# 2020 : THE "YEAR OF AI" AND ITS ROLE IN REVERSING R&D DECLINE

## A WHITE PAPER REPORT

- WHAT IS THE 'YEAR OF AI'? A LOOK AT THE INNOVATIONS AND TRENDS SHAPING 2020
- CAN AI REVERSE THE STEADY DECLINE IN PHARMA R&D OUTPUT? HOW?
- A LOOK AT OTHER MEANS TO REVERSE THIS DECLINE, FROM BUSINESS MODEL CHANGES TO STAFF SHAKE-UPS
- EXPERT OPINION ON AI IN PHARMA AND ITS IMPACT ON R&D

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# INTRODUCTION

The promise of AI, while inevitably enormous in the long run, has been slow in its delivery of real-world improvements to the thousands of sectors it has the potential to benefit. Yet now, at last, the 'year of AI' is being heralded: some have said 2019, some 2020, but in all cases it is without doubt: the promise of computer-assisted pharma is coming to a head.

The pharmaceutical industry has long been foremost in need of the radical change AI offers, but due to a dozen factors has been slow in uptake even of simpler AI and machine learning (ML) processes. Now, as pharmaceutical giants become aware of the potential AI contains, the coming years will see a radical shift in how companies big and small work and strategise.

But does AI have the stunning potential experts have suggested? Can it reverse a decline older than AI itself? Are other methods required in order to fully turn around the industry, or can the miracle of AI, ML and big data alone solve the issues of so many companies in the field?

This white paper aims to answer those questions. With analysis and commentary from leading experts in AI and drug discovery, the validity and potential of this 'year of AI' will be discussed, alongside reflections on the change that will be seen over the next few years and what else will be needed to turn the tide on pharma R&D decline.

We hope you enjoy this white paper, and find the insights contained within valuable to you and your company.

**Joshua Neil, Editor**,
Proventa International



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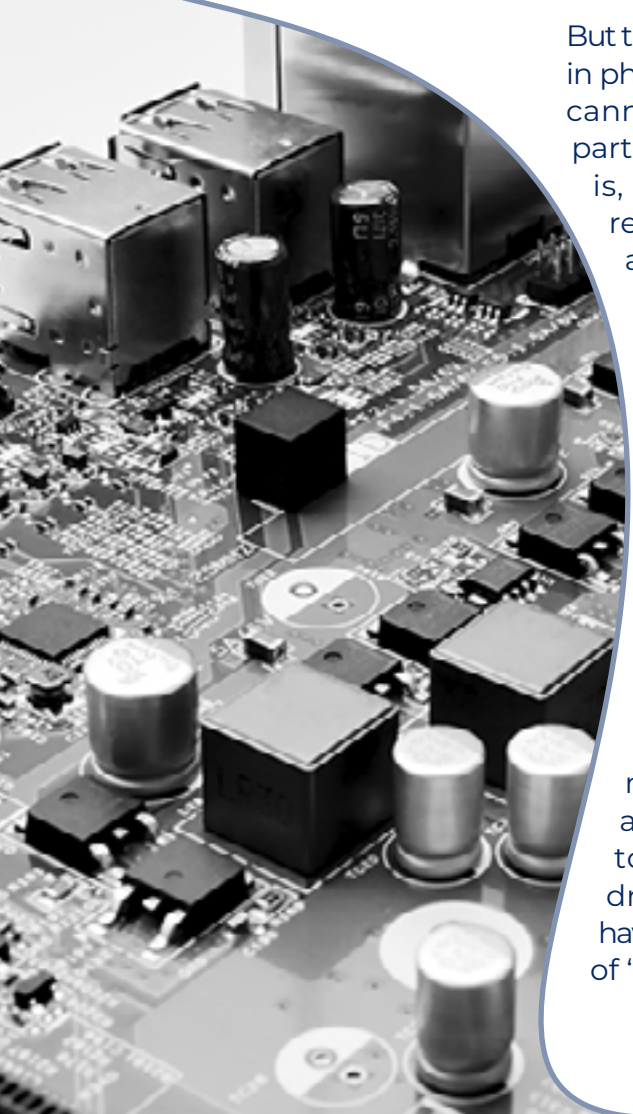
# EXECUTIVE SUMMARY



Both 2019 and 2020 have alternatively been labelled the 'year of AI' for the pharmaceutical industry: the time during which AI and machine learning algorithms finally come into their own and affect real, noticeable change in the sector.

While a number of larger pharma companies have dabbled with the use of AI - notably in data analysis, finding clinical trial patients, ensuring adherence to drug regimes and even attempting the development of entirely new drugs - many have held back from meaningful investment in the area. Up until this point most have been content to rely on traditional methods of drug discovery and using AI only in line with industry development. Until now, the envelope has remained for many firmly unpushed.

But the decades-long decline in pharma R&D productivity cannot be ignored forever, particularly when the industry is, by many accounts, reaching a critical stage at which return on investment will soon vanish completely. New methods and tools are needed to reverse this trend, and for many AI is a key component in this reversal.

With 2020, technologies that for a long time have been tested and dabbled with will come into full, major effect. These include:

- AI in drug design—data mining and intelligent algorithms offer the chance to identify complex, rare drug targets which so far have been missed in preference of 'low-hanging fruit'.
- Deep learning—An increased ability to excel in image and data processing and within the chemical space promises greater global projects and novel opportunities for patient monitoring and recruitment
- AI training models—such as MELLODDY, created to train algorithms on datasets from several pharma giants

The year of AI has seen other changes in the pharmaceutical sector as a whole: a rise in the acquisition of innovative CRO and biotech companies by big pharma, co-opting their software and using it for their own ends; large-scale collaborations between big pharma and smaller innovative biotechs; and the move to top-down AI skillbases, with an increasing number of tech-savvy CEOs and CSOs implementing real changes. These have involved hiring professionals who can fully comprehend the AI situation, and who have the power to transform drug discovery processes.

For the vast majority of experts consulted, AI seems - even on its own - the answer to the decline in pharma. Its ability to radically alter data capture, analysis and processing opens up a thousand possibilities not possible with human work alone. Its hyper-intelligent algorithms have the chance to find countless drug targets and possible drug combinations that would take years to discover without its help. With the effects of AI on patient identification, drug effect prediction and remote monitoring, 2020 - let alone the next five to ten years - could spell a revolution in pharma that brings unprecedented growth to the sector.

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# HISTORICAL DECLINE IN PHARMA R&D

## THE STATISTICS

The decline of progress in pharma's R&D over the last five to ten years is no secret, with its causes many and complex. The main issues facing pharma professionals include rising costs and diminishing returns on investment for each new drug, and crippling failure rates for new compounds in the R&D pipeline. Due to budgetary issues, mergers and acquisitions are increasing as consolidation becomes vital in the industry.

The statistics speak for themselves. Pharmaceuticals' efficiency has been steadily declining since the 1950s, with most drugs costing more than $2 billion to make and push through to approval. A 2013 study by the Tufts Centre for the Study of Drug Development set out to determine the R&D costs of 106 new drugs created by ten different biopharma companies. It found that the average pre-tax cost for each drug up to approval was $2.56 billion, up from the equivalent of $1.04 billion in 2000: an increase of 250% in the 13 years from 2000.

Drugs have a 92% failure rate overall: around 40% of drugs that reach late-stage clinical trials still fail, where the stakes are highest.

Over the last 40 years, the number of drugs which reach the market, per $1 billion of R&D investment, has fallen by a factor of 30, giving the pharmaceutical industry a general return on investment of around 3.2%.

A similar 2018 study by Deloitte found that for 12 biopharma companies reported on, projected returns have more than halved in three years of reporting, now at around 1.9%. The range of values between the top and bottom performers were also narrower than had ever been reported before.

Perhaps the most damning statistics for the decline came from a popular 2017 article by Kelvin Stott, that given pharma R&D's return on investment in the last twenty years, by 2020 internal rate of return would hit 0%: that is, $1 made for ever $1 spent, or breaking even on investment. This trend would then continue downwards, with pharma making losses on every investment unless something radical was done.

> "The main issues facing pharma professionals include rising costs and diminishing returns on investment for each new drug, and crippling failure rates for new compounds in the R&D pipeline.

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# HISTORICAL DECLINE IN PHARMA R&D

## WHY THE DECLINE?

The reason most commonly espoused for R&D's steady decline is one of naturally diminishing returns - the centrepoint of Stott's research. As pharma has found the 'low-hanging fruit' over decades each subsequent drug becomes both more expensive and more difficult to synthesise, given the increased standard of health and reduced number of targets with each successful drug discovery.

One professional, speaking from his expertise as a former Lead in Digital Innovation in a major pharmaceutical company, agreed with this theory. He noted that many major diseases received cures quite quickly, but once these low-hanging fruit had been hit cures became more difficult to find: "They become more difficult because even though companies like Eli Lilly and Biogen have been working on identifying the right compounds or targets to conquer the diseases, they've found no success because they're just not as easy as the ones already conquered.

"In any industry, if you start with a clean slate it's easier to achieve quite a lot. But once you hit the major milestones, achieving the next - in this case diseases like Alzheimer's or Parkinson's - are progressively more difficult."

Peter Henstock, AI and ML Lead at Pfizer, suggested that clinical trials represent a relatively new opportunity for AI. Most of the work in AI within pharma has focused on the drug discovery area, followed by the Real World Evidence. However, there are many opportunities in patient selection, patient engagement, and a number of other areas.

Another suggested reason for the decline relates to diseconomies of scale as a result of pharma's long history of consolidation and scaling-up: it was wrongly believed, some have said, that R&D can be scaled up, industrialised and driven by specific metrics. As R&D units became larger and more complex, what actually resulted was a considerable loss of accountability, creativity and risk-taking attitude.

Evidence for this viewpoint was gathered by an employee of Eli Lilly in 2009, who found that for the last 60-odd years annual new molecular entity (NME) output per company had remained constant, regardless of R&D team size or level of investment. With hugely increasing cost per NME, and the gradual loss of the "low-hanging fruit" that came out of this steady process, it can be seen why the number of NMEs discovered by the large pharmaceutical companies fell from 75% in the early 1980s to just 35% in 2007.

But there are many other reasons circulating for the rising cost and declining returns of pharma R&D: a potentially broken business model; the inherent unpredictability of drug discovery; and tougher regulatory rules which require more testing and evidence before a drug can go to market. There is certainly no one definitive reason given for the issue, which makes finding a solution considerably harder than it otherwise would be.

But looking at the statistics, it is clear that certain truths are self-evident: whatever the reason, pharmaceutical production is suffering, return on investment is faltering and not enough drugs are making it through to market. And the solution to all of these issues seems increasingly to rest on one idea: artificial intelligence and machine learning.

2.1

# WHAT IS THE YEAR OF AI?

The heralding of 2019/2020 as the "Year of AI" extends well beyond the borders of the pharmaceutical sector. While dozens of technological advances are being speculated on as coming to fruition in the near future - functional chatbots, for example, or connected clouds - the centrepieces for all these varied trends and innovations are the core ideas of big data analytics, ML and automation.

All companies are turning to data to function better, whether they are gathering information for research or understanding market patterns. As companies expand and business time requirements become more and more imminent, it is vital for every company that more data is gathered more quickly for them to act with ever-increasing speed. While almost all the world's data has been created in the last few years alone, almost none of this - statistics speculate 1% for unstructured data - is being used effectively. As processing power improves, ML programs will be able to better comprehend, process and analyse a company's data.

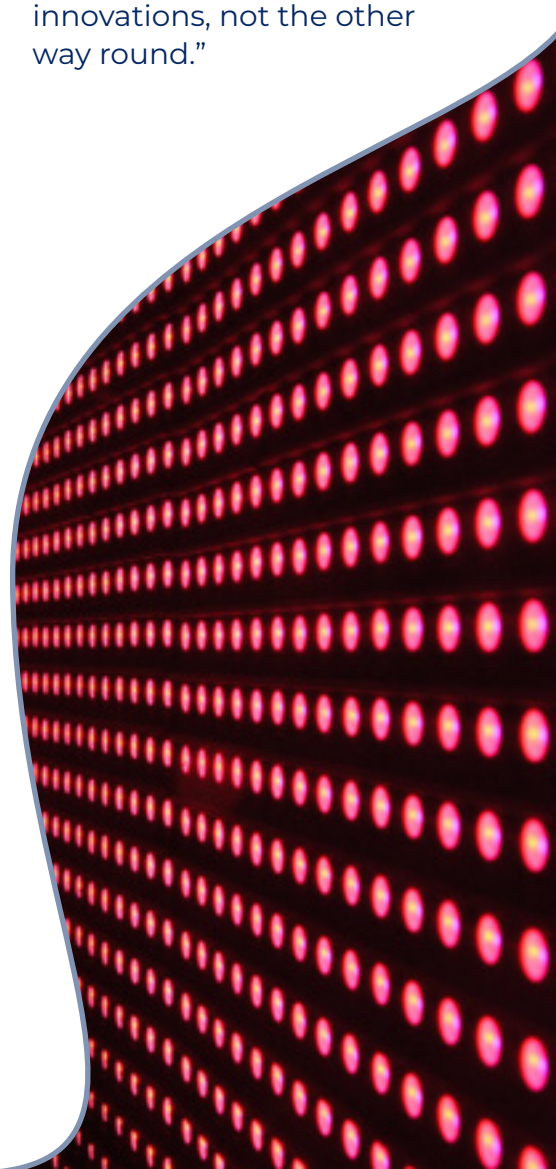
Now, after more than five years of increasing hype as AI developed and slowly began to integrate into the working routine of pharmaceutcal companies, nextyear has been hailed by some as the 'year of AI'.

That 2020 is the start of this revolution in pharma R&D is down to several reasons that before now have been neglected by pharma and biotech companies. Overcoming the hype and initial reluctance to believe in the technology has been a slow process for many businesses, and only at this stage are companies - even some giants - investing in the technology and acquiring the businesses that will allow them to innovate and stay ahead of the curve.

Increasing processing power has also made now the time to invest: AI and ML algorithms, more powerful than ever before, finally have the ability to make a real impact in R&D processes, from mining data to analysing diverse and unstructured information to performing incredible feats of target acquisition and drug synthesis. While other options for reversing the (some say terminal) decline in the R&D pipeline have been proposed by experts, the promise of AI is the one that everyone is looking to as a saviour of the industry. But with problems of its own and the warnings of some that the pharma business model itself is broken, it is yet to be seen whether this 'year of AI' and the years that follow can really reverse the damage done to the pharmaceutical industry, and deliver the benefits that have been promised for so long.

The former Lead in Digital Innovation dissented against the concept however, arguing that the progress of innovative technologies was more dependent on not only the particular domain and industry but also where a particular company was in its journey.

He exemplified this with the argument that CEOs, the individuals deciding whether or not to invest in innovations, would not make the decision to invest $20 million or more based solely on the suggestion of a 'year of AI'. "Instead, they'd look at their business strategy and what they need to provide for their company. For them the objectives are the customer, the shareholders, and how the company can be made more profitable. That's the focus. The business is driving the need for tech like AI and other innovations, not the other way round."



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# CURRENT USES OF AI IN PHARMA

During the early years of AI, which began within the pharma space between 2012 and 2015 with initial instances of deep learning systems outperforming individuals in the yearly ImageNet Large Scale Visual Recognition Competition, big pharma paid little attention. Many believed that it would play out as had the internet revolution before: not only did the internet fail to bring R&D costs down, but it actually increased them. Due to this, some companies were resistant to the notion of deep learning and AI.

This is changing, however: In 2017, Verdict AI ran a survey in which more than 70% of pharmaceutical companies said AI would be very important to them in the near future. Where AI was implemented, it was done in broad, non-specific areas, CEOs and business leaders often choosing to enhance and supplement current processes and technologies rather than take the radical step of replacing them entirely.

That said, AI is having an increasing impact on pharmaceutical operations, with its possible uses many and varied. Examples of areas in which the new technology can have a big impact include data mining, predicting the effects of treatments and in new company acquisitions. A particular instance where AI can make a real, powerful difference to R&D right now is in mining early data to build research

## MINING & ANALYSING DATA

Analysing data from patients, clinics, literature and other sources to find research ideas can hugely change the pharmaceutical industry. Focusing on peer-reviewed, validated data ensures ML algorithms learn correctly and are more accurate, while validation of these simple, structured sources should be a relatively simple thing to do, allowing for updates to the algorithm to be made easily and quickly.

This technology is already in use with several companies looking to mine data from life science sources to improve insights: BenchSci, backed by Google, uses an AI antibody search service for its clients, while AI company Bioz has created the first ever AI-driven search engine for the life sciences.

Regarding analysis, AI can work wonders in this area also: current use examples include BMS' collaboration with Concerto HealthAI, which uses new tech to analyse real-world oncology data; and Novartis' digital transformation, which includes the creation of a predictive analytics platform to assess clinical trial operations.

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# CURRENT USES OF AI IN PHARMA

## DETERMINING PATTERNS AND DRUG REPURPOSING

Nowadays, the overwhelming use of sophisticated AI software within pharma is to detect patterns more quickly and efficiently than humans can. Both Bayer and Merck, for example, use algorithms to analyse image findings from lung perfusion, cardiac and pulmonary vessels, as well as patient notes, to determine risk of diseases such as pulmonary hypertension and allow experts to diagnose individuals earlier for better outcomes.

A good example here is Atomwise, which has used deep neural networks to analyse simulations of molecules, saving scientists time in testing the real thing. In 2015, it used its algorithms to determine which molecules could bind to a certain glycoprotein to treat Ebola. Since 2015, repurposed drugs count for around 2% of all pharmaceutical revenue: by 2020 the market is expected to reach $31.3 billion, up from $24.4 billion five years ago. AI is a facilitator of this boom: while drug repurposing has been conducted for a while, both through knowledge-based discovery and through experimentation, often these are limited in resource and scope.

AI approaches can change this. Such methods are done by training ML algorithms to mine data from a number of different sources, including scientific literature, health records, clinical trials and phenotypic information. Unlike previous methods, AI-based drug repurposing can integrate many different types of data and reveal connections that otherwise would be extremely difficult to determine.

The benefits of such a process are self-evident: the use of drugs already in service removes the need for a second phase one trial, where safety is tested, and renders unnecessary all the cost and time a company usually spends in designing and developing a novel drug. The potential for FDA fast-tracking also speeds up the entire process, and creates the possibility of a much swifter turnaround time for a drug than normal. That said, the AI systems here are only as useful as the datasets they mine: greater industry collaboration and access to new datasets are needed before AI can fulfil its full potential in drug repurposing.

Healx is a good example of a biotech focusing on this area of drug discovery: rather than identifying new molecules and compounds with potential efficacy for treatment, the company uses its AI software to examine drugs already in existence and then to repurpose some to cure other rare diseases beyond the drugs' original intent.

## PREDICTING TREATMENTS' EFFECTS

One of the more complex current uses of AI is to test how drugs will impact patients: automated gathering and analysis of patient data can help understand potential side effects of new drugs, mapping out genes responsible for disease and better predicting how patients will react to treatment. One of the companies pioneering this technology is Verge Genomics.

This application of AI today leads into another: drug dosage optimisation, where analysed data can quickly and efficiently determine the exact level of drugs needed by a patient for a given illness.

CURATE.AI is one example of such a technology being used in the sector today; Reverse-Engineering & Forward Simulation (REFS)-generated ML models are another.

These REFS models are able to identify possible relationships between several factors affecting results, including how a patient can absorb compounds and variations in patient metabolism, by reverse-engineering to find factors affecting patient drug responses and then comparing them with the patient's case. Simulations are then run until the best drug treatment is found for that patient.

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# CURRENT USES OF AI IN PHARMA

## REMOTE MONITORING

A newer use of AI is that of patient monitoring: smartphone apps, wearable devices and even particular keyboards can be used to monitor and interpret patient usage and wellbeing, in some cases reducing assessments of conditions such as motor function from half an hour to a tenth of that time. The need for this technology is evident: a high percentage of patients with chronic conditions still fail to take their medication, compromising the effectiveness of treatment and damaging health outcomes. This becomes even more important an issue due to the increasing complexity of clinical trials in recent decades, requiring even more scrutiny of patients within them.

The AI methods of monitoring patients remotely are numerous: companies have found success through encouraging patients to take clinical-quality images remotely from their phones, using 'smart keyboards' to register patient keystrokes and activity, or use wearable Apple watches to monitor a range of health information as the patient goes about their day-to-day business.

## AUTOMATION

Many large companies are also using the increased computing power to automate many previously laborious tasks: Amgen, Pfizer and Novartis, for example, have collaborated with MIT to automate small molecule discovery and synthesis; Genpact is working with Bayer to automatically extract adverse event data from source documents; and Sanofi has allegedly partnered with Researchably to cut reviews times by automating medical literature reviews.

> The year of AI will be distinguished from what has gone before it by the innovation and complexity seen in the next wave of AI in pharma.

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# THE YEAR OF AI

The year of AI will be distinguished from what has gone before it by the innovation and complexity seen in the next wave of AI in pharma. Pharmaceutical companies will no longer be content to integrate broad AI solutions to their business, supplementing existing processes but not radicalising their internal structure. Now, real and company-wide change will be effected as AI becomes a crucial, all-encompassing part of every company that intends to compete in the sector.

## DRUG DESIGN

Dr. Alex Zhavoronkov, CEO of Insilico Medicine, believes that due to a general focus on sales by many pharma companies, internal R&D will be the area hit first by AI's new wave of innovative technologies.

But how will the adoption of certain technologies or the acquisition of owner companies reverse the decline in pharma R&D? They key is in processing power and speed. ML programs are able to screen thousands of potential drugs and rapidly analyse their effectiveness in stopping current diseases, through deep learning and scrutiny of successful past targets. The main benefit of using AI in this regard is that combinations which cannot work are quickly filtered out, reducing the pool of available options for new drugs and instantly increasing the chance of success.

A perfect example of ML used in this way is Microsoft's 'Project Hanover', in which an algorithm sorts through vast quantities of cancer research data to better personalise medicine for the patient.

According to Microsoft, Project Hanover is an innovation in using ML as 'curation-as-a-service'. Rather than labelling and annotating all data the ML algorithm would be trained on, a combination of deep learning and probabilistic logic allows Hanover to compensate for a lack of labelling and analyse data more effectively than otherwise.

The algorithm's results do still need to be vetted by subject matter experts to ensure success, but as time progresses the algorithm will learn from this assisted curation to improve its own cultivating skills.

Currently, Project Hanover is focusing on the areas of molecular tumour boards, real-world evidence and clinical trial matching. In the future Microsoft suggested the potential for combining machine reading results with causal ML to better facilitate cancer decision support and disease management.

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# HOW WILL AI CHANGE PHARMA IN 2020 AND BEYOND

## ACQUISITIONS

Big pharma companies are beginning to build their own internal expertise, but still there have been few acquisitions of AI startups by big pharma in the past five years, despite credible demonstrations by Deep Genomics that AI can accelerate at least a small part of pharma R&D. Until these acquisitions begin, Dr. Zhavoronkov argues that there will be no 'Year of AI'.

Acquisitions are the easiest means by which new technology and innovation can be brought into a company, and according to Dr. Zhavoronkov companies with clinical-stage assets are likely to be acquired first, despite being perhaps less innovative than other AI companies in the field. This is because, he speculated, once a company moves towards clinical or preclinical work, it moves away from AI innovation, due to a need for a different expertise set and a greater need for value in processes. According to Dr. Zhavoronkov, 2019 is the first year where tangible, credible validation exercises are being held in multiple areas by startups. He mentioned that his own group recently released a major paper in Nature Biotech, in which generative adversarial networks and reinforcement learning were used to create novel molecular structures, validating the research experimentally as proof.

The ability to generate such novel drug candidates requires AI to handle a number of tasks well: it must analyse complex datasets and generate new insights based on them; identify candidates from these insights; analyse data from patient samples to find new biomarkers and targets; predict the affinity of the molecules to bind; and allow filtering for drug-like molecular properties, among other things.

Insilico Medicine's network deploys two deep neural networks against one another: the first takes in certain inputs, such as the desired characteristics of a potential structure such a solubility and bioavailability, and using this discovers molecular structures. The second then analyses and judges these molecular structures to ensure their suitability. Within this conflict, the two networks learn as a result of their competition.

Another company, Deep Genomics, recently revealed a similar project, in which its AI platform AI Workbench identified a new genetic target for Wilson disease and designed a new oligonucleotide therapy, DG12P1, all within 18 months. This therapy will be moved towards clinical studies in the next two years.

A third example of this recent AI excellence can be found in Recursion's announcement that its AI collaboration with Takeda, begun in 2017, has yielded 60 unique indications' worth of new preclinical and clinical small molecules, and new therapeutic candidates for several diseases.

London-based Benevolent AI has been doing research into motor neurone disease. Its AI-led system is able to review billions of sentences and paragraphs from millions of scientific research papers and abstracts.

The AI technology is then able to link direct relationships between the data and regulates the data into 'known facts'. These known facts are curated, and previously unrealised connections made, to generate a large number of possible hypotheses using criteria set by the scientist. The process could save an enormous amount of time and resources during the drug discovery process.

GlaxoSmithKline, meanwhile, signed a $43m deal with British AI firm Exscientia in July 2019. The pharma giant hopes to harness modern supercomputers and ML systems to predict how molecules will behave and how likely they are to make a useful drug, thereby saving time and money on unnecessary tests.

It is evident, then, that takeup of AI and ML algorithms in the industry has slowly increased

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# HOW WILL AI CHANGE PHARMA IN 2020 AND BEYOND

over the last few years: studies still show, however, that less than 5% of healthcare organisations have actually made the move to invest in AI technologies. Despite the many uses of AI today, only as takeup increases and more companies begin to invest will the true potential of the technology be seen

## SHORTAGE OF TALENT AND THE MOVE TO TOP-DOWN SKILLBASES

One of the major difficulties many pharma companies will face in the coming few years is a dearth of industry specialists, many having been rapidly acquired by more traditional IT and AI companies: at present, only around 15.6% of AI-driven drug discovery companies' staff are AI experts.

To combat this lack of AI expertise, as well as to rectify a number of other issues within evolving pharma companies, Dr. Zhavoronkov noted the need for Chiefs of AI to take a more prominent and strategic role in a pharmaceutical company. Often, he said, when companies select their Chief of AI they look for an individual who is embracing AI for the stratification of trials or patient sub-populations, or who excels at text data analysis. What's more crucial - and will be increasing crucial as time goes on - is a pure AI expert who is able to look at the AI situation from end to end, and crucially has the power internally to transform drug discovery processes to incorporate large-scale changes. "You need to put the chief of AI as CEO or CSO of the company."

Dr Henstock agreed with this assertion. He said even since 2019 companies have gone from a place of speculation around moving into AI, to another in which every big pharma company not only seems to have an AI strategy but is implementing it - an extraordinary change in a single year.

With this change he asserted that companies are no longer simply throwing money at whichever company claims it can 'do AI': now groups are being formed, many positions have an active AI component, and he even suggested that given "another year or two" some major problems surrounding AI in pharma would begin to be solved.

A recent study backs up this idea: of the CEOs and board members surveyed across the U.S, Japan and Germany, only 3% had any education or experience in both AI and pharma. Their companies were, however, expected to outperform the market due to this knowledge.

## DEEP LEARNING

Dr Henstock noted that predictive models and algorithms have existed in pharma for more than 15 years now, without changing to a radical extent. The sudden rise of deep learning promises to perform such predictions more accurately - and the technology can be applied to vastly more applications: literature and patent mining, image processing, biology and chemistry problems.

2020 has been posited as the year when deep learning and generative adversarial networks in particular become even more important to companies looking to revolutionise their processes.

Deep Learning consists of a number of hidden layers between input signal and result, with each layer operating independently of its peers but simultaneously. Currently, deep learning is around 10% more accurate at analysing data, from ophthalmology and pathology data to radiology images, than the average physician.

New areas affected include image processing, which is vastly more possible with the AI-granted ability to analyse every single cell on every single slide produced. New algorithms can show details of elements missed by scientists, identify obscure patterns, and determine how individuals are rating the images differently. The same can be said of text, chemical structures and other areas: in all instances new technology allows scientists to

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# HOW WILL AI CHANGE PHARMA IN 2020 AND BEYOND

do different types of experiment than otherwise they would have been able to.

Deep learning has ramifications across the entirety of the pharma area: with greater analytical and predictive ability scientists can institute global, large-scale programs to better run R&D, changing the nature of pharmaceutical problems that currently cannot be answered.

## BIG COLLABORATIONS

Another new trend worth noting is for deals struck between big pharma companies and tech giants, such as the recent five-year collaboration between Novartis and Microsoft, looking to enhance the drug company's research processes through Microsoft's advanced analytics and AI technologies. Other such collaborations include:

- Watson Health and Pfizer - the Watson ML system was intended to boost Pfizer's immuno-oncology discovery rates
- Benevolent AI and AstraZeneca - an attempt to use AI and ML to discovery new kidney disease and idiopathic pulmonary fibrosis drugs
- Iktos and Janssen - Janssen is applying Iktos' virtual drug design technology to a number of its small molecule drug discovery projects, hoping to create deep generative models and develop new applications

As Dr Henstock acknowledges, Insilico Medicine and Benevolent AI are both companies with an 'interesting' business model combining a pharmaceutical company with deeply entrenched AI expertise. He said the industry is eager to learn whether such an approach can transform the pharmaceutical R&D paradigm and outperform big pharma.

He added that one of two things will likely happen in the next few years: big pharma will build substantial AI programs in-house to bring the capabilities of the high tech smaller biotechs, or strategically outsource much of the AI work instead. A sizeable challenge in either case is finding talent who understand both the scientific and AI/deep learning aspects of the problem.

## THE RISE OF CHINA

Commenting on the companies that were performing the most innovative, forward-thinking work in pharma AI at the moment, Dr. Zhavoronkov commented that beyond his own company and certain other biotechs like Deep Genomics, there were a number of innovative companies in China that could not be ignored.

The former Lead in Digital Innovation hinted at the same conclusion when discussing the concept of the 'Year of AI'. "Companies like Baidu and Alibaba have already invested substantially in the AI space, laying out the foundations of the data so their AI and machine learning can take advantage of it. Other countries and companies aren't at that stage yet, either because they want a slower introduction or to see what other companies are doing and invest in successful business cases."

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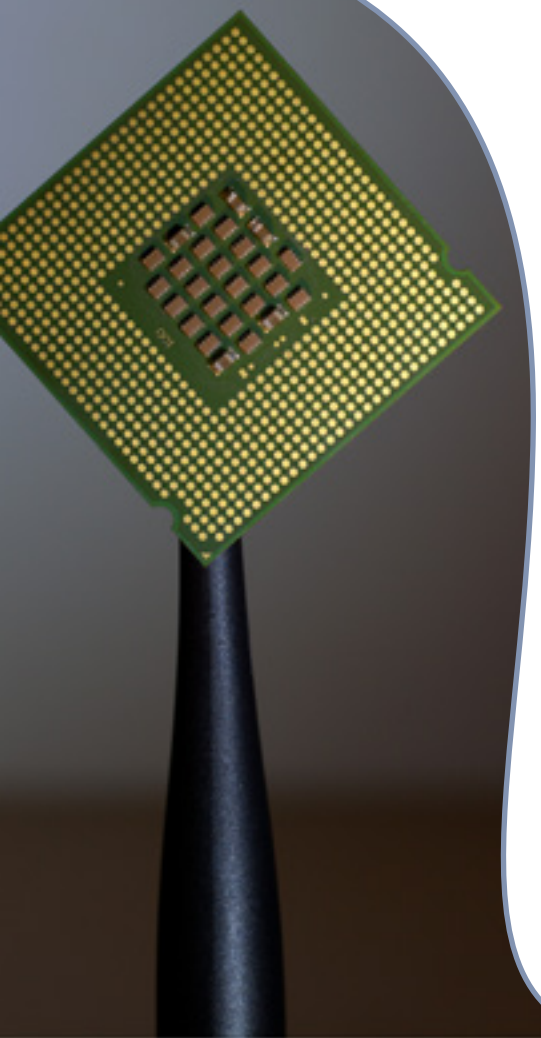
# HOW WILL AI CHANGE PHARMA IN 2020 AND BEYOND



General statistics buoy up these claims, with Chinese investment in biotech and drug discovery rising sharply in 2019 to $1.4 billion, compared to $125.5 million in 2017. In 2017 the Chinese government released an AI strategic plan, declaring the goal of catching up in the AI race by 2020 and becoming a world leader by 2030.

China benefits greatly from the size of datasets created from its population, with reduced privacy laws facilitating greater access than is available in some other countries. It has been bolstered by rapid migration of experts from other parts of the world, and governmental policies which push research forward. However, a lack of core pharmaceutical skills and less intellectual property protection will ensure the catch-up is not as swift as it might otherwise be.

## AI TRAINING MODELS

Another recent development that will continue to grow over the course of the next year is a change in the model used for training AI and ML algorithms to work. Naturally, training such algorithms requires an enormous amount of data to pore over, which in pharmaceutical companies is often either siloed and unavailable or private and sensitive. Furthermore, the data that is available can often be susceptible to biases due to the limited scope of data sources.

In 2019, several pharmaceutical companies and research institutes started the ML Ledger Orchestration for Drug Discovery (MELLODDY) project. This was created to train ML algorithms on a number of private datasets from several major pharma companies, avoiding breaches of privacy and confidentiality with the use of blockchain and federated learning. From MELLODDY, a platform is being made which will use the data to more accurately model promising compounds to take through to later stages of drug discovery and development.

MELLODDY uses Amazon Web Services technology to train and execute ML algorithms for pharma in a secure way. The data is never removed from the company's possession, and no sensitive data is used. Instead, a central dispatcher ensures that a common model is shared by the companies that can be consolidated as the project continues.

Blockchain is used to ensure both privacy and traceability, with all partners approving any contract between dispatcher and ledger before it can go ahead.

> A sizeable challenge... is finding talent who understand both the scientific and AI/ deep learning as-pects of the problem.

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# HOW WILL AI CHANGE PHARMA IN 2020 AND BEYOND

> I think that given all the technology available right new, given the added data provided with better imaging, sequencing, etc, AI has the best chance of improving the situation, as I see it.

## CASE STUDY: INNOVATIVE DEVELOPMENT OF AI IN PHARMA

Dr Zhavoronkov related two case studies of his own company, Insilico Medicine, where AI innovations were tested and outperformed existing methods to improve the R&D field.

In the first, a big pharma company challenged Insilico Medicine to identify novel drug targets in a specific disease area, and also generate the molecules for those targets, within one year. Insilico Medicine used an entirely 'driverless' mode for this test, relying entirely on AI even for target selections.

The first attempt at this challenge was undertaken by a partner of the pharma company, which underwent a process of analysing the targets and buying molecules from chemical libraries. This company, said Dr. Zhavoronkov, had a ten out of ten failure rate with their internal assays. Insilico Medicine, on the other hand, when conducting the same test with the use of their AI scored five out of ten hits very quickly.

A second case study reflected the work published in Nature Biotech, which has since become the fourth most popular paper in the history of the journal. Dr. Zhavoronkov said that one of the company's chemistry partners had challenged Insilico Medicine to generate molecules in record time using specifically the company's generative approach and no human intervention.

The company did so, designing the molecules with only limited chemistry expertise, finding strong drug-like hits. The company performed the test in 21 days, validating on the way with mice and ultimately open-sourcing the data so anyone can repeat the study.

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# IS AI ENOUGH?

Dr Henstock was positive about the impact AI could have on the fabled R&D decline in pharma: “I think that given all the tech available right now, given the added data provided with better imaging, sequencing, etc. AI has the best chance of improving the situation, as I see it.” He added that pharma is nowhere near pushing the limits of AI yet- it will be many years before AI’s potential is exhausted or the current problems inherent to the technology are solved.

The former Lead in Digital Innovation agreed that AI would undoubtedly aid in reversing the pharmaceutical decline, but said it would perhaps not be enough on its own: “The most successful companies are those who are innovating, learning from failures, and are investing in the right tech, people and processes, and trying to do the right thing for patients. So the successes will take advantage of the tech, then the people, then the process.

> “AI will not work at reversing the decline on its own. Everyone thinks AI is a silver bullet, but it isn’t new. We’ve been working with deep learning algorithms since I was doing my bachelor’s degree. The ecosystem has to be there for technology to make a big difference in terms of the bottom line productivity of the company. People are beginning to realise that now.”

But despite its vast promise, and the rapid improvements AI has made in several key areas within pharma R&D, a deeply-held cynicism can still be detected in a number of analysts. This is based mostly around the numerous deeply-entrenched bottlenecks involving the new technologies.

As has already been discussed, while deep learning and ML algorithms have made great strides in other industries where image classification and simple data analysis are all that is needed, takeup in the pharmaceutical industry has been considerably slower. This is due to a number of bottlenecks in the sector, most prominently and famously the scarcity of useful, available data and its siloing in a number of disconnected places.

The quality of the data itself is currently often an issue - as with any area in life science, much of the clinical and research data available is unstructured and without unified format;. Often the data is poorly validated, or often hidden by confidentiality and secrecy clauses by companies unwilling to share their data.

Further issues arise when validating the AI results, particularly stemming from feature-rich datasets with complex findings - determining what AI has found will take both time and manpower to achieve, at least for the near future.

Are other options available? Some have been mentioned as ways to curb the decline: two of the main reasons involve a drive for new talent in the industry, and an entirely new model setting out how the pharmaceutical industry should operate.

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# CURRENT USE OF AI IN PHARMA

## NEW TALENT

The pharmaceutical sector does not only need new talent to transform its fortunes in a failing market: it also needs to reverse a decline in job security as a result of collapsing profits and diminishing returns.

Collecting an understanding of staff needs and knowledge gaps is no longer an arduous or prolonged task. Companies can now use tools to collect data from across an organisation to identify the structure of a current workforce and what improvements should be made in the next five or ten years.

The solution does not lie only in identifying the need for new talent and the space in which it can best be utilised. Today pharmaceutical companies face stiff competition not only from other sectors in which skilled professionals can make more money or greater recognition, but also smaller biotechs and disruptors with a greater focus in one area, an innovative approach to finding and hiring experts and perhaps a flexibility or fresh policy more appealing to young professionals than that found in larger organisations. As has already been discussed, one key means of ensuring better, more relevant talent is hired is to ensure that key issues are focused on in a top-down manner: hiring a CEO or director-level position with a keen interest in AI, for example, can ensure a better strategic understanding of the skills necessary to move the company forward in vital areas.

## ORGAN-ON-A-CHIP

Organs-on-a-Chip (OOCs) are microfluidic cell culture chips, the smallest of which are the size of a coin. These are made of a translucent polymer containing living cells able to completely simulate the microenvironment of an organ or cancer. Over the last two decades, such chips have already been made for the brain, lung, kidney, liver, gut and heart. Since 2017, however, chips have been created to combine several elements together. A 2017 article in Nature showcased an OOC comprising of a heart, liver and lung combination. These models are created using microscale engineering technologies like replica molding and microcontact printing. A silicon-based organic polymer acts as support for tissue attachment and organisation. Their miniaturisation has a number of significant benefits for scientists, from their high analytical throughput to improved performance and facile parallelisation through multiplexing. This is without any loss in automation or precision.

There are some downsides to the several types of OOC, but most of these are far outweighed by their positives. Complex manufacturing technology is needed to create them, with integration of many functions on one chip a difficult prospect. Another particular problem with many OOCs is that there can be too few accessible cells or tissues in the system to fully study using tools such as western blotting or mass spectrometry.

The applications of OOCs in pharmaceuticals are vast, primarily in the R&D space. Using OOCs to test drug candidates as early as possible saves not only time but reduces the enormous costs of prolonged trials that could end up failing. The process of developing and testing a new drug can take much more than $2 billion and an average of eleven years to complete. As such the ability to immediately test a drug in a harmless way in a biological surrogate is a huge boon for professionals, determining critical failures long before the drug would otherwise be introduced into humans (which could have potentially dangerous results).

OOCs are particularly useful where tumours are concerned. As opposed to spheroid formation models or other models used to mimic tumour microenvironments, tumour-on-a-chip models are not limited when predicting a drug's efficacy. Instead,

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# CURRENT USE OF AI IN PHARMA

studying the tumour microenvironment in a controlled way and in real time allows scientists to overcome the problems of other models. It allows them to study the subject across many parameters, such as cell-to-cell and cell-to-matrix interactions within the tumour.

OOCs can be used in both preclinical R&D and clinical trials to rapidly speed up a firm understanding of a drug's effects without risk to patients or huge investments. This is done through high-throughput screening and the mechanistic study of drugs.

Despite the vast benefits potentially offered to the pharmaceutical industry by OOCs, the technology has only just begun to see considerable takeup in the area. Currently, the technology is still too limited to make the difference it promises. Animal models are still often the preferred tool: but coming years will see OOC models replacing current technologies, rather than simply used as an addition to aid in selection.

Limited present functionality and difficulty of manufacture must be removed before such a thing can be achieved. When these technicalities are surpassed, OOCs will begin to have a considerable impact across the pharmaceutical sector, from reducing the crippling time and money concerns of early R&D to speeding up clinical trials with limited risk to patients. It is safe to say that, within the next ten years, OOC technology will be a boon to almost every pharmaceutical company.

## NEW BUSINESS MODEL

The traditional pharmaceutical model, some argue, is unsustainable due to its unpredictability and low-volume, high-cost strategy. The declining returns and loss of performance demands a radical change not simply to one aspect of the business, e.g. the addition of AI or new talent, but instead calls for a total overhaul of the business model employed.

The new model, they argue, would reverse the standard position to become a model of low cost and low risk but high quantities: Under the new model, a new reliance would be placed onexternal collaborators, such as biotech startups, who can instigate a more numerous process of cheap tests more flexibly.

This must, naturally, be complemented by a regime of more hardline approaches to experiments, with a greater focus on statistical analysis of each experiment as it continues: potentially unsuccessful trials must be aborted more quickly to reduce spending, but in such a way that possible successes are not wiped out before their benefits can be shown.

This emphasis on externally-produced quantity ensures little would be done in-house, with pharma companies only beginning to invest considerable time and resources of their own staff during clinical development and the commercial and regulatory steps that follow.

AI still has the potential to help in this scenario, though in this case more for operational activities such as risk assessment or trial planning.

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# CONCLUSION

Dr. Zhavoronkov expressed a firm belief in AI's ability to reverse the recent decline in pharmaceutical R&D. He argued that his own company, Insilico Medicine, has validated their AI drug discovery processes in a number of experiments, and have tangibly out performed alternative methods of discovery. "You just need to have the guts to do an experiment from target identification to clinic," he said, "which is difficult. It requires patient and competent investors who are comfortable with the time taken to do this, and who are willing to take those bets."

This time challenge is a crucial one to the ability of AI to outperform rival methods of discovery and development. Dr. Zhavoronkov noted that he updates his pipeline every half a year, totally changing it. With AI, validation cycles in biology and chemistry are immeasurably longer than those in pictures or imaging or text, due to the need to train the AI on more complex ideas as well as a historic lack of processing power.

With advances in GPU computing, processing power is increasing and training AI is becoming quicker and quicker. However, validation is still a slow process, and courage to make bets and prepare for failures is still a must. Dr. Zhavoronkov said that his company failed a number of times before the Nature Biotech paper was published- for two years or so. While the company is now in a position to trust AI to create good molecules, failure rates still exist with more complex targets. Good companies in the innovative AI R&D space will look to minimise risk as much as possible, and understand that in some cases creating small positive changes in current internal processes is insufficient: pharmaceutical processes must in certain situations be entirely built from scratch.

The near future for AI will be one of some contradictions: a period of significant change, but for some not change enough; a period of increased mergers and partnerships but also one of slow take-up of new processes; AI as the saviour of pharma R&D, but still criticised by many as a fabled 'golden bullet' that will not have the intended effect without wider changes in personnel and attitude.

But what is clear, despite these polarised notions, is that 2020 and the next few years will see unprecedented advances in innovative technology: whether 2020 really is the great year that was promised for AI, or whether change will come more gradually over a larger period of time, the time is now for AI to flourish and change the pharma sector for good. Whether the R&D decline will turn around because of this is yet unknown: and only time will tell.

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# OUR UPCOMING STRATEGY MEETINGS

PROVENTA INTERNATIONAL

| | | |
|---|---|---|
| 11 MAY | - Clinical Operations \| Clinical Trial Supply Chain \| Pharmacovigilance - | SAN DIEGO |
| 1 JUNE | - Chemistry Manufacturing Control - | BOSTON |
| 2 JUNE | - Regulatory Affairs - | BOSTON |
| 3 JUNE | - Biomanufacturing - | BOSTON |
| 4 JUNE | - Cell and Gene Therapy - | BOSTON |
| 29 JUNE | - Biology \| Medicinal Chemistry - | LONDON |
| 30 JUNE | - Oncology \| Bioinformatics - | LONDON |
| 5 OCT | - Clinical Operations \| Clinical Trial Supply Chain \| Pharmacovigilance - | ZURICH |
| 6 OCT | - Biomanufacturing \| Cell and Gene Therapy - | ZURICH |
| 7 OCT | - Regulatory Affairs \| Chemistry Manufacturing Control - | ZURICH |
| 2 NOV | - Oncology \| Bioinformatics - | SAN FRAN |
| 3 NOV | - Medicinal Chemistry \| Biology - | SAN FRAN |
| 5 NOV | - Medicinal Chemistry \| Biology - | SAN FRAN |
| 9 NOV | - Pharmacovigilance - | BOSTON |
| 10 NOV | - Clinical Operations - | BOSTON |
| 11 NOV | - Clinical Trial Supply Chain - | BOSTON |
| 16 NOV | - Oncology - | BOSTON |
| 17 NOV | - Bioinformatics - | BOSTON |
| 18 NOV | - Biology - | BOSTON |
| 19 NOV | - Medicinal Chemistry - | BOSTON |