LESSONS FROM THE GENOME

Arthur Caplan

With Nathan Kunzler

Mapping the Brain

Inspired by the success in mapping the human genome, two significant projects are now underway to map and improve our understanding of the human brain. President Barack Obama's BRAIN initiative (Brain Research through Advancing Innovative Neurotechnologies) and the European Commission's Human Brain Project. Each project is expected to cost about a billion dollars. Both are to be carried out over ten-year spans.

The BRAIN project was, at the time of its initial announcement, explicitly compared to the Human Genome Project. The hope, says the White House, is that the project will lead to a long list of practical applications, including new ways "to treat, prevent, and cure brain disorders like Alzheimer's, schizophrenia, autism, epilepsy, and traumatic brain injury."

Two decades ago similar promises—many not yet delivered—swirled around government-funded efforts to map the human genome. What can our experiences with the genome project tell us, practically—and ethically—about projects to map the brain?

The Nature of the Two Projects

The BRAIN project states that it provides funding to investigators to develop next-generation technologies with the aim of mapping the activity of each of the neurons in the brain. The goal is to develop technologies for monitoring the responses of large populations of neurons with high spatial and temporal resolution. Initially these will primarily be developed in animal models, like flies, fish, and mice, but with an eventual goal of

applications in humans, enabling the study of brain processes, thereby allowing a more accurate study of brain processes from thought and memory to pathologies such as Alzheimer's and PTSD. The list of collaborators includes leaders in neuroscience from all over the United States. Close to half of the initial funding for the initiative is to go to DARPA—the Defense Advanced Research Projects Agency. DARPA's current interest appears to be direct brain stimulation technologies (DBS). This means that a lot of money is being spent on the initiative with an eye toward military use, including DBS for various forms of brain trauma, enhancing or recovering mental functioning, memory modification, brain interfaced prosthetics, and accelerating recovery from brain injuries associated with combat.

The European Commission's Human Brain Project (HBP) seeks to gain insight into the function of the human brain and thereby advance research in neuroscience. It is, however, distinct in the approach being taken. The goal of the HBP is to integrate disparate areas of neuroscience research through innovative informatics and other modalities to create a functional brain simulation. The hope is that functional simulation theories about brain health and pathology can be formulated and tested. The HBP carries less explicit rhetoric about treatments and cures associated with its promotion than does the BRAIN Initiative.

The projects, despite their differences, could prove complementary. Certainly having a neuron-by-neuron map of the brain temporally and spatially would greatly contribute to the ability to create a functional simulation of the human brain. Similarly, information gleaned from simulation using a dynamic model may be key to creating a unifying neuroscientific foundation to guide future research. But there are challenges too, especially when considering the use of new technologies to study the human brain, as opposed to model systems, and it is instructive to consider the history of the genome project to better understand them.

Challenges in Mapping the Human Genome

The first official funding for the Human Genome Project originated with a proposal from then-President Ronald Reagan in his 1987 budget submission to the Congress. It subsequently passed both houses. The project was planned for fifteen years.

In 1990 the two major funding agencies, the Department of Energy and the National Institutes of Health, developed a memorandum of understanding in order to coordinate their mapping efforts. They reset the clock for the initiation of the project to 1990.

Due in part to the prevailing political climate of the United States, which favored private solutions to large-scale projects, there was interest in privately funded alternatives to the HGP. Many felt that private companies dedicated to mapping would find ways to more efficiently and affordably sequence the human genome. Some felt that a project to simply map the human genome was better suited for private enterprise, leaving government funds available for more basic research purposes. Celera Genomics, among other companies, was created in 1998 in partnership with PerkinElmer to perform the mapping work and to profit commercially from the result. Celera quickly became the major competitor to the publicly funded project. The company claimed to be able to achieve the same goals of the project on a faster timetable with a much smaller total budget.

Investors believed they would succeed. Celera Genomics Group stock rocketed after the company, based in Rockville, Maryland, announced in 2000 that it had mapped 90 percent of the human genome. Celera, which began trading at $25 a share, saw its stock price rise to over $200 a share, giving the company at one point a market value of $5.5 billion. Celera's revenue from the sale of genomic sequence information peaked at $121 million in June of 2002.

An issue that came up right away was: who owns the information contained in the genome. Many argued that all genomic information should be publicly available. There was an initial agreement between the public and private groups to share data. This fell apart when Celera refused to deposit their data into a public database—Genbank. This led to a situation where the private project was able to use the data from the public HGP, but the same was not true for the public project in seeking to access the data assembled by Celera, a private, commercial entity. There were no legal grounds for insisting on symmetry.

Meanwhile, the public and private efforts had distinct and different goals. The publicly funded group sought to make human genome information freely available to all scientists across the world in the hope that

they would use the information to further the research they were doing in diverse areas of science and medicine. Those in the privately funded group may have had some desire to share information, but (as shown by the hundreds of patents they filed), Celera initially had a strong desire to retain a good deal of the information it discovered as proprietary. Celera was a commercial entity supported by private investors eager for a return on their money. The notion of sharing data was not one that found any support in the company's early days. Only when it became clear that a vague, low-resolution general map of the human genome had no real commercial value did the company move toward a position of freely releasing that map for public use.

Lessons for Brain Mapping

There is enormous value in biological information, whether composing rough low-resoluition brain maps or subsequently fine-tuning them as more precise information is learned about small individual brain variations. High resolution maps of human genomes will have the greatest value in personalized diagnosis or therapies, including creating drug targets. One key lesson learned from mapping the genome is that access to a rough initial map proved crucial to developing more detailed maps of small individual human differences. Unless ALL data, not just crude initial brain mapping data, is guaranteed to be open and freely available, commercial interests and motivations will, as they have in genomics, drive the evolution of knowledge about the brain. While efforts to map the brain have begun as public, government-funded projects, this does not mean that private entities will not enter the arena and seek to compete with those projects.

Although initial efforts to map the brain may be fueled by public funds, the issue of how "fine-tuned" information that can be used to determine risk factors or emerging disease states in individual's brains, which will require linking data to genetic databases, health records, and health databases, will be handled merits discussion now. What rules will govern the sharing of detailed scans or maps about each individual's brain? Can data be linked from a brain scan to a genome to a database

without an individual's express consent if that person's identity is not 100 percent secure?

What information about the brain can be patented? Recent battles over the patenting of *BRCA* genomic information by private firms show what can happen if these issues are not acknowledged and resolved early on. It is important to keep new advances in neuroscience from bogging down in fights over commercialization and ownership. Such issues need to be resolved sooner rather than later.

Consider a company formed with the promise of offering customers interesting information about their thoughts and/or predictive information about brain diseases they might be at risk of acquiring. Many such companies, some more legitimate than others, are operating now in the sphere of genomics. Some are huge and have proven profitable, like deCODE and 23andMe. Others are small and often make claims that are on the fringes of genomic science. Building on preliminary and incomplete information coming out of the brain mapping projects and related research, we can predict with certainty that new "brain diagnostic," "truth assessment," and "brain detective companies" will begin to proliferate on the web and elsewhere. The emergence of companies that purport to be able to conduct neuromarketing without much in the way of evidence to ground their claims shows what is likely to be in store in short order regarding "truth" analyses.

All these soon-to-come companies need is some form of a scanner, a suspicious spouse or wary potential employer, and a lot of hocus-pocus to say that new knowledge of the brain will permit the detection of adultery, unfaithfulness, unhappiness, or a disposition to theft. Without any control over the use of new information about the brain or advertising claims allegedly based upon knowledge derived from the new projects to map the brain, the projects will create many spin-offs. Not only will there be spin-off information about how to diagnose disease and treat it and what price ought be charged for such benefits of government research, but there will also spin off a host of quacks, charlatans, entrepreneurs, quick-buck artists, and shysters eager to parlay incomplete or rough data about the brain for sale to a public eager to believe in truth machines, windows into one's deepest hidden thoughts and fears, and screens that can weed out the different, the potentially derelict, and the defective in the home, workplace, or jail.

Calls to map the human genome anticipated none of the aggressive commercial exploitation that followed in its wake. There is no reason not to better prepare for the fallout that will surely occur as knowledge of the brain advances.

What Is the Best Source of Funding a Brain Map?

As was seen in the HGP there are distinct advantages to various types of funding. By allowing public or governmental funding many argue that scientists are allowed academic freedom, an ability to proceed in the direction they feel is most promising. But that belief may be naive. The heavy presence of DARPA, the Defense Advanced Research Projects Agency of the US Department of Defense, in the American project all but guarantees that that project will be under pressure to show benefits useful for national security, military application, and the diagnosis and treatment of combat- and military-service-related disabilities and injuries. There appears to be no guarantee that all data collected under DARPA's auspices will be publicly available. DARPA sponsorship may entice brain scientists eager for grant money in a time of tight budgets, but it is important to realize the goals of DARPA may not always overlap the values of scientists used to relying on NIH or NSF support.

When an endeavor like mapping the brain is funded by private industry funds, or even foundation grants, there is a pressure to move in the direction those funders want. A grant from the Alzheimer's foundation is likely to come with strings attached about mapping with an eye toward better understanding Alzheimer's. The same can be said of industry funds. While they can be a valuable source of money for investigators, they also come with a pressure to find commercializable opportunities in the research.

Foundation and industry grants are not without their merits. The idea that they could lead to more efficient and affordable technologies was used to justify the competition between public and private groups that occurred during the HGP project. The fact is that the competition between public and private efforts to map the genome did in fact lead to more affordable and efficient technologies is now very much appreciated by many in the scientific community. However, if brain

projects are fully or partially funded through collaboration with industry to reap the benefits of increased efficiency and translation to application, then it must also be understood that the community of scientists might not be used to working with large corporations, such as GE, Medtronic, Siemens, Johnson and Johnson, Google, and others, and will surely be averse to the demands made on them in terms of proprietary rights as a price for their funding. Large foundations can also make demands that readily create conflicts of interest for those seeking rapid publication and the release of all crude data into public data banks.

Are We There Yet? What Counts as Progress?

Other lessons from the initiative to map the human genome deserve attention as well. The competing projects engaged in mapping the genome did not agree on what would constitute the finish line in terms of announcing success regarding achieving a map of the human genome. Nor did they agree on whose genome or genomes would serve as the template for mapping activities. Often what counted as progress was fiercely debated in public with an eye toward gaining a PR advantage for one side or the other albeit at a serious cost for the public's understanding of what was taking place.

Nor was there agreement on what to map. For example, at the time the HGP was first launched, it was widely assumed that noncoding DNA was "junk" and need not to be taken into account as part of a claim to have "mapped" the human genome. And initially many involved in mapping said that noncoding DNA need not be mapped. But years later, researchers began to realize noncoding DNA played a key regulatory role governing much of the process of epigenesis

When it comes to the human brain, what should we map? Is it a map of the neural connections of the brain, a so-called human connectome? Should the glial matter that makes up as much as 90 percent of the cells in the human brain be included in any map before success is declared? This is an especially important question, looking back on the decision to not include "junk" DNA as part of the human genome. More and more evidence mounts that glial cells are not simply "supporters" of the

neurons, as neurological dogma has held for many years, but are possibly involved in brain processes.

As some have argued, building a connectome is not enough to say the brain has been mapped. We also need to develop technologies that can image the brain dynamically and see what cells and groups of cells are firing with high spatial and temporal resolutions to say anything like a brain map has been achieved.

But what resolution will be sufficient? Spatially, should scientists seek to see individual neurons, groups of 5, areas of 1 mm? What about temporally, do we need to see every second, millisecond, or every evoked action potential?

These questions will undoubtedly be the source of much debate among scientists, but they should begin to be addressed now. Without a consensus on what mapping the brain means, at what resolution it will, and ultimately ought to, be done will not be evident, as it was not when seeking to map the human genome. Battles over credit, ownership, error, and the fulfillment of promises of applicability hinge on reaching an agreement about what the endpoints are. Just as importantly, public support and funding for mapping will pivot on clarity about what endpoints are important and what landmarks along the way have real significance.

The Practical Value of a Map

Those seeking to fund the project two decades ago heralded sequencing and mapping the genome as the way to a very rosy future in which we would secure freedom from all our genetic ailments, the key to a longer, healthier, happier life. Indeed, at the official announcement of its completion, then-President Bill Clinton said it would "revolutionize the diagnosis, prevention and treatment of most, if not all, human diseases."

But while genomic technology may well accomplish these things, it is important to recognize that the true advances regarding the "prevention and treatment" of most human diseases are still decades away. Even now, almost fifteen years after the initial announcement of the completion of the project in 2000, medicine is only just beginning to see technologies that may meaningfully change the way human diseases are diagnosed and treated. The public or Congress or other funders might well feel that

science did not deliver on the big promises made in the name of mapping or that the time frame that was sold was far too optimistic.

Any large-scale project seeking significant public funds risks facing the same problem as, say, building a location for the Olympics such as Sochi, Russia, or constructing a tokamak for nuclear fusion. Mustering public support for any science project that requires billions of dollars, and, at least in the US context, requires persuading a wary Congress, public, and media that wondrous advances in the human condition lie just around the corner if science can only get enough money, requires reasonable achievable goals, not science-fiction-inspired promises. In order not to disappoint the taxpaying public it is important to be wary of the tendency to overpromise in the name of securing funding. Being able to map the brain of a mouse is no more a promise of cures around the corner than is the capacity to map the genome of a mouse.

Whose Brain or Genome Shall We Map?

At the time the HGP was announced there was a great amount of time spent discussing *whose* genome would be mapped and what the consequences of that decision would be. Because the project would be made available freely to the public anyone who allowed their genome to be sequenced would have to understand and accept the idea that their genetic information would be available for all to see. Any genetic privacy they had would be erased.

In the end a decision was made to sequence the genomes of several volunteers but only after a rigorous informed consent process. The Human Genome Project used protocols to ensure that the DNA from several different volunteers was used and that the blood samples from which the DNA would be extracted were de-identified to the researchers using them. Additionally, many more volunteers were recruited than were needed to sequence the human genome, and as such, no single volunteer is actually certain if their DNA is a part of the project or not. While this approach may have worked well to avoid some of the ethical conundrums of genomic sequencing, it may not be as simple as we map the brain.

The question of whose brain to map is centrally important in the current project for reasons both symbolic and scientific. While many

millions of persons have "maps" done of their brains every year for diagnosis or research, at some point a decision must be made about which brain or brains to use as the foundation for a standard brain map. Will we include data from the mentally ill? Will the developmentally disabled be a part of the data pool? Will those who have specific brain diseases be a part of what is brought forward as a "normal" or "typical" human brain, and if not, why not? It seems best to use a group of people that represents a broad section of humanity. This seems to give the best scientific chance of capturing all the important information being sought. It is also, as the HGP found, ethically less cumbersome that choosing the brain of a single, identifiable individual.

This approach, however, may not work. We don't know how different the connectome of each human brain is, and we do not know what sort of variability to expect in a dynamic brain image. It may well be that this variability makes the collected data impossible to pool and de-identify. If brain variability may create issues of brain selection in studying the brain then these issues, which are hugely controversial if they do exist, require public discussion and debate.

Translating New Knowledge of the Brain Will Not Be Easy

No shortage of enthusiasm greeted the first findings to emerge from the crude map of the human genome. Media stories erupted with the promise that "genealyzers" would soon be present in every doctor's office. The Internet also erupted with a parade of scams and nonsensical offerings: genetic testing for predicting athletic performance in children, the best diet suited to a person's genome, ancestry testing, and even the identification of a person's best romantic partner through DNA analysis. So far, little of this has yet emerged from efforts to map the brain. How can we keep brain knowledge from spawning the same sort of hype, confusion, exploitation, and misunderstanding?

Even on some basic concepts, there is already considerable confusion in the general public. Consider the basic concept of brain death—the total and irreversible loss of all brain function—and the recent case of a thirteen-year-old girl, Jahi McMath, who died on December 12, 2013. Her parents had taken her to Oakland Children's Hospital for surgery to

remove her tonsils to help her sleep apnea. Things went tragically wrong (although exactly why is not known). She suffered severe bleeding, a heart attack, and massive hemorrhaging in her brain. Unfortunately, experts in neurology could not find any sign of brain activity after these events. Independent experts who were not treating Jahi did the standard accepted scans and tests to assess brain activity and concluded with certainty that she was brain dead.

Yet months later, the girl remained on a ventilator receiving food through a tube in an unidentified facility—because her parents refused to accept her death because they did not accept "brain death." Unlike those in a coma or in a permanent vegetative state like Terri Schiavo, a Florida woman whose parents fought unsuccessfully with her husband to keep her alive, or Ariel Sharon, the former Israeli prime minister whose family kept him in a coma for eight years, no one recovers from brain death. Brain death is death because the brain can no longer support any key vital functions. Of course no parent would want to accept their daughter's death, but because the public continues to confuse brain death with coma or vegetative state, the McMath family received great support from other families and in the media. Indeed, intensive care units in the United States and other nations sometimes contain bodies that have been pronounced brain dead on machines providing artificial life support at the direction of families who cannot or will not understand brain death.

Brain death is widely misunderstood around the world. A brain map is likely to be misunderstood as well unless great care is always used in explaining the concept.

More broadly, if the genome has taught us anything, it's those working to map out biology, be it genome or brain, have a huge social responsibility. The push to map the brain can't just be about gathering information and discussing ways that information might be applied. Scientists must also debunk hype, allay groundless fears, and anticipate likely ways in which efforts may be made to exploit or dupe the public in the name of knowledge derived from brain maps, studies, and scans.