The Duty of Imagination

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Phi Beta Kappa Oration

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Thank you for the wonderful invitation to give the Phi Beta Kappa Oration this morning. I'm delighted to get to share this special occasion.

I want to start by congratulating the students here not only on being members of the Harvard graduating class of 2019, but on the rarifed distinction of being elected to Phi Beta Kappa at Harvard. You are members of the oldest chapter of America's most prestigious academic honors society, devoted to the promotion of scholarship. You have not merely completed 16 years of education — you have become something very special: a scholar. It is not a prize but an acknowledgement: Whatever else you become in your career, you are a scholar.

It is a tremendous honor — an honor that you will carry forever. I invite you and your families to bask in that honor for a moment. [Pause]

OK, enough basking!

Because I now need to tell you about the fine print that you agreed to when you clicked "Accept" to Phi Beta Kappa — that is, the responsibilities that you took when you became a scholar.

Some people think of scholarship as dusty, fusty, monastic, esoteric. Allow me to dust off the word.

Scholarship is arguably the most transformative force in the world. Scholarship is the sum of two things: knowledge and imagination . . . knowledge and imagination.

- It is broadly understood that "knowledge is power." *Knowledge* is the foundation for all meaningful and lasting change.
- It is somewhat less understood that *imagination* is how we direct the power to make change.

So, I want to talk to you about your "duties of imagination." Whatever you *do* in your life, you have a duty to not just to *do* but to *imagine*. Whatever you *work on*, you have a responsibility to ask about your *work* two questions of imagination:

- What could possibly go right? and
- What could possibly go wrong?

Failures of *execution* tend to get a lot of attention. But, the greater risk often lies in *failures of imagination*. Why? Because humans tend to extrapolate linearly from current conditions. We tend to dramatically underestimate both the *progress* we can make — and the *problems* we can create.

The world moves farther and faster than most people think. My message to you is that, as scholars, you have a special ability and thus a special duty to imagine where things may go — so that we can seize opportunities and avoid pitfalls.

To make this concrete, let me tell you a story — it's a story that spans my own career in my own field of genomic medicine.

Let's begin the story at a pivotal moment:

In June 1986, the Cold Spring Harbor Laboratory chose to hold its distinguished annual international symposium on the topic *The Molecular Biology of Homo Sapiens*. That might sound a bit dry, but it was anything but. On the program was the first public debate on the question: Should we try to sequence the DNA of the entire human genome — that is, read out the human genetic instructions? What we would later call the Human Genome Project. It was also the first scientific meeting at which I had ever been invited to speak.

To understand this pivotal moment, one has to go back a bit in time.

Act 1: In the mid-20th century, the field of molecular biology was born.

• Biologists were able to purify the molecular basis of hereditary information in organisms — proving that it was DNA. But, they had no clue how a molecule could "encode information" and pass it on to from cell to cell, from parent to child.

• On April 25, 1953, the work of four scientists — Francis Crick, James Watson, Rosalind Franklin and Maurice Wilkins — revealed in articles in the leading scientific journal *Nature* that the secret of heredity lay in the double-helix structure of DNA. The two complementary strands each served as a template for the other — they could be unzipped to duplicate the information and pass it on to daughter cells and thereby to daughters . . . and sons. But, they still had no clue about the language in which that information was written.

• In the 1960s, biologists cracked the genetic code. Using elegant test tube experiments, they showed how three-letter codons of DNA specified the amino-acid building blocks of proteins. They knew, in principle, how DNA encoded the blueprints for hemoglobin or insulin. Some declared victory — the secret of life was known! It was time to take on a new challenge, like understanding the brain.

Act 2: But, a younger generation was not satisfied. While biologists knew the answer in principle,they couldn't actually isolate even a single gene or read its DNA instructions.

In the 1970s, scientists at Stanford, Harvard and MIT created the field of recombinant DNA — devising ways to clone individual genes and read out their DNA letters. It had a huge impact — including giving rise to the biotechnology industry.

But, it still left a gaping hole.

While recombinant DNA was powerful, it couldn't discover the genes responsible for human diseases — like cystic fibrosis, Huntington's disease, Alzheimer's disease, schizophrenia, or early heart disease — because you typically had no idea in advance about a disease gene's molecular function and thus no way to recognize it.

Act 3: In 1980, a geneticist named David Botstein came up with a brilliant solution for finding the gene responsible for a rare genetic disease: even if you knew nothing about *what* the gene did, you could find out *where* it was — by comparing the inheritance pattern of the disease in families to the inheritance pattern of genetic markers.

It was a trick long used in fruit flies and yeast.

But, it would require creating a map of genetic signposts across the human genome. The idea of mapping the human genome was born — and it would soon grow into the idea of reading out the entire human DNA sequence.

I met David Botstein only a few years later, and we began working together on extending these ideas from rare genetic diseases to common diseases in the population.

It was David who wrangled me an invitation to speak at the 1986 Cold Spring Harbor meeting — where the great debate on the Human Genome Project took place. I was 28 years old at the time.

So about that debate: It's fair to say that there was a lot of skepticism in the biology community.

• One worry was the cost — it was projected to total at least $3 billion, which some feared would drain funding from other scientific projects.

• A more serious worry was the value: Did we really need to know the sequence of the human genome anyway?

This point of view was best captured by an editorial recounting the debate that appeared in the journal *Nature*, written by the journal's biology editor. I quote:

> Nobody seems to doubt that . . . it can be done in perhaps a century.
> The question is whether it is *worthwhile*. . . .
> As an information resource, the sequence of the human genome is an *extremely doubtful asset*. . . .
> If the skill and ingenuity of modern biology are already stretched to interpret [the handful of known genes] . . ., *what possible use* could be made of more sequences?
>
> *Nature, July 3, 1986*

In short, the editorial argued, the whole would likely be little more than the sum of its parts. What's the point? And, what's the rush?

Many young scientists — myself included — begged to differ. This new generation believed that seeing the complete picture might reveal astonishing new insights and open astonishing new medical possibilities.

To this day, I keep that Nature editorial tacked above my desk to remind me about **failures of imagination.**

Fast forward about 15 years: After some heated debate, the scientific community eventually came around. I signed up to be part of the generation that would take

up the challenge of reading and understanding the human genome. An international collaboration came together involving 20 genome centers in 6 countries—the flagship center was here in Cambridge—that generated data and shared it immediately without restriction. In the late 1990s, we did battle with a company that tried to derail the Human Genome Project so that it could privatize the data. By 2001, we had a rough draft sequence. And, on April 25, 2003, we announced that we had a finished sequence of the human genome.

We chose that data apurpose — it was exactly 50 years to the day after the papers announcing the discovery of the DNA double helix.

We invited to the celebration the legendary Francis Crick, co-discoverer of the DNA double helix. He could no longer travel, but he sent a video. In it, **Crick confessed to his own failure of imagination**. He admitted that, when they discovered the DNA double helix, he had never — in his wildest dreams — imagined that he would live to see the complete reading of the human genetic information.

The completion of the Human Genome Project was indeed a remarkable moment. But what came next is *even more* astonishing.

Fast forward another 15 years to today. What has happened?

The Human Genome Project had required $3 billion and 13 years to read out just one human genome. But it lit the fires of imagination. Powerful new technologies soon appeared. By today, more than 1 *million* human genomes have been sequenced and the cost has fallen from $3 billion to $500 a genome — and will likely hit $100 in the years ahead.

The scientific impact has been remarkable:

• **For Rare Diseases**: David Botstein's idea for discovering the genes underlying rare has now been applied to >4000 rare genetic diseases, revealing their molecular basis.

• **For Common Diseases**: The ideas that David and I discussed in the mid-1980s have — over the past decade — led to >100,000 discoveries of genes associated with common diseases — shedding light on basis of heart disease, diabetes, autism, schizophrenia and Alzheimers.

• **For Cancer**: Applying genomics to cancer has revealed hundreds of new cancer genes — pointing to unsuspected biological pathways and propelling drug development

• **For Evolution**: Comparison to the genomes of other mammals has revealed conserved regulatory controls that evolved 100 million years ago.

• **For Human History**: Comparison to the genomes of homonid fossils has revealed that our ancestors interbred with Neanderthals.

Moreover, scientists can now see how the DNA instructions are read out which genes are activated in different places and times in the body — the biological programs of health and disease.

• At first, we could only do it in bulk — studying a piece of muscle or cerebellum or a tumor.

• But, recently, it's become possible to read the gene activation in individual cells. Five years ago, the first paper reported 18 cells. Today, it's more than 18 million. And, a worldwide project has been launched to create a complete Human Cell Atlas — this generation's successor to the Human Genome Project.

Finally—and totally unexpectedly, reading genomes of bacteria revealed the existence of the now-famous CRISPR systems that are letting us edit genomes in living human cells to correct disease genes. Clinical trials of genome editing are being planned for cancer, muscular dystrophy, heart disease and many other diseases.

Now is the point where I have to confess **my own failure of imagination**. As a young scientist, I was wildly optimistic about what we could learn from the human genome. But, I'm embarassed to say that, never in my wildest dreams did I imagine that we'd get so far so fast — $100 genomes in sight; single-cell biology; CRISPR genome editing — just about 15 years after the end of the Human Genome Project.

All progress depends on imagination — not fantastical dreams, but realistic imagination. Yet, imagining, realistically, "what could go right?" turns out to be remarkably difficult. Reality has a way of outrunning our projections.

If I were a computer scientist, I could have told you a similar story.

• In the 1950s, who would have imagined that that the Brobdingnagian ENAIC computers, which filled entire rooms, would beget iPhones that are >1,000,000 times more powerful, 10,000 times cheaper and fit in your pocket?

• In the early 1990s, few imagined that one could have all the world's information at one's fingertips.

• Even as recently as 15 years ago, few imagined the explosion in machine learning and artificial intelligence that we have seen — making it possible to translate spoken speech from one language to another, or to reliably read CT scans to diagnose lung cancer.

These are all examples of what could possibly go right. But, I also have to call your attention to the second duty of imagination — asking "What could go wrong?" If we're bad at the first question, we're worse at the second.

Computer science provides the most obvious examples:

• At the beginning, we imagined how social media could bring communities together, but we never contemplated how it might tear the world apart. **It was, as we are learning, a spectacular failure of imagination**.

• We were excited that we could have all knowledge about the world at our fingertips, but we never contemplated that the world would have all knowledge about us at its fingertips.

• As we taught computers how to master image recognition, we failed to imagine how easy it would enable some governments to become modern surveillance states.

• As technology expanded our creativity, we didn't think hard about how to handle the fake images, audios, and videos that would become possible.

In biology, there are worries as well:

• How do we make sure that genetic information is not misused? On the positive side, the US passed a law to forbid genetic discrimination in health insurance. But there's lots more to do.

• How do we make sure that our growing ability to engineer cells to prevent disease doesn't someday lead to new kinds of biological weapons?

• And what about human genome editing? It's one thing to try to cure a patient with muscular dystrophy; it's another thing to contemplate modifying the human gene pool by making genetically modified babies with new traits. As you may know, a scientist in China announced last November that he had done precisely that to two twin baby girls. The world is now grappling with whether and when it might be permissible to allow the production of genetically modified children.

In all these cases, the best approach is to anticipate problems in advance — and start thinking of solutions. It's much easier to get out ahead than to play catch up. The first step is imagination.

Finally, I should note that these duties of imagination don't just apply ˜to science and technology. They apply to every human endeavor — economics, politics, education and much more.

So, welcome to the community of scholars. Being a scholar comes with the responsibility to use one's knowledge and imagination to think deeply about where the world is going.

You don't have to do it all. And, you don't have to do it alone—that's why there's a community of scholars. But, you cannot refrain from the work.

Congratulations to all of you. And good luck!