Providing preimplantation genetic diagnosis in the United Kingdom, The Netherlands and Germany: a comparative in-depth analysis of health-care access

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In recent years, preimplantation genetic diagnosis (PGD) has developed into a routine diagnostic procedure in health care. Although during this process, several initiatives have been employed to regulate the procedure, access to PGD may be hampered by the diversity in health-care arrangements or therapeutic cultures in different countries. This article demonstrates how PGD provision practices depend on much more than regulation alone, by providing an in-depth comparative analysis of the provision of PGD in Britain, the Netherlands and Germany. In analysing regulation, organization, selection of indications, and mechanisms and criteria for reimbursement, differences between these countries can be identified. This is important, since differences in PGD provision can have enormous consequences for the access of individual patients in different countries. Somewhat paradoxically, this article concludes that even though differences in access do have serious consequences, they also serve the establishment of PGD. Developing access to PGD in national ‘therapeutic cultures’ can contribute to making PGD routine health care in a way that may not be achievable by harmonizing regulation.

Key words: preimplantation genetic diagnosis / health-care provision / access / policy / comparative analysis

Introduction

In recent years, preimplantation genetic diagnosis (PGD) gradually developed from an experimental test into a routine diagnostic procedure in health care, accommodating this test in the organization of health care and health-care provision to assure patient access. During this process, various policy and regulatory initiatives have been employed to standardize the application, performance and delivery of PGD in European countries. For example, the European Society for Human Reproduction and Embryology (ESHRE) recently issued a number of guidelines and viewpoints, specifying technical requirements to laboratories, indicating best practices for diagnosis and counselling, and highlighting the need of cooperation between genetics and reproductive medicine (Geraedts et al., 2001; Thornhill et al., 2004; European Society of Human Genetics and European Society of Human Reproduction and Embryology, 2006; Corveleyn et al., 2008). Moreover, ESHRE’s Task Force on Ethics and Law explicitly addressed the view that access to and provision of reproductive technologies and PGD should become part of regular health care, in a standpoint discussing whether such technologies should be covered by public health-care arrangements in Europe, and under which circumstances (Pennings et al., 2008). This standpoint alludes to the need to standardize access to PGD under given criteria, in order to provide people all over Europe with access to PGD and to prevent inequality between European citizens in different health-care systems. Yet this wish may be complicated by the variety of arrangements for health-care delivery in Europe. This variety in mechanisms for health-care provision is at the core of this article. The discussion below will provide an in-depth analysis of access to PGD in the UK, the Netherlands and Germany.

This analysis will focus on the, often complex, (provision) practices that shaped and still shape patient’s access to this particular medical technology. The regulation of access to health care, as well as cross-border diversity in PGD, is often analysed in terms of formal government policies and regulations. A considerable number of publications have been looking at variation in regulations and policies for reproductive technologies across countries (Viville and Pergament, 1998; Bleiklie et al., 2004; Knoppers and Isasi, 2004; Dickens, 2008). Most
of these publications classify the investigated policies in terms of permissiveness and restrictiveness, on the basis of who regulates and which aspects of the technologies are regulated. In identifying differences of access to PGD and reproductive technologies as resulting from policy and regulation, such studies imply that regulation is decisive for variation in the delivery of PGD. Related to this view, standardization of applications for PGD and of access to PGD is considered to be achievable through a harmonization of regulations for the delivery of reproductive technologies.

However, practices of PGD performance and provision consist of more than regulation alone (Franklin and Roberts, 2006). To highlight the complexity and historical backgrounds of PGD practices in different countries, this article employs the concept of ‘therapeutic cultures’ (Daemmrich, 2004). This concept indicates how health-care provision practices are shaped by historical developments and interactions between different actors in the area of health care, which have led to nationally specific constellations of health-care provision. Such constellations for the provision of PGD will be discussed below, followed by a discussion of what differences in access mean and how to confront them. As this article demonstrates, understanding and positively valuing these differences in national health-care provision may in the long run serve even better the establishment of PGD as a routine procedure in health care than harmonizing national regulations into a unified, cross-national protocol or regulation.

Materials and Methods

The study of PGD provisions presented in this article is part of a qualitative study of practices of provision for different forms of novel genetic technologies in the UK, the Netherlands and Germany. The central aim of this research is to analyse how innovative developments in genetic science and technology will affect arrangements for health-care provision in these three countries. The countries in Western Europe have been selected on the basis of the different basic types of health-care delivery these three countries. The countries in Western Europe have been selected on the basis of the different types of health-care delivery they represent (Lameire et al., 1999; Burau and Blank, 2006; Van der Zee and Kroneman, 2007), as well as on the basis of their different approaches towards developments in genetics in national health-care policies. These policies were found in policy documents produced by the government or medical organizations. By focusing on the practices of health-care provision of genetic technologies, the study does not assume a linear impact of genetics on health care as can be found in many commentaries foreseeing a ‘genetic revolution’ in medicine (Varmus, 2002; Weinsilboum, 2002; Perpich, 2004). Rather, an in-depth analysis of the practices of health-care provision looks at the different ways new technologies may get incorporated into health-care arrangements, which may entail changes to these arrangements as well as to the technology and its uses. The latter phenomenon is often described as the co-production of science and society (Jasanoff, 2004; Aarden et al., 2008).

To analyse provision practices of PGD in this manner, empirical material has been collected both from clinical practices and from the practices of public health-care provision. This material consists of policy reports, position papers and other documents about PGD provision in the different countries. The relevant documents include legislation, lists of medical criteria, judgements of insurance disputes and contributions to discussions in medical literature. Besides that, 17 semi-structured, in-depth interviews were held with medical professionals (eight in total, including medical doctors, nurses and laboratory researchers) as well as public officials regulating, monitoring and evaluating PGD (nine). Respondents for these interviews were found via two different routes, either via their respective organizations and clinics or via a form of snowball-sampling where new possible respondents were mentioned in interviews. These interviews addressed topics such as regulation of PGD, organization of clinics, the trajectories for individual patients, criteria used for selecting applications, and mechanisms and criteria for financing the procedure. By studying documents of medical professionals and public policy officials, and by interviewing representatives of both groups, the empirical material provides insight into many aspects of PGD provision, further than regulation alone.

In analysing how specific national ‘therapeutic cultures’ relate to access to PGD, this article focuses on three aspects that are of major importance for the practice of health-care provision. These three aspects also serve to provide the basic structure of the country-descriptions. The first part presents the regulations that apply to PGD and the way clinics are organized, indicating the basic infrastructure for the delivery of PGD in the three countries. The second part describes the indications for which PGD is considered to be applicable and, in particular, to what extent medical professionals have autonomy in defining these indications. As this part will show, applications for PGD are identified in positioning the use of PGD in relation to indications for prenatal diagnosis, deciding how to deal with unaffected mutation carriers, and application of preimplantation genetic screening (PGS). The third part addresses the provision in the more strict sense of financing and reimbursing the delivery of PGD. In particular, this section analyses the mechanisms and criteria that are used to decide in which cases PGD will be provided or not.

Access to PGD in the UK

The use/delivery of PGD in the UK is regulated by the Human Fertilisation and Embryology Act of 1990. The major consequence of this Act is the establishment of the Human Fertilisation and Embryology Authority (HFEA), a government body licensing and monitoring centres that perform reproductive procedures in health care. In the HFEA’s Code of Practice, one chapter addresses preimplantation testing, outlining why it falls under HFEA’s remit, and which tasks the Authority has regarding PGD (HFEA, 2007). One of the aspects that distinguish PGD from in vitro fertilization (IVF) in general is that clinics performing PGD not only need a licence for the procedure, but also for the specific diseases for which the procedure will be applied. Several interviewees indicate that the procedure for obtaining a licence for a given indication is not very clear. There is a difference between merely notifying the HFEA when starting PGD on a disease for which the procedure is already applied elsewhere in the UK, and the requirement of presenting extensive documentation for a first application of PGD to a new disease. Especially in the latter case, criteria are unclear, but clinicians indicate that the HFEA usually follows the judgement of the clinicians. This means that decision-making about the indications for which to apply PGD is largely in the hands of clinicians. In addition, Britain has a form of ‘transport PGD’, which means that patients can go to a clinic in their own region to have PGD for a condition that is licensed somewhere else, since samples for testing can be sent to that clinic.

The indications for which PGD can be applied were mainly based on the accepted indications for prenatal diagnosis, although these were not explicitly listed or licensed. This correspondence between indications for PGD and prenatal diagnosis still exists. However, both kinds of indications have started to diverge. This is the result of couples increasingly seeing PGD as a better option than prenatal diagnosis and abortion for preventing diseases with a later onset or
less immediate and serious consequences. Another issue in determining whether to apply PGD is the question of what to do with embryos that only carry a recessively inherited disease or a sex-linked disease and will not suffer from the disease themselves. The general tendency in the UK is not to discard embryos that are only carriers of such diseases. Clinicians, when asked about this practice, put forward both practical and moral reasons. Practically, they argued that embryos, being morphologically suitable for implantation, are relatively rare, which often makes it preferable to implant an embryo that carries a mutation but has a good chance to develop. The moral reasons are indicated by one clinician who considers PGD ‘not a program of eugenics, to try and wipe out genetic disease’ (Interview CB 8, 140207). Finally, PGS is allowed in the UK, but not performed widely. Although most PGD clinics now offer this procedure, some clinicians criticize them for performing PGS for commercial reasons alone, since some studies suggest the procedure does not improve the number of pregnancies conceived by IVF (see also Braude and Finter, 2007; Harper et al., 2008).

Financing and reimbursement of health care in Britain happens within the National Health Service (NHS). A major characteristic of the NHS is that medical care is financed out of general taxation and should therefore be available for individual patients without extra payment. But even though legally there can be no ‘blanket ban’ to entirely exclude a medical procedure from funding (Mason, 2005), not all forms of health care are equally well-funded. This is a consequence of the local allocation of health budgets, where so-called Primary Care Trusts decide for a particular geographical area which health-care provisions will receive funding. As a consequence, the kinds of health care available for individual patients may considerably differ between geographical areas: the so-called ‘postcode lottery’ phenomenon. One medical procedure that receives much media attention with regard to this postcode lottery is IVF (Barnes and Gray, 2005; Anonymous, 2006). For IVF, the National Institute for Health and Clinical Excellence (NICE), an agency developing guidelines for best practice within the NHS, prescribed that three cycles should be made available to couples qualifying under certain criteria (NICE, 2004), but interviewees claim that adherence to this guideline appears to be limited. PGD was explicitly excluded from this guideline of fertility treatments, but a form of postcode lottery exists for PGD as well. A possible explanation for the lack of funding is the low number of procedures performed every year, giving PGD a relatively obscured presence in discussions on budget allocation. In some regions, this problem is solved by annually reserving part of the budget for a specific number of cycles, whereas in other regions applications for funding are made for every cycle anew. Even though patients can have PGD when they pay for it themselves, this is not an option for most couples. Therefore, if funding is not made available, this often means patients cannot undergo the procedure.

Access to PGD in the Netherlands

Regulation on embryo research in the Netherlands was developed long after PGD was first performed, and did not significantly affect the practice of the delivery of PGD. In fact, PGD is regulated by the Special Medical Treatments Act, positioning the use of this test in the area of medical genetics. The Act covers medical procedures that are considered to be experimental or highly specialized and can therefore only be performed at clinics licensed by the Dutch Ministry of Health. The profession of clinical genetics is covered by this legislation, and the 2003 Planning Decree on clinical genetics further specifies that genetic procedures can only be performed at university hospital clinics and PGD in particular only at the Academic Hospital of Maastricht (VWS, 2003), to which a form of transport PGD at two other university hospitals has been added in the last few years, with the genetic testing still being done in Maastricht. The Planning Decree does not limit indications for PGD, other than stating that the procedure can be used for the prevention of serious disorders. As interviewees in the Dutch PGD clinic indicate, the clinic refused to develop a list of indications in order to prevent the existence of a ‘black list’ of serious disorders, arguing that diseases can manifest themselves so diversely that not all forms of a disease are appropriate to apply PGD to. Recently, as a result of a rather fervent public debate about the applications of PGD in the Netherlands, some amendments to the Planning Decree were proposed. The state-secretary for health introduced slightly stricter criteria for PGD (i.e. from applications in the case of raised disease risk to high disease risk), and a formalization of existing practice in evaluating individual cases in the clinic’s working group on PGD (Bussemaker, 2008).

This means that, currently, indications for which to provide PGD are defined by a working group of the Maastricht PGD clinic, consisting of geneticists, gynaecologists and ethicists, on a case-by-case basis. Couples are usually referred to this clinic by geneticists, and are evaluated on the basis of whether clinicians consider the indication for which PGD is requested to be acceptable, whether the clinic is technically capable of performing PGD for this indication, and whether the couple can safely undergo treatment. As in the UK, indications for PGD are similar to the ones for which prenatal diagnosis is applied, with the same view regarding the use of PGD for late-onset disorders. Furthermore, exclusion of mutation carriers is explicitly not considered to be an indication for PGD. Thus, preimplantation screening is not performed at the Maastricht PGD clinic. This was the clinic’s own decision, which was also recommended a few years ago by the Dutch Health Council. In its Report on the use of PGD (2006), the Council advised the government and the parliament not to consider PGS suitable for regular health care (yet), and to wait for the results of a number of studies evaluating this screening method (Gezondheidsraad, 2006). One study that was performed by several clinics in the Netherlands published its results in 2007, which suggest that PGS harms rather than benefits IVF embryos (Mastenbroek et al., 2007). Consequently, it is unlikely that PGS will be practiced in Dutch clinics in the near future. Reimbursement of PGD, as well as other forms of health care in the Netherlands, runs through a statutory insurance scheme, in which individuals pay a monthly, risk independent, premium that gives access to a basic package of health care. This statutory scheme was introduced halfway through the twentieth century, and in recent reforms was changed from a form of social security for people with an income below a certain threshold to a form of insurance covering the whole population of the Netherlands. The Health Care Insurance Act of 2006 and related Planning Decrees mention what should be included in this package in rather broad terms, such as ‘care that is normally provided by a medical specialist’ and which
is according to ‘scientific standards’. What this means for the reimbursement of specific procedures is determined by the Health Care Insurance Board (CvZ), which has the task of ‘package administrator’. This task is derived from the former authority of the Board to judge disputes between insurers and their clients. In this capacity, in 2005 the Board gave some binding advice on the reimbursement of PGD. Some insurance companies refused to reimburse PGD because criteria for the reimbursement of IVF were not met, or because procedures were performed abroad, in centres that did not have licenses from the Dutch Minister of Health. In both of these cases, the Board overruled the insurers’ decision, claiming that IVF is not a separate issue but only part of PGD, and by referring to judgements of the European Court of Justice ruling that patients in the European Union can have outpatient health care in other member states reimbursed (see also Steffen, 2005). In a third case, the Board agreed with an insurance company’s refusal to reimburse PGD for BRCA mutations. The reason to accept this refusal, while overruling claims on other kinds of genetic diseases such as myotonic dystrophy and Marfan’s syndrome, was that BRCA mutations were not considered to be a ‘common’ indication for PGD internationally, a judgement based on whether a specific use of PGD is considered to be standard in international literature. By using this line of reasoning, the largely unspecified criterion of ‘commonness’ is prominent in Dutch PGD provision, thereby constraining the autonomy of medical professionals. Their views on indications that are appropriate to apply PGD may not be shared by insurers and public officials ultimately deciding about reimbursement.

**Access to PGD in Germany**

Regulation of embryo research in Germany is often presented as a quintessential example of restrictive regulation. The German Embryo Protection Act of 1990 bans any use of human embryos created in vitro that do not serve the embryo’s preservation and the establishment of a pregnancy. Although not explicitly mentioned in the Act, several articles are interpreted as forbidding PGD at the moment it is usually performed in clinical practice, namely in the stage of a 3-day-old blastomere, consisting of eight cells (Kollek, 2002; Schwingier, 2003). However, the question whether PGD should be allowed remains under discussion in Germany, in several different arenas. In the main medical journal Deutschs Ärzteblatt, for example, publication of a concept-guideline on how PGD should be performed if allowed, developed by the scientific council of the German Chamber of Physicians led to a lengthy debate among medical professionals (Bundesärztekammer, 2000). In parliament, two different ethics committees were consulted about the status of PGD, the National Ethics Council and the parliamentary Enquiry Committee, which came to opposing views, with the former in favour of allowing PGD, and the latter against it, leading to a continuation of the legal status quo (Deutscher Bundestag, 2002; Nationaler Ethikrat, 2003). Parallel to this restrictive legislation and ongoing discussions, a unique practice of (a different form of) PGD, sometimes described as pre-fertilization diagnostics (Diedrich et al., 2005), has been established in Germany. The Embryo Protection Act only defines an embryo as the entity that exists 24 h after an oocyte has been inseminated, after the fusion of maternal and paternal cellular nuclei. This implicates that genetic testing can then be obtained through polar body biopsy. This allows for an indirect way of testing, looking at rest material originating from the maternal genotype.

As a consequence of the specific organization of health care in Germany into what interviewees call a parallel ‘double structure’ of privately established outpatient clinics on the one hand and mostly public hospitals on the other hand, the further application and reimbursement of this form of PGD takes two different forms, yielding a dual provision practice of PGD in Germany. Indications for PGD differ between the two sectors of health care in Germany. The indications to which PGD is applied in university hospitals are most similar to those in the Netherlands and the UK. Two university clinics providing the German pre-fertilization PGD apply the procedure to a limited number of monogenetic disorders such as Huntington’s disease and fragile X-syndrome (Hehr et al., 2004). These indications, thus, form a minor part of the indications for which prenatal diagnosis is available. With a rather loosely defined criterion of a ‘medical indication’ for abortion, it is possible to end pregnancies should prenatal testing indicate the presence of an affected child. When discussing how unaffected carriers of recessive and sex-linked diseases are handled, German clinicians stress how in their opinion German legislation is unethical in its effects. Because polar body biopsy only looks at maternal DNA, all mutation carriers for recessive and sex-linked disorders will be discarded, although half of these will develop to be either unaffected carriers or healthy girls. University clinics also follow the cautious approach to PGs found elsewhere, and therefore do not offer this procedure. Nevertheless, PGS is performed as a variant of PGD in private outpatient clinics. Most of these clinics are unable to perform a PCR test required for monogenetic disorders within the existing timeframe allowed by the law. The clinics therefore limit their PGD to FISH applied to a few particular chromosome abnormalities. This form of screening for aneuploidies works with standard chemical solutions that can pick up aberrations on about five chromosomes. It is not standardly applied as screening to all IVF embryos, but can be offered as an option to prevent miscarriages or the birth of severely handicapped children, to women of advanced maternal age (over 35 years old).

In reimbursement, the two forms of early stage PGD that exist in German health care are also approached differently by statutory health insurance. The benefit package of this insurance scheme is not laid down in legislation such as in the Netherlands, although broad criteria are prescribed. Decisions about reimbursement of a specific medical procedure are made in the Joint Federal Committee, in which representatives of medical professionals and of statutory insurance funds negotiate about the inclusion of different forms of care. Yet different criteria apply to the different kinds of clinics. For outpatient care, there is a catalogue that explicitly lists which procedures are included. This catalogue, called the Uniform Valuation Scale, is based on techniques for diagnosis and treatments rather than indications, but despite the fact that FISH is included in the catalogue for several forms of genetic diagnosis, polar body biopsy with genetic testing is not. A possible reason why this form of diagnosis is not reimbursed is that it is considered to be a luxurious extra procedure added to PGD that does not meet the broad German reimbursement criterion of ‘medical necessity’. For care in hospitals, decision-making about reimbursement works in exactly the opposite way; procedures that are not explicitly excluded from reimbursement...
ought to be paid by insurance funds. Polar body biopsy has not been excluded from the catalogue, but due to the low number of procedures, clinics have to apply for funding on behalf of the patient in every individual case. After explaining the procedure, it is usually reimbursed by public sickness funds.

**Discussion**

The variation in PGD provision in the three EU countries presented above may have considerable consequences for patients. As has been demonstrated, PGD provision does not exclusively depend on regulation; application and reimbursement of PGD also depends on the organization of clinics, the professional discretion in deciding for which couples to perform the procedure, and the rules and mechanisms for the reimbursement of medical procedures in health care. In Germany, it is primarily restrictive legislation and the double structure of health care that shape access to PGD, whereas in the Netherlands the use of the criterion of ‘commonness’ in health care insurance defines the indications for which PGD is applicable, and in the UK, regional differences in health care funding have a considerable effect on the availability of PGD for individual couples. Variation in health-care provision practices makes PGD fundamentally different in all of these countries, especially from the point of view of individual patients who may end up with different entitlements, opportunities and financial compensation schemes.

However much these differences in terms of inclusion and exclusion of patients in public health-care provision may affect patients and their families, a few examples of situations where PGD may or may not be made available are instructive, e.g. cystic fibrosis age-related chromosomal abnormalities and BRCA. A couple looking for PGD for the diagnosis of cystic fibrosis of their future child may in principle have access to reimbursement of PGD in the Netherlands as well as in the UK, although in the UK that same couple might not have access in practice when living in the ‘wrong’ region. In Germany, it would be hard for this couple to have access to PGD for cystic fibrosis. However, a woman over 35 years old who wants to prevent chromosomal abnormalities before implantation will have access to the pre-fertilization variant of PGD in Germany, although she would have to pay for the procedure herself. The same woman would have access to PGS in most British clinics, but would most likely have to pay for it herself and would not have access in the Netherlands, since it is not performed as regular health care there. In Germany, PGD for women with BRCA mutations is still a long way off, where indications for PGD are narrower than those for prenatal diagnosis. In the UK, some clinics perform PGD for BRCA, which is broadly accessible via transport PGD, but funding still depends on the region. In the Netherlands, PGD for BRCA would not be reimbursed only a few years ago, but may well be in the near future, depending on the Health Care Insurance Board’s evaluation of medical literature and practice internationally. These examples demonstrate how access and exclusion are the result of different health-care provision practices rather than regulation alone. Yet these also highlight how cross-border differences in health-care access is a complicated and pressing matter for the health-care entitlements of citizens of these different countries.

This analysis of cross-national health-care provision practices nevertheless shows that solving differences in health-care provision access through standardized protocols and European regulations is a strategy unlikely to succeed. Rather than assuming that issues of difference in health-care access can be solved by harmonizing regulation supra-nationally, it might be better to understand and address the differences and variations in current national health-care provision practices. Practices of health-care provision are complex in nature and are deeply embedded in historically developed therapeutic cultures. These therapeutic cultures feature as much in the acts of clinicians when prescribing treatments to individual patients, as in processes of policy making regarding medical technologies and shaping reimbursement arrangements. The existence of differences in health-care access and reimbursement across national health-care arrangements may contribute to the embedding of PGD as a routine procedure in health care. Currently, access to PGD seems to develop in ways that are most suitable to the respective different therapeutic cultures. So construed, the paradoxical conclusion we draw is that the cross-national differences may in fact contribute to the process of turning PGD into regular health care. When PGD performance and PGD provision get embedded in national ‘therapeutic cultures’, the procedure might eventually become more well established than is achievable through harmonization at an early stage. This conclusion about the provision of PGD has broader significance; insights discussed in this article may stimulate rethinking the value of diversity for innovation in health care. Equally, it may be most fruitful for innovation in health care to remain aware of the limitations of supra-national harmonization in regulation.

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