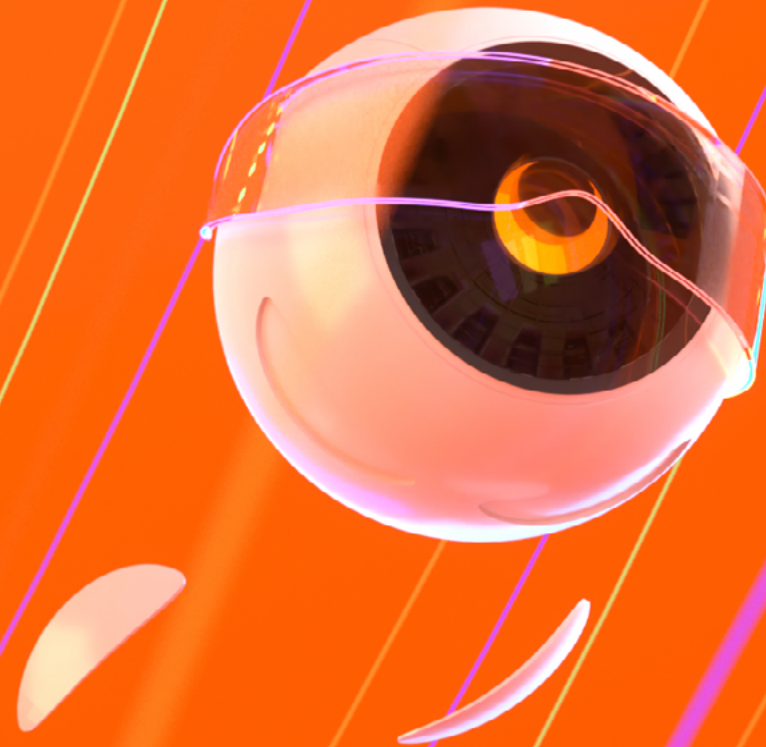


# Investment Recipes

by  AtonRā Partners



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# HARNESS CONTAINERIZED INFRASTRUCTURE

## Ship Software Like Goods

### Deploying software: a historical challenge

Software, once developed, still needs to be tested, and upgrades/bug fixes deployed. For software developers, this has always been a challenge, but recent technological innovations make such processes smoother by providing new useful tools.

- The combination of different hardware and operating systems makes the testing task particularly difficult to perform due to the limitless number of end-users' machine configurations.

### Performance of containerized software

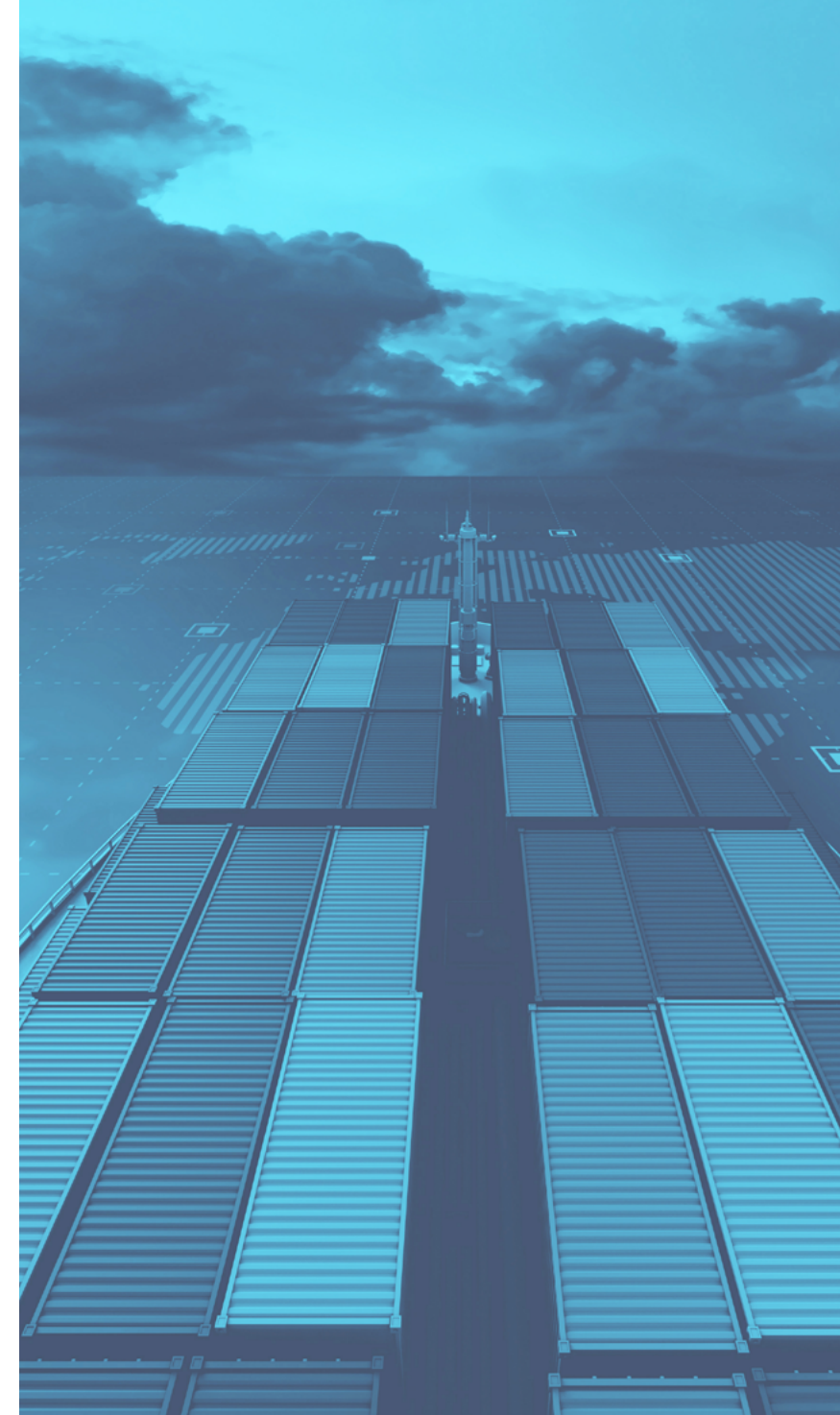
As for the freight industry, no matter what kind of goods are shipped into the container, the ship only manages the box itself. In the software world, « containerizing » means separating the code from the environment in which it runs (OS, hardware specs, etc.).

- Data security and scalability (i.e., the capacity of a system to handle traffic increase) is increased.
- Brings about the DevOps engineering field, responsible for the continuous testing and deployment of new pieces of software codes.

### The benefit of a flexible software “supply chain.”

Software testing, bugs fixing, and maintenance are costly. Flexibility and fast updates are thus critical to reducing such costs.

- Long downtimes are a no-go for any business. DevOps reduces downtime and helps to push quick and efficient software updates to the end-user.
- Docker, a private software company, dominates the software container market.
- Containerized software is the first step. Handling simultaneous and numerous containers is called Orchestration and is the next level in DevOps.



# The Challenge Of Software Deployment

## No silver bullet

For decades, solving the software development problem was the main focus for researchers and IT companies.

- Maintaining software was twice as expensive as developing it.
- Fixing a bug after the software release would cost up to 30X more than during the development phase.
- Discipline and strict organizational procedures could not overcome these structural issues.

## Disparate supporting software environment

The software stack needs to run reliably when moved from one computing environment to another. Although challenging, this is a critical step.

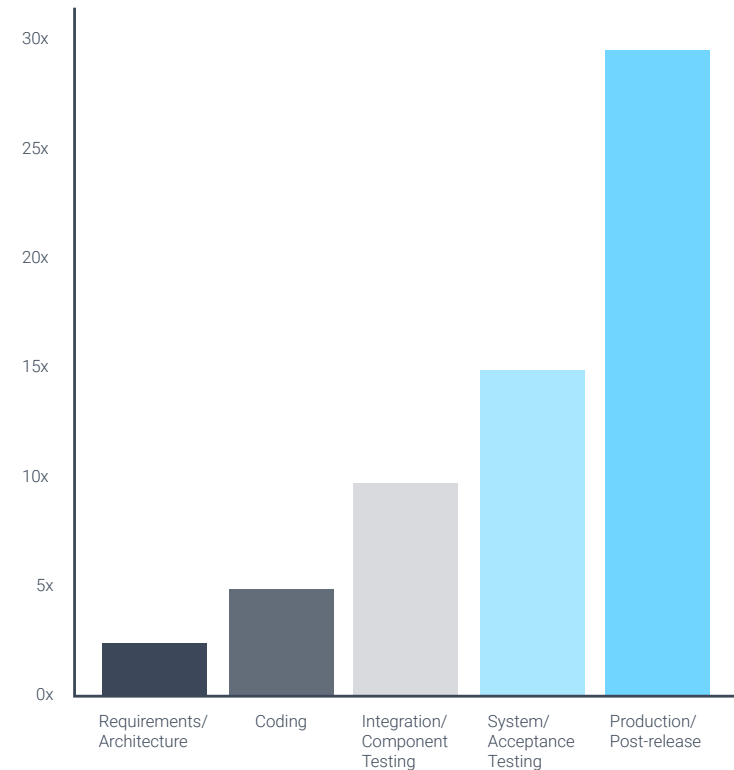
- The number of testing environment possibilities is practically infinite.
- The cost of hardware and the absence of tools made efficient continuous testing impossible.

## An inefficient workaround: Virtualization

Often used in enterprise infrastructure technology, virtualization is a system (called a hypervisor) that “virtualizes” a computer within a computer. For instance, having Windows 10 installed in a MacBook is virtualization.

- The most famous hypervisor is Oracle VM VirtualBox.
- The launch of a full OS and its applications takes several minutes and uses several gigabytes of memory.
- VMs size limits considerably the number of different environments one can have installed on a single machine.

RELATIVE COST TO FIX BUGS, BASED ON TIME OF DETECTION



# Lodging Applications Into Containers

## Containers principles

A container consists of an application plus all its binary and configuration files, bundled into one single package. By doing so, it does not have to rely on a specific operating system (OS) and its underlying infrastructure.

- A container requires 100-1000x less memory than a virtual machine (VM).
- It takes only a few seconds to spin up a container, allowing to add capacity (scalability) and quickly face increasing load.
- Containerization increases scalability up to 100x that of traditional VMs.

## The creation of DevOps tools

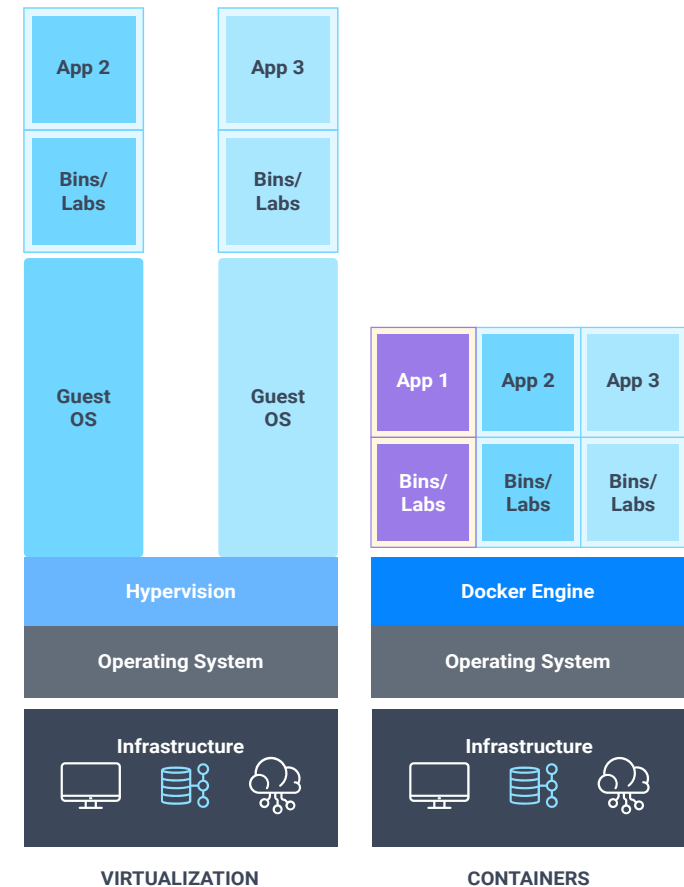
Containerization has made testing and deployment way more flexible. Software containers help standardization and efficiency throughout the “software supply chain”. DevOps is all about handling integration and deployment.

- Continuous Integration (CI), allows merging bits of new software code into a mainstream branch and test it.
- Continuous Deployment (CD), allows deploying and updating software directly to the end-user.

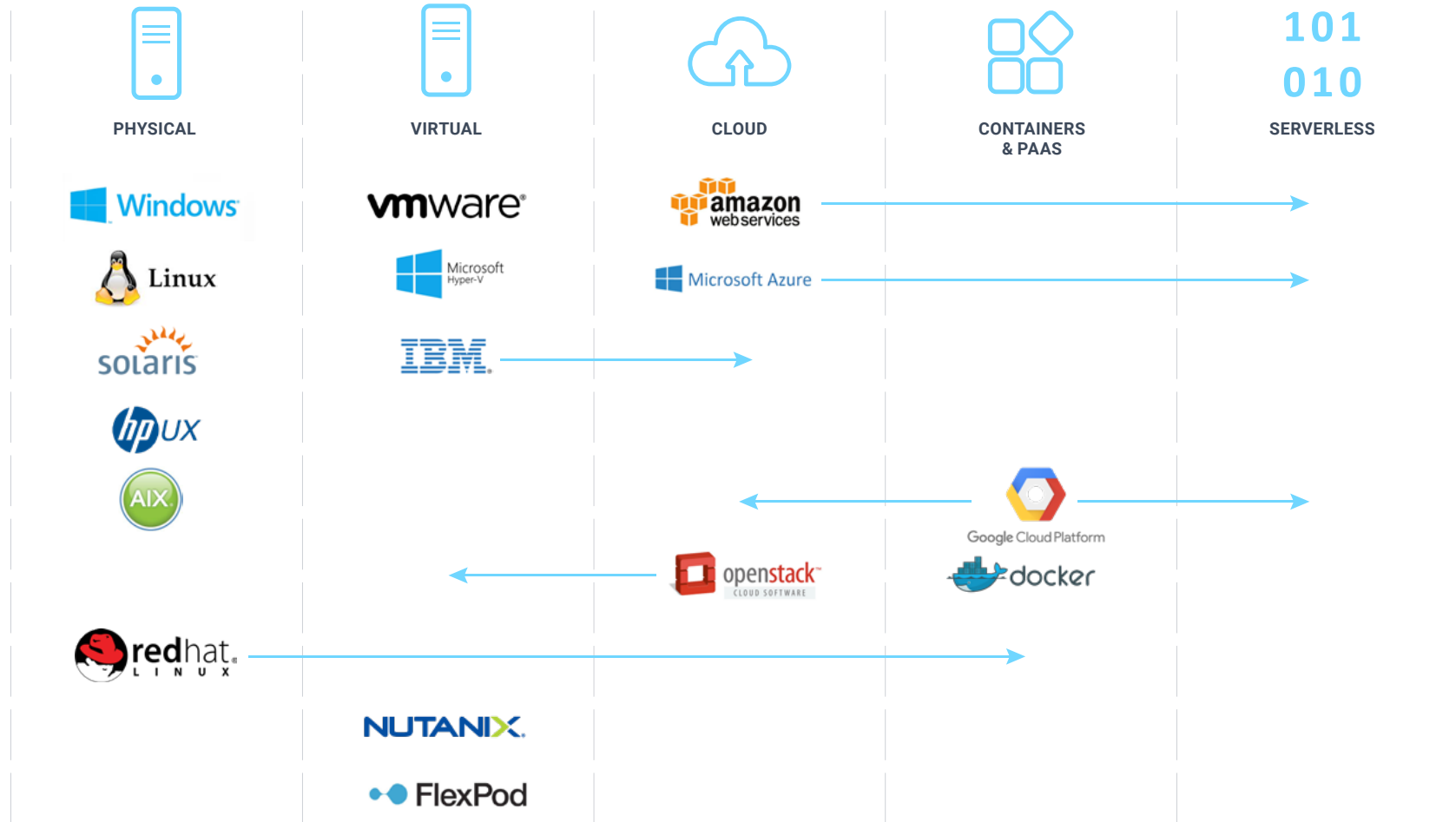
## Isolating data: best practices for a secure and scalable system

The container technology is now also used to isolate functionalities and data. A container is like an impenetrable black box where sensitive data can remain isolated from the rest of the program.

- If a container is compromised, it is trivial to isolate the component from the rest of the application.
- Application updates can be deployed at scale securely and efficiently.



# HARNESS CONTAINERIZED INFRASTRUCTURE



# A Clear Economical Advantage

## The cost of downtime

DevOps optimize the deployment software pipeline, and failing to do it properly can be very costly.

- The average cost of unplanned application downtime is \$1.25 - 2.5bn, based on a \$100k hourly price for infrastructure failure.
- The DevOps market is expected to reach \$13bn in 2025, growing at an average of 18.6% CAGR.

## Docker, the market leader in containerization

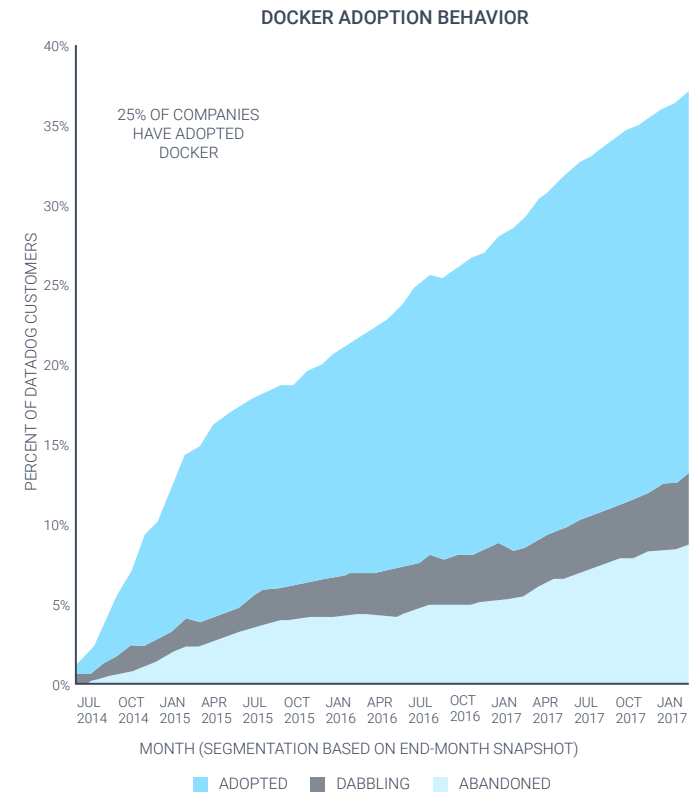
Docker is a platform as a service (PaaS) for Containerization created in 2010 and released to the public in 2013. In 2019, Mirantis acquired Docker's Enterprise business.

- Docker accounts for more than 80% of containers running in 2018.
- In 2018, the global application container market was valued at \$1.5bn and should grow at a 26.5% CAGR rate to reach \$8.2bn in 2025.

## Orchestration: the containers bandmaster

Isolating services is the standard in the software industry nowadays. Each application is containerized and ships through the DevOps pipeline. Different containers live next to each other and can lead to hundreds of instances that need to be simultaneously controlled.

- The most used Orchestration system is Kubernetes (Google), followed by Amazon's ECS and Docker's Swarm. They can handle up to 300K containers installed on up to 5K computers, each one using a unique configuration and system.



## Catalysts

- **KubeCon + CloudNativeCon Europe 2020.** It is the biggest conference in the world for Cloud-Native software and containerized solution. This year, the event will be hosted online from the 17th to the 20th of August.
- **Rancher announced the release of k3s.** The software stack, including Kubernetes, is not necessarily designed to run on heterogeneous computing environments outside data centers. Rancher's solution would increase the potential market for the whole containerized ecosystem.
- **Microsoft, Amazon, and Google now support hybrid cloud.** Google was the last of the big tech to announce a new multi-cloud (hybrid) system, Anthos.

## Risks

- **Snyk raised \$150 Million to find container vulnerabilities.** Even though a container is more secure than a legacy application, it does not necessarily make the whole ecosystem more secure. A flaw in container security could lead to dramatic consequences for Containerization.
- **Weak Profitability.** Even though Docker Enterprise was bought by Mirantis and had raised more than \$250mn in its funding rounds, the company hasn't been profitable yet.
- **A better new technology.** As for every IT technology, leadership is granted until it isn't. Even though Containerization still has room for progress, there is no guarantee that this technology will not be jeopardized by a better one.

## Bottom Line

- Software development and maintenance were dramatically inefficient throughout the last century. The absence of tools for testing and deployment made new release update cumbersome and expensive.
- Containerization created the DevOps role which allows an agile and flexible deployment pipeline (from an average of 4 updates per year to hundreds per day) while ensuring thorough testing. We believe that these new technologies are a huge catalyst for the software market overall and we expect the pace of innovation (and new products hitting the market) to rocket in the next few years thanks to containerization.

### Companies mentioned in this article:

Google (GOOGL US), Oracle (ORCL US), Amazon (AMZN US), Mirantis (not listed)



# GET READY FOR A STRONG CONSOLE CYCLE

## Gaming Console Market Set For A Leap

### Strong growth is expected from gaming consoles

The next console cycle begins in 2020 with Sony and Microsoft launching their new PlayStation 5 (PS5) and XBOX X. Driven by dramatic spec-upgrade, consoles are expected to represent >30% of the videogame industry by 2025.

- The console market is set to grow from \$50bn to \$75bn by 2025, and the whole gaming industry (PC, Mobile, Consoles) to reach \$250bn, up from \$152bn in 2019.
- Compared to the previous versions, new iterations will offer 50% more CPU's clock speed, 2x graphic power, much higher bandwidth, and faster memory support.

### Semiconductors are to profit from more powerful and affordable consoles

Spec-upgrades make consoles an essential option for gamers and will represent a strong source of growth for supply chain players involved in high-performance chip and memory production.

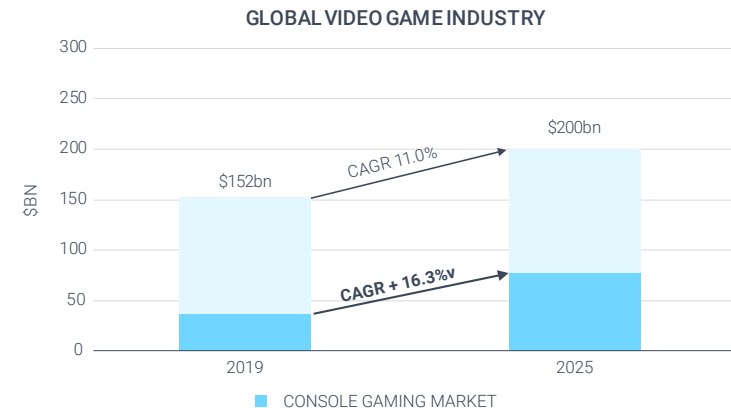
- 8k resolution and ray-tracing (realistic lighting/reflection effects) are impossible to experience elsewhere at the console price point, i.e., the cheapest desktop video card capable of ray tracing costs 80% of the console price.
- After the initial delay caused by COVID-19, semiconductors will continue along the path of strong revenue growth with a five-year CAGR of 16% supported by constant recurring demand.

### AMD to benefit the most

With 20% of sales coming from the semi-custom chip business, AMD will strongly benefit from the upcoming console cycle. Both PS5 and XBOX will upgrade to the AMD Ryzen CPUs and AMD Navi GPUs.

- AMD dollar revenue per console is expected to be a 75% step up from last year's shipments for the PS4.

SOURCE:  
Newzoo, AtonRâ Partners, Xbox, Sony



# AMD CPUs And GPUs Are Essential For Gaming

## AMD wins the race

Choosing the right CPU (Central Processing Unit) is essential for a console manufacturer to ensure a successful life span for its products. While in previous cycles Microsoft and Sony relied on different suppliers, this cycle AMD takes it all.

- AMD offers a complete package of CPUs and GPUs, both compatible and optimized to work together for the best gaming performances.

## Technological leadership pays off

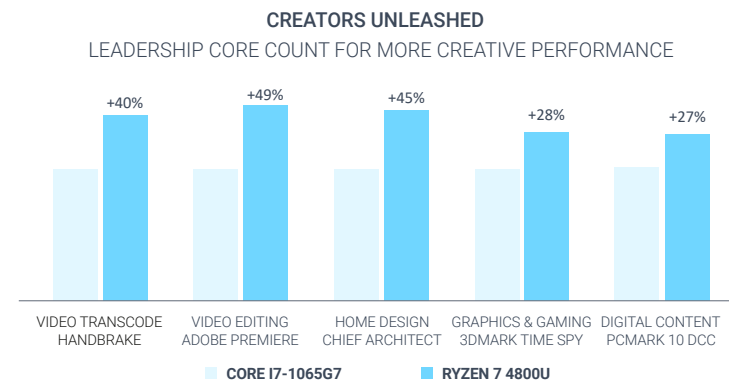
AMD proved itself as the leader of CPUs for gaming. The company triumphs in CPU speed and powerful core architecture - key factors for analyzing CPU performance.

- AMD Zen 2 CPU, designed on the 3rd generation AMD's Ryzen platform, is an eight-core architecture designed on the new 7nm node.
- Its ultra-high clock speed (+50% improvement versus the previous generation) is essential to support extremely high refresh rates present in multiplayer gaming.

## Cross-selling GPUs

AMD is certainly a winner of the upcoming console cycle as no competitor can match the performance of its combined offer for both CPUs and GPUs for a similar price.

- AMD GPU offers the performance of 9,2 teraflops for PS5 (5x improvement over PS4) and 12 teraflops for XBOX coupled with a bandwidth of 512 GB/s and faster GDDR6 memory.
- Both PS5 and Xbox series X consoles will come with an AMD Radeon-based GPU that will have a performance 200% higher than PS4 Pro and 100% higher than XBOX One X.



SOURCE:  
AMD, AtonRa Partners

## Graphic And Storage Memory Are Key

### Graphic memory is a crucial enabler of high-performance gaming

The new generation of consoles will also house a new graphics memory standard – the GDDR6. Evolution of resolution, more detailed visual effects, and multi-display configuration increase dependence on high-memory capacity and memory bandwidth.

- Graphic Double Data Rate (GDDR) memory is used to store data that needs to be quickly accessible by the CPUs and GPUs to be processed during gaming.
- GDDR6 offers a higher bandwidth per-pin at lower operating voltages over GDDR5.

### In 2020 play the memory and semiconductor industry

The long-awaited console release will boost sales not only for AMD but also for other major memory suppliers like Samsung, SK Hynix, and Micron, while Western Digital will deliver ultrafast hard drives.

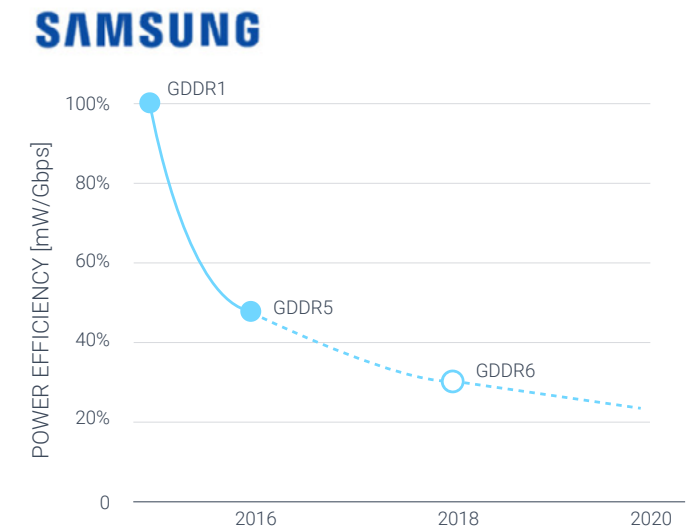
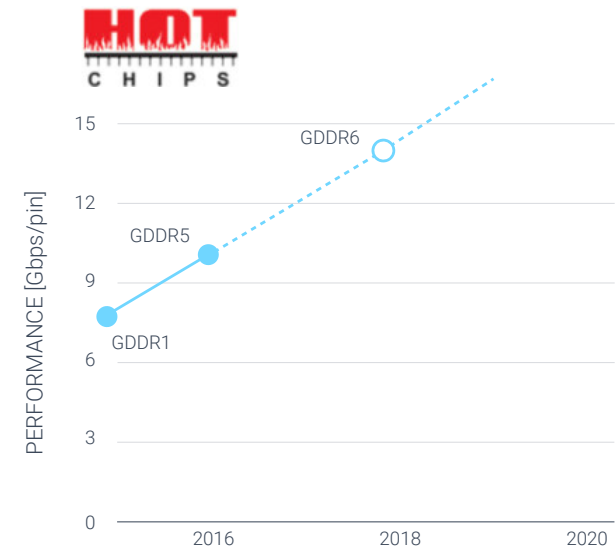
- Graphics DRAM production has remained concentrated in the hands of the three mentioned leaders, who have already announced their GDDR6 solutions.
- Samsung remains the industry leader with more than 50% market share in graphic-DRAM, while Micron expanded from 8% in 2014 to 34% in 2019.

### From memory abundance to scarcity

After having been in oversupply during 2018-19, the graphic-DRAM industry is moving towards an undersupplied environment starting in Q2 2020.

- Expectations are for a 6% YoY growth for the graphic-DRAM industry over the next five years, with a remarkable 18% GDDR6 growth projected for Micron in 2021.

SOURCE:  
[DRAM Market Again Saw Record High Revenue in 2018 but Prices Are Approaching Their Peaks,](#)  
[NAND Flash to Lead All Others As IC Market Growth Returns in 2020,](#)  
 AtonRā Partners



## Catalysts

- **Growing global audience.** Video gaming is becoming more engaging than ever. Boosted by social distancing, users are spending, on average, 51 minutes daily on games, and the worldwide gamer population is reaching 400mn people. This lasting trend would significantly boost console sales.
- **E-Sports.** Growing consistently at 40% YoY Esports revenues have attracted millions of investments into the gaming industry. While many competitions are PC based, consoles are gaining a considerable e-sports share and solidifying their position in the market.
- **Continuing support.** Typically, 2-3 years following the release, consoles receive a small aesthetic and hardware upgrade, that defines how long the cycle will be. Sales would be boosted, and the current lifespan will be prolonged if the upgrade will be judged favorably by consumers.

## Risks

- **Weak console demand.** There is no denying that mobile gaming is gaining traction among consumers, mainly due to price and convenience. If consumers decide that gaming consoles are incorrectly priced or do not offer any advantage, this may be the last console generation.
- **Faster than expected innovation.** The usual lifespan of consoles is 5-7 years, during which they stay viable in terms of performance. If CPUs and GPUs improve exponentially faster than predicted, the current cycle could be short-lived and shake consumers' confidence in the console market.
- **Uncomfortable limitations.** It would be detrimental to console sales if to keep prices "under control" users find too much performance limitation upon the release day in 2020.

## Bottom Line

- The new console cycle begins now, with Sony and Microsoft unleashing a new upgraded console generation. This will be a strong and recurring source of growth for both console players and semiconductor companies involved in memory, CPU/GPU, and electronics.
- New consoles are expected to capture a third of the total Video Game Industry, notably, thanks to switching to AMD processors and graphic units. Other companies to benefit from the upcoming cycle are memory producers such as Samsung, Micron, and SK Hynix.

### Companies mentioned in this article:

AMD (AMD US), Micron (MU US), Microsoft (MSFT US), Samsung (005930 SE), Sk Hynix (000660 KS), Sony (6758 JP)

# ARE HEARING DEVICES CLOSE TO AN END?

## One Of The Largest Unmet Medical Needs

### The global burden of hearing impairment

Hearing loss, the partial or total inability to hear, is one of the leading causes of disability worldwide and is related to age, genetics, exposure to noise, and the use of certain drugs. It leads to severe social and economic consequences.

- Currently, more than 466mn people are living with disabling hearing loss.
- Hearing loss triggers depression, dementia, diabetes, and many more.
- The unaddressed hearing loss is estimated to cost \$750bn annually.

### A widely untapped market

The most common option for the treatment of hearing loss is the use of medical devices such as hearing aids and cochlear implants.

- Hearing devices meet only 10-20% of the global need, given the high cost (on average, \$ 2'300 p/u), the poor quality of sound, and social stigma.
- Cochlear implants can cost up to \$50k and require an invasive surgical procedure.
- Global penetration has reached less than 5%.

### The race to cure hearing loss

The real breakthrough treatment for hearing loss would restore the natural hearing, employing novel approaches such as regenerative medicine and gene therapy. Currently, there are no approved drugs of this kind, but several companies are rapidly making progress.

- Frequency Therapeutics, Decibel Therapeutics, and Akous are running groundbreaking studies to treat hearing loss.

SOURCE:  
[Deafness and hearing loss](#)

THE LEADING CAUSES OF BURDEN BY 2030

2030 Disease or Injury	As % of total DALYs*	Rank
Unipolar depressive disorders	6.2	1
Ischemic heart disease	5.5	2
Road traffic accidents	4.9	3
Cerebrovascular disease	4.3	4
COPD	3.8	5
Lower respiratory infections	3.2	6
Hearing loss, adult-onset	2.9	7
Refractive errors	2.7	8
HIV/AIDS	2.5	9
Diabetes mellitus	2.3	10
Neonatal infections and other	1.9	13
Prematurity and low birth trauma	1.9	14
Birth asphyxia and birth trauma	1.9	15
Diarrheal diseases	1.6	19

\*: Disability Adjusted Life Years – a measure of overall disease burden, expressed as the number of years lost due to ill-health, disability, or early death.

## The Hearing System And Its Disorders

### **Conductive hearing loss involves the mechanic portion**

When the sound reaches the ear canal, it strikes the eardrum, causing its vibration. Behind the eardrum, a chain of 3 tiny bones, the ossicles, transmit the movement to the fluid that fills the cochlea. Problems to this portion of the hearing system prevent sound from flowing correctly. Today, medical devices provide a logical solution to treat the condition.

- Hearing aids, middle ear implants (MEI), and Bone-anchored hearing aids (BAHA) are the existing alternatives.

### **Sensorineural hearing loss involves the hair cells**

The ossicles cause the fluid into the cochlea to move. The movement of the fluid is captured by tiny structures, called hair cells, which in turn activate the auditory nerve. Missing or damaged hair cells are the cause of sensorineural hearing loss (SNHL). As of today, medical devices are the best therapy.

- Cochlear implants and hearing aids are the most common solutions.
- 90% of hearing loss cases are classified as sensorineural.

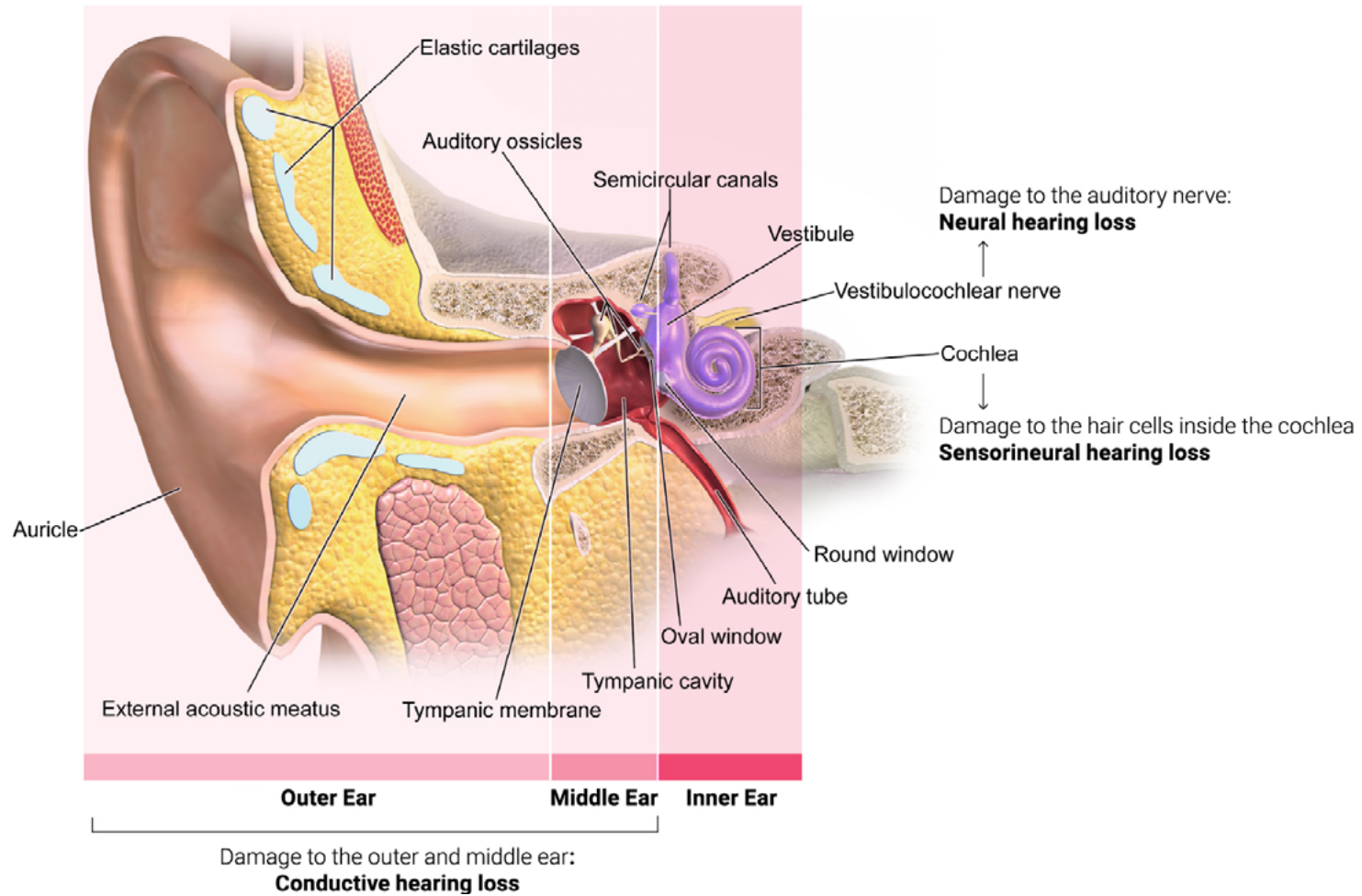
### **Neural hearing loss involves the auditory nerve**

The auditory nerve is responsible for sending the electrical signal to the brain. The brain interprets the message as sound. The absence or damage of the auditory nerve causes neural hearing loss. Currently, only one medical device has been developed to target the condition.

- The problem is usually treated with an Auditory Brainstem Implant (ABI).



# The Hearing System And Its Disorders



## Medical Devices Give Way To Medicines

### Hearing aids

Hearing aids improve the ability to hear by amplifying the volume of the sound. The devices are usually expensive, and most insurance providers don't cover the cost. Starting this year, lower-cost over-the-counter hearing aids are available for people with mild to moderate hearing loss.

- The global market is expected to grow by 4% CAGR over the next five years.
- Sonova has a 31% market share, Demant 30%, Sivantos 19%, GN ReSound 15%.

### Cochlear implants

Cochlear implants are surgically implanted devices that partially restore the sense of hearing of people with moderate to severe sensorineural hearing loss. Implants bypass the damaged hair cells to deliver electrical signals directly to the nerve. Given the invasiveness and the poor quality of sound, their adoption has never taken off.

- The global market is expected to grow by ~1% CAGR over the next five years.
- Australian's Cochlear dominates the industry with more than 60% of the global market, followed by Demant and Med-El.

### A cure for sensorineural hearing loss

A less intrusive solution would make the two above devices obsolete and revolutionize the market. Regenerative medicine, designed for sensorineural hearing loss, has the potential to replace damaged or missing hearing cells.

- When hearing cells are damaged, they cannot grow back. With regenerative medicine, hearing cells regrow, and hearing loss reversed.

SOURCE:

[Percentage of the global hearing aid market as of 2019, by company](#)

Image: Wikipedia





## Disruptive Treatments On The Horizon

### **Congenital hearing loss**

Gene therapy is under investigation to treat congenital hearing loss, caused by DNA changes that result in the production of atypical proteins. The treatment works by delivering a healthy piece of DNA into the hearing cells, enabling them to produce the functional protein and restore hearing.

- 32mn children have hearing loss; 50-60% of cases have genetic roots.
- Decibel Therapeutics and Akouos' programs (respectively DB-OTO and AK-OTOF) are in the preclinical stage of development.

### **Deafness due to chemotherapy**

Toxicity of chemo and radiation therapies can cause damage in the inner ear, leading to hearing loss. Researchers are developing treatments to protect hearing cells from the toxic effects of cancer drugs.

- After treatment with cisplatin, a widely used chemotherapeutic drug, 80% of adults and 50% of children have permanent hearing loss.
- Decibel Therapeutics' candidate, DB-20, is in phase 1b trial to prevent hearing damage in people receiving cisplatin chemotherapy.

### **Degenerative hearing loss**

Scientists are conducting clinical trials to evaluate whether regenerative approaches, which include the use of gene therapy or the activation of progenitor cells, are a viable solution to stimulate the regrowth of damaged hair cells, and thus cure sensorineural hearing loss (SNHL).

- SNHL accounts for 90% of all hearing loss.
- Frequency Therapeutics' leading candidate, FX-322, and Audion Therapeutics' compound LY3056480, are in phase 2.



## Frequency Therapeutics Leads The Race

### Unlocking the regenerative power of the ear

Progenitor cells are human cells found in vivo that hold the potential to regenerate tissues. In the hearing system, these cells are dormant. Frequency Therapeutics is developing a small molecule, FX-322, that hopes to wake them up.

- The compound is injected in the form of gel into the middle ear, overcoming the critical challenges of stem cell transplantation, i.e., delivery and integration.
- FX-322 enables regeneration without the development and manufacturing complexity of gene therapy.

### Frequency therapeutics is playing it loud

FX-322 is rapidly advancing through a phase1/phase2 study. Results already showed encouraging signs of efficacy. In October 2019, the company started a phase 2a clinical trial, with top-line data expected in 2H20.

- Patients experienced a meaningful improvement in word recognition, sound clarity, and no serious adverse effects.
- The company has a partnership (for non-U.S. markets) with Astellas Pharma.

### The next-generation regenerative company

As progenitor cells can be found all over the body, the approach has broader applicability. The company continues to target severe unmet conditions, which usually lead to faster pathways to market

- The next most advanced program is evaluating the progenitor cell approach for multiple sclerosis, which has an Investigational New Drug (IND) expected to be filed in 2H21, that would grant permission to start human clinical trials.
- In 2019, the FDA granted a Fast Track designation for FX-322.



## Catalysts

- **Positive results.** This year, the results of some promising clinical trials (e.g., Frequency Therapeutics' leading compound FX-322) have the potential to validate innovative approaches for hearing loss.
- **M&A and collaborations.** Companies target different types of hearing loss through different approaches. M&A and partnerships could expand the market reach and strengthen expertise.
- **New fast track designations.** Companies in this field are likely to be eligible for a fast track designation. The pathway, granted by the FDA, demonstrates the urgent need to find a cure for hearing loss.

## Risks

- **Trials failure.** Any failure in ongoing clinical and preclinical trials could instill a sense of distrust in innovative approaches or could lead to mistrust in innovation approaches.
- **Hearing Devices Advancements.** If cochlear implants and hearing devices manage to reduce their prices, shrink in size, and overcome technical limitations, they may place themselves as valid competitors to novel treatments.
- **Pricing.** Innovative treatments are usually costly, and without reimbursement, patients may not be able to afford them.

## Bottom Line

- Hearing aids and cochlear implants are still the only available solutions to restore the sense of hearing. Novel therapeutic approaches, such as regenerative medicine and gene therapy, are emerging, with the aim to restore the natural hearing. We could soon experience a radical change in the way hearing care is provided.
- We are carefully monitoring all the medical and technological advancements, most notably in the progenitor cells field, and stand ready to invest in this very promising technology.

### Companies mentioned in this article:

Akouos (not listed), Audion Therapeutics (not listed), Cochlear (COH ASE), GN ReSound (GN DC), Decibel Therapeutics (not listed), Demant (WDH DC), Frequency Therapeutics (FREQ US), Med-El, Novartis (NOVN SW), Sivantos (not listed), Sonova (SOON SW)

# MEET THE SECOND BRAIN

## Microbiota-Brain Axis

### **An enigmatic brain-microbiota relationship**

The microbiota is defined as the collection of the trillions of microorganisms inside (e.g., gut or mouth) or on (e.g., skin) the body. A microbial imbalance (i.e., dysbiosis) may play a role in the pathogenesis of neurological diseases.

- Microorganisms, specifically certain bacteria, synthesize a multitude of molecules that act on nerve cells.
- The gut and the brain are directly connected by the vagus nerve and exchange information through neurotransmitters (chemical messengers) produced in the gut.

### **Bypassing the complexity in CNS (Central Nervous System) R&D**

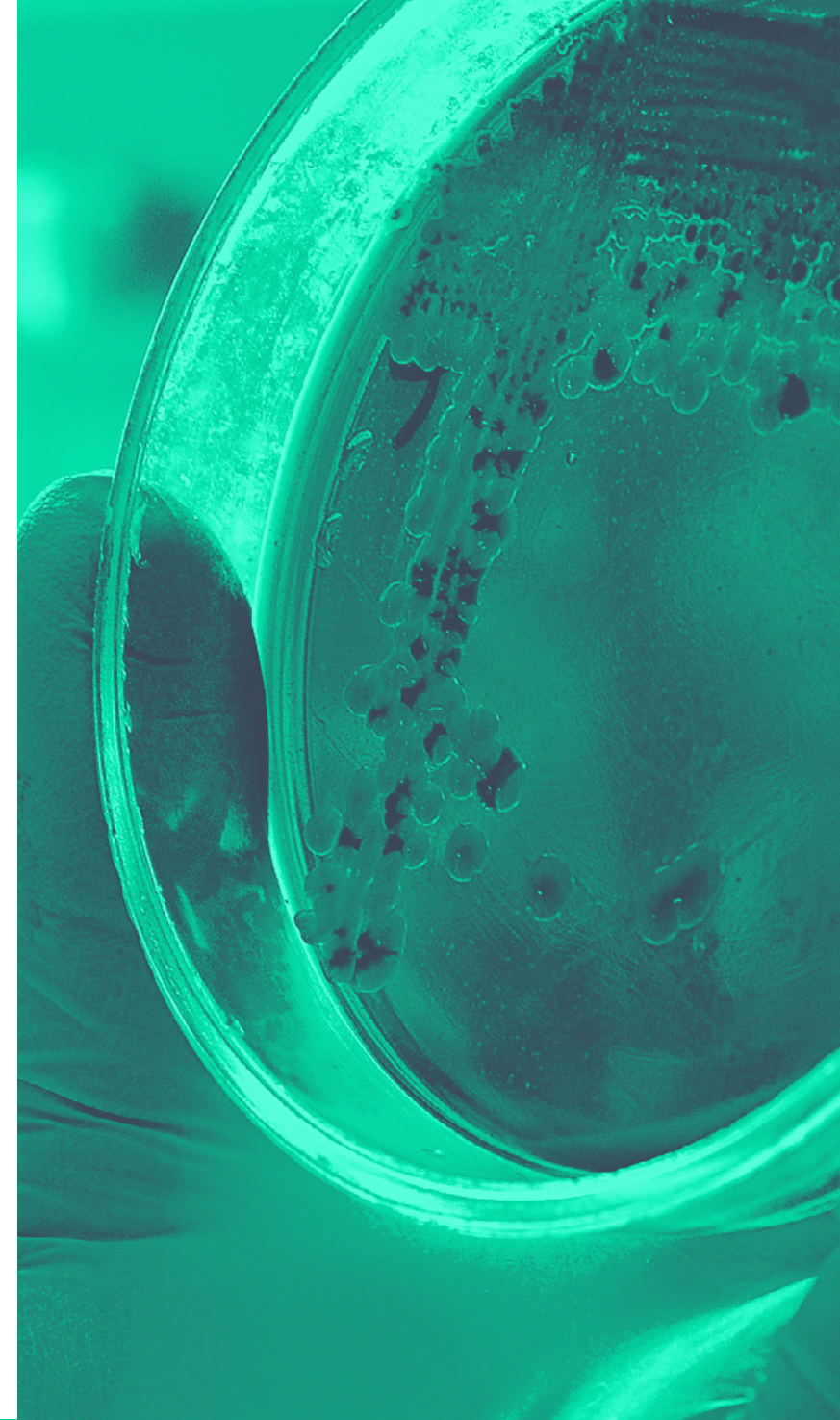
The incidence of neurological illnesses is rising sharply, but no effective treatment has yet been developed. The pathogenesis is still unclear, making targets challenging to identify and confirm. Bidirectional communication between the CNS and microbiota provides new therapeutic targets to explore.

- Delivering the drug through the gut microbiome avoids the current hurdle of passing the blood-brain barrier (BBB), which protects the brain.

### **Differentiated treatments for neurodegenerative diseases**

Two main microbiota are currently studied: those of the gut and the mouth. Most players are still at a preclinical stage (animal testing), and just a few are in clinical trials (human testing).

- Cortexyme is looking to leverage the presence of the oral bacterium *P. gingivalis* in the brain of more than 90% of Alzheimer's patients.
- Axial Biotherapeutics and Kallyope are harnessing the relationship between the gut and the brain and have candidates in autism and Parkinson's disease, among others.



## Three Connected Routes

### The vagal pathway (vagus nerve)

The gut has its nervous system, called the Enteric nervous system, composed by 500mn of neurons. It produces 50% and 95% of dopamine and serotonin, respectively. Through the vagus nerve, neurotransmitters are sent to the brain and influence our mental health.

- 40 neurotransmitters have been identified in the gut.
- Dopamine correlates with Parkinson's disease (low levels), and schizophrenia (high levels).
- Major depressive disorders, as well as autism or Parkinson's, are associated with serotonin.

### The immune pathway

Oral and intestinal dysbiosis (i.e., microbial imbalance) may promote a neuroinflammation response, associated with Alzheimer's and Parkinson's diseases. This inflammation is part of an immune response triggered by an abnormal presence of gut or oral bacteria.

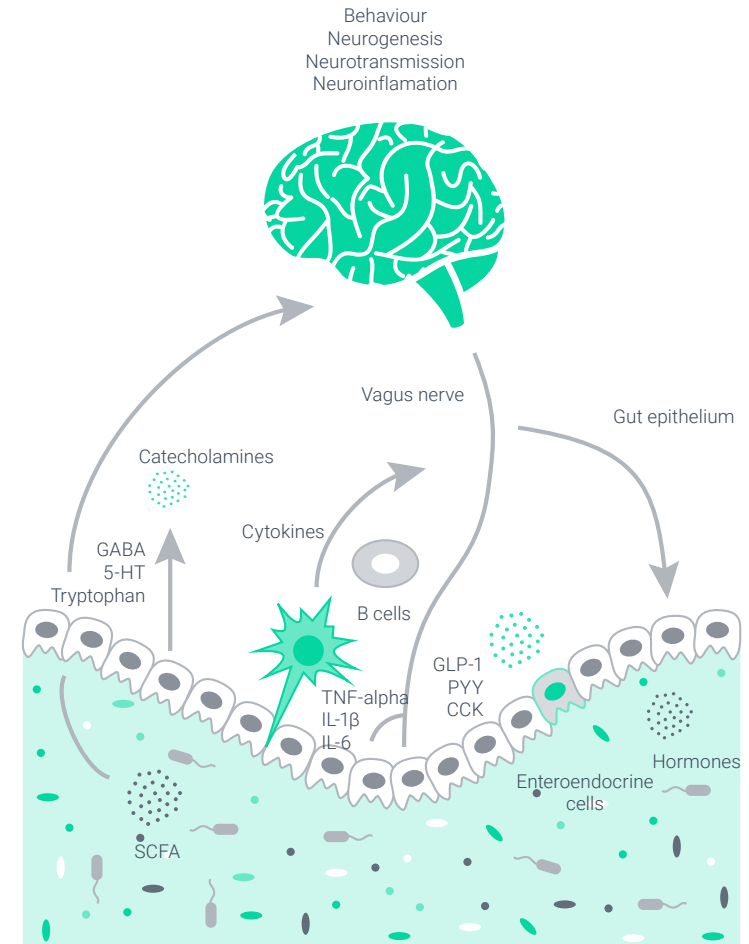
- Cytokines, immune-system signaling mediators, could indicate an intestinal-led inflammation of the brain.
- Chronic inflammation in the brain could lead to damage and death of neurons.

### The metabolic pathway

Metabolites (i.e., SCFA, Short-Chain Fatty Acids), produced by bacteria in the gut, can influence our brain. Metabolites can modulate neurotransmission, the process of communication between neurons.

- Neurotransmitters are released by the neuron and then bind to receptors in another neuron, thus sending a signal through the neural network.
- Enzymes can modulate the production of neurotransmitters. Some metabolites can control the expression of enzymes.

COMMUNICATION PATHWAYS OF THE MICROBIOTA–BRAIN AXIS.



# Succeeding Where It Previously Failed

## A poor success rate in CNS (central nervous system) R&D

Neurological diseases are the world's leading cause of disability-adjusted life years (i.e., healthy years lost due to disability or death), but there is little or no cure available on the market today.

- The success rate in terms of FDA approval for a CNS drug is 8.4% vs. 14.8% for drugs in all other non-neurological indications.
- At more than \$1.3bn to develop a new drug, neurology is one of the most expensive therapeutic areas for R&D.

## The blood-brain barrier (BBB) permeability issue

The blood-brain barrier (BBB) permeability and safety are two reasons why many neurological drugs have failed. Most drug delivery methods are not able to cross the barrier, and even if the drug crosses the BBB, much of it ends up in other parts of the body, causing side effects.

- It is easier to deliver a drug into the gut than directly into the brain.

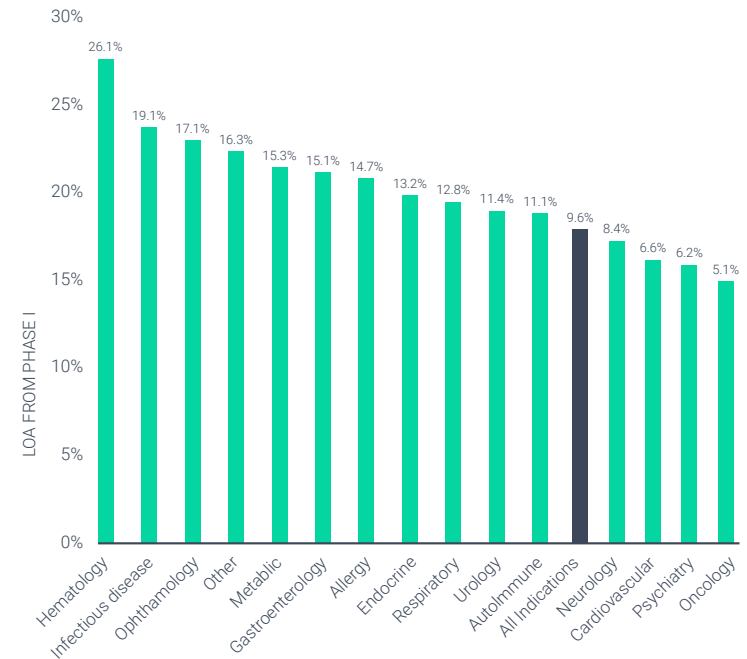
## Early detection and action

The main problem with existing CNS drugs is to target patients as early as possible. Abnormalities in the enteric nervous system can occur before those in the brain. Ultimately, scientists hope to spot (and cure) damage to the enteric nervous system before they see it in the central nervous system.

- 90% of all signals passing through the vagus nerve come from the gut.
- The microbiota and the presence of abnormal bacteria could be used as a biomarker to identify patients at risk.

SOURCE:  
Global Burden of Disease Study, Lancet Neurology, Mullard,  
A. Parsing clinical success rates. Nat Rev Drug Discov 15, 447 (2016)

CLINICAL SUCCESS RATES



# How Do We Target The Microbiota-Brain Axis?

## Targeting the gut microbiota

The trillions of microorganisms in the intestinal microbiota could be involved in many brain diseases. Some misfolded proteins have been observed as traveling from the gut to the brain and are currently being studied for therapeutic purposes.

- Axial Biotherapeutics is testing the role of bacteria in  $\alpha$ Syn protein aggregation, which is associated with Parkinson's disease.
- Kallyope develops a platform to explore all gut-brain circuits and find targets in several disorders (depression, Parkinson's, autism).

## Don't forget the oral microbiota

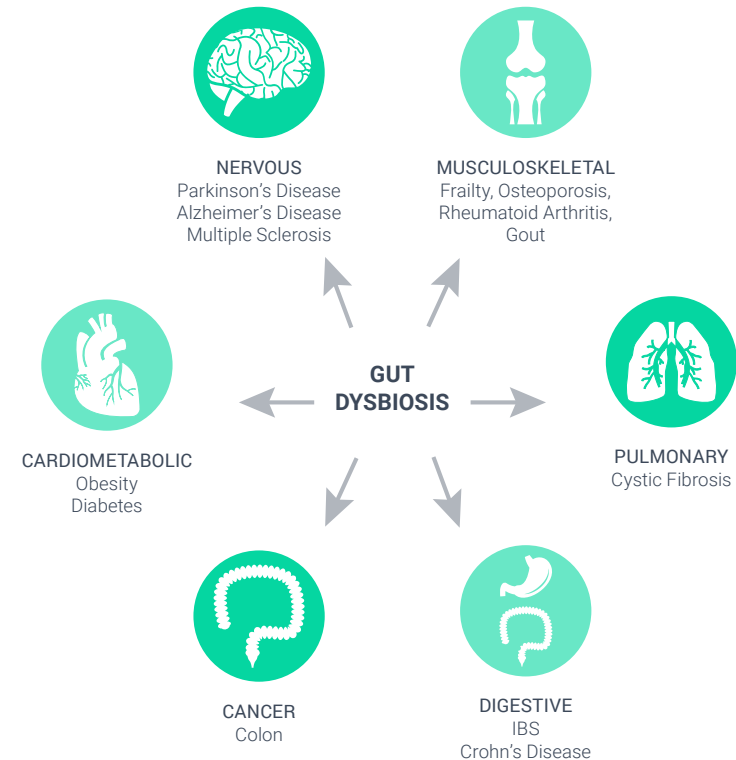
The mouth is the second-largest microbiota after the intestine with 700 different bacteria. The presence of neuroinflammation and immune response related to this microbiota has been observed in the brain of Alzheimer's disease patients.

- Cortexyme's lead product, COR388, targets *P. gingivalis*, an oral bacterium that produces toxins causing neuroinflammation, with promising preliminary data (Phase II/III trial) already been published.
- COR388 showed a significant decreased in the growth of *P. gingivalis*, anti-inflammatory effects and lowered the burden of amyloid plaques, which play a role in Alzheimer's disease.

## Beyond neurological diseases

Several studies showed the role of the microbiota in many other diseases, from cancer to liver disorders. A specific mix of bacteria was found in several tumors, such as bone or pancreatic.

- Second Genome has three pre-clinical and research programs targeting several indications: inflammatory bowel diseases, immuno-oncology, and metabolic diseases.
- Seres Therapeutics has a discovery platform to understand which microbes/ bacteria (absence or overexpression) can cause dysbiosis. The company designs drugs in inflammatory, metabolic, and infectious diseases.



## Catalysts

- **Cortexyme's drug results.** Interim data are expected at the end of 2020 and top-line data in Q4 2021. Any proof of concept in the field would drive the whole sector upwards and may trigger M&A.
- **Microbiome sequencing.** New methods, such as the single-cell sequencing technique, will allow each bacterial genome to be obtained separately. We will be able to understand the individual role of each bacterium.
- **Biogen's potential approval of Aducanumab in 2020.** The potential approval of its drug on Alzheimer's disease could restore investors' enthusiasm for neurological treatments.

## Risks

- **Failure in Alzheimer's disease.** Renewed failures in Alzheimer's disease after recent ones (Lilly, Pfizer) may lead to a binary reaction from investors.
- **The chicken or egg dilemma.** The cause and effect relationship between the microbiota and the brain is not well known. Does the microbiota lead to neurological disease, or does neurological disease lead to changes in the microbiota?
- **A complex community.** Microbiomes are studied in an artificial environment. The wild diversity of bacteria is not well represented in the patient's selection in clinical trials and could lead to misleading interpretation.

## Bottom Line

- The father of medicine, Hippocrates, believed that "all diseases begin in the gut". Two thousand years later, drugs based on the brain-microbiota axis have shown promising initial results and not only from the gut but also from the mouth. Microbiota therapies could provide a differentiated way of treating neurodegenerative diseases, where many biopharma companies have failed so far. Beyond brain diseases, the microbiota is also linked to hundreds of conditions, including cancers.
- With exposure in Cortexyme into the Biotechnology and Healthcare M&A certificates our investors are invested into a promising approach to treating Alzheimer's disease. We recently organized a call with the management of the company, confirming our positive view.

### Companies mentioned in this article:

Axial Biotherapeutics (Not listed), Cortexyme (CRTX US), Kallyope (Not listed), Second Genome (Not listed), Seres Therapeutics (MCRB US)



# THE GROUNDBREAKING SPACE ECONOMY

## Entry Barriers Down, Market Size Up

### Technological disruption in the satellite industry

Satellite technology is experiencing significant changes, disrupting the conventional satellite market. Dimensions, costs, and capacity are where innovation is having the most impact.

- Nanosatellites (or cubesats) are small (10cmx10cmx10cm) and as cheap as \$40k to launch.
- High throughput satellites (HTS) can offer transmission speeds up to more than 100x conventional ones.
- Satellite constellations increase orbit bandwidth by 10x at lower overall costs.

### Expanding application markets

The technological disruption and lower costs in launches foster satellite deployment and open up new applications. Sectors such as agriculture, supply chain, and national security increasingly rely upon satellite for data collection.

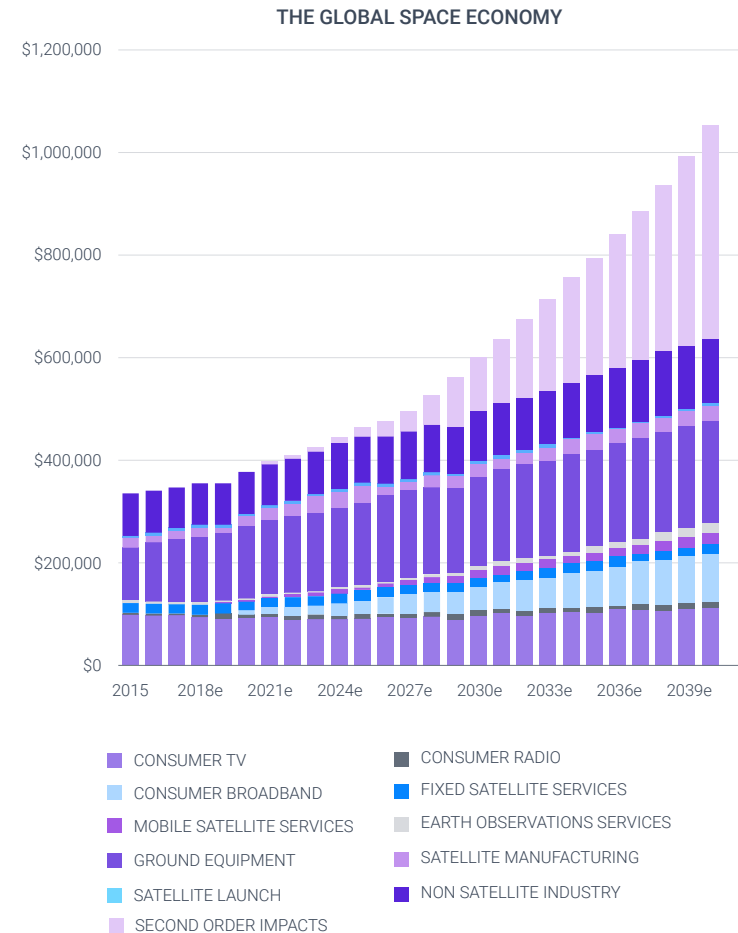
- Reusable rockets brought down launch costs from over \$20'000/kg to less than \$2'000/kg.
- The satellite data services market is expected to reach \$23.4bn by 2025, growing at a 21% CAGR.

### A galactic opportunity

The space economy is facing a steep boost in investments and projects. Its market size is forecast to rise almost three-fold in the next two decades.

- The global space economy will move close to \$1tn in value by 2040, from its current size of \$340bn (2018), a CAGR of 4.6%.
- Private investments created companies worth billions such as SpaceX, Virgin Galactic, or Blue Origin.

SOURCE:  
 UBS Research, Morgan Stanley,  
[Global Satellite Data Services Markets, 2019-2025](#)



# The Satellite Industry

## HTS and CubeSats at the forefront

High throughput satellites and cubesats are the necessary building blocks to complete satellite constellations and achieve broad internet connection.

- HTS provides superior capacity and high data throughput over small surface areas.
- CubeSats allow for cheaply updating the constellation of satellites – the technology deployed will always be up-to-date.

## Ubiquitous broadband internet

Broadband internet coverage for remote areas still lacks even in developed countries. Deploying cables and infrastructure to increase internet coverage is financially challenging in sparsely populated areas. Falling launch costs make internet access via satellite more affordable.

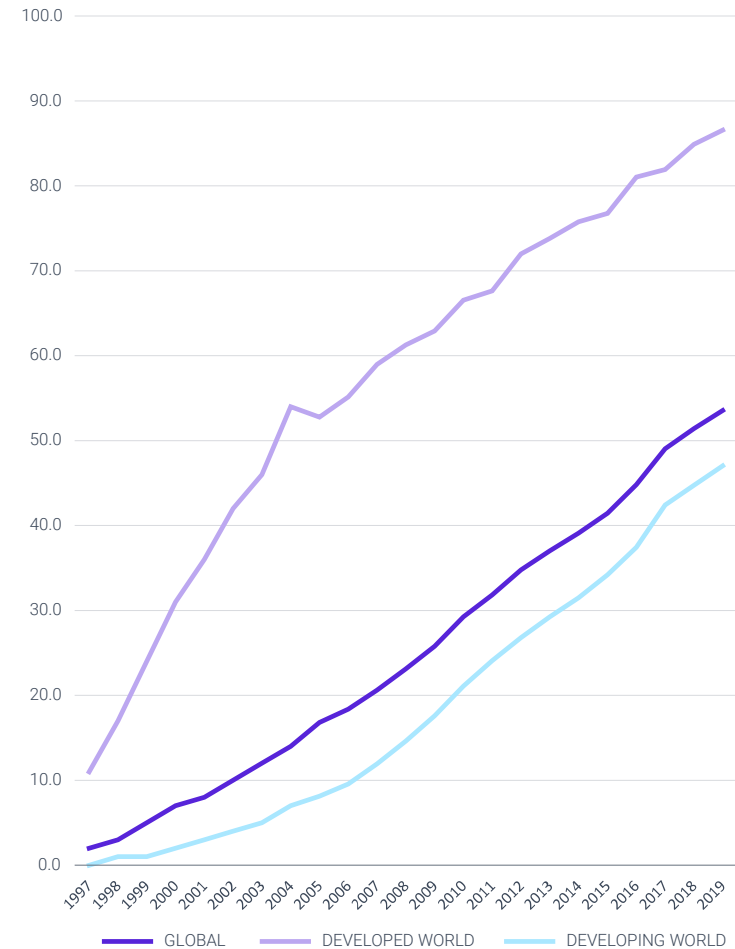
- Three-quarters of the unconnected population resides in just 20 countries – almost 3.6bn people still lack internet connection or do not use it.
- Servicing the unconnected global population is a \$300bn opportunity.

## More satellite, more data, more applications

As connectivity costs fall, satellite broadband will have a broader role in the rising demand for bandwidth expected over the next decades. New applications such as the Internet of Things will drive this surge in demand.

- Deloitte expects the number of satellites in low-earth orbit (LEO) seeking to offer broadband internet to grow 3.5x from 2019, reaching 700 at the end of 2020.
- As an example, the integration of the Global Navigation Satellite System (GNSS) in agricultural machines is expected to reach 35% by end 2020 – up from 7.5% a decade ago.

INTERNET USERS PER 100 INHABITANTS



## Earth Applications From Space Data

### A data-based agriculture

The agricultural sector needs data access. While drones and sensors collect some data, satellites can provide a larger scale. Precision farming thrives on using data to optimize the workflow (see our [10.06.2020](#) issue for more details).

- Farmers can maximize yields, increase productivity, and lower their environmental impact by optimizing the deployment of herbicides and chemical compounds.

### An additional eye for supply chain management

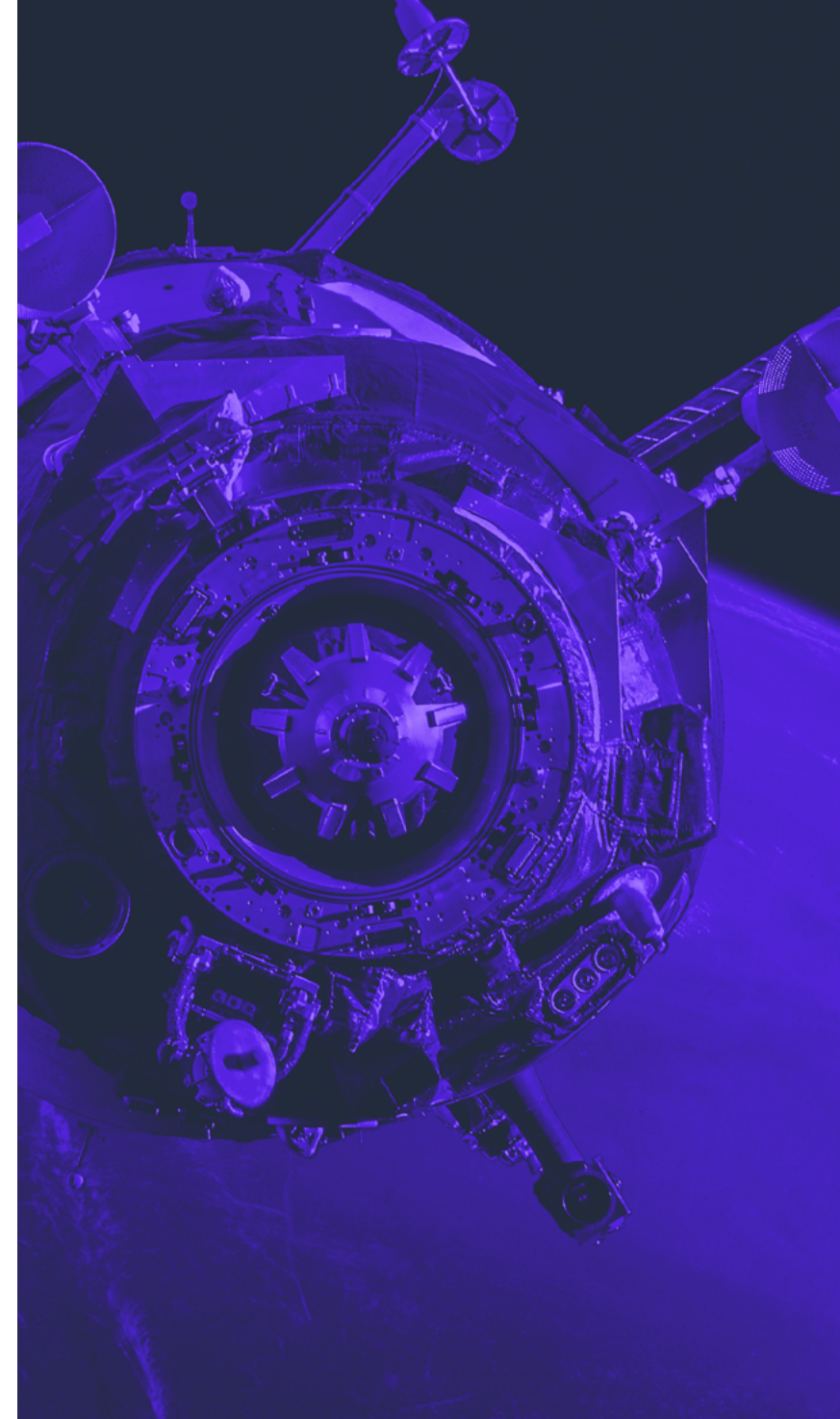
Satellite imagery will be essential also in supply chain management, as it will ease projections made by companies procuring commodities and other goods, as well as to develop models for forecasting and monitor re-routing options.

- Descartes Labs uncovered through its geospatial imagery that soybeans were re-routed to South America from Asia after tariffs hit.
- Computer vision, machine learning, and cloud infrastructure are essential for computers to interpret satellite imagery.

### National space programs benefit as well

Declining costs also benefit national space programs, with National Security and advanced research the main issues being addressed.

- The Hera project (European Space Agency) aims at controlling potential threats from outer space through small satellites.
- NASA is sending nanosatellites to travel into deep space (MarCO-A and -B).



## The Billion-Dollar Club

### Cheaper rocket launch: SpaceX

Manufacturing and launching rockets are undergoing a revolution thanks to SpaceX, the company founded by Elon Musk that is focusing on low-cost satellite launch. Reusable rockets are expected to replace current expendable launch systems.

- NASA used SpaceX to send US astronauts to the ISS in May 2020, ending nine years of reliance on Russia and the Soyuz rockets.
- SpaceX plans to perform 38 rocket launches in 2020, up from 13 in 2019.
- The company plans to expand its Starlink satellite constellation massively, from the current 538 satellites to the at least 12'000 already planned.

### Above the sky level, faster than the sound: Virgin Galactic

Richard Branson founded Virgin Galactic primarily for suborbital space tourism. It will generate the first opportunity to experience space travel for individuals. It plans to add hypersonic flights at a later stage, bringing cities closer.

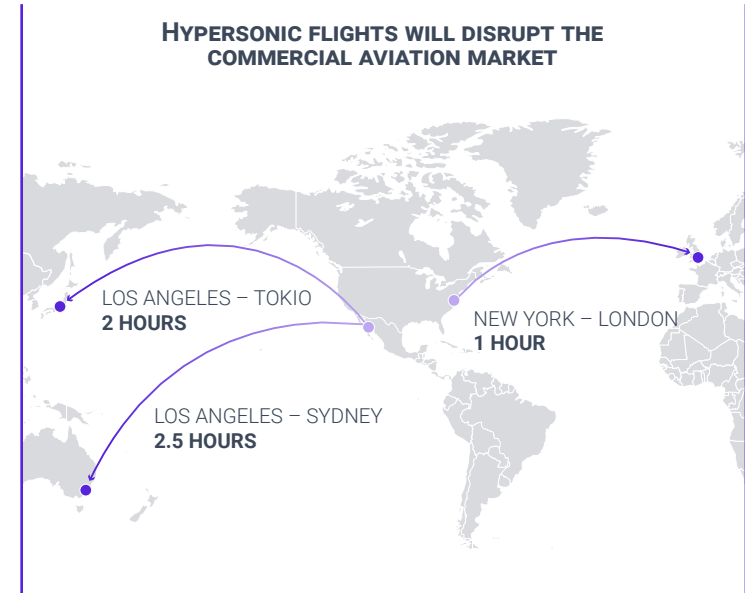
- It received almost 8k reservations for its space travels, priced at \$250k each.
- Space tourism is expected to be worth \$30bn by 2030.
- The first suborbital launch is expected in 2020.

### Closer to the stars: Blue Origin

The company founded and funded by Jeff Bezos aims at enabling private human access to space. It plans to deliver suborbital space flights and eventually aiming to reach the orbital level.

- Its first launch carrying humans is expected in 2020.

SOURCE:  
NASA, Company data  
[Image: Wikipedia](#)



## Catalysts

- **Private equity appetite.** Venture capitalists want to get a slice of the space economy. Private funding for space investments reached a record level in 2019, which should ultimately boost research.
- **OneWeb satellite constellation is going live.** The 650-satellite constellation is under the ramp-up phase. It is expected to start delivering global satellite Internet broadband beginning in 2021.
- **FCC public C-band auction.** The US Federal Communications Commission will commence the auction on December the 8th 2020, a pivotal moment for the future of 5G in the US.

## Risks

- **Space debris.** Adding thousands of satellites in the Earth orbits increases the risks of collisions. Several projects are under development to remove space debris.
- **SpaceX slowing down launch pace.** SpaceX conducted 40% fewer launches in 2019 than in 2018 because of a lack of customers ready to launch. Customers' readiness may hamper the speed of their progress.
- **ExoMars 2020 postponement.** The European Space Agency (ESA) will determine if the mission to search evidence of past life on Mars can take off this year. A set of tests during 1H20 will evaluate if it will be live in 2020 or on hold until 2022.

## Bottom Line

- The space economy is booming – innovations coming from private companies are pushing the wave. New markets such as space tourism will emerge.
- Entry barriers for the space sector are falling. Rockets launch costs are shrinking – this boosts satellites deployment for internet connection and data collection purposes.

### Companies mentioned in this article:

Blue Origin (not listed), Descartes Lab (not listed), OneWeb (not listed), SpaceX (not listed), Virgin Galactic (SPCE US)

# CLEANING UP THE SHIPPING INDUSTRY

## Navigating The Waters Of Cleaner Ships

### What is it all about?

International Maritime Organization issued a new regulation, called IMO2020, whose primary goal is to limit SOx emissions from ships to protect the environment & human health.

- Limiting SOx emissions should prevent 100'000 premature death/year, as it reduces particulate matter responsible for respiratory & lung diseases.
- SOx in the atmosphere can lead to acid rains causing oceans' acidification and harming crops & forests.

### Heavy polluters

Ships have traditionally been using one of the dirtiest existing fuel, known as "bunker fuel", the residual leftover from crude oil distillation. Such fuel contains sulfur, which, when burned, emits Sulphur oxides (SOx).

- IMO2020 aims at reducing SOx emissions by 8.5mn tons/year or a 77% reduction from current levels.

### Greenhouse gas emissions in the pipeline

Beyond SOx, the IMO also intends to align its greenhouse gas (GHG) emissions with the Paris Agreement climate goals.

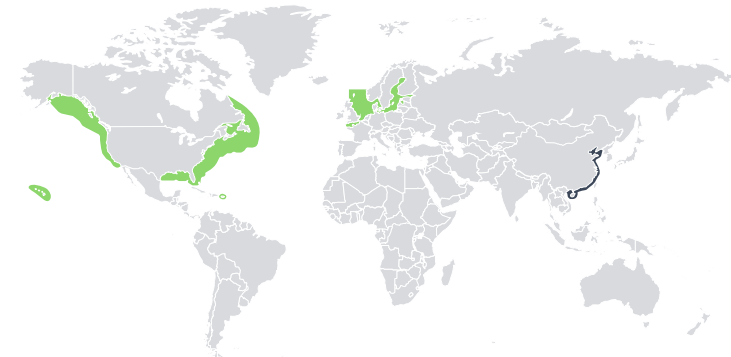
- In April 2018, it adopted an initial strategy aiming to reduce GHG emissions by at least 50% by 2040 (compared to 2008 baseline levels).
- Meeting shipping decarbonization requires the implementation of targeted policies, tackling ships' operational efficiency, supporting the use of low-carbon fuels, and setting a CO2 pricing system for maritime fuels.

SOURCE:

[Global Sulphur Cap 2020](#), DNV GL, 2019

[Sulphur 2020 – cutting sulphur oxide emissions](#)

[Tracking Transport 2019](#)



- 0.50% LIMIT, GLOBAL (MARPOL, 2020)
- 0.10% LIMIT, SECA (MARPOL)
- 0.50% LIMIT, CHINA NATIONAL WATERS (12 NM), 2019

Area	Sulphur limit	Scrubbers
Global	0.50% (2020)	Local restrictions may apply for open-loop scrubbers
SECA	0.10%	Yes
EU	0.10% in all ports	Open-loop scrubbers restricted in some countries
China	0.50% in national waters (12 nm)	Certain restrictions apply for open-loop scrubbers
California	0.10% within 24 nm	No, only with research exemption

# The Road To Compliance

## Economics vary from case to case

Distillates are widely available, but more expensive, low-sulfur residual fuels are price volatile but cheaper than distillates. Installing a scrubber allows to use cheaper high-sulfur fuel oil (HSFO) but requires high investment cost, and the use of Liquid Natural Gas (LNG) requires even higher upfront investments but is cleaner.

- Shipowners need to assess each option on a case by case basis, depending on residual vessel life, routes, usage, etc.

## There is no one-size-fits-all solution

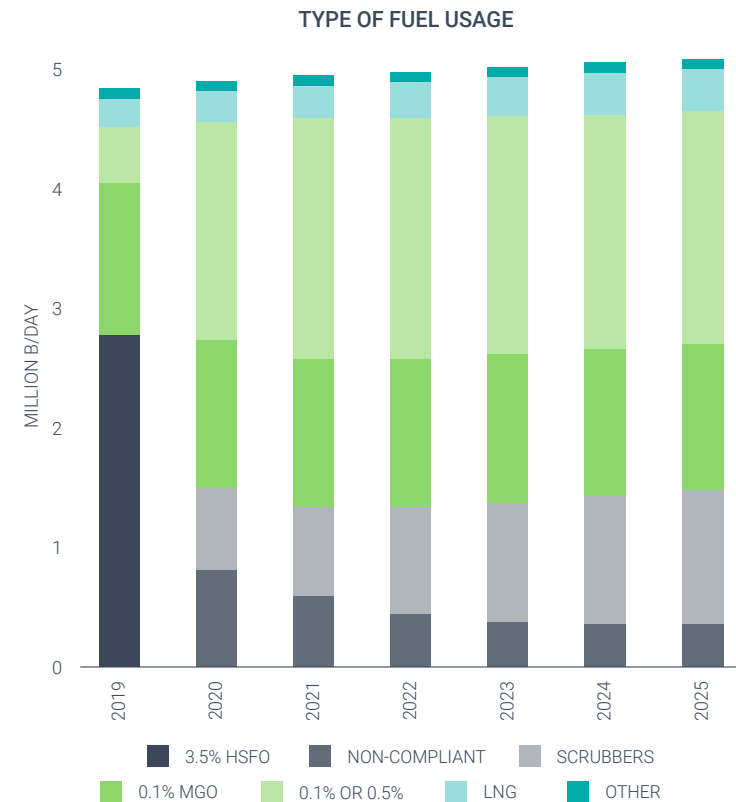
Given the different possible options and shipowners deciding on a case by case, the likely result will be a split across a variety of solutions and providers.

- By 2025, experts expect bunker fuel demand to be split between residual marine fuels (38%), Marine Gas Oil (24%), HSFO + Scrubber (22%), and LNG (8%)

## A niche market

The shipping industry represents less than 5% of the global oil demand. However, big oil suppliers (incl. Shell, Exxon, BP, Total, Sinopec, etc.) have already declared compliant fuels to be available at all major ports.

- Marine vessels consume globally, 4-5mn barrels of oil per day.



SOURCE:  
 IMO 2020 Monthly, BNEF, February 2020  
 Air Pollution and energy efficiency, IMO, 2016  
[Oil price information](#)

# The Road To Compliance

## Fuel prices

While it is difficult to predict future fuel prices, relative price levels, and spreads are stabilizing after some volatility caused by the implementation of the new policy and the COVID-19 related oil collapse.

- Marine Gas Oil (MGO) is the most expensive and High Sulfur Fuel Oil (HSFO) the cheapest.
- Very Light Sulfur Fuel Oil (VLSFO) did spike to \$700/t in early 2020 before falling to almost \$200/t in April. Rates seem to be stabilizing at around \$300/t (exact price varies depending on port location).

## Scrubbers

Scrubber costs vary between \$2-\$10mn depending on size (linked to engine range), type (open/close loop, hybrid), and design (inline/ multi-inlet tower).

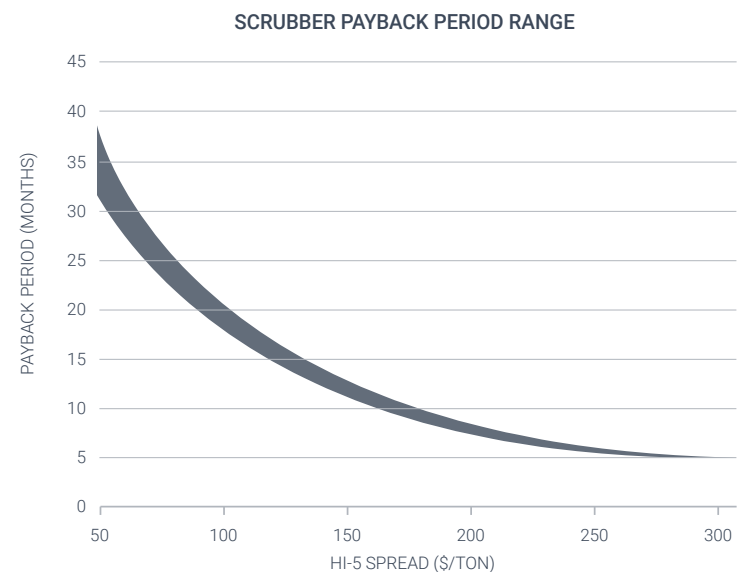
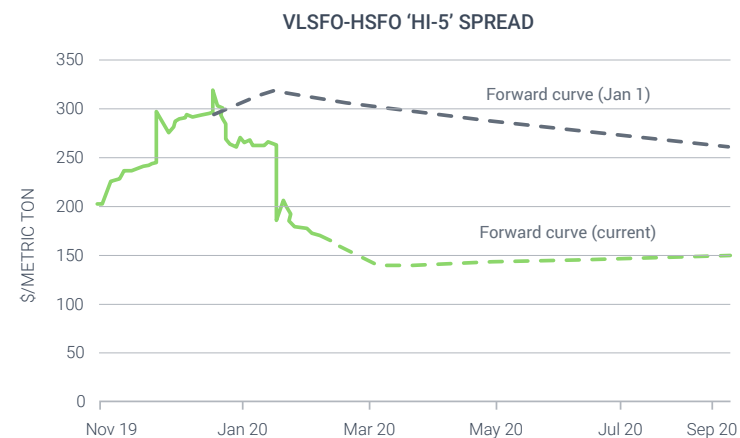
- The two leading scrubber providers are Wärtsilä and Alfa Laval.

## Spreads are key

Economics of each option depends on the price spread between the different fuels used and their availability. VLFO-HSFO spread (called “HI-5” spread) is used as a base to calculate the payback period of installing a scrubber.

- “HI-5” spread seems to stabilize at below \$100 per ton (currently at around \$80 at Singapore port), bringing the scrubber payback period at about two years (vs. less than five months at January’s spread levels).
- VLSFO prices collapsed during the economic downturn while HSFO remained more stable, supported by the seasonal cooling demand in the Middle East.

SOURCE:  
 IMO 2020 Monthly, BNEF, February 2020  
 Oil and Product Markets Monthly, BNEF, May 2020  
 Air Pollution and energy efficiency, IMO, 2016  
 BloombergNEF, [Oil price information](#)





# How To Make Ships Even Cleaner

## Alternative fuels to reduce CO2 emissions

The next major regulatory constraint will be the limitation of CO2 emissions, which are to be cut by 50% by 2040 (from 2008 basis). To comply, more drastic changes will be required, opening the door to alternative fuels.

- CO2 emissions could potentially be reduced to levels below 20g/MJ (vs. current 80-90 g/MJ).
- Shipping fuels with the lowest carbon footprint include methanol (from black liquor), hydrogen (from water), biogas, and biodiesel (from clean sources).

## Energy efficiency or how to consume less fuel

Beyond burning cleaner fuels, ships also need to enhance their energy efficiency. The IMO has set energy-efficiency measures requiring, by 2025, all new ships to be 30% more efficient than the ones built in 2014.

- Improving vessel's energy efficiency comes by improving voyage planning, using waste heat recovery systems, regularly cleaning underwater parts & propeller, replacing propellers with more efficient ones, etc.

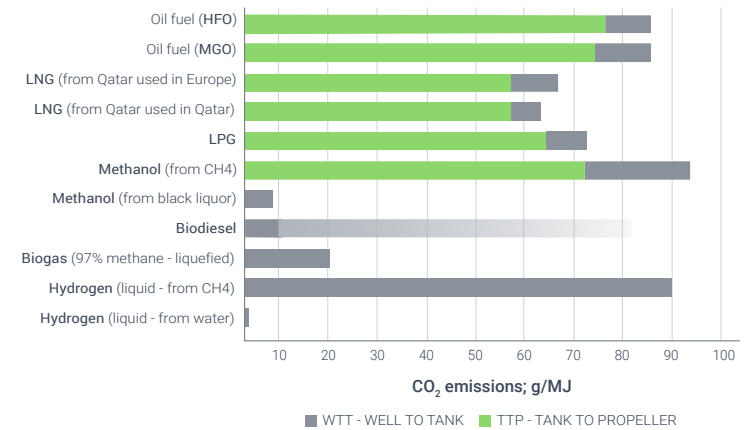
## Going one step further

Looking one step ahead, some nascent technologies might find their way in the shipping industry, including batteries, fuel cells, or wind-assisted propulsion.

- Batteries have great potential for short-distance applications but are technically limited for long-range deep-sea shipping.
- Fuelcell powered ships start to appear with some pilot projects such as the "e4ships" or the hydrogen superyacht to be built by Feadship for Bill Gates.
- Wind-assisted propulsion can be used as an add-on to reduce fuel consumption (efficiency gain up to 20%) but used mainly on slow vessels.

SOURCE:  
Assessment of selected alternative fuels and technologies, DNV GL, 2019  
Image: [gCaptain](#)

CO<sub>2</sub> EMISSIONS OF FUEL ALTERNATIVES IN SHIPPING



## Catalysts

- **Increased international pressure.** E.g., the OCED putting pressure on the IMO by recommending new ships to be 60% more efficient by 2030 or developing & adopting a CO2 pricing system for maritime fuels.
- **Technology transfer.** Increased R&D spending in battery or fuel cell technologies (as seen in China, Europe, and Japan) for road transport can benefit the shipping industry through technology transfer.
- **New Amendment on HSFO.** Starting from March the 1st 2020, ships that are not equipped with scrubbers aren't allowed to carry HSFO in their fuel tanks.

## Risks

- **Falling Gas Prices.** Falling marine gas oil & natural gas prices, driven notably by COVID-19, makes MGO/LNG more profitable and therefore threatens the viability of scrubbers or other alternative fuel options.
- **Lack of control.** Infractions to the new IMO2020 regulation are subject to penalties, which can vary significantly between countries. Since no standardized penalty system exists, enforcement could remain uneven around the world, and some ships might keep using illegal fuel.
- **Lack of cash.** The shipping industry is one of the most affected by COVID-19, and carrier companies might not have the required capital to initiate expensive infrastructure upgrades such as scrubber installation.

## Bottom Line

- The shipping industry is being reshaped to integrate environmental parameter, opening up the door to several cleaner alternative technologies.
- Stricter air pollution and GHG emissions regulations are creating new opportunities for several technologies including scrubbers or alternative fuels, all part of our Sustainable Future universe.

### Companies mentioned in this article:

Alfa Laval (ALFA SS), BP (BP LN), Feadship (not listed), Shell (RDSA LN), Sinopec (386 HK), Total (FP FP), Wärtsilä (WRT1V:FH)

# CHARTS FOR THOUGHTS

## Where Is Corona's Money Gone?

### Retail Missed the Last Bull Market

Following the repeat market crashes of the dot com bust and the 2008-09 financial crisis, retail investors have fled the stock market for the past ten years.

- Cumulative fund flows in Equity Funds have been declining since 2008.
- Only Millennials are increasingly investing, but their share of wealth is only 3%.

### People Received More Money than they Needed

As the Covid-19 crisis struck, State aids to support the workers were exceptional. Although very welcome news for many in dire need, it also provided extra cash to many at a time when spending was reduced by being forced into lockdown mode.

- In 37 states, workers received on average more in unemployment benefits than they would from regular salaries.
- The lockdown brought along the closure of stores, entertainment opportunities, and sport-related activities, including betting.

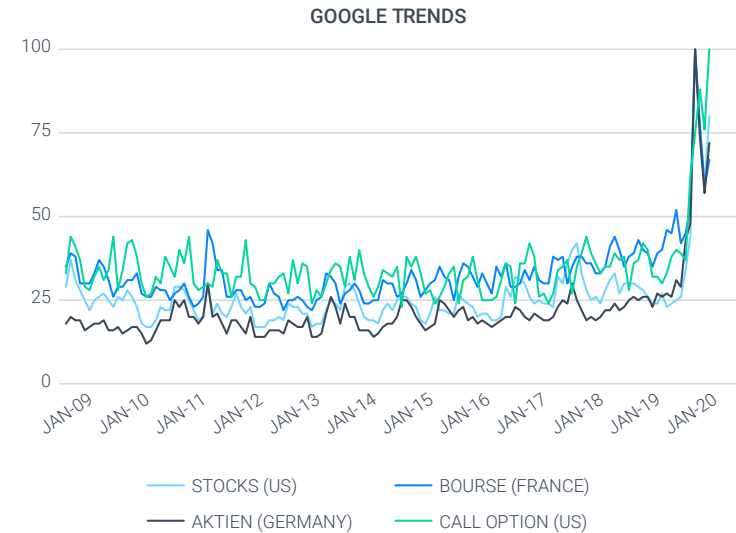
### Flows into Online Trading?

Spikes in Google Trends search item "Stocks" and online brokers' new accounts opening at the moment lockdown was implemented, imply aid money has likely gone to the equity markets.

- The financial impact is likely marginal in the overall scheme of things.
- But it shows how retail investors may be regaining interest for the equity markets, and how quickly they opted for Fintech solutions.

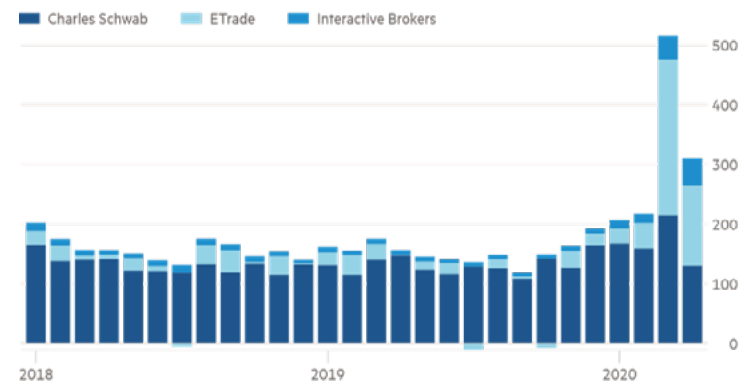
SOURCE:

[Frustrated sports punters turn to US stock market](#),  
[The \\$600 Unemployment Booster Shot, State by State](#)

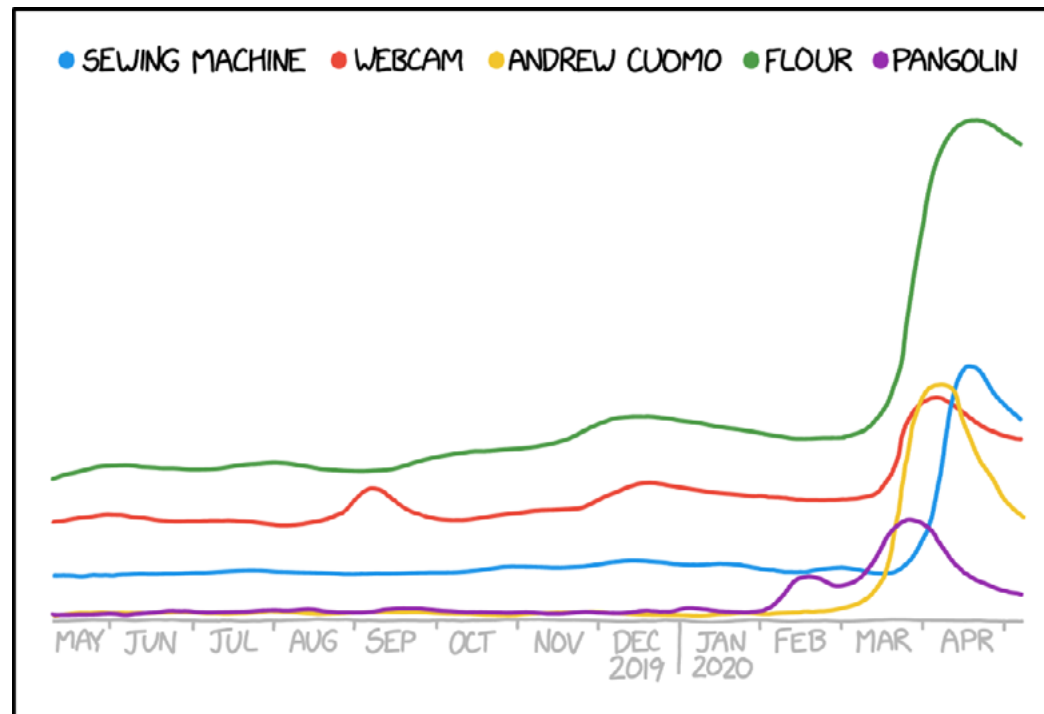


### Online brokers enjoy lockdown boom

Monthly net new client accounts (1,000s)



# CASUAL FRIDAY



I WANT TO SHOW SOMEONE FROM 2019 THIS GOOGLE TRENDS GRAPH AND WATCH THEM TRY TO GUESS WHAT HAPPENED IN 2020.

SOURCE:  
<https://xkcd.com/2302/>

# Invest Beyond The Ordinary

Explore our investment themes:  
[www.atonra.ch/investment-themes/](http://www.atonra.ch/investment-themes/)



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PAYMENTS



BIONICS

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AtonRâ Partners is a conviction-driven asset manager combining industrial and scientific research with financial analysis. AtonRâ Partners focuses on long-term trends powerful enough to be turned into thematic equity portfolios.

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