HealthQuake Summit 2022

Summary of Presentations (Provisional Report)

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HealthQuake 2022: Summary of Presentations

Please note that this is a provisional report only and is subject to revision. The final report will include selected delegate discussion/comments and editorial inferences and comment, and may include revisions based on speaker feedback.

Wayne State University professor emeritus **David Bouwman** opened the Summit with a cogent summary of the state of innovation. Humans, he said, tend to be profit- or prestige-oriented problem solvers who build on pre-existing knowledge to innovate solutions.

Some of that knowledge is overlooked—understandably, given that the volume of new data is exploding exponentially—or misunderstood. When that happens, innovation must either wait—like the innovation of laparoscopy, which took 15 years longer than was necessary—or be hustled down blind alleys by irrational exuberance. Dr. Bouwman opined that quantum computing, for example, may turn out to be a dud, at least for application in healthcare.

The key, for innovator and investor alike, is a prepared yet open mind capable of sorting the wheat from the chaff.

Electronic Caregiver (ECG) Inc.'s chief technology officer **David Keeley** underscored the importance of the evidentiary base—the pre-existing knowledge—to his company. ECG is an innovator in the application of digital touch technologies in healthcare. The company both drives and is driven by a major societal shift in the acceptance of digital technology, a shift that was exacerbated and accelerated by the COVID pandemic.

Patients have become much more educated and sophisticated consumers of digital health, but cultural, geographical, and national policy differences affect what is expected from healthcare systems. Nevertheless, innovation has led to the acceptance of technologies we never thought people would accept. For instance, 10 years ago, allowing surveillance cameras in the home was almost unthinkable. Now, homes are festooned with cameras inside and out, making sure everything is okay.

There has also been a massive increase in the adoption and utilization of voice assistants (Amazons's Alexa and ECG's own Addison, for example) and of wearable health technology. This is all because people are more accepting of the use of technology in their everyday life in general and in their healthcare in particular.

Sometimes, innovation simply leverages pre-existing technology by applying it to previously unconsidered or new use cases and utilizing the data generated to make better healthcare inferences and decisions. But something is missing, and that is data system interoperability and analysis, especially in the context of data streams now being generated by voice assistants, cameras, and smart sensors in the home, clothing, and other wearables such as smart watches.

The goal is not just to improve medical monitoring and diagnosis but to provide the patient—the consumer—with a seamless digital healthcare experience. A lot of "single-lane" solutions are available (e.g., for diabetic, COPD, etc. patients) but ECD is transitioning to multilane and ultimately an omnilane solution that leverages the massive data streams as the systems producing them become interoperable and accessible.

Digital health technology gives consumers more autonomy in engaging with their providers and gives providers more autonomy in delivering appropriate care to their patients. ECG's augmented reality, voice-driven, virtual caregiving system deployed in the home gives patients and their remote providers the capacity to jointly manage their care while providing a wealth of data for ever more personalized care and for continuous quality improvement.

For the future, quantum computing and machine learning/artificial intelligence will increasingly handle the growing data streams and facilitate increasingly pinpoint, targeted, personalized healthcare in real time, giving the provider the ability to respond instantly with solutions exactly tailored to the individual patient.

This is a digital revolution and ECG is proud to be helping to bring it about.

The head of intelligence at Brazil's Ceará Cancer Institute (Instituto do Câncer do Ceará—ICC), **Hermano Rocha**, described the extra burden healthcare systems put on cancer patients, who must work through complex systems of providers and tests and therapies, and on providers who must work within the same systems and, in a 20-minute office visit (that's on a good day) choose from some 700 different treatment types for a patient with lung cancer.

Such complexity challenges human cognitive capacity, and it is getting worse. In 2,000, faculty at one academic medical center were found to have read an average 322 papers per year out of some 550,000 papers published that year. That is less than 0.1% of the new medical literature. It gets a bit easier the narrower the speciality, but not much, and not enough. Such complexity also leads to healthcare consuming increasingly large chunks of GDP.

No matter how you look at it, the current system is unsustainable and must ultimately collapse. ICC decided to take this bull by the horns and installed IBM Watson for Oncology, which has the cognitive capacity to read all the literature and to assess all patients based on their data and the literature, and provide the oncologist with not just one but several ranked, recommended diagnoses, therapies, and follow up prognoses.

Watson has previously tended to be used only in worst-case patient scenarios, not on all patients in a cancer center. ICC is unique in that regard. Watson does not replace the oncologist at ICC, who may see still know or see things Watson cannot and who makes the final decisions. But it has already helped ICC dramatically improve outcomes for its patients and reduced the cost of care.

ICC is working on research projects for the use of Watson in physician training and evaluation, in partnership with Harvard Medical School and Harvard School of Public Health. IBM was also a partner until a new IBM president decided to sell Watson Health. ICC promptly bought it and is working with UnitedHealth Group on fundraising to continue its research projects and further Watson's development.

Rafael Yuste, director of the Neuro Technology Center at Columbia University, noted that neurotechnology is poised to have a revolutionary impact in science, medicine, and society. It is technology that concerns the brain—the organ that generates our mental and cognitive abilities, and our behavior—it generates, essentially, our mind and our humanity.

But with few exceptions most brain diseases (schizophrenia, autism, etc.) essentially remain without a cure because we don't understand their pathophysiology. It is a dark corner of medicine in spite of the heroic efforts of psychiatry and neurology.

The reason has to do with the brain's very complexity. It has close to 100 billion neurons, each connected probably with 100,000 others. The result is a network the size of three global internets running inside our skulls on 20w of power (just enough to power a dim light bulb). Understanding brain disease by looking individually at the 100 billion neurons is like trying to watch a movie in a TV one pixel at a time, only worse.

We now know that the brain generates coordinated activity among groups of neurons. This is an emergent property not present in individual particles. Dr. Yuste's lab has developed methods not only to identify specific neuron groups or "ensembles" whose firing causes a specific behavior but also to manipulate the ensembles through an ontogenetic holographic "piano" they have developed.

Dr. Yuste and colleagues have gotten mice to lick water from a spout by playing the appropriate ensemble "chord" in their brains, effectively taking control of the perception of the animal. In short, neurotechnolgy has now broken into the brain and can decode and manipulate neural circuits at the emergent ensemble level with great precision.

This will enable the pathophysiology of schizophrenia, autism, Alzheimer's, epilepsy and other brain diseases to be uncovered and treated. There is now experimental evidence to support this hypothesis in mouse models of schizophrenia, autism, Alzheimer's, and epilepsy.

In the future, this research may ultimately lead to optical treatment of mental and neurological diseases with pinpoint precision, unlike today's pharmacological approach that doses every single cell in the body. It could also be applied to cancer or any other disease.

The chair of the Fischell Department of Bioengineering at the University ofMaryland, **John Fisher**, spoke about tissue engineering, a fundamentally simple, but in reality very complex, concept.

Craniofacial defects can be treated with autografts or biosynthetic materials, but it would be better to regrow missing tissue, whether it's craniofacial, bone, muscle, soft tissue, nerve, or vascular tissue. Bioprinting is one solution. 3D printing enables this. 3D printing has exploded over the last decade in healthcare and medicine. Prices have tumbled while the portfolio of technologies has expanded greatly, leading to its application in dentistry, surgical modeling, and medical devices, among others.

Printing technologies include stereo lithography and inkjet extrusion. The former, a form of digital light processing (DLP), uses light to harden layers of a photo-curable polymer resin to build a three dimensional object, precise down to about 20 microns. Extrusion-based printing is like building something out of toothpaste as it extrudes from the tube. The resolution is much more modest—about 100 microns at best—but it is the preferred approach to bioprinting, which Dr. Fisher defined as printing cells embedded in a gel.

Extrusion printing takes minutes, vs. hours for DLP printing. It can be applied to cardiovascular, bone, cartilage, dermal, and the nipple areolar complex. A lot of work is under way to address the impacts the printing process has on the viability and ultimate functionality of cells. Culturing the tissues in vitro requires bioreactors to supply oxygen and other nutrients. Bioreactors range from simple flow chambers and microfluidic systems to complex multi-chamber reactors for high volume.

Dr. Fisher's lab has developed and applied such technologies to produce articular cartilage that worked well in rabbits, bone tissues engineered for craniofacial defects, and placental organoids for research into placental biology and its impacts on the developing fetus. It has also bioprinted the nipple areolar complex for women following mastectomy (tissue flaps tend to resorb and many women either do nothing or have a nipple tattoo'd on their chest.)

Commercialization of tissue engineered products and approaches (the nipple areolar complex is a case in point) is hampered by concerns about its complexity. Industry wants simplicity to reduce risk. For that reason, the simpler biomaterials-based approaches may continue to lead over the next decade but cell based products will continue to develop along with the infrastructure to support their complexity. In particular, machine learning will drive both materials development and tissue development and is key to overcoming the complexity challenge.

Vittorio Sebastiano and his colleagues in academia and at Turn Biotechnologies, which he co-founded, are working to reverse the process of cellular tissue and organ aging to achieve longevity or, rather, healthy longevity, This is not just good for the individual, but is necessary for society. Its success will greatly impact individual quality of life, society as a whole, the healthcare system, the pension system, and so on.

Modern medicine has succeeded in slowing down the aging process to some extent but at the expense of longer periods of frailty. Turn Biotechnologies aims to stall the process of aging or even reverse it. Helping people become younger will eliminate many age-related diseases and conditions.

Their method centers on the epigenetic program of cells. Genetic code comprises the words produced by a four-letter alphabet, providing basic instructions to the cells. Epigenetics provide the grammar or syntax—the way the words are put together in a meaningful fashion to have a meaningful message. The cells in our bodies are genetically identical, but brain cells are very different from (say) liver cells because the epigenetic program instructs some cells to turn on the liver genes and turn off neuron genes, and vice versa. They use tame alphabet and the same words, but a different grammar.

Over time, the epigenetic program becomes dysfunctional. We humans gradually transition from a very tightly regulated functional epigenetic program in our younger cells (our younger selves) to a loosely controlled and dysfunctional epigenetic program in older cells (our older selves). The good news is that unlike genetic code, which is digital, epigenetic code is analog, non-binary, with an infinity of programmable, or “tunable" conformations.

We age, but the human species does not. There is no progressive accumulation of aging of the species with every generation. We are all born at age zero because our germ cells are protected from aging by a mechanism that wipes out aging features that would otherwise accumulate over time. That mechanism works continuously in germ cells and in very early embryonic stem cells, which undergo massive epigenetic reprogramming as they grow. This system has worked remarkably well across all species over millions of years. Turn's technology builds upon this insight.

The cloning of Dolly the sheep in the 1990s was conceptually simple. The team at the Roslin Institute removed the nucleus from the egg of a female donor and replaced it with the nucleus from an adult cell taken from the mammary gland of a six-year-old sheep. THe result was an embryo which, when transferred into a surrogate mother, was able to develop into a newborn lamb. The donor cell was from an older sheep, yet Dolly was born an infant. This provided the fundamental basis for Turn's hypothesis. (It is true that Dolly died young, but it was because of telomere shortening, an essentially technical problem that was solved in subsequent clonings.)

But while the epigenetic signature of aging can be reset completely to zero, the process is inefficient. Shinya Yamanaka won the Nobel Prize in 2012 for having demonstrated six years earlier how to turn adult cells (he chose skin cells) back into an embryonic state simply by over-expressing a set of four genes. The theory then was that you could simply take anyone’s cells and reprogram them back to the embryonic state in order to create new skin, or liver, or heart, etc., cells, grow and multiply them in one of John Fisher's bioreactors, and print them into the form of the appropriate organ using his bioprinters, and finally have a surgeon transplant it into the patient.

The problem is that reprogramming the cells to an embryonic state, as happened with Dolly the sheep, changes the identity of the cell. At age 0, a cell has not yet developed an identity as a skin cell or a liver cell. A way was needed to decouple those two things—to rejuvenate the cell without impacting its identity as a skin (or liver, etc.) cell.

Turn found a way by injecting an mRNA cocktail into an old dysfunctional cell. The cocktail was optimized to make a younger version of the cell. Everything about the cell was rejuvenated with the exception of the telomeres, which were not elongated. In published papers Dr. Sebastiano and his colleagues have shown that their method works in four different human cell types, and they are working on many more.

The potential of the technology can be seen in an experiment with satellite cells, a type of muscle stem cell that has the very special capability of self-renewal, making copies of itself to repair an injury in torn muscle. Turn developed a way to isolate satellite cells from the body and keep them in culture for 48 hours, retaining this ability to self-renew and differentiate. They did this in vivo in mice and in vitro in human muscles. They divided each into two groups, untreated and treated. The target cells in the treated groups were treated with the mRNA cocktail for two days then transplanted into an immunocompromised mouse with muscle damage. A month later, upon measuring the muscle for contractility, the researchers were

were just blown away to find that the muscle in the treated mice was as strong as muscle in young mice.

Turn Biotechnologies has demonstrated that it can rejuvenate cells back to a more functional state. It recently closed a fundraising round and attracted three major players to join its team—a stamp of recognition of the potential of its technology.

Wrapping up the Summit presentations, **Mike Tanji**, director and executive officer of the Alliance Forum Foundation and DEFTA Partners, joined us from Japan to describe the mission of DEFTA Partners and a new form of capitalism they call public-interest capitalism.

Some corporations, he showed, are now bigger than countries in terms of their economic and social influence and play a huge role in the world economy and society. In traditional shareholder capitalism, all of their profit goes to shareholders in the form of dividends and buybacks, which makes it very difficult for the money to be spent on innovations.

There has also been a decrease of the labor share of the value their labor has added to the corporation. The gap in earnings between the top 1% and the bottom 90% is already wide and getting wider. The middle class barely exists any more. All this may lead to crime and provides fuel for violence and terrorism.

Capitalism is based on the concept that companies are owned by their shareholders, but the reality is that a company's profit is dependent on its customers, suppliers, employees, and the broader community that provides the basic inputs—the land, the water, the roads, and so on. In that sense, companies are public institutions, and that is what underlies the concept of public-interest capitalism.

For public-interest capitalism to be realized, management should foster entrepreneurship and tolerate greater risk, take the long term view for sustainable growth, and most importantly distribute profits fairly (not necessarily equally) to all who support the company: Employees, suppliers, customers, the community, and —of course—shareholders.

In short, public interest capitalism is based on the concept that a company is a public institution which contributes to society through its business. Its adoption will lead to more robust middle class growth globally and reduce the wages gap.

A drastically revised Statement on the Purpose of a Corporation by the Business Roundtable in 2019 said that "While each of our individual companies serves its own corporate purpose, we share a fundamental commitment to all of our stakeholders." It defined stakeholders as customers, employees, suppliers, communities and shareholders. The theme of the World Economic Forum in Davos in 2020 was also "Stakeholder Capitalism" and the CEO of Salesforce announced that "Capitalism as we have known it is dead."

DEFTA Partners chairman George Hara advised the Japanese prime minister in 2013 that Japan's national goals would be better served by public-interest capitalism and urged the adoption of a policy goal to make Japan the first nation in the world where every person lived a healthy life until his or her last moment. Innovation in technology, policy, and the ecosystem is vital to achieve this goal.

DEFTA Partners' investment fund seeds early stage technologies in the US, Europe, and Israel, as well as in Japan. It has 31 portfolio companies of whom more than 20 are in the US. None has yet successfully exited, but neither has any gone under. DEFTA Partners' efforts have also resulted in a change in the law of Japan that will stimulate innovation in regenerative medicine. The partners do not look for ROI from the fund's investments. They know that a high return is indeed likely, but is not the Fund's primary purpose.

Prime Minister Kishida has introduced the concept of "New Capitalism" as the policy container for what is essentially public interest capitalism.

Dr. Tanji found the innovative technologies discussed at HealthQuake to be really fascinating. He personally does not care to live a long life but he does care that it is a happy and healthy life. Cancer, dementia, and other age-related diseases do seem vulnerable to gene therapy and regenerative medicine and other new technologies.

However, market realities and government regulation, even in the US, make funding difficult for even the most fascinating technology. FDA approval generally requires very expensive and time-consuming clinical trials, adding greatly to risk. Major investment usually only comes in the middle and late stages when the trials have succeeded and FDA approval granted. In such cases an IPO is almost inevitable, followed by merger with or acquisition by somebody bigger. A high ROI is essential. There is not much risk taken at this level.

Competition is another market reality. There are so many different technologies aiming at the same result. It can be very difficult for investors to understand the differences among them. Dr. Tanji tells his students to be sceptical of claims that a new technology is unique. There are 7 billion people in the world, he notes, and you can bet that others have had the same idea as you. The important thing is to try hard, not give up, and take the long view.

Academic research is often hard to commercialize because academic researchers don't have knowledge of the engineering and manufacturing requirements that lie beyond the prototype, no matter how successful the prototype is.

Management is also very important. Get-rich-quick management for the short term will leave a technology stranded. Management must plan for the long term, understand the market realities, and be prepared to change the technology if that is what the market wants. It takes time, patience, and motivation to get a technology into the market and at the bedside. Some markets (countries) may be more appropriate than others in the case of healthcare technologies.

The most important and dramatic technology changes are occurring in DNA sequencing, gene editing using CRISPR cas9, and bioinformatics, driven by IT/AI/robotics/biotech systems and integrated in a "biofoundry."

But in the end, the goal of a healthy and educated middle class in all regions, regardless of religion or race, is the mission of the Alliance Forum Foundation and DEFTA Partners.