

Microarray genetic screening: a prenatal roadblock for life?

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Lancet 2007; 369: 526–29

See [Comment](#) page 440

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Prenatal screening can help prospective parents to have healthy babies. Screening can also provide reassurance that a pregnancy is going well, and can help in management of a high-risk pregnancy. New DNA microarray technologies (also called DNA chip, gene chip, biochip, or gene array technologies), which permit screening for thousands of genetic disorders at once, threaten to disrupt the rationale and purpose of prenatal screening. These developing technologies, which combine microelectronics and molecular biology, are presently used for research, but they could be introduced in medical practice for routine prenatal screening, if and when fetal DNA is recoverable from maternal blood.^{1,2} Already in the USA, one medical college offers additional chromosomal analysis to pregnant women who undergo amniocentesis by use of microarray-based comparative genomic hybridisation to evaluate over 65 genetic disorders at once.³

Once fetal DNA can be non-invasively obtained, screening practices will be able to generate a massive amount of information of uncertain importance. These data might cause more harm than good. Because timely analysis might not be feasible, abortion could seem reasonable to parents who wish to avoid having an unhealthy baby. Despite the best of intentions, the practice of prenatal genetic screening could ultimately undermine its own original purpose, and prevent rather than enable the birth of healthy babies.

The practice of screening in the USA began with the detection of Down's syndrome. Amniocentesis to screen for this syndrome was offered to women aged 35 years or older. Selection of this cut-off age for screening was an attempt to balance the risk that a baby would be affected by a chromosomal disorder with the risk that spontaneous fetal loss would result from amniocentesis.⁴ At present, prenatal screening includes use of maternal blood to test for α -fetoprotein, human chorionic gonadotropin, and β -unconjugated oestriol. Quad screening also tests for dimeric inhibin A. The use of a maternal blood sample rather than amniotic fluid led to the recommendation that all pregnant women should be screened for Down's syndrome and neural-tube defects, such as anencephaly and spina bifida.

Cost-benefit analysis, together with counselling of patients and informed consent, has been used to decide whether any additional disorders should be screened for. Every decision has been made—one disorder at a time—after a systematic examination of its implications by professional associations (such as the American College of Obstetricians and Gynecologists and the American College of Medical Genetics) that make recommendations for clinical application. These recommendations have been informed by the severity of the disorder and the accuracy of the screening interventions. In January 2007,

the American College of Obstetricians and Gynecologists recommended that all women who present for prenatal care before 20 weeks of gestation be offered screening and invasive diagnostic testing for aneuploidy, irrespective of age, and be counselled about the differences between screening and invasive diagnostic testing.⁵

The introduction of DNA microarray technologies that allow screening for thousands of genetic variations at once will make individual decisions about screening for each disorder impracticable and attempt at differentiating screening and testing ineffectual.⁶ How should we meet the challenge created by microarray technology, which has been characterised as “the ideal tool for genetic screening”?⁷

Prenatal screening and its difficulties

Prospective parents want their babies to be healthy. But notions of health, disease, and normality are not straightforward. Such properties cannot be inferred from molecular or genetic reading because they are not the property of genes or molecules per se but of the interaction between the entire organism and its environment.⁸ French philosopher and physician, Georges Canguilhem noted that “science does not dictate norms to life”.⁸ His observation highlights the difficulties of how to establish the health of a fetus at the genetic level, and then to articulate prenatal screening policy on the basis of such a determination.

In the USA, the development of prenatal screening policy has been hampered by increasing polarisation about abortion: in general, the right-to-life position opposes any fetal screening on the basis that it could be used to justify prevention of a birth, whereas the pro-choice position values parental autonomy and favours parents' right to almost unlimited access to information about their fetuses. Because of this controversy, and to avoid charges of eugenics or neo-eugenics, prenatal counselling has generally been non-directive, and respectful of parental decisions.

No overarching rule has been developed to decide whether an existing or a new prenatal screen should be routinely offered to prospective parents. Jeffrey Botkin, for example, has argued for limits to the information that prospective parents can find out about their fetuses, and has suggested that “the standard of disclosure for prenatal information should be designed to prevent harms to parents that are of approximately the same magnitude as the harms of an unwanted pregnancy”.⁹ By this standard, Botkin considers that patients can reasonably be offered screening for such disorders as haemophilia, Down's syndrome, fragile X, sickle-cell anaemia, and cystic fibrosis, which “cause harms to parents in terms of time, resources and efforts”, but not for adult-onset disorders,

such as Parkinson disease, Huntington disease, or breast or colon cancer, which “do not seriously threaten the interests of prospective parents”.⁹

Botkin’s harm-to-parent principle is an attempt to specify which disorders should be screened for prenatally, and which should not. Botkin, however, would permit exceptions to his own rule if prospective parents requested specific information about their fetus. In this regard, Botkin would bow to parental autonomy, but also to his assessment of the minimum legal requirements that he believes judges and juries could set in wrongful birth actions. Because in the USA avoidance of lawsuits is a strong motivator for development of prenatal screening policy, Botkin argues that such considerations make practical sense, even though wrongful birth litigation is inappropriate as a benchmark for clinical-practice guidelines.

The creation of a list of disorders that might be screened for prenatally is, however, not straightforward. Adrienne Asch is horrified at the idea that professionals might categorise specific medical disorders as bad or less bad.^{10,11} She is deeply concerned at the prospect that parents might select their future children by “genetically auditioning them before allowing them to be born”,¹² and fears that creation of such a list would encourage intolerance, hostility, and discrimination in society. Importantly, Asch questions whether routine use of prenatal screening for specific disorders would make it easier for society to pursue a eugenics project. Asch’s moral bottom line is that fetal selection would morally damage parents and children, and is incompatible with the precepts of an inclusive and just society.

Sonia Suter agrees with Asch that abortion cannot be regarded as a treatment for disability. But rather than reject screening, she would rely on comprehensive counselling to educate prospective parents about the complexity and unpredictability of many genetic diseases, and about the meaning, values, extent, and limitations of prenatal screening practices.¹³ She trusts that such counselling could actually inhibit the demand for screening and reduce the number of unnecessary abortions that could flow from it.

The difficulty in development of reasonable approaches to prenatal screening persists, and shows no sign of resolution.^{14–16} This quandary persists not only because patients’ autonomy is afforded high value, but also because health, disease, and normality cannot be scientifically established at the molecular level.

In the absence of policy agreement, practices have by default become market driven, with prenatal screening offered not only for disorders for which professional organisations recommend screening, but also for disorders requested by pregnant women—with the notable exception of sex selection. Screening on demand, with full disclosure of results and non-interference with the abortion decision through morally non-directive counselling, is the US norm.¹⁷

New technology needs a new approach

The introduction of new genetic screening technologies will displace the present model for screening in which the usefulness of genetic screening is assessed one disorder at a time.^{18,19} For example, screening for cystic fibrosis was recommended for routine prenatal use only after more than a decade of discussion. The time and effort needed to examine each of the 1000, 10 000, or 100 000 genetic variations, and to properly inform patients about them would make it impossible. Elias and Annas²⁰ suggested a new model of informed consent for genetic screening, which they labelled generic genetic consent. They argued that acquisition of valid informed consent about all of the hundreds of genetic conditions screened for would not be possible. Thus, a rational approach would be to explain genetic screening in generic terms, and discuss a few examples of disorders, rather than try to explain the implications of hundreds of disorders separately. Informed consent is, of course, important. But it is not relevant until a decision has been made about whether microarray technologies should be used for prenatal screening.

Use of microarray genetic screening is likely to produce a flood of information that is overwhelming, anxiety-producing, inconclusive, and misleading.²¹ Genetic screening of adults can allow time to rescreen, to confirm findings, and to interpret or ignore results. But microarray genetic screening might allow only weeks or even days for a decision on whether or not to terminate a pregnancy.

Furthermore, no screening practices are perfect, and all produce both false-positive and false-negative results.²² Suppose, for example, that genetic variations can be screened with 99·9% accuracy for detection of true positives. For every 1000 fetuses screened, one fetus will be identified as positive for a particular disorder that is not present. If a quick and accurate method can be used to test this finding, a positive identification might not be important. But if no such method exists, false-positive results will present a formidable challenge, since millions of fetuses will probably be screened every year; for 1000 000 fetuses, 1000 will have false-positive findings. And, if we screen for 1000 genetic variations in this population, we will have 1000 000 false-positive results—ie, every fetus will be identified as abnormal. Every child born after such a detailed screening of his or her genes would produce a false-negative result for at least one disorder. Even the attainment of 100% accuracy would not produce a solution, because all human genomes are programmed for death.

The paradox is that the more detailed the search for defects, the less likely it is to produce information that translates into useful knowledge about the health of a fetus. Canguilhem described this search as “genetic inquisition” directed at the suppression of “heterodoc genes”.

“At the beginning we have the generous ambition to spare innocent and impotent living beings the atrocious burden of producing errors of life, at the end there is the gene police, clad in the geneticists’ science....To dream of absolute remedies is often to dream of remedies which are worse than the ill.”⁸

Prenatal genetic screening allows parents to take on the role of gene police, and to erect a roadblock at which they search and examine their children-to-be before birth. Microarray screening technologies give prospective parents and their physicians a means to extract information that they believe, can predict the health of a child. Anomalies that might have remained hidden during a lifetime as “non-activated tendencies in the absence of environmental encounters, and thus could have been ignored”⁸ will now be revealed and assessed by use of microarray technologies. In short, the quest for a healthy baby could cause parents to have no baby at all.

All or nothing?

Widespread introduction of prenatal genetic screening will create implications analogous to, but much more complicated than, those of the so-called incidental findings from imaging studies.^{23–25} Readers of these scans commonly identify anomalies that they cannot explain but have no reason to believe are pathological. If such anomalies were disclosed some diagnostic follow-up would be likely, which, if it involved an invasive test, could actually create a disease that the anomaly did not represent. For example, obstetricians in France have publicly defended their decisions not to inform pregnant women of findings that they believed were inconsequential or inconclusive.²⁶ Genetic screening, however, produces a computer printout of results, which will complicate non-disclosure.

How should we decide whether to adopt microarray technology for prenatal genetic screening? Cost–benefit analysis seems too narrow, and analysis of one genetic disorder at a time is unrealistic. We need a philosophical basis for decision-making. Since screening is population-based, we might reasonably expect that its use should embody social values and further—or at least not undercut—them. In this context, the philosophy of John Rawls is especially pertinent. In his attempt to establish “a workable public conception of justice”, Rawls postulated a group of “theoretically defined individuals” in an “original” position of equality and under a “veil of ignorance”.²⁷ He reasoned that these “free and independent” individuals would have no knowledge of their social class and fortune, and whether they were advantaged or disadvantaged by such contingencies.²⁷ He stated that they would be self-interested and rational and could express their notion of justice, despite not knowing “how the various alternatives of justice will affect their particular case”.²⁷ Rawls’ hypothetical device was to ask these individuals to set the social rules under which they would like to live, and to assess principles of justice solely on the basis of general considerations.²⁷

Although they did not specifically apply Rawls’ approach to prenatal genetic screening, Norman Daniels and his colleagues have used Rawlsian principles to argue that we can exclude from a medical benefit package “tests of uncertain significance [for which] the information provided to the patient may have little value in medical decision making, or may even tend to lead patients into imprudent decisions”.²⁸

To apply Rawls’ ideas to prenatal screening we could consider the interests of physicians, fetuses, and parents in a society that possesses microarray technologies, and assume that each group has no knowledge of the contingencies that set them apart. This veil of ignorance should ensure impartiality, since each member of a group would have to take into account the interests of other groups if they want to be treated fairly.

This theoretical exercise leads us to conclude that physicians would prefer not to screen if the result of screening was the abortion of healthy fetuses; that fetuses would probably prefer not to be screened if so many disorders were examined that their chances of birth were greatly reduced, and that parents would probably prefer not to have to consider large amounts of information produced by screening if that caused them to make poor decisions, or to consider uncertain and complex long-term therapeutic solutions for genetic variations that might not translate into an actual disease in their child. The social values that emerge from this exercise are those of autonomy, fairness, and non-discrimination. Microarray technologies for prenatal genetic screening will probably undermine these values, and thus a decision not to adopt such technologies as standard of care would be reasonable and responsible. Similar considerations might produce different conclusions, however, about the use of microarray screening for preimplantation embryos, neonates, children, and adults.

“Technology, not medicine, is the immediate force behind the quest for the \$1,000 human genome. The new decoding machines are being developed because they are possible, not because hospitals are demanding them, and therefore, the makers of this technology expect that demand will grow as researchers develop new uses.”¹⁷

Similar concerns might apply to microarray technologies, since manufacturers will push for maximum use of their products.

The introduction of these technologies for routine prenatal screening is a global issue. For example, in the UK, “many [prospective parents] given the choice, would probably prefer to have all the information about their baby’s chromosomes that the sample could provide. If a health service cannot afford to provide full karyotyping, then those who want the full range of information may want to pay the extra cost.”²⁹ Unless physicians take a firm position against the use of microarray technologies in the contested terrain of prenatal screening, they will probably have to surrender to parental requests for more

screening—either because they (incorrectly) view consumer choice as equivalent to autonomy or because of (unjustified) concern about wrongful birth lawsuits.

Microarray screening technologies present a dilemma similar to that confronted at the beginning of the human genome project, when the project was resisted on theoretical grounds because of the threat that it would be used to advance genetic determinism and reductionism.^{30,31} Use of microarray screening technologies is based on the belief that we are shaped by our genes, and that our health is moulded by the properties of our genomes. These technologies prompt constant revisions of our view of health, and upward redefinitions of normality that will probably cause more, rather than fewer, abortions of healthy babies. Although the use of microarray technologies for prenatal screening might be intended to help couples have healthy babies, it will undermine not only this purpose, but also the very foundation of the human genome project itself, which is to improve human health.

Conflict of interest statement

I declare that I have no conflict of interest.

Acknowledgments

I thank Frederick Balzer, of the Gene Therapy Program at the University of Pennsylvania, for his insightful comments on current prenatal screening practices and new DNA microarray technologies.

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