

The future of neo-eugenics

Now that many people approve the elimination of certain genetically defective fetuses, is society closer to screening all fetuses for all known mutations?

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Every year, 4.1 million babies are born in the USA. On the basis of the well-known risk of Down syndrome, about 6,150 of these babies would be expected to suffer from this genetic condition, which is caused by an extra copy of chromosome 21. In reality, only about 4,370 babies are born with Down syndrome; the others have been aborted during pregnancy. These estimates are based on a prevalence rate of 0.15% and an abortion rate of about 29% of fetuses diagnosed with Down syndrome in Atlanta, GA (Siffel *et al*, 2004), and Hawaii (Forrester & Merz, 2002)—the only two US locations for which reliable data are available. Data from other regions are similar or even higher: 32% of Down syndrome fetuses were aborted in Western Australia (Bourke *et al*, 2005); 75% in South Australia (Cheffins *et al*, 2000); 80% in Taiwan (Jou *et al*, 2005); and 85% in Paris, France (Khoshnood *et al*, 2004). Despite this trend, the total number of babies born with Down syndrome is not declining in most industrialized nations because both the number of older mothers and the conception rate is increasing.

These abortions are eugenic in both intention and effect—that is, their purpose is to eliminate a genetically defective fetus and thus allow for a genetically superior child in a subsequent pregnancy. This is a harsh way of phrasing it; another way is to say that parents just want to have healthy children. Nevertheless, however it is phrased, the conclusion is starkly unavoidable: terminating the pregnancy of a genetically defective fetus is widespread. Moreover, because none of the countries mentioned above coerce parents into aborting deformed fetuses, these abortions—which number many thousands each year—are

carried out at the request of the parents, or at least the mothers. This high number of so-called medical abortions shows that many people, in many parts of the world, consider the elimination of a genetically defective fetus to be morally acceptable.

This form of eugenic selection is not confined to Down syndrome, which is characterized by mental retardation, a higher risk of various diseases, and a range of major and minor abnormalities in body structure and function. Fetuses with many disorders detectable by ultrasound *in utero* are also aborted. Data from the European Surveillance of Congenital Abnormalities shows that between 1995 and 1999 about 40% of infants with any one of 11 main congenital disorders were aborted in Europe (Garne *et al*, 2005). Similarly, the International Clearinghouse for Birth Defects Monitoring System (ICBDMS; Rome, Italy) provides data for the eight main industrialized (G8) countries. From this data, I calculate that in 2002, 20% of fetuses with apparent birth defects were aborted in G8 countries—that is, between 30,000 and 40,000 fetuses. As a result, many congenital disorders are becoming rare (ICBDMS, 2004) and, as they do, infant mortality rates are also declining. In Western Australia, neonatal mortality rates due to congenital deformities declined from 4.36 to 2.75 per 1,000 births in the period from 1980 to

1998. Half of that decline is thought to be due to the increase in abortions of abnormal fetuses (Bourke *et al*, 2005).

The widespread acceptance of abortion as a eugenic practice suggests that there might be little resistance to more sophisticated methods of eugenic selection and, in general, this has been the case. Increasingly, prenatal diagnosis of genetic conditions is carried out on the basis of molecular tests for Mendelian disorders. There are few published data on the frequency and consequences of such tests, but a recent survey of genetic testing in Italy showed that about 20,000 fetuses were tested in 2004, mostly for mutations causing cystic fibrosis, Duchenne's muscular dystrophy and Fragile X mental retardation (Dallapiccola *et al*, 2006). In Taiwan, screens for thalassaemia mutations have caused the live-birth prevalence of this disease to drop from 5.6 to 1.21 per 100,000 births over eight years (Chern *et al*, 2006).

However, such tests probably do not markedly decrease the mutational burden of a nation's newborns. Usually, a fetus is only tested for a specific mutation when its family medical history indicates that there is a clear risk. If, as must often be the case, parents are oblivious to the fact that they are carriers of a genetic disorder, they will have no reason to undergo a prenatal diagnosis, which is both expensive and invasive. Fetuses are also not tested for *de novo* mutations. However, given that many—perhaps most—parents want healthy children, should all fetuses be screened for many disease-causing mutations?

It is a question that some geneticists are now asking (Van den Veyver & Beaudet,

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2006). They point out that comparative genomic hybridization (CGH) microarrays could be used to screen a single embryo or fetus for thousands of mutations. One type of CGH microarray that is close to clinical application is designed to detect changes in gene copy number across the whole genome (Vissers *et al.*, 2005). These arrays, which are based on bacterial artificial chromosome (BAC) clones, can detect aneusomies—deletions and duplications—of about 100 kilobases in size. Such aneusomies are found in almost all individuals with no negative consequences, but a minority, which affect dosage-sensitive genes, cause disease. A recent study in which 100 patients with unexplained mental retardation were screened for aneusomies gives some indication of the importance of aneusomies in genetic disorders (de Vries *et al.*, 2005). Most of the copy number changes found in these patients were also found in healthy parents or controls and thus were probably not responsible for the disease; however, ten patients had unique *de novo* mutations. Therefore, this study identified a likely—albeit unproven—genetic cause of mental retardation in 10% of patients; a remarkable result for a single screen.

The virtue of a BAC-based microarray is that it can detect novel, as well as known, deletions and duplications; its limitation is that it misses the point mutations that are the cause of many, perhaps most, genetic diseases. Such mutations presumably account for at least some of the retardation in the 90 patients in whom no aneusomies were detected. At present there is no feasible method of screening the genome of a patient for all possible mutations—at least not without sequencing it. However, there is no technical obstacle to constructing an oligo-based microarray able to detect all known disease-causing mutations.

How useful would such a microarray be? More precisely, if a geneticist were able to screen a randomly chosen embryo for all known disease genes, what is the probability that he or she would be able to predict a genetic disease should the embryo come to term and live to adulthood? At the time of writing, the Human Gene Mutation Database (HGMD; www.hgmd.cf.ac.uk) identifies 64,251 mutations in 2,362 human genes that impair health. Most of these mutations are individually rare, but collectively they are very common. Indeed, given that there are

so many mutations, the probability that an embryo is at risk of a genetic disease caused by at least one of them must be quite high.

An individual's risk of suffering from a genetic disease depends on the mode of inheritance of the disease—autosomal dominant (AD), X-linked recessive (XLR) or autosomal recessive (AR)—and the global frequency of the causal mutation. A survey of 567 disease-causing loci from the Online Mendelian Inheritance in Man database showed that about 59% are AD, 32% are AR, and 9% are XLR (Jimenez-Sanchez *et al.*, 2001). Using these percentages with the 64,251 known disease-causing mutations in HGMD, we can estimate that 37,908 are AD, 20,560 are AR and 5,783 are XLR.

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To complete our calculation, we need to know the typical global frequencies of each of these three types of mutation. It is surprisingly difficult to obtain global frequency data for disease alleles; however, Reich & Lander (2001) give the total frequencies of all known disease mutations for 14 monogenic diseases: 4 AD, 3 XLR, and 7 AR. The HGMD then provides us with the total number of disease-causing mutations known for each of these 14 genes, which ranges from 31 for haemochromatosis to 1,262 for cystic fibrosis.

Using these figures, I have calculated average allelic frequencies (Table 1). The fact that AR mutations are more common than AD or XLR mutations makes sense, as selection acts less intensively on them. Multiplying these numbers by the number of mutations in each inheritance class calculated above, while taking into account the mode of inheritance and assuming global Hardy–Weinberg equilibrium, I calculate that the probability of predicting an inherited disease in a randomly chosen human embryo is almost 0.4% (Table 1). Therefore, it should be possible to predict a disease in 1 in 252 embryos.

The prediction of a genetic disease in a fetus does not necessarily indicate that it should be aborted. This decision ultimately depends on the strength of the prediction and the nature of the disease, both of

Table 1 | The probability of predicting a genetic disease in a random embryo if it were screened for all currently known mutations.

Inheritance	<i>n</i>	<i>p</i>	<i>F</i>
AD	37,908	4.9×10^{-8}	1.9×10^{-3}
XLR	5,629	2.4×10^{-7}	6.7×10^{-4}
AR	20,560	2.6×10^{-4}	1.4×10^{-3}
Sum	64,097		3.97×10^{-3}

n is the number of mutations; *p* is the average frequency; *F* is the frequency of humans in which a disease can be predicted. To calculate *F*, I assume global Hardy–Weinberg equilibrium (violation of this owing to population structure tends to inflate *F*). $F(\text{AD}) = np$; $F(\text{AR}) = np^2$; $F(\text{XLR}) = 0.5np(1 + p)$. I excluded *G6PD* from the XLR genes listed by Reich & Lander (2001), and from the mutation total in the Human Genome Mutation Database, because mutant alleles in this gene are so common that its inclusion vastly inflates the number of diseased fetuses, even though homozygotes have only mild health effects. Mode of inheritance: AD, autosomal dominant; XLR, X-linked recessive; AR, autosomal recessive.

which vary greatly among mutations. A female embryo with a single *BRCA1* mutation, which is dominant, has a 68% probability of developing breast cancer by the age of 80 (Risch *et al.*, 2001). Conversely, an embryo with two copies of the *HFE* C282Y mutation, which is recessive, has less than a 1% probability of developing haemochromatosis, a relatively mild blood disease (Beutler *et al.*, 2002). Whether such risks warrant aborting either fetus is a decision to be made by its parents and their clinical advisors, but it should be noted that most of the mutations in the HGMD cause classical Mendelian disorders detected by family linkage studies and so have fairly high penetrance.

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The estimate of the rate of disease prediction that I have given here is crude, but it is probably conservative. For convenience, I assumed a Hardy–Weinberg equilibrium, but in isolated populations or populations with a high degree of consanguinity—for instance, much of the Middle East through to Pakistan—the number of disease-causing homozygotes will be higher than my calculations. In addition, the rate of disease prediction will continue to rise as more and more disease-causing mutations are found. In 2005, 7,017 mutations were added to the HGMD—26% more than in 2004.



Fig 1 | Ultrasound scan to amniocentesis test. Amniocentesis is a diagnostic procedure performed by inserting a needle (seen on the left) through the abdominal wall into the uterus and withdrawing a small amount of fluid from the sac surrounding the fetus. The test can detect chromosomal disorders, such as Down syndrome, structural defects, such as spina bifida (open spine, where the vertebrae fail to close), anencephaly (a condition in which the brain is incomplete or missing), and many rare, inherited metabolic disorders.

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One impediment to a universal, total prenatal screen for all known mutations is the invasive nature of the procedure—it requires amniocentesis (Fig 1) or chorionic sampling to retrieve cells from the amniotic sac—and the traumatic nature of the treatment, which is therapeutic abortion. Perhaps, then, a total mutation screen will not be used in prenatal diagnosis, but rather in preimplantation genetic diagnosis (PGD). This procedure tests embryos produced by *in vitro* fertilization (IVF) for chromosomal abnormalities and specific mutations before implantation, by removing a single cell from the embryo at the eight-cell stage. Healthy embryos are then implanted; poor embryos—showing one or several abnormalities—are frozen or discarded. As in prenatal diagnosis, PGD is generally carried out only when a family medical history suggests that the embryo is at risk of a specific disease (Braude *et al*, 2002). Since its introduction in the mid-1980s, the procedure has spread quickly, although it remains illegal in some countries, such as Germany, which does, however, allow prenatal screens for a range of severe inheritable diseases. Data collected by the European IVF-monitoring Programme for the European Society of

Human Reproduction and Embryology (ESHRE; Grimbergen, Belgium) showed that 1,563 PGD screens were recorded in 25 European nations in 2002, compared with 882 in 2001 (Andersen *et al*, 2006). There do not seem to be any comparable data for the USA, but given the large number of US IVF clinics offering PGD—and the lack of regulation—the number of people across the world who have survived a PGD screen must now number tens of thousands.

How common will PGD become? Is it possible that one day every citizen of an industrialized nation will have survived, as an embryo, a PGD screen? Most commentators who have considered such a scenario—which was portrayed in the movie *GATTACA*—do not think so (Silver, 2000). Their main argument is that PGD—and the need to use IVF—is too expensive, inconvenient and limited in application to ever

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become widespread. They have a point: nature has contrived a cheap, easy and enjoyable way to conceive a child; IVF is none of these things.

However, the difficulties might be exaggerated. A course of IVF in the UK costs between £7,000 and £10,000—expensive, but cheaper than a mid-range car, and trivial compared with the costs of raising a child. Conception rates using IVF are generally lower compared with the old-fashioned method, but that is because many of the women who undergo IVF are relatively old (CDC, 2003). For women under 35 who have no fertility problems, the success rate per cycle is greater than 50%, which is comparable to natural monthly conception rates. However, perhaps the most important evidence against the idea that IVF—and PGD—will not catch on is the observation that it already has. At present, about 1% of Americans are conceived using IVF, and each year 4% of Danes start their life in a petri dish (Nyboe Andersen & Erb, 2006). It seems possible that if the cost of IVF decreases further and the number of PGD screens expands, an increasing number of parents will choose not to subject their children to the vicissitudes of natural conception and the risk of severe genetic disease.

Ultimately, the argument for a universal, total mutation screen will be based on its economic costs and benefits. It is too soon to draw up a detailed balance sheet, but we can suggest some numbers. Congenital mental retardation afflicts about 51,000 children annually in the USA; the Centers for Disease Control and Prevention estimate that each afflicted child will cost the US economy \$1 million over the course of his or her life—that is, a collective cost of \$51 billion (CDC, 2004). This does not include the social and emotional cost that parents assume in raising a mentally disabled child, which all but defy quantification.

Will neo-eugenics spread? Probably. At least it is hard to see what will stop it if, as I claim, it becomes possible to detect all known disease-causing mutations before birth or implantation, if the cost of IVF and PGD declines, and if eugenic screens have clear economic benefits. Some readers might find it peculiar that in this discussion of neo-eugenics, I have not considered the ethical or legal implications with which this subject is generally considered to be fraught. Although I do not doubt their importance, I simply have no particular knowledge of them. Peter

Medawar put it best 40 years ago: "If the termination of a pregnancy is now in question, scientific evidence might tell us that the chances of a defective birth are 100 percent, 50 percent, 25 percent, or perhaps unascertainable. The evidence is highly relevant to the decision, but the decision itself is not a scientific one, and I see no reason why scientists as such should be specially well-qualified to make it" (Medawar, 1966).

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doi:10.1038/sj.embor.7400860