DISRUPTIVE INNOVATIONS VII

Ten More Things to Stop and Think About

Citi GPS: Global Perspectives & Solutions

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DISRUPTIVE INNOVATIONS VII

Ten More Things to Stop and Think About

Kathleen Boyle, CFA
Managing Editor, Citi GPS

In our new report, the seventh in our Disruptive Innovations series, we once again look at some of the leading-edge concepts across sectors and identify new products that could ultimately disrupt the marketplace. This year again, there are a few concepts that have been around for quite a while — nuclear fusion and quantum computing — which have required a technological breakthrough to become reality. With nuclear fusion, we note there has been talk of a solution in the 'next 20 years' for about the past 50 years, but interest in the topic has recently peaked again with the increased global focus on renewable energy and the concept is only one small breakthrough away from becoming reality. Quantum computing is another subject talked about as perpetually on the horizon, but progress is accelerating here and we think that we could be close to a tipping point in technology in the near future.

In healthcare, we once again are spoiled for choice in terms of the ideas and concepts that are quickly coming down the pike. Robotic surgery makes up just 2% of all surgical procedures currently, but with advancements in visualization and robotics, this looks set to accelerate to almost 15% by 2030. Virtual healthcare is just starting to gain a foothold with the advent of telehealth, but going forward, we see it expanding to broader technology-enabled healthcare, spanning from urgent care all the way to chronic condition management and remote surgery — effectively replacing the four walls of a hospital with the patients' home. Gene therapies, which are increasingly being reviewed and approved by regulators have the potential to make untreatable diseases treatable, eliminate some currently treated disease markets, transform the drug payer system, and increase the rate of drug development. Finally, we investigate the benefits and challenges of using probiotics as preventative medicine and an alternative to immune-related drug therapies

There is also a focus on sustainable innovation. Outside of simply emitting less carbon dioxide, we find carbon dioxide removal technology, such as carbon capture and storage/sequestration could be on the near horizon along with carbon pricing. Hydrogen-powered rail could be an indirect renewable energy story as hydrogen-powered trains, using fuel cells, have zero emissions at the point of use and don't require an upgrade to track infrastructure. We also look at new technology initiatives to increase the quality of recycled fibers in order to offset the use of virgin materials in clothing manufacturing and the role that Digital Agriculture can play in ensuring not only cost savings for farmers through increased efficiency, but also as a sustainable solution to increase food yields in order to feed a growing population.

Innovations to Help the Planet and its Inhabitants

$2.3tn

Carbon price revenue generated per year from CO_2 removal

800

Number of gene therapy new drug applications on file at FDA – expect › 200 new applications/year

$15billion

Cost savings from digital agriculture and more efficient fertilizer and pesticide use

15%

Penetration rate of robotic surgery by 2030 (from 2% today)

00

Emissions at point of use and additional track infrastructure required using hydrogen-powered rail

$129.5bn

Expected size of yogurt/probiotic market in 2024 vs. anti-cancer drug market of $236.6bn

3%

Amount of the current clothing supply chain made from recycled materials

5

Number of years in which the U.S. telehealth market is expected to double

Limitless

Amount of carbon free energy generated through nuclear fusion

10

Number of years before large-scale commercialization of quantum computing

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Innovation Clusters and Universities

Kathleen Boyle, CFA
Managing Editor, Citi GPS

In previous editions of our Disruptive Innovations series, we've identified the different characteristics and drivers of innovation. We encouraged enterprises who wanted to innovate to first define what innovation meant to them, then to agree on why they wanted to innovate, their definition of what success looked like, a process to get there, and a commitment to gather metrics which tangibly measure the value innovation was contributing to their organization. We talked about the big company innovation dilemma and Professor Nathan Furr, Professor or Innovation and Strategy at INSEAD, introduced us to the 'Innovator's Method' as a framework for corporates to shift their underlying process towards innovation, the pitfalls big companies get stuck in on their quest for innovation, and the tools corporates can use to overcome these bottlenecks.

We also looked at how the pace of innovation has been accelerating over the past few years while the cost of innovation is falling, helped by technologies such as cloud computing and the Internet, which in turn has lowered barriers to entry and the price of failure. In a world of rapid-fire innovation we found it was slow change that often brings about the most paradigm-altering transformations — the trick is to catch the accelerating, irreversible trends as they emerged.

In our latest edition, we'd like to go back and look at our work on innovation clusters.

Finding the Successful Recipe in Innovation Clusters

Silicon Valley is universally identified as center for disruptive innovation

Silicon Valley is almost universally identified as a center for disruptive innovation. Since the 1970s, the region has been associated with developing the cutting edge technology and blockbuster inventions which have disrupted our everyday lives. Home to the semiconductor, computer software, and electronics industries, the Valley has grown to be one of the largest innovation clusters in the world with outsized importance in both its region and the United States. In 2018, Silicon Valley and the San Francisco Bay area together made up 53.8% of California's patent registrations and 14.8% of total U.S. patent registrations.

Other notable clusters of innovation have emerged across the U.S…

Other notable clusters of innovation are scattered across the U.S. In Boston, the 'Route 128 Corridor', is a technology-based area with nearly 30,000 scientists directly involved not only in high-tech industry but in also biotechnology, pharmaceutical, and clinical research. The Research Triangle in North Carolina is an industrial/research park created by the state to help bring research and development into the area and currently is home to multiple pharmaceutical companies and four out of the top five agri-tech companies.

…and across the globe

Across the globe new innovation clusters have popped up, and while universally less well-known, are still extremely important to their local and regional economies. These clusters also vary in sector expertise with Stockholm known for information & communication technology (ICT), London for FinTech, Shenzhen for communication and electronics, and Tel Aviv for technology. In the U.S., in addition to the clusters mentioned earlier, Austin, Texas has developed as a hub for software development and Pittsburgh, Pennsylvania for robotics.

There is a recipe for success in innovation clusters

The success of regional clusters depends on a number of issues including (1) the availability of adequate skills; (2) good local/regional policy that targets fields with a long comparative advantage and encourages a good open immigration policy that enables access to global talent; (3) low cost structure especially in the early stages of development such as low cost office space and rent; (4) the availability of funding (venture capital, angel investment, federal and state funding); (5) good infrastructure and good lifestyle offering; and (6) proximity to markets and geographical location.[1]

Innovation clusters tend to sit geographically near universities which provide workers with adequate skills

The availability of adequate skills is helped by the proximity of higher education. Although incredibly diverse in geography and culture, we see one common thread running through the innovation clusters we've highlighted above — proximity to higher education. In or around many of the major innovation clusters there is a university which not only supplies a steady stream of talent, but also provides a steady stream of scientific research. Stanford University sits in the middle of Silicon Valley, Duke University and the University of North Carolina are near the Research Triangle, while MIT, Boston College, Boston University, Harvard University, and Northeastern are within the Route 128 Corridor. In London innovation clusters center around both Cambridge University and the University of Oxford. In addition to sharing talented individuals, the proximity of successful innovation clusters and universities allow for the successful transfer of ideas or idea exchanges.

University tie-ups help drive the focus of innovation clusters

In Asia, the innovation cluster around Shenzhen/HK has grown rapidly over the past few decades with business magazine Inc. noting that 90% of the world's electronics originate from there and subsequently labeling Shenzhen as 'the world's factory'. Historically a stronghold of manufacturing, Shenzhen is now shifting its stance to becoming a leader in high-tech innovation. Many of the world's largest information and communication companies call Shenzhen their home which in turn is attracting an increasing number of start-ups and accelerators. Robotics research has recently become a focus of the area and is supported by tie-ups with university groups such as the Shenzhen Institute of Artificial Intelligence and Robotics — a collaboration between the Chinese University of Hong Kong (Shenzhen), MIT, Carnegie Mellon, University of Pennsylvania, Stanford University, Zurich Institute of Technology, and Edinburgh University.

Figure 1. Top 15 Science & Technology Cluster Rankings

Rank	Cluster Name	Economy	PCT Applications	Scientific Applications	Share of Total PCT filings, %	Share of Total Pubs, %	Total	Ranking 2012-16
1	Tokyo-Yokohama	Japan	10,8973	144,559	10.9	1.72	12.62	1
2	Shenzhen-Hong Kong	China/HK	55,433	45,393	5.54	0.54	6.08	2
3	Seoul	S. Korea	39,545	136,654	3.95	0.63	4.58	3
4	Beijing	China	23,014	222,668	2.3	2.65	4.95	5
5	San Jose-San Francisco, CA	U.S.	38,399	88,243	3.84	1.05	4.89	4
6	Osaka-Kobe-Kyoto	Japan	28,027	67,127	2.8	0.8	3.6	6
7	Boston-Cambridge, MA	U.S.	14,364	120,404	1.44	1.43	2.87	7
8	New York City, NY	U.S.	12,329	133,195	1.23	1.59	2.82	8
9	Paris	France	13,426	94,982	1.34	1.13	2.47	9
10	San Diego, CA	U.S.	19,280	34,403	1.93	0.41	2.34	10
11	Shanghai	China	8,736	114,395	0.87	1.36	2.23	12
12	Nagoya	Japan	19,370	23,705	1.94	0.28	2.22	11
13	Washington, DC-Baltimore, MD	U.S.	4,498	117,623	0.45	0.4	0.85	13
14	Los Angeles, CA	U.S.	9,398	68,337	0.94	0.81	1.75	14
15	London	Great Britain	4,070	107,131	0.41	1.28	1.69	15

Source: WIPO Statistics Database, March 2019

[1] Citi GPS Disruptive Innovations IV, July 2016.

Collaboration of Academia and Corporate in Innovation

In the 20th century, a large amount of innovations were the result of work done in research and development centers at large corporate research labs

In the recent past, a significant amount of inventions considered to be disruptive innovations — including the transistor, cellular communication, optical fibers, and synthetic materials — were developed by notable, large U.S. corporate labs, including Bell Labs, IBM's Watson Labs, the Palo Alto Research Center and DuPont's Purity Hall.[2] The rise of these labs within corporate America were driven by three things that occurred in the early part of the twentieth century: (1) chemical firms in Germany became increasingly competitive, which required firms in the U.S. to innovate in order to compete; (2) antitrust issues came into increasing focus, making it more expensive to acquire patents versus discovering them in-house; and (3) increasing competition to American inventions (such as electric lighting) from overseas players.

Changes in corporate structure and regulation in the 1980s drove a decline in corporate research labs…

However starting in the mid-1980s, corporates started to close their research labs and subsequently, the amount of corporate research spending declined. This reversal in trend was initially the result of an increase in competition from accelerating technological change, which reduced the time period available to companies between when made a new discovery and when they successfully turned that discovery into a commercial product. This made it much harder for internal research divisions to be profitable. Corporates also became narrower in scope as investors and activists pushed them to divest non-core businesses, decreasing the need for large, broad-based corporate research labs. Finally, more relaxed antitrust laws made it cheaper to buy innovation versus building it internally, while at the same time that the quality of university research increased. This led corporates to stop spending their money on in-house research labs and focus instead on external options.

…and a decline in the amount of basic research being done at the corporate level

The result of the shift away from internal labs was that the share of research (both basic and applied) in total corporate R&D fell from 30% in 1985 to less than 20% in 2015, despite overall corporate R&D levels being stable.[3] In addition, there has been a decline in the number of scientific articles published by corporates, which is another indication of their shift away from basic and applied research. For American listed firms, the number of publications per firm fell at a rate of 20% per decade from 1980 to 2006 with even more dramatic drops for established firms in higher quality journals.[4]

At the same time, university share of applied research increased as did the number of patents awarded to universities

Given that scientific capability continues to be important for innovation and innovation has continued to accelerate, the decrease in science research spending at the corporate level must have been made up somewhere else. Offsetting this decline was an increase in university research, which steadily rose from 23.8% in 1985 to 33.6% in 2015 as a share of total research while their share in applied research almost doubled from 10.0% to 19.8% over the same time period.[5] This increase was helped in the U.S. by the passage in the 1980s of the Bayh-Dole Act, which allowed the results of federally-funded university research to be owned and exclusively licensed by universities.

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[2] Arora, A., Belenzon, S., Patacconi, A., and Suh, J. (2020), "The Changing Structure of American Innovation: Some Cautionary Remarks for Economic Growth," Innovation Policy and the Economy 20: 39-93.

[3] Ibid.

[4] Arora, A., Belenzon, S., and Patacconi, A., (2018). "The Decline of science in corporate R&D." Strategic Management Journal, 39(1), pps 3-32.

[5] Bouroush, M., (2017). "National Patterns of R&D Resources: 201415 Data Update. Technical Report NSF 17-311, National Science Foundation.

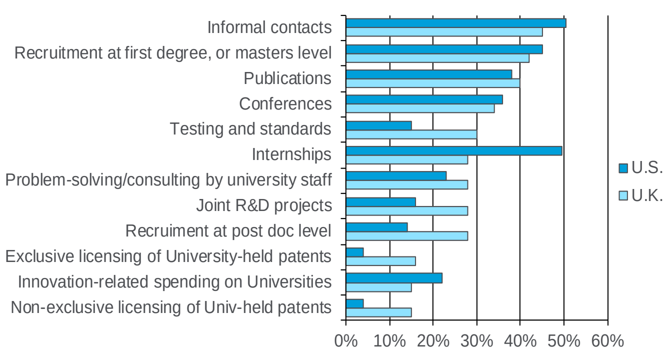
Being able to own and license their own research led to a big increase in the number of patents awarded to universities (from 380 in 1980 to 3,088 in 2009[6]) and in the number of universities starting their own businesses. Despite these gains, corporates still hold the majority of patents but increasingly they cite university research in their patent applications versus their own proprietary research.

Corporates and universities now work together in an innovation ecosystem with a division of labor between research and development

Today, corporates and universities exist in an innovation ecosystem where universities increasingly focus on the science and lab research while corporates focus on the development and integration needed to commercialize the resulting innovations. Academics are split on whether this division of labor is a positive or a negative for future innovation. On the one hand large corporations have greater access to financial resources, can tackle multi-disciplinary problems, and research conducted in a corporate lab is directed toward solving a specific problem. This may result in positive spillover effects by spurring high-quality scientific entrepreneurship.[7]

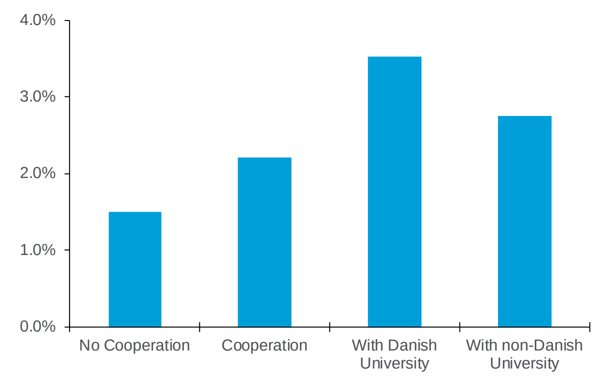
On the other hand there are notable positive spillover effects from academic research on innovation and growth, as universities provide valuable assets to corporates, especially in the form of skills and ideas.[8] According to Schneider & Sørensen, academic research spills over into the rest of the economy similar to corporate research, but with a longer lag, but they find it compliments private R&D rather than crowding it out. Although the link is not always direct or obvious, there are multiple pathways through which academic research affects society. Private sector innovations are promoted most by informal contacts with academic faculty and the recruitment of university graduates is one of the biggest contributors to corporate innovation. Figure 2 shows the results of a survey of firms and their views on university cooperation for the development of ideas and the completion of innovation completion, and highlights that around 50% of the firms rated informal contacts with universities as important. Studies also show firms who employ a higher share of university graduates have a greater amount of innovation, and firms who collaborate more with universities had higher average productivity (Figure 3).

Figure 2. Types of University-Industry Interactions Contributing to Innovation (% of Firms Rating Mode)



Source: Cosh, A.D., Lester, R.K. and Hughes, A. (2006) 'UK plc: Just how innovative are we?', Cambridge-MIT Institute, Cambridge, UK and Cambridge, Mass.

Figure 3. Annual Labor Productivity Growth, 2008-13;Groups of Firms Divided by Type of Cooperation



Source: Community Innovation Survey, 2014, accounting data (FIRM) 2013 (Statistics Denmark)

[6] Arora et. al. (2020).
[7] Arora et.al. (2020).
[8] Schneider & Sørensen (2016), "Contribution of Academic Research to innovation and Growth", prepared for Universities Denmark and Reinhilde Veugelers (2014). "The Contribution of Academic Research to Innovation and Growth. WWWforEurope Working Paper No. 71," WIFO Studies, WIFO, number 50856, June.

Carbon Prices and CO_2 Removal

Combating Climate Change

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Carbon prices — whether explicit as a carbon tax or generated by cap-and-trade systems[9], or implicit in other policies — are seeing accelerating movement, upwards, along with shifting political trends. Combined with other environmental policies, this can provide a significant jolt to the gargantuan but increasingly urgent project of decarbonizing the world to combat climate change.

The surest, fastest, and most cost effective way to reduce the world's carbon footprint could be through carbon taxes or other mechanisms to raise carbon prices, which would make the financing of large-scale carbon capture and sequestration (CCS) more economic. Other mechanisms could involve broader carbon dioxide removal (CDR) pathways, including a larger portfolio of carbon emissions reductions investments, in addition to investments in wind, solar, nuclear, efficiency and conservation, energy storage, and the transition of transportation systems. Carbon prices would also complement a range of other tools within a portfolio of policies, including support for innovation and infrastructure, regulations on emissions, efficiency standards, subsidies and tax credits, and others.

Outside of emitting less CO_2, carbon dioxide can also be removed from the atmosphere

In the fight against carbon, other than simply emitting less carbon dioxide (CO_2) to begin with, CO_2 can also be removed from the atmosphere. Carbon dioxide *removal* (CDR), including carbon capture and storage/sequestration (CCS), takes atmospheric CO_2 and aims to store it underground permanently. Both CDR and CCS are crucial tools, if not the heart, of ways to achieve net carbon emissions reductions, toward, for instance, targets as laid out in the Paris Agreement. They are also particularly important for CO_2-emitting industrial processes, which might otherwise be hard to decarbonize. Costs of CDR and CCS can keep falling (albeit from still high levels) and as more facilities are built, learning by doing can drive costs lower over time. Ongoing R&D can support further technological improvements, while the emergence of clear and higher carbon prices makes CDR and CCS economics more workable in general. Even so, decarbonization will still likely be a heavy lift and requires massive investment in a wide range of approaches.

Carbon prices could represent a market of > $2 trillion per year and carbon tax revenues could be targeted for a variety of uses

Overall, our currently carbon-intensive global economy — and civilization — could be set to shift dramatically. Carbon prices could represent a market/sector of more than $2 trillion per year (using short-term indicative numbers: a $50/t$CO_2$ carbon price multiplied by ~42 GtCO_2 year of CO_2 emissions), which would be ~2.5% of current global annual GDP of ~$85 trillion. Carbon prices could — and/or may need to — go higher, toward $100+/t$CO_2$ over time, reflecting the potential marginal cost of abatement needed to reach climate targets. Where carbon *tax* revenues go is already becoming politically sensitive: they could go toward a combination of dividends to citizens, fiscal deficit reduction, and/or an array of investments in net carbon emissions reduction efforts.

[9] Carbon prices in cap-and-trade systems can of course fluctuate up and down, driven by policy, political, and economic factors, with some downside risks in the short-term from macroeconomic growth concerns, and coal-to-gas switching economics.in the short-term given low global gas prices.

New sectors of the economy could open up as carbon-intensive industries are disrupted

Rising carbon prices covering a greater percentage of global CO_2 emissions, along with policy support for R&D and deployment and the potential for falling costs from learning by doing, can precipitate disruptive changes to existing carbon-intensive industries and open up new sectors of the economy. These could include CO_2 capture, transportation and storage infrastructure and services, CCS + hydrogen, bioenergy + CCS (BECCS), direct air capture (DAC), and natural/biological CDR projects, alongside more established renewable energy and efficiency and conservation.

With clearer market signals from higher carbon prices, financial products and services for carbon emissions reductions projects can thrive. It is questionable whether they could otherwise do so. Transparent and higher carbon values should drive much more favorable project economics. Policy supports such as tax credits (like 45Q for CCS) and other carbon credits (like the LCFS or the proposed CORSAIR) should drive this further.

Carbon Prices Set to Move Higher and Cover Large Portions of Global Emissions

Carbon prices around the world today are mostly low, but we believe they are set to rise rapidly

Carbon prices around the world today are mostly low, but we believe they are set to rise rapidly. Current carbon tax and cap-and-trade systems cover ~20% of global emissions with prices ranging from $1-$127/t and these systems represented $44 billion in carbon pricing revenues in 2018[10]. However, some implicit carbon values are already well higher. California's Low Carbon Fuel Standard (LCFS) sees carbon credits pricing at almost $200/t, for carbon reduction projects that qualify, which now include CCS. And the largest cap-and-trade system, the EU Emissions Trading System (ETS), could see its allowance price move from ~$30/t levels today to ~$50/t by 2021 on the back of policy measures to reduce the supply of allowances and with the market stability reserve (MSR) withdrawing allowances from auctions. (However issues including Brexit, macroeconomic concerns, low natural gas prices, and falling renewables costs could mean downside risks for EU allowances, at times.)

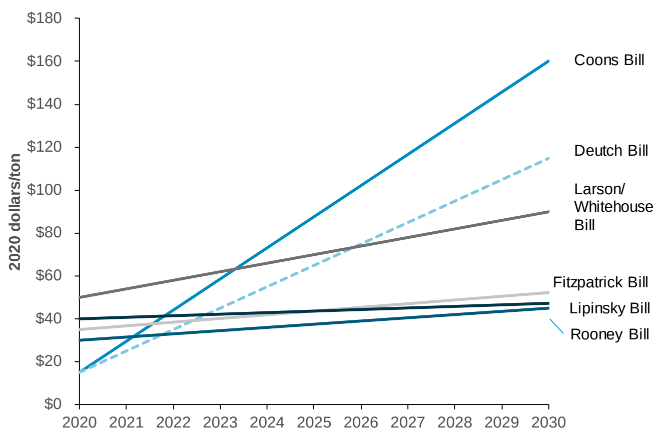
2019 was a year of carbon pricing proposals in the U.S., with six proposed so far and a seventh expected, with several of these bipartisan[11]. Carbon taxes are likely to be a critical element in U.S. elections going forward, with several Democratic primary candidates mentioning carbon pricing in their campaigns.

Carbon pricing proposals have been introduced in the U.S. with the main differences being what the carbon revenues will be used for

The main differences between proposals in the U.S. are in what the carbon revenues are used for — these are a mix between dividends, low- and middle-income assistance, and green energy spending, innovation, and infrastructure. On one level, carbon taxes promise to raise significant revenues, with the U.S. emitting 5.3 billion tons of CO_2 ($GtCO_2$) in 2018, and carbon tax proposals starting in a range of $15-$52/t and rising each year after, implied revenues are $80-$275 billion in year one alone. In addition to the focus from political parties on climate, corporations, including oil majors, are also supportive of the need for climate policy. That said, there are also political challenges to carbon prices, including affordability and access to energy and food, as well as employment impacts, exemplified by the Yellow Vest protests in France, in part fueled by opposition to rising gasoline and diesel prices due to a proposed raising of carbon taxes.

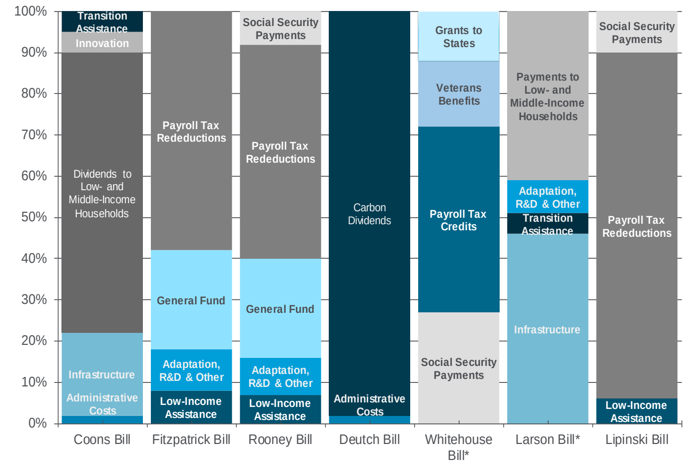
[10] State and Trends of Carbon Pricing 2019, World Bank.
[11] See The Year of the Carbon Pricing Proposal, Resources Magazine.

Figure 4. Carbon Tax Rates for U.S. Federal Carbon Tax Proposals ($/ton)



Source: CGEP Analysis

Figure 5. Use of Carbon Tax Revenues (%)



Source: CGEP Analysis

With higher carbon prices, the economics — and financing — of emissions-reducing projects are boosted. In particular, the U.S. 45Q tax credit (which provides a performance-based tax credit to power plants and industrial facilities that capture and store CO_2) for CCS including direct air capture (DAC), embodies implicit carbon values with a schedule for $22/t today rising to $50/t in 2026 for CO_2 that goes into storage, and $13/t today rising to $35/t in 2026 for enhanced oil recovery (EOR). Meanwhile, California LCFS credits are now pricing at near $200/t, and other than transportation fuels with a carbon intensity (CI) lower than target levels, credits can also be generated by several other carbon reduction activities including CCS. Overall, as explicit and implicit carbon values rise, coal, oil, and gas power generation will see fuels become more expensive in proportion to their CO_2 emissions. This has the side benefit of making solar and wind project economics relatively more favorable and in transportation, improving the economics of electric vehicles (EVs) relative to internal combustion engine (ICE) vehicles. CCS project economics are also much clearer, with cost savings or credit streams corresponding to carbon prices. Energy efficiency project economics also become clearer as does their stream of cost savings, and higher carbon prices may occur alongside other policy incentives for solar, wind, battery storage, CCS, DAC, and CO_2 pipelines and infrastructure.

Removing CO_2 from the Atmosphere and Negative Emissions

CDR is crucial among the portfolio of approaches to reduce CO_2 emissions and keep the world within its carbon budget

The case for CO2 removal (CDR): While it receives less attention than low- and zero-carbon projects (like solar, wind, and efficiency), CO_2 *removal* (CDR) is crucial among the portfolio of approaches to reduce CO_2 emissions and keep the world within its carbon budget. First, as opposed to other pollutants, CO_2 stays in the atmosphere for a long time so prior emissions remain, and can only be effectively reduced by CDR. Conceptually, it is important to differentiate CO_2 that is below ground, and CO_2 that is present in the atmosphere. CDR is defined as the removal of CO_2 from the atmosphere, which would require it to be stored underground over long geological time scales. Meanwhile, most long-term projections of CO_2 emissions factor in CDR as a part of the portfolio of solutions (see below) — the IPCC includes a rise of CDR use in their forecasts for this century to 100-1,000 $GtCO_2$ in order to stay within the 1.5°C scenario with reasonable probability.

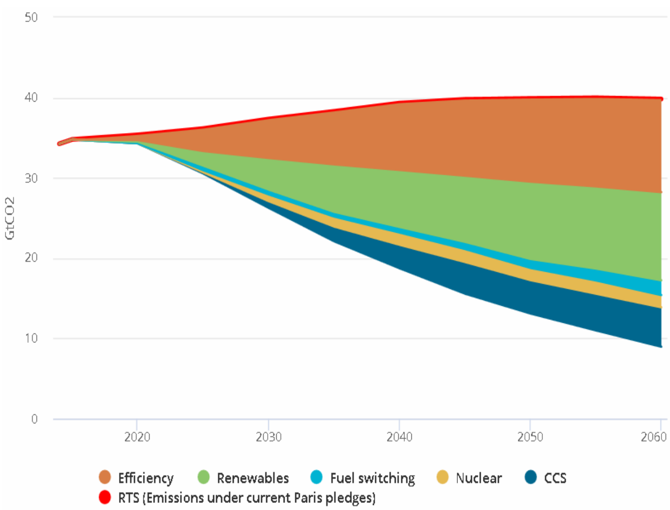
Some of these CDR approaches represent net *negative* emissions, including direct air capture (DAC) and bioenergy with CCS (BECCS), though these technologies and their economics still have some way to go.

Achieving CO_2 emissions reduction targets would likely be faster and less expensive with the inclusion of CDR in the portfolio

Achieving CO_2 emissions reduction targets would likely be faster and less expensive with the inclusion of CDR in the portfolio. And for some industries that are harder to decarbonize, CCS could be crucial — this is important for sectors like steel, cement, and chemicals.

A main pushback against CO_2 removal, and particularly CCS, is that it could give license to emitters to emit more CO_2. This is a moral hazard. However, this is likely to be marginal compared to the significant benefits from a net CO_2 emissions reductions standpoint, with much lower marginal costs of abatement than deploying even more carbon-free power and industry.

Figure 6. The Portfolio of Technologies Contributing to CO_2 Emissions Reductions — CCS is Crucial



Source: OECD, IEA * 2°C scenario

Figure 7. Assessment of Pros and Cons of CO_2 Removal Pathways

Source: ICEF Roadmap 2018: Direct Air Capture of Carbon Dioxide

CDR technologies fall into two broad categories — natural or engineered — as well as hybrid approaches

CDR technologies fall into two broad categories — natural or engineered — as well as hybrid approaches. Natural and biological approaches include reforestation and restoration of wetlands and coastal regions, which tend to have land use and food/fuel competition challenges. Engineered solutions include direct air capture (DAC), which remains a high cost technology; CCS which we discuss further below; enhanced weathering of rocks, which requires significant mining activity; and ocean liming, which might fall foul of marine dumping treaties. DAC encompasses a range of technologies, from chemical to cryogenic to membranes[12]. Hybrid approaches include bioenergy with CCS (BECCS), where biomass is used to generate power and CO_2 is captured and stored, and bioenergy with biochar carbon sequestration (BEBCS), where bioenergy can yield charcoal that can then be used as soil amendment. These approaches can offer negative emissions, reducing atmospheric CO_2, but again face land use and food/fuel issues. DAC, CCS, and BECCS would also require CO_2 transportation and storage infrastructure.

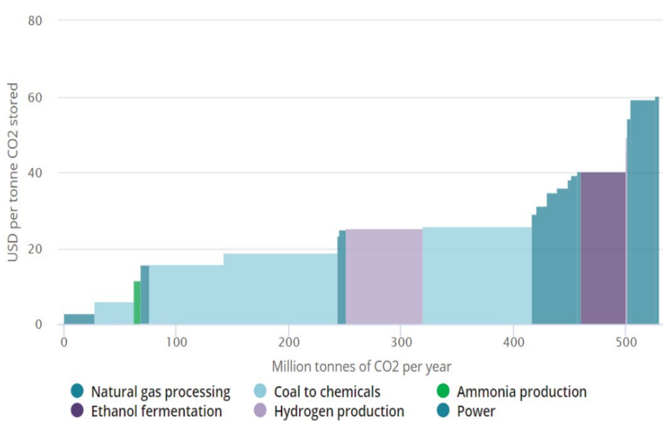
[12] See Direct Air Capture of Carbon Dioxide (ICEF Roadmap 2018).

CCS is a well-known technology

Carbon capture and storage/sequestration has a long history, making it a well-known technology, having been used in some form since the 1970s, though more learnings from widespread deployment is crucial. It could grow explosively as a major, crucial, CO_2 reduction pathway that can be deployed at scale if the price is right. Without a carbon price, CO_2 injection was first used for enhanced oil recovery (EOR), which used gas or water flooding to flush residual oil out of reservoirs. CO_2-EOR was first demonstrated in 1972 in Texas and has been widely used in Norway and Canada. Algeria has had one CCS facility since the 2000s, and others have been completed in Brazil, China, Saudi Arabia, and the UAE. These projects capture the CO_2 from a range of sources, including hydrogen production, fertilizers, chemicals, iron and steel, natural gas processing, and coal-fired power.

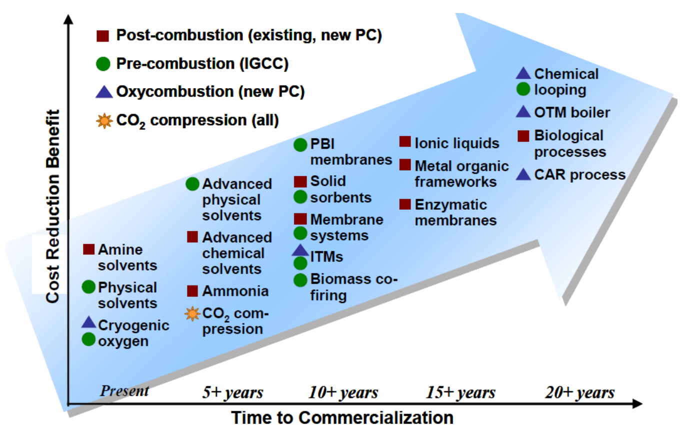
Most use the CO_2 for EOR, but a notable exception today is the Illinois Industrial CCS facility, which opened in April 2017 — a 1.0 Mtpa BECCS project that just puts CO_2 into dedicated storage. All-in-all, as of October 2018, there were some 18 large-scale CCS facilities in operation, with five under construction, with the capacity to inject 40 Mtpa of CO_2 per year. A further 20+ projects are in various stages of development, which could come online in the 2020s. Meanwhile, the failed pre-combustion CCS project at the Kemper coal-fired power plant has been a poster child for concerns over the viability of coal with CCS. However, it is better understood as a case study showing the challenges of deploying young technologies (a new lignite-based pre-combustion CCS project, as opposed to mature pre-combustion technologies) combined with commodity price shocks, in this case much lower natural gas prices due to the surge in shale output. (See Global CCS Institute[13].)

Figure 8. Potential Future Breakeven Cost Curve for CCS ($/t$CO_2$)



Source: OECD/IEA

Figure 9. CO_2 Capture Technologies



Source: DOE

Costs are falling for CDR and CCS technologies

Costs are falling for CDR and CCS technologies, and this can accelerate as carbon pricing leads to more deployment and learning by doing; further policy support in R&D is needed too to bolster this though. For CCS, further R&D and learning-by-doing would help technologies mature more quickly; second-generation CCS technologies could see 20-30% lower costs (RFF[14]), with further n^{th} of a kind (NOAK) projects likely to see further cost reductions. Of the whole CCS process, CO_2 capture represents 70-80% of the total cost of project. Overall, CCS project economics depend on the level of CO_2 concentration in flue gas, where capture is to take place, and the energy penalty incurred with, versus without CCS.

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[13] Global CCS Institute CCS Storage Indicator (2018).

[14] Carbon Capture and Sequestration is needed and improving despite Kemper project shutdown, August 3, 2017.

Key technologies include post-combustion capture based on amine-based solvents; pre-combustion capture; and CCS by oxy-fuel combustion. Emerging technologies are in the areas of advanced membranes, solvents, and adsorbents.

Another emerging technology is carbonate fuel cells: these separate CO_2 from the exhaust gas stream and can generate additional electricity, with a 500MW power plant with a carbonate fuel cell projected to generate an additional 120MW of power, as opposed to current CCS technology consuming 50MW of power.

Using ships to transport CO_2 might make sense too, which could become more cost-effective than pipelines when moving CO_2 more than >2,400km

On the transportation side, the technology surrounding pipeline movement of gas is mature, but using ships to transport CO_2 might make sense too, which could become more cost-effective than pipelines when moving CO_2 more than >2,400km. CO_2 storage approaches are also well understood, with the main storage capacity being considered in deep saline formations, and depleted oil and gas reservoirs. Monitoring, reporting, and verification (MRV) of CO_2 storage performance will be important, including for regulatory frameworks, with both shallow monitoring sensors as well as the potential for more deep-focused monitoring using seismic and pressure imaging, or looking at ground surface displacement from satellites.

New CO_2 Logistics and Utilization Sectors, Financial Products, and Services to Emerge

Financing of low-carbon projects could grow rapidly, with a clear price on carbon and with recognition that CCS is a crucial part of climate mitigation solutions

Financing of low-carbon projects, including CDR and CCS, could grow rapidly, with a clear price on carbon and with recognition that CCS is a crucial part of climate mitigation solutions. Clear and higher carbon prices mean that project financing can be based on a future stream of cost savings (by reducing the carbon tax burden) or earning of credits; the number of projects that are economic and would look for financing could surge. Depending on the type of carbon price that a project faces, carbon price hedging might be needed, particularly in the context of cap-and-trade systems, supporting commodity trading activity. Other policy supports such as tax credits (like the ITC and PTC) are phasing out in the U.S. (though extensions may still be possible), but there could be the potential for an ITC for battery storage, stimulating activity there. Meanwhile, the new 45Q tax credit can mean that there are new opportunities for tax equity investors to enter the DAC, CCS, EOR, space in the U.S., in a similar way that the ITC and PTC allowed for solar and wind projects. Meanwhile, the ability to receive LCFS credits for CCS and EOR projects makes the revenues on such projects more realizable too, rather than requiring a CO_2 offtake agreement of some sort. A key legal challenge is for regulatory authorities to clarify the requirements on monitoring, reporting, and verification (MRV) of CO_2 storage, making sure there are no leaks that would invalidate tax credits, which would adversely affect the certainty of future tax credit-related cash flows of CCS projects. However, this is an eminently manageable technical requirement. Meanwhile, small- to medium-sized carbon emissions reduction projects such as energy efficiency, distributed solar, battery storage in buildings could accelerate with a clear carbon price signal, with the potential for aggregation and securitization that could then be attractive to larger-scale investors.

New sectors emerge, including carbon management, while others face a sunset — or manage a transition.

New sectors emerge, including carbon management, while others face a sunset — or manage a transition. An extensive CO_2 logistical sector looks set to emerge in a full-blown carbon management sector, with CO_2 offtake agreements becoming more common as the CO_2 transportation and storage sector comes into its own. Northwest Europe is seeing a CO_2 management hub emerging, with storage capacity nearby in the North Sea. Decarbonized hydrogen production with CCS can catalyze the rise of a hydrogen-based economy that fuels transportation, industry, power, and heating. DAC and BECCS projects can see further fall in costs and wider adoption. The so-called carbon-to-value (C2V) sector, that is, use of CO_2 for end-markets other than EOR, could pick up, but likely remains small relative to global CO_2 emissions reduction needs, meaning CO_2 storage likely accounts for most of the CO_2 'demand'.

That said, these niche markets that could benefit include urea yield boosting, carbonated drinks, water treatment, pharmaceutical processes, mineral carbonation, and CO_2 concrete curing. On the other side of things, a rising price on carbon and additional policies to accelerate emissions reductions means that carbon intensive sectors are at risk, and need to face a transition.

This happens to have come at a time of hydrocarbons abundance, meaning awkward policy, investment, and business choices between hydrocarbons development and CO_2 reductions. CCS might provide a bridge there, but policies, politics, public opinion, investors, and oil company management themselves already appear to be increasingly recognizing the need for transition. Some competencies from the hydrocarbons sector could translate well, including CO_2 midstream and storage, including offshore, as well as a new hydrogen production and value chain.

Digital Agriculture

Harvesting (with) Data

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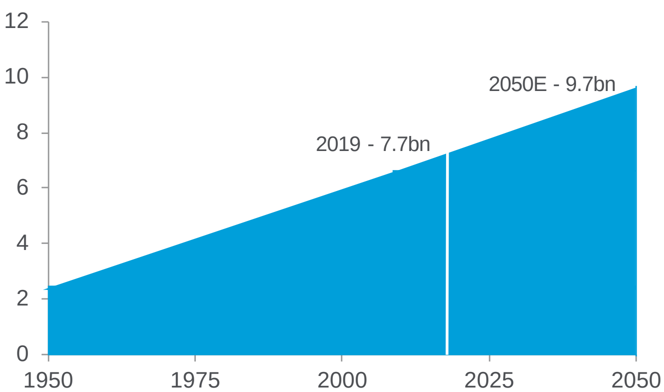
Digital Agriculture (Digital Ag) seeks to use data and machine learning-driven analysis to allow farmers to make the best possible decisions as they manage their fields driving higher yields and cost efficiencies. Eventually full digitization could enable fully-automated farms with human involvement dropping to the mere role of supervision. We are in dire need of sustainable solutions to increase food yields with an estimated 50% increase in food demand required by 2050. Digital Ag offers the best option to sustainably reduce input use while also increasing yields. In terms of impact, Digital Ag solutions, on conservative assumptions, could enable more than $15 billion of cost savings through more efficient fertilizer and pesticide use. Looking longer term, society may have to find a way to re-employ the 28% of the global population still employed in agriculture as automation reduces the need for human labor.

The amount of food humans consume is expected to increase by 50% by 2050

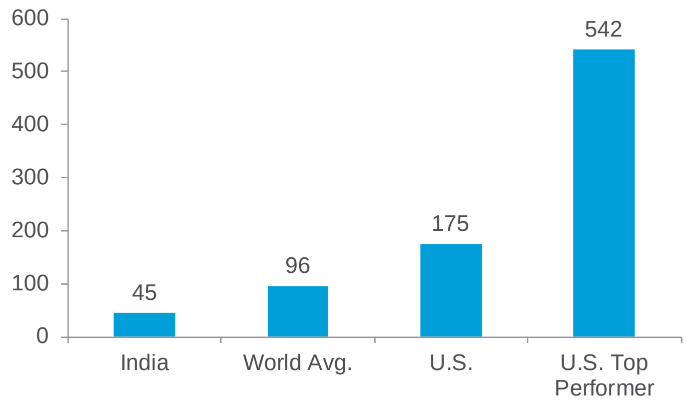
Doing More with Less: Growing populations, rising living standards, and changing tastes are set to drive a 50% increase in the amount of food we as a species consume by 2050[15]. To produce this amount of food without a rise in yields would involve an increase in farmed land greater than the total arable land of the Americas and Europe combined. Moreover, this immense jump will likely have to be achieved with no increase in land utilized, noting flat global acreage growth in recent years, and amidst increasing scrutiny on both agricultural water consumption and CO_2 emissions. The agricultural complex must produce more from less, yields must increase.

Figure 10. Global Populations Growth Slows but Still Trends Higher



Source: Citi Research

Figure 11. Large Yield Gains Are Possible – Global Corn Yields (Bu/Acre)



Source: Citi Research, OECD, Company Reports

The highest yielding corn field in the world can produce 11x more corn than the average Indian acre and 3x more than the average U.S. acre

The good news, luckily, is there is meaningful scope for just such an increase. The highest yielding corn field in the world (found in the U.S.) can produce **eleven times more corn** than an average Indian acre. Indeed it can produce 3x more than the average U.S. acre. Clearly far higher yields are possible, the question then is how they can be achieved.

15 FAO, http://www.fao.org/3/a-i6583e.pdf%20.

Crop yields are a function of two things: (1) a farmer's tools: their seed, fertilizer, pesticides, and equipment; and (2) a farmer's knowledge (i.e., when and how they use their tools): when do you apply fertilizer, and how much, what seed do you use.

In addition to increasing the use of modern tools, yield increases can come from using existing tools better

Clearly, part of the required yield increase will come from wider use of modern tools. But, given increasing scrutiny on pesticides (e.g., glyphosate) and the greenhouse gas (GHG) cost of fertilizers (~20% of agricultural emissions), massive increases look unlikely. The bigger, and ultimately far more environmentally sustainable opportunity comes from using existing tools, but just using them better. The threefold difference between the top performing U.S. farmer and the average U.S. farmer is not in their access to tools, but in how they use their tools.

It is here that digital agriculture is set to massively shift the face of modern agriculture as it enables farmers to make the best possible decision at every stage of the farming process, ensures effective development of the best farming technologies, and eventually enables full-scale automation of the farm.

What is Digital Agriculture?

Digital agriculture consists of technology which capture, process, and deliver insights from agricultural data

Digital agriculture includes a wide array of technologies, but the connecting link is they are all technologies which capture, process, and deliver insights from agricultural data. In turn they allow for step changes in agricultural efficiency by helping farmers use their existing tools in the most efficient way, which in turn secures the best yield. They also ensure the development of the best crop chemicals, fertilizers, and equipment by providing agricultural companies with the data they need to design the exact products required. This technology shift is being enabled by the cheap availability of processing power and data storage, the proliferation of novel data collection systems (e.g., satellites and drones), and consistent and persistent connectivity (e.g., the Internet-of-Things (IoT) and 5G).

We would divide digital agriculture into three discrete sets of technologies:

- **Data Capture & Generation:** Technology used to collect data, e.g., sensors in fields, on animals, or on the plant, or imaging technology enabled through satellites and drones.
- **Data Processing & Management:** Software and hardware systems that aggregate data, store the data, and exchange and share the data in order to deliver insights to the user. Of particular importance here are machine learning technologies which are bringing together a variety of different data sources across geographies and time frames to deliver insights that can match if not exceed the most experienced farmers.
- **Decision Making & Implementation:** Systems that allow you to implement the recommendations generated by data-driven insights. On the software side, this includes farm management systems seeking to integrate all aspects of farm management with incremental data inputs from the field. On the hardware side this involves precision agriculture systems (fertilizer systems that target specific areas) and eventually machine automation.

The impact on the farmer is seen in three discrete areas:

- **Input Management:** The hypothetical fully 'digitized' farm would provide the farmer with granular and timely detail on every relevant farming metric: nutrient levels, humidity levels, pest presence, plant health, soil quality, and weather. This combined with precision agriculture systems, would drive two key efficiencies:

– **Ensure bespoke use of crop inputs:** These data systems generate metrics on an incredibly granular level (i.e., not just for every field but for each plant) and would allow for every plant to receive the ideal inputs at the best time given the soil, weather, and other factors. This level of detail is the difference between an average yield per field, and market-leading yields per field.

– **Reduce use of inputs where not required:** A key benefit, and probably the key initial driver of adoption, will come from the reduction of wasted inputs and thus a reduction in cost. Many inputs are over rather than rather than under-utilized, but with granular data, fertilization, and pesticide application can become far more targeted. Trials utilizing such technology point to a 10-15% possible reduction in fertilizer use under such schemes.

– **Activity management:** Much of farming comes down to timing. Digital agriculture systems seek to marry granular farm data, detailed weather data (the largest Digital Ag platform started as a weather forecasting platform), and machine learning systems to generate the best decisions at a given time.

- **Automation:** The endpoint of these data systems, married with older technologies like GPS navigation, is full-scale automation. In time, fully-centralized data-driven farm management systems will be able to automate all aspects of the growing process (planting through to harvesting), with data input systems playing the historic role of the farmer themselves in terms of deciding when to fertilize, or harvest, or indeed any activity.

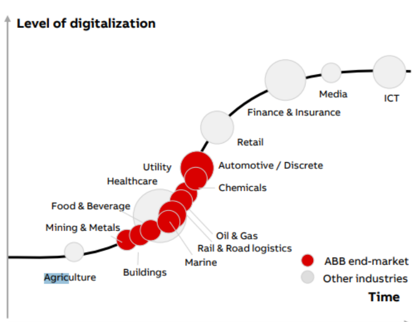
The impacts of technology are not limited to the farmer alone, we note the following potential effects through the rest of the value chain:

– **Data enables better farming tools:** The data generated has value not only for the farmer in terms of managing his own farm, but also for the crop input and equipment provider. With better knowledge, the crop input provider is better placed to create more efficient products, and indeed with increasing detail about individual farmers, more tailored products.

– **Data improves visibility down the value chain:** With better data on yields and crop health, dealers and traders will be better able to manage their own risk and client risk around agricultural products. Food manufacturers in particular would be better placed to manage their cost position.

– **Accountability drives sustainability:** A connected farm would give consumers the ability to know exactly who has produced their food product and how, while also allowing them to more effectively choose sustainable sources.

Figure 12. Digitalization by Industry



Source: ABB

Where Are We Now?

Digital Ag platforms are already spreading across the U.S. and some European markets but the functionality remains well short of its potential. In particular the technology remains piecemeal. The key offerings thus far include:

- **Farm Management Software:** Software that helps a farmer manage their farm, by marrying accounting and business management systems with farm-based data inputs with the intent of simplifying the farm management process.

- **Nitrogen Detection & Prescription Systems:** Systems that combine nitrogen detection (via handheld or infield sensors, or imaging systems), with weather data and predictive analytics to recommend the most effective fertilization process.

- **First-Generation Holistic Platforms:** Some providers are starting to offer more holistic platforms which include the offerings above but also incorporate seed recommendation systems all set in the context of field level yield and health insights.

Agriculture is one of the most under-digitalized industries across the economy

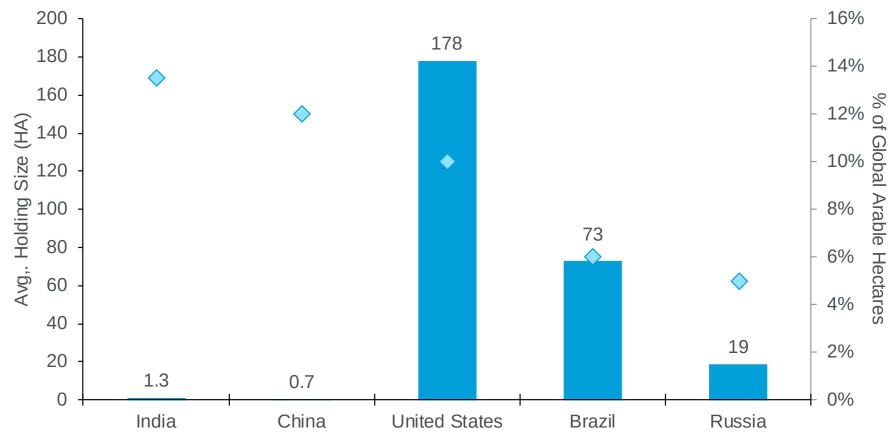
In terms of penetration, numerous industry participants and industry advisors point to agriculture as one of the most under-digitalized industries across the economy. On a macro level there is clearly a long way to go. Looking in more granular detail, the leading provider is looking to have almost 90 million paid acres (<30% of total U.S. acreage) in 2019. However, it does not make clear what kind of product is being utilized, and we note that current products fall vastly short of the potential functionality of a full Digital Ag system, even if R&D pipelines are pushing towards this kind of solution.

Barriers to Adoption?

We see three key barriers to adoption:

- **Prevalence of small scale farming:** The efficiencies and yield gains from Digital Ag systems scale most effectively for large industrial farming operations like those seen in the U.S. and Brazil where around 50-60% of farmed land is in the hands of large farms. However the majority of global agriculture still takes place on smaller holder plots (60%+). This is shifting, but for the time being it will prove to be a limiting factor for broader agricultural digitization.

Figure 13. Small scale Farming Still Dominates Global Acreage Outside of More Industrialized Locations like Brazil and the U.S.



Source: Citi Research, USDA, FAO (2000), Chinese (2009) and Russian (2006) State Census.

- **Cost and lack of full scale technology offering:** The most meaningful efficiency and yield gains will only come from a full-suite technology offering at a reasonable cost. For this to happen we need continued R&D to develop effective software to deliver the correct insights. We will also need lower costs and more widely available sensor and implementation solutions to provide the right data inputs and utilize them effectively.

- **Conservative industry:** Farmers are historically conservative in their approach to newer technologies.

Which Sectors Are Likely to be Affected and What Could the Impact be?

Digitization should lead to higher yields & efficiencies throughout the agriculture value chain

The digitization of the agricultural sector will lead to higher yields and greater efficiencies throughout the agricultural value chain. Understanding the aggregate impact is challenging, but there are a few easier conclusions that can be drawn:

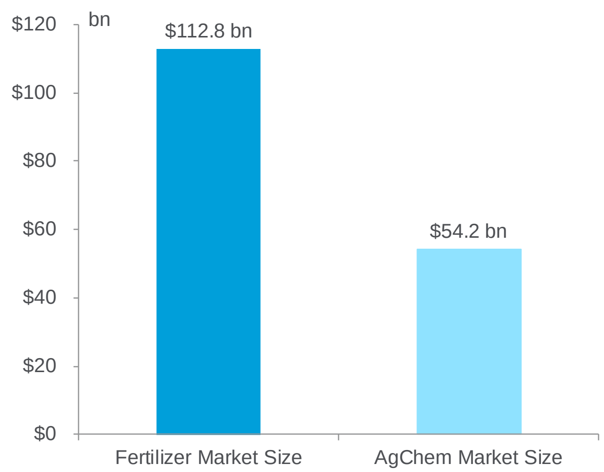
- **Crop input use will likely be reduced:** One of the most attractive aspects of the prospective yield gains to be had from the shift towards digital agriculture is the fact that they will likely come with reduced input utilization. As farmers gain more insight on crop nutrition levels and pest infestations they will be able to be more targeted with their input usage, and in turn fertilizer, pesticide, and particularly importantly, water usage will likely fall.

The implications of such a shift in demand would be large:

- **Fertilizer Market:** We would note that any possible reduction would not affect all nutrients equally, Nitrogen as an example is typically over-applied globally, with potash under-applied. But, looking simply at the issue, if we assume a 10% reduction in fertilizer demand as a function of more precise application (in-line with German trials[16]), that could entail an $11.3 billion reduction in farming outlay on fertilizer in a given year.

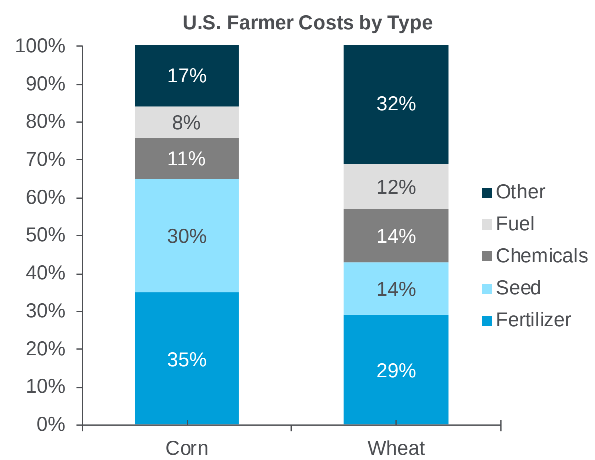
- **Agchem Market:** Agrochemical use (e.g., pesticides) could also be meaningfully curtailed with more precise targeting rather than blanket application. One company has estimated a 90% reduction in pesticide use through the use of its tool that directly identifies weeds within the field and sprays them individually. We judge reductions of this magnitude may fail to fully deal with the infestation, especially given part of the pest may not be visible. But to give some sense of the context again, a 10% reduction in Agchem usage would result in an almost $5.5 billion reduction in agrochemical spend per year.

Figure 14. Crop Inputs Amount to a $165bn Market…



Source: Citi Research, IFA, Philips McDougall, Argus

Figure 15. …and Make Up a Meaningful Proportion of Farmer Costs



Source: Citi Research, USDA

[16] Meyer-Aurich et al (2010). "Optimal site-specific fertilization and harvesting strategies with respect to crop yield and quality response to nitrogen". *Agricultural System*, Vol 103.

We would expect the providers of digital agriculture systems to share in the value generated by such savings, not to mention the incremental value generated by increasing yields.

Agricultural Automation

The other large potential impact from increasing digitization is the reduction of the human element in the agricultural value chain as digitization enables full automation from seed to harvest. This could prove to have a far greater global impact than the simple crop input efficiencies and even incremental yields noted above. According to the World Bank, around 28% of the global population is still employed in agriculture; under a full digitization scenario a large proportion of that percentage would have to find employment in other industries.

Gene Therapies

A Potentially Curative New Treatment Option

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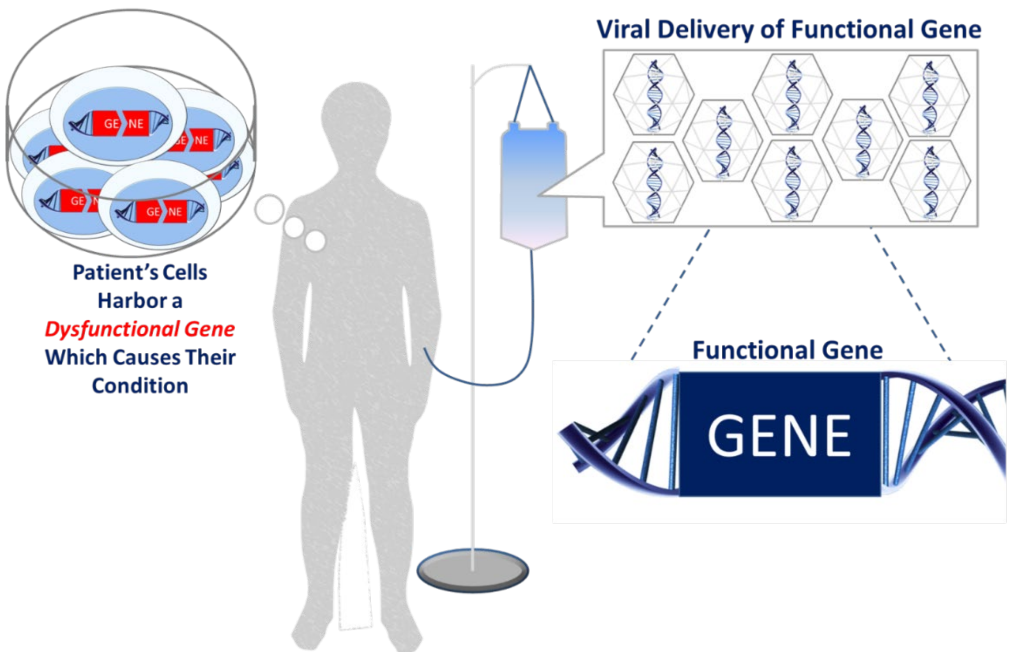
There are thousands of rare diseases that are caused by the DNA of patients' cells having just a single defective gene. Historically, treatment for these conditions has focused on alleviating their symptoms and/or palliative care, while the underlying cause of the condition remains untreated. Gene therapies are a new class of drugs that address the root cause of the condition, the defective gene, and thus may prevent, treat, and in some cases essentially cure the disease. With a single treatment, gene therapies deliver a correct version of the defective gene into the patient's cells using a special virus that has been engineered to deliver the gene. Patients are given these engineered viruses, which infect the patient's cells with a correct version of the dysfunctional gene (see Figure 16). This disruptive innovation to drug design opens the door to many diseases that have been completely untreatable while also potentially disrupting the currently approved treatment landscape.

Figure 16. Gene Therapies Deliver a Functional Gene to Patients Using a Specially Engineered Virus for Delivery



Source: Citi Research

Four Ways Gene Therapy Could Be Disruptive to Healthcare Markets

1. **Many Untreatable Diseases Become Treatable:** It is likely that many new disease markets will be built on the back of gene therapy, as the vast majority of genetic rare diseases lack an FDA approved treatment (see Figure 17). Furthermore, most diseases will likely not be completely cured by gene therapy and as patients live longer they will develop unmet needs that can be addressed with additional products.

Figure 17. Rare Disease Market Size Estimates

Rare Disease Market Size Estimates	
Prevalence Threshold to Classify as Rare Disease	less than 200,000 people affected
# of Known Rare Diseases	~7,000
# of People Affected With A Rare Disease in the US	~25 — 30 million
# of Genes Linked to Rare Disease	~4,000
% of Rare Diseases Without an FDA Approved Treatment	~90%

Source: Citi Research, www.irdirc.org, and https://rarediseases.org

2. **Many Currently Treated Disease Markets May Change or Disappear:** Often, genetic diseases are managed through the chronic treatment of symptoms. Gene therapies have transformative potential for many diseases; some established drug markets are likely to erode as prevalent populations receive these transformative therapies.

3. **Transformation of the Drug Payer System:** Many drugs on the market require chronic administration thus providing sustained multi-year revenues from each patient on the drug. Since gene therapies generally require only a single administration that can last for years, if not indefinitely, the price of each dose is considerably higher than other drugs on the market (see Figure 18). The unique multi-year efficacy that characterizes many gene therapies will necessitate a transformation of the drug payer system as more and more are approved. Two gene therapy pricing models frequently discussed are payment-over-time and pay-for-performance (P4P), both of which are not typically used in current drug pricing.

Figure 18. ~Top 20 Most Expensive Drugs in the U.S. After One Month of Treatment

Drug	Indication	List Price ($) 30-day*	~Annual Price ($)**	Administration
Gene Therapies				
Zolgensma	Spinal Muscle Atrophy (SMA)	$2,125,000	$2,125,000	Intravenous infusion
Luxturna	RPE65 mutation-associated retinal dystrophy	$850,000#	$850,000#	Sub retinal injection
Kymriah	Pediatric acute lymphoblastic leukemia (ALL) and non-Hodgkin lymphoma (NHL)	$475,000##	$475,000##	Ex vivo GT, IV infusion
Yescarta	Adult non-Hodgkin lymphoma (NHL)	$373,000	$373,000	Ex vivo GT, IV infusion
Non-Gene Therapies				
Myalept	Leptin deficiency with generalized lipodystrophy	$64,859	$778,308	Subcutaneously
Ravicti	Urea cycle disorders	$52,756	$633,072	Oral
Actimmune	Chronic Granulomatous disease and severe, malignant osteopetrosis	$47,962	$575,544	Subcutaneously
Oxervate	Neurotrophic keratitis	$47,200	$566,400	Eye Drop
Daraprim	Toxoplasmosis and Malaria	$45,000	$67,500	Oral
Cinryze	Prophylaxis against angioedema attacks for Hereditary AngioEdema (HAE)	$44,141	$529,692	Intravenous
Takhzyro	Prophylaxis to prevent attacks of Hereditary AngioEdema (HAE)	$44,140	$529,680	Subcutaneously
Chenodal	Gallstones in patients not eligible for surgical resection	$42,570	$510,840	Oral
Juxtapid	Homozygous familial hypercholesterolemia (HoFH)	$40,671	$488,052	Oral
H.P. Acthar	Infantile Spasms (IS) and Multiple Sclerosis (MS)***	$38,892	$466,704	Intramuscular injection
Tegsedi	Polyneuropathy of hereditary transthyretin-mediated amyloidosis (hATTR)	$34,600	$415,200	Subcutaneously
Firazyr	Treatment of acute attacks of Hereditary AngioEdema (HAE)	$33,443	$401,316	Subcutaneously
Vitrakvi	Solid tumors with neurotrophic receptor tyrosine kinase (NTRK) gene fusion	$32,800	$393,600	Oral
Sovaldi	Treatment of chronic hepatitis C virus (HCV) infection	$27,728	$83,184	Oral
Viekira	Treatment of chronic genotype 1 hepatitis C virus (HCV) infection	$27,504	$82,512	Oral
Orfadin	Hereditary tyrosinemia type 1	$27,247	$326,964	Oral

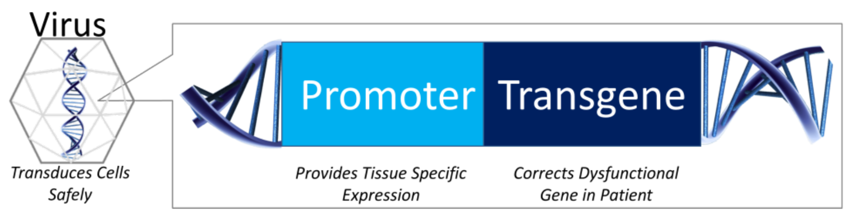
** List price reflects each medication's most common 30-day prescription regimen*
*** Annual price reflects each medication's most common annual prescription regimen*
**** Other indications include rheumatic; collagen; dermatologic; allergic states; ophthalmic; respiratory; and edematous state*
 # Price if for treatment of both eyes
Kymriah has a one-time price of $475,000 for ALL, with a refund if it doesn't work after one month, and $373,000 for NHL (no refund)

Source: Citi Research, Drug labels, goodrx, healthadvances, and xconomy

4. **Faster Drug Development:** Gene therapies may accelerate the speed of drug development while also de-risking their paths to approval.

There are two aspects of gene therapy that may accelerate the speed of drug development while also de-risking their paths to approval. The first aspect is the platform nature of the gene therapy technology. The essential components of a gene therapy are: (1) the **transgene,** the therapeutic/functional gene being delivered to the patient's cells; (2) the **promoter**, which is a region of DNA controlling whether the gene is turned on or off. For example, the appropriate promoter can ensure the gene only makes functional protein in the correct organ or tissue. Similarly, switching out different promoters can change which organs and tissues make functional protein; and (3) the **virus**, which is responsible for infecting the desired cells within body and delivering the transgene and promoter (see Figure 19).

Figure 19. General Components of a Gene Therapy

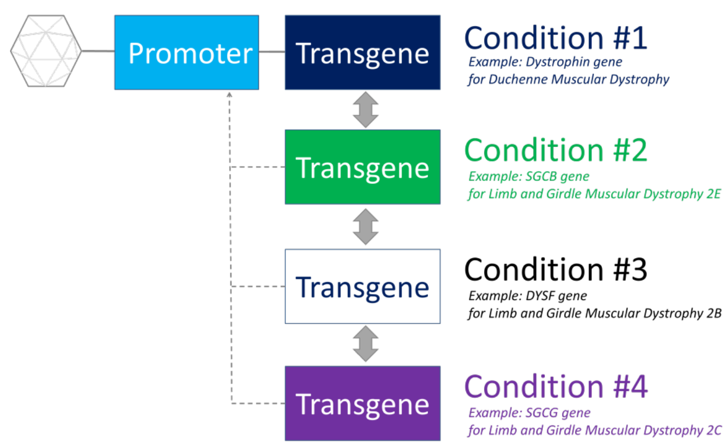


Source: Citi Research

The platform of the technology lies in the relative ease of swapping in various transgenes once the infection capacity and safety have been validated for a virus + promoter combination. Therefore, with a validated virus + promoter combo, one could theoretically treat many different rare diseases by altering the transgene.

For example, muscular dystrophies are a group of diseases that cause progressive weakness and loss of muscle mass and are typically caused by a genetic mutation. A successful virus + promoter combo could potentially treat many different muscular dystrophies depending on which transgene is swapped in (see Figure 20).

Figure 20. Gene Therapy Platform



Source: Citi Research

The second aspect that may give gene therapies a quicker path to approval is a number of FDA-sponsored programs designed to expedite drug development. These include: accelerated approval, breakthrough therapy designation, fast track designation, priority review, and a regenerative medicine advanced therapy designation.

Of particular interest to gene therapies is accelerated approval, which grants approval based on a surrogate endpoint (a test thought to predict clinical benefit but not a direct measure of clinical benefit). There are likely many rare genetic diseases where the expression of a functional gene itself could be an adequate surrogate endpoint and offer a much faster time-to-market than typical lengthy efficacy trials.

FDA is Expecting Many More Gene Therapy Approvals

FDA predicts:
"10 to 20 cell and gene therapy approvals each year by 2025"[17].

In recent years, the FDA has approved Yescarta (2017) and Kymriah (2018), which are cell gene therapies designed to fight cancer, Luxturna (2017), which is a gene therapy used to treat a specific form of blindness, and Zolgensma (2019) the first approved systemic gene therapy used to treat a rare pediatric neurodegenerative disease known as Spinal Muscle Atrophy (SMA).

The FDA has indicated they expect more gene therapies will be approved in the coming years. To prepare for this they plan to hire ~50 new clinical reviewers focused on assessing gene therapies and preparing for *"a surge of cutting-edge products currently entering early development*"[17]. The FDA currently has over 800 gene therapy investigational new drug (IND) applications on file and have publically stated they expect to receive >200 IND applications per year going forward.

Manufacturing and Safety Are Potential Barriers to Entry

- **Manufacturing Lags Behind Gene Therapy — Innovation but Is a Major Focus:** Each viral particle can infect only a single cell so very large quantities of virus are needed for each respective gene therapy. This is particularly true with gene therapies delivered to the entire body systemically. Both manufacturing and total capacity will need to advance substantially in order to support an effective deployment of the next wave of gene therapies. Development in this area is ongoing and is a major focus for the industry. While some companies are scaling out to meet manufacturing and capacity demands others are developing innovative ways to scale-up. Manufacturing approaches will likely be one of the most important pieces of becoming a leader in gene therapy.

- **Manageable Safety Risks Lead to a Favorable Risk/Reward Profile:** A number of serious safety issues have emerged throughout the development of gene therapy. However, many of these have been overcome. As it stands the risk/reward of the currently approved gene therapies is quite favorable. The major emergent safety issues during the development of gene therapy include: (1) cancer, which was a major risk factor in the early development of gene therapy, however risks have been largely mitigated through careful selection of the virus type and through modifications to the virus itself; (2) severe immune reactions, which have emerged in a number of different clinical presentations and typically occur transiently following administration, but the use of various immune-suppressing agents have made many of these safety events manageable; and (3) the loss of the delivered gene over time leading to reemergence of the condition. If the therapeutic duration of gene therapy turns out to be shorter than expectations it could have broad implications for the class by both impacting utilization and pricing power. However, it is clear that in many cases gene therapies provide years of clinical benefit and pre-clinical data suggests gene therapy can lead to long-term gene expression.

[17] https://www.fda.gov/news-events/press-announcements/statement-fda-commissioner-scott-gottlieb-md-and-peter-marks-md-phd-director-center-biologics.

Hydrogen Powered Rail

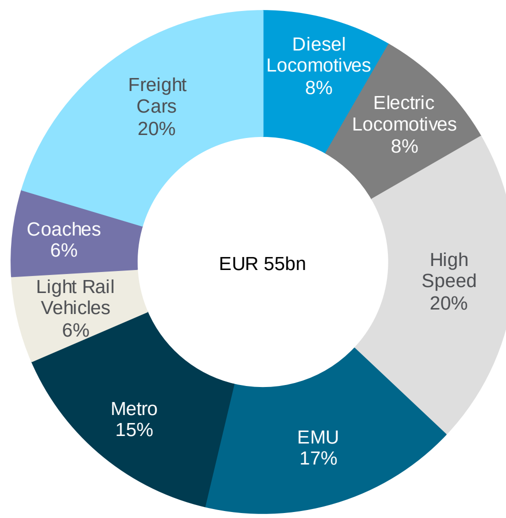
An Indirect Renewable Energy Story

Martin Wilkie
Global Head of Capital Goods Research

Rail transport is typically seen as an environmentally-friendly mode of transportation, with lower grams of CO_2 per passenger kilometer traveled compared to virtually all other methods of transport (including car, bus, and plane). Not all rail transport is green however, since vast parts of the established rail network are not yet electrified, and instead rely on diesel-powered trains. Diesel trains generate carbon dioxide through the burning of fossil fuels, and also emit particulate matter and noxious gases linked to health issues and other environmental concerns, including nitrogen oxides and sulfur oxides.

Railway stations can breach air quality guidelines due to the concentration of diesel trains, with the Rail Safety and Standards Board in the U.K. finding in a 2019 report that nitrogen dioxide levels at two major U.K. stations (London's King's Cross and Edinburgh's Waverley) exceeded annual limits in just two weeks. The report also found air quality inside the train stations was poorer than that in the area immediately outside the stations, attributing the issue largely to diesel trains.

Figure 21. Global Rolling Stock OEM Market Split by Type… We Estimate About Half of Locomotives are Diesel Powered



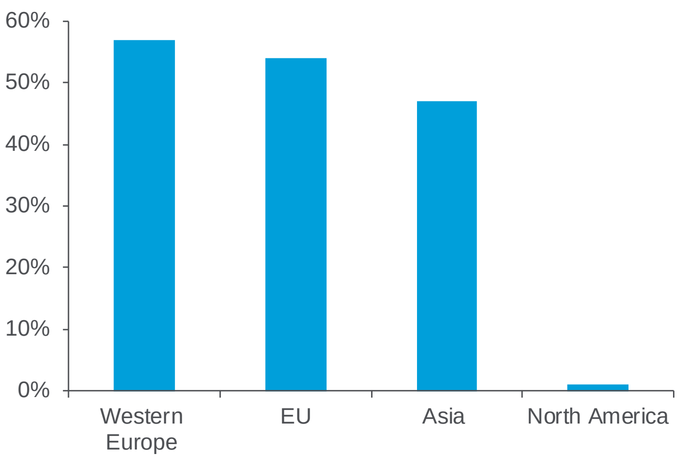
Source: Citi Research, company data based on multiple sources, locomotives market by orders is ~16% of which we assume 50% electric and 50% diesel

Diesel engines still form a large part of the rail market, and represent a key emissions concern

Electrified rail not only has zero emissions at the point of use, it also benefits from the switch to renewable energy, since it uses on-grid power, which is becoming greener as the penetration of on-grid wind and solar energy increases. However, there are limits to the adoption of rail electrification. In Germany only 60% of the rail network is electrified, as measured in track distance. In the U.K. it is only 42%, and at the EU level 54% is electrified. Some of these non-electrified lines are rural and so far less busy, but overall in Europe, 20% of rail volume is still powered by diesel trains. Globally, the penetration of electrification varies enormously by region — only 1% of the U.S. rail network is electrified, while rail electrification has significantly risen in Asia from 34% in 2013 to 47% in 2017 as China has made large investments in both constructing new lines and electrifying diesel lines. India has also been instrumental in the electrification growth, and the Government has approved 100% electrification of railways by 2021-22.

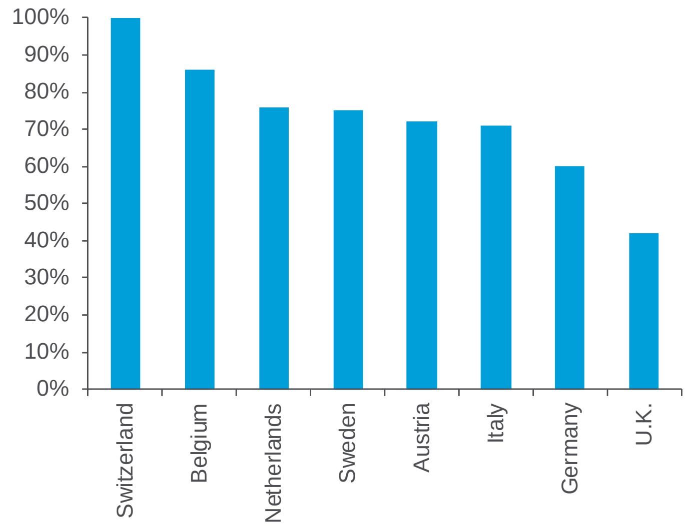
Electrification costs can be prohibitive — a U.K. study of rail electrification costs, through overhead cables or a third rail infrastructure, show costs varying from <£250,000 per single track kilometer to £1.2 million per single track kilometer in two cases. The costs vary enormously depending on associated civil works, especially related to bridges and tunnels.

Figure 22. Western Europe Leads in Electrification; while North America is Far Behind



Source: Citi Research, SCI Verkehr

Figure 23. Within Europe, Switzerland Leads the Pack; While the U.K. and Germany are Below Average



Source: Citi Research, SCI Verkehr

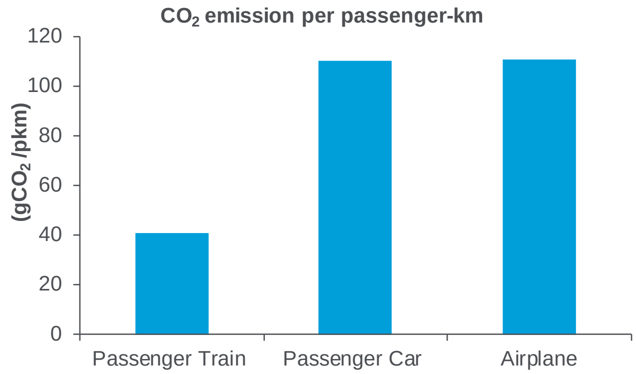
Are Hydrogen-Powered Trains the Answer?

Hydrogen-powered trains, using fuel cells, offer zero emissions at point of use and no required upgrade to track infrastructure

All modern trains are technically powered by electricity, either directly from the grid or through onboard generators; diesel trains have onboard diesel generators for example. In the case of hydrogen-powered rail, onboard fuel cells convert the energy from hydrogen, when paired with oxygen, into electricity. Hydrogen-powered trains, using fuel cells, offer zero emissions at the point of use with no required upgrade to the track infrastructure and the only by-product of running a hydrogen fuel cell is water.

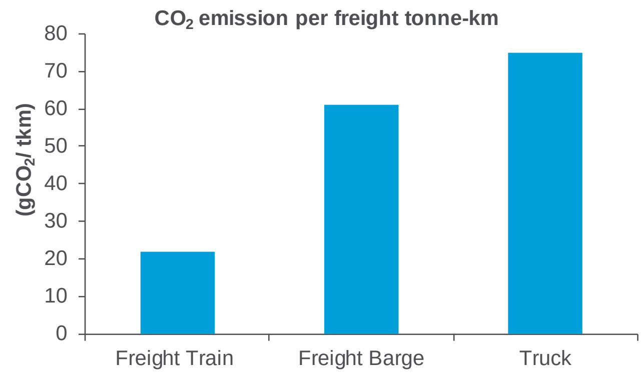
While batteries are becoming the favored environmentally-friendly method for powering the automotive sector, batteries have severe limitations when it comes to rail transport, especially over long distances. Hydrogen fuel cell trains have benefits over batteries, including shorter re-fueling times and better range, and hydrogen as an energy store benefits from virtually zero energy loss in storage.

Figure 24. Rail is Already a Lower Emission Mode of Transport for Passengers...



Source: Citi Research, European Commission

Figure 25. ... and for Freight



Source: Citi Research, European Commission

Adoption is Still in its Infancy

Pilot hydrogen rail and tramway projects have been announced or implemented in Germany and China in the last year, and more recently in the U.K. Falling total cost of ownership (TGCO) means hydrogen technology could replace diesel technology and avoid the high costs of electrification while still driving down CO_2 g/km for rail, and reducing particulate matter and noxious gas emissions.

Four states in Germany have collectively ordered 40 fuel cell-electric passenger trains

Four German states have collectively ordered 40 fuel cell-electric passenger trains. In 2016, the German state of Schleswig-Holstein announced it was to electrify its entire railway network by 2025 using 'hydrail' fuel cell equipment. In 2018, two hydrogen trains entered into commercial service in Germany, as the world's first passenger trains powered by a hydrogen fuel cell. The trains, which can reach speeds of up to 140 km/h and operate on ~100 kilometer of line, are fueled at a mobile hydrogen filling station. The gaseous hydrogen is pumped into the trains from a 40-foot-high steel container, where one tank can power up to 1,000 kilometers. A stationary filling station is scheduled to go into operation in 2021, when a further 14 trains are due for delivery.

The U.K. government announced plans to introduce some hydrogen trains by 2022

Recently, the Rhein-Main transport authority has awarded contracts for hydrogen powered trains, which are scheduled to be delivered in 2022. Separately, the U.K. government has targeted removing diesel engines by 2040, and in 2019, the U.K. government announced plans to introduce some hydrogen trains by 2022. In 2017, China announced plans for a hydrogen-powered light rail service in Foshan.

Opportunity Size Linked to Renewable Energy Penetration

The target market for hydrogen rail is likely to be the diesel-powered market as opposed to already-electrified lines. With electrolysis, hydrogen trains require around two-to-three times the electrical energy of an electric train for each kilometer traveled, due to the energy losses of the cycle, as the energy is required to compress hydrogen to very high pressures for storage.

Despite this apparent inefficiency, there is a clear and valuable symbiosis with intermittent renewable energy sources like wind and solar. Surplus renewable energy can be used for electrolysis meaning this efficiency is not an issue. Wind farm operators can also benefit from diverting to hydrogen production rather than grid supply when power prices are negative. Importantly, hydrogen can be stored on a large scale at low cost, and is suitable for long-term storage (unlike batteries), meaning hydrogen can play an important part in offsetting the intermittency of renewable power generation.

'Clean' Hydrogen is the Main Barrier to Adoption

How the hydrogen used in hydrogen-powered trains is produced will determine its environmental impact

We see adoption as inherently linked to the production of hydrogen from renewable sources. Any hydrogen-powered train is cleaner at the point of use — meaning reduced noxious gases and particulate matter near railway lines and in stations — but the overall environmental impact clearly depends on how the hydrogen is 'produced'. While hydrogen is the most abundant element in the universe, on Earth it is almost always found in compound form, including in water and in hydrocarbons.

According to the U.S. Department of Energy (DoE), there are currently three major ways of producing hydrogen, including reforming hydrocarbons like natural gas or ethanol, fermentation (of biomass), and electrolysis. In electrolysis, electricity is used to split water into hydrogen and oxygen; the electrolyzers in electrolysis can be thought of as fuel cells in reverse. If the electricity used by the electrolysis process is generated from renewable energy then the hydrogen is considered an energy store for renewable energy. This cannot be said of hydrogen produced from (say) reforming natural gas, where CO_2 is a byproduct when steam is used to separate the hydrogen in methane, and where carbon monoxide (initially) and carbon dioxide (ultimately) are byproducts. According to the U.S. DoE, 95% of hydrogen in the U.S. is currently produced by reforming natural gas. According to IRENA, the International Renewable Energy Agency, only 4% of hydrogen globally was produced from electrolysis in 2017.

What is the Effect from Hydrogen-Powered Rail?

We see several sectors benefitting from this technology:

- **Rail rolling stock suppliers:** The replacement of diesel engines with hydrogen-fuel cell powered trains could accelerate the replacement of aging rolling stock in both passenger and freight markets. This may be offset by lower revenues in electrification projects.

- **Renewable energy developers, operators, and suppliers:** The use of clean hydrogen in clean transport applications including rail can create an opportunity for renewable energy projects, helping solve the problems of intermittency and supply/demand pattern mismatches, by providing a method to effectively store clean energy in the form of hydrogen when demand is low.

- **Hydrogen infrastructure:** Including compression, transportation, and storage.

Some sectors that may have risk:

- **Electrical transmission operators and suppliers:** While we don't see hydrogen-powered rail as a major disruptor to on-grid power, at the margin there may be less demand for incremental rail electrification. If clean hydrogen emerges as a mature technology, other energy users either in transportation (heavy trucks, buses) or other areas (buildings, industry) may see a benefit to switching in certain applications, reducing grid power demand.

- **Diesel production and distribution:** According to the U.S. EIA, the rail industry accounts for close to 6% of distillate fuel oil usage by end use in the U.S. While clearly not the largest user, the adoption of hydrogen rail could contribute to declining demand for distillate fuel oils in conjunction with new technology adoption in other areas.

The Evolution of Robotic Surgery

Moving Towards Digital Surgery

Citi Healthcare Research Team

Of the roughly 55 million applicable surgical procedures performed worldwide, we believe over 15 million are already being performed in a minimally-invasive fashion via manual laparoscopy. Robotic penetration, however, still makes up just 2% or so of applicable procedures worldwide. In the years ahead, we expect new entrants and advancements in technology to drive a major acceleration in robotics to nearly 15% penetration by 2030, taking from both laparoscopy and open procedures.

Future robots in surgical applications will undoubtedly be smaller, more portable, flexible, and less expensive

Thinking about the role of robotics in surgical applications needs to evolve from our current image to something very different. Meaningful technology innovation is the major advantage that robotics offer over traditional open and laparoscopic surgery. As we look ahead, future robots will undoubtedly be smaller, more portable, flexible, and less expensive. Invasiveness will also decline as surgery transitions from tissue resection (i.e., removal of a part of tissue) to targeted ablation (i.e., using catheters to create scarring on tissue), driving improved outcomes. Software will be a hugely important enabler of this transition earlier into the treatment paradigm, with the surgeon's role as a manipulator waning and transitioning towards a decision maker. All of this should enable a vastly expanded variety and quantity of procedures to be performed robotically.

Visualization and the Beginnings of Digital Surgery

Major advances in visualization will further enhance robot surgery over the coming years

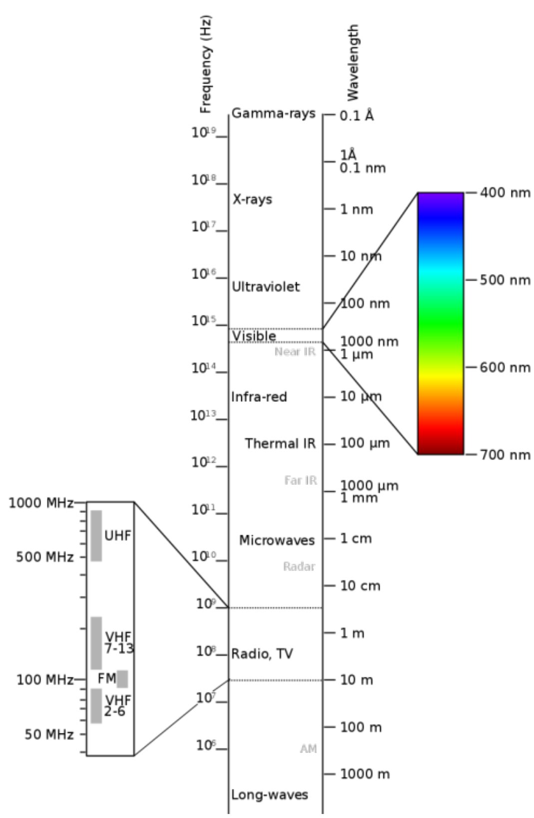
While visualization is already a big advantage of current robotic surgery systems over either open or laparoscopic surgery, we expect major advances in visualization to further enhance robot surgery over the years to come. In fact, if phase one of the superiority of robotic surgery technology over the past 20 years was about advancement in instrumentation, we would argue that the next decade (phase two) of that superiority claim and broader adoption will be mostly about improvement in visualization. Some of the advances in visualization are closely connected with the concept of digital surgery, which we will generally define as converting data in usable digital information. The importance of virtualization and the additional solutions provided by digital surgery in concert can hardly be overstated in regards to the impact on the surgeon experience and on the likelihood of, and consistency of, successful surgical outcomes. Technology on the horizon surrounding digital imaging include:

- **Anatomy Recognition:** Software-enabled anatomy identification using artificial intelligence (AI) and based on prior surgical images. Identification of key anatomical structures today is performed solely by the surgeon. This leaves the door open for operative error, however uncommon. Surgical video data is becoming increasingly available, though there still remain some limitations, mostly legal, to what can be captured. Over time, however, we expect enough images and video data to be aggregated and fed into algorithms for precise and accurate tissue identification. This may help mitigate surgical missteps and may also ease one dimension of cognitive load on the operator. Over time, we suspect these algorithms will become increasingly advanced such that they can evolve into a system that 'guides' a surgeon. Here we imagine the software pointing out key structures to avoid and highlighting possible next steps based on the surgical video feed in real time. A mentor-like system could evolve from effective software-based anatomy recognition, coupled with other technology. These advances are likely to happen gradually and piecemeal with layers of software capabilities being added over time. The longer-term mentoring capabilities are still beyond five years from commercialization, in our view.

- **Tissue Segmentation:** Delineating between different tissue beyond what might be possible by the human eye, enabled by AI and intelligent software. This is another key step that can enable improved surgical performance with a potentially lower cognitive load for surgeons. Tissue segmentation could be based on pre-op images to demarcate anatomy or tumors targeted for resection. Segmentation may be enabled in real-time to provide additional guidance to surgeons beyond what the naked eye can see, and with more precision. We see particular applications in oncology where tumor tissue can be delineated from healthy tissue enabling better margins and greater confirmation that no cancer is left behind.

- **Spectral Imaging:** Using a broad array of electromagnetic wavelengths — beyond just the visible light spectrum that is captured and displayed with endoscopies such as ultraviolet, infrared, x-ray, or combinations thereof to discern tissue characteristics not visible to the human eye. Today endoscopic cameras and the output display rely mostly on the visible light spectrum of red, green, and blue. The image below reminds us that there is a much broader range of electromagnetic frequency than just the visible light portion of the spectrum. Over time, we expect more capabilities to be added to robotic systems to enable the display of anatomical features that may only be visible under different EM wavelengths. Of course, this would need to be translated into something visible to the human eye within the visible light spectrum to be usable. Both of these steps are likely to happen and contribute to some of the development of other features such as anatomy recognition and tissue segmentation.

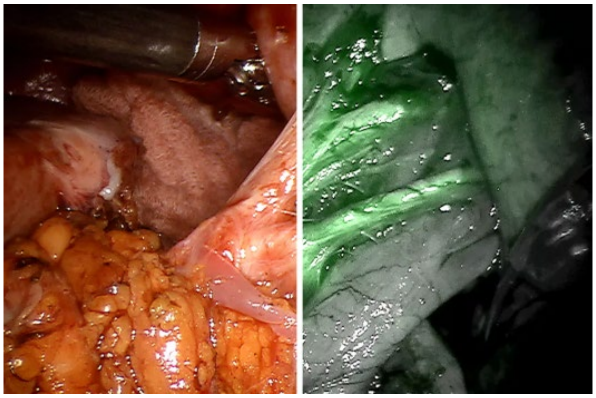
Figure 26. Ultrasound Elastography and Guidance



Source: Citi Research, University of British Columbia (Salcudean et. al.)

- **Imaging Agents:** The use of radioactive or contrast agents to identify specific anatomy. Today's systems use ICG (indocyanine green) in concert with spectral imaging to measure blood profusion and to identify other key structures. The fluorescent ICG molecule is administered intravenously and then a certain wavelength of light is directed at the tissue and bright green color is reflected back. This has been applied to a number of surgeries already, urology and colorectal most notably, but to think applications of the concept stop there is likely shortsighted. Novel imaging molecules are likely to come to market over the next five years that can more specifically target certain structures and tumors with greater precision. The challenges include developing molecular agents that are safely administered in patients, have photon reflective properties that can be isolated using certain EM wavelengths, and then translating that into usable images. This all takes time and so our expectation for next-generation imaging agencies is likely early- to mid-2020s.

Figure 27. Indocyanine Green

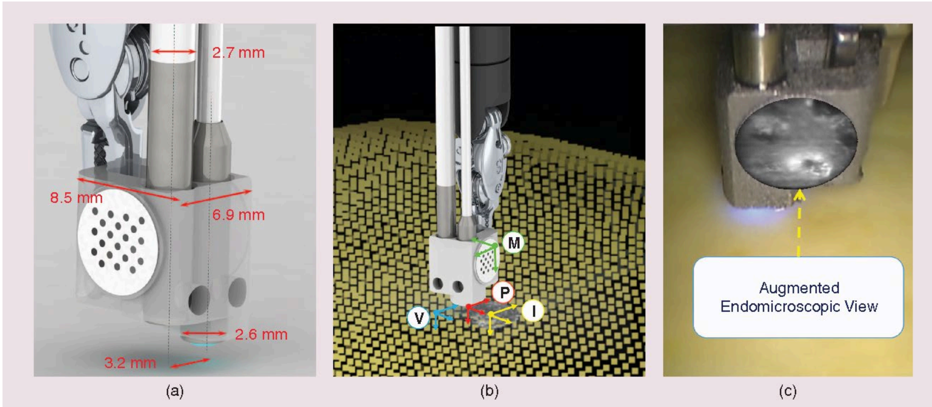


Source: Citi Research, Intuitive Surgical

- **Mechanical Probes:** Instruments can be integrated into robotic systems that measure various tissue characteristics. Further instrumentation development can enable tissue property measure in real-time. As these types of products are commercialized, surgeons will be able to measure the mechanical properties of tissue during a procedure to enable better decision making. Key properties that might be of interest to surgeons, and thus likely in first generation commercial versions, are tissue thickness and stiffness. We imagine these properties can be translated into a score or displayed with colors in the surgeon console giving surgeons greater information to aid in decision making. The foundation of these technologies seems like it already exists today, though the complexity of integrated sensors into an instrument in a cost-effective manner is likely to slow integration. For this reason, we expect these types of features to come to market in the early-to-mid-2020s.

- **Microscopic Imaging:** Augmented endoscopic cameras can be integrated into a surgical system to enable imaging at the microscopic level, a potential benefit for some cases. The concept of magnification is of course not new. Over time we believe there will be different levels of magnification added to robotic surgical systems that can be adjusted in real time. However, seeing at the microscopic level in real time may not be solving a problem that truly exists, and if there is no problem to be fixed and no added benefit, then we shouldn't expect major steps towards integration in the near term. Perhaps longer term there are applications to even more precisely image tumor margins, but realistically, we don't see a major benefit.

Figure 28. Microscoping Imaging



Source: Citi Research, Imperial College London (Yang et. al.)

- **Augmented Reality (AR):** The intersection of reality and synthetic imaging whereby the two are overlayed against each other for better navigation. We think this will have interesting and practical applications in robotic surgery over the next decade. AR is the culmination of many of the technologies and imaging modalities described above, translated into computer-generated 2D overlays and 3D models. These are then made part of a mixed reality landscape where computer-generated models are interwoven with traditional imaging. The challenge of AR is multi-dimensional and each will take some time to solve before being brought to bear in full in robotic surgery: (1) image rendering is highly processing-power intensive meaning, for now, that the rendering likely has to take place before the surgery to avoid what would be a sizeable latency if rendered in real time; (2) AR is extremely difficult in soft tissues where anatomy registration and tracking is compromised by the movement of the anatomy. This leaves only a few likely candidates for AR in abdominal surgery in the medium term including the liver and pancreas.

  Colorectal surgery, gynecology, and urology will likely take much longer to have AR incorporated given the complexity of matching up the overlay with the actual anatomy continuously throughout the surgery. Given this challenge, most AR research to date has been done in head & brain, orthopedic, hepatobiliary, and pancreas, i.e. anatomy that doesn't move much during surgery. Over time we expect these challenges to be addressed, the latter more slowly, enabling AR in real-time in robotic surgery. The benefits will yield a procedure that can be done more quickly and more safely as critical structures such as major vessels, nerves, or other vital tissues are projected onto the patient.

- **Anatomy Registration:** For robotic orthopedic procedures, registering enables an integrated camera system to track surgical tool movement in space, and limb movement for both inter-procedural guidance and assessment of surgical quality before case completion. This is basically a prerequisite of robotic orthopedic surgery as it stands today. Companies are likely to fine-tune the registration process and algorithm to speed registration and to improve the data and analytics that are enabled with motion tracking cameras. Longer term, the more interesting potential technology development is on the analytics side, which could, for example, provide even better feedback on surgical outcomes (bone cuts) and the soft tissue balancing required in a knee replacement surgery. We expect some advancement here but don't expect anything that will change the trajectory of ortho robotic surgery, and we also see limited application across other specialties.

Moving Towards Digital Surgery

The three tenets of digital surgery include: (1) data & analytics; (2) simulation & training; and (3) automation

The move towards digital surgery is both inevitable and near-term: in fact, it is very much already underway and we fully expect that to continue. The three tenets of digital surgery, as we see them include: (1) data & analytics; (2) simulation & training; and (3) automation.

Data & Analytics

Data is pervasive in the surgical care pathway, from imaging to motion tracking in robotics, surgical video, and outcome data. The abundance of data presents opportunities, but the challenge is how to translate the massive amounts of available data into actionable insights. This question is the focus of research and development in the field. Our view is that the right kind of data and analytics will improve surgical outcomes and lower the economic cost of robotic surgery.

Here we focus on three categories or data & analytics: outcome data, economic data, and physical surgical performance data. These, of course, are all intertwined.

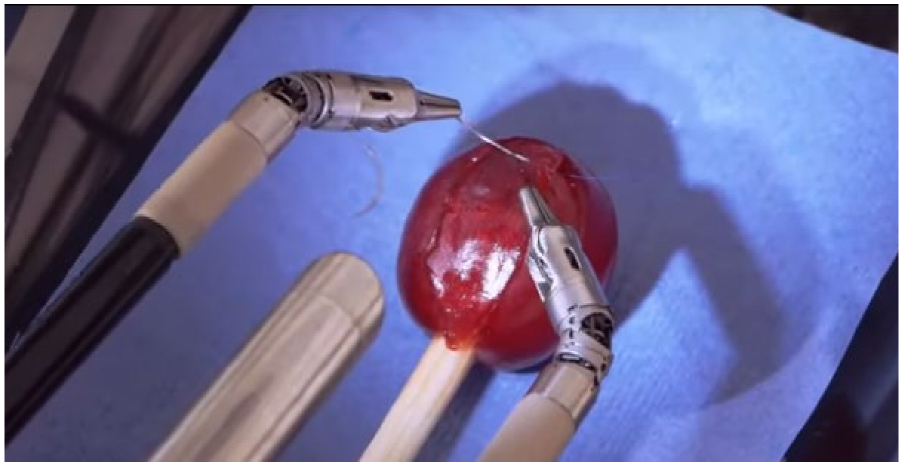
- **Outcome data:** One area already being looked at is increasing informatics to help hospitals assess surgical outcomes and optimize their robotic surgery programs. This is partly done by benchmarking hospital robotic surgical data and help assess surgeon level outcome data to better identify best practices. Another area in which informatics can help is in robotic utilization assessment to make sure the robotic system is being used in the most efficient manner. Over time, we believe surgeons and hospital will have access to case-level robotic data upon completion of the surgery. Rapid feedback is the best way to learn and change practice so the ability to provide this type of case-level feedback in near real time can move the needle for individual surgeons and hospitals. The types of outcome data that might be most interesting to these constituents (beyond economic data) are blood loss, complication rates, conversion to open, 30-day readmission rates and length of stay.

  As the age of digital surgery progresses, we expect the abundance of surgical data available to be better analyzed and delivered back to surgeons and institutions in ways that can be actionable. This has the potential to raise the bar on surgical outcomes and to more empirically grade surgeon competency, driving volume to surgeons and institutions most skilled in their specialty. Of course, this creates some negative outcomes for some surgeons and creates potential legal problems as well, so we believe there are likely to be some bumps in the road towards broader-scale implementation.

- **Economic outcomes:** In similar ways to outcome data, economic data is abundant and can be assessed in a way that delivers actionable insight to institutions. Some of the same outcome measures — like length of stay and readmission rates — are highly correlated to economic outcomes as well. Beyond that, institutions are likely to measure operative time, which is highly costly; instrument use, which can be optimized; and utilization, which can be made more efficient. These analytical tools will be highly valuable to institutions in order to narrow the increased economic cost of robotic surgery relative to open or laparoscopic procedures.

- **Surgical Skills Analytics:** Very much related to the prior topics, programs are being devolved to assess surgeon skill in basic robotic control and more advanced procedural steps.

Figure 29. Surgical Skills Assessments



Source: World Association of Laparoscopic Surgeons

Simulation & Training

In addition to training new surgeons, experienced surgeons will be able to practice new techniques to familiar procedures, or new procedures entirely to hone their skills before a live operation

The process of training a competent surgeon or developing an excellent one begins with nearly a decade of school and fellowship training. But, like in everything, learning by doing is often the best aid in developing skill. Here is where simulation and training come in. Current robotic surgery systems have robust simulation programs built in so a surgeon can practice entire surgical procedures before every operation on a patient. These simulations require extensive knowledge of anatomy to be translated into a virtual setting and then allow for an undefined and infinite number of potential surgical actions to take place; the former is challenging, the latter even more so. Hence, there is much that can be improved with regard to these simulators and the value of enhanced training environments can hardly be overstated. To draw an analogy to aviation, pilots learn to fly commercial plans through books, lecture, and observation. In addition to these learning steps, commercial pilots are required to complete thousands of hours of simulated flight training which makes us more confident to get on an airplane with our family. In surgery, a robust digital surgical environment can massively increase the odds of competence for new surgeons before operating on a patient. As well, experienced surgeons will be able to practice new techniques to familiar procedures, or new procedures entirely to hone their skills before a live operation. Here too, this gives us more comfort before going under the knife, so to speak.

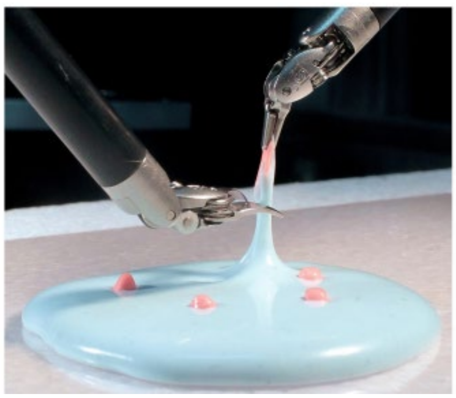
As we assess new robotic systems coming to the market, simulation and training programs become increasingly relevant. To help convert new surgeons into users of these robotic systems, the quality of the training and simulation programs is likely to be a gating factor in their adoption. Broadly speaking, a quality training program and robots virtual reality simulator will raise the probability of commercial success for new robots coming to the market.

Automation

The first surgery task that could be subject to automation is suturing

Surgical task automation is a concept that has been discussed for a long time and continues to be an area of extensive research and can capture much of people's imagination. Its viability in robotic surgery relies on many of the technologies already discussed being perfected, as well as new technologies being developed. We believe it will take the better part of a decade to bring even the simplest forms of automation to the markets. We see certain functions of surgery, suturing for examples, as likely candidates for the initial wave of automation, but not likely for the next five years, at least. After automation of individual processes is proven successful, the focus is likely to turn to reproducing entire segments of a surgery as we know efforts are being made today to break a given surgery down into components that may be more easily automated. This is, of course, even further from fruition.

Figure 30. Surgical Task Autonomy: Debridement



Source: Citi Research, UC Berkeley (Abbeel & Goldberg)

Figure 31. Surgical Task Autonomy: Cutting

Source: Citi Research, UC Berkeley (Abbeel & Goldberg)

Experts believe surgical automation will progress and take over parts of procedures, or even whole procedures. The question then becomes what the role of the surgeon is in that setting. We believe the surgeon's role, many years out, will shift towards decision making and guiding, while the robotic system performs mechanical tasks in an automated way with limited actual decision-making being done by the computer itself.

Nuclear Fusion

The Quest for a Man-Made Sun

David Bieber
European Fixed Income Portfolio Strategy

Francesco Martoccia
Global Commodities Strategy

Edward L Morse
Global Head of Commodities Strategy

Anthony Yuen
Head of Commodities Strategy, Pan Asia

Developing a limitless carbon free energy source is a titanic scientific and technological dream that has mobilized human potential across the globe. If one day this goal is accomplished, it would have colossal economic, environmental and geopolitical repercussions. It would be one of the most disruptive technological changes in the history of the world. Yet despite the promises, the goal of creating more energy output per energy input through controlled nuclear fusion (CNF) has persistently remained a good 20 to 50 years away over the last century.

For almost a century since English astrophysicist Eddington advanced the still utopian idea of mimicking on Earth the processes that power the stars, modern physics has been chasing the dream of mastering nuclear synthesis — combining small atoms into large ones — and unlocking the energy engine that powers the universe. This process, has long been hailed as a source of unlimited energy: unlike fossil fuels, it would rely on a virtually infinite supply of hydrogen isotopes. It is symmetrically the opposite of nuclear fission and extracts energy from merging atoms rather than splitting them.

The new focus on nuclear fusion is being driven by private sector and is focused on cold fusion

After the oil crisis of 1973-74, the incentive to accelerate research and investment in fusion came from the fear of falling into a Malthusian Trap. But that dissipated with the belief that the world did not confront a resource supply gap in an age of hydrocarbon abundance. Urgency diminished over time and now concerns about an oil supply peak have been replaced by a focus on a demand peak and a desire to replace carbon intensive fuels with carbon free fuels. This has given a rebirth to interests in fusion energy. The new focus is not the public but the private sector, not the high temperature traditional fusion but cold fusion. Today's reality is the environmental legacy of ever-growing energy demand from fossil fuels and its impacts on climate change. Last year nuclear plants supplied 2,563 TWh of electricity, sparing the atmosphere some 2.2 Gigatons of CO_2 that would have come from fossil fuels. However, nuclear fission plants have to deal with the high costs of safety, problems of stocking radioactive material, the risks of meltdown, earthquakes, nuclear weapons proliferation, and waste disposal to name a few. Fusion energy would produce no waste, bear no meltdown, proliferation or other risks, albeit the underlying reactions would require extremely precise and controlled temperature, pressure and magnetic confinement

But fusion has not only yet to be proven commercially, but safety concerns abound, over and above fusion's attraction vs. fission-based reactors. As summarized in *Nature* in 2016, the ITER project itself will need to test for accident probabilities, potential hydrogen/dust explosions, the safety of electromagnetic loads, controlling overheating and spillover heating, tritium operational releases, occupational radiation exposure and remaining radioactive waste.

The Process of Nuclear Fusion

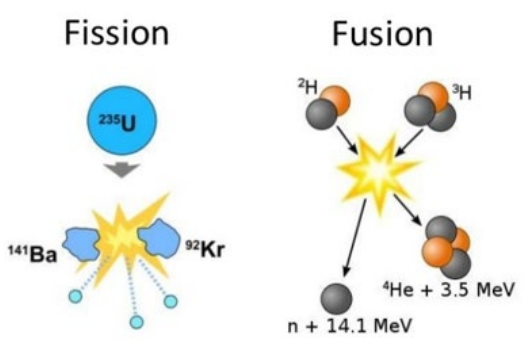
There are two types of nuclear reaction that can occur, namely fusion the process of building atoms from lighter elements, and fission the process of spitting large atoms into small elements. To estimate the energies of nuclear reaction it is useful to ask a slightly different question — how much energy would be required to rip an atom apart into its fundamental components of electrons, protons and neutrons? Clearly energy is positive since the particles are bound together via the forces; hence work is required to break these bonds.

This measure is called the *nuclear binding energy*, with each atom having a different value: the larger the atomic mass, the greater the energy output. In Figure 33 we plot the nuclear binding energy per atom as a function of its atomic mass.

There are two regions in the graph — region 1 where nuclear binding energies increase with atomic mass up to 60 and region 2 where nuclear binding energies beyond 60 are falling. The boundary defines the separation between nuclear fusion and nuclear fission. For atomic masses below 60, energy is required to deconstruct atoms and consequently energy must be released by building atoms (this is called nuclear fusion). However for atomic masses great than 60, binding energy falls as the atoms get bigger — hence by splitting atoms, energy must be released (which is called nuclear fission).

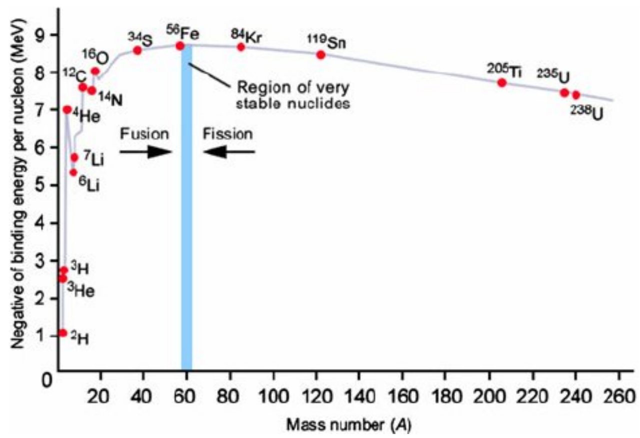
The region where the nuclear binding curve is steepest will have the most energetic nuclear reaction energies (which occurs for atoms with the smallest atomic masses) — this means that building small atoms will release the greatest amount of energy. Indeed nuclear fusion reactions with hydrogen can generate energies that are around 10x higher than a nuclear fission reaction.

Figure 32. Nuclear Reactions: Fission vs. Fusion



Source: Wikipedia

Figure 33. Nuclear Binding Energy per Atom



Source: http://www.dlt.ncssm.edu/tiger

The sun is a giant nuclear fusion reactor

The sun is in fact a giant nuclear fusion reactor. It is mostly composed of hydrogen, which is the simplest and most abundant element in the universe (at 75%). Hydrogen has a single proton with a single electron bound to its orbit. For nuclear fusion to occur there are a number of processes that need to occur.

For nuclear fusion to occur, there are a number of processes that need to occur

The first issue is the large distances between the electrons and protons in an atom — in this state, quantum effects prevent close approach of the protons so no nuclear fusion can occur. A process called ionization occurs in the sun, which removes the bound electrons from the atoms. This works by heating the particles, which results in raising the temperature (or kinetic energy) of the particles so they are moving so fast that electrons get ripped from the atom. This creates a new state of matter called a *plasma* and is commonly referred to as the fourth state of matter after solid, liquid, and gas). The second step is to provide the protons (which repel each other given they are all positively charged) with enough energy so that they can break through the repulsive Coulomb force. Densities of the plasma need to be sufficiently high, or the size of the nuclear reactor sufficiently large to ensure there is a significant probability of a nuclear collision to occur. This why all anthropogenic attempts to reach nuclear fusion rely on gigantic reactors like ITER in France.

Nuclear Magic

When two protons make a close approach, the strong nuclear force takes hold and can fuse them together, releasing energy in the process. However, there are a couple of different reactions that are possible: (1) those that preserve the number of protons; and (2) those where protons number is not conserved. In stars, the second reaction type dominates the initial stages of nuclear fusion — here two protons (hydrogen ions) fuse together and, with a nuclear physics sleight of hand, one of the proton changes into a neutron (a particle with a neutral charge). This nuclear magic is a result of the weak nuclear force (one of the four fundamental laws of nature), without which nuclear fusion in stars would not happen.

The result of proton-proton fusion (p-p) is the creation of Deuterium (D) (an isotope of hydrogen composed a proton and neutron), a neutrino and energy in the form of light (which is why stars shine) — this reaction produces 1.44MeV of energy.[18]

Fusion in the Lab?

To achieve nuclear fusion on earth we need to recreate an environment similar to the sun

To achieve nuclear fusion on earth we need to recreate an environment similar to the sun. The sun is a million times bigger than the earth and hence fusion in the lab creates its own set of unique challenges! To compensate for the lack of size, far higher temperatures are required (than the 15 million degrees Celsius found in the sun) to achieve a reasonable reaction yield. The fusion yields will also be dependent on the type of nuclear reaction that occurs.

The struggle for scientists has been to develop a fusion machine that could deliver more energy than it requires on a steady basis.

The bulk of all research effort in fusion is how to create and confine plasma at the right temperature and density so that nuclear fusion can occur. In the sun, plasma is confined by gravity which creates high density and temperatures for billions of years. This is clearly not something we can do in the laboratory. The struggle for scientists has been to develop a fusion machine that could deliver more energy than it requires on a steady basis.

Magnetic Confinement Fusion

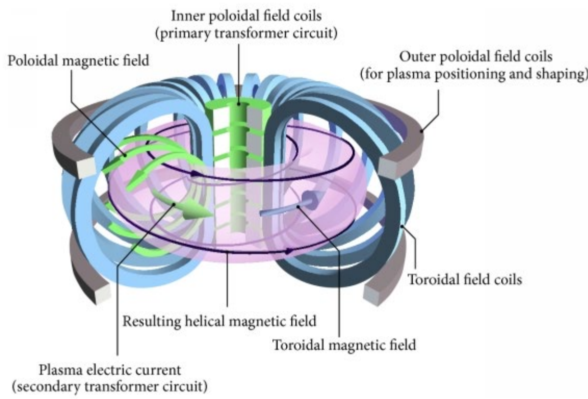
Though scientists began drafting projects for a self-sustaining fusion engine in the 1950s, financing of nuclear fusion experiments flourished only in the aftermath of the 1973-43 oil price shock. It has waned through failure to get anywhere close to a threshold in which more energy is unleashed than is used. When the Argentinian *Huemul* Project team erroneously claimed to have reached nuclear fusion in 1951, it sparked a wave of interest among governments. The same year Stalin approved the Soviet magnetic thermonuclear reactor (MTR) program lead by Lavrentiev, Sakharov and Tamm and the U.S. Government granted $50,000 to Lyman Spitzer to head *Project Matterhorn*, later re-named the Princeton Plasma Physics Laboratory (PPPL). Since the first practical application of nuclear fusion, the struggle for scientists has been to develop a fusion machine that could deliver more energy than it requires on a steady basis.

Magnetic confinement uses the fact that plasma is made up of charged particles and hence can be manipulated and controlled using electromagnetic fiddles. Several models of this engine were theorized to recreate the extreme conditions of pressure and temperature that happen within the core of the sun to ignite the reaction that leads atoms to fuse and free energy.

[18] Temperature is a measure of average kinetic energy – the higher the temperature the higher the energy. In nuclear physics energy is measure in electron volts (or eV) where 1eV is approximately equal to 11,000 degrees Celsius.

For example, the Soviet Tokamac (Russ. **to**roidal'naya **ka**mera s **ma**gnitnymi **k**atushkami — toroidal chamber with magnetic coils), a donut-shaped magnetic containment chambers, emerged as the leading technology to contain the plasma stream. A Tokamak operates by filling the vacuum chamber with a mixture of deuterium and tritium gas. Radio frequency ionizes a gas into plasma, which can then be held away from the vessel walls using electromagnetic fields created by huge external magnets in place around the device.

Figure 34. Magnetic Confinement: Section of a Tokamak



Source: EUROfusion

To heat the plasma to around 100 million degrees Kelvin in order to create the conditions for fusion, there are basically three methods that are employed:

1. **Microwaves:** These incoming electromagnetic waves cause the ions to oscillate back and forth harder and harder, extracting energy from the microwaves.

2. **Current:** Run a massive current through the plasma called Ohmic heating - the plasma conducts but not perfectly, so a lot of heat is generated through electrical resistance. It is literally as if the plasma were a massive fuse.

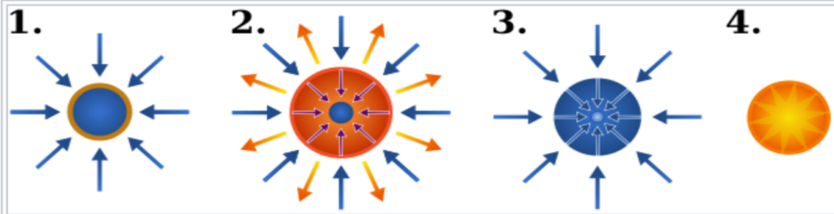
3. **Particles:** Neutral particles are fired into the plasma so that they can penetrate the magnetic field, which then collide with particles in the plasma and deliver energy to them.

This type of device can readily achieve the conditions needed for nuclear fusion — it is well tested and its performance well understood and it is the basis for most fusion programs around the world. The largest tokomak is JET (Join European Torus) based in Oxfordshire, U.K. On 9th November 1991, this device achieved the world first controlled nuclear fusion. In 1997 it produced 16 MW of energy with a current world record Q factor of 0.67 (the ratio of energy input vs output). This will soon be surpassed by ITER (International Thermonuclear Experimental Reactor) based in Provence, southern France that aims to generate more than 500MW. The planning/construction of the international project has been frustratingly slow due to political delays and lack of funding — in 1986 the initial project was approved and it is still in construction.

Laser Fusion

A completely different approach is inertial confinement. This relies on rapidly compressing a pellet of fuel (deuterium and tritium) to incredibly high densities over very short periods of nanoseconds (10^-9 seconds). This is achieved by focusing higher power lasers or X-rays that generate 500 trillion watts[19] over 20 billionth of a second onto the surface of the pellet. As the fuel compresses to x100 times the density of lead, it turns into plasma and heats up to high enough temperatures / pressures to induce nuclear fusion.

Figure 35. Inertial Confinement



Schematic of the stages of inertial confinement fusion using lasers. The blue arrows represent radiation; orange is blowoff; purple is inwardly transported thermal energy.

1. Laser beams or laser-produced X-rays rapidly heat the surface of the fusion target, forming a surrounding plasma envelope.
2. Fuel is compressed by the rocket-like blowoff of the hot surface material.
3. During the final part of the capsule implosion, the fuel core reaches 20 times the density of lead and ignites at 100,000,000 °C.
4. Thermonuclear burn spreads rapidly through the compressed fuel, yielding many times the input energy.

Source: Wikipedia

Over the last decades, significant progress has been made in the development of short pulse, high-energy systems which are the main component of a laser fusion device

Over the last decades, significant progress has been made in the development of short pulse, high-energy systems which are the main components of this fusion device. However major challenges remain, such as how to focus all this energy efficiently in a highly spherical symmetry. There are currently two different approaches being investigated, direct drive, which uses lasers, and indirect drive, which uses X-rays. Ultimately finding the right balance in efficiency, stability and symmetry of the implosion will be crucial in the development toward an economic device. The major research effort for inertial confinement is occurring at two sites - one facility is the Laser MegaJoule in Bordeaux, France and the other is the National Ignition Facility (NIF) at the Lawrence Livermore National Laboratory in Livermore, California, U.S.

The Future of Nuclear Fusion

Given the wide recognition that there was no direct national security advantage to succeeding, scientists from around the world interacted with Soviet scientists in sharing knowledge. Soon the U.S. was leading the race thanks to its human and financial capital — over a 30 year period, the U.S. government committed $15 billion, including $500 million for a single project — and in 1978, the PPPL reached an important milestone — heating the plasma to 60 million degrees Kelvin or even much higher, a level at which Enrico Fermi calculated the reaction would have been self-sustainable. The PPPL remains one of the world's centers for fusion research and is still based on variants and improvements of the original Tokamak design.

[19] Equivalent to five million 100-watt light bulbs.

Alongside progresses done on hot CNF, scientists also advanced the hypothesis that they could unleash fusion's energy forces without resorting to extreme conditions, including ultra-high temperatures, creating the promise of "cold fusion." Already in the early 1980s research began in the private sector on cold fusion. In 1989, two electrochemists, Fleischmann and Pons, claimed to have reached sustained nuclear reaction at room temperature in an electrolytic cell of heavy water whose electrodes were made of platinum and palladium. However early replications of the experiments dismissed the results as flawed in a climate of mistrust and controversy. In the early 2000s independent experiments at Italian ENEA and U.S. SPAWAR reopened the debate and caused a renewed interest in cold fusion research. However, the scientific community is still divided between those who look at it as a cheaper alternative to hot fusion and those who regard it as pure alchemy.

With the end of the energy crisis, hot CNF lost its national strategic importance and funding had to move a more integrated international stage. Once the energy crisis was over by the early 80's, Washington started to radically reduce its budget for fusion. Recognizing the financial needs to pursue joint projects, in 1986 the U.S., USSR, EU, Japan, China, Korea, and India started a joint venture in the south of France to create the largest thermonuclear fusion reactor, the ITER, a $22 billion megaproject expected to increase tenfold by 2035 its output from 50MW of thermal input. Thirty-five countries with more than half the world's population are now involved in this venture. Its sponsors point to the increasing ability to achieve fusion power of more than 100%.

But the recent increase in the objective of finding carbon-free energy inputs has ignited interest in fusion technology within a new class of green-focused private investors. Optimism around this carbon-free technology has spread among venture capitalists eager to rethink the way we produce and consume energy and accelerate the energy transition. *TAE Technology* aims to commercialize energy through CNF: they aim to license proprietary patents and technology to improve margins. Their reactor reached 50 million degrees K this year and is touted to mark a net energy gain in 2023, 2 years ahead of ITER. The company attracted $700M of investments including from the Russian government. Universities including MIT are leveraging their laboratories and know-how to spin-off companies like *Commonwealth Fusion System* (CFS), which received financial support from the Breakthrough Energy Coalition. CFS will shrink the size of the tokamaks employing super magnets made of Rare-Earth Barium Copper Oxide, a new high temperature superconductor. *Helion* Energy, which was granted funds from the NASA, the DOE and DOD, aims at lowering production costs shrinking the reactor's size by merging magnetic confinement technology like in a tokamak and inertial confinement. It is important to notice that all these projects rely on safe source of nuclear energy, which cannot be turned into radioactive dispersal devices, thus limiting nuclear proliferation. Meanwhile, cold fusion, or low energy fusion, keeps attracting private capital.

The elusive Holy Grail of infinite, clean energy has always been 20 years to half a century away ever since scientists started working on it in the 1930s

Huge steps have been made in CNF, but as the paradox of Achilles and the Tortoise, the elusive Holy Grail of infinite, clean energy has always been 20 years to half a century away ever since scientists started working on it in the 1930s. Controlling nuclear fusion would be the dawn of a new era for mankind, where endless, cheap energy is accessible to everyone. It would help the world economy moving towards a cleaner setup without the need for coercive tools like a global carbon tax. But the disruptive consequences of launching fusion successfully would be enormous.

Converting all fossil fuels into stranded assets could unleash dramatic consequences for both countries and countries dependent on their exploitation. That could create domestic havoc across the oil and gas producing countries of the world, with global implications, including social disruption and angry terrorism. The financial consequences to investors in companies exploiting these assets as well as to the companies themselves would also likely carry unprecedented consequences In the immortal words of English romantic poet William Blake "*Energy is the only life, and reason is the bound of energy. Energy is an eternal delight, and he who desires, but acts not, breeds pestilence*".

Probiotics/Personalized Medicine

A Gut Response

Elise Badoy, CFA
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Japan Food, Beverage, Tobacco & Personal Care Research

With medical costs rising around the world, preventive medicine is attracting growing interest. This makes probiotics, which is backed by a growing body of evidence, a promising market. Current global interest in the functions of the intestines stems from the realization that they govern the whole body's immune system rather than simply digesting and absorbing food. They are home to roughly 70% of the body's immune cells. There are some 1,000 different types of intestinal bacteria (the body has 100 trillion in total), which bolster immune function by applying appropriate stimuli to immune cells. Immune cells in the intestines repel germs and viruses that have come from outside the body. They are also transported in the blood to mount attacks on pathogens and viruses in all parts of the body. Recent research has reportedly shown that the degree of resistance to illnesses, such as influenza and pneumonia, is closely linked to intestinal immune cells. Raising immunity requires maintaining the balance of gut bacteria by increasing the number of beneficial bacteria in the intestines while reducing the number of harmful bacteria. Yogurt and probiotic products containing lactic acid bacteria help to maintain this balance.

We estimate the yogurt/ lactic acid bacteria market will grow at a CAGR of 7%, reaching $129.5 billion in 2024

Immune-related drug therapies include anti-cancer drugs, anti-rheumatic drugs, and bronchodilators (in the allergy domain). EvaluatePharma estimates that anti-cancer drugs will post the highest growth between 2018 and 2024 of the three classes with a compound annual growth rate (CAGR) of 11% resulting in a market of $236.6 billion in 2024. For anti-rheumatics and bronchodilators, their 2024 markets are estimated at $54.6 billion and $30.7 billion, respectively. We estimate the yogurt/ lactic acid bacteria market will grow at a CAGR of 7%, reaching $129.5 billion in 2024. There are two key differences between these immune-related drug therapies and yogurt/lactic acid bacteria products. The first is effectiveness and speed of effect, and the second is price. Yogurt does not act fast and it is usually hard to gauge whether an effect was produced or not. However, it is cheap compared with drugs. We think demand for yogurt and lactic acid bacteria products is likely to grow as the effectiveness of intestinal immune cells becomes more widely recognized, and we would not rule out the possibility of yogurt and lactic acid bacteria products taking market share from drugs in the future. Fecal transplants and probiotics have been explored as separate but interrelated potential disruptive innovations for the pharma and biotechnology sectors. Fecal transplants have shown material symptomatic improvements in patents with autoimmune disorders include ulcerative colitis and Crohn's disease.

The attractiveness of probiotics as a product is they are thought to work to ensure a healthy gut (and gut flora) and thus replicate the same effect as antibiotics without the undesirable side effects

The advent of probiotics in the feed additive market has been prompted by the increased scrutiny placed on the use of antibiotics as a growth promoter in feed. The issue being that utilization of antibiotics in feed is leading to greater incidence of microbial resistance and in turn is rendering this highly important category of drugs impotent. As a result the European Union banned the use of antibiotics as growth promoters in the early 2000s; consumer pressure is leading to a similar shift in utilization of these products in the U.S. and across the rest of the world ('antibiotics free' is a desirable claim on products in the U.S.). Antibiotics have a consistently delivered and positive effect on animal growth and feed efficiency as they ensure a healthy gut for the animal. The attractiveness of probiotics as a product is they are thought to work to ensure a healthy gut (and gut flora) and thus replicate the same effect as antibiotics without the undesirable side effects noted above.

How Close Is this to Becoming Reality?

The challenge is to get to the stage with probiotics of personalized nutrition on a scalable basis

Mass-market probiotics are already a sizable market. The challenge is to get to the stage of personalized nutrition on a scalable basis. Probiotics can be added to a range of food products but currently the majority are added to dairy products — primarily yogurt — representing a €21 billion market according to Euromonitor and delivering mid-single digit growth over 2015-2018. There are other possible vehicles for the probiotics, notably plant-based alternatives, which in turn could foster additional growth and higher margins for the food producers involved (or lower prices for the end-consumer). Delivering probiotics via beverages are also an option.

Probiotics are increasingly being included in animal feed and companion animal food

In addition, probiotics are increasingly being included in animal feed and companion animal food. The challenge thus far has been ensuring stability of the probiotic and thus consistent efficacy of the product. The animal feed supply chain is a harsh one in particular, in terms of the various environmental conditions a feed additive has to withstand without degrading, be it heat, aridity, or even physical force. Feed additives therefore need to be stabilized to ensure they retain their efficacy. However, for probiotics, which are made up of billions of living organisms, stabilizing the product so they can withstand the trials of the broader supply chain is a tough challenge.

One solution marketed by a number of suppliers has been to move one step down in the biological chain of effect. Instead of marketing the relevant organism itself as an additive, they seek to isolate the specific beneficial enzymes and proteins that a probiotic organism produces and use these products as a feed additive. These products are in turn far easier to stabilize and thus are more consistently effective.

From a pharmaceutical standpoint, there is a lack of randomized controlled trials sufficient to secure approval of probiotics

From a pharmaceutical sector standpoint, while single arm trials and anecdotal case reports are promising for fecal transplants and probiotics, there is a lack of randomized controlled trials sufficient to secure approval. In addition, the heterogeneity of the stool transplant is likely to create extreme regulatory challenges as well as potential safety concerns from infection with pathogens from the donor. Phase II trials are underway but several are on potential hold given a death and a severe complication following implantation in a trial patient.

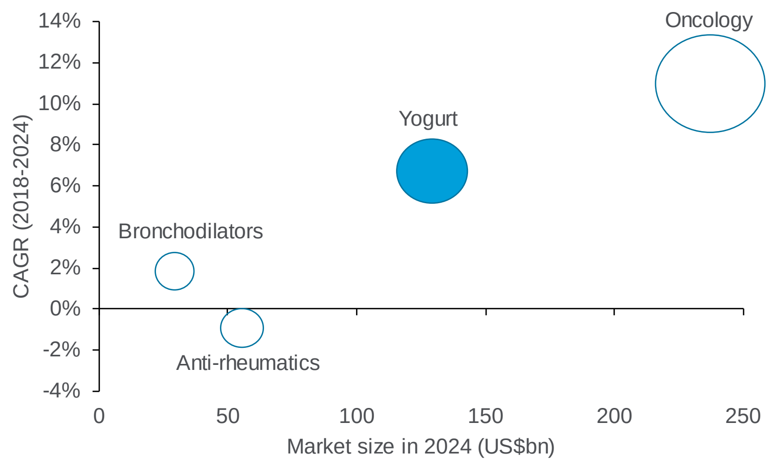
The potential role of probiotics for pharma and biotech companies, is even more unclear. Promisingly, pre-clinical and clinical data with antibiotics have shown that prior exposure materially reduces the efficacy of cancer immunotherapies such as PD1 agents. However, attempts to use probiotics to improve PD1 response rates have demonstrated worse outcomes. The challenges and scientific uncertainties in both these areas makes commercialization a distant and remote possibility.

What is the Potential Market Size?

Yogurt remains the main driver of probiotic market growth. The market for yogurt, the product most commonly associated with probiotics, is expanding. According to Euromonitor, in 2018 the global yogurt market grew 7% year-over-year (YoY) to $87.9 billion (retail price basis). The market has grown at an average rate of 2% over the last five years and 4% over the last 10 years. We believe the acceleration of growth from 2017 may reflect rising global health consciousness. There are three main types of yogurt: drinks, flavored and plain. The market value of each category in 2018 was as follows: yogurt drinks $37.2 billion (+10% YoY), flavored yogurt $33.1 billion (+2%), plain yogurt $17.7 billion (+8%). The CAGRs for these markets over the last five years are: drinks +6%, flavored -2%, plain +4%.

In 2018, yogurt drinks accounted for 42% of the yogurt market, flavored yogurt for 38%, and plain yogurt for 20%. The market breakdown in 2013 was drinks 36%, flavored 46%, and plain 19%, and the breakdown had largely remained the same prior to that. Yogurt drink market growth began to accelerate around 2016.

Figure 36. Size of the Market for Immunotherapy Drugs and Yogurt



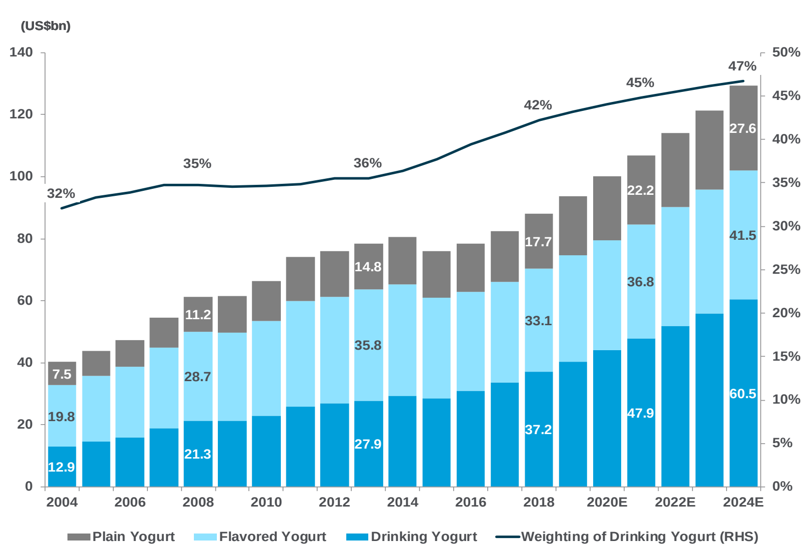
Source: Euromonitor International, EvaluatePharma, Citi Research

Yogurt drink have become the driver of overall yogurt market growth

Yogurt drinks have become the driver of overall yogurt market growth as consumers have shifted from flavored yogurt to yogurt drinks. We believe this reflects factors like the convenience of yogurt drinks, the launch of new products with health benefits, and improvements in taste and quality. Over the next six years, we forecast the global yogurt market will expand to \$129.5 billion, which equates to average annual growth of 7%. In 2024, we forecast a market value of \$60.5 billion for yogurt drinks, \$41.5 billion for flavored yogurt, and \$27.6 billion for plain yogurt.

We forecast CAGRs of 8% for yogurt drinks, 4% for flavored yogurt, and 8% for plain yogurt and estimate yogurt drinks will account for 47% of the overall yogurt market in 2024.

Figure 37. Global Yogurt Market



Note: Based on retail price

Source: Euromonitor International, Citi Research

The feed additive market in aggregate is about $12 billion and growing at 4-5% per year and the medical additives market is worth another almost $11 billion. Probiotic solutions are already on the market for both applications and have the opportunity to take a meaningful share in both markets. Industry experts we have spoken to judge the addressable market for providing a consistent replacement to antibiotic growth promoters at $1.0-1.5 billion, but we note that probiotic's broader offering as a product that improves feed conversion efficiency and intake could allow it to take even more share.

Barriers to Adoption

The largest barrier to widespread adoption is ensuring the technology is refined so it works consistently

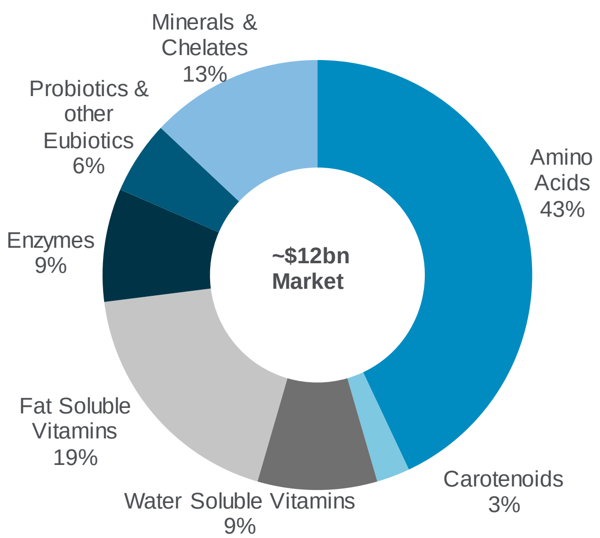
The largest barrier to widespread adoption is ensuring the technology is refined so it works consistently. This industry demands demonstrable benefits, i.e. a consistent improvement in feed conversion efficiency. Once this is demonstrated, large industrial farms will be relatively quick to utilize the product given feed remains the largest cost for protein production.

Beneficiaries

The key beneficiaries in branded food and food ingredients are the companies present in categories where probiotics as a 'claim' can bring better pricing and attract more consumers. The groups that could be challenged among branded food companies are those exposed to categories not skewed to nutrition or wellness (which can include 'acceptable' indulgence), as in those segments where the cost of growth is becoming increasingly high with limited prospects.

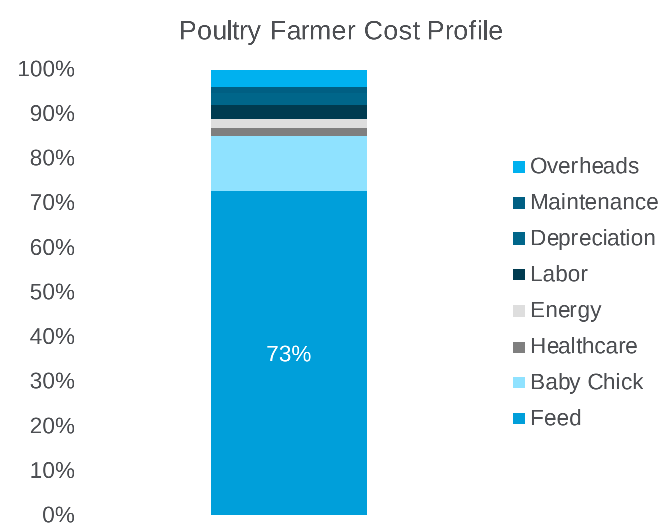
With regards to animal feed, the key beneficiaries look to be the more biologically-focused feed additive producers and those with experience in microbial technology, enzymes, and fermenting. The groups that could be challenged are those who are purely exposed to antibiotics utilized as growth promoters, but we note that most businesses who have exposure to this business area also offer potential replacements (e.g., enzymes or probiotics).

Figure 38. Probiotic Market Size



Source: Citi Research

Figure 39. Poultry Farmer Cost Profile



Source: Citi Research

Quantum Computing

Quantitative Research
Chris Ma
Asia Quantitative Research

Technology Research
Jason B Bazinet
U.S. Technology and Media

Kota Ezawa
Japan Technology

Arthur Lai
Asia Technology Hardware

Andre Lin, CFA
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Hao Yan
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Asia Internet

Quantum computing is a disruptive technology providing a new type of computing power using quantum mechanics. While the basic building block of a classical deterministic computer is the 'bit' which has a binary state of either 0 or 1, the fundamental building block of a quantum computer is the 'qubit', which is a quantum system that can be in a complex combination of 0 and 1 at the same time. Thus, quantum computers can scale to solve problems computationally intractable on classical computers, leading to huge benefits for many industries.

Why Do We Need Quantum Computing?

There are many predictions about the end of Moore's Law — the principle that the speed and capability of computers can be expected to double every two years as a result of increase in the number of transistors a microchip can contain — including from Gordon Moore himself, not because of a lack of desire for more computational power, but rather because of technical, physical limitations. Certainly with the era of big data, IoT, and 5G, we are living in a world where the demand for more computational horsepower is ever increasing.

Quantum computing technology aims to solve the largest and most computationally challenging problems currently out of reach of classical computers, even using the combined power of all existing data centers on the planet. That's not to say quantum computing will replace classical computers, which are better suited for general purpose computational needs. It's highly unlikely that quantum computing hardware would appear in your smartphone anytime soon. However, quantum computing does have specific advantages for applications in a number of industries including pharmaceutical/ healthcare /genetics, chemical/ materials, aerospace, information security, energy, and financial markets.

"If I try to map a caffeine molecule on a normal computer, that computer would have to be over one-tenth the volume of this planet in size. A quantum computer just three or four times the size of those we've built today should be able to solve that problem." – Arvind Krishna, IBM

"*Doubly exponential growth is so singular that it's hard to find examples of it in the real world. The rate of progress in quantum computing may be the first.*" –Dr. Hartmut Neven, Google

How Close Is It To Becoming Reality?

A measure of how close quantum computing is to becoming a practical reality is known as 'quantum supremacy', which is the point at which a quantum computing device can solve a particular problem at orders of magnitudes faster than a classical computer could. One measure of the progress made in quantum hardware is the qubit count, similar to the early days of the CPU race for higher clock speeds in megahertz (MHz). And in a similar vein where clock speeds are not an accurate measure of CPU horsepower, the number of qubits is not a fully accurate measure — not all qubits are created equal. Nevertheless, with the big caveat of all else being equal, the higher the number of qubits, the greater the computational power.

According to the Financial Times, a Google research paper posted in September 2019 claims "their processor was able to perform a calculation in three minutes and 20 seconds that would take today's most advanced classical computer, known as Summit, approximately 10,000 years." While this will be a milestone in the annals of computing history, it won't be a tipping point in which quantum computers will suddenly take over the world. There will be a gradual adoption curve, and quantum supremacy will be a step on the path to many useful applications. Companies that embrace the technology will enjoy strong competitive advantages from more robust solutions, leading to superior optimizations and improved R&D.

Although there are currently multiple competing technologies for quantum computing, there is not yet a clear winner

There are currently multiple competing technologies for quantum computing hardware, and there is not yet a clear winner. The hurdles in quantum computing are largely technical as they are much more susceptible to errors than classical computers. Much of the effort is aimed at reducing or correcting the noise inherent in the quantum process. Some of the key challenges in quantum computing are:

- Temperatures are often required to be close to absolute zero or other extreme conditions;
- Large overheads for error correction;
- Expensive setup and unique materials;
- Precise pulse control;
- Sparse connectivity;
- Coupling with environment and decoherence;
- Faulty gate operations;
- Cross-talk between qubits; and
- Fabrication yields and life cycle.

Because there are many technical challenges, there are a number of competing solutions

As there are many technical challenges, there are a number of competing solutions. Some of these technologies include: superconducting qubits, trapped ions, topological qubits, quantum dots, photonics, neutral atoms, and silicon. While many technical issues remain to be solved, competition has been healthy and rapid progress is being made.

In the meantime, software companies are already at work solving real-world problems by applying quantum algorithms like optimization (adiabatic, Quantum Approximate Optimization Algorithm (QAOA)), unstructured search (Grover's algorithm), factorization (Shor's algorithm), and chemistry simulations (Variational Quantum Eigensolver (VQE), Phase Estimation Algorithm (PEA)). In computer science, there has been a long history of using a physical process as the inspiration for an algorithm. For instance, simulated annealing has been used for decades as a heuristic approach to solve optimization problems. Some machine learning algorithms also have roots in the physical world, such as neural networks and genetic algorithms.

Specialist software developers are acting as the bridge between the multiple hardware platforms and industry. Quantum software developers employ researchers from different fields, including physics, computer science, chemistry, medicine, and finance and partner with many of the various quantum hardware platforms to enable their software to execute on multiple platforms. They also work with industry end-users to develop quantum solutions for their real-world problems. Use cases include: (1) accurate prediction of catalysts' molecular conformation; (2) accurately describing the forming and breaking of chemical bonds for designing next-generation EV battery materials; and (3) accurate prediction of interaction energy for computer aided drug design. Finance uses cases include portfolio optimization, asset allocation, hierarchical risk parity, optimal arbitrage, and swap netting.

We note most software targeted at the quantum opportunity is from specialist vendors or internally developed by leading adopters. We are seeing only primary research and very early commercial applications from the mainstream software vendors, which signals mainstream commercial applications are likely several years away.

Corporates are developing Digital Annealers that can already make user of quantum-inspired algorithms

While the race for quantum supremacy continues, in the meantime, corporates are developing Digital Annealers that can already make use of quantum-inspired algorithms. Essentially, quantum-inspired platforms simulate quantum computers with classical hardware like FPGA (field-programmable gate arrays) and ASIC (applied-specific integrated circuit) chips. In that way, progress from quantum algorithms can already be harnessed.

How Well Does the Market Know About Quantum?

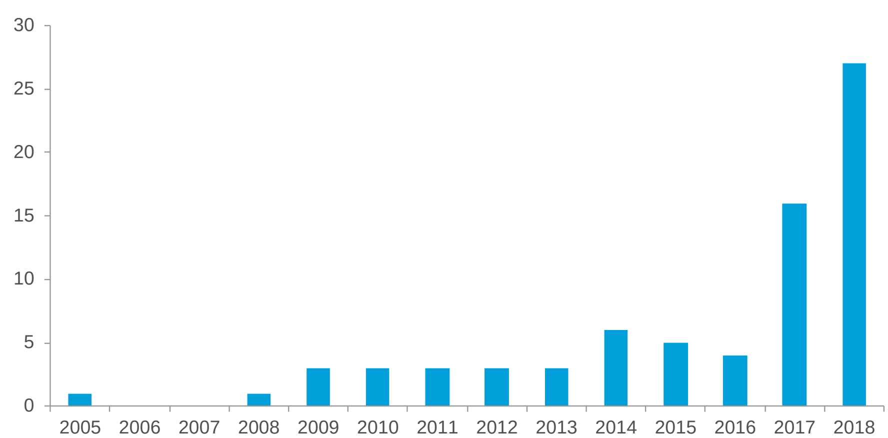
Quantum computing is still early in the hype cycle, though there has been increasing buzz around its promise. Many incumbent technology companies have already invested significant resources into quantum computing research and governments as well have invested billions of dollars into fundamental quantum computing research.

Increasingly, end-user companies are exploring how to utilize quantum computing as a competitive advantage

Increasingly, end-user companies are exploring how to utilize quantum computing as a competitive advantage. What's becoming more apparent to these companies is the classical computing paradigm does not directly port over to quantum computing hardware and instead they need quantum algorithm knowledge in order to apply their use case over to the quantum domain. Much of the technology rests in the software layer that sits on top of the quantum computer and there has been considerable research in this applied quantum algorithm development. Quantum algorithms have the potential to show significant speed advantages over their classical counterparts. This is especially useful for chemical, material, and pharmaceutical R&D where there is strong potential for improvement. Indeed, there has already been a significant increase in research for quantum-enabled chemistry simulation.

"The way I see quantum computing right now in our engagement with 1QBit is that it would give us the opportunity to anticipate what a molecule would do without actually having to make the molecule in the lab." –Peter Margl, Research Scientist, Dow Chemical

Figure 40. Publications in Quantum-Enabled Chemistry Simulation



Source: 1QBit, Citi Research

How Big Could the Opportunity Be?

Quantum computing has the potential to solve computational problems currently out of reach or imperfectly solved by classical computers

Quantum computing has the potential to solve computational problems currently out of reach or imperfectly solved by classical computers. For technology companies themselves, we see this as an augmentation of existing classical technology in the same vein as a math co-processor or a GPU (graphics processing unit) might augment a CPU (central processing unit). Cloud computing providers could potentially democratize the initial high costs of quantum computing, while software providers and technical consulting firms could help the industry translate their problem set into the quantum domain.

The average person may never hear about quantum computers, but they will feel the impact in their daily lives

The average person may never hear about quantum computers, but they will feel the impact in their daily lives from better batteries, more effective drugs, cheaper energy, less risky investments, and less congestion on the highways.

What Are the Barriers to Adoption?

As previously mentioned, there are a number of technical hurdles quantum hardware needs to overcome. True quantum computing hardware will take time to mature and develop, and in the meantime technology companies with quantum-inspired hardware will be a stepping stone to help transition to a quantum computing paradigm.

The initial costs of a quantum computer will put it out of reach of most small companies and even many large companies

The initial costs of a quantum computer will put it out of reach of most small companies and even many large companies. However, quantum hardware can easily be democratized in the cloud so not everyone will need to have their own quantum computer on site except for potentially low-latency applications. Quantum computing lends itself well to software-as-a-service, and this could help overcome the initial high barriers to entry.

Education is another area which will take time, and adoption will be determined by how well companies can learn and develop new software. Software companies and consultants will help companies transition and develop the domain knowledge necessary for quantum computing.

How Does Quantum Computing Change the Industry?

Industry and academic consensus expects quantum computing is roughly 10 years away from large-scale commercialization

The industry and academic consensus expects quantum computing is roughly 10 years away from large-scale commercialization. As we move towards scaling commercial applications, there are still many competing technologies as business models. The hardware design and supply chain remains in the laboratory stage and is still far from mature. Our research indicates there are no hardware vendors in a dominant market leading position. Software development for quantum computing is still in in its infancy, though we have seen robust development in high-end custom-developed software. Development of the software ecosystem at a large scale could lag behind hardware.

We believe the end users who can leverage quantum computing to improve or optimize their operations will be the key beneficiaries from the development of quantum computing. Quantum computing can also boost AI development with quantum neutral networks (QNN). We expect the financial industry, pharmaceutics, chemistry, energy, defense & aerospace, and logistics could be the key sectors who benefit most from the new capabilities. Supercomputer vendors, in particular, are at the forefront of this paradigm shift.

On the other hand, we expect technology development will widen the gap between technology leaders and laggards. Companies in the above mentioned industries who cannot keep up with the new development or utilize the technology could be left behind their peers.

We anticipate the mainstream business model for quantum computing will be an offering available in major cloud computing platforms as an accelerator for certain applications

From our current point of view, we anticipate the mainstream business model for quantum computing will be an offering available in major cloud computing platforms as an accelerator for certain applications. The cloud quantum computing model can reduce barriers to adopt quantum computing with higher flexibility. Cloud computing service providers could offer quantum infrastructure-as-a-service (IaaS) or serverless quantum computing options for developers to leverage quantum computing capabilities in their workflow. We believe the leading cloud service providers are positively geared to quantum computing development and could become key beneficiaries in quantum computing development.

The approaches to cloud quantum computing by key players in the cloud quantum computing field are varied. All researchers in the field are looking to achieve 'quantum supremacy' which is a fancy way to describe the threshold when a quantum computer can outperform a classical computer. Quantum supremacy requires two things: (1) hardware that can process may qubits and (2) low error rates. They are focused on reaching quantum supremacy using superconducting circuits. But there are other approaches — focusing on using trapped ions or utilizing rubidium atoms.

One quantum processor, which some observers believe may be close to achieving quantum supremacy, is said to be a 72-qubit processor with 1% error rates (and far lower error rates of about 0.1% for single-qubit gates). This type of early stage quantum computer is sometimes called a Noisy Intermediate Scale Quantum (NISQ) computer. They are 'noisy' because the error rates are still high and they are 'intermediate scale' because breaking cryptography will probably require a few thousand qubits. The challenge, however, is this: the required processing power doubles every time a qubit is added. Ultimately, millions of qubits with an error rate of less than 0.1% may be needed. As such there is still quite a bit of research that needs to be completed.

In one sense, quantum computing power is similar to that of a GPU — expensive at first with limited/ niche applications and then when it hits volume, it goes mainstream. Initial adoption will likely be in vertical markets like pharmaceuticals, government, and technology. Given these customers are usually large consumers of cloud-based services, there is an incentive for hyperscalers to invest ahead of demand.

In February of 2018, a Chinese corporate/ research institute joint venture launched an 11-qubit quantum computing service and made it available to the public on the Computing Cloud Platform. This quantum computing prototype is targeted to reach 50-100 qubits by 2030.

In addition to quantum computer processors, a Digital Annealer — computer architecture that applies a quantum-inspired computing approach — was introduced in May 2018 as a cloud-based service. The architecture of the Digital Annealer specializes in rapidly solving combinatorial optimization problems it uses digital circuits and its strength lies in its ability to perform stable operations at room temperature (many quantum computers need specialized facilities such as cooling facilities).

Recycled Fiber

What Is the Disruptive Innovation?

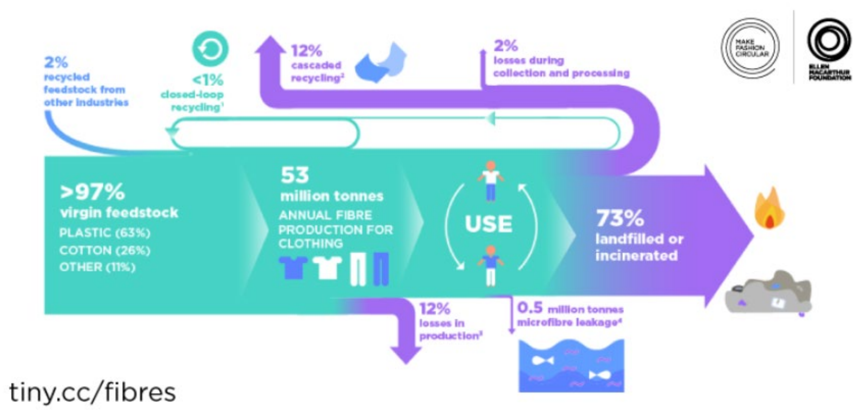
Adam G Cochrane
European General Retail Analyst

Recycled fiber is developed by recycling discarded clothing garments and textiles, chemically breaking down the natural fibers and creating a fiber which can be easily integrated back into the supply chain. While cotton is a natural fiber and is therefore biodegradable, the production process uses up a significant amount of natural resources which could be used for alternative purposes. Polyester and nylon are man-made fibers sharing similar properties to oil-based plastics and more progress has been made on recycling these products, but not to the points it has penetrated the mass market.

The fiber created in current recycling methods isn't high enough quality to be used on its own

Current recycling methods are based on 'pre-consumer' utilizing of unused fabric offcuts from the production process and 'post-consumer' involving manual sorting of garments into color and material before they are shredded and spun into new fabric. The fiber created in this process isn't high enough quality to be used on its own so it is combined with virgin cotton to ensure consistent quality for manufacture.

Figure 41. Current Clothing Supply Chain Sees Only 3% of Clothing Made from Recycled Materials



Source: Ellen MacArthur Foundation

Why Is it a Problem?

Almost 97% of clothing is made using virgin materials given the complexity and cost of using recycled materials

The global clothing industry is a significant consumer of global natural resources whether through water, land, and pesticides for cotton or oil for nylon (an estimated 340 million barrels of oil per year are used in textile production). The Ellen MacArthur Foundation estimates the current clothing supply chain consumes about 10% of the world's energy. Currently almost 97% of clothing is made using virgin materials given the complexity and cost of using recycled materials. Sustainability has focused on increased efficiency and organic products to date but the most significant longer-term development relates to reusing materials to help close the loop on the manufacturing process. Ongoing research into more efficient methods to recycle used clothing are progressing quickly and may have large ramifications down the supply chain for global apparel.

How Close is Recycled Fiber to Becoming Reality?

The technology to recycle used clothing items has been put into production on a relatively limited scale and usually in more upmarket products given its cost. Utilizing plastic waste is more developed as the sortation process is less complex and with significant press coverage more resources have been devoted to it. For example, Parley for the Oceans already collaborates with global brands such as to recycle plastic waste into new sneakers and apparel.

It is becoming ‘trendy’ to be associated with environmentally-beneficial products — consumer adoption will accelerate the adoption of technology across the mass market

It is becoming ‘trendy’ to be associated with environmentally-beneficial products and this consumer adoption will significantly accelerate the adoption of these technologies across the mass market. We look at a few of the current innovations which are at various levels of development:

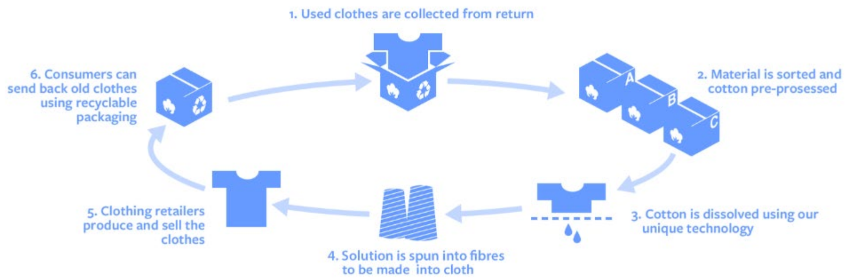
1. Econyl is a product developed by an Italian fabric company which takes nylon waste from landfills and oceans and transforms it back into regenerated nylon. This regenerated nylon can be used through the process multiple times and potentially helping to create the closed loop and circular economy.

2. Scientists at KTH, Stockholm’s Royal Institute of Technology, developed a process to take used clothing, dissolve them, decomposing the cellulose in cotton and viscose and recreating it back into a rayon fabric. The finished product is a form of rayon (which is made from regenerated cellulose fiber) and can be used to replicate natural cotton.

3. Relooping Fashion Initiative uses a process developed by the VTT Technical Research Centre of Finland Ltd to dissolve used clothing and recycle it into cotton. Partnering with companies across the value chain, it is a pilot for a closed-loop recycling system which requires no new raw material products to manufacture new clothing garments.

In adjacent areas to the recycling of used clothing there has been evidence that the idea will be readily accepted by the consumer with quality and durability bigger concerns in other categories.

Figure 42. The Relooping Fashion Initiative



Source: ReloopingFashion.org

How Well-known is Recycled Fiber to the Market?

The step change will be delivered with the shift from 'sustainable and organic' products to recycled products

The market is becoming increasingly aware of the necessity for apparel brands to use more sustainable sources for their production given the severe environmental footprint of apparel manufacturing. The main solution to date is 'sustainable' or 'organic' cotton and a number of high profile brands have increasingly utilized this strategy. The step change will be delivered with the shift from 'sustainable and organic' products to recycled products — especially cotton and polyester — which are responsible for the most environmental issues.

There are a number of charitable and non-profit organizations — such as the Ellen MacArthur Foundation, WRAP (Waste and Resources Action Plan), and Global Fashion Agenda — as well as a number of apparel companies, which are pushing the agenda but recycled fiber remains relatively low profile at this stage. Companies which successfully industrialize the chemical recycling of clothing will open up a significant investment opportunity. Conversely retailers and brands which do not engage in this topic bear the risk of brand damage and the costs of implementing any remedial actions. We don't believe these opportunities and risks are currently priced in by the market.

What is the Size of the Opportunity?

Recycled materials looks likely to take a significant share of the $1.3 trillion global clothing market in the longer term

The global clothing market is estimated to be $1.3 trillion annually and over the long term there is potential for recycled materials to take a significant share of this market. However, with the technology still under development, and the cost differential to virgin raw materials unclear, the proportion of the clothing market that can be addressed is difficult to ascertain.

Longer term, the use of recycled fabrics and plastics could be implemented across a number of different areas such as furnishings, furniture, and automobile interiors. However, it makes sense to focus on the shorter lifecycle products such as clothing first as these products will benefit the most from recycling and closed loop ecosystem.

The opportunity generated by reducing the amount of land devoted to intensive cotton agriculture, the transfer of this land to growing edible crops and the associated cost and resource saving (cotton is a water intensive crop) could also provide significant benefits.

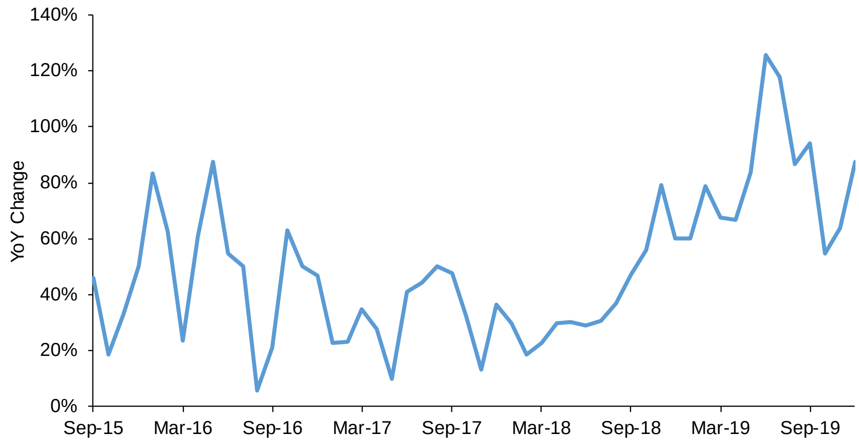
What are the Barriers to Adoption?

The biggest barriers to overcome with recycled fiber largely relate to scaling the adoption rather than the process itself. These barriers include:

1. **Ensuring the quality of the recycled product is acceptable for the manufacturer to replace their existing product without compromising quality:** The new technologies are creating products which do not need to be combined with virgin cotton or plastic and this should allow for direct replacement in the supply chain.

2. **Consumer acceptance of the replacement product:** Consumer demand for sustainable products is not under debate with numerous retailers reporting that organic lines are generally some of their fastest selling lines and the Google Trends analysis below supportive of this. What's harder to ascertain at this stage is the quality element as the majority of recycled products have been introduced at a higher price point to date and it remains to be seen how this is scaled.

Figure 43. Searches for 'Sustainable Fashion' Up Strongly Year-on-Year



Source: Citi Research, Google Trends

3. **The efficient collection of used products:** Existing players in the market have developed a supply chain to collect the raw materials (either from centralized waste collection or ad-hoc recycling) but the scale of this collection would have to be significantly increased to provide the scale we are discussing in recycled fiber. In Germany 75% of clothing waste is collected (although this is largely sent for re-use in other countries rather than recycling) but the rate is much lower in other countries. To increase recycling, end consumers would have to be encouraged to bring their old garments to be recycled with convenient drop off points widely spread. For plastic waste the process may be easier as it has already been adopted in a number of countries.

4. **Intellectual property:** The processes for recycled fiber are currently being developed by private companies and accordingly there will be a cost attached to using this process on a wider scale to pay for intellectual property. Given some of the environmental concerns it may be that new 'open sourced' ideas are generated to ensure a more cost effective adoption.

5. **Global brand adoption:** The change to recycled fiber will likely be driven by increased consumer demand. Large brands and retailers can accelerate this by adopting the recycled product, helping to educate consumers on the environmental impact of recycled fibers compared to virgin raw materials and attempting to manage any price differential between the products.

How Does Recycled Fiber Change the Industry?

Recycling should affect only the use of raw materials in production, not the quality of end product

The technology being developed for recycled fiber should just change the raw materials being used in production and will largely leave the quality of end product unchanged (hopefully in the eyes of consumers). The main impacts will likely be felt in the supply chain with existing products being replaced and with increased recycling of fabric, whether nylon or cotton, it is likely that apparel production will likely move closer to the end market. Over time it makes little sense for recycled material to be shipped to Asia for production into clothing to be largely shipped back to Europe and the U.S. as finished garments.

This will be further accelerated as robotics develop and fashion products are increasingly ‘made to order’ within the end markets. The environmental angle will potentially be accelerated by any global trends towards tariffs on Asian production which further reduces the labor cost advantage currently enjoyed in many of these markets.

For the apparel brands there is potentially scope to gain relative share by accelerating the adoption of recycled products in this growing segment of the market. For fast fashion retailers using more recycled products will help challenge the consumer perception of the negative environmental impact of the brands. We expect larger companies to be able to secure supply earlier and have the resources to invest in these new technologies.

The impact of greater cotton and plastic recycling will potentially be felt across the clothing supply chain including:

1. Cotton farmers could see a significant reduction in demand and in the global cotton price leading to a reduction in cotton planting. Much of the land will have alternative use so there may be a limited long-term negative impact on the agricultural industry which supports up to 250 million jobs globally (and a number of positive ones due to less water and pesticide usage given cotton is intensive in both of these).

2. Cotton production accounts for 2.5% of global arable land but only 5% of all pesticides use with a further $20-30 billion per year of chemicals used in the manufacturing process. The arable land no longer producing cotton will likely move to alternative crops which will offset any decline in pesticide and genetically modified seed sales.

3. Factories producing fiber from raw cotton could potentially be repurposed, but coupled with increases in automation, it is more likely this process is undertaken nearer to the garment collection to limit transportation costs.

4. Finished clothing manufacturing factories in Asia may suffer as production moves closer to the end market although there is growing domestic demand in many of these markets which may provide some offset.

5. Recycled nylon and polyester will require less oil based inputs.

Virtual Care

Making the Unsustainable Sustainable

Citi Healthcare Research Team

At the same time we are witnessing the rise of the on-demand economy, how we deliver healthcare is still practiced in the same way as it has for centuries. We believe stressors to the system — rising healthcare costs, an aging population, and a dearth of physicians — are pushing this hospital-centric construct closer to a tipping point. Combined with evolving consumer preferences, these trends have brought us to the cusp of a transformation in care towards on-demand care, or virtual care.

We are in the early days of virtual care but it should be views as a new distribution system for healthcare

We are already in the early days of virtual care, starting with the advent of telehealth. Going forward, we see virtual care expanding to broader technology-enabled healthcare, spanning from urgent care all the way to chronic condition management and remote surgery — effectively, all the things normally happening inside of the walls of a hospital, but at home.

It is important to note we do not see virtual care as a new standalone field of care, but rather, as a new distribution system for healthcare. Virtual care is the use of enabled technology such as videos, apps, and texts to deliver health services in a way that is independent of time or geography. Just as a company would not have an ‘e-mail department’, we do not expect hospitals will operate a separate ‘telehealth department’ in the future.

The Traditional Model of Care is Unsustainable

We are approaching a tipping point with our current healthcare model

We are approaching a tipping point with our current healthcare model as a confluence of factors including the aging population, rising healthcare costs, developing market expansion and a shortage of clinicians is driving the model to be unsustainable. We see the shift to healthcare technology as a necessary step to offset this trend and help the sector transition to a more sustainable model of care.

Healthcare Costs are Rising

Global healthcare spend is projected to reach $10 trillion by 2022 (Deloitte), with the United States encompassing nearly 40% of that spend.

The U.S. domestic healthcare market is the largest private-sector industry in the U.S.

According to the Centers for Medicare & Medicaid Services (CMS), U.S. domestic healthcare was a $3.6 trillion market in 2018 by annual spend, making it the largest private-sector industry in the United States. To put this scale in context, $3.6 trillion of annual spend puts healthcare at three times the size of the global payments industry (~$1.2 trillion according to BCG), approximately six times larger than the domestic defense industry (~$610 billion), and nearly 45x the amount of domestic bank IT spend (~$78 billion).

Figure 44 below shows the acceleration in U.S. healthcare expenditure. Costs are projected to accelerate by over a full point in the coming decade, driven by expanded coverage, aging population demographics, and cost inflation within the system. To put this growth in context, healthcare spends compound annual growth rate (CAGR) of 5.5% is more than double the rate of U.S. GDP growth at 2%.

Figure 44. Total National Health Expenditure Growth is Accelerating

Source: Centers for Medicare and Medicaid Services

On a per capita basis, the U.S. spends over $10,000 on healthcare, or nearly 1.5x the OECD (Organization for Economic Cooperation and Development) median. Despite that outsized figure, the U.S. lags other developed countries in healthcare efficiency, equity, and lifestyle.

Virtual care could generate $10bn of savings across the U.S. healthcare system, helping bend the cost curve for healthcare

We see virtual care as a way to reduce costs in the healthcare system, both through improving efficiencies and by moving lower-acuity patients into cheaper venues of care (the average cost of a telehealth consultation is ~$40 vs. the cost of an in-person visit at ~$125). According to an Accenture study, virtual health use in three leading care scenarios — annual patient visit, ongoing patient management, and self-care — could generate economic value across the U.S. health system of approximately $10 billion annually over the next few years.

We Do Not Have Enough Physicians

One significant problem on the horizon for the U.S. is a shortage of healthcare providers as the number of new physicians fails to keep pace with growing healthcare demands (e.g., an aging population and expanded healthcare coverage). According to the American Association of Medical Colleges, the U.S. will face a shortage of more than 40,000 primary care physicians in the next decade. Given limited supply and increasing demand, the incidence of physician burnout is also expected to increase during the same time period.

While incentive programs can help bend the growth curve for providers, in the near term we will need technology to help fill the gaps in demand. Virtual care's ability to extend provider reach and efficiency will be a necessary first step to balance the market.

Population Dynamics are Changing

By 2035, retirement aged people will outnumber children for the first time in U.S. history

The population of the U.S. is aging. By 2035, the number of people aged 65 and older will outnumber the number of children below the age of 18 for the first time in the country's history. Combined with a higher incidence of chronic disease among seniors, this creates a far greater demand for healthcare services, which will outstrip supply.

Remote care solutions can keep seniors out of higher cost, higher acuity care while also creating less disruption in their day-to-day activities

The aging population dynamic expands beyond the U.S. — the number of people aged 65 or older is projected to reach over 2 billion by 2050, with people aged 60 and older outnumbering both youths and adolescents from ages 10 to 24. This suggests the potential for greater strain on the global healthcare system, creating a need for more efficient care through technology. We forecast remote care solutions extending care into the home, giving physician's greater breadth of coverage while also keeping seniors out of higher cost and higher acuity areas of care.

At the same time, the healthcare system is experiencing an influx of younger patients — millennials will become the largest generation in 2019. This segment of patients grew up surrounded by online-enabled consumer convenience tools: online banking, e-Commerce with free two day shipping, telecommuting and online food delivery. Looking through this tech-enabled lens, today's healthcare services delivery model is an antiquated and foreign experience.

We expect the younger patient population will bring their consumer lens to healthcare choices, resulting in greater cost consciousness and an increased focus on end patient experience. Flexibility provided by telehealth fulfills this demand, as it allows for real-time access to care with minimal travel friction.

The Early Days of Virtual Care

While virtual care may seem like a relatively nascent concept, we are already in the early days of virtual care with consumer adoption of tech-enabled healthcare solutions growing at a rapid clip. Accenture's 2019 Digital Health Consumer Survey showed 29% of consumers have used some form of virtual care, up nearly 40% from 2017 usage figures.

As mentioned in the population trends above, this rapid adoption is consumer led, i.e., healthcare consumers want these changes. Today's consumers are able to fulfill many of their needs through a tap or a swipe, and are increasingly expecting their healthcare services to mirror that experience.

We cover some of the early use cases below, starting with the entryway to virtual care: telehealth.

Telehealth as an Early Application

We define telehealth as the use of telecommunications technology to deliver clinical healthcare services remotely.

We are already in the early days of virtual care, starting with the advent of telehealth. Telehealth itself has evolved, originating as a phone call-based urgent care substitute and business-to-business (B2BP) doctor solution and progressing to encompass direct-to-consumer video chat apps, remote patient monitoring, and specialty care solutions. Despite this quick evolution, telehealth itself is still a nascent industry, with domestic utilization rates in the low single digits.

We define telehealth, or telemedicine, as the use of telecommunications technology (voice calls, two-way video, e-mail, electronic communications, etc.) to deliver clinical healthcare services remotely.

The Center for Connected Health Policy (CCHP) segments telehealth into four categories: mHealth, remote patient monitoring, store-and-forward care, and live video.

1. **mHealth**, or mobile health, is defined as healthcare practice and education supported through a mobile device. Examples can range from targeted text messages to promote healthy habits, wearables, and disease outbreak warnings.

2. **Remote Patient Monitoring** (RPM) entails the use of technology to enable patient monitoring outside of a clinical setting. An RPM program will involve the collection of medical and health data then transmitting it to an external monitoring center, such as a primary care setting, hospital, or nursing facility. RPM allows for both lower cost of care from reduced readmission rates and improved quality of life for patients as it allows for greater independence.

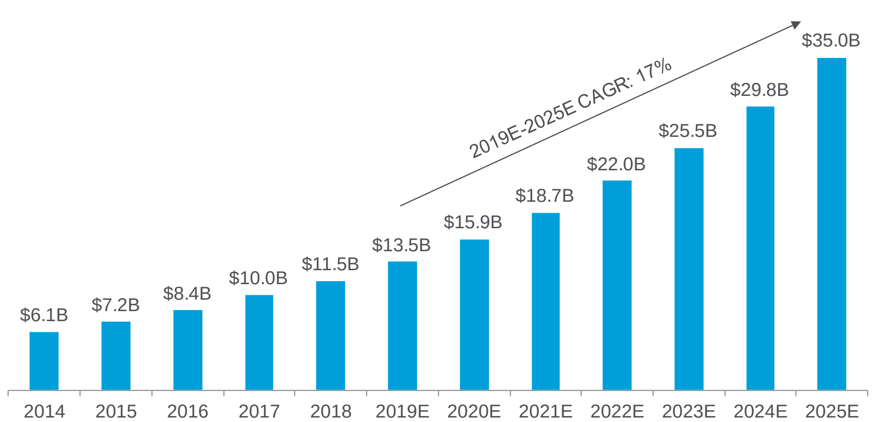
3. **Store-and-Forward Care**, or asynchronous care, entails the transmission of pre-recorded health information (i.e., photos, x-rays and text) to a provider through a secure electronic message, such as an app or an email. Treatment/services are rendered outside of a real-time interaction, making this form of telemedicine popular for specialty care where there is more limited access to specialists.

4. **Live Video**, or synchronous care, involves a real-time two-way audiovisual interaction between a patient and a provider to provide consultative, diagnostic, and treatment services. This is the definition most popularly thought of as telehealth, with audiovisual technology allowing for remote access to healthcare providers.

The U.S. telehealth market is projected to more than double over the next 5 years

Now that telehealth has established a foothold, the telehealth market is in rapid expansion mode. As shown in Figure 45 below, the U.S. telehealth market is projected to more than double over the next five years.

Figure 45. Telehealth Market Revenues (2014-2025E)



Source: Grand View Research, Statista, Citi Research

Other Use Cases

Streamlining the Exam

Pre-visit telehealth solutions enable the streamlining of in-person doctor's appointments, providing both expedited care delivery as well as cost savings by replacing manual processes with technology.

Applications of digital health solutions on the front end include electronically onboarding a patient via a portal vs. paper forms, collecting symptoms data (often with the use of a chat bot vs. an in-person clinician), and identifying potential diagnoses and treatment plans prior to the visit. In hospitals, augmented reality can be used as a navigation tool. This future solution solves important issues as, around one-third of first time hospital visitors get lost or confused at the hospital and a quarter of hospital staff report being confused about critical locations, according to Deloitte Digital.

Armed with virtual care tools, we believe providers can restore medicine to patient-facing appointments and move away from the data verification portion that has begun to dominate appointments since the introduction of electronic health records.

Lowering Accessibility Barriers

Telehealth adoption allows for broader access to care. This can range from access to primary care visits in regions where primary care physicians are more limited, to increased access to specialists despite geographic limitations. Access limitations can either drive patients to higher cost settings or worse, prevent patients from getting the care they need, which should incentivize payers to include telemedicine as part of their coverage.

No-shows due to accessibility issues are a significant but often overlooked pocket of spending in healthcare, with virtual care freeing up this spend. The impact from no shows can be staggering — a National Academies of Science study from 2005 found that ~3.6 million patients miss appointments each year, while a 2016 BMC Health Services Research study found that providers lost $4.1 billion of revenues due to no-show patients. By lowering the need to travel for appointments and eliminating the need for data gathering checkups through remote sensors and data aggregating apps, virtual care can dramatically lower this cost.

Remote Monitoring

Growth in remote patient monitoring has helped reduce cost in the healthcare system by solving for data-gathering follow up appointments and increasing real-time communications around disease progression. From a patient perspective remote monitoring also improves quality of life by reducing the amount of time needed at a hospital, allowing patients with acute conditions the dignity of a more normalized schedule.

Remote patient monitoring can improve upon care for patients with chronic conditions and reduce hospitalizations for a population that makes up the majority of hospital admissions

Remote monitoring is particularly valuable in treating patients with chronic conditions, such as diabetes and hypertension. Notably, ~60% of Americans have at least one chronic condition, but chronic diseases account for ~81% of hospital admissions. In these scenarios, rehospitalization often occurs due to gaps in communication or transparency around the patient's condition, augmenting the cost of care. Wearables that track heart rate, connected scales, and mobile apps allow for an easier two-way flow of information, keeping patient care up to date and patients out of the hospital.

The youngest patients can also benefit from remote monitoring. Every year 10-15 percent of infants are admitted to the neonatal intensive care unit (NICU), often due to preterm birth. The cost of a premature birth to payers is typically about 10x the cost of an uncomplicated birth — and a significant driver of the cost is that, traditionally, these infants spend long periods of time in the NICU until they are deemed well enough to go home. Many times, these infants are not medically complex but require key vitals, such as weight and feeding progress, to be monitored by their care team at the hospital.

Remote monitoring apps and platforms allow these patients and parents to stay connected with their care teams, providing metrics, keeping the care team aware of important trends, and allowing neonatologists to conduct virtual rounds. Proven benefits include a shorter length of stay, improved clinical outcomes, increased patient satisfaction, and far lower cost.

Remote Surgery

Robotic surgical systems were first introduced to facilitate complex surgeries in a minimally invasive manner, controlled by a surgeon from a console across the room. The advent of remote surgery answers the question: does it matter if the operating console is one room over, or one state over? With advances in connectivity solutions, the answer more and more is no.

Remote surgery and robotic surgical systems are not new, with the first transatlantic remote surgical operation completed in 2001. However, we believe advances in technology will allow for the democratization of remote surgery, making it available to the broader public.

The need for robust connectivity network technology is paramount for remote surgery adoption; in 2001, the first transatlantic surgery required exclusive private use of a connection and redundant fiberoptic ATM lines to minimize latency and optimize connectivity. With the rollout of 5G, high quality, real time data transfers will now be more easily accessible, allowing for fewer lag issues over greater distances. This could expand access to a leading surgeon beyond the reach of a car or plane, but to where ever a network connection is available—across the globe, or even to the ISS (International Space Station).

Where Can Virtualized Healthcare Take Us?

Changing Healthcare from Pull to Push Function

Longer term, we believe healthcare technology will evolve from just monitoring and producing healthcare data that can be analyzed by a clinician, to actually doing the analysis itself. This essentially will change healthcare from a pull function to a push function.

As tech evolves, it can proactively connect us with care when we need it vs. waiting for when we feel sick to contact a doctor

Healthcare services operate as a pull function today. When we feel sick we put in an inbound request to our provider systems, setting off the care management process. This has parallels to the early days of mobile email — with pull coding, the initial network communication requests for data originates from a client. In effect, a user would have to open their inbox to set off a request for their messages, resulting in some lag from the initial point of access to reading email.

In a push function, the system is always on and actively transfers messages. In the email example, this gives us active notifications on our smartphones when there are messages waiting for us. In the context of healthcare, this could mean our remote sensors or wearables detect discrepancies in our metrics, and notify us we are beginning to get sick before symptoms have progressed to a level where we are aware of it. Paired with the 2,310 exabytes of healthcare data projected to be produced in 2020, a powerful patient-centric technology can be created that keeps us healthy rather than helping us recover from illness.

The more things change, the more they stay the same: while the introduction of tech put doctors in a data-collecting role, the evolution of tech will free up doctors for care.

The shift from a pull to a push function will have broader implications on today's limited clinician capacity, freeing up time to put the humanity back into healthcare. Less time will be devoted to data collection and diagnoses, and more time can be put into care.

The Democratization of Healthcare

The evolution of virtual care has broader implications beyond the U.S. healthcare system. Virtual care will be able to democratize healthcare, bringing quality care to people in every corner of the world. Half of the world lacks access to essential health services, with broad gaps in care availability across Sub-Saharan Africa, Southern Asia and even the more rural regions of developed nations.

Virtual care can not only extend a doctor's reach across the globe, but it can help automate the front end of care through artificial intelligence, similar to an extended version of today's AI-enabled chat bots. This allows for a truly scalable entryway into the health system. Further, these automations can potentially help extend first-world healthcare knowledge around illness prevention and treatment, globally.

Barriers to Adoption

1. **Regulatory tailwinds:** The U.S. Senate passage of the CHRONIC Care Act in September 2017 shows there is regulatory momentum for telehealth. The act allows for broader telehealth benefits in Medicare Advantage plans, allows Accountable Care Organizations (ACOs) to cover telehealth, and expands the use of telemedicine for stroke and dialysis patients. Current regulation requires private insurers to include telehealth coverage across 31 states and the District of Columbia, with recent parity law expansions in North Dakota, Nebraska, and New Jersey.

2. **Regulation:** Despite recent momentum, regulation remains the greatest limiting factor for telemedicine. Current state licensing laws can prevent clinicians from practicing telemedicine across multiple state lines, while comprehensive policies for telehealth reimbursement has yet to surface due to the nascent industry's limited cost and quality data.

3. **Reimbursement:** As mentioned above, comprehensive telehealth reimbursement policy does not yet exist, with the industry only currently reimbursed in the commercial sphere. We believe further expansion into government payers is likely, with CMS recently finalizing telehealth expansion into Medicare Advantage plans. Reimbursement remains at a discount for telehealth services compared to in-person care, creating a headwind to telehealth expansion in many health systems; however, this may change over time, such as with Georgia's recent telehealth parity bill. As reimbursement becomes more liberal, we will soon reach an inflection point not only for patients, but for providers signing up for the service.

4. **Technology:** Although artificial intelligence and machine learning have already made inroads into healthcare, we believe it is still early days for the sector due to data siloing and heterogeneity. As we progress towards greater data standardization and aggregation, we expect virtual care solutions will also progress in lock step. Other technological advances, like the roll out of 5G, should help extend the reach of virtual care.

5. **Consumer awareness:** Telehealth remains a nascent industry, with comparatively low consumer engagement compared to other channels of care. Broader telehealth utilization remains in the low single digits, reflecting this.

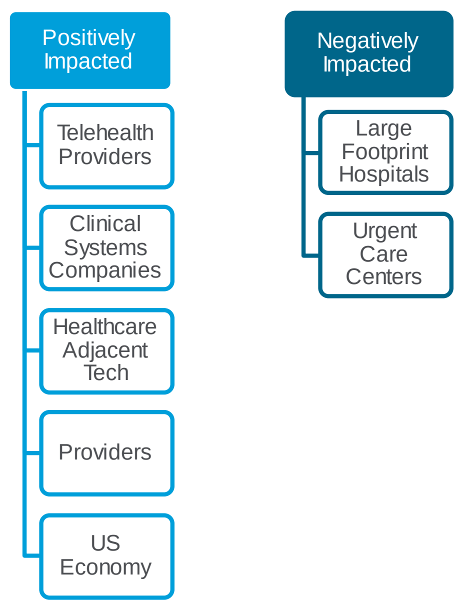
How Does Virtual Care Change the Industry?

We see the implications of virtual care as broadly positive. Domestically, the solutions increase quality of care, improve speed of care delivery, and lower cost within the health system, all while enabling a higher quality of life for patients while receiving treatment. On a global basis, virtual health solutions democratize access to care.

Depending on adoption, virtual health's greatest areas of pressure could be on health systems with a large footprint and urgent care providers. Importantly, while these care constructs could be under pressure, we do not believe it will extend to clinicians working within these systems. Given the provider shortage, it is likely that these clinicians will stay employed in more virtual-adjacent roles.

We detail the specific winners and losers from the emerging telehealth trend below.

Figure 46. How Does Virtual Care Change the Industry?



Source: Citi Research

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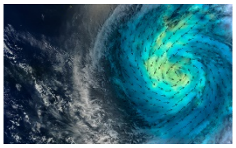

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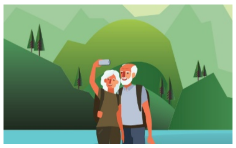

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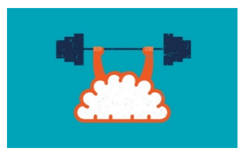

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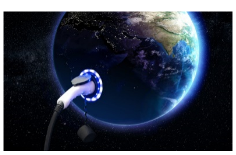

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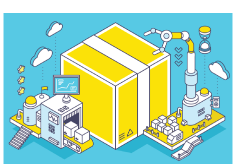

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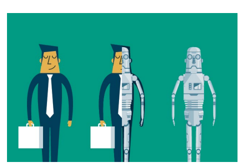

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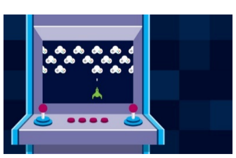

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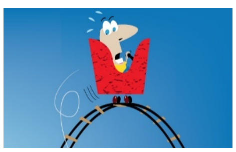

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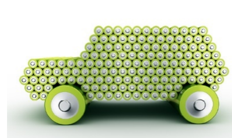

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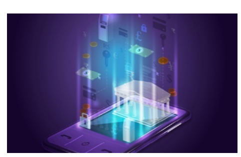

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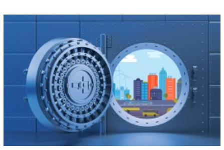

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Key Insights regarding the future of Disruptive Innovation

INNOVATION

Growing populations, rising living standards, and changing tastes are set to drive a 50% increase in the amount of food humans consume by 2050. / Digital agriculture includes a wide array of technologies which capture, process, and deliver insights from agricultural data allowing step changes in agricultural efficiency by helping farmers use their existing tools in the most efficient ways to secure the best yield.

SUSTAINABILITY

Carbon dioxide is problematic for the environment because it stays in the atmosphere for a long time, meaning prior emissions remain and are additive. / In the fight against carbon, other than simply emitting less CO_2 to begin with, CO_2 can also be removed from the atmosphere through carbon capture and storage/sequestration (CSS) and carbon dioxide removal (CDR). Carbon taxes could finance these removal pathways.

TECHNOLOGY

Despite a shift to an on-demand economy, how we deliver healthcare is still practiced in the same way as it has for centuries. / We see virtual care expanding to broader technology-enabled healthcare, spanning from urgent care all the way to chronic condition management and remove surgery – basically all the things normally happening inside the wales of a hospital, but at home.