LLOYD'S

Emerging Risks Report 2018
Understanding Risk

A new lease of life
Understanding the risks of synthetic biology

Imperial College London Consultants

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Executive summary

Despite the huge number and diversity of naturally-occurring living things in the world today, they represent only a tiny fraction of the organisms that could theoretically exist. Over the past few years scientists have been trying to develop altered or wholly new organisms using biotechnology for a range of applications, including disease prevention and treatment, fuel, chemical production, crop resistance and even space exploration.

In recent years this work has increasingly been referred to as synthetic biology, although there is a number of different definitions in common usage. Lloyd's first explored the topic in 2009 in its report: 'Synthetic biology: influencing development'. This 2009 report concluded that: "Synthetic biology is in its infancy and the first commercial applications are likely to appear as incremental to traditional genetic modification… Depending on the pace of development we might expect to see fully commercialised outputs from synthetic biologists in full production within the next 10 years."

Today, there are a number of commercial synthetic biology products in the market but development is limited by immature technology, processes, breadth of activity due to the number of potential applications and regulatory uncertainty. However this is no different to any other emerging technology at this point in its development lifecycle. Many of the technical solutions needed for the successful development and deployment of synthetic biology are now available but they tend to be discipline specific, and therefore are not often reusable in other areas.

As the technology continues to develop, it is important for insurers to consider the extent to which they wish to be, or may already be, exposed to potential systemic risks associated with synthetic biology. To assist the Lloyd's market, this report introduces the subject of synthetic biology, describes some the new developments and applications since 2009 and sufaces the potential risks and opportunities that exist now and in the future.

Developments since 2009

The market has continued to grow, with estimates of $1.1bn in 2010 (OECD, 2011), $5.2bn in 2015 (Singh, 2014), to forecasts of $38.7bn by 2020 (Sumant, 2016). A number of new established commercial entities have emerged out of the start-up and spinout companies that were formed off the back of early research discoveries. This first wave of companies have seen a significant increase in capital support. Industry research estimated that equity funding to private synthetic biology companies topped $1bn in 2016, with some start-ups seeing funding rounds of more than $100m (CB Insights, 2017).

The university synthetic biology research sector also remains strong and government investment in academic research has continued, although there are signs this is starting to plateau. Governments are also investing in regional centres of excellence.

In parallel, other industrial sectors have begun to adopt synthetic biology technologies. Currently, the main products on the wider market are those that enable synthetic biology research (i.e. reagents, equipment, and tools that are used to develop new synthetic organisms).

There are also companies using synthetic biology to establish biosynthetic platforms to manufacture different types of products. These operate in a variety of markets including healthcare, chemicals, biofuels synthesis, agriculture, food, materials, textiles and other consumer products. At the other end of the scale, reduced costs and commercialisation are lowering the barriers to entry, so 'DIY-bio' is much easier to participate in than it has been in the past.

Global resource scarcity and sustainability continue to drive innovation in synthetic biology, made possible by technological developments in the field. Organisations such as the Bill & Melinda Gates Foundation are funding synthetic biology research to tackle societal problems such as disease. Technological innovation and the bio economy are now a key part of the international strategy to overcome global challenges.

In the commercial markets, biomedical companies are using synthetic biology to secure product supply chains and new applications in frontier areas such as space exploration are also being developed.

In general, regulatory frameworks have not changed substantially since 2009. However, there is increasing awareness that synthetic biology can create products that do not conform to standard regulatory paths and there are ongoing discussions about the need to change regulations for these products.

One barrier to this work is the fact that none of the commonly used definitions of synthetic biology are rigorous, and it is not possible to draw a clear distinction between synthetic biology and biotechnology in a way which is agreed by academic and industrial practitioners, or which could underpin a legal distinction.

Key findings

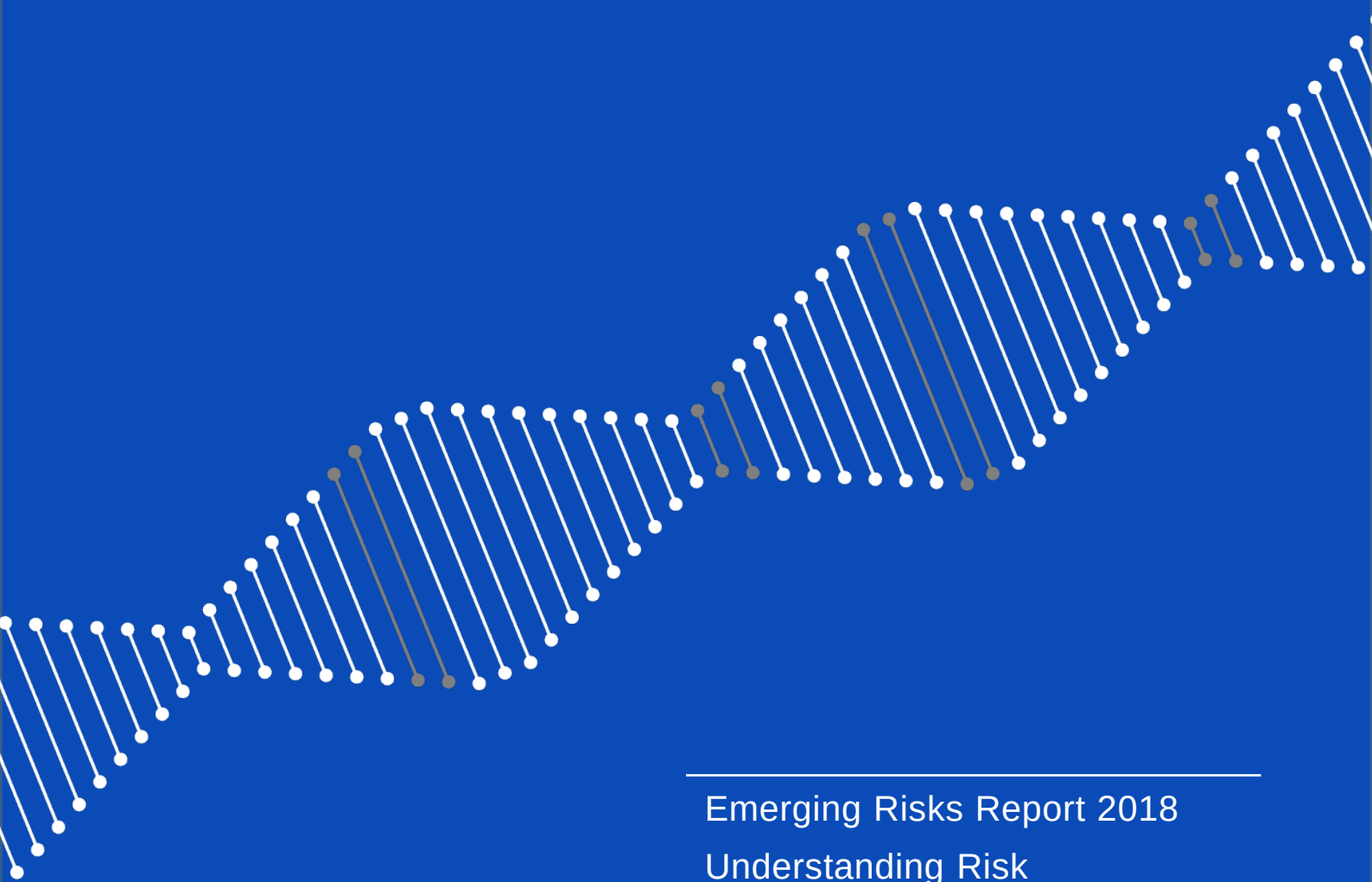
The report contains a number of key findings on the potential risks associated with synthetic biology:

- Risks associated with synthetic biology research include accidental release of biological organisms (bioerror), construction of biological weapons (bioterror), and the unintended consequences of biological research. The likelihood of bioerror and bioterror are low relative to unintended consequences. At present there is a high degree of uncertainty about the types of things that can go wrong, let alone the probability of these risks occurring.
- Technology and automation is reducing the amount of skill, knowledge and time needed to create new synthetic biology applications. This trend raises concerns around traditional risk management in the field, and all businesses should be aware that synthetic biology applications may enter their sectors without explicit notification. This may already have happened.
- Currently, synthetic biology products are regulated by type without regard for the way they were developed. For example, medicinal products are regulated as medicines, food products according to food regulations and so forth, and the associated laws and regulatory approval processes apply. There is currently no distinction between products made using synthetic biology and those made with other types of biotechnology.
- Increasingly sophisticated synthetic biology technologies are now being developed with characteristics or consequences that fall outside the scope of conventional assumptions. This requires careful consideration to ensure risks are being properly assessed.
- More debate and discussion about synthetic biology is required. Focus groups should be held, involving the public (including a diversity of views), the biotech industry, security advisors, developing countries, governments/regulators, insurers and research scientists, to ensure all views on synthetic biology are listened to and understood. Transparency and greater public awareness will remain of increasing importance as regulation develops and new synthetic biology applications make their way to market.

Next steps for insurers

- Synthetic biology enables more modifications to organisims and on a larger scale than was previously possible. This means there is a higher probability that the boundaries of what is currently achievable will be exceeded. Insurers should consider using scenario and counterfactual analyses to assess the impacts of potential disruptive events when evaluating risks.
- The risk profile of synthetic biology is changing as it develops. Commercialisation and digitalisation of research are enabling faster development and there are new developments on the horizon such as gene drives (*see p22*) that will push the field further still. Insurers should ensure they include appropriate limits and keep a close watch on developments as bio-innovation is adopted in more and more sectors.
- Insurers and manufacturers could work together to support the responsible development of new synthetic biology technologies.
- Insurers should consider developing existing and new risk transfer solutions to underwrite the synthetic biology sector. While biomedical and life sciences insurance may act as a starting point for those wishing to enter this market, new insurance solutions will need to be developed to support research and development and protect consumers.
- Insurers and brokers must discuss the potential risks openly with companies. Health and safety, product liability and third-party liability risks will all need to be assessed. Transparency and collaboration are going to be important going forwards (Kerr, 2016).

Introduction



1. Introduction

Synthetic biology is variously described or treated as the application of engineering principles to genetic modification; or a generic set of tools, technologies and approaches (essentially services) for achieving biotechnology objectives; or as simply a synonym for biotechnology, with no meaningful difference between the two.

While the main commercial developments of synthetic biology are in traditional areas of biology, such as pharmaceutical development, there are more and more examples emerging out of the lab and into the real world. Therefore, it is useful to see how synthetic biology has developed to understand:

- Common definitions
- What activities and developments fall into this sector
- Why it is gaining increasing interest, and
- Why all classes within the insurance sector should keep a watching brief

Common definitions

Some of the confusion around the boundaries between synthetic biology and other applied biology fields comes from the fact that scientists have been using approaches related to synthetic biology for years, including recombinant DNA technology, metabolic engineering and directed evolution.

None of the commonly-used definitions is rigorous, and it is not possible to draw a clear distinction between synthetic biology and biotechnology that would be widely agreed between academic and industrial practitioners, let alone one sufficiently unambiguous that it could be used to underpin a legal distinction.

Synthetic biology is the design and construction of new biological parts, devices, and systems, and the re-design of existing, natural biological systems for useful purposes.

- Nature *(2018)*

Synthetic biology is an emerging area of research that can broadly be described as the design and construction of novel artificial biological pathways, organisms or devices, or the redesign of existing natural biological systems.

- The Royal Society *(2007)*

Synthetic biology is the engineering of biology: the synthesis of complex, biologically based (or inspired) systems which display functions that do not exist in nature. This engineering perspective may be applied at all levels of the hierarchy of biological structures – from individual molecules to whole cells, tissues and organisms. In essence, synthetic biology will enable the design of 'biological systems' in a rational and systematic way.

- High-level Expert Group, European Commission *(2005)*

Since the previous report in 2009, the university research sector in synthetic biology remains strong and government investments in academic research have continued, although there are some signs this is starting to plateau.

In parallel, existing industries have begun to adopt synthetic biology technologies, albeit at a slower pace. Currently, the main products on the market are those that enable synthetic biology research (i.e. reagents, equipment, and tools that are used to develop new synthetic organisms).

There has also been a wave of new start-up and spinout companies based on early research discoveries. The first of these are beginning to enter the marketplace and they have seen a significant increase in development capital in the last few years.

What is clear is that synthetic biology is a field with high potential for growth, and widespread cross-cutting applications. There are also important challenges and opportunities that have shaped its development, and that will need to be overcome for it to progress.

Factors driving momentum

- New technologies: are lowering barriers of entry and could be coupled with further automation to optimise processes. The first human genome took ten years and $3bn to achieve. Today it costs $1k.

  Scalability and economies of scale have opened up development to start-ups and enabled DIY-bio where users are not restricted by government or academic funding. While this encourages commercialisation, it also offers capabilities to malicious actors.
- Finance: industry research estimated that equity funding to private synthetic biology companies topped $1bn in 2016, which is helping drive market forecasts to an estimate of close to $40bn by 2020.
- Political awareness: The Sustainable Development Goals are one example of the recognition by governments to consider sustainability and innovation to answer global challenges. This is also leading to the growth of centres of excellence where developments are clustering.
- Diverse and pressing needs: from securing global supply chains to responding to the impacts of climate change, synthetic biology is a potential solution and enabler of many topics, in limitless sectors.
- Consumer empowerment: information, equipment, and skill levels required for entry are more accessible, and in an increasingly digital and connected world more and more applications are possible.
- Standards and frameworks: the increasing drive for more information to be made accessible and the rise of open source frameworks, conversations around intellectual property, and the development of legal tools to do so are also being seen in the bio-world.

1.1 The development of bioscience

The properties of living things are controlled by information stored within them and inherited from one generation to the next. Understanding of this principle developed gradually over centuries and early forms of this understanding have underpinned selective breeding since ancient times.

There is a very long history of living things being used for critically-important purposes: from crops and farm animals providing enough food to support the development of agricultural societies, population expansion and ultimately industrial societies; microbial fermentations to produce bread, alcoholic drinks and dairy products; medicinal compounds from plants; and the microbial treatment of wastewater to support sanitation that enabled the development of large towns and cities.

To understand the current state of knowledge and applications it is useful to know how this sector has come about, and where there is still large potential for developments to occur.

1.1.1 Natural selection

The beneficial properties and limitations of natural organisms arise from natural history: living things compete for limited food, water, space and opportunity to reproduce. Competitive success varies among individuals in a population, and those better-suited to their environment have more successful offspring and descendants. This is the core evolutionary principle known as natural selection, or ‘survival of the fittest’. Today’s plants, animals and microorganisms have been gradually shaped by this evolutionary pressure for billions of years.

1.1.2 Artificial selection

Natural selection and selective breeding can both cause changes in animals and plants. The difference between the two is that natural selection happens naturally, but selective breeding only occurs when humans intervene. For this reason selective breeding is sometimes called artificial selection (Diamond, 2002).

Humans have been breeding animals and plants with the most desirable characteristics for thousands of years. For example, the fattest pigs and the cows with the highest yield of milk were chosen for breeding. Fruits and vegetables were carefully selected and those that have

grown fuller than others were used as the prime source of seeds for the following harvest.

Over many generations, selected properties can be successfully improved. However, the process is slow and is limited to acting upon variation which initially arises naturally. Furthermore, there is little control over other genetic changes occurring in parallel and indeed the intended changes in some properties may be linked to defects in others, as observed in health issues in various breeds of dogs.

1.1.3 Biotechnology

Our ability to understand, alter and improve living things changed dramatically in the twentieth century as scientific advances revealed how the information which controls traits is stored inside cells using DNA (*see Box 1, p11*), and technological advances provided the ability to 'read' and 'write' that information. Biological science and medicine were transformed, and a complex new era of rational genetic engineering began, no longer limited to selective breeding of traits which arise by chance.

Reading DNA and creating biocode repositories

Reading DNA (known as DNA sequencing) has been possible since the 1970s, but for many years was limited to reading short stretches of a few hundred DNA 'letters' (bases) at a time. Recently, especially in the last decade, it has become routine to use new technologies to quickly and cheaply read all the millions of bases of DNA information of any organism. There has been explosive growth in the amount of DNA sequence information in repositories, which represents a vast resource available to synthetic biology.

Writing DNA: from cut-and-paste to design-by-AI

In the 1970s, at the same time as reading DNA first became possible, early approaches to writing DNA also emerged, known as recombinant DNA technology, which involved combining one piece of DNA with another, often from two different organisms.

At first, these were relatively crude ‘cut-and-paste’ procedures, like tearing parts of pages from a book, or copying fragments of computer code starting or ending mid-line. Although limited, recombinant DNA technology was powerful, allowing breakthroughs such as the 1978 development of a microbe which produced the insulin required by diabetics, replacing the traditional supply from pig pancreas (Goeddel et al., 1979).

Later, the approaches became more precise, as the development of PCR (polymerase chain reaction) technology made it easier to copy and combine only chosen parts of DNA sequences (like whole paragraphs from a book, or whole modules of computer code), and to edit them in the process.

Later still it became possible and then routine and cheap to obtain any DNA sequence from scratch, essentially without design limitations, thanks to the development, commercialisation and commoditisation of chemical DNA synthesis.

It is now equally easy to obtain a DNA sequence whether it is an exact replica of a sequence found in nature, or an edited version of a natural sequence, or from an extinct organism, or an entirely new sequence which has never existed before. Many consider commercialisation of DNA synthesis to be a key milestone in the development of synthetic biology.

Finally, academic researchers and synthetic biology companies are now exploiting the flexibility of DNA synthesis and advances in AI to design and optimise DNA sequences using computer-aided design and machine learning algorithms, reflecting the ongoing development of synthetic biology beyond the limitations of manual design and human intuition and into an information science.

Inserting the code into the program

There is a variety of ways to insert recombinant DNA into cells, with different methods required for different types of organisms, from simply mixing cells with DNA to firing DNA into plant cells using gas-propelled projectiles. The key constraints are that DNA must physically enter cells and at least some cells in a population must survive the process.

While inserting DNA into cells is simple and routine for some types of organisms, for others it is more difficult, or has not yet succeeded. For many types of organisms, DNA insertion has not even been attempted, which adds to the uncertainty around risk factors that are discussed later in this report.

Besides physical transfer of recombinant DNA into cells, further steps may be involved in achieving particular types of genetic modification, such as deletion of existing genes or stable integration of new DNA with the existing DNA in the cell, the genome (*see Box 1, p11*).

A wide variety of genetic modification approaches of increasing sophistication have been developed over many years. Among the most recent and widely known are the CRISPR (Clustered Regularly Interspaced Short Palindromic Repeats) technologies, which can be considered a key enabling development as they allow precise genome editing in more complex organisms where it had previously proven difficult.

This includes some higher plants and animals – including humans – and has opened the door to a new phase of development potential.

Key enabler: New technologies

CRISPR/Cas9 is a system found in bacteria and involved in immune defence. Bacteria use CRISPR/Cas9 to cut up the DNA of invading bacterial viruses. Researchers have used this functionality to change any chosen letter(s) in an organism's DNA code.

The CRISPR part of the name comes from repeat DNA sequences that were part of a complex system telling the scissors which part of the DNA to cut.

At a very high level the process can be simplified to 'find, cut and then paste'. This is done by Cas9, which is the technical name for the virus-destroying 'scissors' that evolved in bacteria (Crossley, 2018). It gives scientists the ability to delete or swap out pieces of a genome in order to change or eliminate traits.

This gives the ability to replace decades of selected breeding in one step. Although it is important to know that it is far easier to carry out selective breeding than CRISPR, and that skill, knowledge, and equipment are all key requirements.

CRISPR genome editing is allowing users to create cell and animal models that can be used to accelerate research into diseases such as cancer and mental illness.

The technology is lowering barriers to entry and could be coupled with further automation to optimise genetic engineering.

While this opens up the potential further developments, it also offers the same potential to malicious actors to engineer or edit biological agents or toxins (Dunlap and Pauwels, 2017).

1.1.4 Synthetic biology

The developments in gene modification technologies as described above, have facilitated the rise and continued evolution of synthetic biology.

One of the first examples of the application of synthetic biology was the production of the antimalarial therapy artemisinin in yeast by introducing additional genes encoding the biosynthesis of artemisinic acid from natural fatty acid precursors.

Although artemisinin can be extracted from a natural plant source, wormwood (*Artemisia annua*), this is a commercial crop and there were problems with cyclical over- and undersupply based on the changes in demand for the plant from year-to-year. This led to large fluctuations in prices and influenced farmers to switch to other more financially reliable crops.

The ability to synthesise the drug in yeast was considered and developed with the aim of allowing for a constant supply, which would enable the price of the drug to stabilise and decrease the cost per dose (*see Box 2, p12*).

1.2 Recent developments

Increasingly ambitious synthetic biology research has pushed the boundaries of techniques for DNA synthesis and for insertion of recombinant DNA into cells. Researchers are now able to synthesise individual genes, through to entire chromosomes, or even entire genomes. These endeavours remain difficult and time-consuming, but great progress and successes have been demonstrated since the 2009 report.

The area of synthetic genomes is in its infancy, but has huge biotechnological potential to develop Genetically Modified Organisms (GMOs) without the constraints of natural organisms, and with new types of features which function at the genome scale. The defining aspect is that these features could not be achieved through conventional small-scale genetic modifications.

Just as advances in chemical synthesis created new drugs, industrial materials and energy sources in the 19th and 20th centuries, new biological molecules and living organisms have the potential to do the same now. For example, synthetic biology has large potential is managing and securing global supply chains.

Researchers around the world are exploiting synthetic biology in its applied form - engineering biology - to make new products, services and tools in response to societal challenges and opportunities.

There has also been a drive towards founding new commercial entities such as start-up and spinout companies based on early academic research discoveries. The first wave of these is beginning to enter the marketplace and there has been significant increase in such investments in the last few years. This has been facilitated through the digitalisation of biology, and the development of tools and knowledge, and is described in Section 2 (*see p14-23*).

Box 1: Nature's information systems

DNA (deoxyribonucleic acid) is the information storage medium within the cells of all living things.

DNA is physically composed of many units of four different types of molecular 'letters' (bases) of DNA (A, T, G and C) chemically linked together in a linear chain to form long DNA molecules. Information is embodied by the order (sequence) in which these letters occur in a DNA molecule. This is similar to the way information is embodied by the order of 1's and 0's in computer data storage.

Genes are the key organisational units of DNA sequences. Each gene contains precise, complete instructions for how to synthesise a specific type of molecule with a particular structure and function, using a simple information encoding system that is essentially common to all organisms and is well understood.

Genes also contain instructions for when and where the specified molecule should be made by a cell, and in what quantity. These 'regulatory' instructions are less straightforward, as they are encoded in a variety of different ways, which are less consistent between different organisms.

In DNA, there is no truly empty or blank storage space, as every position is occupied (by an A, T, G or C). Even the poorly-understood sequences between genes, historically referred to a 'junk DNA', have been found to have functional roles.

Organisms typically contain thousands of genes, each of which can be hundreds, thousands or tens of thousands of bases long. There are many genes on each long DNA molecule, which is physically packaged to form a dense structure called a chromosome to save space.

The entirety of an organism's genetic material, including all its genes and chromosomes, is known as its genome, and usually contains millions of 'letters' (bases) of DNA. Every cell of an organism (with special exceptions) contains a complete copy of the whole genome, but only a particular subset of genes is needed in any given type of cell.

Genes can also influence one another, and can cause cells to influence one another, building up complex networks of interactions that ultimately give rise to complex tissues, organs and whole organisms.

Cells are constantly 'reading' (transcribing) many genes in parallel, but do not normally 'write' DNA. In nature, DNA is essentially a 'read-only' information storage medium. DNA is copied very accurately between generations when cells divide and when organisms reproduce. In nature, DNA sequences change only very slowly by evolution based on rare copying errors (mutations).

This system for how information is stored, inherited and acted upon by cells is entirely natural, but can now be used for the storage, inheritance and action of modified or entirely artificial, synthetic sequences designed by humans.

Box 2: Artemisinin anti-malarial drug

One of the first examples of the application of synthetic biology was the production of the anti-malarial therapy artemisin. Artemisinin is a natural product that can be processed from the wormwood bush *Artemisia annua*.

Use of the plant to treat malaria is described in ancient Chinese medicine and it remains so effective that it is still used in modern times as part of combination therapies.

Artemisinin is obtained by extracting it from the plant on a commercial basis, but there are difficulties maintaining a constant and sufficient supply. Sweet wormwood requires up to ten months from sowing to harvest, and its yield and quality vary depending on weather, region, growing practices, and market conditions. These issues lead to fluctuating prices and can influence farmers, predominately based in China and Vietnam, to switch to other more reliable crops. Farming continues to contribute to the global supply. These factors add to the challenges of countries looking to manage and reduce their malaria risk, which in turn puts a strain on their ability to plan and execute responses.

Applying synthetic biology

Scientists have been able to utilise synthetic biology to introduce additional genes that instruct yeast to produce artemisinic acid from natural fatty acid precursors (reviewed in Paddon and Keasling, 2014). By synthesising the drug to enable a reliable supply, the project sponsors aimed to stabilise costs, with the end goal of decreasing the cost per dose.

The synthetic yeast strains are now being used for the industrial manufacture of artemisinic acid in partnership with Sanofi, who have agreed to manufacture and sell the drug at cost. Initially, Sanofi have a capacity to produce 60 tonnes per year. They were also prequalified by the World Health Organisation, who recommended Artemisinin-Based Combination therapy (ACT) as the standard treatment for malaria worldwide in 2001 (Bollack, Martel and Pantjushenko, 2014).

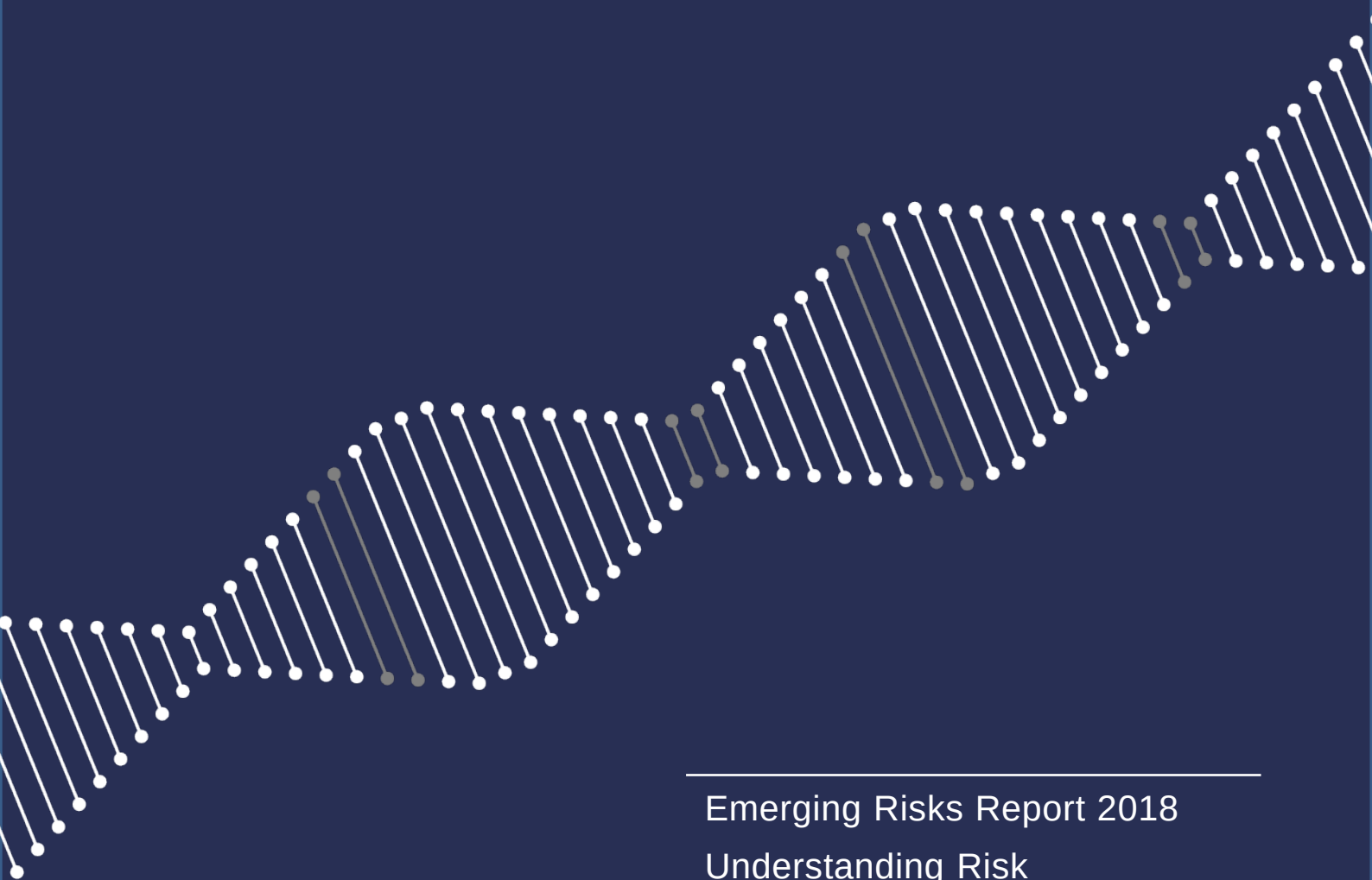
Development challenges and risk insight

The development of yeast strains capable of producing artemisinic acid took 13 years to develop and involved ~150 full-time equivalents (Keasling, 2014) and $43m from the Gates Foundation under their goal to tackle critical societal issues (Time, 2007). During refinement The National Research Council Canada Plant Biotechnology Institute also gave royalty-free access to a gene it discovered to make the process even more economically feasible.

The project required iterative design to increase yields to a level where they could be considered sufficient for industrial manufacturing. Some of the methods in the project have also been perceived as closer to traditional biotechnology than synthetic biology. This raises a factor to be aware of given how closely linked developments are, and how end products might be classified from a regulatory perspective. Currently there is no distinction (*See Section 5, p43*).

The end result is volumes and concentrations of the product (titres > 25 g/L) that are sufficient to support industrial manufacturing. It is hoped that the lessons learned can be applied to the synthesis of other drugs to reduce the time needed from concept to development. Researchers from the lab are currently using the same technology to produce biofuels and bioproducts from plant matter biomass (Paddon and Keasling, 2014).

Current applications



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2. Current applications

Since the 2009 report, the application of synthetic biology has continued to grow.

There are six sectors where innovation is consolidating and where applications have been either envisioned, are in development, or are in the process of being commercialised:

1. Healthcare
2. Nutrition
3. Manufacturing
4. Energy
5. Consumer products
6. Services enabling research and development

While instances might be specific to one sector, there are also companies using synthetic biology methods to establish biosynthetic platforms to manufacture a number of different types of products.

These operate in a variety of markets including healthcare, chemicals and biofuels synthesis, agriculture and food, materials and textiles, and other consumer products.

There is real potential for products to be out in the market for years, with the worst-case, extreme loss scenario being the next asbestosis. While this is an extreme example, Lloyd's minimum standards require there to be formal processes to communicate material uncertainty to nominated committees and the board.

Insurers and brokers will need to quickly develop understanding of the risks and opportunities of this new sector (Welfare and Clift, 2017).

Risk insight

While it is not true for all instances, there are specific types of gene modification where products created through synthetic biology or gene editing technology are considered distinct from GMOs and do not need to confirm to the labelling requirements manufactures must adhere to in that area.

While this distinction is likely to cover off legislatory semantics in the short-terms, further regulatory developments are expected to be needed to deal with the unique aspects of synthetic biology.

Companies must be open to discussing potential risks with brokers and carriers – transparency and collaboration are going to be key going forwards (Kerr, 2016).

Health and safety, product liability and third-party liability risks will all need to be assessed. While biomedical insurance may act as a starting point for those wishing to enter this space, new insurance solutions will need to be developed to secure developments and protect consumers.

See *Section 5, p43* for further details.

2.1 Healthcare

To date, the most developed examples of market penetration occur in the healthcare industry for two main reasons:

- The applications lend themselves to biological solutions, and are extensions of well-developed markets.
- The healthcare/medical sector has high-value added products, which make the development of bio-based processes economically feasible.
- In the healthcare space, products include engineered bacterial therapies (Synlogic, Prokarium), cell and gene therapies (Poseida Therapeutics), nucleic acid therapies (Moderna Therapeutics), and proteins and small molecules (GlaxoSmithKline, Teewinot Life Sciences, Sanofi, (*see Box 2, p12*)).
- At present the number of companies manufacturing healthcare products is larger than those manufacturing other classes of products, likely reflecting the favourable economics of manufacturing such high-value products. Potential future developments include microbiome management, diagnostics, regenerative medicine and cognitive healthcare and genome editing.
- While widespread public acceptance across all applications may still be far off, public acceptance tends to be unevenly distributed with greater acceptance in areas like disease treatment (Kinder and Robbins, 2018).

Biologics

Biologics (biological therapeutics) including antibodies, cell therapies, and stem cell therapies. Under development by biotech companies and major pharmaceutical companies.

Stage of development: Trial and commercial

Outlook: Markets developing subject to demonstration of safety

Experimental approaches

Experimental new approaches including genome editing for health and disease, tissue and organ-scale regenerative medicine, therapies using viruses or bacteria. Under research, with some clinical trials.

Stage of development: Lab and trial

Outlook: Speculative, subject to societal acceptance

Pharmaceuticals

Pharmaceuticals similar to existing types of products, but manufactured more reliably, cheaply or with modifications, such as the anti-malarial drug Artemisinin produced by Amyris and Sanofi.

Stage of development: Trial and commercial

Outlook: Markets mature

Diagnostics

Diagnostics which are cheap and robust to deploy outside laboratory environments and offer rapid development and detection of new and emerging threats.

Stage of development: Lab, trial, and commercial

Outlook: Markets established, but new applications emerging

2.2 Nutrition

Global challenges of resources scarcity, growing populations with changing diets, and increasing awareness of supply chain fragility around food system shocks, have led of continued interest and growth in this sector.

Potential uses have been identified in food production processes, developing new products that can be grown more sustainably and with better food yield, and around pest-control practices in the management and reduction of invasive species (Kinder and Robbins, 2018).

As well as the more obvious applications, synthetic biology is being considered and tested by stakeholders to enable developments in other sectors.

For example, NASA is developing on-demand nutrients through hydratable, single-use packets that contain microbes engineered to produce target nutrients for human consumption during deep space travel (Mahoney, 2017; Huynh, 2017).

One instance they will be looking to trial is also designed to reduce a defined and recognised health risk, and is currently working towards testing on the ground:

"The first demonstrations of synthetic biology nutrients will employ yeast engineered to produce Zeaxanthin when activated. Zeaxanthin is a carotenoid, which is an important antioxidant for ocular health, a known risk for astronauts who spend extended periods of time in space."
– NASA (Mahoney, 2017)

A review of food-related scenarios carried out in the 2017 'Stochastic modelling of liability accumulation risk' study (Lloyd's and Arium, 2017), demonstrated that while there have been few recent large historic food-related events in the developed world, there appears to be potential for significant future losses (*see Box 3, overleaf*).

While casualty risks accumulate in a variety of different ways and may affect many lines of business, it remains important for insurers to approach casualty risk accumulation systematically.

Food sources

Food (human and animal), engineered crops and livestock, synthetic meat, algae as a primary food source.

Stage of development: Lab and trial

Outlook: Speculative, subject to societal acceptance

Food processing and production

Food processing enzymes, recombinantly produced enzymes used in food production, but not main constituent of food, e.g. Cakezyme by Novozymes.

Stage of development: Commercial

Outlook: Markets mature

Additives

Additives (flavours and fragrances), 'natural' routes to flavours and fragrances currently made by chemical synthesis, e.g. Evolva's yeast-based vanilla.

Stage of development: Lab, trial, and commercial

Outlook: Emerging area with good economic prospects

Box 3: Food-related scenarios in the 2017 ‘Stochastic modelling of liability accumulation risk’ study

– Near misses: In the Sudan 1 red-dye loss, products were recalled before reaching the consumer. The UK 2013 horsemeat scandal turned out to be mislabelled food rather than harmful food.

  Both “near miss” events demonstrate the cascading effect of ingredients through the supply chain and widespread distribution across national boundaries.

  Formal analysis of the events and asking counterfactual questions about these near-misses could help underwriters get significant additional insights into extreme losses and reduce future market surprises (Woo, 2016)

– Food-related losses in the less developed world: In 2008, a nitrogen-rich substance known as melamine was added to milk, particularly infant formula, affecting tens of thousands of infants in China.

  Melamine had sometimes been illegally added to food products to increase their apparent protein content and it is known to cause renal failure and kidney stones in humans and animals (International Risk Governance Council, 2010).

– Food-related losses in previous decades: In 1973, a fire-retardant chemical called polybrominated biphenyl (PBB) accidentally got mixed into livestock feed.

  The accident was not recognised until long after the bags had been shipped to feed mills and used in the production of feed for dairy cattle. Studies estimate 70-90% of people in Michigan had some exposure to PBB from eating contaminated milk, meat and eggs.

  The Michigan Department of Community Health (MDCH) says the “overwhelming majority of those who were exposed to PBB received very low levels”. However, some individuals had higher exposure (40 years after toxic mix-up, researchers continue to study Michiganders poisoned by PBB, 2014).

– Food-related emerging risks: There are a number of emerging risks related to food additives (e.g. phosphates and nitrate), to plasticisers used in food packaging (BPA), to other technology introduced into the food chain such as nutraceuticals and to changing society awareness such as the amount of sugar and salt in food.

Source: (Lloyd’s and Arium, 2017)

2.3 Manufacturing

Some of the reasons driving interest in this sector include manufacturing chemicals and compounds at a low cost with minimal environmental impact, being able to create new materials or reliably manufacture known elements at scale.

The chemical industry generates more than $5trn per annum and its wide array of products are incorporated into more than 95% of the world's manufactured goods (American Chemistry Council, 2018). The largest market segment is the provision of basic and intermediate chemicals such as ethylene, propylene, butanediol, and butadiene (Lammens et al., 2017).

The industry has many challenges, including rising prices, price volatility, availability and the overall sustainability of routes dependent upon petrochemicals. Cost-competitive renewable routes to these important building blocks are being actively sought by the chemical industry, and they are using synthetic biology to do this.

Another class of products are small molecules such as solvents, plastics, biofuels, and other industrial 'platform' chemicals. Many companies in this space produce both fuels and other chemicals in a biological analogy to the petroleum refinery where different products are made from different fractions of petroleum and the cost of fuels is offset by some of the other products which have higher value.

Some of the companies in this space include Green Biologics, the Renewable Energy Group (who acquired the start-up LS9 in 2014), Lanaztech, and Oakbio who synthesize chemicals from carbon dioxide captured from the environment.

The current challenge in manufacturing is the ability to create bulk chemicals without the need for petroleum inputs. This will require producers to adjust manufacturing techniques for renewable inputs (such as biomass) and to develop new processes that use biology and/or environmentally friendly chemistry to do the conversions. Synthetic biology has never been attempted on such a large, commercial scale.

Bio-equivalent of chemicals

Biologically derived versions of chemicals currently derived from petroleum products: fuels, plastics, solvents; some existing commercial entities (Green Biologics, Lanzatech, Renewable Energy Group), but also start-ups and academic research

Stage of development: Lab, trial, and commercial

Outlook: Markets developing, highly active area of research due to potential impact

Additives

Additives (flavours and fragrances), 'natural' routes to flavours and fragrances currently made by chemical synthesis, e.g. Evolva's yeast-based vanilla.

Stage of development: Lab, trial, and commercial

Outlook: Emerging area with good economic prospects

Materials

Biologically derived versions of materials currently derived from petroleum products, new materials with enhanced properties, hybrid/smart materials that respond to environmental cues. Strong investment by governmental and defense organisations

Stage of development: Lab and trial (mainly lab)

Outlook: Speculative, subject to discoveries and market emerging

2.4 Energy

Following on from the points raised around manufacturing, current energy and chemical needs are generally met by the extraction and processing of fossil fuels.

Yet with growing global concern and actions to limit their usage requires identification and development of new technologies to create cleaner, sustainable alternatives (Minton and Green, 2015).

The adoption of the Sustainable Development Goals and 2015 Paris Agreement have brought renewed focus on the need for innovation to meet the challenges of sustainable and inclusive development (Rijsberman, 2018; Esposito, 2018).

The scale of the challenges is immense, yet many of them could be met with the application of biology. Sustainable fuels for aviation and freight are particularly important and challenging, as they are currently difficult or impossible to replace with electric motors using renewable energy.

There are research and development initiatives which focus on these fuels specifically (InnovateUK, 2018b; a).

Improving conventional biofuel production

Research to improve conventional biofuel production (ethanol made from corn in the USA, ethanol made from sugar cane in Brazil, biodiesel made from palm oil) is incorporating synthetic biology approaches to improve performance and increase utilisation of low-cost inputs such as wastes.

Stage of development: Lab, trial, and commercial

Outlook: Markets mature but linked to subsidies and oil price

New biofuels

Advanced biofuels, including ‘petroleum replica’ products and other advanced fuels such as energy-dense chemicals suitable as jet fuels have been shown to be made by engineered microbes in laboratories.

Stage of development: Lab

Outlook: Speculative, economic feasibility very challenging

2.5 Consumer products

Despite the potential public concern over genetically-modified foods, there are a number of companies using synthetic biology to produce materials and textiles including Modern Meadow (growing leather), Bolt Threads (creators of an engineered spider silk tie) and Colorifix (production of dyes with biological systems).

Taxa has product lines that include engineered fragrant mosses and glow-in-the-dark plants for the home consumer. Glowee produces a lamp that is powered with luminescent bacteria with the aim of providing light in places without electricity or reducing electrical consumption.

Moving beyond industrial applications

Engineered spider silk tie (Bolt Threads), glowing plants (Taxa), laboratory grown leather (Modern Meadow)

Stage of development: Lab and trial

Outlook: Speculative / specialist, subject to market emerging

2.6 Services enabling research and development

One class of products are those that enable synthetic biology research by others including reagents, equipment, and software tools that university and/or industrial researchers purchase to use in their own applications.

This has allowed researchers to focus on idea generation rather than having to invest time and money in developing equipment and foundational laboratory reagents.

Process innovation

New and existing companies supporting biotechnology R&D have incorporated synthetic biology technologies, providing a range of enabling services from DNA synthesis (e.g. ATUM) to cloud-based tools (e.g. Benchling) to laboratory materials (e.g. New England Biolabs).

Stage of development: Commercial

Outlook: Market established, continuing to develop with expanded product lines

DNA synthesis companies, which offer synthetic genes with user-defined sequences, form a large part of this space. As DNA synthesis has been commoditised and the price has fallen, the former premium DNA synthesis supplier DNA 2.0, recently renamed ATUM, has increasingly diversified into higher-value offerings.

Examples include long-established companies such as Eurofins MWG Operon and Integrated DNA Technologies, as well as new companies that have developed technological innovations to enable massively upscaled synthesis and decreased costs (such as Twist Bioscience).

Some of the start-ups in this area have been acquired by others, for example Gen9, which was acquired by Gingko Bioworks in early 2017 and GeneArt, which is now part of Thermo Fisher Scientific.

Reagents

Related to this are reagent suppliers, such as New England Biolabs, Finnzymes, Promega, Fermentas, and others who manufacture molecular biology enzymes, purification kits, and other laboratory consumables needed to do research in this area.

These companies have long supplied the biotechnology and biological sciences research markets, but are now also offering new product lines to the synthetic biology market.

Equipment

Similarly, there are companies that manufacture the equipment used to conduct research, many of whom historically served the biotechnology research market, but some of whom have developed new products. An example of the latter is Bento Lab, who are developing a small-scale, portable molecular biology laboratory that fits in a laptop bag.

There are also a number of companies who manufacture laboratory equipment aimed a high throughput experimentation and automation such as Labcyte Inc who make acoustic liquid handling devices for distributing very small volumes of liquid and AnalytikJena whose Cybio line focuses on automated liquid handling.

Software tools

Finally, also part of this space are companies that design software, bioinformatics, or automation support platforms that are used in the design or construction of synthetic organisms. The software and automation facilitate experimentation and accelerate the pace of development of new synthetic organisms.

Examples here include Benchling, a spin-out from the Massachusetts Institute of Technology, and Desktop Genetics, a spin-out from the University of Cambridge, both of whom offer software for DNA sequence design and manipulation, as well as Synthace whose software Antha supports automation and offers laboratory information management systems.

Outsourcing research and process development

Another class of companies within this segment are contract research organisations (CROs) who develop manufacturing processes, cell lines/strains, host organisms, or DNA sequences on behalf of others, that is, they are paid to do research to support another company's product development.

This model has operated in the biopharmaceutical industry for some time, with companies like FujiFilm Diosynth Biotechnologies, Lonza Biologics, and others developing manufacturing processes for molecules discovered in basic research elsewhere.

In synthetic biology the concept has been expanded into new product areas with companies such as Gingko Bioworks and Conagen offering similar services for the production of small molecule products. There are also companies who develop new host cell lines (or 'chassis') for use in synthetic biology such as Synthetic Genomics (primarily bacteria) and Horizon Discovery (primarily mammalian cells).

A small number of companies develop new DNA sequences (or 'parts') for others as part of contract research, such as SynPromics, which offers bespoke design of promoters for different host cells so that transcription of genes can be controlled to desired levels.

2.7 Future developments on the horizon

Current GMOs feature the conceptually simple, if not necessarily technically simple, addition and/or removal of genes, causing the addition and/or removal of the associated traits.

Increasingly sophisticated synthetic biology technologies are now being developed with characteristics or consequences that fall outside the scope of conventional assumptions, and these require careful consideration to ensure risk is properly assessed.

Two examples currently on the horizon to be aware of are gene drive technology and human genome editing.

2.7.1 Gene drives

The rate and extent of the spread of a gene through a population depends on the advantage or disadvantage the gene gives an organism. Organisms that reproduce sexually have two copies of every gene, one received from each parent, which can be the same or different. In turn, only one of the two copies is passed on to each offspring.

The natural passing on of genes is random, so particular genes only accumulate in a population if they cause organisms to be more reproductively successful. This is known as Mendelian inheritance, which is fundamental to normal population genetics.

Given that synthetic genes are unlikely to confer a competitive advantage to organisms in the natural environment and are very likely to confer at least a slight disadvantage, the Mendelian inheritance pattern means that the spread of synthetic genes in the wild would be self-limiting. Gene drive is a new technology that causes synthetic genes to be inherited differently (The National Academies, 2016).

When an offspring receives a natural copy of a gene from one parent, and a synthetic gene equipped with gene drive technology from the other parent, the gene drive then actively copies the synthetic gene in some cell types (chosen by design), 'overwriting' the natural copy of the gene. The result is that the offspring then has two copies of the synthetic gene with the gene drive, which will be passed on to any offspring.

This means that synthetic genes with gene drives can spread through a population, increasing in frequency, even if they cause a reproductive disadvantage. This concept is currently being explored for disease control.

Box 4: Disease control

Several types of mosquitoes transmit human diseases, among which malaria and dengue fever are particularly important, difficult to control, and cause great suffering and loss of life.

Gene drives for mosquitos have recently been designed to cause little or no disadvantage to offspring receiving a copy of the gene drive from only one parent, but to cause sterility in females which receive the gene drive from both parents.

This design is intended to allow the gene drive to spread rapidly through populations until it accumulates to a high level, at which point the population numbers will crash, with little opportunity for mosquitos to escape this fate through natural selection.

The aim is to deploy this system in the environment to rapidly reduce the mosquito population to below the threshold level that supports the spread of diseases like malaria and dengue fever, and therefore to massively reduce or even eliminate these diseases.

Gene drive technology is highly controversial and has been termed ‘extinction technology’ by some segments of the media (Thomas, 2016). The ‘super-Mendelian’ spread of gene drives through populations means that natural selection cannot be relied upon to limit and contain gene drives in the same way as conventional GMOs. Moreover, a technically ideal gene drive system could in principle wipe out the target species altogether over the course of a few years, either in a particular region or even worldwide (The National Academies, 2016).

The elimination of malaria and dengue fever are exceptionally worthwhile goals, but it is not trivial to weigh these against the uncertainties surrounding gene drive technology, and the new kind of interventions in the natural world they represent.

Finally, gene drive technology can be considered ‘dual use’, as besides the disease control objectives for which it was developed, the same technology could be put to malign use as a type of bioweapon by targeting other species, which in principle could include humans. A moratorium on gene drives was proposed, but a meeting of the UN Convention on Biodiversity in 2016 rejected it.

2.7.2 Human genome editing: from genetic diseases to designer babies

There are many inherited (genetic) human diseases with a wide range of severity and implications for quality and length of life. Some of these diseases can be treated to alleviate symptoms, but none can be cured by conventional medical approaches, because the problem lies in the patient’s own genes.

This can lead to medical treatment over long periods of time, or even the entirety of the patient’s life; but also typically means that the disease-causing gene(s) may be passed on to the patient’s children. The development of genome editing technologies is changing the status quo by opening the way to more effective gene therapy, an approach which aims to cure genetic diseases by correcting defective genes in cells within a patient or embryo.

Gene therapy is not a new concept, but previous approaches to achieving gene therapy have a variety of serious limitations. Recent genome editing technologies, particularly CRISPR, provide the necessary precision to move this from fiction to reality.

Genetic manipulation of human cells in patients or embryos is controversial. To some, any such intervention for any reason is ethically unacceptable, although many are supportive of the approach being used to treat serious diseases, alleviate suffering, and prevent inherited diseases being passed to future generations.

However, genome editing technologies are not technically limited to genes involved in genetic disease.

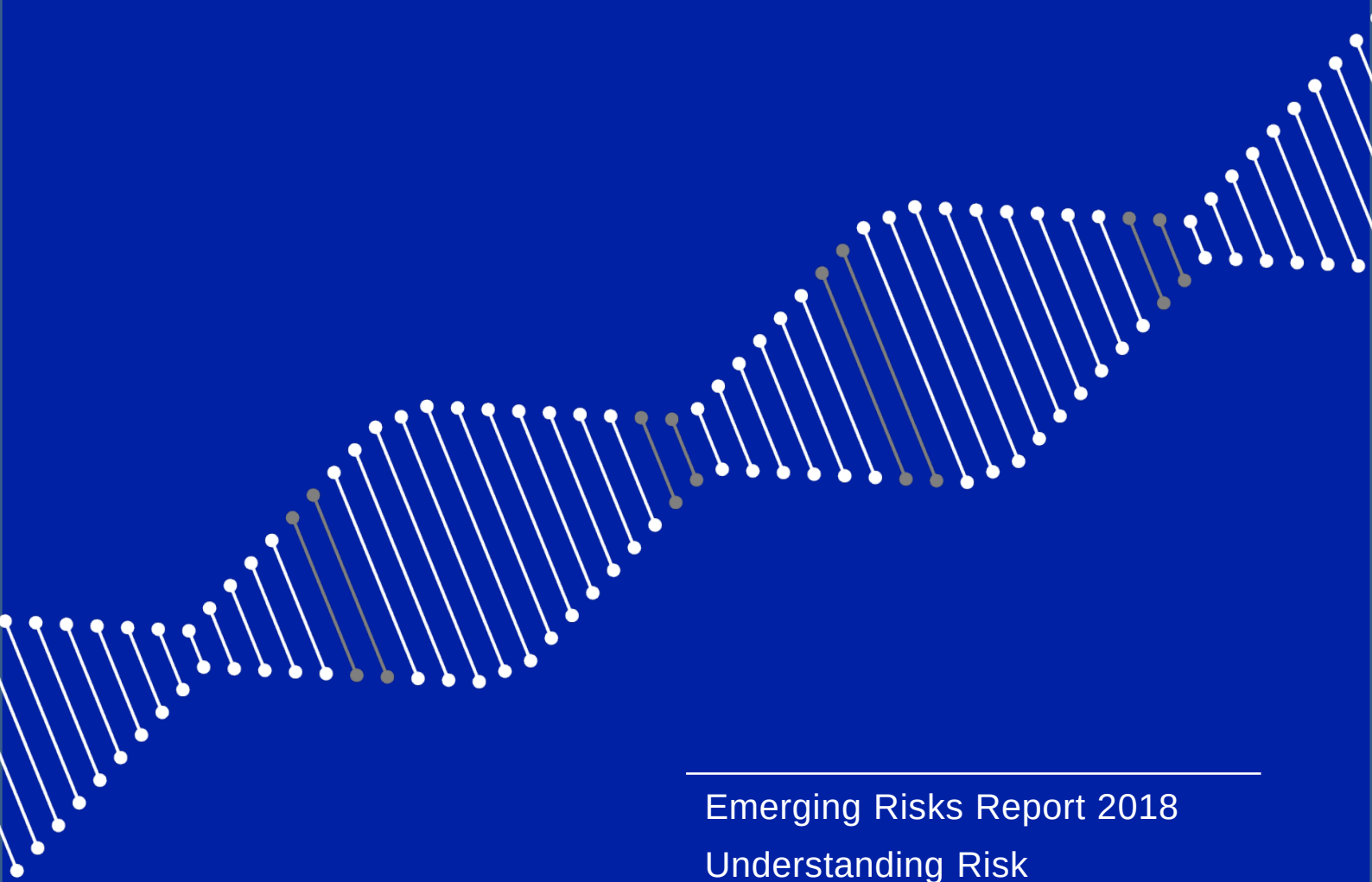
The same approaches could equally be used to edit, remove or replace any genes, responsible for any trait. In principle, genome editing in embryos could be used for any trait parents might wish to seek or to avoid for their children, for which the term ‘designer babies’ has been coined. Any such use is likely to be far less publicly acceptable than genome editing for the treatment of disease (King, 2017).

Least controversial among these might be essentially aesthetic choices such as eye colour, hair colour, body shape or size; essentially the genetic equivalent of cosmetic surgery, albeit performed on the unborn without consent. However, more controversial genes could be targeted, such as those involved in skin colour, intelligence, gender or personality traits, among others.

The argument for genome editing in embryos as gene therapy to treat or eliminate genetic diseases is persuasive. The research is therefore likely to continue, and increasingly to proceed to clinical use. However, as the technology developed for this purpose could also be used for designer babies, there is great need for public discourse and regulatory oversight.

From today’s perspective, it seems likely that this practice would be widely rejected as unethical, but even small numbers of practitioners and a single regulatory jurisdiction in the world allowing designer babies would be highly significant.

Stakeholders driving development



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3. Stakeholders driving development

The following sections describe how synthetic biology has been developed in areas academic research, commercial research and development, and DIYBio, and some of the key enabling programmes and geographic regions where innovation is clustering.

Since the previous report in 2009, the university research sector in synthetic biology remains strong and government investments in academic research have continued, although there are some signs that this is starting to plateau as it matures. In parallel, existing industries have begun to adopt synthetic biology technologies, albeit at a slower pace.

Key enabler: Finance

The market continues to grow, with forecasts of $1.1bn in 2010 (OECD, 2011), $5.2bn in 2015 (Sumant, 2016), to future estimates of $38.7bn by 2020 (Singh, 2014).

Industry research estimated that equity funding to private synthetic biology companies topped $1bn in 2016, with some start-ups seeing funding rounds of more than $100m (CB Insights, 2017).

As well as companies, governments are also facilitating investment in regional centres of excellence. At the other end of the scale, economies of scale and commercialisation are lowering the barriers of entry, and DIY-bio is easier to access.

The early activity in synthetic biology was research-focused and universities played a large role. However, given the applied nature of the field and parallels with biological sciences, it is perhaps unsurprising that many of the research results have the potential to be developed into industrial processes or products.

Although the field is less than two decades old, there is already a significant amount of commercial activity referred to as synthetic biology, and sectoral studies from commercial research entities are available.

Risk managers and insurance market practitioners may find the ‘Synthetic Biology Project’, a useful resource for exploring and monitoring the entities and applications developing in their markets (Synthetic Biology Project, 2018). Established by the Woodrow Wilson Center for Scholars, the website maintained a global map of groups involved in field. This covers universities and other research laboratories, as well as companies active in this sector.

New to the scene since the 2009 report is the advent of DIY-bio, where entry barriers have been lowered in terms of price, technology, and knowledge, to allow developments to occur outside academic and commercial institutions.

3.1 Academic research

Synthetic biology began as an academic research field around the year 2000. Therefore, much of the early work has been associated with universities with funding from government science funding bodies, charities, and later, industry, as grant awards to academics.

A large number of research funding initiatives have been established across the world and have been used to establish teaching and research programmes, which have produced novel applications or tools that have furthered the field.

United States

In addition to traditional research funding streams from the National Science Foundation and the National Institutes of Health, specialised synthetic biology funding programmes were initiated by the U.S Defense Department through the Defense Advanced Research Projects Agency (DARPA)) and by the Department of Energy. Both programmes had emphasis on using synthetic biology to develop routes to synthesise chemicals and materials.

The DARPA programme, called Living Foundries, had two components. The first, ‘Advanced Tools and Capabilities for Generalizable Platforms’, focused on

developing tools and methods that would enable researchers to construct new systems quickly and at a lower cost, and enable more complex systems to be developed. This was an investment aimed at facilitating platform technologies that could be used by many researchers in different application areas.

The second component, '1,000 Molecules', sought to utilise the tools developed from the first programme to engineer systems for the production of molecules with relevance to defense purposes or the bioeconomy. As of the time of writing this programme is still ongoing and the first round of funded projects should be reporting in 2018 (Wegrzyn, 2018).

The Department of Energy programme has been in collaboration with the Joint Genome Institute, and is also focused on biosynthesis of molecules, in particular on developing sustainable alternatives for the production of chemicals with the aim of securing resilient supplychains (US Department of Energy Joint Genome Institute, 2018). The overall aim is to accelerate metabolic engineering and discover new enzymes for the use of lignocellulostic biomass and carbon fixation as feedstocks to produce fuels and chemicals.

United Kingdom

Initial funding for synthetic biology came from the Engineering and Physical Sciences Research Council who established the Centre for Synthetic Biology and Innovation at Imperial College London in 2009. Building on this, the Biotechnology and Biological Sciences Research Council established the "Synthetic Biology for Growth" programme in 2012 (Biotechnology and Biological Sciences Research Council, 2012).

This funded an additional six research centres around different application areas (headed by the Universities of Bristol, Cambridge/John Innes Centre, Edinburgh, Manchester, Nottingham, and Warwick) and made infrastructure investments in gene synthesis technology in five different locations (at the Universities of Edinburgh and Liverpool, the Earlham Institute, Imperial College London, and the MRC Laboratory of Molecular Biology).

Finally, to facilitate the translation of research discoveries and integration of synthetic biology into existing industries, an Innovation and Knowledge Centre (IKC) was established in 2013, called SynbiCITE. SynbiCITE is a public-private partnership based at Imperial College London that currently involves 17 UK universities, local and regional governments, and industrial partners of various types including start-ups, small and medium enterprises, and large multinational companies.

Mainland Europe

Funding activities included the ERASynBio (European Research Area Synthetic Biology) Network, which involved 14 European Countries and was tasked with coordinating synthetic biology activities, training, and investment across Europe. Participating countries were Austria, Denmark, Finland, France, Germany, Greece, Latvia, Netherlands, Norway, Spain, Switzerland, and the United Kingdom with observers from the US (ERA-SynBio, 2016). Research project grants were made through managed calls as part of the Framework Programme 7 and involved multiple partners in different countries.

In 2016, the European Commission adopted a co-funding strategy for the areas of synthetic biology, systems biology and biotechnology in recognition of the overlap in these research areas. The ERA-NET 'Cofund Biotechnology' (ERA-CoBiotech) announced its first round of funding in April 2017 with two further calls expected (ERA-CoBiotech, 2018).

Asia

There has been significant investment in synthetic biology research programmes in Asia, most notably in China and Singapore.

The Chinese government established the national Key Laboratory of Synthetic Biology in 2008 with a set of milestones for synthetic biology research for the next 20 years. The focus of the Key Laboratory is on development of computational platforms and databases of synthetic parts with applications in the synthesis of chemicals and materials as well as the development of drought-tolerant plants (Shanghai Institute for Biological Sciences, 2018).

Key enabler: Automation

In the biology of the future, researchers will be spending their time in the designing and learning stages, with machines undertaking the build and test phases, where they are quicker and more accurate than a human could expect to achieve.

There are researchers designing computer systems that allow users to design at a high level the function required, and much like a complier, software will select and build together the components to make it happen.

In addition, the '973 Program', which aims to give China a competitive edge in various areas of science and technology via basic research funding, has invested $38m in synthetic biology to date (Moshasha, 2016).

In Singapore, the National Research Foundation has invested in synthetic biology research and training, with a focus on translation of research discoveries into products, including forming a consortium of major research institutions in the country with partners from industry (Primer Minister's Office Singapore National Research Foundation, 2018).

2.2 Commercial research and development

Most of the early new commercial entities were university spin-out or start-up companies seeking to capitalise on discoveries from government-funded research. This has been part of a drive by research funding sources to enable impact from research and has provided a driver to accelerate translation for research to development.

For example, a recent report from SynbiCITE suggested that 146 start-up companies had been formed in the period between 2000 and 2016, 111 of which were still active and 12 of which had been acquired (SynbiCITE, 2017). The review also found four synthetic biology companies on the Alternative Investment Market of the London Stock Exchange.

Many of the new commercial entities have raised significant funding from venture capital funds. In the first half of 2017, over $500m was invested in synthetic biology companies (Stevenson, 2017).

In addition to new commercial entities, existing companies have been adopting synthetic biology methods into their normal workflow to accelerate the pace of research and development. Many of these have become partners in research centres and consortia, which facilitates better exchange of ideas between academia and industry.

Existing reagent supply companies have also marketed new products aimed at the synthetic biology research market, such as the 'HiFi DNA Assembly Kit' marketed by New England Biolabs and various laboratory tools for genome editing.

The availability of products like these underpins further academic and industrial research and can increase the pace at which new biological systems can be engineered by providing reliable and robust reagents to perform basic tasks, allowing the end users to focus more attention on design and analysis.

Key enabler: Time compression

Sequencing (reading) DNA used to be done by hand and eye with a slide ruler and a sheet of polyacrylamide gel, and the first human genome was published in 2003 and took ten years and $3bn to achieve; today, it costs $1k (Esposito, 2018).

Today, there are companies that manufacture equipment that will sequence 18,000 genomes a year, 49 a day at $1k a genome. Digitalisation has facilitated leaps in biology, and these are only accelerating.

Geographies of commercial development

Commercial activity in synthetic biology is geographically diverse, although clusters of activity occur on the East and West Coasts of the US, in the UK, and in China. These are often in proximity to universities with a large research presence in the field, reflecting the proliferation of spin-out companies and concentrations of expertise.

Key enabler: Developing standards

There has been concerted effort to explore standards since the 2009 report. NIST and BSI are both active in developing standards around measurement and data transfer.

Other examples include the BioBricks Foundation, which has been working on standardising biological parts and systems, and OpenPlant – a UK research council funded initiative – who have been examining barriers to development and developing solutions.

The two groups have also been working in partnership to develop and promote the Open Material Transfer Agreement (OpenMTA), a legal tool for sharing DNA parts and other biological materials that provides provenance tracking and specifies terms for access, attribution, reuse, redistribution and non-discrimination (OpenPlant, 2017).

The aim of this is to reduce or eliminate costs to further development, with specific aims around enabling researchers in less privileged institutions and world regions (OpenPlant, 2018).

2.3 DIYBio: Do-it-yourself synthetic biology

As synthetic biology becomes more accessible, and awareness increases, there is also a growing research community engaging in synthetic biology non-professionally, outside of academic or industrial laboratories.

The so-called DIYBio movement often operate out of ‘hackspaces’ that provide basic laboratory equipment for individuals to design their own experiments. DIYbio and the democratisation of biology research were stated goals of many of the early pioneers in the field.

Key enabler: consumer empowerment
Information, equipment, and skill levels required for entry are all falling, and in an increasingly digital and connected world more and more applications are possible.

The concept of a DIY community is prevalent in technology fields, and often, the hackspaces have advisory boards connected with the field and are supported by donations from universities, companies, and individual membership fees. The governance of DIYBio and hackspaces is discussed in more detail below (*see Section 4, p34*).

As well as semi-formal defined hackspaces, basic synthetic biology is accessible to the average consumer. For example, in the United States, Ward’s Science, a manufacturer of classroom science supplies, offers a synthetic biology kit for $140 (Brewster, 2016).

One product allows students to create cells that emit a ripe-banana smell, whilst another allows the creation of different coloured cells. These are extremely simple use cases for teaching school science.

In the UK, a DNA printer now costs under £700 and BentoBio is developing a laboratory platform the size of a laptop that would enable portable synthetic biology experiments. DNA printers provide a device to receive, download and print DNA instructions, essentially ‘printing’ outputs. The platform is currently in beta testing (Welfare and Clift, 2017).

Box 5: Paper based diagnostics

One area in which synthetic biology was initially applied is the development of low-cost, portable biosensors for the detection of pathogens and environmental pollutants. Synthetic biology solutions were sought for two main reasons:

1. Current analytical assays often involve high tech equipment that is expensive and the assays are slow, laborious and not well suited to field deployment. For example, diagnosis of pathogens usually requires culturing of the organism, amplification of its DNA, or antibody-based diagnostic tests.
2. Biological systems have naturally evolved the capability to sense their environment and adjust gene expression in response. Thus, there is a naturally occurring source of DNA parts from which such biosensors can be constructed.

A team led by Professor James J Collins at the Massachusetts Institute of Technology have developed a portable biosensor system based on paper dipsticks and freeze-dried extracts of cells containing gene circuits for the detection of different emerging pathogens such as the Zika and Ebola viruses. The biosensors were designed to produce a colour change upon detection of the pathogen, which means that they can be read by eye.

The paper dipsticks are very light weight, easy to distribute, and cost about $0.10 per test to manufacture. The reaction to produce the colour change is relatively quick, leading to diagnosis in approximately 2-3 hours, which is much faster than conventional detection methods for these pathogens (Pardee et al., 2016, 2014).

More importantly, the gene circuits were designed to be modular so that different parts of the circuit can be reused in new designs without having to reengineer the whole system. Therefore, they can be easily customised for the detection of new diseases in the event of an outbreak.

For example, the group estimates that it took just 6 weeks to adapt the test for Ebola virus for the detection of Zika (McAlpine, 2016). Going forward, Professor Collins has suggested that the process could become even faster – perhaps as rapid as one week – from identifying a new pathogen to manufacturing the test.

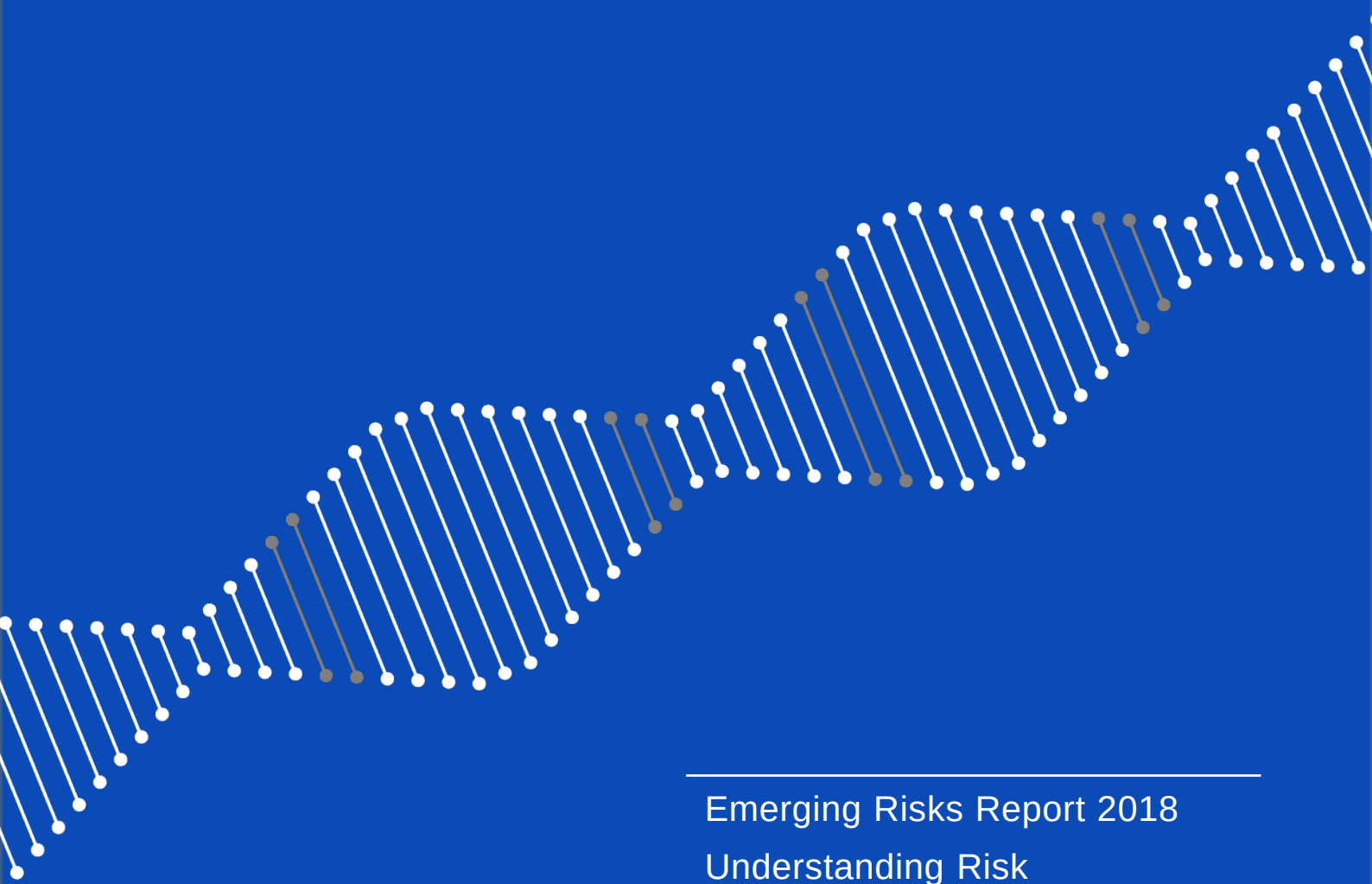
Risk insight

Overall, this case study is a good example of technology development in synthetic biology, where generic platforms are created and can be expanded to a wide variety of new applications rapidly and with lower research and development costs.

It also illustrates how synthetic biology can be used to provide information for decision makers promptly to enable them to trigger a response. This could enable the international and insurance community to prearrange response plans by using financial instruments, so identification across a defined number of points could trigger a prearranged response plan, which is financed by insurance. The diagnostic sticks could be part of the decision-making process - they aren't the solution, but they help make it happen.

A recent example of how a lack of pre-established responses can escalate costs comes from the World Health Organisation. Their research estimates that the outbreak of Ebola in West Africa would have cost $5m to contain when it was first detected in Guinea in 2014, but this figure increased exponentially to $1bn eight months later (Boseley, 2016; Woo, 2015). Recognition of this problem has led to the development of a pandemic financing facility, and this concept could be replicated in response to comparable barrier problems.

Risk pathways



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4. Risk pathways

There are a number of risks associated with biotechnology and synthetic biology research, and as applications become more widespread and the development cycle shortens it is useful to understand how risks might arise.

In the 2009 report Lloyd's highlighted 13 risk factors that insurance professionals should think about when considering what might go wrong and how. These remain aspects to consider, and are referenced throughout the report where applicable to give context where thinking has moved on, especially around ethics:

Box 6: Risk factors from the 2009 report, 'Synthetic biology: influencing development'

1. Terrorism: new technology and the ground-up approach may significantly increase the ease with which such groups can create harmful pathogens.
2. Rush to market: large companies and governments have invested significant sums into research and need to get a return on investment
3. Confusion of regulation: many governing bodies are involved in regulation of biotechnology; however there is no specific regulation, and many unique aspects.
4. Self-regulation aims: those involved in the development of new discoveries may have difficulties in considering concerns of outside stakeholders in the concern around early regulation limiting innovation.
5. Engineering and ethics: borrowing heavily from terminology and processes closer to engineering, there are concerns that the technical mind-set may not sit well with the biological and social aspects.
6. Hackers and real viruses: in the computing world we have seen 'hackers' produce viruses because they can, and there is concern that just because something can be developed, this may emerge here.
7. Creation of monopolies: while companies' intentions may be benign, monopolies can lead to international political tensions.
8. Unexpected gene transfer: although efforts are made to prevent the unwanted transfer of genes to other species this has been shown to occur by a number of other routes in other comparable developments.
9. Unexpected release: containment measures can and will fail, and harm could occur even if outbreaks are contained.
10. Evolution: organisms may behave as expected in the short term, but organisms evolve and you can't plan and mitigate for the unexpected.
11. 'We don't fully understand': despite the steps forwards in understanding there are still many known unknowns, and an unknown number of unknown unknowns.
12. Ecosystem effects are hard to predict: changing a single organism has many uncertainties and predicting how those changes will interact with wider ecosystems is staggering.
13. Moral and ethical issues, the backdrop to litigation: this area is highly emotive, with public stakeholder groups having lobbied against what they may perceive as comparable developments, whether this is for amoral, ethical, financial, social or environmental reasons.

(*Source: Lloyd's 2009*)

One of the biggest developments since the 2009 report is around the widespread emergence into a large number of sectors. This has increased the risk of unintended consequences, which will likely vary between sectors with uncertainty and potential impacts remaining high.

The risk pathways include three major categories:

- accidental release of biological organisms resulting from bioerror
- deliberate construction of biological weapons defined as bioterror
- and potentially unintended consequences of biological research

For the latter, many of the risks are not predictable and there is a high degree of uncertainty about the types of things that can go wrong and how this might happen, let alone the probability of these risks occurring. However, this risk category contains some of the higher probability events. The following sections outline current thinking within the sector by those involved in it.

For the insurance sector and wider risk management professionals, the use of scenarios and comparable past examples is a useful tool for considering any sector and the risks that may arise. To aid thinking there are examples in each risk pathway of past events that could be used in scenario development.

4.1 Bioerror

'Bioerror' refers to unintentional consequences of biological discovery leading to disastrous consequences. In general, two scenarios are often envisaged, and they fall into the category of low probability, potentially high impact. Of the two, accidental release scenarios are of the higher likelihood.

In the first, scientists accidentally create something they do not understand, and it escapes into the world to cause damage. One analogy often invoked outside the sector is the fear of a self-replicating 'grey goo' taking over the world that was put forth at the advent of nanotechnology.

The commonality between synthetic biology and nanotechnology is that the technology is new and therefore is likely to not be fully understood. There is increasing interest in the synthetic biology community around the importance of communicating the science to alleviate some of these fears.

The second scenario proposes that the risks are correctly understood, but that containment measures designed to prevent release of Genetically Modified Organisms (GMOs) fail. An example of this could be sterilising waste from biological experimentation. Some scenarios of this type have occasionally occurred but these kinds of instances are infrequent (*see Box 4, overleaf*).

There are several reasons why those within the synthetic biology community believe that events from bioerror are of low probability, but potentially high impact. Most notably, scientific research often builds incrementally on prior knowledge.

Researchers are unlikely to jump from the current state of knowledge to something so revolutionarily different that understanding would change in such a way that mitigation methods don't have time to catch up.

> Risk insight
>
> This belief will need to be challenged as the sector expands, developments move on to more complex organisms and field deployments, and regulation struggles to keep pace.

Second, safeguards are in place to ensure that research is conducted safely, and oversight is in place. For example, within a university, safety committees review and approve all research involving living organisms.

Additional review is given to projects involving genetic modification to consider whether additional risks are incurred due to the modifications proposed. This does not preclude malicious actors from facilitating developments, and this concept is described in the bioterror section.

> Risk insight
>
> With barriers to entry lowering, enabling technology, and sectors with limited biotechnology experience seeing developments taking place, it is important to map uncertainty and fill knowledge gaps and explicitly consider potential risks in conjunction with stakeholders.

Third, research involving human subjects must undergo an additional internal review to ensure that the rights of participants are not jeopardised. In the US this is called internal review board or IRB, and individuals enrolled on such studies must give 'informed consent' meaning that:

- The study aims and goals are described to them
- The limits of their participation are made clear
- Participants must sign that they both understand the proposal and agree.

These control factors make it unlikely that a study that is high risk would pass both IRB review and be able to enrol human subjects.

Risk insight

This relies on strong governance, oversight, and control procedures being implemented, and incentives for development not overriding safety.

Therefore, it may be important to consider these factors and consult local regulatory guidance when making underwriting decisions.

4.1.1 Accidental release

Accidental release due to failed containment measures is more probable, as containment measures do occasionally fail (*see Box 7, below*) although these tend to be low frequency events.

Risks are mitigated by solid and liquid waste from research laboratories being sterilised and incinerated as routine procedure and the equipment for doing so is tested and certified annually.

In addition, personal protective equipment is worn by researchers and plant operators to prevent contamination of skin and clothes that could result in accidental release to the community via personnel. However, occasionally, these containment measures fail, resulting in accidental exposure to organisms outside the research facility.

This concept is best described as the 'Swiss cheese model of accident causation' by James Reason, who stated that when all the holes in the slices line up, failure will occur (Reason, 2000).

Risk insight

In general, the bioerror risks apply equally to other types of biological research, such as biomedical infectious disease research, and are not necessarily greater for synthetic biology.

There is thinking within the insurance industry from biomedical and life science insurance that could be used as a starting point when considering risks and policy coverage. This covers companies that design, develop, manufacture or supply products or provide supporting services to industries ranging from pharmaceutical and biotechnology, to cosmetics and food supplements.

Concerns tend to be raised about synthetic biology because it enables a larger scale of modifications to organisms than was previously possible. Therefore, there is a higher probability that the boundaries of what is currently possible will be exceeded, and the use of scenario analysis and counterfactuals around potential events should be considered when evaluating instances.

Box 7: Accidental release, Pirbright Animal Facility risk insight

In August 2007, an outbreak of Foot and Mouth Disease occurred in rural England. When analysed, the virus was molecularly identical to that used at the Pirbright animal research facility. Investigations later showed that the outbreak was linked to a faulty drainage pipe that was not properly maintained allowing escape of the live virus, when then was spread on the tires of vehicles leaving the site to a nearby farm. The drainage pipe linked the research laboratory waste stream to the chemical inactivation tanks designed to decontaminate waste, meaning that containment measures failed.

Three different groups were using the virus on the site: a governmentally funded research laboratory (Institute for Animal Health), and two private vaccine manufacturers (Merial Animal Health Limited and Stabilitech Limited). Because the drainage pipes were shared, it was not possible to link the release to a single group.

In total, 1581 animals were culled to control the outbreak. Although the agent released was not genetically modified and therefore not an example specific to synthetic biology, this illustrates the type of consequences that can result from the accidental release of biological organisms when containment measures in a research laboratory fail (DEFRA, 2007).

How did risk management change?

Recommendations following the subsequent investigation included that the drainage pipe should surrounded by a secondary containment system as an extra measure to prevent accidental release. More importantly, it was suggested that a single unified regulatory framework should be developed to regulate both human and animal pathogens in the UK, given the similarities in risk of release and consequences of disease, but the disparities in the legal frameworks operating for each.

In 2008, the regulatory approval process for handling animal pathogens, inspection, and enforcement was transferred from Department of the Environment, Food, and Rural Affairs to the Health and Safety Executive. However, ultimately a fully unified legal framework for handling both types of agents was not possible because of inconsistencies in primary legislation underpinning the regulations in each case and issues around devolution of powers. However, harmonisation has been agreed through a non-legal framework to help create consistency going forward (Health and Safety Executive, 2015).

DIYBio considerations

With respect to containment failures, the DIYBio/Hackspace activities where there may be less training with respect to safety and less oversight tend to be raised as a concern. However, hackspaces – also referred to as makerspaces within the community – are often closely associated with university activities, which may in some instances provide a degree of oversight.

They are subject to the same regulations with respect to the creation, use, and disposal of GMOs as other research facilities and have access to the standard containment measures commonly found in other laboratory settings in academia and industry.

Risk insight

Conversely, a segment of the community of DIYBio self-identify as 'biohackers', who can be considered part of the philosophical continuity hacker movement in the field of computers and networks (Chardronnet, 2017).

While it is hoped that developers in the bio-industry will be more responsible than their IT equivalents where risks are concerned, there is no evidence to the contrary.

Automation and the development of cloud computing for decentralised processing also raises the potential for users to not require traditional workspaces to perform experiments, and these spaces may fill that role. As with the advent of any industry touched by digitalisation, data and network security should be considered along with the full remit of potential cyber risks.

Regardless of the users, property use should be considered when underwriters evaluate property risks – familiarity with terminology in this section may be useful to consider when dealing with policyholders.

4.2 Bioterror

Bioterror refers to the deliberate construction and release of a biological agent with the intention of inflicting illness or casualty on a population. However, making the organism is only one part of weaponisation of biological agents and additional technology, for example to aerosolise or spread the organism, is often not easy for lone actors to access.

Bioterror experts suggest more risk comes from state-based programmes to develop bioweapons on a national level. These programmes have significantly better funding and access to scientists and engineers with expertise in technologies to weaponise agents. International laws such as the Geneva Protocol and the Biological Weapons Conventions are intended to prevent state-based bioterror programmes (Bradley, 2013). However, the fear is that these are insufficient to deter rogue states from research and development in this area, and concerns have been raised recently around suspected events.

Box 8: The art of the possible

Information on potential bioweapon agents has never been more accessible, for example, it is theorised that the remaining smallpox strains are secured in two labs, one in the U.S and one in Russia, yet the complete genetic sequence is available to anyone with an internet connection (Dunlap and Pauwels, 2017).

One example to be considered is the successful recreation of the horsepox virus – a relative of smallpox – using synthetic biology by Professor D. Evans, which has reignited debate in this space around regulation and controls as the effort cost an estimated $100K, took only six months, and "did not require exceptional biochemical knowledge or skills, significant funds or significant time" (World Health Organization, 2017).

All information necessary to sequence and generate the virus was publicly available, and Professor Evans – a member of the World Health Organization's smallpox scientific advisory committee and Vice-Dean, Research at the University of Alberta, Canada (University of Alberta, 2018) – cited the primary limiting factor as the length of time required by the commercial company that performed the DNA fragment synthesis.

Details are still emerging and should be considered when available for scenario analysis and risk factors across insurance lines that may be impacted by these developments.

As with bioerror, the risks associated with bioterror can also apply to biomedical research and previous incarnations of biotechnology research.

The new concern with synthetic biology relates to the scale of modifications possible as well as the idea that making biology easier to engineer for researchers makes it easier to engineer for everyone, including those with motives to use biology for harm (DoD, 2017).

Almost all states have the capacity to produce biological toxins that can be used as weapons. Emerging technologies mean that access to the tools needed to create potential bioweapons are no longer restricted to well-funded government or academic programs, and that feasibly it is possible that a non-state group or malicious

actor may need to be considered, increasing the risk from bioterror (DoD, 2017).

Despite this, in general biological weapons are not likely to be more effective than conventional weapons, especially given their legal and moral unacceptability, so the real risk may well remain comparable with that of Chemical Biological Radiology Nuclear (CBRN) weapons – low but any potential impacts being very high. As with any extreme event, consideration of potential risks is encouraged, and insurance understanding could aid stakeholders.

See the 2016 Lloyd's study '*Use of Chemical, Biological, Radiological and Nuclear Weapons by Non-State Actors*' for emerging trends and risk factors. The study also includes a series of scenarios that could be adapted for considering risks in this space (Lloyd's, 2016).

On the other side, these same advances also have the potential to enhance detection, develop medical countermeasures, provide materials for protective equipment and reduce the destructive and disruptive capacity of Chemical Biological Radiological and Nuclear (CBRN) weapons (Lloyd's, 2016; Aftergood, 2017).

For example, first responders need a portable, simple to use, and timely device for detecting the presence of biological and chemical agents (Saito et al., 2018), and the concept illustrated in the Ebola detection paper strips could be adapted for this kind of application.

Researchers are already working on more complex systems of chemical weapon detection, and a team at the University of Osaka and co-workers have developed a prototype of an integrated automated portable device. All parts of the device are assembled in a compact 300mm × 300mm × 300mm and 12.8 kg container. The device runs with a 24-V battery power source and is connected to a tablet screen (Saito et al., 2018).

Risk insight

While there are easier technologies to cause harm, lowering barriers of entry and even the smallest potential for harm has led to more stakeholders considering potential risks, and how they might be mitigated.

One example of this is an assessment currently underway by the U.S National Academies of Sciences, Engineering, and Medicine at the request of the U.S. Department of Defense's Chemical and Biological Defense Program (CBDP) (Niiler, 2017).

The project will involve the development of a strategic framework to guide an assessment of the potential security vulnerabilities related to advances in biology and biotechnology, with a particular emphasis on synthetic biology (The National Academies, 2018).

Public results are due in 2018 and are anticipated to provide a current state of knowledge that may be useful in considering scenarios and risk factors. Some have also commented on the potential to guide regulations on federally-funded research labs. However, as was illustrated in Section 3 (*p25 onwards*), development is occurring across the world and experts are highly mobile and in demand.

In the meantime, readers may also find the October 2017 Wilson Briefs' of interest, as it outlines two scenarios to 'show avenues that may be exploited to avoid current governance roadblocks and create a pathogen or toxin with Weapon of Mass Destruction potential' (Dunlap and Pauwels, 2017).

4.3 Unintended consequences

Despite the concern over bioterror and bioerror, these are both low probability scenarios from synthetic biology research or even biological research in general. In fact, the more likely adverse scenarios are results of unintended consequences of the deployment of synthetic biology.

A few of the more foreseeable examples of unintended consequence are discussed below. However, uncertainty is high, and it is difficult to refine because synthetic biology is emerging into a large number of sectors with different impacts, leading to different risk profiles. Mapping uncertainty and filling knowledge gaps remain important suggested actions as more examples emerge.

Therefore currently, consideration should be given on a case-by-case basis of the individual factors involved and extreme, but plausible, scenarios considered when evaluating what role risk transfer could be applicable.

Release

Many of the solutions to the human needs discussed in the first section would rely on technologies that are used outside of the laboratory/industrial manufacturing setting and therefore would qualify as deliberate release of an engineered organism (*see Boxes 8 and 9, overleaf)*.

Examples include therapeutics taken by patients, engineered organisms for bioremediation of the environment, engineered crops, and gene-drive organisms that are released to control a wild-population (*see Section 2.7.1, p22*).

Currently there are some regulations in place to deal with these types of technologies that have been developed using traditional biotechnology, although there is no globally consistent standard.

For example, to undertake a clinical trial in the European Union using a gene therapy product, in addition to informed consent of the participants (via the equivalent of the Internal Review Board), demonstrating successful tests of the product in animal studies (pre-clinical) and healthy volunteers (Phase I), companies must also apply for a license for experimental release.

One example that could be considered in countries like the U.S where regulation is implemented on a state-by-state basis, or even at a global level, is the approach currently taken in the EU. The EU member state in which the release is requested must notify the EU of all applications, which are placed on a register held by the Joint Research Centre of the European Commission (2018).

The rationale behind this is that the patients who receive the therapy may shed genetically modified organisms and/or genetic material after they leave the clinic and that others may come into contact with this material. Some of the case studies (*see Boxes 8 and 9, overleaf*) discuss types of organism release and some of the unintended consequences that could result.

Box 9: Intentional release of engineered mosquitoes

Mosquitoes act as a disease transmission vector in a number of diseases including malaria, Dengue fever, Zika and West Nile virus. Current risk management measures include netting, reducing standing water/ breeding sources, and insecticide spraying.

Another strategy that has been proposed is to release engineered mosquito populations – either to control the number of mosquitos or to influence their ability to be vectors for disease. This could have wider benefits of reducing pandemic risk from vector-based diseases.

Oxitec is a UK biotechnology company that originated as a spin-out of the University of Oxford and was acquired by a commercial entity – Intrexon – in 2015. Oxitec manufacture genetically-modified mosquitoes and other insect vectors to release into the environment to block disease transmission. Different variations have been proposed, such as technology to engineer mosquitos to express antibodies against the targeted disease so mosquitos become immune through to gene drive technology that causes lethality (*see Section 2.7.1, p22, for information on gene drives*).

In the case of Oxitec, they have engineered male mosquitoes of the genus *Aedes* rendered sterile through a gene that prevents their offspring from developing, causing them to die (Phuc et al., 2007). These are then released into the population, where they mate with natural females, but produce no viable offspring, thus depressing the population numbers. Previous attempts to make sterile insects by irradiating male mosquitoes and then releasing them into the wild had been conducted, but it was difficult to manufacture these insects in the number required to impact disease transmission (Alphey et al., 2013).

Oxitec mosquitoes have been used in field trials in Brazil, Panama, and Cayman Islands and interest in this type of technology has accelerated due to the Zika virus outbreaks. World Health Organisation (WHO) has recommended an increase in the number of field trials and risk assessments of this and related technology (Radford, 2016).

Regulation and public policy

In 2016, the US state of Florida voted on a referendum regarding a trial in the Florida Keys, but the vote was split and the trials did not proceed. The main arguments against the technology surround the potential for ecological problems due to the disruption of native ecology or the risk that the released organism outcompete natural species leading to a loss of biodiversity.

In the example of the mosquitos, it can be argued that they act as a food source for aquatic animals and so if are eliminated could disrupt the food supply of other organisms. There is also concern that once the niche occupied by *Aedes* is free that something worse could move in. For example, in Florida the main organism discussed in this context is the Asian Tiger Mosquito, which can also carry Dengue fever.

One additional potential concern with engineered insects is that they will not necessarily remain in the area in which they were released and therefore, consideration of the unintended consequences from the geographic spread of engineered organisms is needed.

The responsibility for regulatory approval of the engineered mosquitoes in the United States was initially thought to rest with the Food and Drug Administration (FDA). However, in October 2017, the FDA clarified that as the mosquitoes themselves were not meant for the diagnosis, treatment, or cure of disease, the regulatory approval should rest with the Environmental Protection Agency (US Food and Drug Administration Centre for Veterinary Medicine, 2017).

Box 10: Intentional release of engineered therapeutic, Synlogic

Synlogic (recently merged with Mirna Therapeutics and trading on the stock exchange) produces engineered bacteria as probiotic dietary supplements aimed to treat diseases. The initial focus of the company was on rare and orphan disease such as phenylketonuria and urea cycle disorders, with additional planned therapies in inflammation, cancer, and liver diseases (Synlogic, 2018).

The reason for choosing orphan diseases initially was to have a smoother path to regulatory approval by the FDA. The therapies for phenylketonuria and urea cycle disorders are currently in or about to start clinical trials, and if these are approved, it will create a precedent for additional products.

Although their engineered therapies will be shed by patients, Synlogic have designed their products with the idea of limiting the risk of accidental exposure to non-patients. They self-describe their technology as ‘organic microbes’ as they have chosen host organisms that naturally reside in the human digestive tract as the basis for engineering. Instead of creating a therapy that would colonise the digestive tract and remain alive inside the patient (with the associated complications), they have designed a product that is administered daily.

The bacteria have been engineered to not be able to replicate outside of the laboratory and only express synthetic DNA when in the body. This Synlogic believe this gives clearer information about dose, that is, the dose is limited to what the patient ingests without needing to factor in cell survival and population growth. It also limits undesired side effects because if these occur, the patient stops taking the product and the bacteria are cleared within a day. The net effect of Synlogic’s design choices is that they are able to avoid engineering cells with complex circuitry, which they believe lowers risk.

Risk insight

Overall, this approach could serve as an interesting model for how to consider product design as a risk management mechanism, although ecosystem effects are hard to predict, and the human body is a highly complex, uncertain environment.

Artificial, human-made environments

Organisms naturally adapt to their environment, regardless of whether that environment is natural or not. Human activity often creates environment that are wholly artificial, or artificial with respect to certain organisms. Humans have introduced numerous plant and animal species to geographical locations in which they would not naturally be found. In some cases, these species thrive and even outcompete native species, becoming invasive. Examples include cane toads and prickly pears in Australia, Dutch elm disease in North America, Japanese knotweed in the UK and elsewhere, and rabbits in New Zealand. This phenomenon also occurs with microorganisms.

The widespread use and overuse of antibiotics in human medicine, animal medicine and as a growth supplement in animal feed has created environments in which microorganisms resistant to antibiotics are more successful, causing the development and spread of antibiotic resistance.

In some cases (such as food poisoning by Campylobacter (Angulo, Nunnery and Bair, 2004) there is evidence that this can spread from animals to humans, making human diseases more difficult or even impossible to treat. Improved 'stewardship' of antibiotics is now encouraged, and use of antibiotics in animal feed is now restricted in jurisdictions including the EU and USA.

Risk insight

The close proximity of ill people in healthcare settings, many of whom are taking antibiotics, creates an ideal environment for certain disease-causing organisms.

The prevalence of some organisms depends largely on such environments. For example, the hospital 'superbug' *Clostridium difficile* was barely known a few decades ago, but rapidly became a major cause of serious hospital-acquired disease in numerous countries, specifically due to the use of antibiotics in healthcare settings.

This artificial, human-made environment may also allow the spread and evolution of escaped GMOs, therefore it is key that any human testing or introduce into populations is well considered and monitored closely. While the potential for risk is high here, there is also the potential to develop new antibiotics that could change the risk profile of diseases.

Socio-economic disruption

New technologies are often disruptive in ways that are unforeseen before they are invented. One type of such consequences can be negative economic impacts on existing markets/suppliers. In some instances, this can be problematic, depending on the identities of the suppliers. One example here is artemisinin (*see Box 10, overleaf*).

While this example is specific to artemisinin, these types of risks are difficult to predict as interdisciplinary economic modelling is not a well-developed field, and supplychain modelling is still evolving. In an academic setting, they might be explored through 'Responsible Research and Innovation' frameworks, which ask academics to consider a wide range of stakeholders when they design research projects. However, in industry there is no overt mandate to consider unintended consequences that do not impact on product or societal safety.

Social pressures/consumer backlash against a product, which is usually after the product has been released, and the rise of social media and shareholder action groups has made this an area of concern for businesses and governments.

At a national level, the United Nations 2015 Sustainable Development Goals have also raised questions around value sharing to consider how benefits and costs of bio-innovation should be distributed across stakeholders, regions and generations (Rijsberman, 2018; Esposito, 2018).

Box 11: Artemisin's unintended consequences

The synthesis of artemisinic acid in yeast was one of the early examples of synthetic biology and has widely been discussed as a model success story for the power of the synthetic biology approach. However, even this example resulted in some unintended consequences, which illustrates the potential for diverse impacts of technology on society.

The two unintended impacts of artemisinic acid production in yeast that have emerged are both economic. First, there has been a negative impact on farmers who used to derive income from growing *Artemisia annua* as a crop plant (Thomas, 2013). Initially, synthetic artemisinin was intended only as a supplementary mechanism for production with a goal of evening out fluctuations in the supply. However, recently it has been suggested that it should replace farmed sources entirely, since it simplifies the supply chain and prevents growers from selling to manufacturers of monotherapies that tend to drive the development of parasite resistance. This could, in effect, force farmers to grow other crops as they become unviable commercially.

The second unintended consequence is derived from the manufacturing agreement that was signed with Sanofi. Because it has been agreed that they will manufacture at no loss, the price of therapies containing the synthetic artemisinin will not decrease below a certain level (the level at which Sanofi makes its operating costs back), meaning the therapy will still be unaffordable for many patients (Peplow, 2016).

As a consequence, the Gates Foundation invested in a further set of 10 projects in 2018 to try and decrease costs further. These will explore alternative hosts beyond yeast and new methods to achieve the final conversion of artemisinic acid to artemisinin, which is currently done with photochemistry (Peplow, 2018; Phuc et al., 2007).

These unintended consequences could be viewed as an unpredicted risk that would not have been considered at the start of the project. Similarly, unforeseen risks may emerge for other applications of synthetic biology.

4.5 Risk management

Bioerror and bioterror scenarios involving the release of GMOs could have very serious consequences. However, concern about these issues is limited among biologists and biotechnologists for practical and theoretical reasons.

Practical safety and containment measures are ubiquitous, part of research culture, and required by law. These include several categories of containment laboratory facilities suitable for different types of organisms, the use of personal protective equipment, and rigorous disposal of biological materials involving the destruction and sterilisation of GM organisms before disposal.

Expertise in biological systems and natural environments leads many researchers to assess that the release of typical GMOs would have limited, containable consequences, as opposed to runaway catastrophic consequences, and therefore to judge that the responsible development of synthetic biology is justified.

Two key aspects underpin this view. Firstly, in terms of their genetic composition, natural populations and ecosystems are not generally static or fragile systems particularly sensitive to the appearance of new DNA sequences. In contrast, they are dynamic and robust systems in which vast numbers of genetic variants constantly arise and are exchanged between individuals and even between species, particularly mediated by viruses and bacteria. Secondly, typical GMOs are generally very fragile relative to naturally-occurring organisms, or at least have properties that cause some competitive disadvantage, such as a slightly lower growth rate. Taken together, these points suggest that natural populations and ecosystems are generally very resistant to invasion by GMOs or their DNA.

A typical GMO in a research facility is laboratory strain of a microorganism genetically modified to add or remove a gene for study purposes. If accidentally released, say into soil or a water course, such a GMO would not even be expected to survive for long, much less to successfully compete with native organisms. Some GMOs are more robust and are only slightly less vigorous than natural organisms. However, in the fiercely competitive environments of natural ecosystems, even slight weaknesses are enough to cause the elimination of an organism by natural selection.

Regardless of the survival of the GMO itself, foreign DNA sequences from GMOs may be assimilated by other organisms. However, if such a foreign DNA sequence gave any organism an advantage in a given ecosystem, then that DNA sequence or a similar one would probably be present already, because genetic material has been prolifically generated, recombined and widely exchanged naturally throughout the whole history of life on Earth.

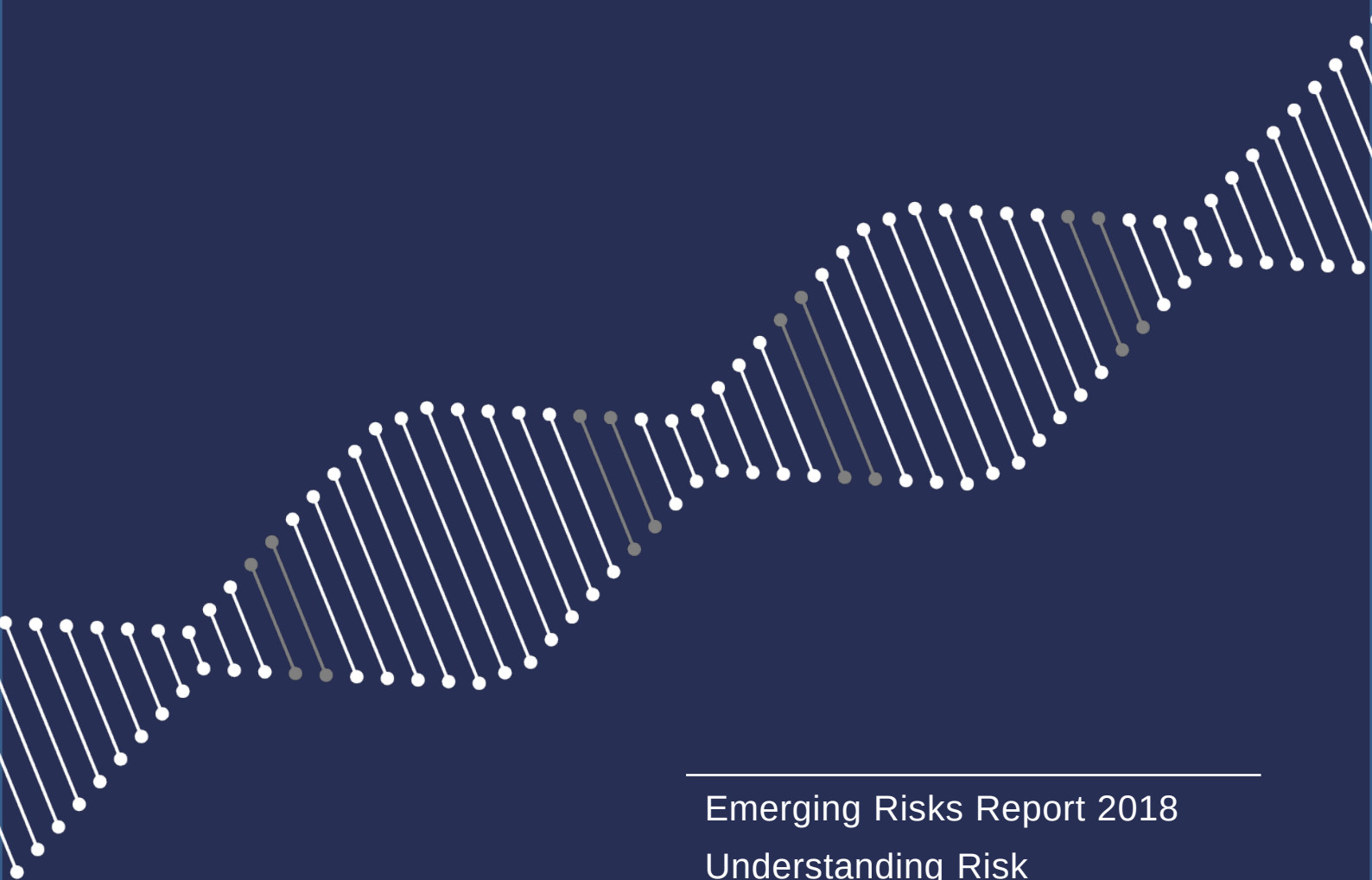
This perspective is neatly summarised by the influential classic microbiology tenet, first published in 1934, that "Everything is everywhere but the environment selects" (De Wit and Bouvier, 2006).

The above views are widely held, but do not mean that concerns are not raised and acted upon by researchers. When recombinant DNA technology was first developed, the first practitioners in this field chose to quickly self-regulate through a moratorium on the technology until the risks and hazards could be assessed. The Asilomar Conference on Recombinant DNA in 1975 presented and discussed these issues and proposed principles and guidelines for the research using recombinant DNA technology. These ultimately shaped the regulatory frameworks which have been used and developed since (*see Section 5, p43*).

It is also possible to design synthetic organisms with safety in mind *(see Box 9, p38)*, for example by engineering cells to be unable to replicate outside of an industrial facility due to an engineered nutritional requirement or a ‘kill switch’, or by modifying the ‘language’ of the genetic code so that even if sequences from engineered organisms are transferred into natural organisms, they will not function.

It is important that researchers remain informed and review their understanding and assessment as new synthetic biology technologies are developed and applied. This is especially true if such developments are at odds with the underlying assumptions above (*see Section 2.7, p22*).

Regulation



Emerging Risks Report 2018

Understanding Risk

5. Regulation

As described briefly in the previous section, research in academia and industry is governed by a set of regulations for the use of biological organisms, genetic modifications of these organisms, disposal of waste after experiments, and research involving human participants. These provide a framework within which researchers must operate to ensure research is conducted safely and provide a degree of oversight as to which experiments can and cannot be done.

In general, regulatory frameworks have not changed substantially since the 2009 version of this report. However, there is increasing awareness of the fact that synthetic biology can create products that do not conform to standard regulatory paths and there have been discussions about modifications to regulations needed for existing products.

Currently, synthetic biology products are regulated by type without regard for the way that they were developed, for example medicinal products are regulated as medicines, food products according to food regulations and so forth, and the associated laws and regulatory approval processes apply.

There is no distinction between products made using synthetic biology approaches and those made with other types of biotechnology. Full discussion of the regulations governing different classes of products is outside the scope of this document.

One common element of most synthetic biology products is that they involve genetic modification at some point within the production process; either the end-product itself may be a modified organism or an engineered organism may be used to make the product, which is then purified before use.

This is also a feature of most products of modern biotechnology. Therefore, most countries have regulations surrounding the safe use of genetic modification technologies already in place. These usually focus on the parameters for contained use and deliberate release of engineered organisms and the mechanisms needed for decontamination of waste associated with producing and using genetically modified organisms.

Current regulatory frameworks generally consider an organism to be genetically modified, and hence subject to regulation, based only on whether foreign DNA is present in the organism produced, not whether foreign DNA was used inside the organism during its development. This means that specially-designed synthetic DNA can be inserted into cells in order to achieve certain types of genome editing, such as the deletion of a gene, as long as the synthetic DNA is later removed.

In a recent example, the US Department of Agriculture confirmed that a type of mushroom generated in this way was not considered to be a regulated GMO (Waltz, 2016).This is not necessarily intuitive, and is probably not what the general public might expect from a food product described as non-GM.

Although the strategy of regulating products by class is logical and simplifies the routes to product approval, it may not be sufficient in the long term. Recently, some products have been proposed that do not have a clear lead agency for regulation because they theoretically can belong to multiple product classes or because they are different enough from pre-existing products to not have an obvious precedent for regulation.

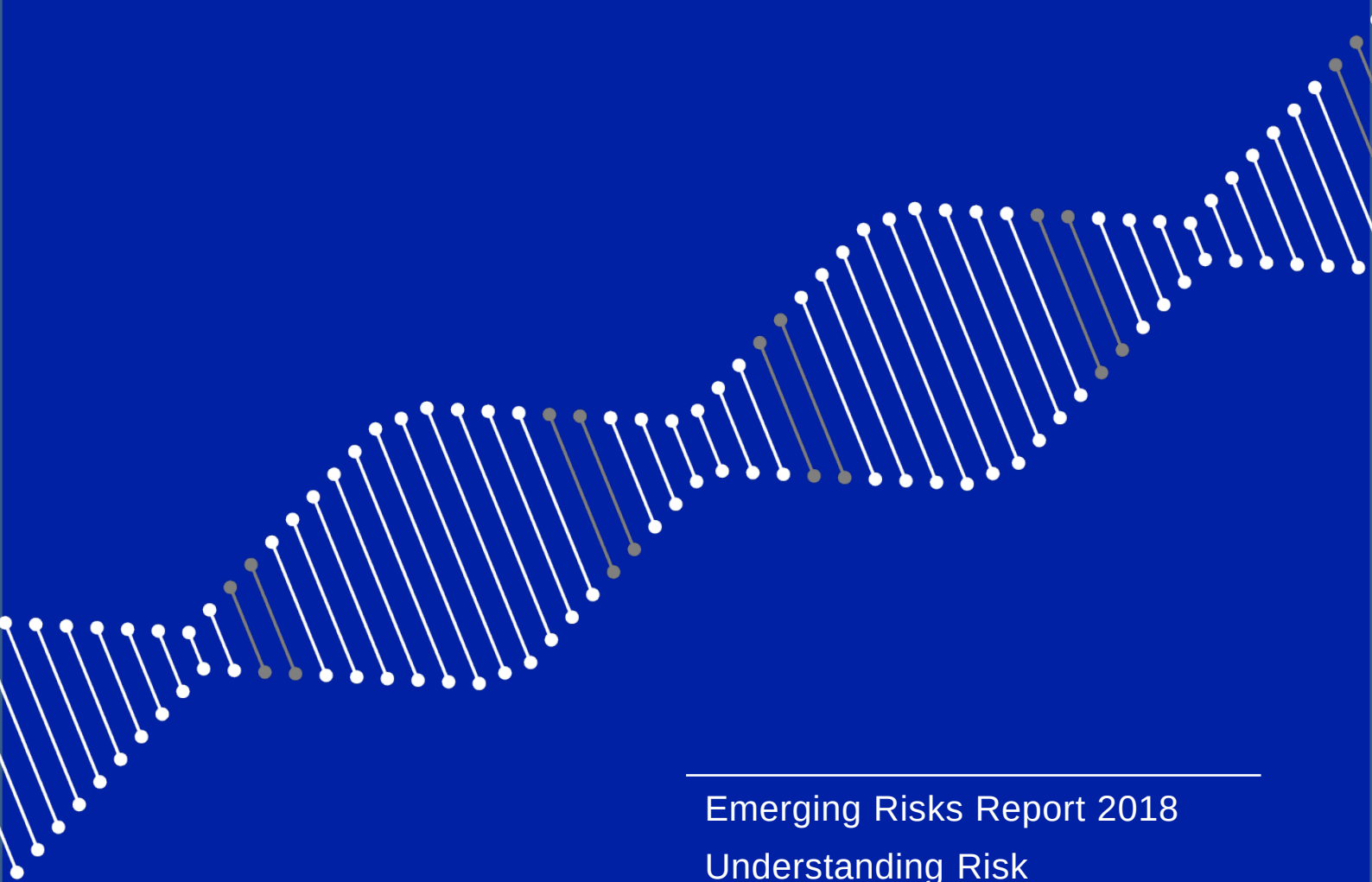
One example is the GM sterile male insects example (*see Box 9, p38*), which in the United States was first thought to fall under the jurisdiction of the Food and Drug Administration, but has since been reassigned for consideration by the Environmental Protection Agency (US Food and Drug Administration Centre for Veterinary Medicine, 2017).

In the UK, GM insects would be regulated under the European directives for contained releases and transboundary movements of genetically modified organisms. However, the House of Lords Science and Technology committee has recently questioned whether this should be reviewed.

They have also noted that the research and development of this technology is happening largely outside the countries in which it would be deployed (such as areas with large endemic populations of mosquitoes and high incidence of diseases such as Dengue Fever and malaria) and have therefore proposed that it may be more appropriate to develop international frameworks for regulation and governance (House of Lords Science and Technology Select Committee, 2015).

New technologies emerging that will allow for genetic modifications on the very large scale (in particular whole genome synthesis) and provide the potential for highly complex products to develop. Therefore, current regulations may not be adequate for all future uses of synthetic biology and require periodic review and refreshment in order to ensure they consider risks from new products as they are developed.

Conclusion



6. Conclusion

Scarcity trends continue to drive innovation, and this has been enabled by technology developments. Global trends such as sustainability have become areas of focus, and new frontier areas are being raised. What is clear is that synthetic biology is a field with high potential for growth, and widespread cross-cutting applications.

In general, the bioerror risks apply equally to other types of biological research, such as biomedical infectious disease research, and are not necessarily greater for synthetic biology. There is thinking within the insurance industry from biomedical and life science insurance that could be used as a starting point when considering risks and policy coverage, but there are large unknowns still to be explored.

Concerns tend to be raised about synthetic biology because it enables a larger scale of modifications to organisms than was previously possible. Therefore, there is a higher probability that the boundaries of what is currently possible will be exceeded, and the use of scenario analysis and counterfactuals around potential events should be considered when evaluating instances. See ‘Reimagining History’ for more details.

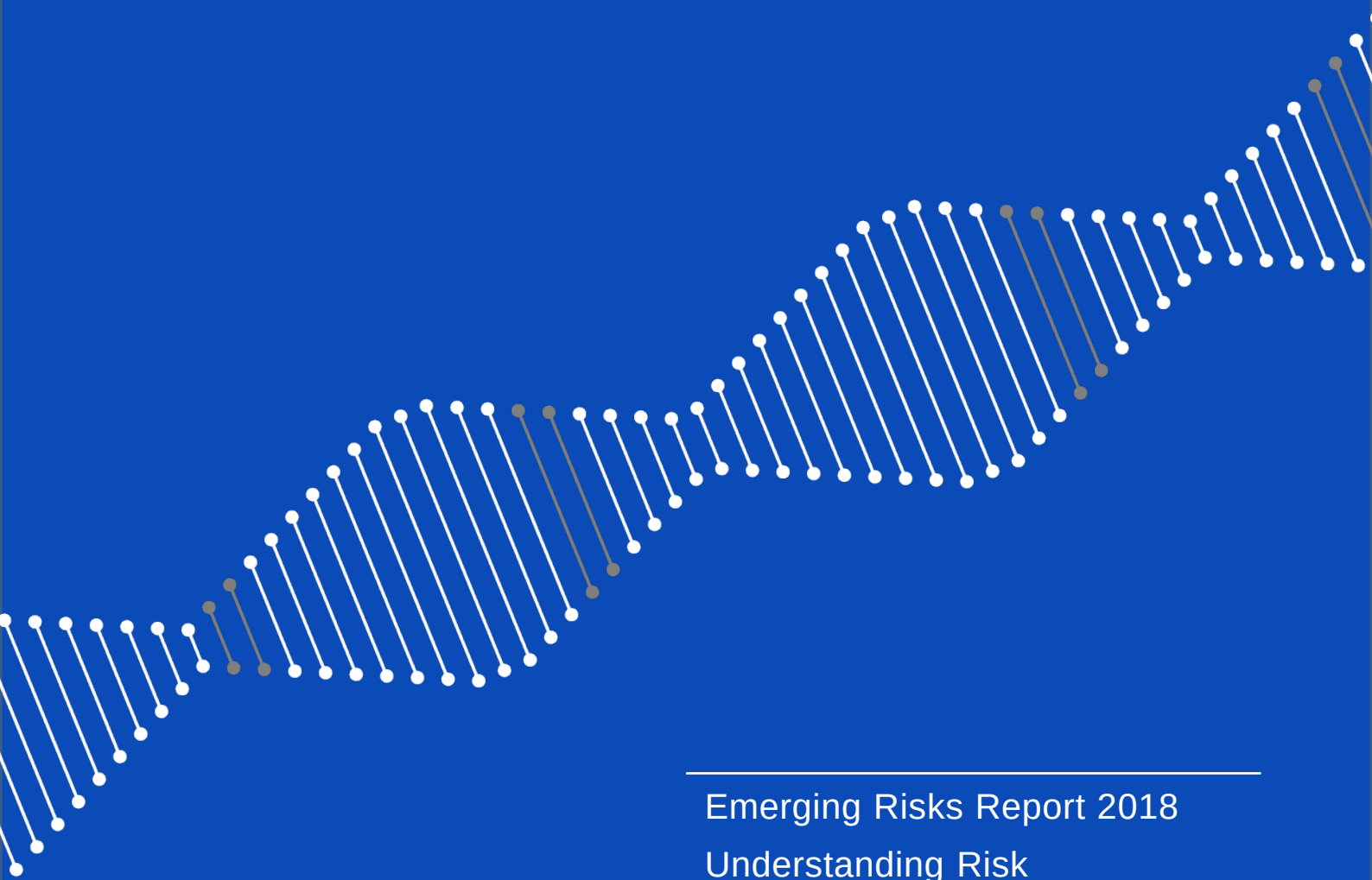
Commercialisation and digitalisation of research is enabling faster development, and there are new developments on the horizon such as gene drives (*see Section 2.7.1, p22*) that may push the field further forwards. These developments are also changing the risk profiles, and uncertainty is not narrowing but growing with each new development.

As the technology continues to gather pace and interest it has never been more important for insurers to consider the extent to which they wish to be exposed to such systemic risks, and scenario thinking and current biomedical and life sciences insurance tools may serve as a starting point. Action can be taken to support the responsible development of these new technologies, and there is potential for existing and new risk transfer solutions to be developed to underwrite this progress.

Companies must be open to discussing potential risks with brokers and carriers – transparency and collaboration are going to be key going forwards (Kerr, 2016). Health and safety, product liability and third-party liability risks will all need to be assessed. While biomedical and life sciences insurance may act as a starting point for those wishing to enter this space, new insurance solutions will need to be developed to secure developments and protect consumers.

The inclusion of appropriate limits continues to be a prudent approach and keeping a watchful eye on developments is advisable as bio-innovation emerges into more and more sectors.

Key conclusions of the 2009 report



Emerging Risks Report 2018

Understanding Risk

7. Key conclusions of the 2009 report

The following section outlines the key points raised in the 2009 report and the current state of play to illustrate the changes that have taken place:

1. Synthetic biology is a new and exciting technology

Humans have engaged in selective breeding for millennia and in genetic modification since the 1970s; however the new science of Synthetic Biology promises a step change in our power to shape life. Using this new technology, it is possible to engineer life from the ground up allowing the formation of organisms with genetic code not found in the natural world.

The technology is still in its infancy and arguably a few years behind Nanotechnology (the subject of a previous Emerging Risks Team report). However, we are already seeing some commercial examples and can expect growth over the next 10 years. This presents an opportunity for insurers; but as this report discusses also some risks to monitor and manage.

Current state of knowledge

Technology and understanding has continued to develop, with activity moving out of the lab into commercial applications and testing. Currently, the main products on the market are those that enable synthetic biology research (i.e. reagents, equipment, and tools that are used to develop new synthetic organisms).

There has also been a drive towards the founding of new commercial entities such as start-up and spinout companies based on early research discoveries. The first wave of these commercialised entities is beginning to enter the marketplace and there has been significant increase in such investments in the last few years.

Commercialisation and digitalisation of research is enabling faster development, and there are new developments on the horizon such as gene drives (*see Section 2.7.1, p22*) that may push the field further forwards. These developments are also changing the risk profiles, and uncertainty is not narrowing but growing with each new development.

2. Scarcity trends will drive innovation

There are 850 million undernourished people in a world with a population growing at more than 6 million per month. Already over 50% of people live in urban dwellings and estimates suggest this will rise to 60% by 2050 when the population will reach 9 billion. Many believe that Synthetic Biology will be one of the transformative technologies necessary to combat climate change, energy shortages, food security issues and water deficits.

By rewriting the genetic code, it may be possible to make plants disease resistant, and salt, heat and drought tolerant. The cost of large scale biofuel production and some medicines could be reduced as engineered bacteria produce the raw materials. Such scarcity trends represent a powerful need for technological development and therefore it is critical that we ensure responsible innovation.

Current state of knowledge

Scarcity trends continue to drive innovation, and this has been enabled by technology developments. Global trends such as sustainability have become areas of focus, and new unconventional areas such as synthetic biology to enable space exploration are being raised. After steady decline over a decade, global hunger levels appear to be on the rise with an estimated 815 million classified as undernourished in 2016, up from 777 million in 2015 (FAO, 2017).

The subject continues to remain an area of interest and groups such as the Gates Foundation are funding tangible developments for societal issues, and biomedical companies are using it to secure product supply chains, such as the Artemisinin example discussed in Box 2 *(see p12)*. Sustainability and inclusion is also at the heart of the United Nations 2015 Sustainable Development Goals, and technological innovation and the bioeconomy are part of the international strategy for meeting challenges.

3. There is no single set of regulations

There is no consistent global view on the appropriate approach to regulating Synthetic Biology; public opinion on the use of this technology appears to differ regionally. Within regions it is typical that there are several agencies with potential jurisdiction over processes using the new methods.

It would be useful (as in the case of nanotechnology in the US) if a single body was set up in each region to oversee and coordinate the approach and to aim for global consistency. The data for a traditional risk analysis will often be lacking in which case a precautionary approach is appropriate when the risks are potentially very high.

Regulations should require developers to consider low probability, high impact events as part of the risk management process. The use of Synthetic biology should be tracked carefully and labelling be introduced if it is used directly in food.

Current state of knowledge

In general, regulatory frameworks have not changed substantially since the 2009 version of this report. However, there is increasing awareness of the fact that synthetic biology can create products that do not conform to standard regulatory paths and there have been discussions about modifications to regulations needed for existing products.

None of the commonly used definitions of synthetic biology is rigorous, and it is not possible to draw a clear distinction between synthetic biology and biotechnology that would be widely agreed between academic and industrial practitioners, let alone one sufficiently unambiguous that it could be used to underpin a legal distinction.

Currently, synthetic biology products are regulated by type without regard for the way that they were developed, for example medicinal products are regulated as medicines, food products according to food regulations and so forth, and the associated laws and regulatory approval processes apply. There is no distinction between products made using synthetic biology and those made with other types of biotechnology.

4. There are valid concerns and actions should be taken to address them

There are fears that, as the ease of use of the technology develops, terrorists or criminals could procure segments of seemingly innocuous DNA and then recombine the pieces into bio hazardous substances. Alongside this “bioterror” there are also concerns around “bioerror”; the accidental release of synthetically engineered organisms that could lead to environmental or health problems.

Ecosystem effects are hard to predict and there have already been examples of unexpected gene transfer between GM crops and their nearby natural neighbours. Although scientists have made great leaps in their understanding of genetics in recent years there is still much we do not understand; unexpected results regularly arise. It is important to map the current uncertainties and set up research programs to fill knowledge gaps around the risks.

Current state of knowledge

The greatest change from the 2009 report is the increasing recognition of the potential impact around uncertainty of the types of things that can go wrong, let alone the probability of these risks occurring. Risks associated with synthetic biology research continue to include accidental release of biological organisms (bioerror), construction of biological weapons (bioterror), and potentially the unintended consequences of biological research. Many of the risks are not predictable.

Technology and automation is reducing the skill, knowledge, and time needed to create novel applications of synthetic biology. This trend raises real concerns around traditional risk management in the field, and all classes of business should be aware that applications may enter their sectors without explicit notification if activity is not already taking place.

5. Debate amongst key stakeholders is essential

A common complaint is that the views of all stakeholders are not taken into account. Some fear the creation of monopolies in food and energy production; others object to the concept of “patenting life”. Focus groups involving the public (including a variety of religious views), biotech industry, security advisors, developing countries, governments/regulators, insurers and research scientists should be held to ensure all views are understood.

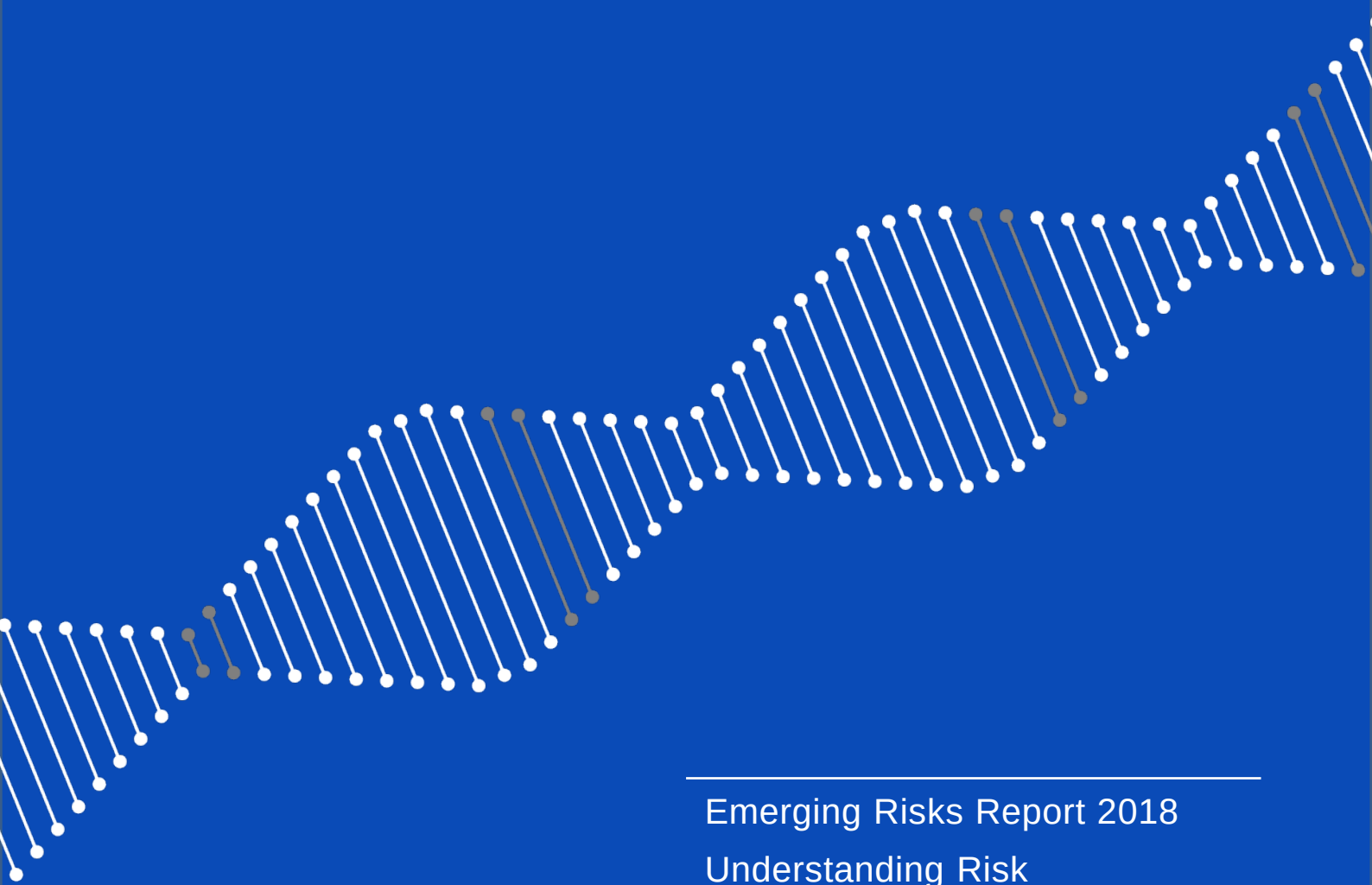
Some adverse scenarios (for example widespread and potentially irreversible ecological damage) might lead to large scale aggregations of liability though this would be decided in the courts if it were to occur. Insurers should consider the extent to which they wish to be exposed to such systemic risks; the inclusion of appropriate limits may be appropriate. For now, keeping a close watch on developments is advisable.

Current state of knowledge

This remains a key area of consideration and more literature and examples of debate amongst stakeholders can now be found to provide an evidence base. There is still a need to encourage broad debate before it becomes embedded, especially considering the widespread developments across sectors. Transparency and greater public awareness will also remain of increasing importance as regulation develops and more examples of synthetic biology applications make their way to market.

Companies must be open to discussing potential risks with brokers and carriers – transparency and collaboration are going to be key going forwards (Kerr, 2016). Health and safety, product liability and third-party liability risks will all need to be assessed. While biomedical and life sciences insurance may act as a starting point for those wishing to enter this space, new insurance solutions will need to be developed to secure developments and protect consumers.

References



References

Aftergood, S. 2017. Synthetic Biology and the Chem/Bio Threat [online]. Federation Of American Scientists. Available at: https://fas.org/blogs/secrecy/2017/05/dod-cbw-2017/

Alphey, L., McKemey, A., Nimmo, D., Neira Oviedo, M., Lacroix, R., Matzen, K. and Beech, C. 2013. Genetic control of Aedes mosquitoes Pathogens and Global Health, [online] 107(4), pp.170–179. Available at: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4001467/

American Chemistry Council 2018. Total revenue of the global chemical industry from 2002 to 2016 (in billion US dollars). Available at: https://www.statista.com/statistics/302081/revenue-of-global-chemical-industry/

Angulo, F.J., Nunnery, J.A. and Bair, H.D. 2004. Antimicrobial resistance in zoonotic enteric pathogens Rev Sci Tech, 23(2), pp.485–496.

Biotechnology and Biological Sciences Research Council 2012. Synthetic Biology for Growth Programme [online]. Available at: https://bbsrc.ukri.org/research/programmes-networks/synthetic-biology-growth-programme/

Bollack, L., Martel, S. and Pantjushenko, E. 2014. First antimalarial treatments produced with semisynthetic artemisinin enter market. Available at: http://www.path.org/news/press-room/685/

Boseley, S. 2016. Escalation of Ebola crisis could have been avoided, says World Bank president [online]. The Guardian. Available at: https://www.theguardian.com/global-development/2016/jul/18/ebola-escalation-could-have-been-avoided-world-bank-president-jim-young-kim-pandemic-financing-facility

Bradley, L.D. 2013. Regulating weaponized nanotechnology: how the international criminal court offers a way forward Georgia Journal of International and Comparative Law, 41(3), pp.728–729.

Brewster, S. 2016. Homebrew biology kit brings synthetic biology to the masses New Scientist. [online] Available at: https://www.newscientist.com/article/2076666-homebrew-biology-kit-brings-synthetic-biology-to-the-masses/

CB Insights 2017. Grapeless Wine And Cowless Milk: 60+ Synthetic Biology Startups In A Market Map [online]. CB Insights. Available at: https://www.cbinsights.com/research/synthetic-biology-startup-market-map/

Chardronnet, E. 2017. The MIT Media Lab takes leadership of the DIYbio community [online]. Makery. Available at: http://www.makery.info/en/2017/10/10/le-mit-media-lab-prend-le-leadership-sur-la-communaute-diybio/

Crossley, M. 2018. What is CRISPR gene editing, and how does it work? [online]. The Conversation. Available at: http://theconversation.com/what-is-crispr-gene-editing-and-how-does-it-work-84591

DEFRA 2007. Foot and Mouth Disease: Government Statement in response to investigations into the probable release of FMD virus from Pirbright. Available at: http://webarchive.nationalarchives.gov.uk/20081106100151/http://www.defra.gov.uk/animalh/diseases/fmd/investigations/pdf/govstatement_fmd2007.pdf

Diamond, J. 2002. Evolution, consequences and future of plant and animal domestication [online]. Nature, 418, p 700–707. http://www.nature.com/articles/nature01019

DoD 2017. The Department of Defense Chemical and Biological Defense: 2017 annual report to Congress [online]. Department of Defense. Available at: https://fas.org/irp/threat/cbw/cbd-2017.pdf

Dunlap, G. and Pauwels, E. 2017. The Intelligent and Connected Bio-Labs of the Future: Promise and Peril in the Fourth Industrial Revolution [online]. Wilson Briefs. Available at: https://www.wilsoncenter.org/sites/default/files/dunlap_pauwels_intelligent_connected_biolabs_of_future.pdf

ERA-CoBiotech 2018. ERA-CoBiotech [online]. Available at: https://www.cobiotech.eu/

ERA-SynBio 2016. ERASynBio Initiative [online]. Available at: https://www.erasynbio.eu/

Esposito, M. 2018. World Economic Forum White Paper: Driving the Sustainability of Production Systems with Fourth Industrial Revolution Innovation [online]. World Economic Forum. Available at: http://www3.weforum.org/docs/WEF_39558_White_Paper_Driving_the_Sustainability_of_Production_Systems_4IR.pdf

European Commission 2005. Synthetic Biology: Applying engineering to biology [online]. Nest High-level Expert Group. Available at: http://www.synbiosafe.eu/uploads///pdf/EU-highlevel-syntheticbiology.pdf

European Commission 2018. Deliberate Release and Placing on the EU Market of GMOs - GMO Register [online]. Available at: http://gmoinfo.jrc.ec.europa.eu/

FAO 2017. SOFI 2017 - The State of Food Security and Nutrition in the World [online]. Available at: http://www.fao.org/state-of-food-security-nutrition/en/

Health and Safety Executive 2015. Background on the regulation of specified animal pathogens [online]. Available at: http://www.hse.gov.uk/biosafety/background.htm

House of Lords Science and Technology Select Committee 2015. Genetically Modified Insects. Available at: https://publications.parliament.uk/pa/ld201516/ldselect/ldsctech/68/68.pdf

Huynh, M. 2017. Webcast of Astrobiology, Synthetic Biology, and the Future of Life [online]. NASA Astrobiology Institute. Available at: https://nai.nasa.gov/articles/2017/9/27/live-webcast-of-astrobiology-synthetic-biology-and-the-future-of-life-sep-28-9am-et/

InnovateUK 2018a. Beginner's Guide to Sustainable Aviation Fuel published [online]. InnovateUK. Available at: https://www.ktn-uk.co.uk/news/beginners-guide-to-sustainable-aviation-fuel-published

InnovateUK 2018b. First stage winners of the Future Fuels for Flight and Freight Competition announced [online]. InnovateUK. Available at: https://www.ktn-uk.co.uk/news/first-stage-winners-of-the-future-fuels-for-flight-and-freight-competition-announced

International Risk Governance Council 2010. Emerging risks: Melamine-tainted milk in China Emerging food safety risks: Melamine-tainted milk in China. [online]. Available at: http://irgc.org/wp-content/uploads/2012/04/Emerging_risks_Melamine.pdf

Keasling, J.D. 2014. Testimony Before the Subcommittee on Research and Technology Committee on Science, Space, and Technology United States House of Representatives. Available at: https://docs.house.gov/meetings/SY/SY15/20140717/102525/HHRG-113-SY15-Wstate-KeaslingJ-20140717-U1.pdf

Kerr, M. 2016. Gene Editing: The Devil's in the DNA [online]. Risk and Insurance. Available at: http://riskandinsurance.com/gene-editing-devils-dna/

Kinder, J. and Robbins, M. 2018. The Present and Future State of Synthetic Biology in Canada [online]. Available at: https://iog.ca/docs/The-Present-and-Future-State-of-Synthetic-Biology-in-Canada.pdf

King, D. 2017. Editing the human genome brings us one step closer to consumer eugenics The Guardian. [online] Available at: https://www.theguardian.com/commentisfree/2017/aug/04/editing-human-genome-consumer-eugenics-designer-babies

Lammens, T., Spekreijse Jurjen, Puente Ángel, Chinthapalli, R. and Crnomarkovic, M. 2017. Report with opportunities for bio-based chemical feedstocks and intermediates in the chemical industry. [online]. Available at: https://www.roadtobio.eu/uploads/publications/deliverables/RoadToBio_D11_Bio-based_opportunities_for_the chemical_industry.pdf

Lloyd's 2016. Use of Chemical, Biological, Radiological and Nuclear Weapons by Non-State Actors: Emerging trends and risk factors [online]. Lloyd's. Available at: https://www.lloyds.com/~/media/files/news-and-insight/risk-insight/2016/cbrn.pdf

Lloyd's and Arium 2017. Stochastic modelling of liability accumulation risk [online]. Available at: https://www.lloyds.com/~/media/files/news-and-insight/risk-insight/2017/stochastic_modelling.pdf

Mahoney, E. 2017. Synthetic Biology: 'Worker Microbes' for Deep Space Missions [online]. Available at: https://www.nasa.gov/content/synthetic-biology

McAlpine, K.J. 2016. Paper disc can quickly detect Zika virus in the field Harvard Gazette. [online] Available at: https://news.harvard.edu/gazette/story/2016/05/paper-disc-can-quickly-detect-zika-virus-in-the-field/

Minton, N. and Green, E. 2015. C1net conference (January) [online]. Available at: https://c1net.co.uk/wp-content/uploads/2018/04/cf1-abstract-book.pdf

Moshasha, S. 2016. The Rapid Growth of Synthetic Biology in China [online]. Available at: https://synbiobeta.com/rapid-growth-synthetic-biology-china/

Nature 2018. Synthetic biology [online]. Available at: https://www.nature.com/subjects/synthetic-biology

Niiler, E. 2017. The Pentagon Ponders the Threat of Synthetic Bioweapons [online]. WIRED. Available at: https://www.wired.com/story/the-pentagon-ponders-the-threat-of-synthetic-bioweapons/

OECD 2011. Future Prospects for Industrial Biotechnology [online]. Available at: http://www.oecd-ilibrary.org/science-and-technology/future-prospects-for-industrial-biotechnology_9789264126633-en

OpenPlant 2017. Open MTA [online]. Available at: https://www.openplant.org/openmta/

OpenPlant 2018. Vision [online]. Available at: https://www.openplant.org/vision

Paddon, C.J. and Keasling, J.D. 2014. Semi-synthetic artemisinin: a model for the use of synthetic biology in pharmaceutical development Nature Reviews Microbiology, [online] 12, p.355. Available at: http://dx.doi.org/10.1038/nrmicro3240

Pardee, K., Green, A.A., Ferrante, T., Cameron, D.E., DaleyKeyser, A., Yin, P. and Collins, J.J. 2014. Paper-Based Synthetic Gene Networks Cell, [online] 159(4), pp.940–954. Available at: http://dx.doi.org/10.1016/j.cell.2014.10.004

Pardee, K., Green, A.A., Takahashi, M.K., Braff, D., Lambert, G., Lee, J.W., Ferrante, T., Ma, D., Donghia, N., Fan, M., Daringer, N.M., Bosch, I., Dudley, D.M., O'Connor, D.H., Gehrke, L. and Collins, J.J. 2016. Rapid, Low-Cost Detection of Zika Virus Using Programmable Biomolecular Components Cell, [online] 165(5), pp.1255–1266. Available at: http://dx.doi.org/10.1016/j.cell.2016.04.059

Peplow, M. 2016. Synthetic biology's first malaria drug meets market resistance Nature, 530, pp.389–390.

Peplow, M. 2018. Looking for cheaper routes to malaria medicines Chemical and Engineering News, 96(11), pp.29–31.

Phuc, H.K., Andreasen, M.H., Burton, R.S., Vass, C., Epton, M.J., Pape, G., Fu, G., Condon, K.C., Scaife, S., Donnelly, C.A., Coleman, P.G., White-Cooper, H. and Alphey, L. 2007. Late-acting dominant lethal genetic systems and mosquito control BMC Biology, [online] 5, p.11. Available at: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1865532/

Primer Minister's Office Singapore National Research Foundation 2018. Singapore Consortium for Synthetic Biology [online]. Available at: http://www.nrf.gov.sg/programmes/technology-consortia/singapore-consortium-for-synthetic-biology

Radford, T. 2016. WHO paves way for use of genetically modified mosquitoes to combat Zika The Guardian. [online] Available at: https://www.theguardian.com/world/2016/feb/16/who-paves-way-for-use-of-genetically-modified-mosquitoes-to-combat-zika

Reason, J. 2000. Human error: models and management. BMJ (Clinical research ed.), [online] 320(7237), pp.768–70. Available at: http://www.ncbi.nlm.nih.gov/pubmed/10720363

Rijsberman, F. 2018. This is what you need to know about the bioeconomy [online]. World Economic Forum. Available at: https://www.weforum.org/agenda/2018/04/can-a-nature-based-economy-help-us-drive-green-growth

Saito, M., Uchida, N., Furutani, S., Murahashi, M., Espulgar, W., Nagatani, N., Nagai, H., Inoue, Y., Ikeuchi, T., Kondo, S., Uzawa, H., Seto, Y. and Tamiya, E. 2018. Field-deployable rapid multiple biosensing system for detection of chemical and biological warfare agents Microsystems & Nanoengineering, [online] 4, p.17083. Available at: http://www.nature.com/articles/micronano201783

Shanghai Institute for Biological Sciences, C.A.S. 2018. Key Laboratory of Sciences, CAS, Introduction [online]. Available at: http://www.sippe.ac.cn/klsb/eindex.asp

Singh, R. 2014. Synthetic Biology Market (Products, Technologies, Applications and Geography) - Size, Share, Global Trends, Company Profiles, Demand, Insights, Analysis, Research, Report, Opportunities, Segmentation and Forecast, 2013 - 2020 [online]. Allied Market Research. Available at: https://www.alliedmarketresearch.com/synthetic-biology-market?synthetic-biology-market

Stevenson, C. 2017. 22 Synthetic Biology Companies Have Raised Half a Billion Dollars in 2017 SynBioBeta. [online] Available at: https://synbiobeta.com/synthetic-biology-funding-2017/

Sumant, O. 2016. Synthetic Biology Market Size & Industry Report 2020 [online]. Allied Market Research. Available at: https://www.alliedmarketresearch.com/synthetic-biology-1520-market

SynbiCITE 2017. The UK Synthetic Biology Start Up Survey. [online]. Available at: http://www.synbicite.com/news-events/materials/uk-Synthetic-biology-start-up-survey-2017/

Synlogic 2018. Synlogic [online]. Available at: https://www.synlogictx.com/

Synthetic Biology Project 2018. Global Growth of Synthetic Biology [online]. Available at: http://www.synbioproject.org/inventories/maps-inventory/

The National Academies 2016. Gene Drives on the Horizon: Advancing Science, Navigating Uncertainty, and Aligning Research with Public Values. [online]. Available at: http://nas-sites.org/gene-drives/

The National Academies 2018. Project: Strategies for Identifying and Addressing Biodefense Vulnerabilities Posed by Synthetic Biology [online]. Available at: http://www8.nationalacademies.org/cp/projectview.aspx?key=49835

The Royal Society 2007. Call for views: Synthetic biology What is synthetic biology? [online]. The Royal Society. Available at: https://royalsociety.org/~/media/Royal_Society_Content/policy/projects/synthetic-biology/CallForViews.pdf

Thomas, J. 2013. Synthetic anti-malarial compound is bad news for artemisia farmers The Guardian. [online] Available at: https://www.theguardian.com/global-development/poverty-matters/2013/apr/12/synthetic-malaria-compound-artemisia-farmers

Thomas, J. 2016. The National Academies' Gene Drive study has ignored important and obvious issues The Guardian. [online] Available at: https://www.theguardian.com/science/political-science/2016/jun/09/the-national-academies-gene-drive-study-has-ignored-important-and-obvious-issues

Time 2007. The 2006 TIME 100: Bill & Melinda Gates [online]. Time. Available at: http://content.time.com/time/specials/packages/article/0,28804,1975813_1975846_1976564,00.html

University of Alberta 2018. Vice-Dean of Research - Faculty of Medicine & Dentistry [online]. Available at: https://www.ualberta.ca/medicine/about/governance/vice-dean-research

US Department of Energy Joint Genome Institute 2018. DNA Synthesis Science Program [online]. Available at: https://jgi.doe.gov/our-science/science-programs/synthetic-biology/

US Food and Drug Administration Centre for Veterinary Medicine 2017. Clarification of FDA and EPA Jurisdiction Over Mosquito-Related Products: Guidance for Industry. Available at: https://www.fda.gov/downloads/AnimalVeterinary/GuidanceComplianceEnforcement/GuidanceforIndustry/UCM533600.pdf

Waltz, E. 2016. Gene-edited CRISPR mushroom escapes US regulation Nature, 532, p.293.

Wegrzyn, R. 2018. Living Foundries [online]. Available at: https://www.darpa.mil/program/living-foundries

Welfare, R. and Clift, E. 2017. Synthetic biology: crash course [online]. Kennedys Law LLP. Available at: http://www.kennedyslaw.com/article/synthetic-biology-crash-course/

De Wit, R. and Bouvier, T. 2006. ‘Everything is everywhere, but, the environment selects’; what did Baas Becking and Beijerinck really say? Environmental Microbiology, 8(4), pp.755–758.

Woo, G. 2015. Fighting Emerging Pandemics With Catastrophe Bonds [online]. The RMS Blog. Available at: http://www.rms.com/blog/2015/01/28/fighting-emerging-pandemics-with-catastrophe-bonds/

Woo, G. 2016. Counterfactual disaster risk analysis (article in press) Variance. [online] Available at: http://www.variancejournal.org/issues/articlesinpress/Counterfactual-Woo.pdf

World Health Organization 2017. WHO Advisory committee on variola virus research: report of the eighteenth meeting, 2–3 November 2016, Geneva, Switzerland [online]. World Health Organization. Available at: http://www.who.int/iris/handle/10665/255211