Biomedical ethics 2.0: redefining the meaning of disease, patient and treatment

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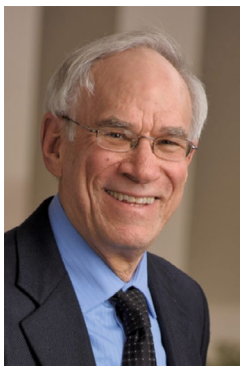
The foundations of biomedical ethics were established in the 2nd half of the 20th century, but issues associated with medical practice continue to evolve from new technologies. Recent progress in genomics and genome engineering has changed the meaning of the basic words of medicine: disease, patient and treatment.



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Three trends came together and gave rise to modern biomedical ethics — biomedical ethics 1.0. First, the technological advance of placing human bodies on external life support made separation of the human person from the human body a practical matter for the first time in history. Second, successful in vitro fertilization created embryos outside a woman's reproductive system and gave practical meaning to the question: when does a clump of human cells become a person and, regardless, what moral status does a clump of human cells deserve? Finally, the increasing use of human bodies for experimental research caused inherent conflicts of interest for those using patients as subjects.

Formal discussions of medical ethics arose initially in response to abuses of human subjects for research taking place through the 19th and 20th centuries (prominently including medical experiments on prisoners during World War II and the Tuskegee syphilis experiment) and were materialized in the form of official documents encompassing the *Nuremberg Code*, *Declaration of Helsinki* and *Belmont Report*. More generally, the foundation for ethics in the common practice in medicine often begins with publication in 1979 of *Principles of Biomedical Ethics* (now in its 8th edition), which laid out four key principles for the emerging field: respect for autonomy, non-maleficence, beneficence and justice.

Bioethics 1.0 emerged because of new ways of understanding what it means to be human. Now, with the rapid progress of molecular biology, and in particular the advances in genomics and genomic engineering, we are facing a need to 'upgrade' to biomedical ethics 2.0 to accommodate to the changes taking place in the ordinary language of medicine.

Historically, disease is related to how a person feels — 'dis-ease'. The person suffering from certain symptoms consults a health-care provider, hoping to correct the problem. In this scenario, the person knows first that something is wrong because of the symptoms experienced. However, now, with the advances in biomedical technologies, a person can be diagnosed with the disease even if not feeling 'dis-eased': one goes in for a routine medical checkup feeling fine, only to learn that things are not as they should be (cholesterol too high, blood pressure too high, bone density too low and so on). Beyond the routine laboratory tests in place to monitor our health, the genomics revolution of the 21st century now makes it possible for basically anyone to analyse their genome. With this increased availability of genomic data, a set of characteristic genetic features has become sufficient to identify a disease for which one is at risk, even before any physiological changes occur. With this definition, one can discuss disease in relationship to any stage of human life beginning with the fertilized ova or embryo. Furthermore, because everyone suffers from their own set of 'original' diseases — the disorders for which they are at risk — genomics pervasively medicalizes the human condition and poses a question: when does a disease start?

Genomic medicine also changes what being a patient means. Historically, a patient refers to a single person. From the genomics perspective, the patient can range from one cell (fertilized ova) or a small cluster of cells not yet in the reproductive system (in vitro fertilized embryos) to many bodies linked by their genetic pedigree (one family). Contrary to classical medicine that targets already existing conditions, in the era of genomic medicine, embryos will be the best potential patients, as they allow corrections of the disease before any damage has occurred. However, embryos are highly controversial 'patients' given societal disagreements regarding their moral status, and treatment of embryos in genomic medicine frequently is linked to socioeconomic discrimination and even eugenics (see also below). At the other end of the scale, genetic information about an individual always has implications for other family members and genetically related groups (for example, tribes),

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which become secondary patients. In this context, if an individual family member has been tested for some disease, what responsibilities do health-care providers have to inform the individual's family members about their own genetic risks? If an individual family member wants to be tested for some disease or diseases as part of a research project, what responsibilities do researchers have to ask permission from the individual's family members?

Furthermore, the meaning of treatment in genomic medicine varies according to disease and patient. For cancers and other multifactorial illnesses, genomics provides the path to precision medicine to clarify diagnoses and help select treatment options. These treatment options include novel, still mostly experimental, interventions, which are highly costly and may eventually be available only to a very limited number of patients. For single-gene inherited disorders, the meaning of treatment bifurcates according to whether a disease is already present or only a potential risk. Beginning in the 1960s, metabolic screening of newborns for the genetic disorder phenylketonuria made it possible to treat the condition by dietary intervention. Another metabolic screening test, this one for adults, beginning in the 1970s, made possible identification of carriers of Tay-Sachs disease. No conventional treatments or ameliorating lifestyle options were then or have since become possible. The only medical benefit of the screen has been preventing the disease in future generations by avoiding having children. However, with the use of genomic sequencing of in vitro-fertilized embryos to identify the carriers of Tay-Sachs disease (or a variety of other genetic disorders) and non-invasive prenatal testing for fetal genetic signatures in the mother's blood to detect chromosomal abnormalities such as Down syndrome, genomic medicine now makes it increasingly possible to 'prevent' the disease by discarding the embryo or by terminating the pregnancy. Such approaches of preventing the birth of at-risk individuals as a means to treat genetic disorders puts genomic medicine in direct ethical conflict with multiple segments of society including the disability community; those opposed to terminating pregnancies; and those opposed to destroying embryos. Indeed, treatment by preventing the at-risk person switches the focus of genomic medicine from making people better to making better people and enters the domain of eugenics, an outcome predicted by the U.S. Congress Office of Technology Assessment in their 1988 report about consequences of the human genome project.

Another emerging aspect of treatment in the era of genomic medicine is gene editing, which has had some success in correcting single-gene hereditary disorders in newborns. However, this strategy is limited once disease-associated genetic differences are expressed throughout the body. Therapeutic gene editing prenatally could circumvent this limitation coming back to the discussion of embryos as ideal 'patients' for genomic medicine. Nevertheless, gene editing to correct embryo genetic disorders, while possible in theory, in practice will be far in the future and will raise a whole new set of ethical considerations, in particular those pertaining to eugenics, owing to the possibility of not only the treatment of embryos, but also embryo improvement through genomic engineering.

How eugenics develops in the future remains to be seen. In the classic movie *Gattaca*, the hero Vincent expresses one view of eugenics when he says, "my real C.V. was in my cells" (DNA), describing a society where your genes determined your future. A very different view was expressed in a 2018 paper about genetic analysis of social class mobility: "the long-term goal of our sociogenomic research is to use genetics to reveal novel environmental intervention approaches to mitigating socioeconomic disadvantage". These alternative trajectories of eugenics — on the one hand determining what one can accomplish and on the other hand determining how to enhance what one can accomplish — will become the focal point in the evolution of genomic medicine and a key challenge for biomedical ethics 2.0.

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