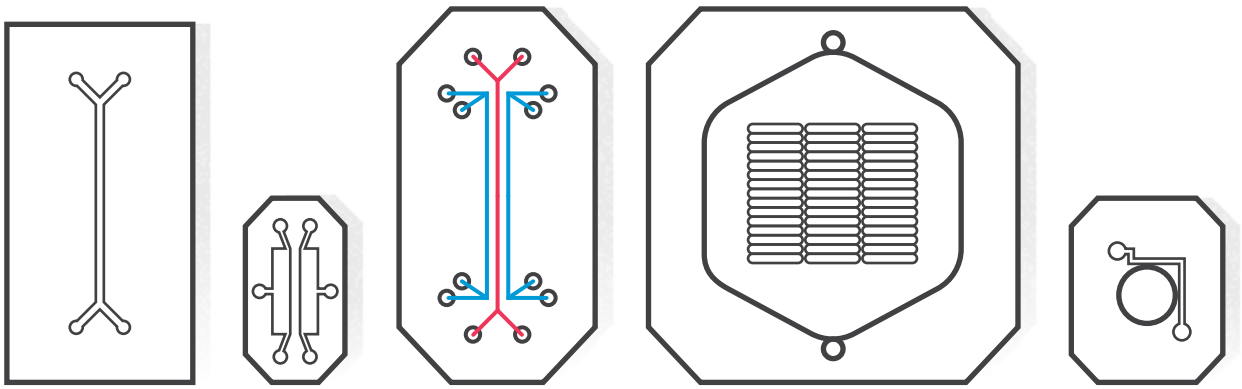
5 OUR THOUGHTS ON SELECT TECHNOLOGIES AS APPLIED TO THE INNOVATION FRAMEWORK

The partnership-driven innovation model proposed in this whitepaper could cover a wide range of technologies. It is therefore impractical to cover every topic in detail. However, there are five technology/platform innovations that we think will have most impact on an innovation strategy. Successfully integrating these innovations in appropriate functional areas will offer a significant competitive edge to biopharma companies.

5.1 MICROFLUIDICS AND SIMULATION FOR PERSONALIZED THERAPY DEVELOPMENT

In vitro testing has always been known for inefficiency in the drug discovery process. However, lab and animal testing are the only option to form a decision model for clinical validation of a new drug. Even with the increased understanding of animal tumor models and the ability to partially simulate the drug response in humans, in vivo testing often fails to accurately predict the response in humans. There is a strong case for industry-wide adoption of an alternative platform for in vitro testing that can offer cost and time efficiency with a tangible increment in accuracy to predict human response.

The technology that has potential to fundamentally change this stage of drug discovery process is organ-on-a-chip. This is a multichannel microfluidic chip that is lined with organ specific tissues to mimic real-life microarchitecture of the organ and its functioning. Multiple organ chips can be combined with functional and therapeutically relevant interfaces such as blood brain barrier or lung airways to simulate and test the impact of the drug at a system level.

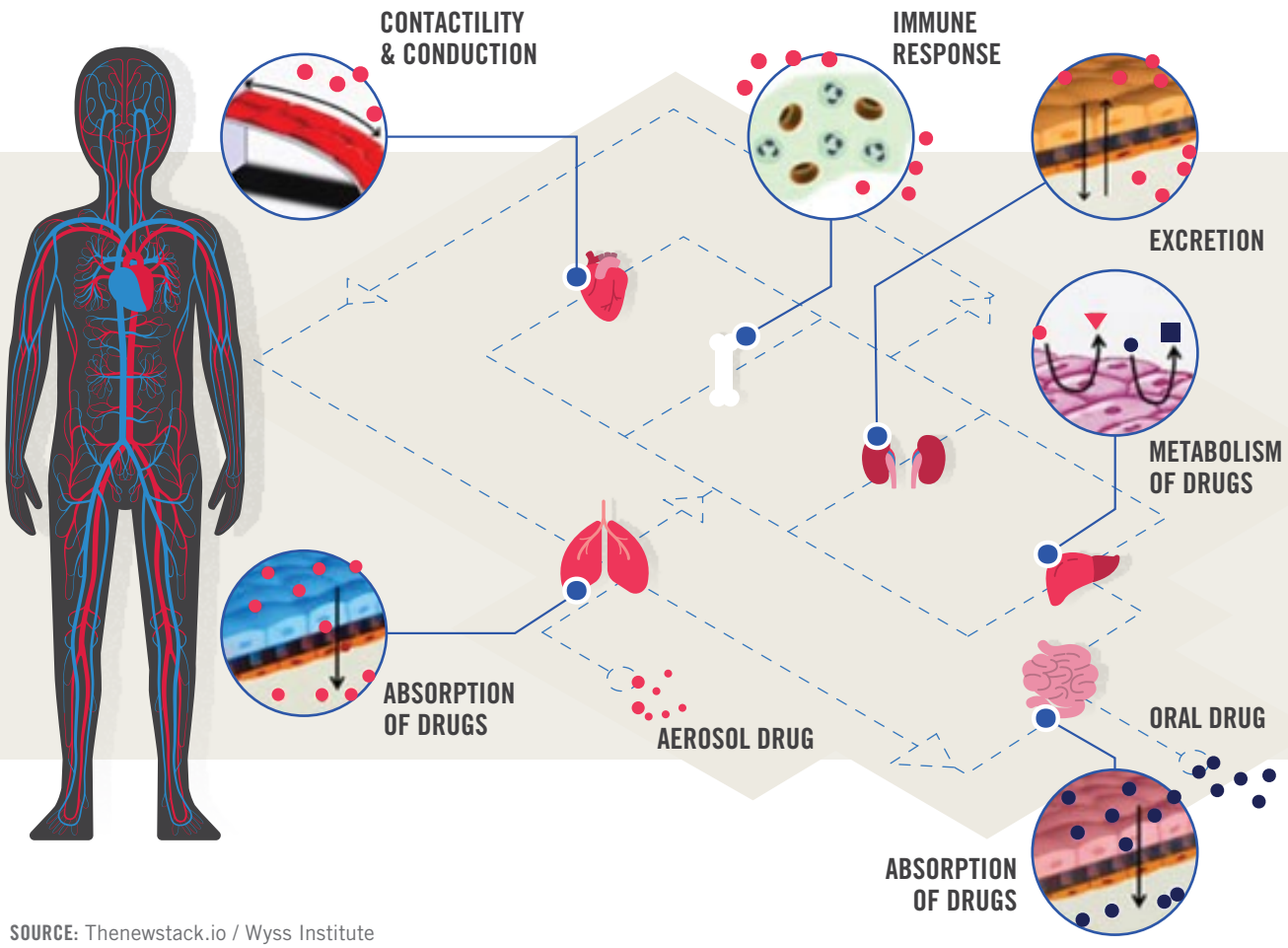


SOURCE: Thenewstack.io / Wyss Institute

In theory, the response to a drug through the entire body can be simulated, to an extent, by using these organ specific chips and relevant interfaces. It has the potential to provide unprecedented micro-level understanding of the drug response and interdependencies of different organs that impact the PK/PD profile of a drug in humans.

These chips revolutionize the pace of drug discovery for mutation specific cancers and other rare diseases. The same technology could be a foundation block for personalized medicine. A tumor environment taken from a patient can be lined in the microchip to test different drugs or a combination of different drugs to identify the best treatment protocol for the patient.

The technology is rapidly maturing and the IP for the hardware may remain with the companies or institutions pioneering the technology. Partnering with them could provide a valuable platform for drug discovery. However, biopharma can build a proprietary IP of simulation and decision models of a multi-organ system and develop their own essays to calibrate the predictive models, based on the outcomes yielded by the off-the-shelf organ-on-a-chip systems provided by these partners. It is not the use of this platform that will offer the competitive advantage, but the ability to develop a proprietary testing and decision model that will offer competitive advantage to a biopharma.



SOURCE: Thenewstack.io / Wyss Institute

5.2 IOT FOR PROFILING, SCREENING AND DIAGNOSING

There are factors that could potentially influence the early risk profiling and screening of cancer and, for that matter, a number of other diseases. One is the omni-present IoTs in our homes and on our bodies, and the second is the rapidly declining cost of genome sequencing.

Consumer electronics and computing powerhouses might assume the role of 'relationship owners' with future patients for biopharma companies. They'd provide granular understanding of lifestyle behaviors, preferences and other comorbidities that have potential to influence risk profiling of the patients. Consumer wearables and IoTs present in our homes, offices and cars could provide a channel to understand the high risk 'consumers" at a very early stage.

These technology powerhouses could be the keepers of massive amounts of consumer/patient data that identify risks at birth based on the genetic profiling of the child – as well as parents, based on genetic testing. Pre-pregnancy genetic tests of parents and post-delivery genetic tests of babies are, at present, voluntary in the US and limited to small patient populations which can afford to pay. However, the declining cost of genome sequencing and the business model of data driven companies may enable widespread, or even free, access to genetics tests. The business model would permit recouping those costs in the form of analytics products and services provided to pharma companies downstream.

Cataloging cultural, behavioral and geography-specific aspects through the many IoTs that have and will continue to penetrate our home, schools, workplaces and even public places, might help create a very robust understanding of a patient's risk profile. This can ultimately form a base for screening and diagnostic strategies for their ultimate end-users – biopharma clients and physicians/hospital systems. With both being reimbursed on value-based outcomes, they will find the insights and analysis of pre-diagnosis data quite a compelling tool in maximizing their business results.

Up to the point where a consumer is identified as a patient, biopharma companies can safely rely on these technology partners to bring actionable data without taking part in the upfront investments in infrastructure. It would be a service focused business model that would provide flexibility for both biopharma as well as the technology partners to engage at appropriate levels.

However, biopharma could invest or at least co-invest in building infrastructure, platforms, hardware and analytics tools – starting with clinical trials and subsequently for monitoring of treatment response in a commercial setup. At a point where the consumer is identified as a patient, biopharma would assume the primary relationship and would control what type of technologies, hardware and decision support tools are deployed, during clinical trials and the commercial setup, that directly engage with patients, physicians and trial administrators.

Company-wide infrastructure, with the ability to collect data from connected drug delivery platforms, wearable sensors, consumer devices and hospital systems at a more granular level, is something that all biopharma should consider as a part of their innovation strategy. It is highly likely, considering the reimbursement dynamics and other strong macro drivers discussed earlier, that the business case to invest in oncology will be more compelling than any other therapeutic area.

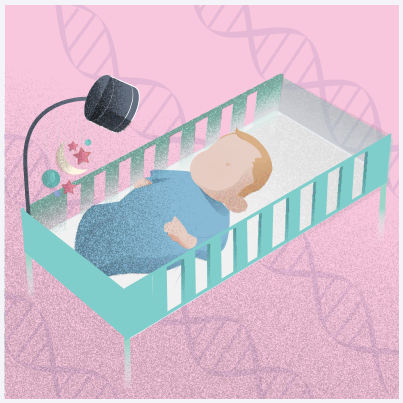
This is probably the only way to authoritatively demonstrate the ongoing value of drug treatments while maintaining a meaningful role in care delivery and benefiting from all the core competencies of technology partners.

Integrating diagnostic steps in the end-to-end treatment delivery would be an equally important task but easier than driving the internal transformation discussed above for biopharma companies. The primary reason is that cancer diagnostics and the diagnostics industry as a whole saw a revolution of sorts in the last decade. The innovation infused in the industry was largely backed by technology savvy startups that went on to become major industry players. This set the pace of innovation for traditional diagnostic players who have largely transformed themselves into much more sophisticated players than they were 20 years ago.

Biopharma can safely continue to rely on established diagnostic players for developing and maturing lab-based tests for testing and staging of the cancer. Established screening technology providers will continue to drive innovation in radiology. For now, there aren't any signs that these players will leave any unmet need for biopharma to dive into themselves.

The area where biopharma would require active engagement is the diagnostic capabilities needed for drug specific treatment response monitoring. From the workflow point of view, it may not have the luxury of time – and leveraging traditional lab-based testing may not be the most ideal solution. Specifically, this applies to drugs that are biomarker dependent or response dependent and not a fixed dose regimen. A number of antibodies, ADCs and specific gene targeting medication, plus some combination IO drugs might fall into this category. In those cases, it might be vital for biopharma companies to invest in drug specific diagnostic technologies. It may come in the form of investment in startups, licensing of assays or even developing tests in-house in the case of certain rare types of cancers.

BUILDING A PATIENT SPECIFIC RISK PROFILE



AT BIRTH

Genome sequencing at birth can provide insight into inherited risks and other mutations that could indicated elevated risk or probability of cancer.

AT SCHOOL

Exposure to carcinogens, pollutants at school where a child may spend a significant amount of time and may have other activity specific risk factors.

AT HOME

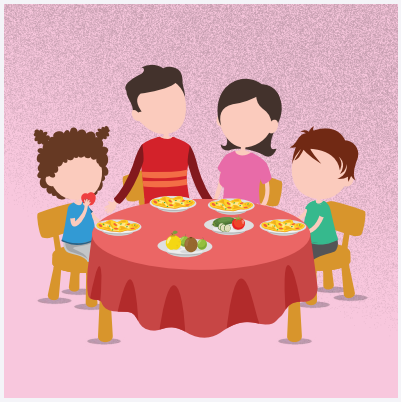
Risk factors and exposure at dwelling which may include a high level of magnetic fields, EPA sites or any other factors directly impacting health.

AT WORK

Occupation specific hazards that directly impact exposure to known carcinogens at elevated levels.

AT PRIMARY CARE

Access to quality of care, geography specific factors, socio economic factors that govern access to quality preventive care and disease awareness.



AT DINING TABLE

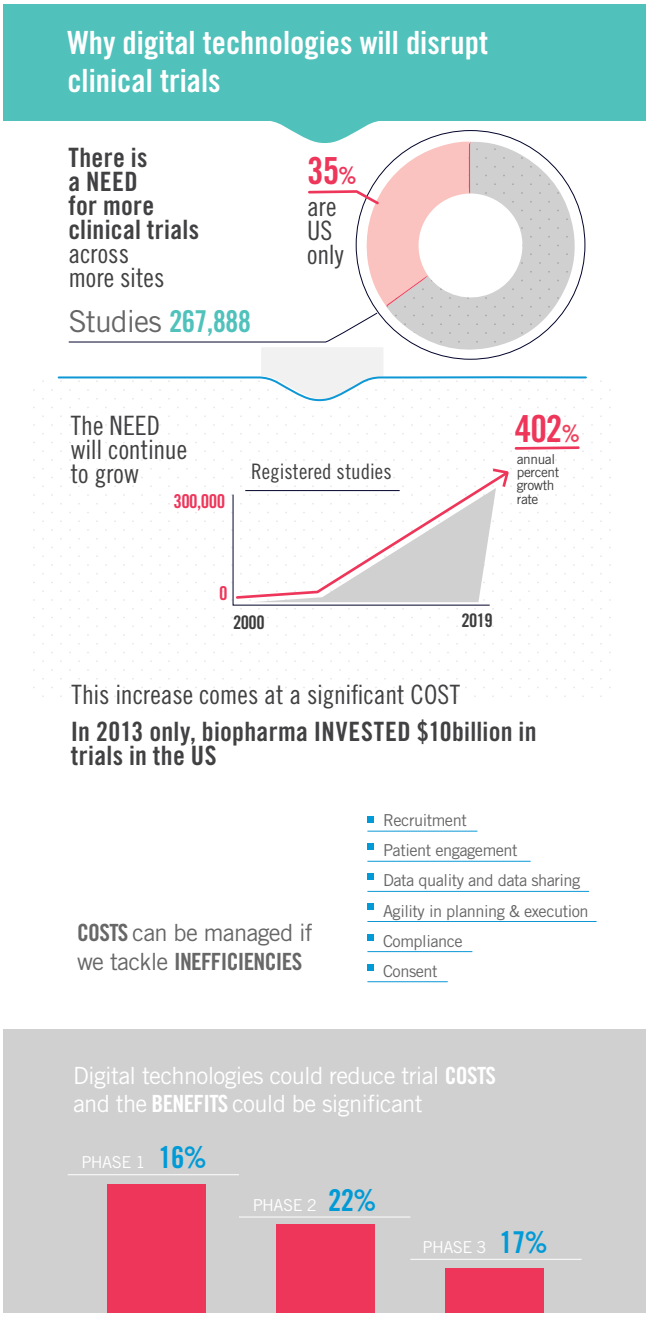
Personal food habits, dietary preferences / likings, socioeconomic factors governing access to quality food and water.

5.3 CLOSED LOOP CONNECTED PLATFORMS FOR NEXT GENERATION CLINICAL TRIALS

As discussed earlier, we believe the clinical trials related process, infrastructure and methodologies are rapidly evolving. Even though RCTs may remain the gold standard for clinical trials, for therapeutic areas such as oncology where there are numerous different types of cancers with unique molecular level differentiators, adaptive platform trials are soon going to gain widespread acceptance. And with that comes the need to overhaul the operational infrastructure for trials. As discussed before, adaptive platform trials can test multiple drugs at once, individually or in combination for the same indication, or one drug for multiple indications. This can potentially shorten to less than a third the lab-to-launch time for a portfolio of drugs or a drug for a portfolio of indications.

However, to be executed successfully, it requires much more granular and meticulous data collection and infrastructure to analyze the data in more complex ways than the simple end points of RCTs. It also requires infrastructure to manage such complex operation. And therefore, the closed loop connected trial management system with a partner who can provide analytics and computing horsepower becomes necessary.

Even if we were to assume that most trials will continue to operate on RCT principles, the sheer number of new drugs and the average cost per patient for trials, which for oncology tends to be 20%-30% higher, provides a business case for change. Ultimately the cost of clinical trials should not be the limiting factors in the number of drugs being tested.



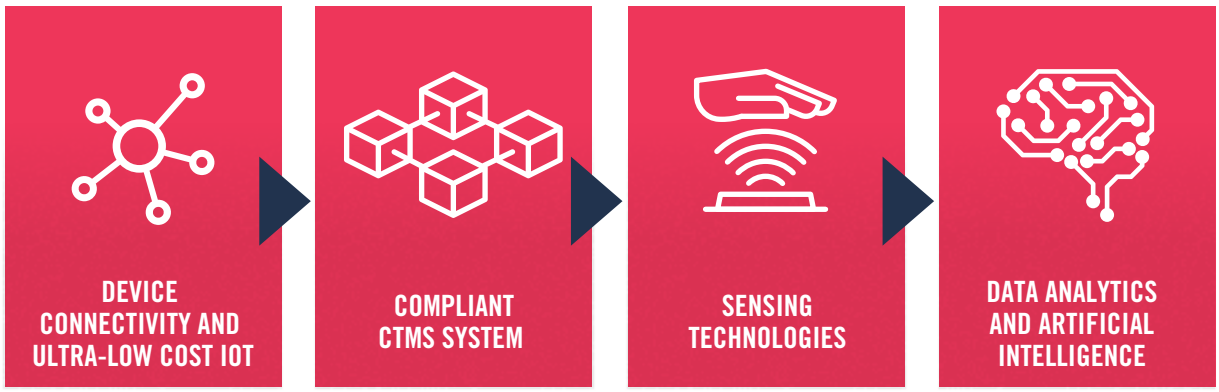
If the aim of the biopharma is to build a robust HEOR case for a drug, developing infrastructure to digitize the clinical trial and to partner with an established AI/analytics player is the logical next step in the innovation process.

Connected drug delivery devices and smart primary packaging are increasingly becoming the stepping-stone of this transformation process. Improving adherence and reducing dependencies on patient reported outcomes can ultimately contribute towards the successful trial result. However, the biggest assets it can generate are the continuous or frequently collected data points when coupled with other sensors and wearables. Ultra-low cost connectivity hardware has reduced the overall cost of integrating such devices and sensors to a much lower level than it was just few years back.

While biopharma may not have the appetite for developing and validating a new sensor, startups and technology players are filling that unmet need at rapid pace. This has provided endless opportunities for data capturing. Integrating such sensors and wearables as a part of overall clinical trial infrastructure, or as a part of the closed loop system that drives the administration of therapies, can offer great deal of agility in operating the trial and level of data driven insights that can help physicians make better treatment decisions for every patient enrolled. Datasets can also enable more complex adaptive platform trials, ultimately yielding much more efficient trial timetables and massive savings in operating costs.

The part that brings all the essential elements together – connected devices, sensors, cloud connected wearables and analytics and reporting tools – is the CTMS platform. The relationship between CTMS platform providers and biopharma will evolve from 'ERP vendor' to 'strategic partnership'. In order to stay competitive, the CTMS platform providers will have to adopt the same innovation framework to ensure their readiness for changes that their most valuable clients and partners will soon be pushing for.

"Ultra-low cost connectivity hardware has reduced the overall cost of integrating devices and sensors to a much lower level."



5.4 ROBOTICS AND MANUFACTURING AUTOMATION FOR ATMPS

This then represents a challenge for advanced therapies, as a large part of the health econometric analysis of these approaches relies on the possibility of distributed manufacture. Achieving this goal will be impossible without significant innovation in manufacturing platforms. There have been some innovative approaches by equipment vendors and CDMOs to semi-automate elements of the cell and gene therapy production workflow, but even these solutions have significant drawbacks in terms of usability and capex requirements. Pharma companies are starting to invest in developing bespoke systems for closing and automating the cell and gene therapy production process.

Another solution to the challenge lies in greater collaboration with suppliers of components of these therapies, for example viral vector manufacturers and nucleic acid producers. In turn many of these suppliers have had to very quickly adapt to the challenges around rapidly expanding their production capabilities and upscaling at the same time as improving quality standards necessary for successful clinical and commercial launch. Again, there is a body of experience from bioprocessing which is a useful base for these companies, but cell and gene therapies require additional skill sets on top of those necessary for production of biologic drugs. Another significant challenge is the lack of available skilled workers who understand the requirements and process for making these advanced therapies. This has been identified by a number of industry bodies as one of the major constraints on the growth of advanced therapies. In turn this provides another driver for the move to bespoke, closed automated systems for production of these therapies.

It can be seen, then, that pharma companies in addition to strengthening and deepening their existing relationship with CMOs and other vendors, also need to develop new relationships with innovative hardware companies, software companies and early stage biotech companies in order to be able to create and produce a product which is suitable for use at an appropriate price point, with acceptable quality, in a time scale which is commercially attractive. Many of these sorts of organizations are unfamiliar with the rigmarole of engaging with pharma companies and in particular pharma procurement departments, and this cultural barrier serves to hinder progress until such time as both sides have a greater appreciation of each other's imperatives and capabilities.

This combination of complex manufacturing processes, the extreme reliability demanded by batch sizes of one, the lack of an available skilled workforce, and the drive to reduce cost and improve patient access means that automation is a critical factor in the success of this field. We are also starting to see automation enter the development process earlier than had traditionally been the case for small molecules or biologics. The impressive efficacy of cell and gene therapies means that regulators are starting to approve products for commercial launch on the basis of a much smaller body of trial data then was historically necessary. This in turn means that it is essential for therapy developers to avoid the trap of using a manual process for production of their drug product with the expectation that they will have time during an extended clinical development program to go back and automate the production process. Instead it is now essential to automate at the very start of clinical trials, which in turn has implications for capex budgets and investor appetite for significant investment before clinical proof of concept has been achieved.

5.5 AI AND ML FOR TREATMENT SELECTION AND MONITORING

The potential impact of Artificial Intelligence (AI) and Machine Learning (ML) on medical imaging, genomic profiling, clinical development and personalized medicine led to an article in Nature that tagged them as among the decade's most disruptive technologies in the field of cancer care.

While research in AI/ML has greatly improved the sophistication and capabilities of data processing algorithms, a great deal of success can also be attributed to the massive increase in computing power at much lower cost. In the medical arena, the utility of AI and ML is highly dependent on the quality of data. The ability to collect data at a more granular and more frequent level with the help of better quality sensors, high resolution, always-on wearables and personal devices, as well as the new generation of diagnostic and surgical devices, also contributed to improving the outcomes of AI/ML deployment in various medical functions.

"Many of these sorts of organizations are unfamiliar with the rigmarole of engaging with pharma companies."

PRIMARY CARE

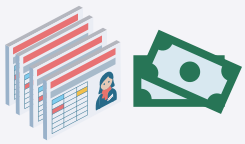
Family doctors will operate in a more efficient, and more personal way.

Chatbots can provide an efficient, first line for healthcare organizations

Chatbots complement first line care, making simple preliminary diagnoses, potentially offering solutions or helping to make appointments with a doctor or nurse.

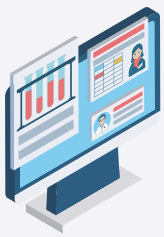
'Physician's assistant' AI collates patient data from medical history and wearables

This provides clinical decision support using all the data available to it and based on the latest collaborative research. It is used as a support – the final decision remains the responsibility of a qualified doctor.



Health insurance will take account of more and more information

Some people may be reluctant to share their data but many will choose to opt-in as insurers provide discounted healthcare. Insurers use of medical data is likely to be regulated to ensure that the market is not undermined by precise information on risk factors for serious conditions.

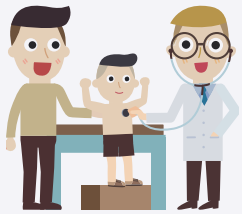


Healthcare will be about stopping people getting ill, not making ill people better

New technologies will monitor your day-to-day condition using voice assistants, wearables and implantables. Organizations will actively reach out to those who need it, rather than waiting for patients to come to them. This move to proactive, outcome-led care will fundamentally change the way healthcare providers, insurers and payers interact.

Organizations will increasingly rely on more effective use of data

As an example, the combination of AI image recognition and human radiologist offers a step change in diagnosis as faster, more accurate results become available.

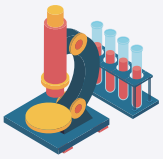


Reduced admin means a greater focus on interacting with patients

Currently upwards of 30% of time is spent on administrative tasks. An AI assistant can reduce this, and help organizations place a greater emphasis on patient interaction.

PERSONALIZATION OF CARE

Bespoke care will become the norm rather than the exception.



Discovering new drugs becomes more efficient

New candidate compounds can be selected for trials with the use of AI, streamlining the current process. Our catalogue of medicines will continue to grow.

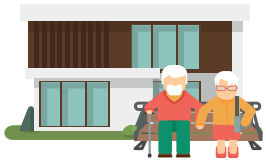
Data lakes and AI techniques uncover emerging health trends

Big datasets gathered from research and development, medical records and wearables across many individuals will form the basis of 'data lakes' that will be used by medical researchers, public health experts and pharmaceuticals as sources for their ML algorithms to discover new insights and uncover emerging trends in public health.

Treatments are delivered on an individual basis

Although adding a layer of complexity for organizations, modelling to produce precision medicine which targets treatments to an individual will significantly increase the effectiveness of treatment and reduce wastage.

Gene mapping insights start to become commonplace, feeding into AI assistants in a collaborative system.



CARE IN THE HOME

Medical and social care will be increasingly decentralized and delivered in the home.

Vulnerable patients can remain in their home for longer

There will be demand to stay at home, where virtual friends and chatbots can help in everything from tackling loneliness to reporting accidents.

In combination these will help people maintain independence longer, and change the relationship between these individuals and organizations.

Earlier discharge from hospital is enabled by the smart home

Sensors and devices providing safety features and assistance in the home ensure that the recovery progresses as planned. This will mean only the acutely ill will need to remain on hospital wards, there would be less need to keep patients 'in for observation overnight'.

Medication will be taken more effectively

Personal AI assistants and smart drug dispensers in the home will help monitor and enforce medication regimes for the forgetful or busy, with data being fed back to medical professionals to intervene if required. Money spent on treatment is more likely to have the intended effects.

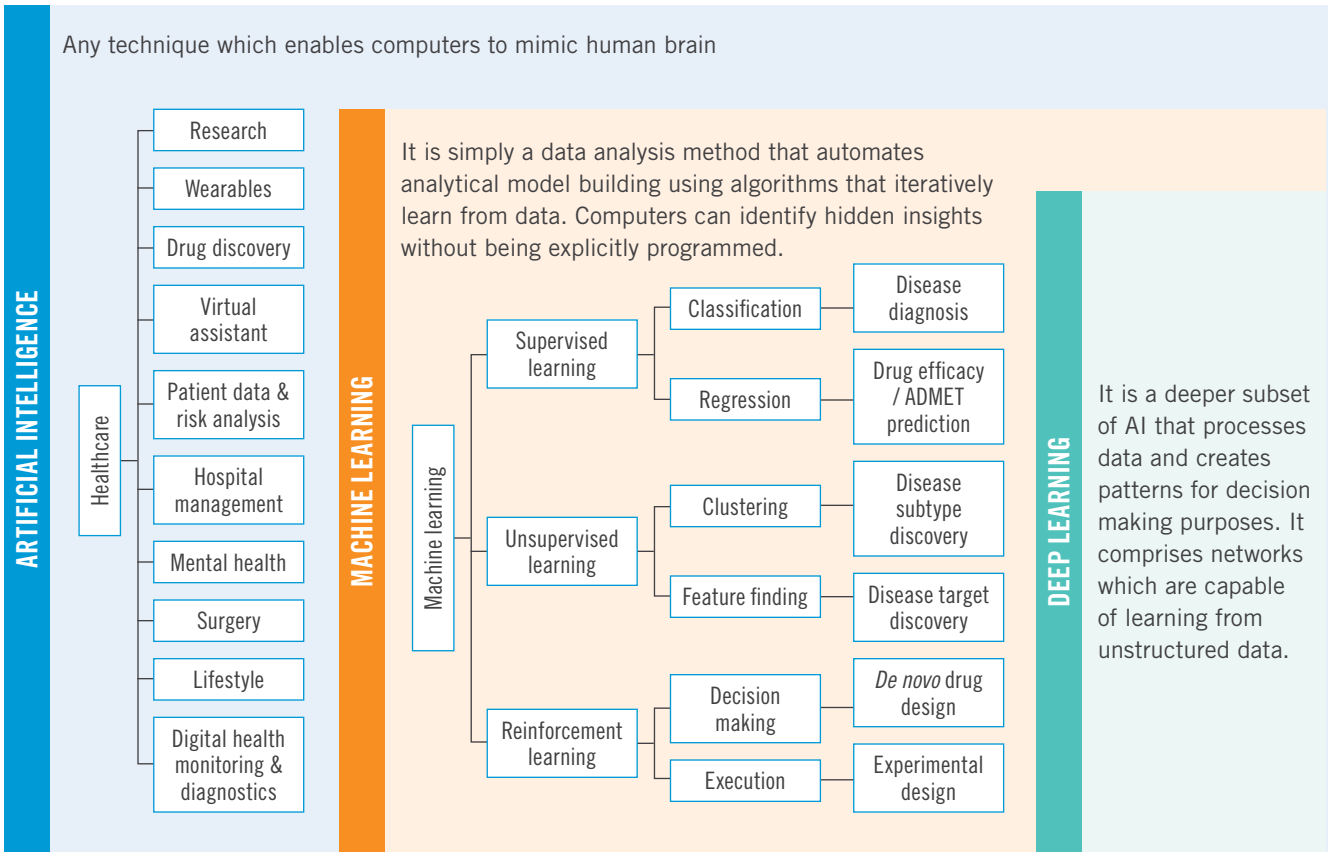
SOURCE: Cambridge Consultants whitepaper – AI: Understanding and Harnessing Potential

MEDICAL IMAGING

The application of image processing algorithms is one of the most widely recognized capabilities of AI. Digital images of radiological and diagnostic tests can be put through ML architecture to evaluate pixel-level or broadband RF (ultrasound) data to precisely detect and classify tumor characteristics and staging. Many endo/colonscopic videos can also be analyzed for potential signs of tissue growth in small or difficult to navigate areas. AI has already demonstrated its utility in surgical oncology to improve the accuracy of tumor margin visualization and planning. It is also being experimented with to predict outcomes based on the tumor imaging analysis and the immune-oncology drug regimen being used to treat it.

CLINICAL

Another use case for ML algorithms is in drug discovery. The task of finding a new drug within vast 'chemical space', which is believed to be as big as 1060 molecules, is a challenging task. Any technology that can assist in target identification, drug design and drug repurposing can greatly improve R&D efficiency. AI platforms can revolutionize pathway identification by greatly reducing the time to explore the search space. Some of the relatively recent methods developed to beat humans at Go, a game with 10172 outcomes, are being generalized to this task using genomic data and biochemical characteristics of molecules, in turn improving the hit rate of successful drug development[5]. AI platforms have also shown capability to predict toxicity of unknown compounds based on the relevant data of a known chemical compounds library. All of this experimental research can provide great deal of R&D efficiency that will ultimately lead to the development of better drugs at a dramatically quicker pace.



SOURCE: Drug Discovery Today

TREATMENT DELIVERY

From the patient's quality of life point of view, the most impactful role AI could play is in delivering personalized treatment with cocktails of drugs in real time based on numerous biomarkers. AI can have a significant impact on the patient specific outcome when deployed to first identify the optimum combination of drugs – specifically the new class of immune-oncology drugs – and then deliver the combination of appropriate drugs in real time based on how the tumor/disease is responding and how well the patient is able to tolerate the drug.

It can improve outcomes not just by the use of an optimal mix of drugs, but also by potentially reducing drug resistance and hence providing the ability for the patient to benefit from the drug for a longer period. With the help of modern sensor enabled wearable devices, it is possible to deploy AI platforms to drive such real-time drug dosing decisions. Until we find a cure, AI deployed in this manner can significantly improve quality of life for cancer patients and potentially help us push certain types of cancers to a 'chronic condition' status where patients can live a near normal life.

"With the help of modern sensor enabled wearable devices, it is possible to deploy AI platforms to drive such real-time dosing decisions. Until we find a cure, AI deployed in this manner can significantly improve quality of life."

5.6 IMPLANTS AND ADVANCED DEVICE PLATFORMS FOR COMPLEX DRUG DELIVERY

As evident from the innovation framework discussion, there are several factors that will govern the transition of drug delivery technologies from traditional IV or PFS. Difficult to treat cancers may require localized delivery, others can require a prolonged dosing regimen, even to extending throughout the life of a patient, and some may require multiple drugs being administered in parallel or sequentially.

Specific types of drugs may have formulation challenges and as a result may need a complex dose preparation process before they can be administered via IV or SC. Some patient populations will by definition need better QOL in the interests of societal productivity, while others may need features that improve QOL due to their age group.

Geographic factors may also impose some requirements to deliver therapies in a certain manner. Combining all these factors – along with the need to build robust outcomes data – will make a compelling case for revisiting the drug delivery device portfolio and evaluating the capabilities gap. Below are the technology and design enablers that biopharma can evaluate against their pipeline of drugs to build a development strategy that plugs the gap.

Delivery technologies, interventional systems and implants have been researched for many years for other therapeutic areas such as diabetes, pain management and autoimmune disorders. However, for oncology this would mark a major shift in treatment delivery strategy. As already highlighted, with macro factors at play and an ever-expanding pipeline with unique physiological properties and cancer targeting modalities, these design and technology enablers must be an integral part of the drug/portfolio-specific lifecycle strategy.

Wearable drug delivery systems are widely available as off-the-shelf solutions. However, depending on formulation characteristics and indication specific situations, such solutions may require major changes in key components, including the needle insertion system, primary container and sterile fluid path as well as the drug dispensing module. If the intent is to leverage the platform as a part of connected ecosystem for treatment monitoring or adverse event monitoring, adding connectivity and communication via the cloud and other controlling sensors would require major changes in the device architecture.

	REMOTE DRUG DELIVERY	ADVERSE EVENTS MONITORING	DIFFICULT TO FORMULATE DRUGS	COMBINATION THERAPIES	LOCALIZED DELIVERY	PROLONGED DRUG DELIVERY	QOL / POPULATION SPECIFIC
Wearable delivery system	●		●	●			●
Closed loop connectivity & sensors	●	●					●
Auto-reconstitution	●		●	●			●
Automated drug mixers			●	●			
Minimaly invasive delivery systems					●	●	●
Active / passive implants					●	●	
Active implants with sensing		●			●	●	

Closed loop connectivity can certainly enable newer types of treatments being delivered in a home setup. It can also enable newer patient groups to receive treatment in a home setup that was not possible due to the possibility of user errors or an adverse event occurrence. A sensor controlled closed loop delivery system can monitor vitals during the drug administration and can either pause, stop or even inject antidote in case of adverse events. It can also monitor each step of drug preparation and self-administration in a patient population that may need additional checks, or where training decay is a possibility due to age or frequency of dosing.

Automated reconstitution and automated drug mixers can enable challenging formulations to be prepared in a hospital or clinic setup to reduce the burden on treatment workflow. It can also ensure accurate drug mixing for expensive formulations. Automated preparation, or at least an automated check at the end of the process, is critical to guard against the consequences of a wrongly prepared/mixed drug having a catastrophic effect on the patient. Automated reconstitution integrated as part of a wearable delivery system can enable the administration of combination therapies. If enabled with real-time connectivity, it can also be used to administer biomarker dependent combination therapies as opposed to fixed dose combination therapies.

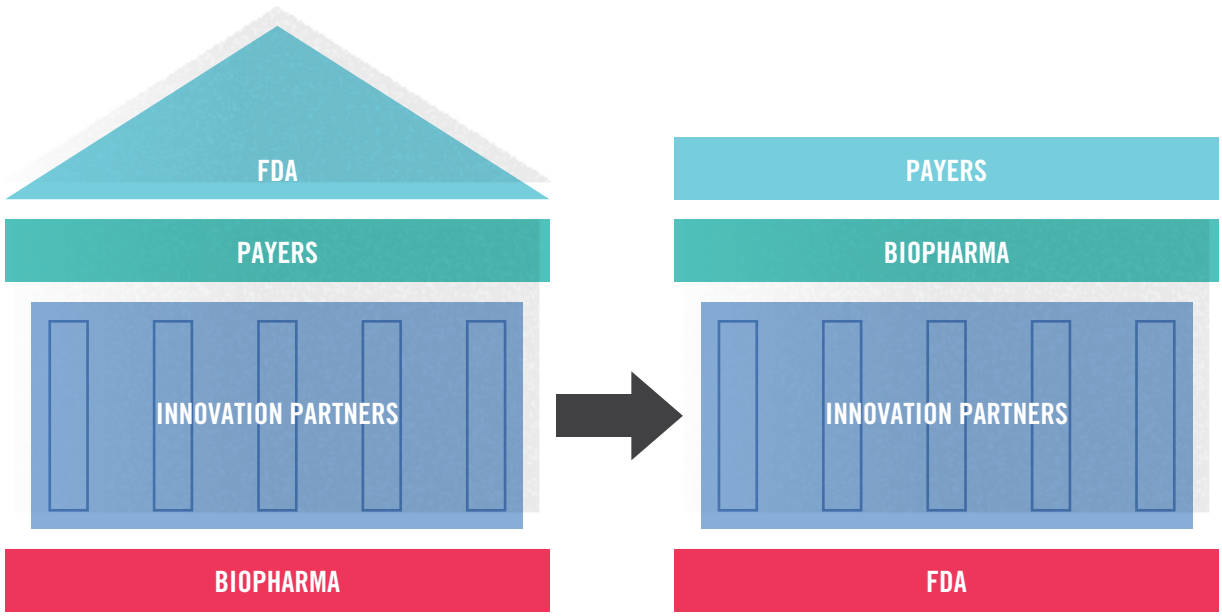
A number of drugs that may require prolonged treatment to a localized tumor environment may be able to be leveraged by implants. Miniaturized implants loaded with a high concentration for multiple doses with a lifespan of a number of weeks to even a year are possible. Such an implant delivery system can be designed to deliver drugs on demand or at regular intervals. If equipped with appropriate sensing mechanisms, it can also be designed to deliver drugs in response to specific cellular or tissue level activity. Implants are suitable platforms for difficult to access organs such as the bladder, colon, head, neck and brain. Such organs can also be treated with minimally invasive/interventional systems repurposed to deliver drugs when the dosing regimen is infrequent. These systems can also be relevant for certain populations such as pediatric patients and patients with other severe comorbidities.

6 BRINGING IT ALL TOGETHER – ENVISIONING THE RELATIONSHIP OF INNOVATION PARTNERS WITH PATIENTS AND CAREGIVERS

In the current setup, we see payers and the FDA as two major orchestrators of the oncology therapeutic area. However, with the increased complexity in the drug discovery, treatment delivery and monitoring process – and considering the number of players involved – our thinking is that biopharma will play a more central role in bringing all these innovations together. That could include, directly or indirectly, being the driving force behind system-wide changes in care delivery and regulatory frameworks.

For several good reasons, it is essential for biopharma to take a central role in integrating innovations at every step of drug development, care delivery and analytics. All the current and new partners in the process can form a pillar for the rapid evolution of the entire ecosystem. But biopharma must evolve from being the foundation of it all to the intermediary for all technology innovation partners and the payers. Unless biopharma takes this role of getting everyone paid for their contribution, it will be an inefficient system where push and pull for reimbursement will be a drag on the innovation process.

The FDA as a regulatory agency can take a foundation role for the entire ecosystem by issuing high-level guideline and regulatory pathways for innovation to be introduced in research and care delivery. This would involve a transformation of sorts at the FDA which is beyond the scope of this whitepaper.



PRIMARY CARE
Lifestyle computation
Genetic profiles and testing

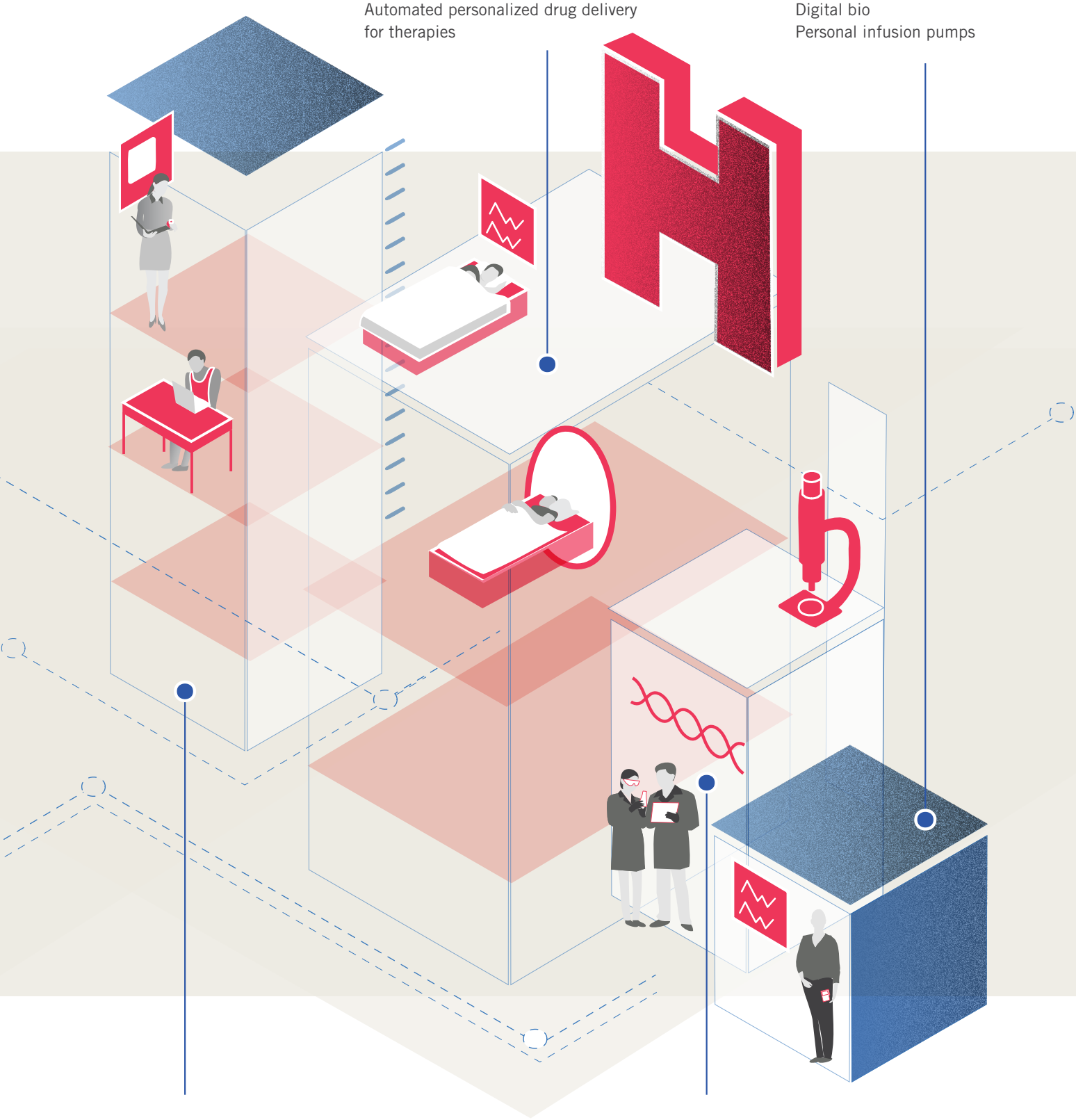
PHARMA COMPANY
Rapid drug discovery
Personalized chip testing

DIAGNOSTIC FACILITY
DNA testing

HOME CARE
Sleep monitoring
Mirror monitor
Fridge screen with
Health suggestions

SPECIALTY HOSPITAL
AI imaging
Advanced visualization & navigation surgery
Automated personalized drug delivery
for therapies

REMOTE CARE AT HOME
Clinic drug delivery
Home monitoring of vital signs
Digital bio
Personal infusion pumps



WORKING SPACE
Smart watch
Wearable clothing

PHARMA BIOTECH PLAN
Cell/gene therapy

7 CONCLUSION

Oncology as a therapeutic area is going through fundamental changes. These changes – driven by macroeconomic, competitive and scientific factors – are taking us many steps closer to making cancer a chronic condition, while keeping the overall cost of care within manageable boundaries.

The impact of these changes is being felt across the industry and by every player involved in this therapeutic area. The overall care ecosystem is bound to feel the need to evolve, innovate and grow.

Our proposed innovation framework provides these ambitious players, many of them our existing clients and partners in innovation, a clear and efficient approach to integrate next generation engineering and technological innovations in their R&D and commercialization strategy. The framework can also help them identify gaps in their existing capability and infrastructure so they can prepare a transformation plan that is future ready. That future will see transformative changes across the care pathway to enable more integrated, transparent and individualized care delivery.

At Cambridge Consultants, we remain committed to evolving and innovating ourselves to stay ahead of the curve during these transformative times in the oncology therapeutic area. We have time and again demonstrated our ability to partner with some of the most agile industry players throughout their innovation lifecycle. Such unparalleled capabilities to collaborate on an end-to-end basis across the value chain is our core strength.

8 APPENDIX

A OTHER RELEVANT CAMBRIDGE CONSULTANTS REPORTS AND WHITEPAPERS

- **AI:** understanding and harnessing the potential
- **Technology enablement:** a new paradigm for oncology patient therapy empowerment
- **Clinical trials:** how technology is driving digitisation
- **Liquid biopsy:** current and future utility
- **The new FDA:** navigating the moving line between consumer & medical

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5 https://www.nature.com/articles/s41587-019-0224-x

About Cambridge Consultants

Cambridge Consultants is regarded as a world-leader in product development, engineering and technology consulting. We work with companies globally on some of the most challenging strategy, innovation and product development projects. With a team of more than 900 staff in the USA, the UK, Singapore and Japan, we have all the in-house skills needed to help our clients – from creating innovative concepts right the way through to taking their product into manufacturing.

Medical technology is a core strength of our business. We specialize in helping companies achieve the ambitious or seemingly impossible. We work with some of the world's largest blue-chip companies as well as with some of the youngest, innovative start-ups who want to change the status quo fast. We follow ISO 13485 certified medical product development processes. Our end-to-end projects deliver prototype hardware or software and trials production batches and transfer to manufacturer. We fully support our clients through the regulatory approval process of the product we develop. Equally, our technology consultants can help you to maximize your product portfolio and technology roadmap.

Our teams help clients transform global patient care via enabling technology, focusing on developing tailored medical products and services for the unique unmet needs of patients, care givers and healthcare professionals. As part of our ongoing commitment to global medical innovation, we would be pleased to hear your feedback on the content of this report, and to discuss your views on the future.

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For more information, or to discuss your product innovation challenge, please contact:

Harshal Shah, Head of Oncology Innovations
Global Medical Technology Division
harshal.shah@cambridgeconsultants.com

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