Whenever a patient needs a blood transfusion, the ABO blood types—classic genetic markers—are used to identify the best match of blood. Tissue typing before transplantation and Rhesus factor testing are other examples. Trastuzumab (Herceptin; Genentech) has recently been licensed for treating some types of breast cancer. It is a humanised monoclonal antibody against the HER2 receptor and has been licensed together with a specific test (Herceptest) to identify the appropriate subgroup of patients who overexpress the HER2 receptor in the tumour tissue.[2] This is the direction that pharmacogenetics is likely to take drug treatment.

Most observers agree that this technology will affect medical practice—in some diseases—within five years (see p 1031)[3] Moreover, pharmacogenetics is associated with fewer ethical problems than other medical applications of genetics, such as presymptomatic diagnosis of highly penetrant single gene diseases with no treatment currently available—the scenario that dominates ethical issues in genetics.

What is the role of industry in this area? Companies are responsible for developing most new medicines or devices, so it is important to consider how they can collaborate with academics to expedite new therapies. Pharmacogenetics is increasingly driven by industrial researchers, partly because of their ready access to clinical trial data on which pharmacogenetic research can be carried out. The rigours of drug registration require a high level of data quality (and hence high cost) that few academic groups can afford.

Counterintuitively, industry can also provide leadership in procedures such as consent for such studies. For example, the need to establish clear procedures for generating and handling genetic information in the context of pharmacogenetic research has led to a cross industry group proposing standard definitions under which such research can be carried out (see www3.diahome.org/committees/pharmacogenetics/mission.asp). This has been welcomed by ethics committees and regulatory authorities, who find the current diversity of terminologies and approaches confusing (see, for example, www.emea.eu.int/pdfs/human/regaffair148300en.pdf). The usefulness of such an approach can be seen from the recent agreement of the Pharmacogenetics Research Network, funded by the US National Institute of General Medicine, to adopt these definitions as their standards (www.pharmgkb.org/pdfs/model.pdf).

In addition, industry is at the forefront of initiatives to use modern communication tools, such as the internet, to allow patients to provide samples for future research yet retain control of them in the light of future developments. When technology is evolving rapidly the research outlined in an original consent form can easily become superseded. If a valuable research resource is not to be lost, efficient methods of maintaining contact with patients to ask for further consent need to be developed. Possible approaches under consideration include having DNA samples and patient contact details held by an independent third party, who can release DNA for research after contacting patients using email or the internet.

Increasingly, the common needs for research tools of both industry and academic researchers are leading to joint activities. A successful recent example is the SNP Consortium, a grouping of 13 companies, five leading academic centres, and a charity (the Wellcome Trust) established to identify 300 000 single nucleotide polymorphisms in the human genome and make the information public as a research tool for all. This map, now available on the web (http://snp.cshl.org/index.html), will be a central tool, allowing genetic markers that affect disease susceptibility or drug response to be identified more rapidly. This should help to speed up the implementation of pharmacogenetic tests. There may be other lessons to be learnt from this initiative as it was managed to industrial timelines, identified five times more single nucleotide polymorphisms than originally conceived, and still finished ahead of schedule and under budget.

Both industry and academic researchers want to bring innovative solutions into clinical practice to improve health care. It is important that the skills of both are used to ensure the benefits from genetic research are delivered sooner rather than later.

Alun McCarthy *European head*

Drug Development Genetics, GlaxoSmithKline, Greenford, Middlesex UB6 0HE (admc2740@gsk.com)

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Preimplantation genetic diagnosis

Needs to be tightly regulated

Pregnant women whose babies are at risk of having a genetic condition serious enough to warrant consideration of termination of pregnancy may be offered prenatal diagnostic tests such as amniocentesis and chorionic villus biopsy. For some couples, however, such tests are not acceptable, and preimplantation genetic diagnosis is an alternative.

Preimplantation genetic diagnosis involves testing the early embryo after in vitro fertilisation. One or two cells (blastomeres) are removed at biopsy from the preimplantation embryo at the 6-10 cell stage (day 3 of development), thus allowing replacement into the uterus of unaffected embryos.

Preimplantation genetic diagnosis can be offered for three major categories of disease. Firstly, it can be used to determine the sex of the embryo for sex linked disorders where the specific genetic defect at a molecular level is unknown, highly variable, or unsuitable for

BMJ 2001;322:1008–9

testing on single cells—for example Duchenne muscular dystrophy.[1] Secondly, it can be used to identify single gene defects such as cystic fibrosis, where the molecular abnormality is testable with molecular techniques after polymerase chain reaction (PCR) amplification of DNA extracted from single cells.[2] Thirdly, it can be used in chromosomal disorders, where fluorescence in situ hybridisation has been developed to detect a variety of chromosomal rearrangements, including translocations, inversions, and chromosome deletions.[3] Some potential parents who carry a chromosomal rearrangement may never have achieved a viable pregnancy before requesting preimplantation genetic diagnosis if each previous conception resulted in a chromosomally unbalanced embryo which miscarried spontaneously.

Preimplantation genetic screening for aneuploidy (Down's syndrome and other trisomies) is not licensed by the Human Fertilisation and Embryology Authority in the United Kingdom, though it is offered elsewhere, including the United States and Italy.

It has taken over 10 years for preimplantation genetic diagnosis to become established, and only five UK centres are licensed. A preimplantation diagnosis cycle is a major undertaking for any couple, and the psychological, medical, and financial costs are considerable. A single cycle costs £4000-7000 (US$6000-10 500) (including drugs). About half of British patients obtain some NHS funding.

Recently the European Society of Human Reproduction and Embryology published results on 886 couples undergoing 1318 cycles of preimplantation genetic diagnosis over seven years.[4] Most couples had already had pregnancies, but fewer than 25% had healthy children. Over a quarter had one or more children affected with a genetic condition and a similar proportion had a spontaneous abortion or underwent termination after prenatal diagnosis. In about a third of cases the genetic indication for preimplantation genetic diagnosis was combined with subfertility, necessitating in vitro fertilisation or intracytoplasmic sperm injection. The reported pregnancy rate was only 17% (detection of fetal heart beat per cycle started), but this is improving: in our centre, established in 1998, the rate is 33%.[5] The European study reported four misdiagnoses after tests using PCR; these were detected at prenatal diagnosis, which was performed on 116 of the 236 fetal sacs (49%).[4]

The high incidence of multiple pregnancies after preimplantation genetic diagnosis is a concern (33% from the European data). Probably a maximum of two embryos should be transferred. Data so far suggest that children born after preimplantation genetic diagnosis do not have a higher incidence of congenital malformations or neonatal problems than children born after "regular" intracytoplasmic sperm injection, but they need to be followed up systematically through childhood.[4]

In the United Kingdom the Human Fertilisation and Embryology Authority has a central role in regulating preimplantation diagnosis, and each centre must obtain a licence for every test offered. The submission of multiple applications is time consuming and there is a debate in the UK about whether over-regulation is stifling service development. The authority's strong guidance is important, however, in such a new and controversial area. The virtually unregulated provision of preimplantation diagnosis in other countries, where sex selection for "family balancing" and HLA typing is performed, risks bringing the whole technique into disrepute.

To offer a safe effective service, a multidisciplinary team needs to be established, including specialists in in vitro fertilisation, clinical geneticists, genetic counsellors, cytogeneticists, and molecular biologists. Laboratories should participate in external quality assessment. The UK's tight regulation should reassure people worried that preimplantation diagnosis might lead to "designer babies." Establishing a similar degree of regulation internationally will depend on the motivation of individual governments and clinicians.

Frances A Flinter *senior lecturer in clinical genetics*

Centre for Preimplantation Genetic Diagnosis, Guy's and St Thomas's NHS Trust, London SE1 9RT

FAF is a member of the Human Genetics Commission genetic testing subgroup which advises the Department of Health.

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The promise of human genetic databases

High ethical as well as scientific standards are needed

Genetic databases are now helping elucidate gene function, estimate the prevalence of genes in populations, differentiate among subtypes of diseases, trace how genes may predispose to or protect against illnesses, and improve medical intervention. They achieve this by bringing together several streams of data about individuals: molecular genetic data; high quality standardised clinical data; data on health, lifestyle, and environment; and in some cases, genealogical data.

The main strategy with genetic databases is to search, often by statistical brute force, for correlations, then use the genetic focusing to guide mechanistic, pharmaceutical, and other investigations. Searching for

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