Journal of Medical Ethics 1999;**25**:200–203

Genetic screening with the DNA chip: a new Pandora's box?

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Abstract

The ethically controversial option of genetic population screening used to be restricted to a small number of rather rare diseases by methodological limitations which are now about to be overcome. With the new technology of DNA microarrays ("DNA chip"), emerging from the synthesis of microelectronics and molecular biology, methods are now at hand for the development of mass screening programmes for a wide spectrum of genetic traits. Thus, the DNA chip may be the key technology for a refined preventive medicine as well as a new dimension of eugenics. The forthcoming introduction of the DNA chip technology into medical practice urgently requires an internationally consistent framework of ethical standards and legal limitations if we do not want it to become a new Pandora's box.

(*Journal of Medical Ethics* 1999;**25**:200–203)

Keywords: DNA microarray; genetic screening; eugenics

The development of molecular techniques for genetic analysis and the deciphering of the human genome have provided tools for the diagnosis of a rapidly growing number of heritable diseases. Genetic diagnosis, however, differs from clinical laboratory diagnosis in two fundamental aspects of ethical relevance: clinical laboratory diagnosis aims at disease-associated parameters that arise only after the onset of the pathologic organic process, whereas inborn genetic anomalies that cause heritable diseases are independent of the somatic course of the disease and thus generally are detectable anytime in the patient's life and even prenatally. This dissociation between genetic disposition and somatic disease allows the diagnosis of late-onset hereditary diseases many years before the onset of symptoms as well as the detection of individual risk factors disposing to multifactorial disease. This *predictive* aspect of genetic diagnosis opens new perspectives for preventive medicine but also for genetic discrimination.[1]

Moreover, molecular genetic diagnosis allows the detection of heterozygous mutations of recessive disease genes. These genetic alterations are completely compensated by the functioning second copy of the respective gene and thus insignificant for the mutation carrier's own health but may bear a risk for offspring to be sick. As an example, one out of twenty whites carries a heterozygous mutation in the cystic fibrosis gene which, by itself, causes no health problems. However, children whose parents are both heterozygous for cystic fibrosis have a 25% risk of being homozygous and, if so, of suffering from serious lung and pancreatic disease. Consequently, the molecular genetic proof of heterozygosity can determine the decision of a couple not to have children or to request a prenatal diagnosis in case of a pregnancy. This *prospective* dimension of genetic diagnosis that goes beyond individual health care may support autonomous reproductive decision making but also bears the danger of external encroachments on parental autonomy.

Ethical acceptance of genetic screening programmes

The technological feasibility of detecting heterozygous carriers of recessive diseases leads to the question to what extent heterozygosity tests should be applied in clinical practice. Three basic strategies can be taken into account:

- Individual diagnosis within affected families, for example, for siblings of a patient who suffers from cystic fibrosis;
- Screening within unaffected families offered to pregnant women and their partners, couples planning to have children, or premaritally in populations with a high heterozygote frequency for the respective disease[2–4];
- comprehensive population screening for all individuals at the age of reproduction.[5]

The ethical evaluation of these strategies shows substantial international differences. The search for heterozygotes within affected families is unanimously accepted worldwide with broad consensus on the individuality of the decision to undergo the test and emphasis on the *right not to know*.[6] Population screening for heterozygotes, on

the other hand, is still a matter of controversy.[7-8] More than one million people have already participated in screening programmes for Tay-Sachs disease in Ashkenazi communities in North America, Australia and Israel[3]; a National Institute of Health consensus statement advocates cystic fibrosis heterozygote testing for the prenatal population and couples currently planning a pregnancy but not for the general population.[9] In Europe, genetic screening is regarded with more reserve. In particular, geneticists in the German-speaking countries still object to the introduction of population screening programmes and even to pilot studies, with historical reference to the abuse of genetics in Nazi Germany.[10] Anyway, there is broad international consensus on the importance of voluntariness and medical secrecy as well as the rejection of any kind of discrimination resulting from unfavourable test results.[11] Moreover, there is widespread concern about the extreme amount of educational work required to obtain informed consent from participants in large-scale genetic screening programmes.[12]

Doubt about confidentiality and the danger of "genetic discrimination" are discussed as well in the context of predictive genetic screening. Data on individual genetic risk factors such as disturbances of fat metabolism predisposing to atherosclerosis or resistance to toxic factors at the workplace would be of great interest to insurers and employers.[13] Genetic tests as a prerequisite for jobs or life insurance are not yet within sight due to ethical concerns[14] and, most of all, not yet realistic because of the lack of scientific knowledge about the complex interactions of genetic and environmental factors.

It may be said that the application of genetic screening programmes is, at present, mainly limited by a shortage of technological and financial resources. At today's state of genome analysis, only a few hereditary diseases and risk factors are accessible to genetic analysis. Moreover, the cost of mutation analysis using conventional techniques of molecular genetics (for example, DNA sequencing or single strand conformation analysis) is a major obstacle to the introduction of extensive screening programmes. Consequently, the development of faster and cheaper technologies for large-scale gene analysis has been at the centre of interest of the genome business for the last few years.

Technical principle of the DNA chip

Earlier than expected even by most experts, the "DNA chip" appears to overcome the technical limitations of genetic mass screening through the synthesis of computer and DNA technologies.[15 16] A silicon chip, as used for microelectronic circuits, is photochemically covered by a microarray of exactly defined short sequences of synthetic DNA; a thumbnail-sized chip can harbour up to 400,000 different such oligonucleotides. These standard sequences can be simultaneously checked for identity with the corresponding sequences of a proband's genome; the evaluation is done automatically with a computerised laser scanner. The whole procedure only takes a few hours. This "massively parallel" approach to genome analysis addresses a huge amount of genetic parameters from one blood or tissue sample in a single step.[17] Thus it is ideally suited for the rapid and cheap identification of mutations in disease-relevant genes. Of particular interest is the fact that even heterozygous mutations are readily detected, thus making the DNA chip the ideal tool for genetic screening. Any human tissue is suitable as the DNA source, including chorionic villi for prenatal testing.

A variety of DNA chips are already available for genome research and microbiology, but also, still at laboratory scale but mass-producible, for the fully automatic detection of mutations in the hereditary breast/ovary cancer gene BRCA1 or in the cystic fibrosis gene.[18 19] The price of a DNA chip is now about £50 but is rapidly declining. The involvement of large companies such as Hewlett-Packard and Glaxo Wellcome leaves little doubt that the technology will soon be put on the market - with or without a concomitant ethical discussion. The developers are optimistic that within a few years they will be able to offer the automatic analysis of any given individual's complete genetic complement by a set of DNA chips.[17]

Key technology for a new eugenics?

With its enormous power and efficiency, the DNA chip is about to open new ranges of application to genetic diagnosis which had been thought to remain matters of theoretical discussion for a long time to come. As Stephen Fodor, principal inventor of the chip, coins it: "The applications appear to be only limited by imagination".[17] In terms of fact, the DNA chip allows the testing of many more genetic parameters in a much shorter time and at much lower prices than conventional gene analysis.

It is an unquestionable blessing for clinical medicine: the increased efficiency and cost reduction by already available chips for HIV resistance analysis in AIDS therapy[20] or differential diagnosis of mitochondrial myopathies[21] is evident and should not be a matter of ethical dispute.

A more difficult field of work for the chip developers is the analysis of genetic determinants

involved in the pathogenesis of common multifactorial diseases like atherosclerosis and diabetes, which have been frustrating for researchers because of the complexity of interacting factors.[16] The expected outcome may serve as an example of the dichotomy of scientific revolutions in general: the, previously impossible, identification of the genetic factors underlying schizophrenia may provide psychiatrists with powerful new drugs, but it also provides employers and insurers with ethically questionable parameters for aptitude tests. The discussion about genetic discrimination[22 23] will surely take on new aspects.

To me, the most problematic point is that the DNA chip is the ideal tool for the widespread establishment of genetic screening programmes. Today's supply of heterozygosity screening for young couples is restricted to cystic fibrosis and a few rare diseases that are confined to specific populations. The chip, however, will broaden the spectrum of analysable parental traits practically *ad libitum*. Moreover, prenatal testing for a battery of predictive parameters such as cancer dispositions or neurodegenerative diseases from a chorionic villus sample will be no problem anymore.

Consequently, the idea of prenatal screening of fetuses has already come to the attention of DNA chip developers.[15] A chip design with probes for interesting traits, be they pathological or, conversely, desired, has got what it takes to become a million-seller. The combination of DNA chip screening with preimplantation diagnosis might be the logical next step towards high-tech eugenics.

The subjective choice of genetic traits that are considered as prenatal selection criteria may blur the distinction between preventive medicine and striving for the "perfectly designed" child. After cost-effectiveness analyses have proven that genetic screening can produce considerable savings even for rather rare diseases which require expensive therapies for affected patients,[24] there is little doubt that health insurers will support extensive screening programmes. The widening of the diagnostic spectrum may also reinforce the already widespread public opinion that the birth of handicapped children should be prevented.[25] Ultimately, the exclusion of prenatally testable conditions from health insurance cover might serve as a sanction instrument for a new kind of economically motivated negative eugenics that may well become popular in an era of declining prosperity.

Conclusion

The emerging, powerful DNA chip technology, with its possible impact on medicine and society, urgently requires an interdisciplinary discussion about its benefits and ethical problems, particularly with respect to its application for genetic screening. Whatever the results may be, the cornerstones of the discourse are evident:

The introduction of the DNA chip is unavoidable. The scientific and commercial driving forces behind it are very strong. Taking into account the undisputable benefits of the technology for research on causal therapies for previously incurable diseases, it is not even desirable to try to stop the development. Anyway, it is a general lesson from history that powerful new technologies can at best be regulated but never prohibited.

The discussion must aim at an international ethical consensus. Unequal ethical standards between different countries lead to medical tourism and class medicine, as we had to learn from organ transplantations. Someone who wants to circumvent restrictive national laws on embryo transfer today must travel and pay a lot; someone who, in the future, wanted to undergo a genetic test prohibited at home would have to pay a lot as well but would only have to send a blood sample to a laboratory anywhere in the world.

The discussion must soon begin. The technical development of the DNA chip is already advanced; the first systems are now being introduced into medical practice. The cloned sheep Dolly only recently demonstrated that a surprising *fait accompli* does not at all improve the quality of the ethical discourse.

Acknowledgement

I wish to thank Professor Klaus D Zang for fruitful discussions and continuous support.

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