



CFO-Summit

TEIL IIX

Von Misha Angrist

Deciphering man – and what it means to us

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In almost every country on Earth and repeatedly from different standpoints, discussions are being held and committees formed in order to explore the ethical boundaries of knowledge concerning the human genome. For scientists, this is a boundless field with vast possibilities. Yet it is exactly this vastness that makes research in this area and its findings so incalculable.

But it is not just the fear of opening Pandora's Box that makes many queasy. When it comes to knowledge we already have, the question of what is ethical still arises? Everything that is doable? Is the economization of life going too far?

Misha Angrist, a psychologist and biologist with a focus on genetics, has been researching the unique human genetic code for the last five years. He is an assistant professor at the Institute for Genome Sciences and Policy at Duke University, a private university in Durham, North Carolina, and examines in particular the ethical, legal and social aspects associated with deciphering genomes. He has decoded his own genome and published it online for all to see as part of the Personal Genome Project. He

deeply believes that a great deal of good can come of this and that the world can be made a little better because it will be healthier: treatments can be developed only when genetic defects and the genetic causes of major diseases are known.

But developing treatments also means being able to make a choice about such things as artificial insemination. The discussions and entrenched positions involving pre-implantation diagnostics clearly demonstrate this. Yet the negative selection processes can be extended to other areas as well: in selection interviews for insurance policies, in placement on waiting lists for urgently needed operations and in the allocation and rationing of life-prolonging measures. Is it conceivable that at some point we may select life partners based on the attractiveness of their genetic code. Or not?

The questions remain: who has the right to make decisions about life and death, and are there criteria for making "objective" decisions at all. What can the human race do and what can it not do? What may it do? What is the price of more knowledge?

Everything that I'm made of, I put online

Is knowledge a blessing or a curse? How much do I really want to discover about myself? What is better left unknown? Do I want to know what diseases are lurking in my future? Can I handle that kind of information? May embryos be examined in these terms? What can be done with this knowledge? What is ethical? Who has the responsibility to make such decisions? Are we once again crossing a knowledge boundary that will lead to another paradise lost?

In 2007, I became part of a study to understand what our genes say about us – and how they can be used against us.

I was born in 1964. While I continue to make peace with social networking, I still think of myself as too old to be an organic part of the exhibitionism on YouTube, Facebook, Twitter and MySpace. At best I am a poseur. I play in an occasional rock band with some other 40-somethings, and while we have a MySpace page, none of us is terribly adept at using it. In my band we will post pictures or movies of ourselves, but almost always with ambivalence, as we find them to be dorky, pretentious or otherwise embarrassing. Like any other collection of 45-year-olds still writing songs and performing them in dingy college-town bars on Friday nights for a dozen of their most patient, loyal and sleepy friends, we are narcissists and stultifyingly vain, to be sure, but hey, at least we're discriminating.

„People believe in the magic of genes and buy into the idea that they are the deepest secrets of our being.“

Much as I want to hide my potbelly (probably a sign of insulin resistance and determined by genes acting in concert with ice cream), I agreed to make my genome – the DNA sequence that I inherited from my parents and that is uniquely mine just as yours is uniquely yours – an open book. And if you want

to study my phenotype – my health records, my ongoing struggles with depression and my infatuation with selective serotonin reuptake inhibitors, or my dubious diet, for example – then go ahead, knock yourself out. It's all out there, with more to come, on the Internet. For doing this, I and the other participants in the Harvard-sponsored Personal Genome Project have been lauded for our “bravery” by friends and colleagues, derided for our elitism and egotism by some social and genome scientists, and largely ignored by the medical establishment.

Are we – were we – really so brave? One of my favorite thinkers on this topic, Stanford law professor Hank Greely, said not long ago, “People believe in the magic of genes and buy into the idea that they are the deepest secrets of our being. But maybe my credit card records come closer to being a deep secret of my being.”

As of mid-2010, few “whole” human genomes had been sequenced – certainly no more than a few hundred. But in the next couple of years – or months – there will be thousands more, at least some of which will be widely shared with researchers or anyone else who's interested. And the “genome-lite” version – having a half million or 2 million DNA markers analyzed for a few hundred bucks by private companies rather than a full sequence – is already a cheap commodity entrenched in the marketplace, much to the chagrin of many doctors and geneticists and to the befuddlement of regulatory agencies.

What will this real-time experiment in science and radical openness mean? DNA sequencing may soon be cheap enough and reliable enough to make personal genomics as pervasive as cellphones, iPods and LASIK surgery (assuming that, like those things, DNA sequences are actually useful).

Nightmare scenarios include identity theft and the loss of insurance.

But cheap sequencing and the widespread sharing of genomic data will also bring with them “unintended consequences,” card-carrying bioethicists’ second-favorite phrase behind “slippery slope.” Nightmare scenarios include identity theft and the loss of insurance.

On the other hand, even the leftiest and most passionate of civil liberties advocates would have to concede that genetic discrimination is relatively rare: The two most notorious cases occurred several years ago. In one, Burlington Northern Santa Fe Railway was found to be surreptitiously testing its workers for a genetic variant thought to predispose to carpal tunnel syndrome (it doesn’t – the company couldn’t even figure out how to discriminate right); the railroad settled with 36 workers for \$2.2 million in 2002. In the other high-profile case, the Lawrence Berkeley National Laboratory was accused of having tested several of its employees for syphilis, sickle-cell anemia and pregnancy without their con-

sent. The lab settled in 1999, again for the magic sum of \$2.2 million.

One presumes that in both cases the employers would have used positive test results (pregnancy?!) to justify denying the employees’ insurance, raising their out-of-pocket costs for health benefits, or perhaps even firing them. Again, two cases do not an epidemic make. But, as a former mentor of mine used to say, “Absence of evidence is not evidence of absence.” Despite the lack of litigation, it may be that the temptation for employers to go all actuarial on their current and future employees is still too great.

In 2005, for example, a higher-up at Wal-Mart floated the idea of discouraging less healthy people from applying to work at the company, as a way of holding down healthcare costs. In her memo, the vice president noted that Wal-Mart workers tend to develop obesity-related – and partly genetic – diseases such as diabetes and heart disease at a higher rate than the national population (at the time, less than 45 percent of Wal-Mart’s employees had company health insurance).

More disturbing, in 2007 an exposé in the Los Angeles Times revealed that the U.S. military regularly practiced genetic discrimination. On a number of occasions servicemen and servicewomen with genetic conditions have found themselves kicked to the curb, with the armed forces arguing that in such cases they bear no responsibility for the soldiers’

health and disability benefits: You may have lost a limb in Fallujah, but your retinitis pigmentosa is preexisting, so, you know, sorry. Military doctors were said to discourage their patients from getting genetic tests.

As I worked through the drafts of my book (from which this passage is excerpted), the world kept changing. The military has since revised its draconian policies on pre-existing conditions. And in May 2008, the Genetic Information Nondiscrimination Act (GINA) passed both houses of Congress and was signed by President George W. Bush. Twelve years in the making, it was the end of a long and tortuous road for patient activists and a rare kumbaya moment in Washington in the post-9/11 Bush era.

And I was gonna put my entire DNA sequence on the Web?

But GINA was not and will not be a panacea: It is limited to employment and health insurance. It says nothing about life, disability or long-term care insurance, all of which are likely to be of greater interest to insurance companies and to Alzheimer's patients and their families. Thus, if an insurer wants to deny you coverage or charge you exorbitant fees because you carry two copies of the APOE allele that raises your risk of developing Alzheimer's 15-fold, GINA can do nothing to influence those insurers.

And its power over employers will be tested. Recently Pamela Fink of Fairfield, Conn., found out that she carried a mutation in BRCA2, one of the two most powerful hereditary breast cancer susceptibility genes. Despite years of glowing reviews from her employer, MXenergy, after she shared her results with her bosses, she was demoted and eventually fired.

And I was gonna put my entire DNA sequence on the Web? In August 1996 I sat among a crowd of hundreds of other graduate students at Case Western Reserve University. As in most graduations, there was a palpable euphoria in the air. It was a rare cloudless summer day in Cleveland, an aging industrial city in northeast Ohio arguably most famous for a serpentine river that once caught fire. I made giddy small talk with the guy behind me in line as we waited our turn to make a brief procession across the stage, each of us feeling uncomfortable and a bit fraudulent in our caps and baggy gowns, anxious to shake hands with a dean we'd never met and take our elaborately adorned pieces of paper to be framed.

I wasn't going to win any prizes for originality or brilliance, but to my mother's and my own surprise, I had stuck it out and gotten my doctoral degree in genetics. I had spent the previous five years studying a rare birth defect called Hirschsprung's disease, named for the 19th-century Danish physician who first described it. The Hirschsprung's patient has great difficulty moving his bowels past the part

without nerve cells – everything stalls. Unlike most other strongly genetic diseases, Hirschsprung’s disease is highly treatable. Although most Hirschsprung’s babies will grow up to lead normal lives, they are forever susceptible to severe constipation and potentially life-threatening infections of the bowel.

I took some measure of satisfaction in knowing that I was helping to elucidate the biology of the disease.

Hirschsprung’s is a stand-in for other complex diseases: that is, ones caused by some mixture of genes and the environment. I was part of one of two teams that found a major clue leading to the identification of the most important susceptibility gene.

At some point during my first postdoctoral year, laboratory science began to lose its luster. I looked at those around me and saw the lives they were leading: the grant applications, the boring meetings, the parade of mind-numbing seminars, and the neurotic graduate students who required some mysterious combination of hand-holding, babysitting, thoughtful mentoring and tough love. It was not nearly as much fun as it used to be.

And I was Hirschsprunged out. I took some measure of satisfaction in knowing that I was helping to elucidate the biology of the disease and that my work might play some small part in creating better diagnostics or therapies. But somehow it wasn’t enough. As tragic diseases go, I suspect even most Hirschsprung’s families would admit that their plight was not in the same league as those with a loved one suffering from Lou Gehrig’s or late-stage lung cancer or Tay-Sachs. Instead, here was a genetic disease that was actually treatable or, as personal genomics partisans like to say, “actionable.” At the time I wondered if anyone really cared about what we were doing. Genetic research has been – and continues to be – criticized for throwing lots of resources at rare diseases, and I suppose I worried that I was part of the problem.

The genetic aspects of the disease I studied were fascinating, but we were a small, insular community studying a small, mostly treatable disease affecting one in 5,000 kids. Meanwhile, molecular genetics was changing at a pace that, more and more, left me dizzy and exhausted. The seminars I attended may as well have been in Esperanto. I was falling behind. Science had revealed to me with much clarity that I was now a full-grown, 33-year-old dinosaur. Staying in the game would mean assimilating massive amounts of biochemistry, deep and broad computational skills, or both. Genetics was becoming genomics, a digital science, and one ought to have had more of a quantitative clue than I did. I had a choice: I could change or die.

I decided to die.

I left laboratory genetics. I worked as a market researcher, feckless financial manager (I know those words seem redundant these days), biotech consultant and science editor. Over the next seven years I rarely thought about Hirschsprung's disease. Once in a while I might stumble upon a paper by my advisor's group or other people I knew describing some novel finding that, if I really followed the paper trail, I might be able to trace back to my own work 10 to 15 years earlier.

But in 2005, Hirschsprung's reappeared in my life in a sudden, unlikely and disturbing way, like a drunken ex turning up at one's wedding. Wielding a knife. On Dec. 14, the eve of my mother's birthday, my nephew Jesse was born with a dilated colon. Three days later he was diagnosed with Hirschsprung's disease.

I knew the question was both clinical and existential, though I could supply neither type of answer.

What did it mean? my family wondered aloud. I knew the question was both clinical and existential, though I could supply neither type of answer. What was going to happen to my brother's new son and my parents' last grandchild? I hadn't a clue. I immediately became the Expert, though I remembered lit-

tle. I was as flummoxed as my family was, but out of love, hubris and a desire to be a hero, I did not betray my ignorance. I took my thesis off the shelf for the first time in years. I sent e-mails and made phone calls to people who still "did" Hirschsprung's. I reread articles about pediatric surgery techniques, the details of which I'd once known cold.

As my heartbroken and sleep-deprived brother and sister-in-law watched their new baby go in and out of the hospital again and again, I was overtaken by a sort of numbness, a paralysis. How strange – how impossible! – that the rare disease I'd devoted eight years to understanding was suddenly no longer an intellectual abstraction, a genetic problem to be solved in a lab or on a computer. Someone in my family was to have five surgeries over the first year of his life, with still more to come. Someone – or someones – in my family had to change colostomy bags and purchase boatloads of strange dietary supplements and be on constant guard for signs of infection.

I thought of my previous incarnation and the Hirschsprung families who would occasionally call the lab. I remembered their need to tell me their stories. I remembered feeling awkward at not being able to empathize. My two-plus years of training as a genetic counselor had failed me. I knew more about Bayesian risk estimates than I did about what to actually say to the grief-stricken mother of a sick newborn. I was mostly useless. But how could I pos-

sibly empathize? I was not one of them. Now I wondered about Jesse. What if he carried one of the mutations I had identified 10 years earlier? What if my brother did? What if I did? And what did it mean?

God, I decided, was screwing with us.

I called my brother on the phone one day. He was tired and loopy after another night on the foldout chair in the hospital. “How’s it going?” I said. An absurd question and a pretty feeble conversation starter. “Why,” my brother wanted to know, “couldn’t you have done your graduate work on the gene for large penises?”

I tell it because it points up the fact that all human genomics is personal – that is to say, it is finally about us.

I tell the Hirschsprung’s story not to elicit sympathy, though my brother and his wife surely deserve it in spades, as do all the other parents who’ve ever had to watch their babies tethered to tubes in the pediatric intensive care unit, terrified and uncertain about what the coming days might bring. Nor do I tell it because it strikes me as so metaphysically improbable, though, despite knowing better, I remain convinced that it is. I tell it because it points up the fact that all human genomics is personal – that is to say, it is finally about us.

Mothers and fathers can negotiate almost anything: marriage, money, careers, sex, cooking, laundry, the Netflix queue, who gives the dog a bath. What they can’t negotiate are their own genomes (although with techniques such as preimplantation genetic diagnosis, a few are beginning to negotiate the genomes of their children). Occasional strange cases notwithstanding, every parent gives his or her biological child 50 percent of that child’s DNA. And every one of us, regardless of ZIP code, membership in an executive health program, or religious affiliation, carries at least a handful of harmful mutations that may or may not manifest in us or in our children, should they inherit them as part of that 50 percent.

Yes, Jesse’s Hirschsprung’s disease was an unlikely event – on the order of one in 5,000. But unless we get hit by a bus or succumb to an infectious disease, eventually almost all of us are the numerator, the “one in” something – cancer, heart disease, diabetes, Alzheimer’s. Genes are rarely the final arbiter of these late-onset chronic conditions, our understanding of them remains woefully inadequate, and they probably don’t constitute the secrets of our being, but there’s no denying the importance that heredity plays in them.

One of the promises of personal genomics is that it will tell us exactly what we are at risk of becoming the numerator for. One of the dangers is that it might also tell our insurers the same thing while not being actionable. It will provoke suspicions and

perhaps ulcers and force us to think about our destinies in terms of probabilities, as though we are watching the tote board at a Las Vegas sports bookies a few minutes before kickoff.

How will I die? It might also tell us something about various “positive” traits – intelligence, memory, musical aptitude, athletic ability – and how we measure up ... or down. What will we do when our entire genomes are no longer abstractions but palpable bits of information we carry in our pockets?

A growing number of people are opting to find out. With some trepidation, I became one of them.

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