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REALIZING THE PROMISE OF IMMUNOTHERAPY

A GLOBAL PLAN FOR ACTION

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REALIZING THE PROMISE OF IMMUNOTHERAPY A GLOBAL PLAN FOR ACTION

Report of the WISH Immunotherapy Forum 2020

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FOREWORD

After decades of grueling research and investment, immunotherapy is now poised to revolutionize the treatment of an array of conditions affecting millions of people around the world. Some cancer patients – who only a few years ago would have faced certain death – are now achieving complete remissions after undergoing immunotherapy. Clinical trials are revealing crucial roles for immunotherapies in combating conditions from rheumatoid arthritis to Alzheimer’s to infectious disease, including the COVID-19 pandemic. Breakthroughs are happening every day, and we may only be at the beginning of this wave of innovative treatment.

Yet this exciting field is not without its challenges. Costly empirical research is required to tailor drugs to specific patient profiles to achieve the most effective responses and reduce the risk of potentially severe side effects. Patients may be enrolled in multiple clinical trials or be exposed to potentially substandard therapies in control arms of these trials. Health systems may struggle with the high cost and complex infrastructure needed to deliver treatments. Governments and policymakers often have limited data on clinical efficacy and cost-effectiveness of treatments when determining which therapies to cover.

This report outlines the key pillars to unlock the promise of immunotherapy and the challenges faced by stakeholders in each area. It concludes with a number of recommendations for governments, regulators, communities, businesses and institutions to maximize the benefits of immunotherapy. Together, we can harness this innovation to improve the health and wellbeing of millions of families worldwide.



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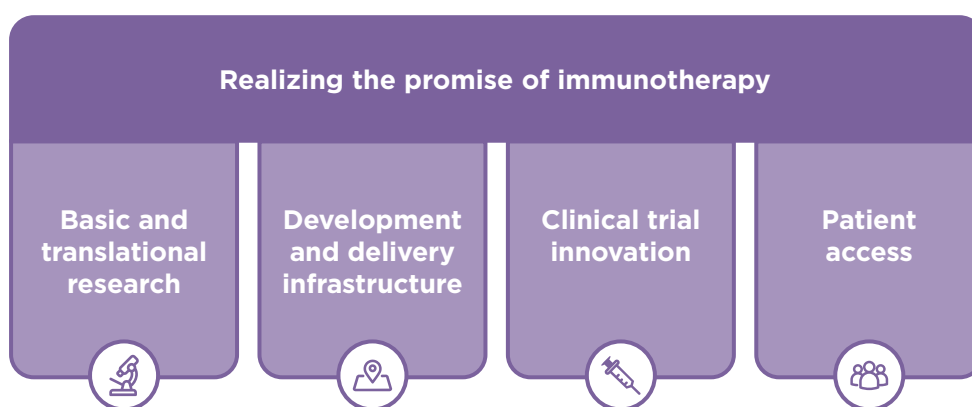
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EXECUTIVE SUMMARY

Immunotherapies stimulate or suppress the immune system to treat disease. While this field is not new, we are now at a point of exceptional opportunity. A number of therapies – primarily for cancer – have shown unparalleled clinical benefit, while countless trials are showing promise for the treatment of a wide range of conditions. However, we are far from unlocking the full potential of this field, which could have a positive impact on the health and wellbeing of millions of citizens across the globe.

This report identifies four key pillars (summarized in Figure 1) that must be addressed to maximize the impact of these treatments.

Figure 1. Framework for realizing the promise of immunotherapy



- We must continue to encourage basic science innovation and work to translate these discoveries into clinically meaningful results. Understanding how the immune system works is essential for developing ways to design new immunotherapies, yet this research is complex and requires investment to support and inspire innovation.
- Immunotherapy can require complex – and often costly – development and delivery infrastructure. For low- and middle-income countries (LMICs) in particular, providing basic therapies can be a challenge, and more complex therapies require extensive testing and monitoring.
- Immunotherapies present several challenges to the standard clinical trial model, including: limited translatability of preclinical results from testing in cells or mice; multiple concurrent trials; and limited ability to project benefits to the wider population. Clinical trial innovation is therefore critical.

- Revolutionary treatments will have no effect if patients cannot access them. It is crucial that patients are able to access immunotherapy innovations as soon as they are proved safe and effective, while balancing the often high cost of these treatments.

The report concludes with eight recommendations for stakeholders to implement to realize the full benefits of immunotherapy:

- 1.** Use innovative approaches to support discovery research.
- 2.** Facilitate translation of academic research.
- 3.** Reduce infrastructure burden for cell therapies.
- 4.** Establish Centers of Excellence to attract trials across all economic backgrounds.
- 5.** Support collaborative trials.
- 6.** Create frameworks for the use of observational data.
- 7.** Enable experimentation with novel pricing and payment mechanisms.
- 8.** Develop a national health strategy for immunotherapies.

SECTION 1. THE PROMISE OF IMMUNOTHERAPY FOR CANCER AND BEYOND

Box 1. Rikki's story, 2015: Immunotherapy for advanced oral cancer

After experiencing what he believed to be a never-ending sinus infection, in 2015 Rikki was diagnosed with oral cancer, affecting his tongue. He went through several months of grueling chemotherapy and radiotherapy, rendering him exhausted, unable to eat solid food and struggling to care for his children. Despite the treatment, a scan in February 2016 revealed that the treatment had not worked; his cancer had advanced and was spreading.

Doctors thought that the only option may be to remove Rikki's entire tongue, rendering him mute and possibly needing a feeding tube for the rest of his life. But Rikki turned out to be eligible for a trial combining two different immunotherapy drugs, called checkpoint inhibitors.

Within just a couple of months of the experimental treatment, Rikki was able to start eating solid food again, and he had the energy to play with his children. By July 2016, Rikki was given the happy news that he was cancer-free.

Source: Adapted from UC San Diego Health¹

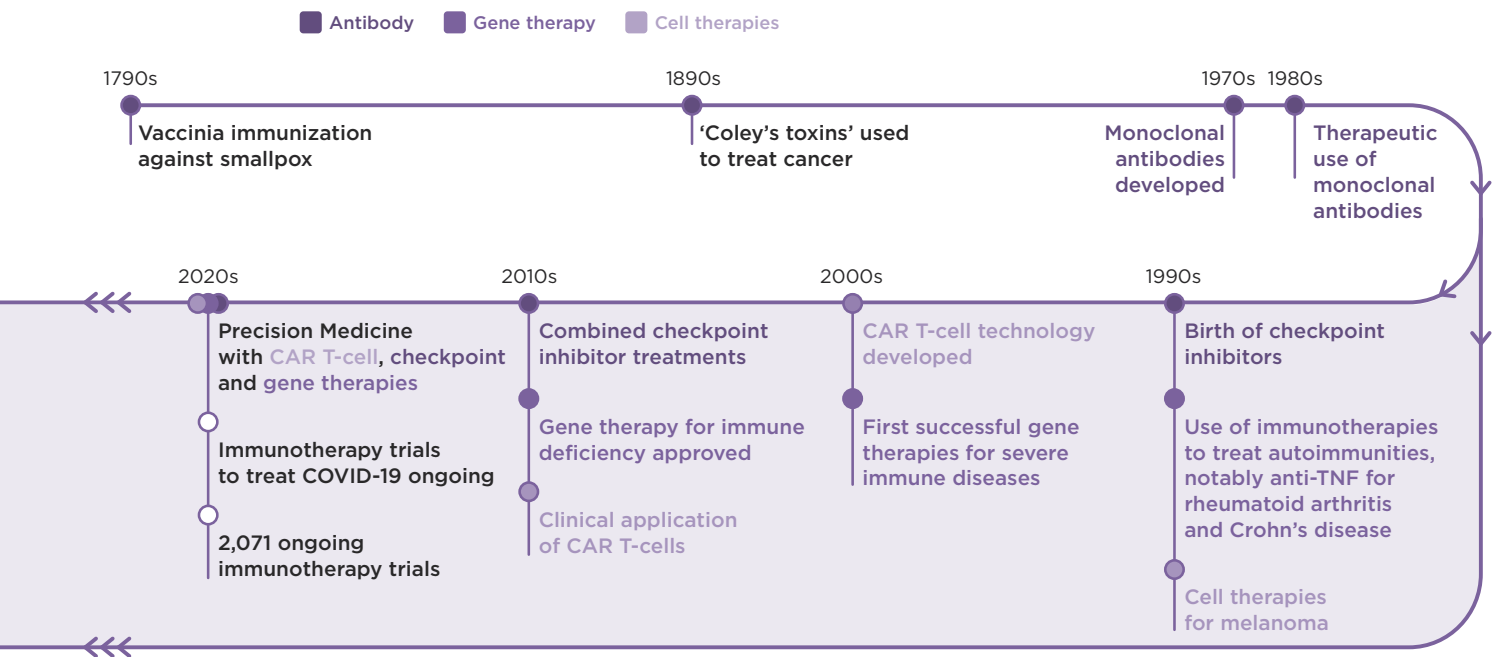
Immunotherapy – using substances to stimulate or suppress the immune system to help the body fight cancer, infection and other diseases – is arguably the most exciting and dynamic field in biopharmaceuticals today.² With the potential to harness the power of our immune system, immunotherapy provides new options in treating previously incurable and life-limiting diseases. Approaches that modify a patient's own immune cells to turn them into targeted weapons have demonstrated astoundingly effective responses in patients who previously failed multiple lines of therapy. (See [WISH 2018 Report on Precision Medicine](#) for further examples.) Despite these breakthroughs in clinical benefit, the field presents meaningful challenges to all healthcare stakeholders: patients, providers, innovators, health systems and governments.

See WISH 2018 Precision Medicine Report, pages 11-12.

A pivotal point for immunotherapy

The concept of immunotherapy is not new (see Figure 2).³ Yet the last decade has seen a paradigm shift in the use of immunotherapy to treat an expanding range of diseases, and immunotherapy is a growing research area.^{4,5} The aim of this report is to provide evidence-based solutions for governments, funders and policymakers to catalyze the discovery, development and delivery of immunotherapies globally.

Figure 2. Timeline of progress in immunotherapy



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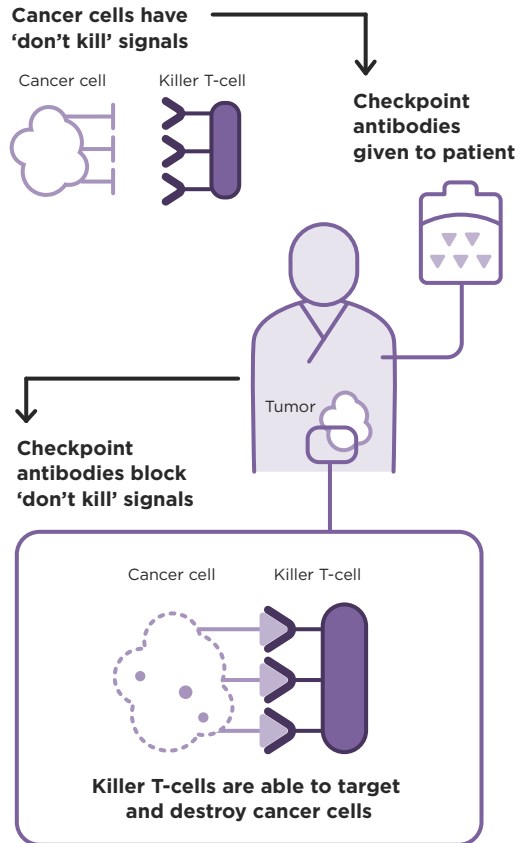
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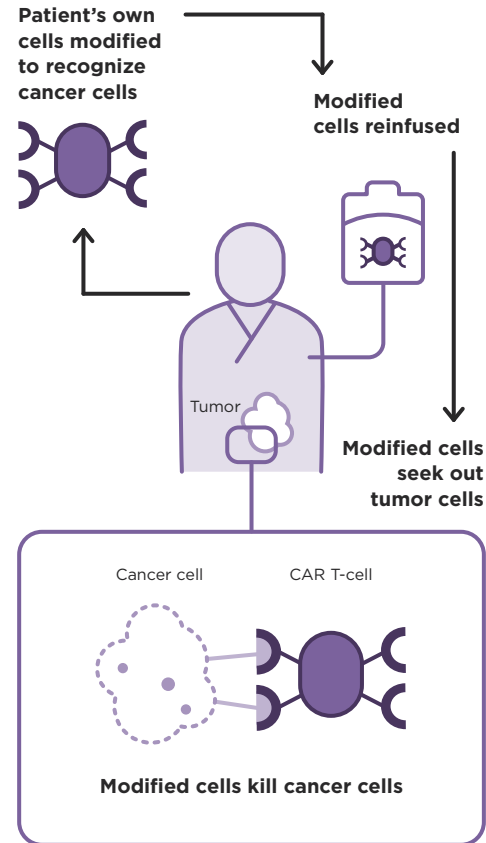
The success of immunotherapy in the last decade is the result of many years of research. This innovative field encompasses a broad range of treatments that engage the immune system in different ways. As of October 2018, 13 products in this regulatory group – known in Europe as advanced therapy medicinal products and in the US as cell and gene therapy products – had received EU authorization.⁶ Though many therapies are under development, checkpoint blockade/inhibitors, cell therapies, and gene therapy have shown particular promise (see [Figure 3](#)).

Figure 3. Promising immunotherapies

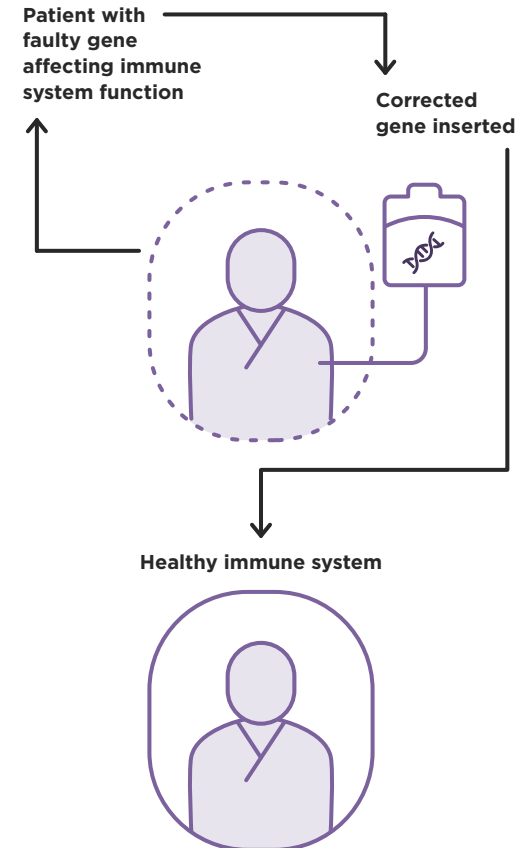
CHECKPOINT BLOCKADE



CAR T-CELL THERAPY

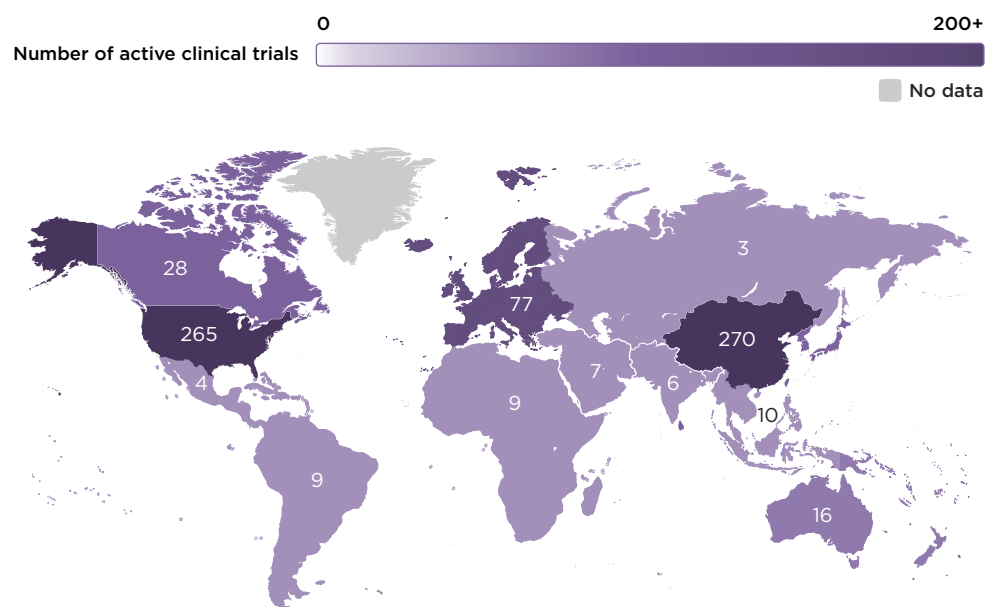


GENE THERAPY



Checkpoint inhibitors are one of the most exciting developments in cancer treatment in the last decade.⁷ Checkpoint inhibitors work by removing the immune system's 'brakes', enabling it to launch a more effective attack.⁸ While not a cure-all, checkpoint inhibitors are dramatically improving the quality of life and survival for many. Examples include chimeric antigen receptor (CAR) T-cell therapies, where a patient's own immune cells are engineered so that they target specific cancer cells.⁹ Two CAR T-cell therapies (Kymriah and Yescarta) received approval in the US and the EU by 2018, and there is ongoing development for a range of cancer types (see Figure 4).¹⁰ Gene therapy, another promising type of immunotherapy, involves correcting a faulty gene or introducing a new gene to fight disease.¹¹

Figure 4. Active clinical trials of CAR T-cell therapies globally (as of July 2020)



Source: US National Library of Medicine¹²

Each of these treatments has experienced different levels of success and has unique challenges in clinical development, manufacturing, delivery, and patient access.

Increased therapeutic applications of immunotherapy

As new immunotherapies rapidly emerge, it has become clear that they have an expanding range of applications, including infectious diseases where the immune system can overreact – such as COVID-19¹³ – and auto-immunity. This growing list includes rheumatoid arthritis, inflammatory bowel disease, psoriasis¹⁴ and multiple sclerosis.

Scientists are also exploring the exciting potential to treat neurodegenerative diseases, such as Alzheimer's, by modulating the immune response. There is increasing recognition that cell- and gene-based immunotherapies have immense potential for treating genetic diseases (see [Box 3. Margaux's story](#)).

SECTION 2. CHALLENGES TO REALIZING THE FULL PROMISE OF IMMUNOTHERAPIES

Box 2. Emily's story, 2012: CAR T-cell therapy to treat childhood leukemia

Emily developed a blood cancer called acute lymphoblastic leukemia when she was only five years old. When it returned after intense rounds of chemotherapy, doctors initially thought that Emily was out of options and would not survive.

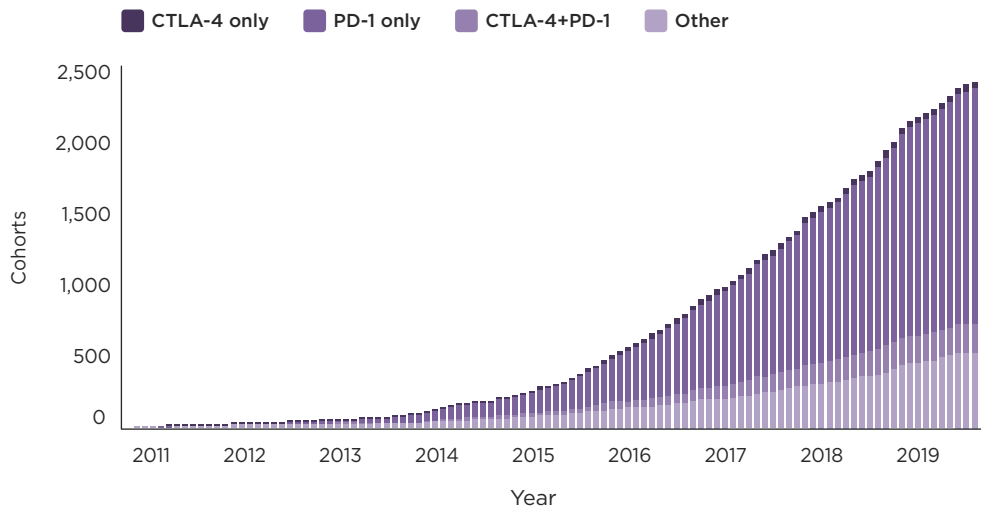
Emily's parents searched for cutting-edge treatment options and learned of a trial for a new type of cell therapy called CAR T-cell. The therapy entailed harvesting a type of blood cell called a T-cell from Emily's blood, using a virus to reprogram the T-cells to recognize leukemia cells, and then transferring these back to Emily where they could destroy the cancer.

Incredibly, just three weeks later, Emily was in complete remission – and with the reprogramed T-cells persisting in her blood, has stayed that way since. She is now an ambassador for the immunotherapy that saved her life.

Source: Adapted from Children's Hospital of Philadelphia¹⁵

While there has been an explosion of activity in immunotherapy (see Figure 5), we have yet to unlock its full potential.

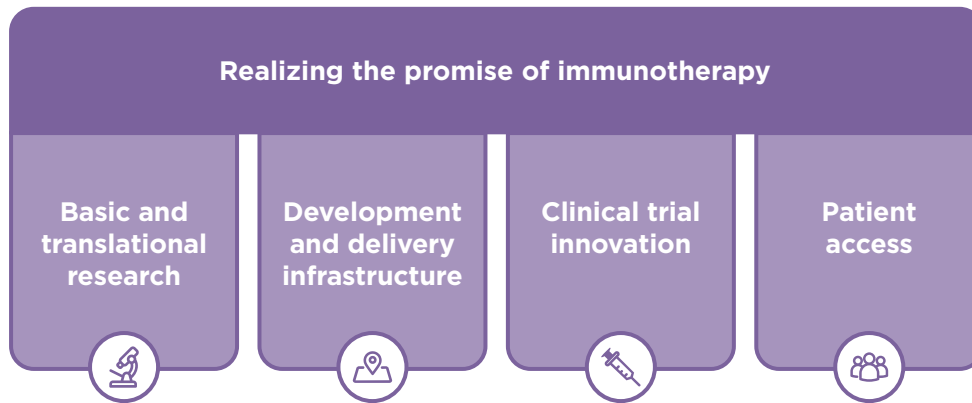
Figure 5. Number of immuno-oncology trials started by year



Source: US National Library of Medicine¹⁶

As shown in Figure 6, we have identified four key pillars to realize the promise of immunotherapies: basic and translational research; development and delivery infrastructure; clinical trial innovation; and patient access.

Figure 6. Framework for realizing the promise of immunotherapy



The following section explores the fundamentals of each pillar, including the challenges that need to be addressed.



Pillar 1. Basic and translational research

Translating basic science innovation into clinically meaningful results is complex and requires research environments that support and inspire innovation.

Understanding how the immune system works through basic science is essential for developing ways to design new immunotherapies. Many innovative drugs that changed the way patients are treated came from creative, ‘blue-skies’ research. One of the antibodies that is now revolutionizing the field of cancer immunotherapy powerfully illustrates the importance of fundamental research (see [Case study 1](#)).¹⁷ The challenge lies in finding ways to support exciting and innovative science that may open new avenues for combating disease by harnessing the immune system.

Another challenge is how best to overcome the long lead times that are often seen between scientific discovery and the delivery of a new treatment. Analysis has shown an average of around 12 to 14 years between a therapy entering the ‘discovery’ stage of drug development and its first approval, if it is successful.¹⁸



Pillar 2. Development and delivery infrastructure

Providing infrastructure to ensure the efficient development and delivery of immunotherapies is challenging. Newer therapies – including cell therapies that work by taking the patient’s own cells, altering them, and returning them to the patient – require significant infrastructure to manage the rare but potentially serious side effects.^{19,20,21} Currently there are fewer than 200 sites in the US, for a population of 331 million (in 2020), that can offer commercial cell therapy to patients, and even fewer in other countries (for instance, only around 10 in the UK).^{22,23}

The challenge is even greater in LMICs where resources are scarce. More complex therapies often require extensive testing and monitoring, putting further strain on these health systems. With immunotherapies, side effects are often a result of the patient’s immune system overreacting.²⁴ This requires the administration of other therapies, often in hospital, which is uniquely challenging in LMICs.^{25,26} The lack of developed infrastructure acts as a barrier to carrying out clinical trials locally and addressing the needs of different countries.



Pillar 3. Clinical trial innovation

The immunotherapy revolution has highlighted limitations and opportunities in the standard design of clinical trials.

First, preclinical model systems, such as cells in dishes or mice, can only offer limited predictions on how a drug may work in patients; understanding the complexity of these therapies requires trials in people. Often, multiple companies carry out trials on the same or similar technologies, but use different designs and metrics for success. This makes it difficult to combine results from similar trials and slows down the process of validating a treatment.²⁷

Also, understanding how the therapies can benefit the wider population, outside the constraints of a trial, is challenging. Even after clinical trials are complete, many questions may remain about the longer-term effects of treatments.²⁸ For example, it is not always clear how long benefits last and why treatments can stop working in certain individuals. We must work to develop more effective systems and frameworks to collect and interpret data that can answer these questions. (See [WISH 2018 Report on Data Science and AI](#) for further information.)

There are a number of phases in a clinical trial which can take years to complete (see [Figure 7](#)). These phases gather evidence on how effective a treatment is, whether it is better than existing treatments, and on its safety. A challenge facing regulators is therefore how to accelerate this process without compromising patient safety, while also maintaining rigorous standards necessary to prove a treatment's worth.

See [WISH 2018 Data Science and AI Report](#), page 17.

Figure 7. Drug development pathway, U.S. Food and Drug Administration (FDA)

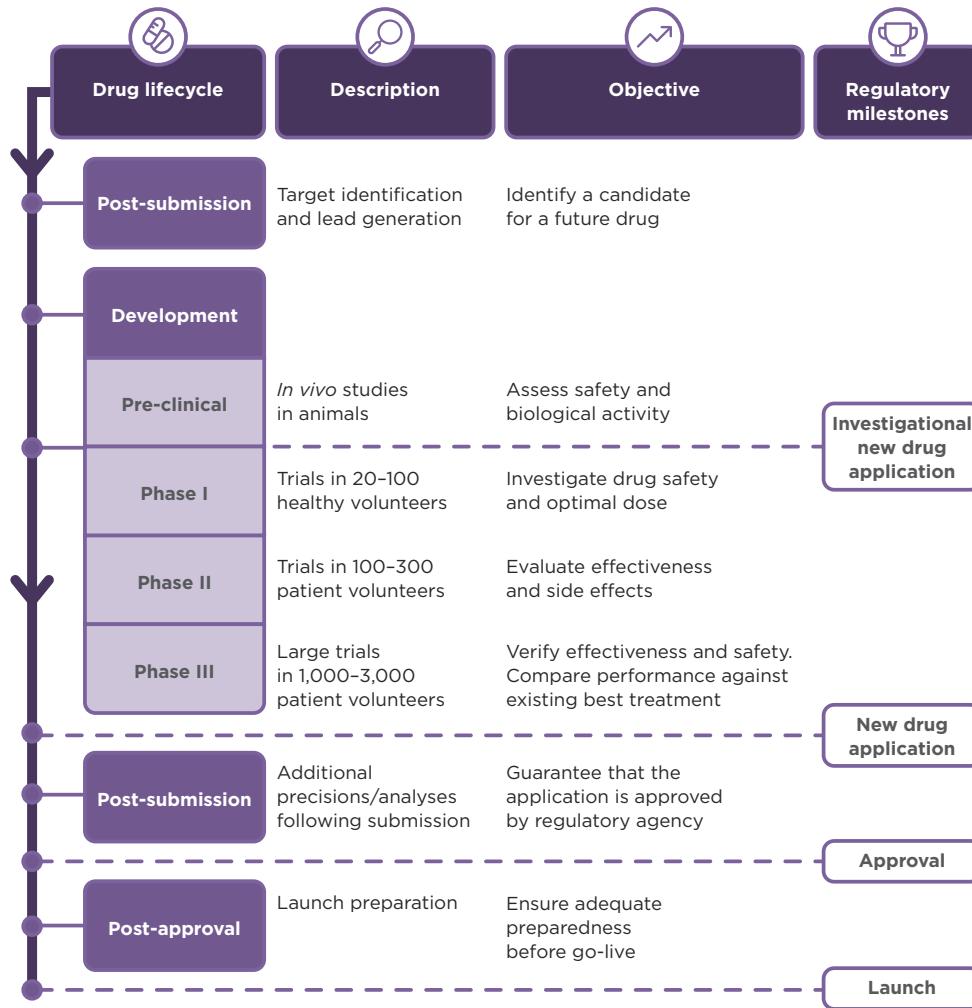
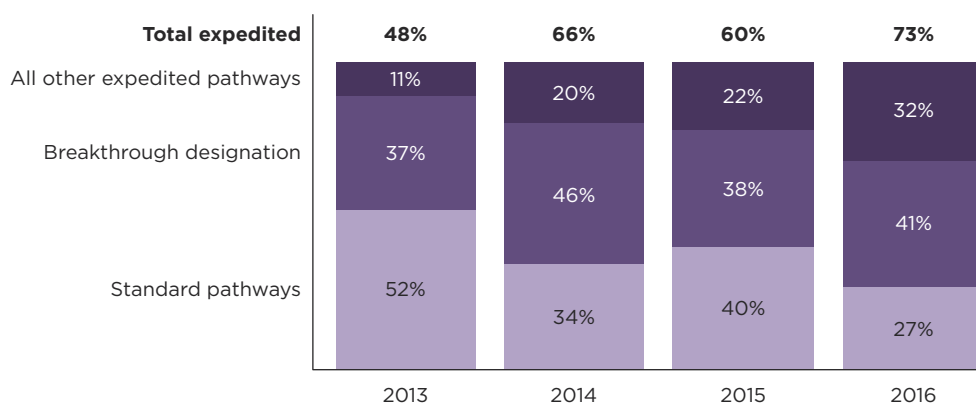


Figure 7a. Drugs approved on expedited pathways,* percent of new drugs approved



Source: US Food and Drug Administration^{29,30}

* Including Fast Track, Breakthrough, Priority Review, and/or Accelerated Approval. Each of these designations helps expedite the speed of the development and/or approval process and is designed to help bring important medications to the market as quickly as possible.



Pillar 4. Patient access

Once a safe and effective treatment has been developed, it must be readily available and affordable so that patients can access it.

Immunotherapies have demonstrated important incremental changes in patient outcomes across different types of disease.³¹ This has resulted in an increasing use of accelerated approval programs,³² where therapies are approved based on Phase 2 clinical studies. These studies often use less-definitive milestones than traditional Phase 3 studies – for example, looking at the number of people who respond to a treatment instead of measuring survival.³³

The ability to accelerate approval creates a challenging balance for health technology assessment agencies, which set reimbursement rates. The earlier the treatment is made available in the development life cycle, the more difficult it is to demonstrate its clinical benefit and safety. Patients who have run out of options should have access to therapies that show very promising signals. However, immunotherapies can be very expensive and can cause side effects, so it is vital to be sure that they are effective.³⁴

Novel immunotherapies can range from roughly \$100,000 per year to more than a \$1 million in the US for a cell therapy (including hospitalization).³⁵ Therefore, immunotherapy can dramatically increase costs when compared to traditional treatments, which may have inexpensive generic versions available.³⁶ As innovative therapies, most immunotherapies do not yet have their equivalent of generics ('biosimilars'),³⁷ magnifying the issue for LMICs which often do not have the resources to provide even the relatively cheaper generic treatments to their populations.

Also, infrastructure must be in place to ensure that patients receive the right drugs to improve the chances of treatment success. This requires the ability to access diagnostics to predict whether a patient will respond to a particular therapy.³⁸ These factors all add to the burgeoning costs of immunotherapies.³⁹

SECTION 3. POLICY RECOMMENDATIONS AND CONCLUSION

Box 3. Margaux’s story, 2014: A gene therapy cure for a fatal immune disorder

Margaux, born in 2013, suffered a severe lung infection within weeks of birth that left her struggling for air and fighting for her life. While her condition stabilized, she was left with the grim diagnosis of a fatal immune disorder often referred to as ‘bubble baby disease’ because those affected must be kept in bubble-like protection to survive. Margaux’s life became one of isolation and careful sterility, while her parents lived in constant fear of an accidental exposure that could cost Margaux her life.

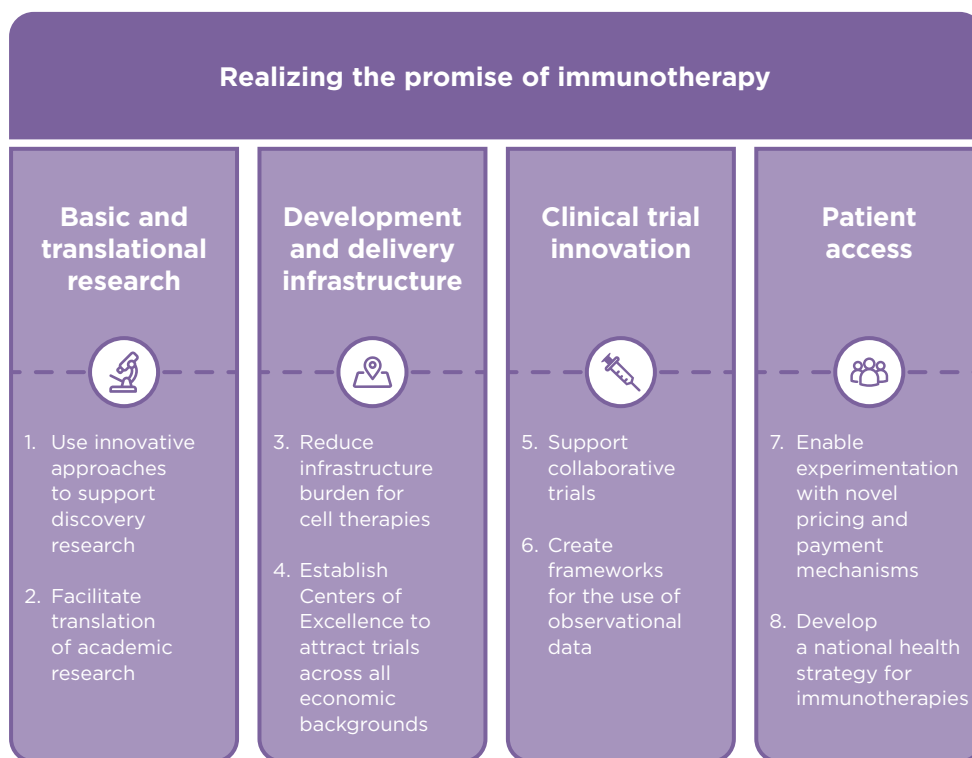
While treatment with a stem cell transplant was possible, finding a matching donor proved difficult. Luckily, in 2014 Margaux was able to try a groundbreaking gene therapy approach. For the experimental therapy, researchers first extracted and purified Margaux’s blood stem cells. They then corrected the faulty gene responsible for the illness by using a modified virus to deliver a functioning version of the gene to the cells. These modified cells were then infused back into Margaux.

These repaired cells have enabled Margaux to develop a healthy immune system and respond to vaccines. After spending the first years of her life in isolation, Margaux is now able to play with other children and start kindergarten.

Source: Adapted from Vale and Leake (2018)⁴⁰

There is no one single solution to these challenges. Solving them will require support from governments, regulators, communities, businesses and institutions. Below, we outline eight recommendations to help these stakeholders drive innovation and maximize the benefits in the field of immunotherapy (as summarized in Figure 8).

Figure 8. Recommendations for realizing the promise of immunotherapy



Pillar 1. Basic and translational research

Recommendation 1: Use innovative approaches to support discovery research

At the root of all novel immunotherapies (and clinical breakthroughs more broadly) is the freedom to succeed in innovative, creative, fundamental science (see [Case study 1](#)). Yet it is not always obvious where the next revolutionary innovation will come from. Therefore, it is vital for governments and funding agencies to support fundamental science, even if the clinical benefit is not immediately clear.

Support can include multidisciplinary centers and convergence science clinics that unite basic and clinical sciences, such as Australia's Walter and Eliza Hall Institute of Medical Research.⁴¹ This could also include better exchange programs for scientists and clinicians to expand learning opportunities which would help to foster future collaborations and ongoing partnerships.

It is also important to support the general public's scientific education, for example, through awareness campaigns that showcase the value of fundamental research and the importance of public involvement to help shape research. The long lead times between discovery and application can be frustrating and difficult for people to understand. However, it is important for the public to have scientific literacy to ensure their buy-in and engagement with research. (See [WISH 2018 Report on Design in Healthcare](#) and [WISH 2015 Report on Communicating Complex Health Messages](#) for further information.)

See [WISH 2018 Report on Design in Healthcare](#), page 10.

See [WISH 2015 Report on Communicating Complex Health Messages](#), page 4.

Recommendation 2: Facilitate translation of academic research

We recommend that governments and funders help catalyze the translation of novel discoveries into the clinic in a number of ways:

- Align basic science with clinical needs by co-locating scientists and clinicians or creating Centers of Excellence that can innovate in this area.
- Partner with professional bodies to support scientists navigating regulatory hurdles to translate discoveries.
- Streamline regulatory pathways to enable investigators to generate the evidence needed to demonstrate benefit and accelerate approval.

These actions are particularly important for novel types of immunotherapies, as it can be challenging to obtain outside funding until proof-of-concept has been demonstrated.⁴² The European Medicines Agency's Priority Medicines (PRIME) scheme, for instance, supports drug developers by optimizing research plans so that evidence generated in trials is robust. This enables faster assessment of medicines and brings potentially life-changing treatments to patients sooner.⁴³



CASE STUDY 1. FOUNDATIONS OF CANCER IMMUNOTHERAPY

The importance of blue-skies research

James Allison, considered one of the founders of the field of cancer immunotherapy, won the 2018 Nobel Prize in Medicine for his work on CTLA-4. Allison and his lab team discovered that the molecule CTLA-4 puts the ‘brakes’ on the immune system, preventing it from launching attacks on the ‘self’.⁴⁴ While many groups tried to use CTLA-4 and other similar molecules to treat autoimmune disease (which have also been quite successful), Allison connected the understanding of the fundamentals of the immune system and the role it plays in cancer – a wildly different approach to the standard chemotherapy drug treatments of the time. This meant it was challenging to get pharmaceutical companies to invest in the early research.⁴⁵ Yet nearly 15 years after Allison first demonstrated that a CTLA-4 antibody cured 90 percent of mice of cancer, the first CTLA-4 blocker, Yervoy (ipilimumab), was approved.^{46,47} Cancer immunotherapy is now an essential treatment, including for those with advanced disease, and the therapy of choice for many different types of cancer.

Allison has repeatedly stated that the discoveries of cancer immunotherapy represent the triumph of science and the value of research, even if it does not immediately lead to scientific or clinical success.⁴⁸ His work demonstrates the need to support hypothesis-driven research that might go against the current best thinking.



Pillar 2. Development and delivery infrastructure

Recommendation 3: Reduce infrastructure burden for cell therapies

With cell and gene therapies holding great promise to treat conditions from cancers to blood-based diseases such as beta thalassemia, it is important that governments focus on reducing the significant infrastructure burden and associated cost.^{49,50} Strategies include:






- enabling faster experimentation and iteration in early stage clinical trials (see Recommendation 2 for more details).
- relaxing some manufacturing standards for early-stage cell therapies.
- working with researchers and companies to create a framework for approval of new devices that can provide these therapies on site.⁵¹
- supporting development of cell therapies that can be better controlled and thus mitigate the sometimes severe side effects.^{52,53}

Decision-makers should also facilitate a co-ordinated approach between healthcare providers, as the small number of eligible patients can create additional barriers to success in fragmented health systems. Uniting expertise through the establishment of formal networks can also expedite research and translation. The recently launched Advanced Therapies Network in the UK, for example, supports knowledge sharing between academic and industry leaders working in cell, gene and tissue therapies, with the aim of accelerating discoveries and patient access.⁵⁴

Recommendation 4: Establish Centers of Excellence to attract trials across all economic backgrounds

Much immunotherapy development has focused on diseases that are common in high-income countries. However, underlying genetic and environmental differences between countries, and consequently the prevalence of different diseases, can vary significantly (as shown in Figure 9). Therefore, it may not be clear whether therapies that are effective in high-income countries are as effective in the rest of the world.

Figure 9. Prevalence of cancer types, by country

Indication (per 100,000)	 US	 UK	 Qatar	 China	 Uganda
Breast cancer	81.5	70.0	10.8	20.9	7.0
Lung cancer	81.1	77.2	3.5	52.7	2.0
Liver cancer	10.3	9.4	2.2	41.1	3.3
Non-Hodgkin lymphoma	27.0	24.4	1.8	5.0	4.6
Cervical cancer	5.8	4.9	0.8	6.6	10.3

Note: Incidence per 100,000 population in 2016, not standardized for age.

Source: Institute for Health Metrics and Evaluation⁵⁵

We recommend the creation of Centers of Excellence (specialist centers with access to innovative therapies) which will advance patient health – particularly in LMICs – by facilitating local research and in-country trials. The infrastructure and resources within these centers provide a range of benefits⁵⁶ including:

- infrastructure to study the most prevalent diseases in the local population.
- increased testing facilities to match patients to the right therapy, thereby increasing the likelihood of treatment success.
- an increase in the number of trials conducted locally, expanding access to new medicines.
- lower costs for clinical trials.

As a more efficient investment of limited resources, centers offer LMICs the infrastructure to meet the demands of newer treatment options, as exemplified by the Tata Institute of Social Sciences, Mumbai in India.⁵⁷

Centers may also engage with global partners to speed their growth and build local capacity. Partner organizations could include academic centers, pharmaceutical companies, or other governments. For example, Croatia has partnered with Roche to establish an institute for personalized medicine.⁵⁸ The partnership includes both testing and training for physicians to interpret the results and provide cutting-edge care. In Germany,

the charity Deutsche Krebshilfe (German Cancer Aid) has supported the development, qualification and approval of Oncology Centers of Excellence with the help of international review boards.⁵⁹



CASE STUDY 2. UGANDA CANCER INSTITUTE - A CENTER OF EXCELLENCE

A global impact on cancer care

Uganda is a successful example of an LMIC establishing a Center of Excellence,^{60,61,62} and has a long history of leading research in cancers disproportionately seen in sub-Saharan African populations, such as Burkitt's lymphoma. This was first described in Uganda in 1958 by surgeon Denis Burkitt who demonstrated one of the first effective uses of chemotherapy for cancer, showing that Burkitt's lymphoma responded to a single dose of Cytosan (cyclophosphamide).^{63,64}

The Uganda Cancer Institute (UCI) was founded in 1967, with support from the US National Cancer Institute, largely to treat Burkitt's lymphoma. By starting with one high-impact disease and gradually expanding its remit, the UCI was able to partner with leading cancer institutes across the globe to advance science. At the same time, the Institute was able to build in-country capabilities to preserve talent and provide better treatment to the Ugandan population, and now the other countries within the East African Community region.⁶⁵

UCI is a leading cancer center in sub-Saharan Africa and its discoveries have had a global impact on cancer care. One ongoing collaboration, with the Fred Hutchinson Cancer Research Center in Seattle, Washington, led to the establishment of an advanced facility with a suite of the latest research and clinical infrastructure,⁶⁶ including:

- a training center to develop the next generation of Ugandan oncologists.
- a molecular diagnostics lab to guide treatment selection and research.
- a biorepository that collects samples from cancers that are rarely seen in the US or EU.
- a full suite of research labs that enable in-country research and development.

There are currently more than 30 ongoing studies across a range of cancers.⁶⁷



Pillar 3. Clinical trial innovation

Recommendation 5: Support collaborative trials

Governments and policymakers can stimulate progress in immunotherapy development by supporting innovation in trial design. Platform trials are one example. These trials test different compounds in parallel using the same protocol and comparator (control arm). This enables straightforward comparisons of multiple therapies, while reducing the number of patients required for the control arm. This in turn allows more patients to receive potentially innovative drugs and reduces the cost. The trials also benefit from improved patient identification, as there is a standard procedure for enrolling patients based on disease characteristics. Platform trials therefore discourage excessive testing of the same hypothesis while enabling flexibility and rapid decision-making.⁶⁸

The experience and innovative methodologies developed in these studies have enabled rapid start-up of a number of COVID-19 platform trials in response to the global pandemic.⁶⁹ This includes SOLIDARITY (see [Case study 3](#)).⁷⁰ Another example is the I-SPY group, which is using its network of sites that traditionally study breast cancer to create an I-SPY COVID trial. In response to the pandemic, the trial began in weeks, rather than the months or years that standard trials usually take.⁷¹

Developing policies and processes that make it easier to connect patients to experimental therapies will also support this effort and quickly bring new drugs to patients who have no other options. For example, the US-based Emily Whitehead Foundation has a patient portal to help translate the information contained in government-run databases of clinical trials into an easy-to-understand format.⁷²



CASE STUDY 3. GLOBAL COLLABORATION FOR COVID-19

A model for future innovation

The global COVID-19 crisis has enabled innovation and a reimagining of ‘business as usual’, particularly around data sharing and collaboration across geographies and stakeholders.

Stakeholders have demonstrated a willingness to share data more rapidly and more openly than ever before. For example, Nextstrain, an open sourced global initiative for genetic data has enabled scientists to understand the spread of the virus that causes COVID-19 more rapidly.⁷³ The World Health Organization (WHO) has created a data repository called the COVID-19 Technology Access Pool (C-TAP), which aims to compile and share COVID-19 related knowledge, intellectual property, and data. TransCelerate, a non-profit founded by pharmaceutical companies to share control-arm data, has also created a platform to rapidly share patient-level data from experimental arms of COVID-19 related trials.⁷⁴

We have also seen impressive global collaboration in the area of clinical trials. WHO’s SOLIDARITY trial is a global platform trial (see Recommendation 5) to rapidly and efficiently test therapies for the treatment of COVID-19 across the globe. A number of interventions are being compared against standard of care, with more than 100 countries involved or interested in taking part (as of July 2020). The global collaboration and the emphasis on equity is vital.⁷⁵

Recommendation 6: Create frameworks for the use of observational data

Data gathered outside of research, known as observational data, can help to bridge the gap between clinical trials and clinical practice. When combined with insights from clinical trials, observational data can help assess the true impact of treatments in wider populations and under real-world conditions. These insights provide a greater understanding of who may benefit from a treatment, identify new applications, and track long-term effects.⁷⁶ This can also help build necessary evidence for the approval of a treatment (see [Case study 4](#)).

Observational data is already being used to replace a placebo control in some mid-stage studies. These methods can be applied to cancers with few treatment options and where immunotherapy holds great promise, and where it can be challenging or unethical to enroll patients onto control arms.^{77,78}

Fully realizing the potential of observational data will require government support. This can include co-operative engagement of regulatory authorities to create consistent frameworks and standards for the best use of data, which can flexibly evolve with changing needs.⁷⁹ Examples include the German regulatory authority, the Paul Ehrlich Institute and professional scientific societies such as the American Society of Clinical Oncology (ASCO) and the European Society for Medical Oncology (ESMO).⁸⁰ These organizations ensure data quality, allow timely access without prohibitive cost, protect confidentiality, and homogenize data collection across countries to enable comparisons. They are clear about the benefits of these data sets to reassure the public, and develop real-time feedback to inform policy and clinical decision-making.



CASE STUDY 4. THE CANCER DRUGS FUND (CDF) IN THE UK

Earlier access to promising treatments

The UK has a single payer system that places importance on equity of access across its population and uses cost-effectiveness as part of its decision-making process. The National Institute for Health and Care Excellence (NICE) decides whether most new drugs will be reimbursed under the National Health Service (NHS) in England and Wales, and the conditions for use.⁸¹ To be recommended for reimbursement, a new drug must achieve a specific threshold for cost-effectiveness. Assessing this involves considering the incremental impact on overall survival and quality of life compared to current treatments. This is at odds with the trend to approve more immunotherapies through early access mechanisms based on mid-stage trials that do not measure, or have not yet achieved, overall survival.

The UK has created the CDF to provide an interim access solution before final NICE approval.⁸² Where uncertainty around effectiveness prevents the drug from demonstrating cost-effectiveness, NICE can refer the drug to the CDF while waiting for further data on efficacy to emerge.⁸³

This enables reimbursement through a separate fund for a specified amount of time. After that time, the benefits and cost-effectiveness of the therapy are reassessed. NICE includes more mature information from clinical trials, observational data or experience within the NHS. This is used to decide whether to move the therapy to routine commissioning. This approach encourages biopharma companies to work with the NHS to complete their post-marketing commitments in a reasonable timeframe, while providing broad and early access to potentially innovative therapies.













Pillar 4. Patient access

Recommendation 7: Enable experimentation with novel pricing and payment mechanisms

To mitigate rising healthcare costs, many stakeholders are exploring novel reimbursement mechanisms. Traditionally, healthcare has been priced under a fee-for-service concept. For drug prices, payment is based on the number of pills or vials used.⁸⁴ There are many types of novel pricing and payment mechanisms that aim to move away from this model (see [Figure 10](#)). Each has its own benefits, disadvantages, and implementation requirements, and governments need to understand the nuances and implications of each. (See [WISH 2015 Report on Delivering Affordable Cancer Care](#) for further information.)

See [WISH 2015 Delivering Affordable Cancer Care Report](#), page 29.

Figure 10. Types of novel pricing and payment mechanisms

				
Name	How it works	Example	Region	Description of example
Outcomes-based payments/pay for performance	Manufacturer provides rebates, refunds or price adjustments if the medicine fails to meet pre-agreed outcome targets at the individual patient level	Retigabine (ezogabine), an epilepsy treatment	France 	Payment is dependent on the length of response
Risk sharing	Manufacturers reimburse a proportion of the cost of the medicine if outcomes are not achieved	Sacubitril/valsartan (Entresto), a combination heart failure drug	US 	Pricing is tied to the ability of Entresto to reduce hospitalizations in heart failure patients
Cost-sharing arrangement	Price reduction for initial treatment cycles until it is clear whether a patient is responding to the medicine	Sorafenib (Nexavar), a treatment for primary kidney cancer	Italy 	50% discount for the first two months, reimbursed if response continues
Price cap/floor	Maximum spend either per patient or per year is negotiated with a payer	Ranibizumab (Lucentis), an antibody treatment for age-related vision loss	Germany 	Agreement to cover costs in excess of an annual cap, with the Pharma company taking on the risk for more prescriptions or additional dosing
Tenders	Competitive bidding for access to reimbursement	Sintilimab (Tyvyt), a checkpoint inhibitor drug used to treat Hodgkin lymphoma	China 	Bidding for access to a market instead of relying on only cost effectiveness

We recommend that governments work with biopharma companies to test different payment mechanisms. This is the only way to learn what works in each unique ecosystem, and it is important to involve all stakeholders in discussions. This will likely be an iterative process and requires flexibility from all parties as new challenges are identified. Philanthropy can also play a role.⁸⁵

One novel pricing mechanism is outcomes-based payments, where the payer is only responsible for paying when the therapy works.⁸⁶ This means that parties must agree on what ‘works’ means: for how long and how well must a treatment work? They must also agree on how to measure whether a therapy is working and who is responsible for tracking its progress. Patients do not always stay in the same place during treatment, so parties must agree on what to do if a patient moves in or out of their system.

Overcoming these hurdles requires governments to partner with other stakeholders to build the right infrastructure.⁸⁷ For example, much of the data required is not already routinely collected within a healthcare system. Governments can put mechanisms in place to track outcomes at the patient level, enabling outcomes-based payments. Building the right mechanisms is an important step toward the vision of paying for outcomes instead of doses.



CASE STUDY 5. VORETIGENE NEPARVOVEC (LUXTURNA) GENE THERAPY TREATMENT

Addressing the risks of high-cost treatments

Luxturna is a gene therapy that treats a rare form of blindness and can be curative for many.⁸⁸ Luxturna requires only a single treatment over the patient's lifetime. At a price of \$850,000 per patient, it represents significant cost challenges to the healthcare system. The price may be difficult to justify when it is unclear if an individual will benefit or not. In addition, the high, one-time cost is challenging for health systems to manage and presents a risk to providers when payment comes through reimbursement from insurers. To mitigate these issues, Spark – the biotech firm that makes Luxturna – offered three different payment programs:⁸⁹

- 1.** An outcomes-based pricing model. Payers are responsible for paying the full cost up-front. If the patient does not benefit, Spark will provide rebates based on outcomes at 30 days, 90 days, and 30 months.
- 2.** An 'installment plan' offered to patients who have insurance through the government. In the US, this is the Centers for Medicare & Medicaid Services. For these patients, Spark spreads the price of the drug over several years.
- 3.** Spark sells Luxturna directly to the commercial payer or specialty pharmacy. This way the provider does not have to pay for the drug up-front, thereby reducing their financial risk.

Recommendation 8: Develop a national health strategy for immunotherapies

Given the challenges in developing and delivering innovative immunotherapies to broad populations, it is important for each country to create a national strategy. This should consider what is most important, given the conditions within the country, including disease prevalence and the current state of infrastructure, and identifying where there are major gaps in capacity, knowledge and resources.

By implementing a well-thought-out framework, each country can focus their resources on the initiatives that will make the largest difference to their population. Strategies should include a plan for developing the infrastructure required to deliver on the priorities for immunotherapies.

Broadly, a robust developmental framework should (but is not limited to):



Identify

- disease trends.
- technological and workforce capability and capacity requirements.



Develop

- standards for the provision of immunotherapy.
- core national guidelines and patient information that can be adapted locally.
- research capability and capacity by identifying international research collaborations and mentorship.



Deliver

- core training and education programs for nurses, doctors and pharmacists working in oncology.
- education for primary care and urgent care settings.



CASE STUDY 6. A STRATEGIC FRAMEWORK TO IMPLEMENT ADVANCED IMMUNOTHERAPIES

Qatar

In 2011 Qatar launched *The National Cancer Strategy, A Path to Excellence*, a five-year plan designed around the patient pathway to transform cancer care in Qatar.⁹⁰ A companion document, *The Qatar National Cancer Research Strategy, 2012*, set out a framework to develop world-class basic, clinical, and translational cancer research while developing national capacity and capability.⁹¹

The complementary strategy delivered excellent cancer outcomes in a compact timeframe. It provided a clinical environment that could accommodate and support advances in cancer immunotherapies. The parallel development of a supportive research infrastructure permitted basic and translational immunological research development.

The establishment of formalized multidisciplinary teams, along with external expertise, enabled internal clinical capability development, particularly in molecular disease characterization and diagnostics, while collaborations with international partners simultaneously increased the research capability and clinical service development.

The establishment of the Qatar Cancer Research Partnership ensured that collaborations across academic partners could maximize the available skills, technology and resources while avoiding duplication. It also ensured that cancer research focused on areas that would have the biggest impact across Qatar, including immunology.⁹²

This clear, stepped, developmental approach could be adapted to deliver a similar framework for establishing core immunology services for LMICs.

Conclusion

Immunotherapies hold immense promise to benefit patients who suffer from an array of different diseases. Governments must make meaningful policy changes to catalyze discovery, development and delivery of immunotherapy globally to maximize the potential of these transformative treatments.

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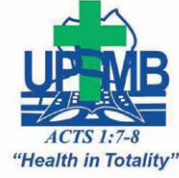


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