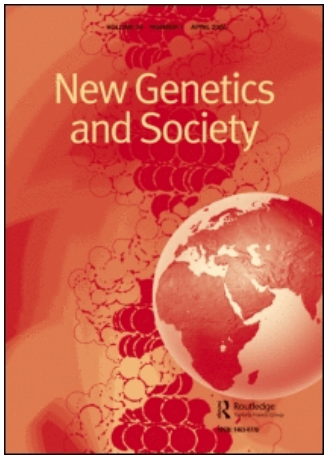

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Genomics and self-knowledge: implications for societal research and debate

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ABSTRACT *When the Human Genome Project (HGP) was launched, our genome was presented as our 'blueprint', a metaphor reflecting a genetic deterministic epistemology. Eventually, however, the HGP undermined rather than strengthened the understanding of genomes as blueprints and of genes as ultimate causal units. A symbolical turning point was the discovery that the human genome only contains ~22,500 genes. Initially, this was seen as a narcissistic offence. Gradually, however, it strengthened the shift from traditional genetics and biotechnology (i.e., gene-oriented approaches) to genomics, i.e. genome-oriented or systems approaches, emphasizing complexity. The 20th century can be regarded as the century of biotechnology and of the gene. Its history demonstrated that the will to know (notably: to know ourselves) has never been a disinterested affair: it is driven by a will to improve (notably: to improve ourselves). In this article it is claimed that, as genomics takes us beyond a genetic deterministic understanding of life, this must have consequences for societal research and debate as well. Policies for self-improvement will increasingly rely on the use of complex interpretation. Therefore, the emphasis must shift from issues such as genetic manipulation and human enhancement to issues involved in governance of novel forms of information.*

> Many tasks lie ahead if we are to learn how to speak
> the language of the genome fluently. (Francis Collins, 26 June 2000)

> We simply do not have enough genes for the idea
> of genetic determinism to be right. (Craig Venter, 26 June 2000)

Introduction: self-knowledge = self-improvement

'Know thyself' was a famous admonition inscribed on Apollo's temple at Delphi in ancient Greece. Self-knowledge was regarded as the ultimate goal of all knowledge-directed activities, but also as pivotal for gaining access to the world around us. The Self was considered a microcosm, mirroring the world at large. The ancient admonition was taken up by the neo-classicist poet Alexander Pope (1688–1744) in a frequently cited section of his *Essay on Man*:

> Know then thyself, presume not God to scan,
> The proper study of mankind is man. (Pope, 1924/1959, p. 189)

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When on 26 June 2000, during their famous Press Conference at the White House, Bill Clinton, Francis Collins and Craig Venter declared that the Human Genome Project (HGP) was rapidly approaching its completion, Collins, as director of the International Human Genome Sequencing consortium (IHGSC), cited these very lines in his address. After a long journey of exploration, we will finally be able to know and explore ourselves.[1] He described the human genome as 'our own instruction book' and as 'the draft of the human book of life'. Moreover, he expected that this tremendous progress in self-knowledge would provide us with effective tools, indispensable for fighting diseases such as cancer. Genomics would enable us to significantly improve the human condition.

This shift from knowledge to power is important. Our desire to understand both ourselves and the world around us has never been a completely disinterested affair. Even fundamental research programs are inspired by a *Will to Power* (Nietzsche). This, at least, was the a priori conviction of philosophers such as Friedrich Nietzsche (1844–1900) and Michel Foucault (1926–1984). Research is oriented towards improvement and control. We are determined to acquire knowledge with regard to something in order to gain power over it, to adapt it and transform it. We want to know in order to master, change and ameliorate. And this is particularly true when it comes to self-knowledge. We want to know ourselves in order to master, modify, improve ourselves. Self-knowledge is directed towards self-reform. In ancient Greece, Plato used mathematical knowledge in order to produce a reformed type of human being. His dialogue *Politeia* draws up the contours of a science-based curriculum encouraging the improvement of individuals on the basis of ancient geometry (Plato, 1930/1999; Jaeger, 1959). From a Nietzschean or Foucauldian perspective, the drive towards self-improvement and self-control is what various socio-cultural programs emerging in the course of centuries, varying from medieval Christian asceticism to 20th-century social engineering (Skinner, 1948/1976), have in common. And as science and technology evolve and self-knowledge deepens, new tools for self-improvement are bound to emerge, much more powerful no doubt that the type of science-based education recommended by Plato.

As the HGP came off ground, the 25-century-old quest for human self-knowledge seemed to be entering a decisive stage. The human genome was regarded by many as our 'blueprint'.[2] And it seemed logical to argue that once we have unravelled and sequenced this blueprint, we will at last be able to know ourselves. Moreover, if Nietzsche and Foucault were not mistaken, the mapping of this 'blueprint' would provide us with new prospects for self-mastery and self-modification. One of the authors adopting this line of thinking was Peter Sloterdijk (1999). Starting with Plato, he describes human history as a series of efforts towards self-amelioration. Initially, 'soft' techniques, notably education (teaching people to read and write) were applied. This was part, Sloterdijk argued, of the humanistic program that had been an influential civilizing force in human culture for many centuries. But now, in the genomics era, the high tide of the life sciences, much more powerful tools ('hard' techniques) will become available. Sloterdijk refers to them as *anthropotechnologies* and argues that we

better start thinking about how to apply these technologies rather than claiming that, in the name of 'human dignity', the development of such a repertoire should not even be considered. Sooner or later, we will be forced to move beyond the restricted strategies of traditional humanism. The logic behind his argument is, once again, that remarkable progress in the field of knowledge will inevitably be used to further our *self*-knowledge and will, eventually, and by necessity fuel our desire to improve ourselves.

In this article I will argue that, although the human genome project (HGP) did have a significant impact on our self-understanding, it turned out to be a different one than was initially expected. The HGP was originally seen as the culmination of what has been called 'the century of the gene' (Fox Keller, 2000). It was devoted to mapping all the genes on the human genome—our blueprint or genetic program. Yet, as the HGP and other genomics research activities progressed, the researchers involved made a discovery that may be regarded as more or less inevitable—in the sense of predictable: a standard event in the basic narrative of scientific inquiry, namely, the recognition that the world is much more complex than was expected at first, when the program initially set off. What I mean is that eventually, the HGP has *undermined* rather than strengthened our understanding of the genome as our blueprint and of genes as ultimate causal units. The belief in the existence of series of more or less mono-causal relationships between genes and traits has lost much of its credibility. The HGP has forced researchers to thoroughly reconsider the role and function (and indeed, even the ontological status) of our genes. The question I will consider in this article is what the philosophical implications of this (more or less unexpected) outcome must be for the way we see ourselves and think about ourselves, notably when it comes to prospects for self-improvement. My contention will be that genomics research has acquired an epistemological profile *sui generis*, fundamentally different from traditional genetics and biotechnology, and that this calls for a completely different and revisited agenda for ethical and societal debate in comparison to what was initially envisioned. Whereas a good deal of contemporary societal debate is still framed in the language of the 1990s, genomics research forces us to address new challenges and to really move the debate into the 21st century.

The century of the gene: between parentheses

The 'century of the gene' started in 1900 with the rediscovery of the work of Gregor Mendel (1822–1884). Some years later the term 'genetics' was introduced, and in 1953, around the middle of the century, Watson and Crick discovered the structure of DNA. Finally, in 2000, it was proudly and officially announced that the HGP was rapidly approaching its completion. These are the cardinal points, the markers so to speak of the gene-century. The rediscovery of Mendel's work and the (almost) completion of the HGP are its *parentheses*. Furthermore, the claim of Nietzsche and Foucault that knowledge is directed towards self-knowledge and, eventually, towards self-control seems to be confirmed by the history of genetics. Almost from the very outset, geneticists began to think about possibilities for applying

Mendel's laws to human beings.[3] The exact relationship between genetics research and the (real or envisioned) applications to mankind is, of course, a highly complicated and controversial one. The eugenics movement of the first half of the 20th century has gained a highly problematic political reputation, to put it mildly, and not undeservedly. Eugenics has become a term of abuse and researchers involved in recent developments such as 'community genetics' exert themselves to emphasise the extent to which their research endeavours differ from traditional eugenics—the basic difference being that whereas (in terms of policy) eugenics focussed predominantly on 'top down' interventions by governmental bodies and state authorities, the focus of community genetics and public health genomics will be on empowering individuals to make their own choices ('bottom up'). Yet, the shadow of eugenics is still clearly noticeable.

An impressive recent analysis of the intricate relationship between genetics and eugenics is Simon Mawer's book (half biography, half novel) on Mendel (Mawer, 1998). On the one hand, it is a story about a molecular biologist who suffers from achondroplasia (dwarfism), a monogenetic (autosomal dominant) genetic 'defect'. His life's work is devoted to discovering the 'gene that caused him' and, eventually, to developing the tools that will allow mankind to cleanse the gene pool of this defect (that is, his research objective is basically the extermination of dwarfism, of individuals like himself). Yet, fictional accounts of the vicissitudes of this bizarre molecular biologist alternate with biographical descriptions of and reflections on Mendel's life and work. The novel is an acute analysis of, but at the same time a critical reflection on, the idea that we *are* our genes—that is, genetic determinism.

Throughout the 20th century, from the rediscovery of Mendel's work via the discovery of the structure of DNA up to the launching of the HGP, the deterministic idea that we *are* our genes has been a recurrent theme. It is, so to speak, an important element in the 'score' of this century of the gene. Yet, it has always been contested, mitigated and counter-pointed. Indeed the nature-nurture controversy has been one of the major ideological and scientific quandaries of the 20th century, and if we say that the 20th century was the century of the gene, we should not take this in the sense that genetic determinism was its dominant creed, but rather in the sense that in the context of the nature-nurture controversy, 'nature' became more or less identical with 'genes'. Ironically, however, it was the fate of the HGP to undermine rather than confirm the idea that we *are* our genes. But before addressing this issue in more detail, it must be emphasized that the 20th century was not only the century of the gene, but also of biotechnology. In its final decades, a powerful synthesis came about between biotechnology and genetics. Genomics research (as a successor to traditional genetics) was initially expected to consolidate this synthesis.

The century of biotechnology

Around 1900, biologist Jacques Loeb (1859–1924) voiced the idea that nature must be regarded as raw material, to be modified and improved by biological

engineers (Pauly, 1987). Biology's core objective, Loeb said, is the improvement of nature. Why accept existing biological constraints as given? Why not use biological knowledge in order to improve life and—eventually—ourselves, much more directly and effectively than we have done so far? Why not prolong the human life-span or opt for artificial instead of sexual reproduction? These ideas, articulated in interviews in magazines were futuristic extrapolations of his research with model organisms such as sea urchins. By manipulating the chemical composition of their environment, Loeb managed to induce 'artificial parthenogenesis' (non-sexual reproduction) and concluded that, in the end, artificial reproduction in 'mammals' (i.e., humans) would be possible as well. Children born without male involvement would free future women from the necessity of associating themselves with men in order to become mothers. Although in the context of his experiments the actual power of science over nature was still rather limited, the ideological *framing* of his research (and the recognition of its potential impact for society) was clear enough. The famous first chapter of Aldous Huxley's *Brave New World*, describing the 'Central London Hatchery and Conditioning Centre', consciously echoes Loeb's ideas. Huxley's novel is a classic effort to describe the atmosphere of discontent that biotechnology incited in broad circles. The first chapter describes how the chemical environments of embryo's kept in vitro are systematically manipulated in order to adapt them to societal demands and the chapter actually contains some references to Loeb's views.[4] The basic goal of biotechnology was clear—evidence-based amelioration of human nature: (self-) knowledge is power.

The same biotechnological impetus was apparent in the work of other biotechnologists, such as Hermann Joseph Muller (1890–1967). Building on his laboratory research (exposure of fruit flies to radiation in order to inflict, and study the effects of, mutations) he envisioned a program for the improvement of the human species. In the 1930s he even went to the Soviet Union where a large-scale political program for improvement of human beings had been launched and where he offered his ideas. The advent of Lyssenkoism, however, hampered genetic research in Russia. Communists regarded genetics as a reactionary science, as it predicted the re-emergence in future generations of undesirable traits that political regimes set out to suppress. Lyssenko's ideas were more in tune with communism, focused on the manipulation of environmental factors such as: exposure (of plant forms, but this could also apply to human beings) to extreme conditions, for example, cold. Muller and Lyssenko shared the basic belief that biotechnology will provide us with powerful tools for improvement and, eventually, for self-improvement. Yet their actual research results were not at all sufficient to support these grand societal claims. Biotechnological research as it had evolved so far did not really give them the tools that would allow them to realize their visions.

When in the 1970s the biotechnological revolution finally took place, and tools for effective manipulation of species became available, the socio-political landscape had dramatically changed. Totalitarian regimes that had nourished dreams about science-based improvement of the masses and the people, had

given way to much more open societies, where the setting for biotechnology had altered from top-down and large-scale manipulation (as envisioned by Huxley, Lyssenko and others) to bottom-up strategies for empowerment of individuals. Although some of the technologies announced in *Brave New World* really became available (notably IVF), they were not used for grand programs in the context of 'biopolitics' (mass improvement) but rather for allowing individuals to solve their personal problems (such as childlessness). Moreover, biotechnology (notably in the context of improving crops and livestock) had now unequivocally shifted its focus of attention from manipulating environments to manipulating genes: the 'wedding' of biotechnology and genetics (Bud, 1993, pp. 163ff.).

As biotechnology really became powerful, during the final decades of the 20th century, it incited a considerable amount of societal uneasiness and discontent. Critics considered Western societies as much less open and individuals as much less autonomous and free to choose than proponents of biotechnology suggested. New biotechnologies were seen as potential threats to reproductive autonomy and the environment. In public debates over biotechnology, references to 'brave new world' frequently arose. Whereas scientists emphasized the societal prospects and promises of biotechnology (fighting hunger, improving health, generating economical benefits) there was a substantial amount of hesitance towards, or even downright rejection of, biotechnological products among the public, especially in European countries. Indeed, the late 1990s have been described as the 'years of controversy' (Gaskell & Bauer, 2001). Two events, the announcement by Jacques Loeb at the beginning of the century and the growing resistance towards biotechnology during its final decade are the parentheses, so to speak, of the 'century of biotechnology'.

These two story lines (the synthesis of genetics and biotechnology on the one hand and the controversies this synthesis incited on the other) set the scene for the launching of the HGP. As flagship project of genomics research, but in close connection with other efforts to sequence the genomes of 'model organisms' (Drosophila melanogaster, C-Elegans, the laboratory mouse), the HGP would constitute the final act. The wedding would come to fruition, as new and powerful tools for biotechnology would finally become available. New prospects would be opened up for knowledge (including self-knowledge) and amelioration.

The subsequent debate over the societal impacts of genomics developed in several directions. On the one hand, the genomics researchers themselves in their societal communications tended to focus on short-term benefits and moderate goals such as crop improvement, the production of healthier foods and better medicines as well as the fight against hereditary disease. Others, however, notably novelists and philosophers, went a step further. Peter Sloterdijk's announcement of the advent of anthropotechnologies was already mentioned. Another voice deserving to be mentioned here is Michel Houellebecq (1998) whose novel *Elementary Particles* aroused much response. While criticizing technologies of the self that individuals experimented with in the 1960s, such as drug use and sexual liberation, he propagated the idea that now, at the turn of the millennium, we are really entering a new era, in which much more powerful and science-based

technologies will become available for self-improvement, leading us far *beyond* humanity as it had developed so far, on the basis of evolution and history. Although not many details are given in terms of exactly *how* this self-transformation, this leap into post-humanism will be achieved, the message is nonetheless clear enough.

Another line of thinking belonging to this trend has baptized itself 'transhumanism' (see <http://www.nickbostrom.com/>). The objective is to set the stage for genetic enhancement, not by fighting monogenetic defects, but rather by using genomics to achieve positive intellectual enhancement (learning capacity, alertness, creativity, intelligence, social cognition, empathy, etc.). Opponents to this idea (and this includes authors such as Leon Kass (2002), Francis Fukuyama (2002) and Jürgen Habermas (2003)) are dismissed as 'bio-conservationists'.

It is the objective of this article to point out that this line of thinking, however intriguing or disquieting as a *thought experiment*, is actually mistaken and misguiding in a rather fundamental way. Genomics research is neither about fighting monogenetic health problems nor about cognitive enhancement through anthropobiotechnologies. In order to really address the ethical and societal challenges involved in genomics research, we must first of all try to define its epistemological profile much more precisely. Genomics is not about modifying organisms, nor about finding the genes that will enable us to improve ourselves, but rather about understanding and managing massive files of information concerning complex processes and interactions. And once we realize this, it must affect the framing of our agenda for philosophical and societal debate. Grand ideas about genetic enhancement of humanity as such have more or less become outdated by the way genomics research has actually developed. However futuristic these ideas may sound, in terms of their basic premises they are actually still part of the mindset of the 20th century. The real challenges of genomics research will have to be framed in a rather different manner. It will not take us beyond humanity (for the time being at least), but it *will* take us beyond the ideals and discontents of biotechnology and genetic modification as envisioned during the final decades of the 20th century. Genomics research in general and the HGP in particular did not have the outcome they were initially expected to have. It is time to revisit our societal agenda and to go beyond the clichés of the biotechnology debate as it evolved in the 1990s. We will not enter a post-human era, but we *will* be confronted with a situation that is, in important respects, without precedent—and for which we better prepare ourselves.

The Human Genome Project

On February 2001, the International Human Genome Sequencing Consortium (directed by Collins) in collaboration with its competitor (Celera Genomics, directed by Craig Venter) published 'working drafts' of the sequence of the human genome in *Nature* (IHGSC, 2001)and *Science* (Venter *et al.*, 2001). In the opening lines of the IHGSC article, the HGP is presented as the completion of the century of the gene: 'The rediscovery of Mendel's laws of heredity in the

opening weeks of the 20th century sparked a scientific quest to understand the nature and content of genetic information that has propelled biology for the last hundred years' (IHGSC, 2001, p. 860). This perspective is taken up again in the concluding section: 'The Human Genome Project is but the latest increment in a remarkable scientific program whose origins stretch back a hundred years to the rediscovery of Mendel's laws and whose end is nowhere in sight' (*ibid.*, p. 914). These quotes put the century between its proper parentheses. During the last quarter of the century, moreover, the focus had shifted from deciphering genes to sequencing genomes, from a focus on single genes to a willingness to take a 'comprehensive' or genome-oriented view (*ibid.*, p. 862). The challenge from now on would be to transform information into *understanding* (*ibid.*, p. 914). Indeed, the HGP is presented as a turning point: the completion of the 20th century and the beginning of the 21st. Now that the human genome has been sequenced ('structural genomics'), the emphasis will shift to understanding the intricate complexities of gene *function* ('functional genomics'). In other words, the HGP is not a conclusion, but rather a starting point for future research of a completely different type.

The HGP was launched in 1988, with James Watson as its first director, although the formal initiation took place on 1 October 1990. The ultimate goal was to compile a complete list of all human genes, a 'periodic table' for biomedical inquiries (IHGSC, 2001, p. 892). In 2000, while announcing that the HGP was approaching its completion, Clinton stated that he regarded the genome as a kind of *map* while Blair (via satellite) referred to it as 'the working *blueprint* of the human race'. It was heralded as 'the first great technological triumph of the 21st century'. Clinton and Collins also indicated that the knowledge generated by the HGP will give us immense *power*. What more powerful form of self-knowledge can there be than the ability to read 'our own instruction book'?

From a philosophical perspective, the HGP raises a whole series of interesting questions, ranging from the issue of commercialization to the meaning of authorship in the genomics era. While the *Nature* publication of Watson and Crick had been a two-author article, IHGSC's article listed 249 authors and Venter's publication 285. Clinton and Blair emphasized the importance of both collaboration and competition. James Watson (1968) had already described science as competition between rivaling teams, and the HGP has been described as a 'Genome War' by James Shreeve (2004), a metaphor that reflects the tremendous increase in scale, for while the structure of DNA was discovered by two researchers, engrossed in an unofficial research quest (more or less dropping out from their official research assignments), the HGP was a large-scale, multi-centre, multinational, acutely managed research program. It was a competition moreover between two styles of research, in terms of *methodology* (the more conservative 'hierarchical' versus the controversial 'whole-genome' shotgun approach) and *funding* (public versus private funding). Eventually, however, both teams came to regard one another as 'complementary' (see <http://www.genome.gov/10001356>).

Thus, while the HGP can be looked at in various ways, I will focus on one aspect only, namely, the fact that in the course of the HGP, something remarkable has happened. Initially, estimates of the number of genes on the human genome tended to vary greatly. Figures ranging from 80,000 to 200,000 genes were given. Walter Gilbert (1992) had suggested that the human genome contained something like 100,000 genes. The 'pleasing roundness' of the figure apparently led to it being widely quoted and adopted (IHGSC, 2001, p. 898). James Watson (2002) had mentioned 248,000 genes as a probable figure. In 2000, an estimate of 120,000 genes was still proposed (Liang *et al.*, 2000), but more modest estimates (40,000 genes) were also circulating. In 2001, IHGSC's official estimate was reduced to ~31,000 genes. But in 2004, in the landmark paper that described and discussed the finished version ('build 35'), covering 99% of the human genome, a more or less final estimate was given (IHGSC, 2004). Apparently, the human genome contains ~ 22,500 genes. Gert-Jan van Ommen (2005, p. 931) stated that this finished version will serve as a 'firm foundation for biomedical research in the decades ahead', a robust resource for future research. He was somewhat astonished by the fact that in this 'final' paper the human gene count was corrected to an estimate of 22,500.[5] This was something of a disappointment indeed, not only in comparison to previous (and intuitively more convincing) estimates, but also in comparison to the number of genes on the genomes of other model organisms such as Drosophila melanogaster (~14,000 genes), Caenorhabditis elegans (~19,000 genes) and Arabidopsis thaliana (~25,000 genes). Van Ommen (2005, p. 931) remarks: 'one almost wonders what . . . *does* set us apart from flies and worms'.

In its own comment the Consortium agrees that the number of genes is modest ('only about twice as many as in worm or fly', IHGSC, 2004, p. 860), but this is explained by saying that human genes are 'more complex, with more alternative splicing generating a larger number of protein products' (IHGSC, 2004, p. 860). Yet, ambivalence is clearly noticeable. On the one hand it is said that, in various ways, genome characteristics (size, number of genes, tRNA genes, etc.) do not seem to correlate well with 'organismal complexity'. On the other hand, the authors remain inclined to stress, for a variety of reasons, the uniqueness of the human genome: standing 'in stark contrast to the genome of other organisms' (IHGSC, 2004, p. 882). Mere gene number does not confirm this. The number of genes remains something of a surprise—counter-intuitive, at least.

The surprisingly small number raises an intriguing philosophical question: how can the genome of an organism able to create a highly complex, artificial environment, a technological world, a 'technotope', contain such a small number of genes? While we are exploring and unravelling the structure of the universe and reshaping our environment at an unprecedented scale and pace, the genetic basis for our unique talents and creativity remains unclear. On the level of our genome, we do not seem that different at all. Our uniqueness and otherness is not reflected by our genes, at least in terms of number.

This astonishment may give rise to at least three different lines of argument. The first one can be referred to as 'replacement'. Complexity must be there,

but we must look for it *elsewhere*, for example in the remarkable functional plasticity of human genes. Complexity is not a matter of quantity, but rather of intensity, of intricate pathways. This is the position taken by the Consortium, and seems to be the dominant trend among life scientists in general.

The second line of argument can be referred to as 'disenchantment'. Apparently, we are not that different after all. As Venter (http://www.genome.gov/10001356) phrased it during his White House speech: 'We . . . have many genes in common with every species on Earth . . . we're not so different from one another. You may be surprised to learn that your sequences are greater than 90 percent identical to proteins in other animals . . .'. Indeed, the HGP simply confronts us with yet another 'narcistic offence'. As Sigmund Freud (1917/1947) explained in his famous essay, scientific research inevitably confronts us with findings (such as Copernican heliocentrism and Darwinian evolution) that challenge our belief that we are somehow different. One could add that after Copernicus and Darwin, science has continued to generate narcistic offences of various kinds. The HGP is simply another proof of the vulnerability of our narcistic overestimation (Vollmer, 1992).

A third strategy, the one I will subscribe to in this paper, can be referred to as 'reframing'. If we look at the HGP more carefully (take a 'second look'), our complexity, the idea that we are somehow unique, is confirmed rather than denied. From a philosophical point of view, the 'disenchantment' argument is not wholly convincing. Of course we must remain alert to narcistic biases in our self-image. And undoubtedly, biological research has demonstrated that, as *biological organisms*, we are not that different. Nonetheless, it is clear that we have introduced something without precedent: a technological culture that allows us to inhabit a world of our own making. No other organisms have engaged in such activities (or only in rudimentary ways). No other organisms have addressed issues such as heliocentrism, evolution or genomes. Indeed, no other organism 'has sequenced its own genome!' (Collins, 2006, p. 125). No other species could even consider such a possibility. Due to our remarkable openness to the world, we are the only living beings that are able to *offend* themselves, to challenge appearances—even their own self-image. Although there is continuity (on the biological level) between us and other species, there is (on the cultural level) an evident gap as well. And still, apparently, we do not find our remarkable creativity and intelligence reflected in our genome.

In a famous article in the *New York Times*, Stephen Jay Gould (2001) also addressed this issue. According to Gould, the HGP's final result, in terms of gene number, was not disappointing, but *reassuring*. It changed the way we think about our genome in relationship to ourselves. Initially, the HGP project was seen as the final confirmation of genetic determinism and of its logical counterpart, genetic reductionism. Both research strategies were moved by the desire to discover mono-causal relationships between genes and traits. Genetic determinism claims that single genes determine discrete traits and, pushed to its extreme, the basic objective of genetics is to discover a gene for every possible trait. Genetic reductionism, on the other hand, works the other way around, but on the basis of the same belief: there must be a gene to every trait we are interested

in. Initially, the HGP was regarded as the culmination of this line of thinking. It was seen by many as 'the culmination of the reductionist approach characteristic of molecular biology' (Vicedo, 1992). According to Gould, however, writing in 2001 and reflecting on an estimate of $\sim$ 30,000 genes in the human genome, this has now become impossible. The HGP makes clear that human complexity cannot be generated by 30,000 genes (let alone 22,500 genes). The HGP has undermined 'the old view of life embodied in what geneticists literally called (admittedly with a sense of whimsy) their 'central dogma': DNA makes RNA makes protein—in other words, one direction of causal flow from code to message to assembly of substance, with one item of code (a gene) ultimately making one item of substance (a protein), and the congeries of proteins making a body'. According to Gould, the collapse of the doctrine of one gene for one protein, and of one direction of causal flow from basic codes to species characteristics, marks the failure of reductionism for biology. He writes: 'Biomedical research over the past decade has been dominated by a genetic determinist understanding of disease and the discredited doctrine of "one gene, one protein". One thing the human gene map does tell us is that there are ten times as many proteins as genes. Genetic determinism is dead' (Gould, 2001). The HGP has frustrated the intuitive assumption that there must be a relationship somehow between organismal complexity and gene number. It seems impossible that 22,500 genes are enough to package all the information needed to become a human being.

This issue is also taken up by Adam Wilkins in an editorial comment in *Bio-Essays*. He points out that the human genome project has 'not only been a story of massive technological innovation and high scientific accomplishment but also a history of grand pronouncements' (Wilkins, 2001, p. 561). As the sequencing process nears completion, hyperbole gives way to more realistic statements and this clearly also pertains to the decreasing estimates of gene number. Wilkins is critical of a statement made by Craig Venter saying that the surprisingly low gene number shows that we are 'not a product of our genes' and that 'the wonderful diversity of the human species is not hard-wired in our genetic code—our environments are crucial' (Venter, 2001, p. 1). In his comment, Wilkins emphasizes that this is, of course, a simplification. We should not address this issue in terms of either/or. He agrees that to a certain extent the belief in genetic determinism belongs to the past and that the HGP has contributed to this development. Reported identifications of single genes for traits such as criminality and gender preference have lost much of their former credibility. Downstream causal flow from gene to trait is much more complicated that genetic determinism was willing to accept. The trajectories from genetic information to behaviour involve 'intricate and complex chains of events'. Quite a range of different products can emerge from one single gene. Hence, simply knowing the gene number of an organism is not a measure of complexity. The nature-nurture dichotomy that was so influential in scholarly and political debate in the 20th century has become grossly outmoded. We have finally moved beyond this dichotomy, this either/or.

Thus the impact of the HGP is the reverse of what was originally expected. In 1992, as the project was in its early stages, Gilbert suggested that the HGP would lead to 'a change in our philosophical understanding of ourselves'. Indeed, 'to recognize that we are determined. . .by a finite collection of knowledge that is knowable will change our view of ourselves. It is a closing of an intellectual frontier with which we will have to come to terms. Over the next ten years [we will understand *deeply* how we are] dictated by our genetic information' (Gilbert, 1992, p. 96). We now know that things have taken a different turn. The HGP has rather been the *opening up* of frontiers. It has taken us *beyond* genetic determinism. Yet, terms like determinism and reductionism, used somewhat loosely perhaps in this section, are complicated and highly controversial, especially in philosophical circles. In order to put this discussion in its proper perspective, we must therefore consider the concepts of 'genetic determinism' and 'genetic reductionism' in some more detail.

Beyond reductionism? On defining genomics

A strong initial motivation for the HGP was to relate biological features to the structure and function of small sets of genes or, ideally, to individual genes (Gierer, 2002, p. 25). Gradually, however, this reductionist approach gave way to a 'systems' approach emphasizing the interplay of large numbers of genes, and the involvement of complex networks of gene regulation. According to Gierer, contemporary genomics research may even be called 'holistic', if the term is not used in a pejorative sense. Indeed, the history of biology can be seen as a chronic struggle, an oscillation between reductionism and holism. And genomics, although initially inspired by a more or less reductionist style of thinking, has shifted the emphasis again towards 'holism'. Most aspects of human life cannot be explained in terms of monogenetic causation. The typical bottom-up approach of molecular biology is not sufficient, a top-down, holistic or systems approach is indispensable.

But what exactly do we mean by concepts like 'reductionism' and 'determinism'? In the context of the life sciences, reductionism may mean a variety of things. At least three basic definitions of the term can be distinguished, namely: ontological, epistemological and pragmatic reductionism. Ontological reductionism is the belief that all phenomena in nature can ultimately be reduced to a limited number of causal units (for example genes, or—ideally—elementary particles). These primal causal units are regarded as determinants of everything else.

Epistemological reductionism is the belief that eventually all forms of knowledge can ultimately be reduced to knowledge claims belonging to one basic discipline. In the context of biology, epistemological reductionism would be the belief that eventually all biological knowledge claims can be reduced to or translated in terms of genetics. Both ontological and epistemological reductionisms are philosophical positions: guiding ideas or *a priori* convictions. In principle they cannot be empirically proven.

Pragmatic reductionism is different. It does not contain grand ontological claims about nature as such, but basically says that, although the real world is no doubt tremendously complex, it will be difficult if not impossible to do justice to this complexity in the context of laboratory research. In order to understand a particular phenomenon, the relationships between a limited number of determining factors will have to be studied. Not because scientists believe that this is all, or that everything is determined by (or can be explained on the basis of) a limited set of mono-causal relationships, but simply because the number of factors that can be meaningfully studied in a laboratory setting is limited. Once the relationships between these factors have been established, researchers will try to extrapolate their research finding to the real world, in the expectation that, out there, things will prove much more complicated. In other words, reductionism is a methodological requirement. It is basically a (highly successful, but from a philosophical perspective rather problematic) research *strategy*.

The idea behind genomics, however, is that this may no longer be the case. Because of completely new research tools that have become available (high throughput analysis, bioinformatics, computational biology, micro-array research) it has become possible to study and analyze complex relationships *within* a laboratory setting. Genomics allows us to simultaneously study the function of *all* the genes on the genome of an organism, in interaction with its environment. In other words, whereas traditional genetics was about a limited number of genes, genomics is about a whole genome comprehensively. And whereas biotechnology was about transferring or deleting single genes (genetic modification), genomics will focus on understanding complex systems.

The conceptual counterpart of reductionism is the term 'complexity', a key word in contemporary genomics research (as well as in many other contemporary research areas). What is complexity? Nobel Prize winner Murray Gell-Mann (1929–), famous for his discovery of the quarck, has argued that complex systems cannot be seen as determined by the behaviour of elementary particles. In his book *The Quarck and the Jaguar*, he writes: 'The laws of biology do depend on the laws of physics and chemistry, but they also depend on a vast amount of additional information. The science of biology is very much more complex than fundamental physics... (Gell-Mann, 1994, p. 115). Although physics and chemistry are evidently important, eventually complex living systems have to be studied on their own level of complexity. Moreover, complexity does not simply mean that things are very 'complicated' in the sense that many factors are involved. Rather, complex systems are 'systems that display properties that are not predictable from a complete description of their components, and that are generally considered to be qualitatively different from the sum of their parts'.[6]

In framing a definition for genomics, the term complexity can hardly be absent. But what exactly is genomics? In editorials commenting on the publication of the 'working drafts' in 2001, genomics is 'the beginning of a new approach in biology'[7] and a 'fundamental advance in self-knowledge'?[8] To what extent and in what way is genomics really 'new'?

The question 'What is genomics?' is not at all a trivial one (Delsi, 1988; Harris & Buckler, 1997). Different and often incompatible answers have been given by various experts. And the way we answer this question will have consequences for the way we think about our genome, as well as for the ways in which the debate over the societal aspects of genomics will have to be framed. The term *genome* was first used by H. Winkler in 1920,[9] but the neologism 'genomics' is of a much more recent date. It was coined in 1986 by Thomas Roderick as the title of a new journal and as a name for what is nowadays regarded as structural genomics: mapping or sequencing the genomes of model species. The editorial inaugurating the journal *Genomics* in 1 September 1987 was entitled, 'Genomics: A New Discipline, a New Name, a New Journal'. Although the genome was regarded as a blueprint, it was clear or course that sequencing a genome will not immediately tell us what the functions of particular genes are. Therefore, the focus of genomics was bound to shift sooner or later from structural to functional genomics. Whereas structural genomics can be seen as a continuation of genetics in the sense that it is still about detecting and locating genes, functional genomics is different in that it has taken a global, genome-wide or systems approach (Hieter & Boguski, 1997, p. 601). It is characterized by high throughput or large-scale experimental methodologies combined with computational analysis of data. Genomics is a converging field where genetics, molecular biology and bioinformatics come together and the DNA Micro-array is its basic tool, its basic symbol. It expands the scope of biological investigation from studying single genes to studying 'all genes ... at once in a systematic fashion' (Hieter & Boguski, 1997, p. 601). In the context of this shift from *genes* to *genomes* it became clear that in order to understand the function of genes, a mono-causal, reductionist approach is not very helpful. Functional genomics gradually moved into the practice of analyzing the interactions of large numbers of genetic and environmental factors. In other words, there was a shift from 'genetic determinism' (we *are* our genes) to 'understanding complexity' (studying complex interactions between 'nature' and 'nurture').

The philosopher John Dupré (2004) in a recent article also stresses the newness of genomics in comparison to its predecessor, 20th-century genetics. The *epistemology* of genomics is different. In the context of genomics, it has even become questionable whether the 'gene' is a meaningful concept at all. According to Dupré, the genome does not seem to contain anything that corresponds to traditional conceptions of genes. Despite its historical development out of genetics, genomics represents 'a radically different kind of scientific project' (Dupré, 2004, p. 320). It has undermined the ontological status of the gene, a construct that has lost much of its former usability and credibility. It may even become obsolete. Although we still talk about genes, and although through mass media we still learn with considerable regularity that scientists 'discover' genes, genomics forces us to reconsider the meaning of this concept. According to Dupré, the fact that in contemporary discourse 'genetics' is being replaced with 'genomics' is not merely a rhetorical move. The genome is completely at odds with a 'reductionist epistemology' that has been rendered obsolete (*ibid.*, p. 336).

The shift from a traditional monogenetic to a multi-factorial orientation is also apparent on the level of applied research. The reductionist approach was (and will continue to be) useful for studying traditional monogenetic health problems, such as Huntington's Disease or particular forms of cancer. Most human health problems, however, are multi-factorial. They are the emergent outcome of complex interactions between genetic and environmental factors, between (genetic) constitution and life style. Therefore, genomics has been regarded as a 'quantum leap in the life sciences' (van Ommen, 2002). In the genomics era it no longer seems viable to hunt for an 'intelligence gene' (IGF2R on Chromosome 6) or an 'aggression gene' (Pet-1).

The shift from genes to genomics, from 'genetic determinism' to 'understanding complex systems' is apparent in other areas as well, such as plant genomics. The difference between plant genomics and biotechnology is that genomics does not focus on genetic modification of organisms (gene transfer). Rather its basic objective is to understand and make more intelligent use of complex systems, to interact with them in a more intelligent and informed way. The same goes for a newly emerging, converging field called ecogenomics,[10] aimed at understanding the metagenome of the soil, which comprises the genomes of all soil organisms. A systems approach is vital for understanding complex soil properties such as fertility and resilience. It will support a more sustainable use of soil, interacting with nature more carefully and intelligently. In all these examples the claim is made that genomics, in comparison with 'traditional' biotechnology, has an epistemological profile *sui generis*. However, to the extent that knowledge is power, and to the extent that the will to understand is driven by a will to improve, one may also argue that this distinction between classical genetics and biotechnology on the one hand and genomics on the other is relative in the sense that, in the context of applications (for example in agriculture), the difference may blur. How questionable and/or rhetorical is the newness of genomics?

Definition politics

The claim elaborated in the previous section that genomics is really something 'new', differing significantly in terms of epistemological profile from traditional genetics and biotechnology, is highly controversial. Skeptics point out that actually, there is much continuity between these research practices. Although technologies for doing laboratory research have changed, the basic mind-set remained the same. Genomics is considered a buzzword, introduced for strategic reasons (in order to ensure massive funding, or in order to forego unfavorable associations with genetic manipulation in the public realm). Rather than moving beyond genetic determinism, genomics will eventually reinforce a deterministic view. This is a common line of argument among critics: genomics will eventually strengthen 'geneticalisation'. Instances of 'genomics news' (announcements of research results in public media) continue to focus on genes as ultimate causal constituents.

In the case of pharmacogenomics, for example, Hedgecoe (2003, p. 514) has argued that it must not be seen as a term representing a new area of research, but rather as 'a rhetorical device used to gain support among policy makers and funders for particular research topics and technologies'. Genomics is a dubious neologism, a label for what is actually a 'hype'. According to Hedgecoe, there is no real difference between pharmacogenetics and pharmacogenomics. Both study the impact of genetic differences that affect drug metabolisms (in terms of effectiveness and side-effects). He concludes that 'rather than representing a distinct research discipline, the term pharmacogenomics is a rhetorical strategy used to enlist support through association with the word *genomics*' (*ibid.*, p. 528).

I find this argument not convincing. Although it is certainly possible to indicate various continuities between pharmacogenoetics and pharmacogenomics, the basic epistemological difference as it was fleshed out above is nonetheless obvious, also in this case. Whereas pharmacogenetics relies on detecting single candidate genes, the emphasis in pharmacogenomics will be genome-oriented (interactions between large numbers of genes). As a subfield within genomics, it confirms the shift from a monogenetic to a more holistic approach, discussed above. Of course, these are 'ideal types' in the Weberian sense, and in concrete instances the theoretical distinction may well be less clear. And of course, research teams involved in pharmacogenetics will sometimes, for strategic reasons, undeservedly claim that they are involved in pharmacogenomics, thus adding to the confusion. Although these problems are real enough, it does not imply that the distinction *as such* is completely rhetorical. Although rhetoric undoubtedly plays a role, this should not divert our attention from what is, epistemologically speaking, the key issue here. I agree with Hedgecoe that genomics is strictly speaking not a new discipline or field. Rather, 'genomics' points to an epistemological shift *within* a number of disciplines or research fields: from a monogenetic to a (comprehensive) genomics orientation. A new style of research is introduced, based on new tools but also involving a different mind-set.

Reductionism and complexity in *Jurassic Park*

The shift from genetics to genomics is also reflected in one of the most important *literary* reflections on genomics, namely Michael Crichton's (1991) novel *Jurassic Park*. In this highly successful science novel, a company called InGen developed a sophisticated genetic engineering facility on an island in Central American where regulation is absent. A team of researchers was hired for setting up a theme park in a resort—a private Jurassic zoo of large dimensions. They achieve this by remaking Jurassic dinosaurs with the help of supercomputers using paleo-DNA extracted from blood preserved within mosquitoes entombed in fossil amber. The Jurassic animals, whose ecology has vanished, are introduced into an environment as 'Jurassic' as possible: a tropical forest area. Thus, in *Jurassic Park*, dinosaurs (the flagship species of palaeontology) have become experimental animals and palaeontology itself, the study of extinct life, is transformed overnight into an

experimental discipline. Excavations are no longer needed. When Alan Grant, an outstanding palaeontologist brought in to assess the safety of the resort, is confronted with living versions of his favourite organisms, he immediately realises the epistemological significance of this event. Palaeontological quandaries that occupied his mind for years, such as the issue of whether dinosaurs were warm-blooded and caring animals, are now easily resolved by merely looking at these 'surprisingly active' organisms:

> Grant's field of study was going to change instantly. The palaeontological study of dinosaurs was finished. The whole enterprise—the museum halls with their giant skeletons and flocks of echoing school children, the university laboratories with their bone trays, the research papers, the journals—all of it was going to end. (Crichton, 1991, p. 84).

The revivification of vanished life forms, based on a reconstruction of their genomes, is less absurd than it may appear at first glance: the idea has inspired serious research efforts—although most of them are directed at bringing back Holocene or Pleistocene species (such as mammoths discovered in Siberian permafrost). Notwithstanding a certain tendency towards exaggeration, Michael Crichton, a Harvard graduate, tends to be well-informed when it comes to contemporary laboratory life and cutting-edge research in the genomics era. His novels are usually well documented and based on substantial research. He is *au courant* with the latest developments in American (notably West Coast) science. His novels may be regarded as 'scenario studies'.

In one of his essays, Stephen Jay Gould (1996) submitted *Jurassic Park* to a critical assessment. Although it fails the test in terms of scientific scrutiny, this does not make the work completely nonsensical, says Gould. DNA is not a geologically stable compound and even if bits and pieces of dinosaur DNA could be sequenced, he argues, it is unthinkable that the geological record would somehow have managed to preserve the complete genetic program of an organism. In Crichton's novel, computational biology is called in to fill in the gaps with the help of frog genes but, as Gould emphasises, this whole idea evolves out of a 'deterministic' and 'reductionistic' prejudice. It will never be possible to make an organism from just a few percent of its codes. Indeed:

> An amalgamated code of, say, 80 percent dinosaur DNA and 20 percent frog DNA could never direct the embryological development of a functioning organism. This form of reductionism is silly. An animal is an integrated entity, not the summation of its genes (Gould, 1996, p. 227).

To a certain extent, however, this is acknowledged by Crichton himself. Although in his novel it is possible to bring extinguished species back to life again, using paleo-DNA as their 'blueprint', the novel eventually incites its readers to question a genetic deterministic view on life. In the end, the novel demonstrates how such an adventure, based on a deterministic understanding of life, will inevitably go wrong. First of all, animals become ill, suffering from

the effects of exposure to a post-Jurassic environment. But before long, other things go wrong as well. Notwithstanding its initial reductionism, the novel's moral message is that we should not underestimate the complexity of life.

In the novel, a mathematician is added to the list of characters to play the role of critical referee. It is no coincidence that complexity is his favourite subject. From the outset, he is overtly sceptical about the experiment and challenges its deterministic premises. His arguments are borrowed from chaos theory. Enterprises such as this will never go as planned, he claims. Their course will prove unpredictable. Complex sequences of events will never proceed as they are expected to. Sooner or later, something will get out of control and the enterprise will lead to completely different results than was foreseen by those who designed it. Notably, *containment* will prove impossible. Life (and this goes for revivified Jurassic life as well) has the inherent tendency to spread, to disseminate. The project has taken its precautions, but they rely on a deterministic logic. A gene was inserted so that the animals would be unable to manufacture the amino acid lysine. It had to be administered to them and for that reason they were supposed to be unable to survive in the outside world. But Malcolm's prophecies come true. Dinosaurs do manage to escape from the resort, satisfying their want of lysine in unexpected ways, thereby endangering the ill-prepared outside world. At the beginning of the novel, they have already entered the world of normal people, already left the experimental premises from which they originated. Thus eventually, the novel challenges rather than endorses genetic determinism.

Reframing the debate

Genetic determinism has gained substantial popularity in the public sphere, through metaphors such as the genome as 'blueprint' and the 'hunt' for genes. According to critics, such as Dorothy Nelkin and Susan Lindee (1995), these metaphors encourage a deterministic interpretation of genetics, inciting discriminatory effects throughout society.[11] Gene talk in mass media is thought to strengthen a reductionistic understanding of our genome, biologically deterministic and socially discriminatory, equating human beings with their genes (Lippman, 1992). Although these concerns may have sounded plausible some years ago, we must now acknowledge that they are actually outdated. The implication is that public debate as it has evolved in recent years is not yet addressing the challenges and concerns that will really be generated by genomics. In other words, the agenda for public debate needs to be updated. Otherwise, it may loose much of its critical potential.

On the basis of an epistemological analysis of genomics research, the conclusion must indeed be that it is time for the agenda of public debate to be reset in a different direction. The epistemological shift that is inherent in the transformation of genetics to genomics should also affect the agenda of public discussion and policy development. Current debates are to a large extent still addressing themes that were popular in the 1990s, doing so in the vocabularies of the 1990s, reflecting the logic of genetic determinism. If we want to take genomics

seriously, it is time to try to move the debate into the 21st century. The focus of attention should therefore move from issues such as 'genetic modification' and similar discussions, focusing on *single* genes, to issues involved in the use of and understanding of large-scale genomics information.

On the level of healthcare, for example, the focus should no longer be on issues involved in screening for monogenetic (and therefore rare) health disorders, providing information for specific target groups and individuals at risk. Rather, the focus should be on the challenges involved in research on multi-factorial (and usually much more common) health problems, generating information that will be relevant for virtually everyone. In theory, genomics information may empower individuals to manage their own health conditions through prevention—gearing diet, lifestyle, professional career, etc., to their genetic profile. But will individuals be willing and able to use these new forms of information? Will new types of intermediaries and consultants emerge to assist them in their choices? And *who* will have access to and be able to use this information? Will genomics research really empower individuals to manage their own life, or will it rather encourage top-down forms of exclusion and discrimination, for example by employers and insurance companies? These are the issues to be addressed, on the basis of a recognition that genomics information will be different in important respects to other types of health information.

I find it not realistic to believe that the Olympics of the future will be dominated by 'genetically modified athletes' (Miah, 2004). It is much more likely that they will be dominated by genetically 'normal' athletes working in close collaboration with teams of experts who know how to make use of genomics information in the context of diets, training programs, nutritional supplements ('nutriceuticals') and 'genetic doping'. Or, to use another example, the 21st century will not be a 'brave new world' where 'super employees' will be artificially produced by means of genetic modification. What is much more likely is that in the near future, various possibilities for pre-employment genetic screening (PEGS) will affect the course of professional careers. We must start thinking, in an anticipatory manner, how we are going to address these issues, how we may use these possibilities in fair and legitimate ways. Genomics will be about the equitable and intelligent use of complex information, rather than about manipulation. In order to address these challenges, it is important to move the public and policy debate beyond the restricted stereotypes of genetic determinism (its promises and fears). ELSA genomics should not be about genetic modification of humans, but rather about how to govern the use (storage, management, access, and interpretation) of genomics information in a transparent and justifiable manner.

Francis Fukuyama (2002) has depicted transhumanism as a major threat to human culture. He proposes to determine the unique genetic human constitution (our 'Factor X') as something to be preserved. According to Fukuyama (2002, p. 171), there is a genetic endowment that allows us to become human, distinguishing human beings 'in essence from other types of creatures'. Obviously, both transhumanism and its critics (such as Fukuyama) start from the same idea: that we apparently *are* our genes, and that we can modify ourselves (for

better or for worse) by adding, deleting or preserving genes. If there is something we can learn from genomics research and the HGP it is that the causal trajectories from genes to traits are generally speaking much too complex for such scenarios to be credible. Information governance, rather than gene-based anthropotechnologies, will become the core issue—as policy strategies will increasingly be *informed* by the outcomes of genomics research.

Notes

1. See <http://www.genome.gov/10001356>.
2. For a critical analysis of the blueprint metaphor (among others), see Nelkin and Lindee (1995).
3. Cf. Kevles (1985). The term eugenics was introduced in 1883 by Francis Galton. Eugenics had been 'waiting' for genetics, so to speak and (in the early decades of the 20th century) was eager to put it to use.
4. Loeb's work was well-known when Huxley wrote his novel. It was described for example in the biological text book, *The Science of Life*, written by H.G. Wells in collaboration with his son (G.P. Wells) and Julian Huxley (brother of Aldous). The authors ask themselves for example whether artificial reproduction will also be possible in 'mammals' (humans)—'There is no reason to suppose that it is not...' (Wells, Huxley & Wells, 1931/1938, p. 509).
5. '[T]he human genome seems to encode only 20,000–25,000 protein-coding genes' (van Ommen, 2005, p. 931), ' On the basis of available evidence, our best estimate is that the total number of protein-coding genes is in the range 20,000–25,000').
6. See *Nature Biotechnology*, 1999 (1), p. 511.
7. See *Science*, 2001, p. 1153.
8. See *Nature*, 2001, p. 813.
9. See *Genomics*, 1997, 45: 244–9.
10. See <http://www.genomics.nl/homepage/research/innovative_clusters/ecogenomics/>.
11. Others have raised serious doubts about this line of reasoning, notably, C. Condit (1999).

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