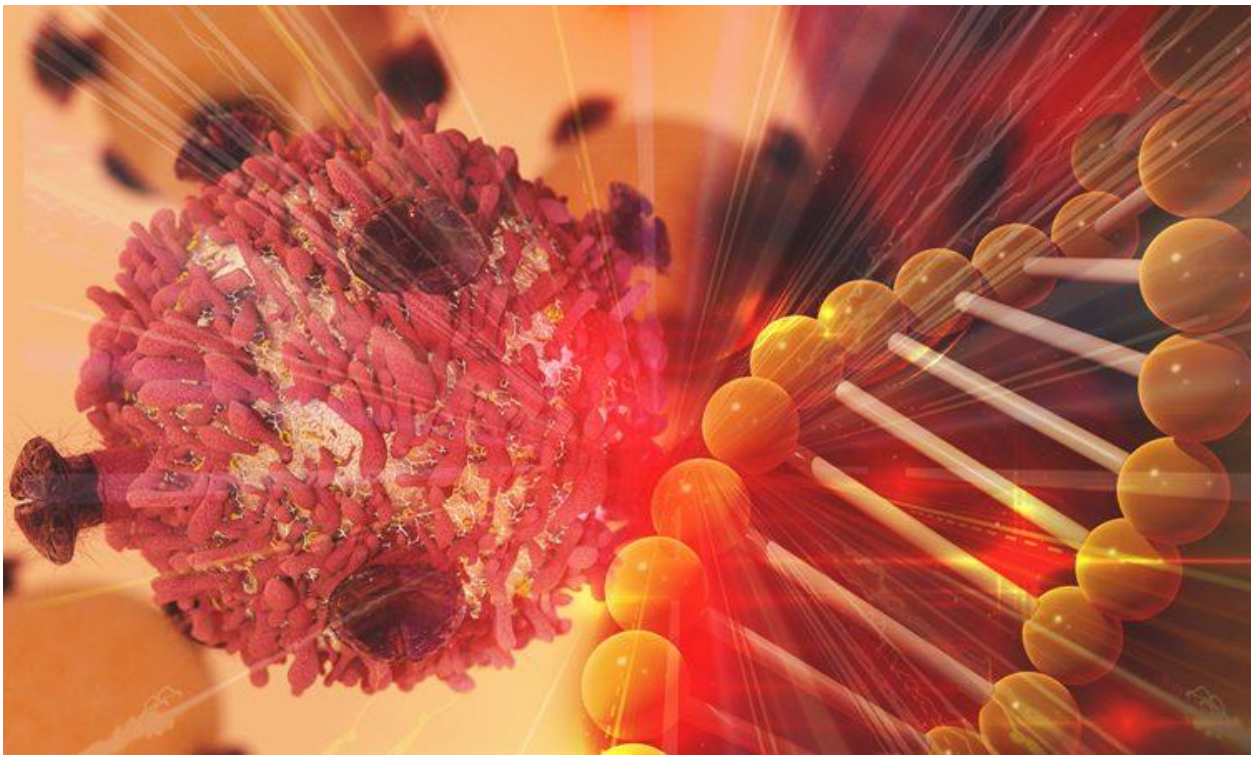


How India can lead the charge in curing cancer

—and build a trillion dollar medical industry

Vivek Wadhwa — Carnegie Mellon University, College of Engineering

Keith Flaherty — Harvard Medical School

Nabeel Bardeesy — Harvard Medical School

Siddhartha Mukherjee — Columbia University, Irving Medical Center

Mitesh Borad — Mayo Clinic

James Doty — Stanford Medicine

thinkINDIA

Contents

Cancer is the second-leading cause of death globally, taking 9.6 million lives every year, according to the World Health Organization. In 2018, there were 1.6 million new cases of cancer in India, with 1300 lives lost every day. Yet, whilst Indians are at the forefront of medical research in the West, India as a country is a laggard in researching and curing the condition; the vast majority of its cancer patients receive no or inadequate treatment; and its researchers make few contributions to the field.

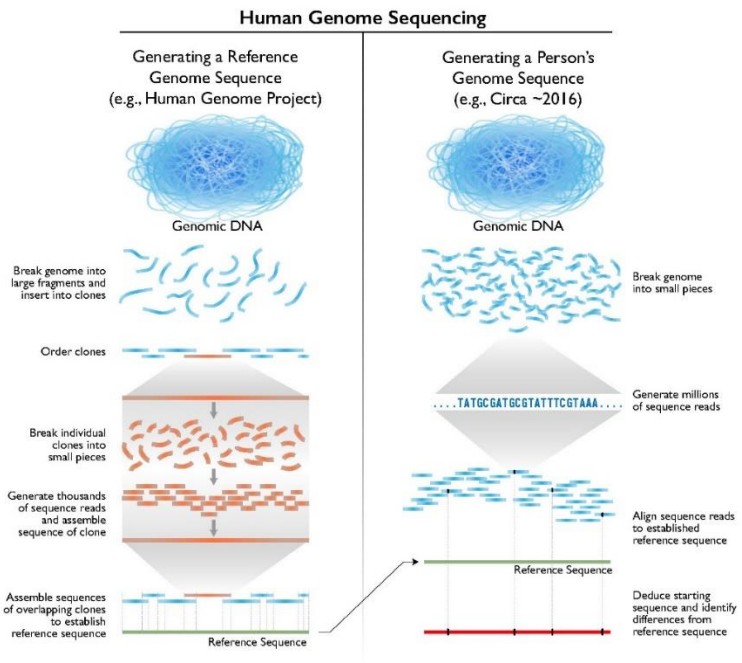
This can all change. Thanks to advancing technologies, India has the potential not only to provide its people with the most advanced medical care but also to cure cancer itself. It can lead the world in research and innovation and lay the foundation for a trillion-dollar medical industry. It can also create a platform upon which to research its traditional sciences, in particular Ayurveda, which may hold the keys to long-term health and longevity by strengthening the microbiome. All of this can be done by 2025 with an investment comparable to the cost of the Mangalyaan and Chandrayaan-2 missions.

To achieve this, we propose that India launch the largest clinical-research experiment in world history and use technologies such as genomics, synthetic biology, sensors, 3D printing, and AI to analyse data and develop treatments. Not only will this provide direct benefit to a hundred thousand cancer patients; the discoveries that emerge will benefit billions and incidentally will lead to the creation of hundreds of startups and fuel global innovation in the medical sciences.

Technologies that are making a cure for cancer possible

Next-generation sequencing

There is a growing army of small molecules and compounds available to treat cancer, from commonly available and off-patent drugs to fusion inhibitors, tyrosine kinase inhibitors, and checkpoint blockers. Yet they only work on a small proportion of patients, and matching them is essentially guesswork. With next-generation sequencing (NGS), we can better identify the broader landscape of somatic mutations, and understand what works where.



Since the Human Genome Project reached completion in 2003, sequencing technology has advanced exponentially. The field is now entering an era of so-called "third generation" NGS, capable of large-scale, real-time sequencing at a fraction of the original cost. Fifteen years ago, the Human Genome Project cost just shy of 3 billion dollars. Now, scientists can run samples for whole-genome sequencing for as little as US$400; soon, it will cost as much as a blood test. Targeted sequencing using small gene panels is even more effective today for routine use and can provide more clinically actionable results at a fraction of this cost.

This opens up an era of crowd-sourced, data-driven, participatory, genomics-based medicine. Today, medicines are prescribed on a "one size fits all" basis. When a particular medication causes a significant negative reaction in a small part of the population, it is prevented from being available to anyone. In the future, expect to see doctors prescribing and selecting the most patient-appropriate medicines based on a person's DNA (the field of "pharmacogenomics").

Cancer is a "genomic disease". Instead of classifying cancers by the tissue where they are first detected — colon, breast, or brain — it can be categorized by its genomic characteristics and treatments selected based on the signature of different mutations. This approach enables treatment of patients by the most effective medicines and minimization of undesirable side effects. Based on recent experience in the largest genomically-guided clinical trial mounted to date, 18% of patients could be directed to US FDA approved therapy based on NGS, and an additional 18% assigned to investigational therapies already showing promise in specific genetically-defined subgroups. These percentages are rising every year, but shed light onto populations with particularly high unmet need.

In 2015, the potential for "delivering the right treatments, at the right time, every time to the right person" inspired President Barack Obama to launch an initiative called "precision medicine". The initiative called for public–private collaborations to collect information about and sequence the genomes of a million Americans and had a budget of $130 million. This budget was increased to $290 million in 2018, and the research programme was renamed "All of Us". For the full project, which will run for a decade, Congress has authorized $1.455 billion. Additionally, Congress passed the 21st Century Cures Act in 2016, authorizing the NIH to spend $1.8 billion to fund the Cancer Moonshot, which aims to eliminate cancer.

As of summer 2019, All of Us had enrolled only 175,000 participants, fewer than one-fifth of the total number of participants the project is aiming for. The NIH expects to sequence 20,000 genomes in 2019, and only limited data will be available for analysis by scientists. This program is not offering treatments or cures to patients, but just gathering basic data.

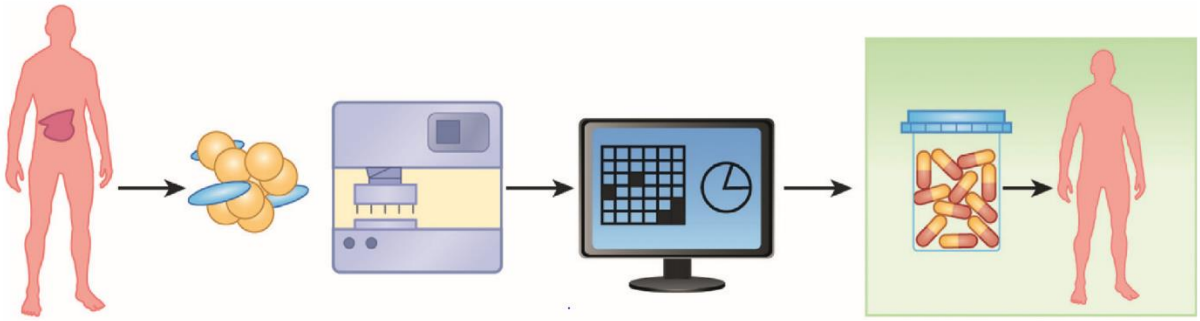
India has an opportunity to leapfrog U.S. initiatives and find a cure before the data-gathering projects are halfway complete. It can do all of this for less than 1/10 of what the U.S. is spending just in data-gathering.

3D patient-derived organoids

Advances in stem-cell biology have heralded a revolution in biology and medicine. The most exciting development has been the creation and use of three-dimensional (3D) structures, known as organoids, which emulate development and tissue organization and resemble organs in the body.

Organoids are 3D cell-culture systems that replicate some of the structural and functional characteristics of an organ. They provide the ability to study organ-level biology in models that mimic human physiology more closely than the 2D cell cultures or non-primate-animal models that have been traditionally used by researchers. They allow for testing thousands of drugs to find ones that might work in these organoids before deploying them on patients.

Organoids can be grown with high efficiency from patient-derived healthy and tumour tissues. They are developed by explanting dissociated patient-derived cells into a semi-solid extracellular matrix and expanding these cells in growth-factor-enriched medium. They have the distinct advantage of growing in three dimensions, and they often recreate the endogenous architecture of the tissue from which they were derived, reproducing the in vivo tumour environment more closely than 2D cell cultures do.



Personalized Cancer Models for Target Discovery and Precision Medicine

Carla Grandori and Christopher J. Kemp

Trends in Cancer

Organoids have an astounding success rate in predicting which drugs will work on the patient, as documented in a 2018 paper in *Science*, "Patient-derived organoids model treatment response of metastatic gastrointestinal cancers". It found them to have 100% sensitivity, 93% specificity, 88% positive predictive value, and 100% negative predictive value in forecasting response to targeted agents or chemotherapy in patients. Compare this with the 3.4% historical success rate of oncology clinical trials.

Once created, organoids also last longer than patient tissues or cells grown in most other test media. In a study of liver cancer, human primary liver-cancer–derived organoid cultures for disease modelling and drug screening 3D organoids maintained the histological architecture, gene-

expression patterns, and genetic makeup of the original parent tumour for nearly a year after in vitro expansion.

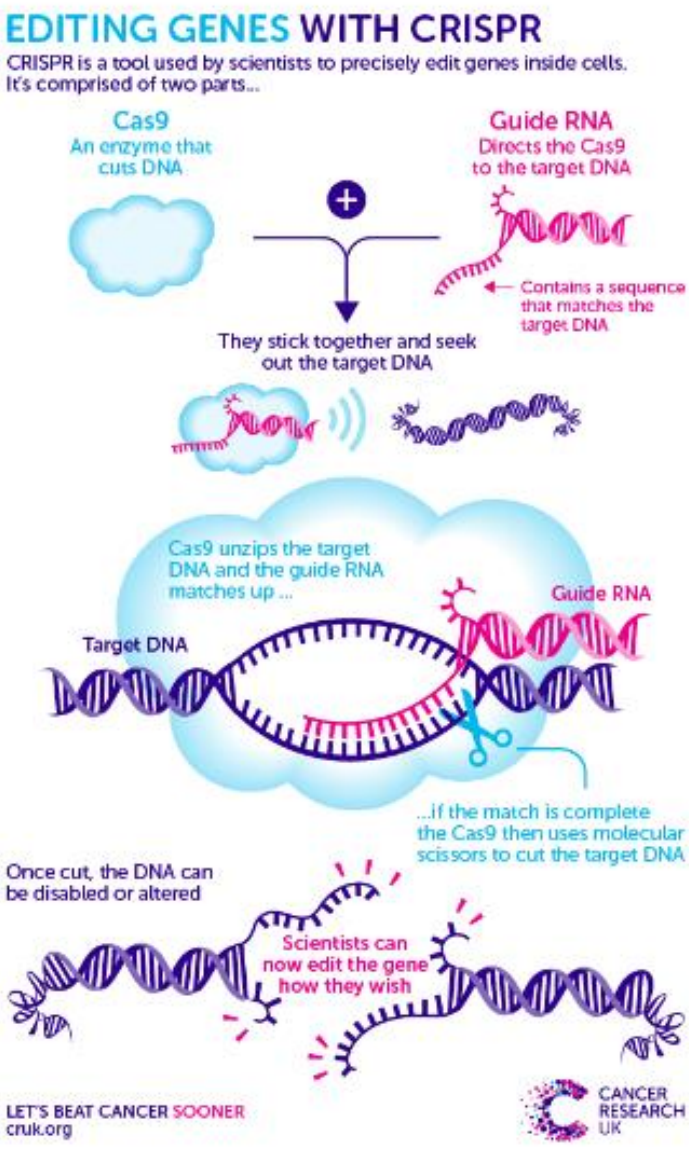
The challenge for 3D organoids lies in testing immunotherapies. An immune response is dependent on the immunogenicity of tumour cells: the ability of an antigen or epitope to provoke an immune response. In tumour cells, this is partially determined by antigens that result from mutations (called neo-antigens). Testing immunotherapies with organoid-like structures requires the replication of the immune system and structural microenvironment, which is extremely difficult.

Farcast Biosciences, formerly known as Mitra Biotech, which has its R&D team in Bangalore, says, however, that it is making significant headway with its CANscript platform, "a human, immune-relevant ex vivo model that allows researchers and drug developers to understand the performance of novel agents, such as oncolytic viruses, in human tissue, providing an informed approach to clinical development and patient response". Farcast claims to recreate the in vivo tumour microenvironment, maintaining the heterogeneity of the tumour and preserving its immune compartment. When this works, it will exponentially accelerate progress toward a cure for cancer.

With organoids, India could safely test the most advanced drugs on the tumours and provide patients with treatments that have a very high chance of success. It can create the largest and most comprehensive clinical testbed of tumours and become the global epicentre of medical research.

Genome editing with CRISPR

One of the most powerful of new medical technologies is CRISPR: clustered regularly interspaced short palindromic repeats. Discovered by scientists only a few years ago, CRISPRs are elements of an ancient system that protects bacteria and other single-celled organisms from viruses, acquiring immunity to them by incorporating genetic elements from the virus invaders. CRISPRs evolved over millions of years to trim pieces of genetic information from one genome and insert it into another. And this bacterial antiviral defence serves as an astonishingly cheap, simple, elegant way to quickly edit the DNA of any organism in the lab.

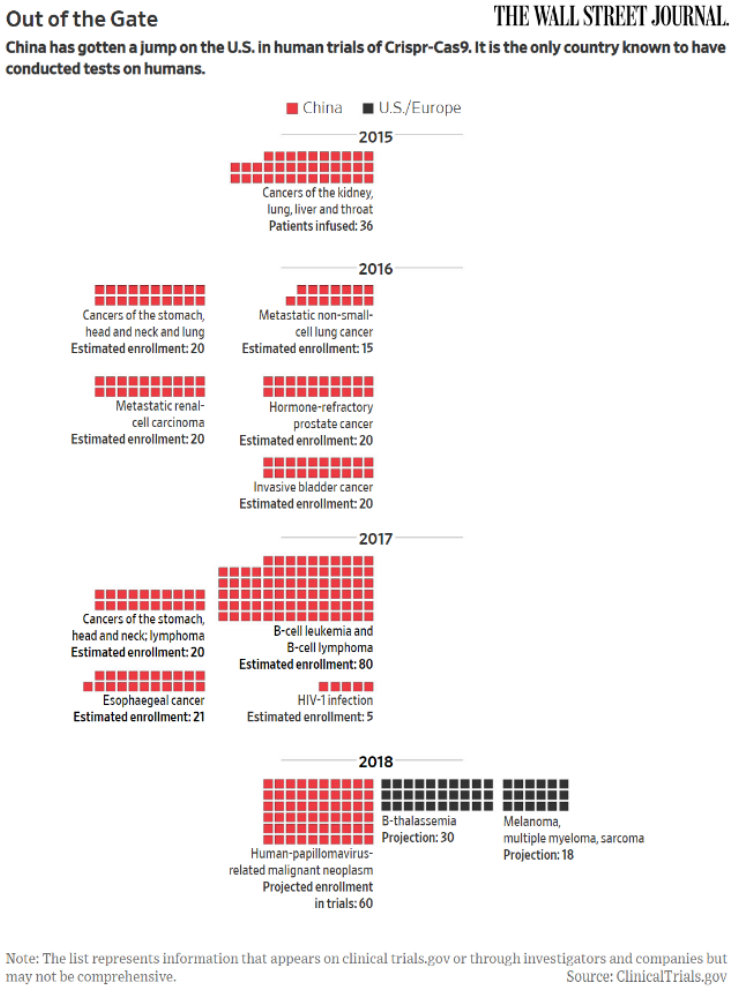


Until recently, experimenting with DNA required sophisticated labs, years of experience, and millions of dollars. The use of CRISPRs has changed all that. CRISPRs work by using an enzyme — Cas9 — that homes in on a specified location in a strand of DNA. The process then edits the DNA to either remove unwanted sequences or insert payload sequences. CRISPRs use an RNA molecule as a guide to the DNA target. To set up a CRISPR editing capability, a lab only needs to order an RNA fragment and purchase off-the-shelf chemicals and enzymes — costing only a few dollars.

Because CRISPR is cheap and easy to use, it has both revolutionised and democratised genetic research. Thousands of labs all over the world are experimenting with CRISPR-based editing projects. China has taken the lead, largely because it lacks the regulations and moral constraints that other countries abide by. Its largest applications are in agriculture, but researchers there are also applying the technology on a large scale in animals, including the altering of pig organs for human transplants. And China is aggressively exploring genome editing in medicine, with a particular focus on cancer.

CRISPR in cancer

Researchers at Sichuan University in China were the first to inject a cancer patient with cells that contained CRISPR-edited genes in October 2016. An oncologist at Sichuan University in Chengdu delivered the modified cells into a patient with aggressive lung cancer as part of a clinical trial at the West China Hospital.



The Wall Street Journal reported in January 2018 that at least 86 cancer patients in China have had their genes edited. This number is likely to be in the thousands by now. In the U.S., the first clinical trial to use CRISPR in a cancer treatment began in September of that year at the University of Pennsylvania. A patient's T-cells, a type of immune cell that circulates in the blood, were altered to make them more efficient at fighting certain kinds of cancer cells. There are 19 such studies listed on the U.S. government's clinical-trial database as of October 2018.

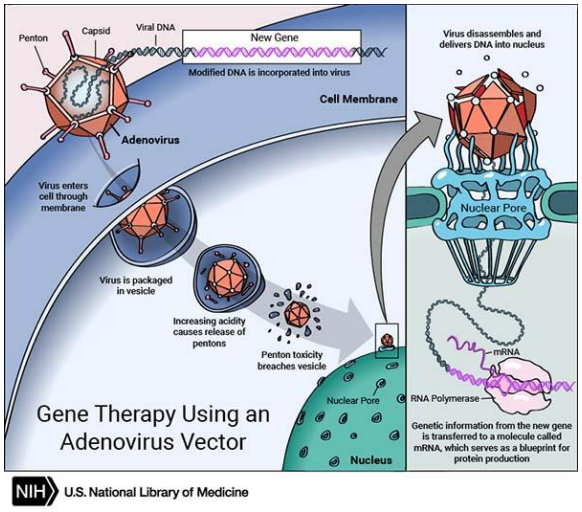
The T-cells are typically filtered out of a patient's blood and modified using CRISPR in the laboratory. They are then reintroduced into the patient's body via injection to target cancerous cells and reduce tumour growth.

Other applications of CRISPR in cancer research and treatment include modelling patient cancers by editing specific genes using CRISPR-Cas9 in vitro to create test beds, to identify new and relevant cancer targets, to understand how cancer drugs actually attack tumours, and to engineer viruses that attack cancerous cells.

With the cost of the core technologies being so low and widely available, with mathematical and engineering skills being abundant in India, and with the large test beds that we are proposing that India create, there is nothing to prevent India from leapfrogging both China and the U.S. in using gene editing technologies to treat disease — and doing so in a highly ethical way.

Cell and gene therapies

Advances in synthetic biology are enabling the development of gene and cell therapies which bring the promise of new treatment modalities for incurable or difficult-to-treat diseases.



Gene therapy introduces genetic material into cells to compensate for abnormal genes or to make a beneficial protein. The transferred genetic material changes how a single protein or group of proteins is produced by the cell. Cell therapies transfer intact, live cells into a patient. The cells can originate from the patient (autologous cells) or a donor (allogeneic cells).

Recent FDA and European Medicines Agency approvals in these technologies have been recognized as watershed events. But the costs are beyond affordable for the vast majority of patients. For example, Bluebird Bio was granted the go-ahead to market its gene therapy for the blood disorder β-thalassemia. It costs $1.8 million. Spark Therapeutics received FDA approval for the first gene therapy to treat an inherited disease, a form of congenital blindness, and it costs $850,000—or $425,000 per eye. These can prevent a lifetime of suffering, but only for the very rich.

This current paradigm is anti-patient, unaffordable, and requires the arduous movement of patient specimens in and out-of-care locations.

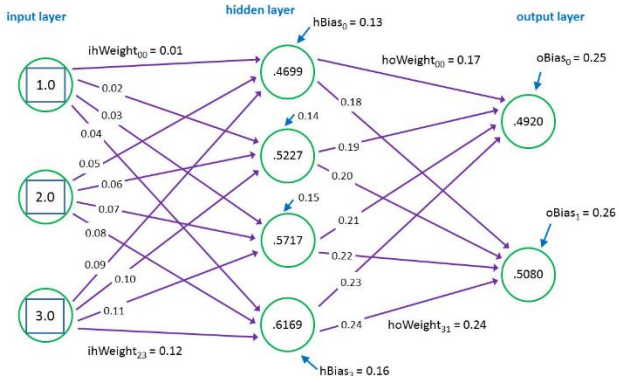
India has the opportunity to create an end-to-end (discovery to implementation) paradigm, perform scientifically cutting-edge and provide ethical and affordable solutions in cell and gene therapies. What is needed is a model akin to that of Aravind Eye Hospitals, which emulates the service efficiency of McDonalds and reaches millions of people.

Aravind began performing surgeries on a large scale with treatments being free or heavily subsidized for the poor. After perfecting new treatment methods in its hospitals, it began sending doctors to remote villages to conduct eye camps. Aravind says that its unique assembly-line approach increases productivity tenfold. The organization performs nearly half a million eye surgeries or procedures every year and has helped more than 56 million patients to date. This is the scale at which cancer needs to be treated.

Artificial intelligence and data

An analysis published in *Nature* of roughly seven million records in the PubMed database of peer-reviewed biomedical and life-sciences literature revealed that there are 147,978 connections between 322 symptoms and 4,219 diseases and that these represent 98.5% of all symptoms and 95.0% of all diseases. The authors of the study of the Human Symptoms Disease Network found that the symptom-based similarity of two diseases correlated strongly with the number of shared genetic associations and the extent to which their associated proteins interact — and that the diversity of the clinical manifestations of a disease can be related to the connectivity patterns of the underlying protein interaction network.

In other words, symptoms, diseases, genes, and proteins are all linked in a complex web. The key to curing disease may lie in the analysis of these data for correlative patterns. Human beings have difficulty in seeing such complex patterns, but this is what Artificial Intelligence (A.I.) excels in.



A.I. programming techniques use neural networks, which are modelled on the human brain, in which information is processed in layers and the strength of connections between these layers depends on what is learned. This is called deep learning, because of the increasing numbers of layers of information that are processed by increasingly faster computers. These enable computers to recognize patterns. As they are exposed to more training data, they become more accurate and begin to see things that humans can't.

The A.I. learning techniques are broadly dichotomized into *supervised* and *unsupervised* learning. In supervised learning, a labelled dataset of inputs and outputs is used to train the system. The algorithm attempts to learn a general rule that maps input to output. Supervised learning algorithms can learn patterns in data for classification and regression; unsupervised learning algorithms use unlabelled data with the goal of discovering structure in the data. Unsupervised learning algorithms are often used to simplify or organize data.

A.I. enables the analysis of vast heterogeneous datasets to diagnosis disease burden, predict patient outcomes, and tailor disease management. It can also be used in smartphone apps and wearable devices to develop "digital biomarkers" that can explain, influence, and predict clinical outcomes.

A.I. and cancer: seeing better

One of the most popular applications of A.I. today is in image recognition, which confers on a machine the ability to interpret the input received through computer vision and categorize what it "sees". Image recognition is being used to develop self-driving vehicles, mobile check deposit, and recognize people in photos.

Studies have demonstrated A.I.s' ability to classify malignant skin-cancer lesions with higher sensitivity and specificity than a panel of 21 board-certified dermatologists. The ability has been used to detect polyps during colonoscopy, and breast malignancies in screenings, at close to human

accuracy. It has also shown promise in detecting radiographic anatomical features of malignancies with a better accuracy than clinicians can reliably achieve. Whilst clinicians have found extranodal extension of tumours in the head and of neck-cancer lymph nodes notoriously difficult to diagnose radiographically, an A.I. model demonstrated greater than 85% accuracy in identifying it on diagnostic, contrast-enhanced CT scans. Google's Lymph Node Assistant algorithm demonstrated 99% accuracy in spotting features of tumours that have metastasized—which human pathologists overlook in as many as 62% of the cases when under time pressure.

A.I. and clinical outcomes

Various studies have shown that the analysis of electronic health records can significantly advance clinical research and better inform clinical decision-making. An analysis of Mount Sinai Hospital records was able to predict the development of a variety of diseases, including cancers of the prostate, rectum, and liver, with 93% accuracy over all. An analysis of 1.1 million medical records from the State of Maine identified nearly 54,000 people who were at high risk of getting lung cancer and would benefit from preventive care.

A.I. can also help predict cancer-treatment toxicity and identify the biochemical pathways in the tumour cells that predict sensitivity or resistance to immunotherapies. In one study, machine learning was used to predict side effects of polypharmacy combinations based on databases of protein-protein and drug-protein interactions. In another study, scientists used machine learning to analyse gene sequences and molecular data from breast tumours in order to reveal crucial differences among cancers that had previously been lumped into one type. They found that two of the types were more likely to respond to immunotherapy than others.

Cleveland Clinic is using machine learning to combine medical scans and electronic health records, generating personalized radiation therapy dosages for cancer patients. Dosing guidelines in traditional therapies do not take specific information about a patient's individual risk factors or tumour characteristics into consideration. Cleveland Clinic uses the patient's medical-imaging data and clinical risk factors to determine a unique radiation dose for each patient. It claims that this has reduced negative side effects for patients and reduced treatment failures to less than 5%.

The key to advancing these technologies is to gather more data, and this is one of the objectives of the grand experiment we are proposing to India. The more data available for analysis, the better the A.I. algorithms become and the sooner scientists can develop revolutionary treatments.

3D-printing medicine

3D printing is being used produce a wide variety of products, including toys, clothing, cars, and even houses. And it has been used to create personalized prosthetics, dental implants, and artificial organs. It also holds incredible promise for producing bespoke medicines.

In 2015, Aprecia Pharmaceuticals produced the first 3-printed tablet that was approved by the FDA. It reformulate an anti-epileptic medication, Levetiracetam, by laying down thin sheets of powdered medication and droplets of water-based liquid that bind these layers together at a microscopic level, resulting in a highly porous structure that cannot be achieved via traditional manufacturing. This structure causes the pill to dissolve in seconds upon contact with saliva, helping patients who can't swallow pills. Not all drugs suit this method of delivery, but there are other approaches to 3D-printing medicines that can.

In a paper published in *Science Magazine* in January 2018, "Digitization of multistep organic synthesis in reactionware for on-demand pharmaceuticals", researchers at The University of Glasgow detailed a method that enables a 3D printer to synthesize pharmaceuticals and other chemicals from simple, widely available starting compounds fed into a series of water bottle–size reactors. This could enable the synthesis of almost any compound — anywhere in the world.

A 3D-printed reactor makes medicines on demand.
SERGEY S. ZALESSKIY AND LEROY CRONIN

As the authors explained, "The manufacture of active pharmaceutical ingredients (APIs) is vital for modern health care, yet critical drugs are regularly manufactured for a finite period in a limited number of sites. The manufacture of chemical products — whether bulk, fine, or specialty chemicals, such as APIs — is currently based on a model whereby a central plant is exclusively designed for the manufacture of the product, or range of products, sold by that particular company". They proposed a concept whereby the large-scale manufacturing process of complex fine chemicals, such as APIs, is augmented by distributed, point-of-use manufacturing in self-contained cartridges of medicines fabricated using 3D-printing technologies.

Such an approach could produce 3D-printed "polypills" that combine multiple drugs in fixed-dose formulations such that each drug has a unique release profile — some releasing upon ingestion, and others taking much longer to dissolve and enter the bloodstream of the patient.

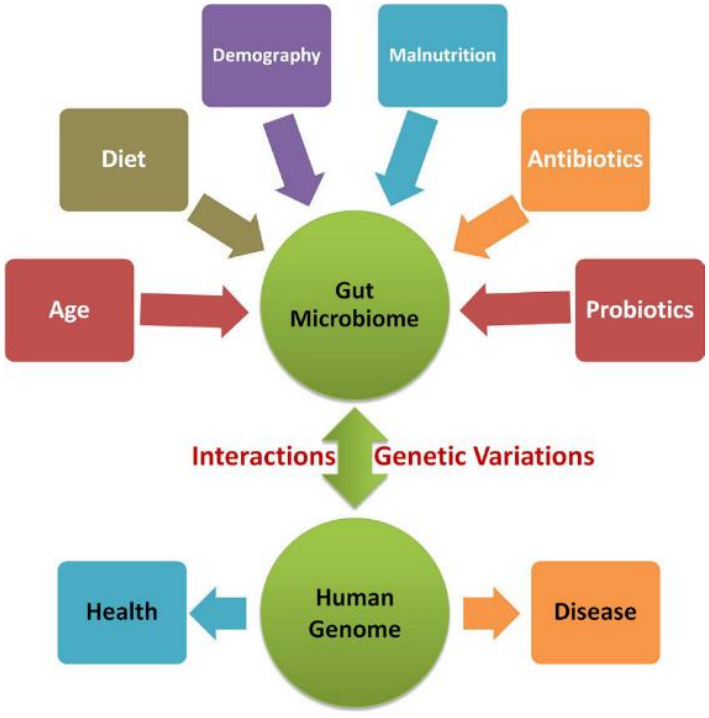
Technologies such as this would allow custom formulations of different combinations of cancer (and other) drugs and remove dependencies on pharma companies. India could provide the most advanced drugs in combinations and dosages suiting patients individually

Microbiome: Taking science back to the wisdom of Ayurveda

The next big medical frontier is on the horizon: our microbiomes, the bacterial populations that live inside our bodies. We may think we are just made up of cells, but in reality there are somewhere between two and ten times as many microbes in our body as human cells. The microbiome may be the missing link between environment, genomics, and human health.

Many children are born with genetic predispositions to type-1 diabetes. Though some of those infants become diabetic in their earlier years, others do not. A key reason for this may lie in the microbiome. In February 2015, researchers from M.I.T. and from Harvard University released the results of the most comprehensive longitudinal study yet of how the diversity and types of gut flora affect onset of this type of diabetes. The scientists tracked what happened to the gut bacteria of a large number of subjects from birth to their third year in life, and found that children who became diabetic suffered a 25 percent reduction in their gut bacteria's diversity. What's more, the mix of bacteria shifted away from types known to promote health toward types known to promote inflammation.

This is one of hundreds of studies in dozens of diseases and the results consistently indicate that the bacteria in our intestines have a strong effect on our health. In fact, manipulating the microbiome may even become more important than genomics and gene-based medicine. Unlike genomics and gene therapy, which require a relatively heroic effort to induce physiological changes, tweaking the microbiome appears to be relatively straightforward and safe: just mix up a cocktail of the appropriate bacteria, and transplant it into your gut.



Credit: Rituja Saxena, Indian Institute of Science Education and Research Bhopal

What you eat, too, can affect what is in your gut. A study published in the journal *Nature* found that changes in diet can cause dramatic shifts in the microbiome within three or four days. They noted variability not just in the abundance of different kinds of bacteria, but also in the kinds of genes they were expressing; and there were alterations in the volume of bile acid secreted. They also found that bacteria native to foods we eat such as cheeses or meats can handle the bile bath and colonize our guts when we eat them.

As the American Society of Clinical Oncology (ASCO) notes, "the human body's microbial community is thought to have such intricate and profound effects on human health that it is often referred to as the hidden organ. By evolving together over thousands of years, indwelling microbes and their human hosts have developed a mutually beneficial

relationship. The relationship is so intertwined that one can think of the human body as one superorganism made of both human and microbial cells…When it comes to cancer, the body's microbes can be both harmful and beneficial. Although certain microbes may promote cancer growth, others seem to bolster the body's immune defenses against cancer or help cancer treatments work better."

A team of 40 scientists and three hospitals led by researchers at Sanford Burnham Prebys Medical Discovery Institute, for example, published a paper in *Nature* that identified 11 bacterial strains that activated the immune system and slowed the growth of melanoma in mice. The study also revealed microbiome-related markers that may help detect the condition and its response to checkpoint inhibitors.

Various studies have found links between the abundance of specific organisms that comprise the microbiome and the risk of colon, squamous cell, and esophageal cancers. One study of 383 patients with head and neck squamous cell cancers noted that the tendency to develop these cancers was associated with current tobacco smoking; consumption of moderate to high levels of alcohol; and presence of human papillomavirus type 16 in the oral cavity. And they found that an abundant amount of Corynebacterium and Kingella bacteria in the oral cavity was associated with a decreased risk of such cancers.

Based on the weight of the emerging evidence, ASCO concludes that although there are still many questions to answer about the microbiome, it is known that a lifestyle involving a well-balanced diet and exercise can promote a diverse microbiome associated with good health. "In the future, cancer care may even include an analysis of the patient's microbiome at diagnosis to inform personalized treatment planning", it says.

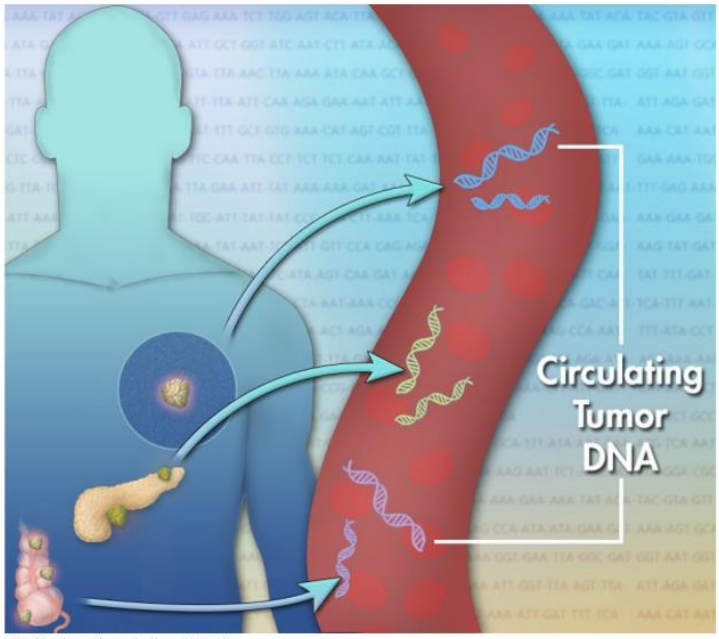
This is what Ayurveda, an Indian medical science, has prescribed for thousands of years. The digestive system and microbiome, only now being acknowledged by modern science as a key component in the regulation of physical and mental well-being, have long been an area of critical importance within the Ayurvedic system.

Developments in the microbiome are taking Western medicine into a world of holistic medicine very much like the systems of Ayurveda and its derivatives. For once, doctors aren't looking to halt symptoms and alter organs; they are being forced to look at the human as a complex ecosystem. The very foundations of allopathy — with drugs having effects opposite to the symptoms of interest — are being challenged by the new research in the microbiome. A realization is setting in that you must look at the organism as a whole rather than merely at the symptoms of a disease or disorder.

Circulating tumour cells and Cell-Free/Circulating Tumor DNA (ctDNA)

Circulating tumour cells are often called "liquid biopsy", because of their ability to facilitate disease diagnosis and their usefulness in monitoring treatment responses and predicting clinical outcomes. Cancer cells release circulating tumour DNA (ctDNA) into the bloodstream. With the next-generation sequencing technologies, this can now be quantified and examined in a simple blood test.

Scientists have discovered that dying tumor cells release small pieces of their DNA into the bloodstream. These pieces are called cell-free circulating tumor DNA (ctDNA).



Credit: Jonathan Bailey, NHGRI

Obtaining a sample of the tumour tissue (biopsy) for genetic analysis or organoid creation may not be possible if the tumour is difficult to access, as when it is in the brain or fragmented over different parts of the body; ctDNA may provide a viable alternative. Its use can be effective in diagnosing cancer; in testing treatments; and in regular monitoring of treatments: a decrease in the quantity of ctDNA suggests that the tumour is shrinking and that treatment is successful. With the information that can be obtained in real time, it could serve as a "surrogate tumour biopsy".

There are not enough data available yet to validate the effectiveness and accuracy of ctDNA tests in most cancers. Scientists argue that well-designed, prospective, randomized, multicentre clinical trials coupled with robust CTC methodologies will be necessary in order to confirm that changes in therapy based on CTC evaluation will make a significant difference to patient outcomes.

With the patient data that India's grand experiment can provide, and by comparing sequencing data from biopsies to sequencing data obtained from the blood, this entire field of medicine could advance exponentially and offer safer and simpler methods of detection, prevention, and monitoring.

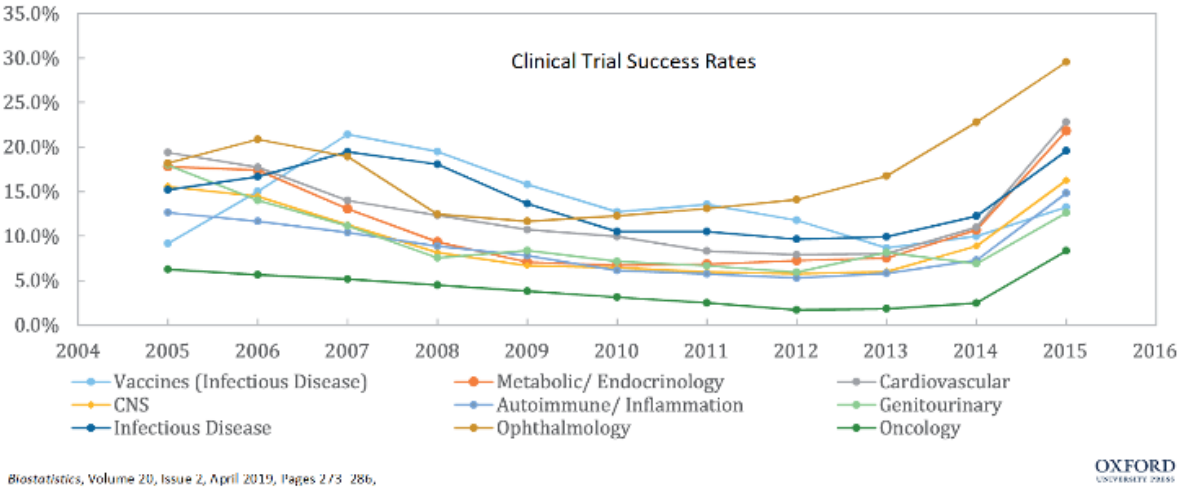
Fatal problems with America's medical research system

Humans as guinea pigs

As Siddhartha Mukherjee explained in an op-ed for the *New York Times*, "The Search for Cancer Treatment Beyond Mutant-Hunting", precision medicine held great promise, especially with the exponential drop in price of genomic sequencing. As Mukherjee explained it: "By identifying the mutant genes in cancer cells, the logic ran, we would devise new ways of killing the cells. And because the exact set of mutations was unique to an individual patient — one woman's breast cancer might have mutations in 12 genes, while another breast cancer might have mutations in a different set of 16 — we would 'personalize' cancer medicine to that patient, thereby vastly increasing the effectiveness of therapy".

Yet, since some initial successes, there have been few breakthroughs in this field. To bring the promise of mutation-directed therapies to life, researchers had commenced two kinds of trials: "basket trials", in which different forms of cancer (e.g., lung, breast, and stomach) containing the same mutations were treated with the same drug and lumped into the same "basket"; and an "umbrella trial", in which cancers were divided into different subtypes according to genetic mutations, each subtype being targeted by a different medicine and treated with therapeutically distinct drugs.

Basket trials had limited success, with some cancers showing response rates as high as 42% and others showing none. The umbrella trials were even more disappointing, with the majority of clinical trials failing completely. A notable limitation of the first generation of basket trials has been the ability to investigate only single-agent molecularly targeted treatments. Mukherjee likened these experiments to the old joke about the drunk looking under the lamppost for his lost wallet, because biomedical scientists were looking under the sequencing lamppost, where the "light is brightest" — that is, where the most data can be obtained as quickly as possible.



Indeed, a study by the Massachusetts Institute of Technology, "Estimation of clinical trial success rates and related parameters", which analysed 406,038 entries of clinical-trial data for over 21 143 compounds from 1 January 2000 to 31 October 2015, found that oncology clinical trials had a 3.4%

historical success rate (in comparison with 13.8% for all drug development programs). All of these numbers are grim for the patients.

As explained by Keith Flaherty in a paper he coauthored for *Nature Reviews Cancer*, "Precision medicine for cancer with next-generation functional diagnostic", genome-based cancer therapeutic matching has been limited by incomplete biological understanding of the relationship between phenotype and cancer genotype. The advances in NGS technologies enabled cancer biologists to identify tens of thousands of mutations in patient tumours. This revolutionized our understanding of the origins of cancer. With thousands of cancer genomes having been sequenced, we reached the "long tail" of mutations that occur in only a minor subset of patient tumours, suggesting that the majority of "low-hanging-fruit" driver mutations that affect populations of cancer patients large enough to justify drug-discovery efforts have probably been identified.

As well, the methods used to test drugs on tumours have been flawed. Cancer-testing models that are commonly used, such as cancer cell lines and primary patient-derived tumour xenografts, only poorly recapitulate the patient's tumour; as a result, many drugs that perform well in these models ultimately fail in clinical trials. These models have provided important insights into the basics of cancer, but their generation is time-consuming, and they do not reliably model pathogenic processes in patients. The histological complexity and genetic heterogeneity of human cancers are not reproduced in the mouse models, for example. And derived cell lines undergo substantial genetic changes and no longer exhibit the genetic heterogeneity of the original tumours. The complexity of cancer requires multi-agent regimens.

This limitation can be addressed by functional testing of live patient-tumour cells exposed to potential therapies using "next-generation" functional diagnostic technologies. The key is to integrate functional testing with next-generation sequencing and immuno-profiling to precisely match combination therapies to individual cancer patients.

Effectively, the U.S. clinical-trial system has been turning humans into guinea pigs in a game in which they have a less than 10% chance of survival. India has an opportunity to flip the U.S. model on its head by functionally testing various therapies on live patient-tumour cells — accelerating the progress of technology and bringing the potential to dramatically increase the patient survival rate.

One size doesn't fit all

Traditional western medicine is generally prescribed on a one-size-fits-all basis. Doctors do try to take factors such as a patient's age, weight, sex, and liver and kidney function into consideration, but drugs come in fixed dosage increments. As well, doctors usually don't have a basis for departing from recommended dosages, because although generally drugs are generally tested on a large (if relatively homogeneous) population, those tests do not seek, and cannot demonstrate, the relationships between the detailed state of an individual test subject and his or her responses to the drug. Any one medication may have its intended effect in one person but not in another, and may cause severe side effects in some.

Age, lifestyle, and health all influence drug responses, and so do genes — as is emerging in a new field of medicine called pharmacogenomics, the study of how a person's unique genetic makeup influences his or her response to medications. The same occurs in cancer: the basis of the selection of drugs and dosages for patients is a generalization of responses in clinical trials. Given the extreme side effects of most medications, however, such a generalized approach can be fatal.

And then, there is a need for novel combinations of drugs. As explained in a paper co-authored by Keith Flaherty in *Cancer Discovery*, "High-Throughput Testing of Novel–Novel Combination Therapies for Cancer: An Idea Whose Time Has Come", combination therapies are also essential to address the genetic complexity, plasticity, and heterogeneity of tumours and to overcome resistance mechanisms that confound single-agent approaches. The paper noted that today we are well-equipped to address many of the scientific, clinical, and collaboration challenges that have existed historically; but that the pace of testing rational combinations is modest. The authors' analysis showed that the volume of clinical trials testing multiple investigational pipeline agents ("novel–novel" combinations) is dismally low, as out of approximately 1,500 phase I to III investigational combination trials initiated in 2014–2015, only 80 were for novel–novel combinations, and only nine of those involved more than one company.

As well, there is an opportunity to greatly expand the range of therapies through "drug repurposing" or "drug repositioning", a strategy predicated on the re-use of existing licensed drugs upon different medical indications. These drugs are rarely tested in clinical trials, because the pharma companies sponsoring the trials don't have any incentive to promote drugs from which they derive no profits.

The Anticancerfund, a Belgium-based non-profit organization, has published a database of non-cancer drugs that can provide great benefit in treating cancer — alone and in combinations. Testing this on a large scale will likely lead to the discovery of many inexpensive and powerful treatments for cancer.

The grand experiment that we are proposing to India will exponentially advance progress in this field by enabling the high-throughput testing of hundreds of thousands of drug combinations upon organoids. The challenge that will remain is to procure investigational drugs. For this, too, there may be a solution.

The role India can play in curing cancer—and transforming medical research

One of the biggest hurdles to curing cancer is obtaining data to understand the correlations between the genome and disease and the drugs that are used to treat them. It will take a decade or more to collect these data in the West, and China is unlikely to share the data it has. Fewer than 10% of patients in the USA enter clinical trials, and even when they do, the data are not shared broadly with researchers, because of onerous privacy regulations and the vested interests of companies running the clinical trials.

India could create an abundance of data with a trial of the size we are suggesting.

The cancer spectrum in India and Asia is distinct from that in the west, as are the genomic features of the population. In hepatocellular carcinoma (HCC), for instance, one of the leading malignancies in Asia, significant differences exist between eastern and western populations on many key aspects, contributing to different treatment outcomes and challenges in clinical-trial design and data interpretation. Genomic studies have identified significant differences in tumour mutations and signatures among different groups of patients who have HCC with various etiologies.

As one would expect, clinical research in the West is largely focused on the types of cancers that are prevalent there; so India needs to research its own maladies.

As well, the U.S. clinical-trial system is geared toward the needs of the pharma companies that largely fund cancer research. Here are some of the inherent problems with this:

- The pharma companies' motivation is to have their drugs FDA approved, so the trials they support are for specific drugs and dosages that lead to this. There is no flexibility in dosages and combinations of drugs for patients; their choice is to take it or leave it.
- Large proportions of patients are excluded because of rigid qualification criteria of clinical trials and their inability to reach the few test centers.
- Placebos, which are commonly used in newer cancer treatments, make clinical trials a game of Russian Roulette for a third or more of the participants. In double-blind studies, investigators do not even know which patient is receiving which treatment, and the outcome for the placebo-receiving patient is nearly always death.
- Off-patent and inexpensive drugs, and any other approaches that bring in no profits to clinical trials' sponsors, are not tested even when there is substantial anecdotal evidence of efficacy.

India, with its size and scale of research, can do what no other country can. With no legacy companies, infrastructure, and interests to protect, it can rethink and dramatically advance medical research — and make it more equitable to all.

India's grand clinical-research experiment

We propose that India launch the largest clinical-research experiment ever undertaken, which provides free treatment to 100,000 cancer patients over a three- to five-year period. This would be conducted at approved, qualified medical centers across the country.

The process would start with a collection of detailed medical records and exams of the patients, stored on a secure central server. All patients would then undergo physical biopsies of the tumours, and/or liquid (blood-based) biopsies if sufficient tumour samples are not available. From these, new research labs will do the genetic sequencing of the tumours and grow 3D organoids when sufficient tissue samples are available. Based on the genetic sequence, dozens, perhaps hundreds of chemotherapies, targeted therapies, and non-cancer drugs that show promise for anticancer activity — as well as combinations of them — would be tested.

The medical history, genetic information, and organoid test results would be shared on a secure website with select groups of scientist world wide, who will be asked to suggest additional drugs and combinations to be tested on organoids. They will also be asked to recommend immunotherapies to test on a basis of clinical evidence that they influence the patient's particular tumour mutations.

With A.I.-based analysis tools, NGS results can be used to create personalized prescriptions that are 3D-printed into polypills — enabling combination of multiple drugs in fixed-dose formulations with each drug having a unique release profile, some releasing upon ingestion and others more slowly dissolving and entering the bloodstream.

As far as procuring the drugs goes, global pharma companies should be asked to donate their drugs in exchange for medical data of the patients whom these are given to. If the companies don't want to make their drugs available, then they should be replicated from the core chemical compounds detailed in the patent and FDA filings of the drugs using 3D printers. Indian companies should also be encouraged to create biosimilars for drugs that pharma companies refuse to make available. (The greatest expense in developing biosimilars is in clinical testing — which, with 3D organoids, can be done rapidly and inexpensively.)

The contribution that patients would be asked to make would be their medical data and detailed daily logs of their health, shared via smartphone apps. We envisage that these data will be shared with university researchers around the globe, who can advance the development of treatments, as well as with Indian startups seeking to develop cures.

We expect that the medical revolution would begin as soon as year two of this project, when data start to become available and breakthroughs begin emerging. Tens of millions of lives will be saved — beginning with those of the vast majority of the participants.

About the authors

Vivek Wadhwa

Vivek Wadhwa is a Distinguished Fellow and adjunct professor at Carnegie Mellon University's College of Engineering at Silicon Valley and a Distinguished Fellow at Harvard Law School's Labor and Worklife Program. He has been a globally syndicated columnist for *The Washington Post* and other publications and author of *Your Happiness Was Hacked: Why Tech Is Winning The Battle to Control Your Brain – and How to Fight Back*; *The Driver in the Driverless Car: How Our Technology Choices Will Create the Future*; *The Immigrant Exodus: Why America Is Losing the Global Race to Capture Entrepreneurial Talent*; and of *Innovating Women: The Changing Face of Technology*. Wadhwa has held appointments at Duke University, Stanford Law School, and Emory University.

In 2012, the U.S. Government awarded Wadhwa distinguished recognition as an "Outstanding American by Choice", for his "commitment to this country and to the common civic values that unite us as Americans". He was also named one of the world's "Top 100 Global Thinkers" by *Foreign Policy magazine* in that year; in June 2013, he was on *TIME magazine's* list of "Tech 40", one of forty of the most influential minds in tech; and in September 2015, he was second on a list of "ten men worth emulating" in *The Financial Times*. In 2018, he was a recipient of Silicon Valley Forum's Visionary Award for his contributions to Silicon Valley's technology ecosystem.

Keith Flaherty

Dr. Flaherty is Director of Clinical Research at the Massachusetts General Hospital Cancer Center, and Professor of Medicine at Harvard Medical School. As described in the more than 300 peer reviewed primary research reports he has authored or co-authored, Dr. Flaherty and colleagues made several seminal observations that have defined the treatment of melanoma when they established the efficacy of BRAF, MEK and combined BRAF/MEK inhibition in patients with metastatic melanoma in a series of New England Journal of Medicine articles for which Dr. Flaherty was the first author.

Dr. Flaherty also has been a leader in assessing and identifying mechanisms of de novo and acquired resistance to BRAF inhibitor therapy and clinically evaluating next generation inhibitors, work that has had implications for resistance to targeted therapy regimens used to treat other malignant diseases. He is the principal investigator of the NCI MATCH trial, the first NCI-sponsored trial assigning patients to targeted therapy independent of tumor type on the basis of DNA sequencing detection of oncogenes. He serves ECOG as chair of the Developmental Therapeutics Committee and in 2013 was appointed as ECOG Deputy Chair for Biomarker Science. Dr. Flaherty joined the NCI Board of Scientific Advisors in 2018 and AACR Board of Directors in 2019. He serves as editor-in-chief of *Clinical Cancer Research*.

Nabeel Bardeesy

Dr. Nabeel Bardeesy is an Associate Professor of Medicine at the Harvard Medical School and the Massachusetts General Hospital Cancer Center where he holds the Gallagher Endowed Chair in Gastrointestinal Cancer Research. He is co-director of the Harvard Cancer Center Specialized Program in Research Excellence in Gastrointestinal Cancer. He received his PhD in Biochemistry from McGill University and conducted his postdoctoral training at the Dana-Farber Cancer Institute on pancreatic cancer biology.

Dr. Bardeesy's laboratory focuses on pancreatic and biliary tract cancers. His work is concentrated on three primary areas: The development of model systems that recreate the genetic building blocks of these cancers; defining the role of altered cell differentiation in cancer formation; and the identification of targeted therapies tailored to a patient's individual genetic makeup. Many of his former trainees are successful researchers at institutions around the world. His work is supported by major grants from the NIH and Dept. of Defense, awards from the V Foundation for Cancer Research, Samuel Waxman Cancer Research Foundation, and TargetCancer Foundation, and partnerships with pharma. He serves on the Scientific Advisory Boards for the Cholangiocarcinoma Foundation and the Forbeck Foundation.

Siddhartha Mukherjee

Hematologist and oncologist Siddhartha Mukherjee was born in New Delhi, India. He holds a BS in biology from Stanford University, a DPhil in immunology from Oxford University (where he was a Rhodes Scholar), and an MD from Harvard Medical School. He completed his internal medicine residency and an oncology fellowship at Massachusetts General Hospital. Dr. Murkherjee is an assistant professor of medicine at Columbia University Medical Center. He lives in Manhattan with his wife, artist Sarah Sze, and their two daughters.

His Pulitzer Prize-winning book, *The Emperor of All Maladies: A Biography of Cancer*, tells the story of cancer from its first description in an ancient Egyptian scroll to the gleaming laboratories of modern research institutions. A three-part documentary series based on the book, directed by Barak Goodman and executive produced by Ken Burns, debuted on PBS. The film interweaves a sweeping historical narrative with intimate stories about contemporary patients and an investigation into the latest scientific breakthroughs.

Mitesh Borad

Dr. Mitesh Borad is currently an Associate Professor of Medicine at Mayo Clinic College of Medicine and Science. He also serves as the Director of the GI Cancer Cellular, Gene and Virus Therapy lab, Director of the Liver and Biliary Cancer Research Program and Deputy Director, Biomarker Discovery Program at the Center for Individualized Medicine at Mayo Clinic. Dr. Borad concurrently serves on the National Cancer Institute's Hepatobiliary Task Force, an appointment he has held since 2011. Prior to joining Mayo Clinic, he spent three years as a Drug Development Scholar/Genomics Medicine Scholar at the Translational Genomic Research Institute, where he worked closely with world-renowned experts, including Dr. Daniel D. Von Hoff.

He earned his B.S. in Biomedical Engineering (summa cum laude) from Boston University and his M.D. from the University of Medicine and Dentistry of New Jersey. Subsequently, Dr. Borad obtained his internal medical training at Cedars-Sinai Medical Center and completed his Medical Oncology Fellowship at Tulane University School of Medicine.

James Doty

James R. Doty, M.D. is a Professor in the Neurosurgery Department at Stanford University School of Medicine and the Founder and Director of the Stanford Center for Compassion and Altruism Research (CCARE) of which His Holiness the Dalai Lama is the founding benefactor. He obtained his undergraduate degree from the University of California at Irvine and medical degree from Tulane University. Dr. Doty completed neurosurgical residency at Walter Reed Army Medical Center in Washington, D.C. and is a Fellow of the American College of Surgeons and the International College of Surgeons. He served 9 years on active duty service in the U.S. Army.

Dr. Doty maintains a broad neurosurgical interest and is one of the pioneers in the use of stereotactic radiosurgery utilizing the CyberKnife. He is an expert in the surgical treatment of benign and malignant tumors of the brain and spinal cord. Dr. Doty is also an expert in minimally invasive (minimal incision surgery) and complex spine surgery. He has published extensively in the areas of spine and stereotactic radiosurgery.

Formerly he was CEO of Accuray (NASDAQ: ARAY) manufacturer of the CyberKnife stereotactic radiosurgery device. He is an advisor to the Fogarty Institute of Innovation and is an Operating Partner for Capricorn Healthcare and Special Opportunities Fund (A Jeffrey Skoll Fund).

As a philanthropist. Dr. Doty has supported health clinics throughout the world and groundbreaking neuroscience research. He has endowed chairs at multiple universities including Stanford and the chair of the Dean of Tulane Medical School, his alma mater.

For the last several years, his interest has focused on understanding the neural basis of compassion and altruism. He collaborates with a number of scientists in a variety of disciplines including

neuroscience and psychology at Stanford and multiple universities throughout the world. Dr. Doty is the senior editor of the recently published Oxford Handbook of Compassion Science.

He is the author *Into the Magic Shop: A Neurosurgeon's Quest to Discover the Mysteries of the Brain and the Secrets of the Heart* that has now been translated into 40 languages, is a New York Times bestseller and has won multiple awards. Dr. Doty speaks throughout the world on the power of compassion to change lives.