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From Icelandic family sagas to Neanderthal genes

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Who are we? Where do we come from? Such questions have intrigued people since time immemorial. Only the tools used to dig through the past have changed.

Photo: Einar Nilsen

For days, Reykjavík has been shrouded in dense fog. However, as we step out of the headquarters of DeCODE genetics, the clouds are breaking up. A rainbow arcs from the big grey building, across the city centre and all the way up to the Hallgrímskirkja church.

It is said that at the end of the rainbow lies a pot of gold. In the basement, underneath all the laboratories, lie blood samples from more than half of the population of Iceland in a gigantic freezer, where they are handled by the two robots named David and Goliath. The privately owned business that was acquired by Amgen in 2012 also has access to huge amounts of health data from all those who have donated blood.

The idea of mapping out the entire nation's genetic material by exploiting the Icelanders' interest in genealogy occurred to the neurologist Kári Stefánsson in 1996 (1). A well-functioning healthcare system gave access to medical information dating back to 1915. The family trees of Icelanders since the first settlement in the ninth century were collected in a national database. The online version is called Íslendingabók and can be freely used by Icelanders who want to find out who their relatives are. This combination of access to medical records, family trees that go back more than 1200 years and genetic sequencing from a small and relatively homogenous population remains unique in the world. Within a few years, it became possible to reveal hundreds of genetic variants that were associated with disease. The population's genes could be

traced back to the Norwegian Vikings and Celts, and the development of drugs adapted to the genotypes of individuals – so-called precision medicine – gained momentum.

Without what started as a small business enterprise on a volcanic island in the North Atlantic, the Nobel Prize in Physiology or Medicine for 2022 might not have gone to Svante Pääbo (2). The mapping of the genome of the extinct human species *Homo neanderthalensis* and discovery of the previously unknown species *Homo denisoya* would have been impossible without the Human Genome Project. What was the model for the mapping of the genome of *Homo sapiens sapiens*? It was the population-based genetic research in Iceland.

In the wake of scientific breakthroughs, ethical dilemmas often follow. By 2015, the genome from a sufficient number of Icelanders had been sequenced to allow a very precise prediction of the genetic variation in the population as a whole – including those who had not participated in the study (3). In some populations, there is an entire range of mutations in the BRCA-1 and BRCA-2 tumour suppressor genes, which greatly increases the risk of a number of types of cancers, especially breast and ovarian cancer in women. In Iceland, there is only one single founder mutation in each of the genes. These mutations can be traced back to the time when Norwegian Vikings were crossing the sea to colonise the island. The BRCA-1 mutation is rare, but the BRCA-2 mutation accounts for approximately 40 % of the cases of familial breast cancer in the republic (4). Approximately 2 400 Icelanders, 0.8 % of the population, are carriers.

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Kári Stefánsson, who claims to be able to trace his ancestry back to Egil Skallagrimsson (5), wanted to inform all the study participants about the risk of cancer. However, Icelandic legislation did not permit this, in part due to the Oviedo Convention from 1997, which seeks to ensure that scientific and medical progress does not come at the expense of human rights (6). Article 10 describes 'the right not to be informed'. All patients have the right to be informed about their own health condition, but they shall be able to choose for themselves whether or not to have this information.

Knowledge allows people to choose. Carriers of BRCA-2 mutations can choose to be closely followed up with mammography. They can also have breasts and ovaries removed preventively. Not everybody wants to know, however. While a decision not to know can subsequently be reversed, the opposite is impossible: once you have learned something, you cannot revert to a state of ignorance. Receiving information about pathogenic mutations can therefore be a harrowing experience for individuals, with implications not only for the person concerned, but also for future generations.

Digital technology can apparently give control of personal health data back to the individual. DeCODE genetics established a website for study participants, where they *can* find out whether they are carriers of the BRCA-2 gene. Those who receive a positive result are offered genetic counselling and a repeat gene test to make a definitive diagnosis. As of the end of May 2019, more than 46 000 Icelanders (19 % of the adult population) had registered on the website, and 352 had received a text message about a positive BRCA-2 gene test (7). A little more than half of them sought out genetic counselling. The majority had a negative emotional reaction upon receiving the message, but many of them later expressed gratitude for having learned that they carried the pathogenic mutation.

In Norse mythology, Bivrost, another name for the rainbow, is the bridge between the realm of the gods and the human world. When Francis Collins, the head of the National Human Genome Research Institute in the United States, announced that the human genome had been mapped, he referred to it as 'the book of life' (8). Knowing the sequences of the human genome is like being able to read our own instruction manual, previously known only to God, he said. But with divine insight comes great responsibility. The challenge is no longer how we will gain access to more genetic information. The challenge is to use this knowledge in the right way.

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