Deutscher Ethikrat

Öffentliche Anhörung

Praxis der Präimplantationsdiagnostik im europäischen Vergleich

Berlin, 16. Dezember 2010

Berlin-Brandenburgische Akademie der Wissenschaften
Leibniz-Saal, Markgrafenstraße 38, 10117 Berlin

Simultanmitschrift

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Donnerstag 16. Dezember 2010
13:30 bis 17:30 Uhr

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Begrüßung

Prof. Dr. iur. Edzard Schmidt-Jortzig, Vorsitzender des Deutschen Ethikrates

Ich begrüße Sie zu unserer Anhörung heute Nachmittag zu den Erfahrungen europäischer Nachbarstaaten bzw. überhaupt zu europäischen Regelungshoheiten mit dem Thema Präimplantationsdiagnostik. Alle wissen, dass es hier zu Entscheidungen im deutschen Parlament kommen soll, und deswegen freuen wir uns auch besonders, dass verschiedene Abgeordnete des Deutschen Bundestages heute unter uns sind. Auch Sie herzlich willkommen, und ein ganz besonderes Willkommen gilt natürlich unseren vier Sachverständigen, die ich für den Deutschen Ethikrat jetzt nur ganz pauschal begrüße, Ihnen herzlich danke für Ihr Kommen. Im Einzelnen wird die Begrüßung und die Vorstellung unserer Gäste dann Herr Kollege Catenhusen vornehmen, dem ich jetzt auch für die weitere Durchführung unserer Anhörungsveranstaltung das Wort gebe.

Wolf-Michael Catenhusen, Mitglied des Deutschen Ethikrates

Lieber Herr Schmidt-Jortzig, liebe Mitglieder des Ethikrates, verehrte Gäste, meine Damen und Herren! Wir führen heute eine internationale Anhörung zum aktuellen Stand der Arbeiten mit und der Entwicklung von Präimplantationsdiagnostik, denn wenn wir unser Votum vorbereiten, dann müssen wir auch wissen, wie in der Wissenschaft und in der praktischen Anwendung die Perspektiven zurzeit vor allem in unseren Nachbarländern aussehen. Zunächst wird Herr Dr. Luca Gianaroli als Präsident von ESHRE eine Einführung in die aktuellen Perspektiven und Entwicklungen auf dem Feld von Präimplantationsdiagnostik geben. Er wird eine halbe Stunde Gelegenheit haben, seine Präsentation vorzunehmen. Dann werden wir die Möglichkeit haben, Fragen zu stellen. Der Ethikrat, das will ich gleich sagen, hat sich an dieser Stelle heute Morgen darauf verständigt, dass auch angesichts der Hochrangigkeit und des Informationsgehaltes unserer heutigen Anhörung auch Mitglieder des Deutschen Bundestags oder der Bundesregierung die Möglichkeit erhalten sollen, wenn sie wollen, einige Fragen zu stellen. Denken Sie nur bitte an die Knappheit der Zeit, und zunächst sind natürlich dann erst mal mit ihren Fragen die Mitglieder des Ethikrates dran.

Dann werden wir in einer zweiten Runde die Experten aus Belgien, aus Großbritannien und Frankreich ihre Erfahrungsberichte geben lassen, und zwar in einer Präsentation von drei mal 30 Minuten. Dann gibt es die Möglichkeit, den Rest der Anhörung bis um halb sechs mit Fragen und Diskussionen zu verbringen, denn aus unserer Sicht macht es Sinn, auch Fragen an die drei Personen, das heißt Fragen an internationale Vergleiche hier einbringen zu können.

Soweit zum Ablauf. Jetzt darf ich zunächst ganz herzlich in unserer Mitte Herrn Dr. Luca Gianaroli begrüßen. Er ist seit letztem Jahr Präsident der European Society of Human Reproduction and Embryology, ESHRE genannt. ESHRE ist für die Transparenz der Entwicklung auf diesem Feld eine unverzichtbare Informationsquelle, auch für die deutsche Wissenschaft, und sorgt für eine weltweite Vernetzung der Wissenschaft auf diesem Gebiet. Sehr geehrter Herr Dr. Gianaroli, ich bitte Sie nun, mit Ihrer Präsentation zu beginnen. Danke schön.

Thematische Einführung

Dr. Luca Gianaroli, Vorsitzender der European Society of Human Reproduction and Embryology (ESHRE)

Thank you very much, Mr. Chairman. Thank you to the members of the committee and to the members of the parliament who are here. My

task today is to present to you the state of the art of this technology and these techniques. And I would just like to mention that the largest data collection in the world on this technology is due to the activity of the European Society of Human Reproduction and Embryology. So much of the data I will show you refers to this activity, which spans more than 11 years. For those of you who are not familiar with this technology, we can remove genetic material from the ovocyte before it is fertilized, from the ovocyte once it is penetrated by the sperm, from the embryo in the development stage and from the trophectoderm of the blastocyst. This removal of material is comparable to what is done in biosynthesis. There are pros and cons concerning this technique, which are summarized here.

[Slide 3]

As you can see, of course, if we compare what is called PB, we have no embryo mass reduction; several days are left for analysis because we can work for a few days before the embryo is transferred and do not encounter the problem of mosaicism, which means in some cases that one cell could represent the entire embryo. If we remove a cell from the cleavage stage embryos, both male and female contributions can be analysed. If the answer is not correct, it is possible to have a second biopsy, maybe the day after or at the blastocyst stage. If we work on blastocyst, i. e. on the trophectoderm, we have several cells available for analysis and there is no embryo mass reduction, so the embryo is not touched, because, as mentioned before, only the cells that are going to form the placenta are analysed. So the advantages of polar body biopsy of cleavage embryos and blastocysts are listed there as polar body. Of course, we have nothing from the paternal contribution, and that implies, for instance, that we have one pathology that can apply to a female or a male for instance, a translocation, the same pathology can be diagnosed if the carrier of the programme is a female; the same pathology cannot be diagnosed if the carrier of the programme is a man. At the cleavage stage, we have the disadvantage, as I mentioned before, of the reduction of the mass embryo and the risk of having one cell that does not represent the entire embryo. The disadvantage of the blastocyst, for which more technology is needed, is that we have only a few hours to produce a diagnosis in the exam. This is the state of the art at the moment in Europe.

[Slide 4]

Here is the data from the consortium I mentioned. The majority of the around 25,000 diagnoses registered at our consortium that have been carried out so far, up to 2007, were on cleavage stage embryos, much fewer at the blastocyst stage and slightly more at the polar body stage. The trend is changing: there is a decrease in cleavage embryos and an increase in blastocyst biopsy and polar body biopsy. I'll go back to this later.

[Slide 5]

This map is not completely correct because we have to take into consideration that polar body biopsy is also part of the PGD or PGS. So here we have just list the countries that allow embryo biopsy and blastocyst biopsy. And there is a slight mistake because Switzerland is not actually considered part of Europe, but it should be because it follows the same rules as this country. So here you can see the countries that participate in the consortium and, as you see, some of the countries are not in Europe, so they represent part of the worldwide scenario. But most of the countries in Europe that deal with PGD report their data to our consortium.

[Slide 7]

And here are the numbers.

[Slide 8]

You see, the number of centres that participate in data collection increased over the years, and then there is a stabilisation of the number of centres, which are now just under 60. In the toolbars, you can see the number of IVF and ICSI cycles registered at our consortium; we are now at around half a million cycles per year.

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And in the red bar, the contribution of PGD. As you can see, we are talking about a few thousand diagnoses run each year across Europe for the countries mentioned and the centres I have just presented to you. So a few thousand every year. When we look at the number of cycles again,

[Slide 10]

you see that there has been an increase since the beginning, and now we are talking about roughly 6,000 cycles every year run in Europe.

[Slide 11]

This graph shows what we consider very important data. It is the mean number of cycles, of patients that each centre treats using PGD or PGS. As you can see, there is an increased number for the specialised centres involved in this branch of reproduction medicine. In other words, the number of centres increases the specific number of diagnoses every year.

[Slide 12]

This is slightly complex, but it shows that the implantation rate is the hard bit for us, so the clinical pregnancies established after the embryo transfer. And OR means the pregnancy rate for ovocyte recovery, that is a surgical manoeuvre we need to recruit ovocytes. And ET is embryo transfer. So, in other words, the number of pregnancies per embryo transfer is of course higher because it is one stage more advanced than ovocyte recovery. You can also see that there is an increasing term of success rate along the years, which remains quite stable.

[Slide 13]

Which are the indications? Here you have more than 27,000 analyses that have been done, collected by the consortium that give you an idea of the indications. The majority of the indications are for aneuploidy screening, so-called PGS, I'll go back to that later on. I would like instead to concentrate on translocation, monogenic disorders and X-linked disorders. As you are aware, the small slice of sex selection belongs to countries outside Europe. You are probably aware that ESHRE was probably the first international society not to consider the application of PGD for sex selection as appropriate. And despite that, of course, we collect data from those countries that send us the data which, as I said, are non-European countries.

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PGD can be carried out for any disorder in which the gene responsible for the disease has been identified. This seems a very simple observation, but we have to bear this in mind because any disease, as long as we know the origin of the problem, can be diagnosed. So, that will also explain some of the slides after this in which we have an extremely long list of severe diseases, just because, as long as we know the origin of the disease, we can make the diagnosis.

[Slide 15]

I don't think it is in the interest of this committee to go to the technical part, at least for the routine. I would just like to mention that, when we work on PGD, what we need is, of course, to have the genetic material, to lyse the cell, to use a PCR to amplify the genetic material we have, which is very small, and then to restrict, with what we call nested PCR, the area in which we want to make the diagnosis. Then there are some novelties I have been asked to present, and then we can analyse the mutation, the

pathology we are studying. So this is principally, in a very simple and schematic way, how it works in genetic laboratories.

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And just to give you an idea, this is what we have once we have the analysis and we make the sequencing of the test. Here, in this case, we are talking about a problem related to beta thalassemia, and this is what we see in our instruments. For instance, here you see a normal allele and a mutated allele. Based on this, we can diagnose whether the genetic material, or the carrier of the disease, is actually affected. Whether or not the disease is there.

[Slide 17]

In terms of clinical application, you can see some of the disorders here that have an estimated prevalence in Europe. The reason why I put this short list here is not to make a comprehensive list but to say that when we think about Europe and we think about prevalence of a disease in Europe, maybe this is not the correct way to think because there are areas, and again I take thalassemia as an example,

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there are areas in the world, and specifically in Europe and specifically, in this case, for instance, some region of Italy in which it is true that 1.5 per cent of the global population are carriers, but it is also true that you can go up to 12, 15, even 20 per cent of carriers of this potential disease in some areas, in this case of Italy. So, the prevalence, consider it as a prevalence in a continent or in a country, which doesn't necessarily mean that there is the same prevalence in an area of a country of Europe. Let us look at some results just to give you a very simple concept.

[Slide 19]

Again, the pregnancy rate, clinical pregnancy rate, for ovocyte recovery, for embryo transfers. So, the blue bar for ovocyte recovery is lower than the bar for embryo transfer. As you can see, these are the numbers of diagnoses for cystic fibrosis, for beta thalassemia. What I would like to stress is that the difference in terms of pregnancy between ovocyte recovery and embryo transfer is due to the fact that by making this selection, so making PGD, you have a certain amount of patients who do not reach the capability to have their embryo transferred. So, they break off the treatment before the embryo transfer because there are no embryos available. All embryos are pathological, none of the embryos are transferrable. So, that's why you always have a difference between embryo transfer and ovocyte recovery. And the more severe a disease, the less chance the patients have of having an embryo transferred. And if the patient is at an advanced reproductive age, let's say 38, 40, she produces fewer eggs, which implies she has less chance of having an embryo transferred.

[Slide 20]

Here you have an example of autosomal dominant and, again, I include only the most important ones, such as Huntington's, myotonic dystrophy, neurofibromatosis. And again, you can see that for some disorders, for instance, for myotonic, the possibility of a patient falling pregnant once the embryo is transferred is decent, but often there is no chance of transferring this embryo.

[Slide 21]

Here are other diseases that don't mean much, but look at the number. More than 1000 are considered other diseases and when you look at the list

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it is enormously long because many have been diagnosed only once, twice, three times, ten times over the period of the ten years in which we have been registering this data. And this is

due to the fact that they are difficult diseases, rare diseases, and they are exposed to this technique only quite rarely.

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The section of the specific X-linked disease, again, I've just included some of them, for instance, haemophilia or the Duchenne, and again, you see that, for instant, for the fragile X that once there are embryos, the chance of the patient falling pregnant is high, but again, not many of them reach the capability to have the embryo transferred. When we look at the, I'll skip this one, I just wanted to say that when we look at PGD use for chromosome abnormalities,

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then we have structural abnormalities and numerical abnormalities. And that means translocation, deletion, inversion and numerical are those with altered karyotype. For instance, an exceeding number of chromosomes.

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So, translocations are represented quite largely in male and female and, according to the type of translocation, we have two different systems. When we are talking about Robertsonian translocations which, as you see, affects only these specific chromosomes, we just use probes that count the chromosomes. When we have reciprocal translocation, however, and I'll come back to this later, we have a variety of technologies – the one most used at the moment is the last one, so-called centromeric and telomeric probes. And this is a technique used most around the world. What does it mean? It's quite simple.

[Slide 28]

Here is an example of normal chromosomes, what we call derivates in which reciprocate, or a piece of one chromosome, is fixed on data, and vice versa. And what we have is the possibility to mark these chromosomes with specific coloured probes. And then, the reading under the microscope, the number of probes that we can see. So, just to give you an example, if we look, for instance, at this picture in the first one, the laser pointer is not very powerful, so the first section, as you can see, is all normal. We have a basal translocation in the second panel. And it is interesting to note that, with this technique, we are unable to discriminate between normal and balanced, that means anyway a phaenotypically normal individual if you use this technique. While, for the pathological one, the so-called unbalanced, as you can see, there is, for instance, in this case, only one green spot, so we are able to make the diagnosis between unbalanced and normal, and unbalanced and balanced. But we are unable with this technique to discriminate the two upper, normal and balanced.

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If we look at the data again from a clinical point of view, here it is even more evident, when we concentrate on the reciprocal translocation, that they are very difficult patients. Most of these patients have gone through repeated abortion before entering this treatment and the pregnancy rate, again, is not very high, also based on the fact that very few embryos are usually available for diagnosis and for transfer.

[Slide 30]

Here I've put the data from only the last register, so 2007, again for chromosome abnormalities based on the fact that for the first year, we are also able to track miscarriages. And, of course, since the aim or goal of this treatment is to have babies born, possibly have babies born, as you can see, some of these, some of these abnormalities, like reciprocal translocation, have quite a high incidence also of miscarriage, because most of the time, they are also linked to other abnormalities. So, the strategy is not only to look into the specific chromosomal aberration, but also to look at all the panels of the chromo-

somes to try to detect the other abnormalities involved.

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A few words, because it still uses a lot of energy, is the so-called PGS, so Aneuploidy screening with the idea to screen those embryos that, being chromosomally abnormal, would either never implant, or if they implant, they would go through an abortion.

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Here, you have the numbers and, as you see, mainly in the table on your left, they are very large numbers, they cover more than 50 per cent of the entire world than in Europe. Up to now, this technique has been applied at the cleavage age, at the cleavage stage embryo mostly, and has not been proven, as you will hear later on, to be clinically, from the statistical point of view, significantly important in increasing the number of healthy babies born. Stressing the point that this data is only related to one part of the technique, so when one cell is removed from the cleaved embryos. There are new technologies now that I will briefly mention later on that seem to have a possibility to rediscuss this technology from the clinical point of view.

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Here, just to give you an idea of the technique of PGS applied to two major indications, that is advanced maternal age, i.e. patients over 39, 38, 39, and advanced maternal age and also with another factor or what we call poor prognosis patients in terms of success.

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Here, you see the results as you saw before from monogenic disorders in terms of clinical outcome and in terms of pregnancy rate for ovocyte recovery or for embryo transfer along the years. And a few words now about pregnancies before we go on to the area of misdiagnosis. Here is what we have. We have a total of over 5,000 generated pregnancies. Some of the pregnancies are lost to follow-up. According to our experience, most of the pregnancies lost to follow-up are those without complications. The patients are not easy to track. And, as you can see, it is quite a small minority of all the work done, anyway. There are terminations of pregnancies, miscarriage, ectopic pregnancies there. The number of deliveries is more than 4000, and you see the number of deliveries in terms of singleton, twins and triplets.

[Slide 37]

Here is statistical data that may be, well, the picture is not very nice, but all in all, we do not see any difference in terms of statistical data between the babies born by PGD and the babies born by other techniques such as IVF or ICSI.

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When we look at the malformation, again, we have some data that is of interest because you see the figures and, again, all the malformations have been incorporated, including the minor ones and, again, comparing this data, we have stratified this data for the age of the patients, there are no differences in terms of numbers, a percentage of malformations with ICSI or IVF babies born that, of course, in much larger registries. So, we still have to bear in mind the small number here.

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Neonatal complications at birth are mainly related to twins and triplets and, again, this follows the general concept of multiple pregnancies and that is, again parallel, to what we already know for the other techniques and, of course, talking about PGD, that means diagnosis, there are misdiagnoses and I think this is probably the most important part of the entire procedure.

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Misdiagnoses, if they occur, are due to technical failure and, here,

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I have summarised for you the registered report of misdiagnoses, but I would like to summarise what we have. For monogenic disorders, out of more than 6000 embryos transferred, we have nearly 1000 embryos implanted with ten misdiagnoses, which stand for one per cent of the embryos that I have shown to be able to give rise to a pregnancy. For X-linked diseases 1.7, for translocation it is much lower, we have put in place new strategies to make this technique even more reliable, and we have 0.3 per cent for PGS. Here, you have the outcome of the misdiagnoses, most of them end up in abortions, in termination of pregnancy. But what is more important is that the technique is now reliable, between 99 and 99 point something per cent.

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I would like to conclude with a few words on new technologies, if I am permitted, because this seems to be what I was asked for. And, of course, new recent advances means just to pick up and take the picture of a running movie, so maybe some of the things that I am going to tell you now that are published or under publication will be superseded by different technologies in six months or one year.

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So, at the level of biopsy, technical biopsy, there is one important piece of information that is, we can remove polar bodies and blastomeres without affecting the embryo, the cleavage of the embryo. So, two manoeuvres can be done in the same fertilized ova cycle.

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In this case, we had unknown oversize, so there was no diagnosis. If we remove the cell, the blastomere, then we can make the diagnosis.

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Here is data that was published some years ago in which the combination of polar body and embryo biopsy does not affect embryo viability. Another point which is very important and has been carried out by this group, this is our own group, but the other thing that is very important that has been carried out by the Brussels group, is to prove, or intend, to find the best way to make the diagnosis in a cleavage embryo, so whether to remove one cell or two cells

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The most important part of this work is to be able to prove that when we compare the one-cell biopsy, that is the left column, with two cells, with the group III which there are, there is no biopsy done, what you see is that removing one cell does not affect the capability of the embryo to implant when it is compared to the non-biopsy group. While there is a decrease, of course, if you remove two cells. But I think that the most important consideration is to prove that removing one cell at this stage does not affect the potential of the embryo to implant when we compare it to non-biopsied embryos. And this, I think, is another piece of information that is important from the decisional point of view of these techniques.

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If you want to remove a cell at the blastocyst stage and you are working on trophectoderm biopsy, as I mentioned to you before, apart from some technical skills that are needed, the time to make the diagnosis is very short. Removing trophectoderm cells, it seems, do not affect, again, the potential of the embryo to be implanted.

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Here are two data, one from Australia and the other from, again,

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a different group in which the implantation rate is 44 per cent, that is quite substantial. Again, assimilating the concept, the mechanical removal of the cell does not affect *per se* the potentiality of the embryo to be implanted.

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Cryopreservation.

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There are many reasons why we need to cryo-preserve or it could be needed to cryopreserve embryos. Prior to biopsy, for example, in cases of hyperstimulation for the patients, after the biopsy, to give us more time to perform the diagnosis, after the biopsy and the diagnosis where fresh embryos have been transferred but unaffected surplus embryos are there. So, there is a need to freeze embryos.

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And when we look at the literature, data from the conventional technique, that is slow freezing, it proved that it was suitable and it was possible to cryopreserve biopsied embryos. But the real advantage or the real advance in this technique is the use of vitrification.

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That, as you are aware, is a modification of the slow freezing technique, or we can say a completely different technique. And what I want to point out is that, when we compare ongoing pregnancies and births in terms of pregnancies, you see that with vitrification, we have a higher chance of these embryos surviving and giving rise to a birth. So, we consider this technique to be probably the most advanced technique at the moment, or the technique of the future.

[Slide 55]

Microarray. To finish with microarray. Microarray is a new technology that has been imported and applied to PGD.

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It's technically, it's – it's too German for me. So, it's a simple technique that, the concept is, anyway, to compare the DNA that we need to test with a normal DNA and once we have it, we label it, we expand this DNA, because, of course, we need a large amount of DNA to make the diagnosis, we put together the two DNA so we hybridise them and then we read on specific slides. And what we read is very simple, once that all the process is done, we can all do it, because what you have is yellow, green and red. If you have yellow, it means there is no variation. If it is green, it means we lost DNA and if it's red, we gain DNA. So there is extra DNA.

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So this is the general principle and you end up with this chart in which you have, for instance, euploid female genetic material.

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An aneuploid with different chromosomal abnormalities, as you can see, there is an extra 6 chromosomes, an extra 22, a loss of chromosome 5, 14, and so on.

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Is this technique reliable? Apparently it is.

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A study was performed recently with the assistance of one of your universities in which all the process was done on polar bodies for specific testing and it was done producing a protocol that took only 12 hours, and was able to give an answer. This test was done on a certain number of polar bodies and, without telling the whole story of the study, I just want to say that there is the possibility to use this technique with 92, 94 per cent reliability. It is interesting because you can discriminate polar bodies, you can discriminate pathologies inside the ovocyte and, of course, this can also be applied to

embryos. Here is the total amount of polar bodies that have been examined in this test; there is more data coming to prove what I am saying. There are two different types of use of microarray while one is what you have just seen, that is a CGH and the other one is NIPS. The difference between the two is the way in which we use bacterial clones of the polymorphes, but at the end of the day, the process is very similar. So, these are technicalities that only increase the quality of the work. And this is the state of the art. Here, you see a different chart that you have seen, just an example of the NIPS microarray. So what you have, then you have to count all these little dots instead of having the peak or the decrease.

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Karyomapping is the last technicality that I want to show you, which can be used to discriminate different pathologies including, for instance, normal and balanced translocation. It has a problem: it needs the genetic material of the father and the mother of the subject we are studying. So, we have the infertile couples, but we also need to have the mother and the father of the two patients' genetic material to make it reliable. It is very precise but, as I told you, it has this bias.

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To conclude, the NIPS microarray can be used, and this is the first report as far as I know in the literature in which you can use this technique for combining PGD, so it makes the diagnosis of monogenic disorder and also tries to avoid chromosomal abnormalities like those chromosomes that are more involved in abortion or are more involved in syndromes that all of us know, like Down's Syndrome or other syndromes. So this is the first report proving that the way in which we are going will probably make the things even more sophisticated. I would like to finish here because these are just other examples, and I think I'll spend all my remaining time with the last slide, which has a lot to do with my practical work as a clinician and I'm showing you, I skip this one, because we've been through this already, I'm showing you what is actually clinical work.

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Here, you have the list of patients who visited a clinic for PGD: 16 were infertile, 81 had no proven fertility, 105 of them were fertile. Among those fertile couples, 78 had at least one termination of pregnancy and 57 had affected children born. In these couples we interviewed for PGD, the history of the babies born, for those of them that were not there at the time of the interview, is little before is the reason of their death. So, this is just an example of what a clinic faces when it starts to apply this system. And I would like to mention that there are now very precise guidelines that have just been published on the different aspects of these technologies and, of course, they need to be updated every two or three years, but they describe step by step what the best clinical practice is at the moment we know that we consider should be put in use in any clinic that is going to work in this area. Thank you very much and sorry for making it a little bit longer than expected.

(Beifall)

Erste Fragerunde

Moderation: Wolf-Michael Catenhusen, Mitglied des Deutschen Ethikrates

Wolf-Michael Catenhusen [Mitglied des Deutschen Ethikrates]: Schönen Dank, Professor Gianaroli. Ich würde jetzt vorschlagen, dass zunächst Mitglieder des Ethikrates Fragen an Herrn Gianaroli stellen können. Herr Taupitz.

Prof. Dr. iur. Jochen Taupitz [Mitglied des Deutschen Ethikrates]: Von mir ein herzlicher Dank für Ihren eindrucksvollen Vortrag. Ich habe

drei Fragen. Die erste Frage richtet sich dahin, wie viele Embryonen man sinnvollerweise oder mindestens für eine PID, PGD benötigt. In Deutschland gibt es nach verbreiteter Auffassung die Regel, dass maximal drei Embryonen innerhalb eines Zyklus hergestellt werden dürfen. Die Frage an Sie: Ist es, wenn man diese Dreierregel aufrechterhält, gleichwohl sinnvoll, mit diesen drei Embryonen eine PID durchzuführen und damit dann eine Auswahl vornehmen zu können?

Die zweite Frage richtet sich an die Blastozystenbiopsie. Sie haben gesagt, dass man nur wenige Stunden Zeit hat, um diese Diagnose durchzuführen. Auf der anderen Seite ist es, wenn ich es richtig verstanden habe, sinnvoll, die PID so spät wie möglich durchzuführen, weil dann die Gefahr der Mosaikbildung nicht besteht. Können Sie diese kurze Zeitspanne erläutern, warum man tatsächlich nur so wenig Zeit hat? Und daran anschließend natürlich die Frage: Kommt man mit dieser kurzen Zeitspanne in der Praxis in der Regel wirklich hin?

Die dritte Frage richtet sich auf die Fehldiagnosen. Wenn ich Sie richtig verstanden habe, haben Sie die Fehldiagnosen geschildert, in denen ein Kind als gesund identifiziert wurde und sich später herausgestellt hatte, dass es doch geschädigt ist. Gibt es Zahlen für den umgekehrten Fall, dass ein Embryo zu Unrecht als geschädigt identifiziert wird über die PID und gleichwohl sich hinterher überraschenderweise herausstellt, dass der Embryo nicht geschädigt war?

Prof. Dr. rer. nat. Stefanie Dimmeler [Mitglied des Deutschen Ethikrates]: Thank you very much for the nice presentation. I have a specific technical question with respect to the detection of mutations. I can understand if microarrays, for example, would be helpful in detecting chromosome translocations, but I wonder about specific mutations and maybe your statement regarding that a deep sequencing would be better and whether there is any technique where we can get really reliable results for severe mutations and risk genes with one single cell RNA.

Prof. Dr. rer. nat. Regine Kollek [Mitglied des Deutschen Ethikrates]: Meine erste Frage hat mir Herr Taupitz schon aus dem Mund genommen, die Frage nach der Anzahl von Embryonen, mit denen man sinnvollerweise startet, wenn man eine Präimplantationsdiagnostik machen will. Der ESHRE-Bericht verzeichnet ungefähr sieben Embryonen im Durchschnitt. Glauben Sie, dass man so viel braucht oder dass man auch mit weniger anfangen kann? Meine zweite Frage ist: In zehn Jahren wurden laut ESHRE-Bericht ungefähr 90 Blastozystenbiopsien durchgeführt. Warum waren es nur so wenige?

Dr. Luca Gianaroli [Vorsitzender der ESHRE]: I think there are two questions that are almost the same, related to the number of embryos. So, how many embryos do we need to make a diagnosis? Here we have what we know from classical medical genetics in which, for instance, when we go for monogenic, we say there is a 25 per cent chance of having an affected baby, a 50 per cent chance of having a carrier baby and a 25 per cent chance of having a normal baby. But these apply from the Mendelian point of view of the clinical work. But, in fact, we know that there are families with a tendency to produce more affected or more abnormal embryos, and vice versa. And there are some pathologies in which this occurs more or less. So, the number of embryos that are needed, and this then fits to the question related to: Is number 7 the real number or the gold standard? So what we know is that, of course, from the efficiency point of view, the more embryos we have to analyse, more chance we have of giving that patient the possibility of having a healthy embryo in her womb. So this is a general

concept. But it is also true that this varies according to families, the disease and mutations within the same disease. So, I don't think that we have a gold standard or a prefixed number of embryos that are the best number to be used. It is also true, and we have to bear this in mind, that many of our patients are at the older stage of their reproductive age, over the age of 38, 37 and they very rarely produce many embryos. In this case, there are a few strategies. Some include, for patients with few embryos, to freeze those eggs that are collected, fertilized, and accumulate after two or three ovocyte recoveries then look at all of them and make the diagnosis. We have to consider the fact that, every time the diagnosis is done, even for one embryo, the time, the cost and the length of the procedure is very, very high. It doesn't change much if we have to do the analysis on three embryos or on five embryos or on one embryo, but the results are completely different. So this is one aspect. The second aspect is that, as you are aware, between 2004 and 2009, in Italy, the law was only designed to generate a maximum of three embryos. So, PGD was not forbidden but, in fact, when we tried to do PGD with three embryos available, it was such a disaster in terms of not only the result, but also in terms of cost, obliging patients to come back many times to repeat stimulation, to repeat ovocyte recovery, that we abandoned it. When I say we, I mean the two groups that were trying at the time to do PGD on embryos, of course, with three embryos available. The misdiagnoses, so-called reverse case, so the question is, the misdiagnoses I presented to you vary between 1 per cent and 2.03 and the question was, but do you have a reverse? So, what, do you have data in which you have diagnosed a wrong embryo and in fact it was a healthy one? We only have a set of data that is important in terms of numbers for embryos analysed for chromosomal abnormalities. And the reason why we have this is that the large number of embryos that have not been transferred have been analysed, so all of them that were not transferrable because they were considered pathological, were analysed. And there, we found a percentage of mosaics that was varying between 5 and 10 per cent in which the cells we analysed did not represent the chromosomal pattern of all the other cells. And then we came to the conclusion that doing preimplantation genetic screening on cleavage embryos is not the correct way to do it. Either, possibly, and we are accumulating data, you do it at the fertilized egg stage, or you do it at the blastocyst stage, exactly as when you do *chorionic* sampling, eight, ten, eleven weeks after the embryos have been implanted. The single mutation risk of analysis, that was your question, if I understood correctly, we have to say that, as we have seen. the misdiagnosis varies in terms of percentage according to the mutation and the difficulty of the diagnosis. If I understood correctly, your question is: if you combine more than one mutation, is there a risk for so-called difficult patients that this 0.5 percent rises to 1 percent? The reason why you will never have 100 per cent complete, correct diagnoses is mainly the problem related to the machinery, that, at the end of the day, we have to use these analysers. They can be as refined as possible, as sophisticated as possible, but still, they cannot guarantee, and there, there is no human error, they cannot guarantee 100 per cent diagnosis. So, the last point, as I understood it, is why only few blastocyst biopsies have been carried out so far. Two reasons, one is technical. Embryo, blastocyst biopsy was tried originally 15, 18 years ago in a university centre, but it was abandoned, because, at that time, it was very difficult to remove the cells without damaging the entire system. A few years later, lasers came along and now that lasers function perfectly, micro lasers in this case, you can remove the cells with almost 100 per cent capability to keep the embryo completely intact. But this is a new technology and, furthermore,

the time you need, as I mentioned before, to make the diagnosis before the blastocysts expand, so the time in which we can transfer the embryo back again, is limited to 12, 14, 15 hours. Some groups were scared of being unable to make the diagnosis, and since embryo freezing for blastocysts is not yet readily available, as I showed you, that's the reason why the data you have seen that, I insist, are related to 2007, showed this small amount of blastocyst biopsy, but the trend we have now, that there is a huge increase in blastocyst biopsy around Europe with the combination of laser, possibility to vitrify the blastocyst successfully and the shorter time for the diagnosis. I think I have answered all of the questions.

Wolf-Michael Catenhusen [Mitglied des Deutschen Ethikrates]: Ich schlage vor, dass wir jetzt eine zweite Runde machen.

Prof. Dr. theol. Eberhard Schockenhoff [Mitglied des Deutschen Ethikrates]: Die Regel in Deutschland, dass man pro Zyklus nur drei Embryonen übertragen darf und entsprechend auch nur herstellen darf, hat den Sinn, dass man verhindern möchte, dass es überzählige Embryonen gibt. Denn das wird als moralisches Problem angesehen, dass man einen Embryo erzeugt schon in dem Wissen, dass er wahrscheinlich keine eigene Lebenschance bekommen wird. Meine Frage ist: Wenn Sie bei der PID sinnvollerweise deutlich mehr als diese drei erzeugen wollen, damit die Chance steigt, dass Sie nachher einen gesunden zum Transfer haben, könnte es ja auch sein, dass Sie mehr als einen gesunden haben. Vielleicht haben Sie so sehr Glück in Anführungszeichen, dass Sie fünf, sechs oder sieben gesunde haben. Und wenn man jetzt davon ausgeht, dass die Selektion unter Embryonen etwas Problematisches ist, dann ist das doch ein schwieriges Ergebnis. Was machen Sie dann, wenn Sie eine Schwangerschaft eingeleitet haben und es bleiben von Ihnen als gesund getestete Embryonen übrig? Wie verfahren Sie dann?

Prof. Dr. rer. nat. Regine Kollek [Mitglied des Deutschen Ethikrates]: Ich habe eine Nachfrage bezüglich der Blastozystenkultur. Wie ist die Lebensfähigkeit und Entwicklungsfähigkeit der Blastozysten? Wie viele sterben nach dem fünften Tag ab?

Frau Prof. Dr. med. Christiane Woopen [Mitglied des Deutschen Ethikrates]: Herr Gianaroli, Sie haben uns sehr vieles über die genetische Diagnostik und das Screening gesagt. Liegen der ESHRE auch Daten vor oder erhebt sie das systematisch, was an morphologischen Untersuchungen im Embryonalstadium vorgenommen wird? Es gibt ja unterschiedliche Scores, anhand derer man die befruchteten Eizellen im Vorkernstadium und später anhand der Entwicklungsgeschwindigkeit usw. beurteilt und danach entscheidet, ob der Transfer durchgeführt wird oder nicht. Liegen Ihnen dazu systematische Daten vor, inwiefern das tatsächlich mit einer höheren Schwangerschafts- oder am besten noch Baby-take-home-Rate einhergeht?

Wolf-Michael Catenhusen [Mitglied des Deutschen Ethikrates]: Ich will noch eine Frage von mir anschließen. Sie haben auf die fehlende empirische Validierung einer höheren Erfolgsrate bei der Schwangerschaft durch PGS hingewiesen. Warum werden dennoch fast zwei Drittel der Präimplantationsdiagnosen in Richtung PGS durchgeführt? Warum ist der Anteil trotzdem so stark?

Dr. Luca Gianaroli [Vorsitzender der ESHRE]: What do we do with the surplus embryos if they are considered normal? From the technical point of view, this has little to do with the PGD itself, of course, because it depends how important *per se* each single embryo in each single state or in each single culture is. What I can tell you from the data we have in those countries where

embryo freezing is allowed in routine IVF and ICSI, we generally have a variety according to the patient's indication, the age of the patient, we have roughly between 15 and 22, 23 per cent of the cycles in which embryos are frozen in routine IVF and ICSI. When we look at the data in which we freeze surplus embryos after PGD, the number falls to 3, 4 per cent. So the number of embryos, the number of cases in which we have surplus embryos, is much more limited because of the previous selection compared to routine IVF and ICSI. So, this is the only data available. You know that in some countries, you can freeze embryos, you can, under certain circumstances work with other projects with these embryos. For instance, in Italy, and that, I think, is peculiar, I think it's the only country at the moment in Europe since the law has been amended, but only part of the law, we cannot destroy embryos, so we freeze all the embryos, also the pathological ones. But that is just to give an example of how the different laws make then apply the different techniques. The only data available is that if you use PGD or PGS, the number of cases in which you need to freeze is much lower than the routine. You can tune stimulation to reduce the number even more, if this is one of the goals. Blastocyst culture. We know, and again mimic what's happening in nature, that the number of eggs that are able, once fertilized, to develop into an embryo, a viable embryo, depends on many factors. For instance, if you have a patient with endomytriosis, these patients *per se* produce eggs that are less viable so they are fertilized but they have less chance of going to blastocyst. So there are differences according to the subcategories of patients. All in all, 50, 60 per cent of the embryos develop to blastocyst. Among those that develop to blastocyst, there is a certain amount of embryos that have chromosomal abnormalities or that have genetic disorders relating to implantation that, even if you transferred them at the stage of blastocyst, they would never implant. So the average is between 50 and 60 per cent. Of course, you need to have a perfect standard, a high standard laboratory to produce 50, 60 per cent. A lot of work has been done trying to compare morphology of the embryo and chromosomal abnormalities and also, morphology of the fertilized eggs. So, the egg and the potential of implantation are related to chromosomal abnormalities. There is evidence that you can detect, in a not very precise or sophisticated way, the possibility of the embryo, looking at that from the morphological point of view, developing to blastocyst and implanting. But the accuracy of the morphology *per se* varies according to capability and knowledge between 50 and 60 per cent of prediction. That is far below the 90 or 95 per cent of the techniques we are talking about. So there is a trend, there is a capability to predict in terms of morphology, but it is not sophisticated enough to be used as the only routine to predict implantation. Why so many PGS? So, first of all, I would like to remind you that within the scientific community, the reason why PGS has been kept separate from PGD is that, while PGD has the need to try to make a diagnosis, PGS, by definition, screening has the concept to try to increase the chance of an infertile couple having a pregnancy in a shorter time. So the rationality between PGS is, since we know that many, even nice-looking, embryos from a morphological point of view do not implant in many, and possibly a large majority of them do not implant not because of the uterus but because of the chromosomal abnormalities of the embryos, let's screen the embryo, let's detect which of the embryos are more prone to success. So that's the reason why PGD was born as a concept. And the reason why it was continued to such a great extent is because the majority of the clinics, 98 per cent, 95 per cent of clinics , don't deal with PGD, as you have seen. They only deal with infertile couples and this was or is considered a tool to increase the

success rate of the infertility clinic. So that's the reason why. In 2008, a few papers were published showing that there was no clinical proof for doing preimplantation and genetic screening at the 8-cell stage, but if you look at the data, also from our consortium from 2008, you still see that the majority, 54 per cent of the cycles, were done because of PGS, so there is a clinical tendency to work on this area that has very little to do with the diagnosis, with the preimplantation diagnosis, but has to do with the chance of helping infertile couples to get pregnant as quickly as possible, reducing the number of repeated cycles. Once again, from the data that we have, if you do this at the 8-cell stage, we don't have strong enough data to say that is the right tool.

Wolf-Michael Catenhusen [Mitglied des Deutschen Ethikrates]: Thank you very much und jetzt die Frage, wenn so ein, zwei Abgeordnete jetzt noch Fragen stellen wollen, jetzt hätten Sie die Möglichkeit. Aber wir haben ja gleich noch die Runde mit den drei Ländervertretern, dann herzlichen Dank, Herr Gianaroli, für Ihre Informationen. Wir werden Sie dann ja in der Schlussdiskussion wiederum einbeziehen. Ich darf nun in unserer Mitte begrüßen Professor Paul Devroey. Er ist klinischer Direktor des Zentrums für Reproduktionsmedizin an der Freien Universität Brüssel. Er war auch als Vorsitzender der European Society of Human Reproducting and Embryology der Vorgänger von unserem, von Herrn Professor Gianaroli. Wir freuen uns jetzt sehr auf Ihre Informationen über PGD und PGS in Belgien. Wir bitten Sie um Ihre Präsentation.

Beiträge der externen Sachverständigen

Prof. Dr. Paul Devroey, Zentrum für Reproduktionsmedizin am Universitätskrankenhaus Brüssel

First of all, I would like to say that I am extremely honoured to be invited to give this information to you. And I received several questions from your board. And I translated your questions to considerations of PGD. Because the core business of this work is, of course, preimplantation genetic diagnosis for well-known monoclonal diseases. In Belgium, it has been, I would say, extremely well regulated since 1993, because in Belgium, which is a small country, as you know, there are seven recognised centres for human genetics and there are 15 centres for reproductive medicine. PGD can only be performed if both are present in the same institution, the same university.

[Slide 2]

Two, there is a large group of, I would say, healthcare people around, such as the very important role of psychologist. Within the law, we also have to ask advice from the Ethics Committee, which is institutional, which means that every big institute, every university does have an ethics committee and, of course, there are also some *ad hoc* committees available for some very special cases. There has been a kind of a legal framework since 1993. According to the list, and I think, Dr. Gianaroli has alluded to that, according to the list, I would say it is a rational approach and you have seen all of the very heavy, strong diseases around.

[Slide 3]

And, of course, if this embryo is a carrier of this disease, it is not replaced. In our institute, for instance, we have about 100 indications now, because some of the indications are extremely rare, with only one or two cases available. And

you have to develop new probes to detect. And, of course, it makes sense that only a genetically normal embryo is replaced according, as you heard, to the morphology, which we can adjust according to certain criteria. So, for my understanding, it's a quite transparent process to perform PGD on a routine basis. The question I was asked was: What about PGS? PGS is a totally different story.

[Slide 4]

And what I can say, and I fully agree with what Dr. Gianaroli said, is that mosaicism is our enemy and it is also a kind of chromosome rearrangement which has been fully documented in several papers, in Nature, etc. The problem is that if you screen, then you take a cell, which is called the blastomy, but this cell is not always representative of the entire embryo. And this is the big problem. That's why I think that PGS on day three embryos is not the thing to do. And I fully agree with what you said, Dr. Gianaroli, that we have to go to different stages, such as polar body, for instance.

[Slide 6]

This is, I think, a very informative paper produced in our department. Well you see that, when you replace one embryo, you know, in Belgium, we always replace one embryo to avoid multiple pregnancies. And you see here that the delivery rate was exactly the same in the control group where no PGS was performed, surprisingly enough, and in the group where PGS was performed, it was also 40 per cent plus, but exactly the same, exactly similar, which means that from the clinical viewpoint, probably, mosaicism rearrangement is present.

[Slide 7]

So how do we replace them, was the following question. It is very, very logical. There is nothing special behind it. You do the genetic analysis, one does the morphological evaluation and then, if genetically and morphologically normal, one embryo is replaced. Because, if you think about the health of the children, the health of the women, one embryo should be the golden standard. So, the use of one blastocyst is of paramount importance, I guess, which makes a high implantation rate, as we show you, of about more than 40 per cent in that study. And also, the process is very, very simple and there are almost no complications according to children's behaviour.

[Slide 8]

What is the role of the different people in the process in our institute? Well, first of all, the patients go to the geneticist for the genetic diagnosis. And you heard from the previous speaker that most of these women have a very heavy loaded diagnosis system with interruption of pregnancies, most of them, one, two, three, four times, sometimes they have children who died after delivery, etc. So, it's a very long history, but this is a crucial point. We need a correct genetic diagnosis. And then they have a meeting with the fertility doctor to see if they can be treated, if they can be stimulated, which are the conditions, and then they always go to the psychologist. Because some of them really need help to make a decision and also to have some support in the decision-making. And sometimes there is disagreement between these three people. It's only if A B C D are correct, because sometimes you have to go to the ethics committee, that we can perform the technique. So the couples will only be taken into the process if the entire team is absolutely in consensus whether the patient has to be treated or not. It is a very transparent process, but sometimes extremely difficult to take the decision. Extremely difficult. And sometimes you don't know what you really, you have to do to accept this couple with the misery they have in the past or not.

[Slide 9]

The following question was put to me: Is research regulated in Belgium? Research is regulated by law. By a kind of two systems, a kind of institutional local ethics committee. So it means that you have advice, you have a project for research, you have to give it to your local institute, there are about 20 local institutes in Belgium, most of them are universities. And if you have a goal, if it is a positive answer, then you have to go to the national law of embryos, which is a kind of national committee. Again, we say Yes or No. And I really think that Belgium has a very good system in following up what's going on. Because in Belgium, any time you have a patient who has to go into the system, who has to be treated, you have to contact the minister of health, who will give you a number. And you are obliged, according to that number, to give, it's blinded, of course, you are obliged to give the results of what you have done. So in Belgium, we have a total monitoring system, where all cycles are included, because that's the way it has been built up. And I think that Dr. Gianaroli has reported to you extremely well the ESHRE consortium, which I think is a unique opportunity to gain an idea about European data. To be honest, it's easy to organise because it's quite straightforward, I guess.

[Slide 10]

Have there been publications on PGD? Well, you heard from the previous speaker that there have been many publications. There are many data collections, many, many diseases have been described. Our own centre has 52 peer reviewed publications so far about all the work we have performed on PGD. We receive many grants nationally and from the European Research Council. And also we have different PGD theses available where we try to analyse our research.

[Slide 11]

What about success rates? Success rates, this is a paper we published in Human Reproduction in 2009 where you see that the observed cumulative pregnancy rates after three cycles is about 50 per cent. But again, be aware that the most important point is female age. Female age means that if you're 40 or 40+, you have a significantly less chance than when you're, for instance, 35 or 38 or less than 25. It is of crucial importance that women are treated at a young age. I think it makes a lot of sense.

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And if you look at the data for the young population as expected cumulative pregnancy rates, you see that you have about 70 per cent cumulative pregnancy rates. So, let us say that this a quite effective way of performing.

[Slide 13-16]

The list of diseases. I know there's a big debate about the list. About strong, severe, mild, but if you look at all these diseases, most of them, or almost all of them, are quite severe diseases which have built up over the years since 1993. And, of course, if you make a list one day, then you're blocked. Because if you find a new disease which is very rare, it's not in the list so you cannot treat it. So, you should have a mechanism by a panel of experts to negotiate about the list. I think it's a crucial point. Otherwise, you kill the system. I know that one of the most important points is children follow-up. You will all agree with me that – why do we do this work? To have children who are in good health and good fate.

[Slide 17]

That's why, from the beginning of our work in 1992 also with the ICSI technique, Intra-Cytoplasmic Sperm Injection, we have followed thousands of children. These are the first 500 children published very recently in Human Reproduction in 2010. You see that the major

information between PGD children and ICSI children is almost similar. And we have another publication now which has not yet been published, presented orderly in the with 1 000 children, and it confirms exactly the same. But look again at the bottom line of this slide. Embryo biopsy does not add risk factors for the health of singleton children after PGD. It is of crucial importance. If you think that you have three cycles in Germany, also for routine IVF, we have, you replace three embryos, you have many, many multiple pregnancies in Germany. And on top of that, you have many selective reductions. Because too many embryos are replaced. Let's look at the facts. But the bottom line is that we should try to go for singleton pregnancies. Because the perinatal death rate in multiple pregnancies is such that both caution and long-term follow-up are required. It is written very clearly in the paper from 2010.

[Slide 18]

Are there future trends in PGD? Well, I think, an increase in genetic diseases and of the technology, I think Professor Gianaroli has explained that fairly clearly. To my under-standing, if you look at it from a health perspective viewpoint, singleton pregnancies and deliveries after replacement of one fresh blastocyst. And also, we will not forget, with the new technologies available today, I think the vitrification of blastocysts is excellent at the moment, that probably for those who are not pregnant after the fresh replacement, after the fresh replacement, they could replace after freezing and thawing a frozen vitrified blastocyst. But again, I would say, I would go for one. Because, once it is frozen, it is frozen, you don't lose anything. And I think it is of paramount importance for the future that all children born with this technology are carefully followed-up. I think it's of crucial importance to know the final result of this work. Have there been discussions in Belgium?

[Slide 19]

Very, very little. Because the laws we have, we agreed on the indications, how to make the list, we agreed about the methodology, we were transparent with the results because we have a prospective monitoring system. We have the minister of health who knows exactly, exactly, how many embryos are replaced, how many children are born. And we have published from the beginning. And we have to give it to the minister of health. It's obligatory by law, the health of the children. You cannot start a second cycle if you have not given the result of the first treatment cycle.

[Slide 20]

CODA. CODA means, when I was preparing this talk and thinking to myself: How should I structure it? I retold the entire system. It's at the end of the day when you go to bed, you say: What did I do today? to yourself. I think that, anyhow, PGD should be a transparent request. I would say, the medical geneticist should clearly design for you, for the couple, the disease which is present, and I can do that with the knowledge they have. I think we have to go for a correct and safe methodology. And if you think about all these poor women who have to interrupt pregnancies, today, we have a system methodology available which avoids interruption of pregnancy. Which I guess, I'm not a woman, but if I see all the women suffer, we have to provide a plan. And I think that vitrification of the vitrified blastocyst leading to singleton deliveries, one by one, or one at a time, is of crucial importance. And let me say, maybe one emotional word. It's about cross-border medical care. It's a shame. It's really a shame. Because I remember two things. First of all, only rich people can do that. It's not fair. Two, I remember when I was in the clinic at 7 o'clock in the morning, a couple from Germany, with a little paper with my name written on it. Unable to speak English, French, trying to have a normal

child after two interrupted pregnancies. I mean it's the cause of shock for so many people or quite dramatic. So I think, in Europe, we should try to limit cross-border medical care. Thank you.

(Beifall)

Wolf-Michael Catenhusen [Mitglied des Deutschen Ethikrates]: Herzlichen Dank für diese Informationen auch zum Schluss, für dieses Plädoyer. Wir gehen jetzt über zur Präsentation der Situation in Großbritannien. Dazu darf ich ganz herzlich in unserer Mitte Frau Prof. Dr. Emily Jackson begrüßen. Sie ist Rechtsprofessorin an der London School of Economics and Political Science. Für uns von besonderer Bedeutung: Sie ist seit 2008 stellvertretende Vorsitzende der Human Fertilisation and Embryology Authority, einer Einrichtung, die sowohl Regulierungsentscheidungen als auch Kontroll- und Zulassungsentscheidungen trifft, also zum Teil Entscheidungen trifft, die in anderen Ländern durch den Gesetzgeber getroffen werden. Und deshalb, Frau Jackson, sind wir froh, dass Sie da sind, und wir bitten Sie um Ihre Präsentation.

Prof. Dr. Emily Jackson, Vizevorsitzende der Human Fertilisation and Embryology Authority (HFEA)

Thank you very much and thank you for the invitation to give me the opportunity to explain how we regulate PGD in the UK. As you said, I'm not a scientist, I'm not a clinician, so I'm not so good at answering those clinical questions, but I hope I can answer questions about the British law. So, the provisions in the UK, the basic provisions are contained in the Human Fertilisation and Embryology Act 1990, which is our big flagship piece of legislation, which has been substantially amended in 2008. Largely, in relation to this issue, to put the rules governing PGD on the face of the statute, because before then, they were developed by the HFEA. Effectively, there are three things, three types of embryo testing. One, the first one is PGS, testing for an abnormality that affects an embryo's capacity to develop in a live birth, the second is PGD and the third is sexing an embryo for the purposes of screening out sex-limited diseases. And the basic rule governing PGD in the UK is contained here, that it is only possible to obtain a license to carry out PGD if the HFEA is satisfied that there is a significant risk that the person will develop a serious disability, illness or other serious medical condition. So, as a basic rule, it hasn't actually changed from being put on the face of the legislation, but that's where it is now. So I wanted to say something first about how this works in practice.

[Slide 5]

In a sense, there are two stages here. A centre that wants to carry out any sort of embryo testing must get a license to be able to do any embryo testing at all. And for that, you have to have suitable facilities, equipment, competent staff, validated processes, proper patient information and consent forms and a multi-disciplinary team, obviously containing geneticists. So, that's in order to do the testing. You used to have to do a sort of family-specific application.

[Slide 6]

Now, once a centre has been licensed to carry out PGD, it can do so for any of the conditions that are listed on the HFEA's website, and I've got that web link here to where that list is held. Now, if the centre wants to carry out PGD for a condition which is not on the list, then it must be specifically applied for. So, it's a kind of, there is a licensing at the centre for competency in doing the process and there is a licensing of the condition, each condition must be separately licensed. Every time a centre does PGD for the first time for one of the conditions on the list, it has to notify the HFEA. If a centre is authorised to carry out PGS, it can do so for all chromo-

somes, though I'll say something later about PGS. So, it used to have to be family-specific. The applications we used to get have been on the HFEA since 2003, so I've sat on quite few license committees. They used to involve a specific family, obviously anonymised. Now, that is no longer the case, it's the condition, not the family. Usually, of course, a centre is making an application to be able to do a new condition because it has a specific family in mind but the application doesn't mention the family. So, the centre has to provide evidence of those legislative criteria, these are the two limbs of the test, significant risk and serious abnormality. Before it goes any further, a lay summary of the condition is published on the website and one of the reasons for this is a sort of public transparency. Before a decision is made, anybody can comment on the application, on the condition that is proposed and, in particular, patients, carers of patients, any interested party can make representations to the HFEA, which are then part of what the license committee considers.

[Slide 7]

And just to give you a snapshot, these are the conditions currently on the website awaiting consideration. So, anybody who has any specific views about those conditions, particularly as to seriousness, can write in and make representations about that. Importantly, it is not just a question of a scientist saying that the condition is serious, every application is sent out to peer review, which will involve usually at least two clinical geneticists to say what they think about issues around seriousness. And, important issued about treatability, too.

[Slide 8]

So, they give their view. Patient, views of patients groups can also be sought on exactly the same questions. But the ultimate decision about whether a condition should be licensed is for the Authority's Licence Committee. Once approved, it's published, as I say, on this list on the website and PGD centres can then, are also notified and can then offer it, though with restrictions, that I'm going to come back to.

[Slide 9]

So, this list that is on the website is reviewed at least every five years. I think, a really important thing to say about this list is it's very much a living list. Conditions can come off as well as go on. So, if there is new evidence about treatability, for example, that it's no longer seen as a condition which meets the criteria, a condition can come off. So, it's very much not set in stone once it is on the list that's not necessarily true for all times. There are some things which are still case-by-case or family-specific. One is late onsets, low penetrance disorders, cancer susceptibility genes, for example, and the other is preimplantation tissue typing, colloquially known as save your siblings, where you are trying to find out if the embryo has, is a good tissue match for a existing sibling.

[Slide 10]

Okay, now, of course, clearly, the two limbs of the test, significant risk, serious condition, require some interpretation. It's not obvious what we mean by significant risk or serious condition. And so, the Licence Committee has issued an "Explanatory Note" explaining how it makes these decisions. Significant risk is, in a sense, the easier of the two and this is down to penetrance. So, whether or not there's full penetrance, i. e. if you have this abnormality, you will get the condition, if you have this, you will get the condition, or incomplete penetrance. In relation to seriousness, there's a number of these slides, there's a range of factors that the Licence Committee takes into account when making a judgement as to seriousness. And it is ultimately a judgement. So, age of onset, symptoms, is it fatal, life threatening, is the condition treatable?

[Slide 12]

If it is treatable, what does that treatment (entail), how invasive is it? What are the effects of the condition on quality of life?

[Slide 13]

And variability of symptoms. I'm going to say more about this in a minute, but, clearly, one of the big issues is that within a condition, there can be variability, they can range from really severe to perhaps milder. So, the Licence Committee has to take that into account and perhaps the most important thing is the last point on this slide that there may be times when some forms of the condition meet the statutory criteria and some forms don't. And I'll say a bit more about that in a second.

[Slide 14]

Where is the condition, not the family circumstances, that the Committee will look at the highest penetrance figure and it will look at the most serious manifestation. But what's really important to bear in mind there is that it does not mean you can do it for the milder version. I'll explain how this works in practice. So, this is how they look at the condition but there's a sort of, as well as the Licence Committee making a decision as to whether or not to licence the condition, there is a whole other stage of regulation in the UK which is that the clinics are bound by the HFEA's Code of Practice. And they must only carry out PGD if the particular family's manifestation meets the seriousness criteria.

[Slide 15]

So, the centre itself must follow the Code of Practice when deciding whether to offer PGD to a particular family. So if, for example, a clinic were to do PGD for a condition which was considered to be mild and not within the Code of Practice criteria, there would be a breach of the Code and there's various sanctions that can be taken against them for that, the most serious of which, of course, is the removal of their licence.

[Slide 16]

Okay, so in terms of statistics, it doesn't happen very often in the UK, PGD. The new conditions, on average, about two per month are received by HFEA to be considered by the Licence Committee. These are new conditions which haven't been done before. In 2008, just over 200 cycles, this is a tiny proportion, as was evident from the early above it's a tiny proportion of all IVF cycles. Again, a tiny proportion of all IVF, about 66 babies in 2008.

[Slide 17]

PGS, as has been said, is a controversial technique. Basically, because with the methods we have at the moment, the evidence really is not robust. So, this is the Licence Condition attached to all licences in centres in the UK, which means that before you offer PGS to someone, you've effectively got to tell them, with written information as well as orally, that it is unproven and the FISH, in particular, is not effective at increasing live birth rates. And what's really important here, and it's a difficult thing to explain to patients, particularly with repeated miscarriage, which is one of the main indications in the UK, is that you may be able to test for a whole range of chromosomes on abnormalities, you may be able to reduce the risk of miscarriage, but that doesn't mean that you're going to be able to provide somebody with a live baby. Because the more you test for, the fewer the number of embryos that are available for transfer. So, there are relatively few PGS cycles going on in the UK.

[Slide 18]

Morphological analysis, all centres carry out visual morphological analysis and this is for regular IVF as well. I wasn't sure, whether in relation to this question, what might be also relevant is the idea, it's a new idea in many

ways, which is that you can test culture media in order to find out something about how the embryo is developing. That's treated differently in the UK from visual analysis. And you do need authorisation from the authority if you're going to use culture media tests to try to discover how the embryo is developing.

[Slide 19]

Counselling. All patients receiving IVF, including PGD, must be offered counselling. And the HFEA Code of Practice provides that patients must have access to a genetic counsellor. In many ways, as I think it's been indicated by previous speakers, this is redundant because most of the families, they get as far as the fertility clinic for PGD have spent years in contact with regional genetic services. They have had an enormous amount of genetic counselling before they get anywhere near a clinic for PGD, because largely, they will have had affected pregnancies and very sick or dead children. So, there is a need for genetic counselling, but most of them have received a great deal of this already.

[Slide 20]

In relation to whether there is controversy in the UK about this, there is, obviously there's a whole range of views on relation to all forms of IVF and PGD in particular. The big change really recently in the UK was the 2008 amendments, which put all the rules for embryo testing on a statutory footing. So, our piece of legislation in 1990 didn't actually mention PGD, so rules were developed by the HFEA and our highest court suggested that that was within the HFEA's scope of authority. So, the statute essentially adopted the previous criterion of substantial risk of serious abnormality. This is the Health Minister in the House of Lords during the passage of the Bill. This, in a sense, it's the same as it was before, statutory ban on sex selection for no medical reasons. The Bill makes it explicit that the condition is that it has to be serious. So, in a sense, the law was amended but the substance of the rules did not change.

[Slide 22]

In terms of recent trends, I think there certainly is greater public awareness, an interest in PGD, and sometimes I think there is within the public an idea, certainly within the popular press, an idea that you can do PGD for many things that you can't do PGD for. An idea that this is something that almost anybody could have rather than this much narrower group of potential patients. You have to have a particular known genetic mutation in their family. Another issue, I think, for the HFEA and for clinics is that clinics on the HFEA have tended to focus on the infertile as the patients who are of greatest concern. These are different types of patients and there is perhaps a need to accommodate their needs as well. There is also this difficult issue that PGD is expensive. It's time-consuming and difficult. It is sometimes available within the NHS in the UK. But, unfortunately, prenatal testing and abortion is much cheaper. So obviously, it is cheaper to do PNG so for a woman it may be preferable not to go down that route.

[Slide 23]

In terms of variability of seriousness, I'm going back to this question, we've got lots of examples within our list of conditions where you've got an umbrella condition and only subgroups are licensed. Niemann-Pick is quite a good example. Nieman-Pick Type A, the child will usually die before the age of 3. Niemann-Pick Type B, slow growth, many, not all, able to lead a full and normal life. So, in the UK, Type A is approved, Type B is not. And I think this is a really good example of why regulation can be quite a good way of drawing a line and saying: This meets the criteria, this doesn't.

[Slide 24]

Publication of data. We publish all of the PGD conditions, all of the OMIM numbers and there is

this issue of confidentiality. The HFEA used to say there might be situations where publishing the condition could identify patients because there are some genetic disorders, obviously, which are so rare that there may only be one, two families in the UK with that condition. There is a provision for a centre to make a case that the condition shouldn't be published on the bounds of confidentiality. This hasn't happened yet, so at the moment all conditions are on the list.

[Slide 25]

In terms of future trends, I think one thing that we're saying is declining use of sex selection to avoid sex-specific conditions because, clearly, if you are able to test for the condition, you enable more embryos to be available for transfer. So you can transfer unaffected males rather than ruling out all males in order to avoid a condition. That's already happening. In a sense, a new issue for the HFEA is the management of this list system, the moving away from case-by-case licensing. So, the HFEA is having to police clinic decisions about seriousness once the condition is on the list. Finally, tissue typing, HLA-typing and late onset conditions, currently, they are case by case, family-specific. Among the questions for the future is whether that might be reviewed and they might be regulated in the same way as ordinary PGD.

(Beifall)

Wolf-Michael Catenhusen [Mitglied des Deutschen Ethikrates]: Herzlichen Dank, Frau Prof. Jackson. Wir werden nun den Überblick über verschiedene Regulierungen und Praktiken in den europäischen Ländern mit einem Bericht aus Frankreich abschließen. Dazu darf ich ganz herzlich unseren Kollegen, Prof. Patrick Gaudray, begrüßen. Er ist Mitglied auch des französischen nationalen Ethikrates. Herr Prof. Gaudray ist Forschungsdirektor am Centre national de la recherche scientifique und wir freuen uns auf Ihren Bericht, denn der französische nationale Ethikrat ist intensiv in die Vorbereitung der Überprüfung des Loi bioéthique, die ja alle fünf Jahre in Frankreich erfolgt, eingebunden, das heißt auch, der Ethikrat hat im letzten Jahr dort eine Stellungnahme abgegeben. Bitte.

Prof. Dr. Patrick Gaudray, Mitglied des Comité Consultatif National d'Ethique (CCNE)

Thank you, Mr. Chairman. Yes, actually, when I was asked to come here today, I was a bit afraid because the situation in France is moving quite quickly and changing a lot, and I thought that maybe I was not the best person to give you a message which would be clear since I followed up the entire story since our recent time. Anyway.

[Slide 2]

That's why I start with a sort of history of PGD in France. Actually, it started three years after the birth of the National Ethics Advisory Board, in French CCNE, which issued an opinion in 1986 saying that PGD shouldn't be performed. It was relatively clear. And it stayed like that until the first bioethics law or almost the first bioethics law in 1994, when PGD was first authorised with many ethical issues which were still totally open, and not many answers had been given even by the CCNE, the ethics committee in France. And actually, you see that opinions have been issued, one, two, three, four, five, five different opinions have tackled the issue of PGD with the CCNE. The first one that opened the possibility of PGD was in 1998, was an opinion where PGD was considered as a possibility to help couples who were suffering and to help very severe conditions not to be present in babies to be born. And the second issue, but still, there was sort of a moratorium which was proposed to really study the ethical impact of the opening up to PGD. Actually, I've heard many, many things so far this afternoon about what could be done,

what we are able to do. And actually, I've not, maybe I've not understood correctly, but I've not heard many issues raised in terms of ethics, bioethics and really only on ethical grounds. So can we, are we enabled to do what we can do? In 2002, CCNE went back and revised the moratorium and decided that PGD was acceptable under certain conditions which were stated in the law in 2004 when the bioethics law was revised for the first time in France. It doesn't seem to work. Okay. So, the French law really considered the advice positively, for once, the opinion that the National Ethics Committee had issued. And the thing was really to give a frame to PGD and, in fact, there are several things I will come back to later on, I don't know where I push here.

[Slide 3]

I would come back to those Multidisciplinary Prenatal Diagnosis Centres which are really major things in this process to allow a couple to have a prenatal, preimplantation genetic diagnosis. The other thing which was really stated in the CCNE opinion is that it has to address to high probability of giving birth to a child affected by a genetic disease, particularly severe, and I will come back to that later and recognised as being incurable at the time of diagnosis. And this is still the major thing around which those Multidisciplinary Centres are really assessing the fight for the couples who request PGD. This genetic disease has to be present in the parents or in direct ascendants of the child to be born. And we will come back to those issues of late onset that are life threatening and we will see how we do exclusion PGD in France. And lastly, but it's a very important, very crucial point, the hospital must be specially, specifically authorised to perform PGD by the Biomedicine Agency. This is a major national agency created by the 2004 Bioethics Law which is in charge of all biomedicine issues and which gives authorisation for transplantation, for in vitro fertilisation, for PGD, PND, etc. So, first those Multidisciplinary Centres, I don't want to go into detail about this, you can read about it. There are quite a large number of such centres in France, more than 50. They are in mainland France and also abroad, in Martinique and Guadeloupe and Reunion. And they represent an assembly of competences, it's a multi-disciplinary assembly which really has geneticists, doctors, fertilisation specialists, etc. But multidisciplinary means multi-medical disciplinary people, it means that there are no representatives of patient associations, no real psychological doctor who is not related to MD. Those centres take part in the framing of the activities of PND and PGD, that's very important. And, specifically, their role is to help the medical teams and the couples in the analysis, the decision-making and the follow-up of the pregnancy. I consider this to be essential so that the process can proceed on a good basis.

[Slide 5]

CCNE has written this sentence, I put it here to make a relation between PGD and PND. In fact, to avoid facing the moral problem of abortion, which is really a major issue which is still heavily debated in France, by circumventing it by the use of PGD is to refuse to see that, in fact, the difficult decision of abortion protects us from the temptation of in vitro genetic sorting. And I will come back to this.

[Slide 6]

So PND, what are the figures for PND when I refer to those Multidisciplinary Centres? So, you see it's relatively stable for a long time, I mean, there are under 30,000 files which are open and you see that the abortions which are authorised are also very constant for a long time. The centres give decisions, which are this number of decisions, which is also stable, as well as a number of meetings. There are meetings once a week on average.

[Slide 7]

Those are the indications, also for PND, but it's important to see the numbers. We are talking about almost 7000 persons, couples.

[Slide 8]

When it comes to PGD, I mean, the figures are much lower. We are speaking about 50, in 2008 71 births after PGD. So the numbers are low but the ethical issues are very high. And the debate is really tense in France and especially now, as Mr. Chairman said, we are engaged in the revision of the bioethics law. I mean, the debate is really very active, I can tell you that in the journals and in discussions and within the CCNE, the discussions go along very, well they are quite tense. So, that was the assessments.

[Slide 9]

What about the refusal? Because, if those committees have the ability to refuse some files, why do they refuse? Mostly actually on technical problems. Difficulties are a possibility to have medically assisted reproduction. Very few refusals about the motivation of the couples, but still, those are the numbers and they increase slightly, those ones increase slightly from 2007 to 2008.

[Slide 10]

What is very significant is that now, the centres are more and more able, and there are only three, or four centres, I should say, in France, because there are two hospitals in Paris, one in Strasbourg and one in Montpellier. I live in the west of France and there is nothing. So people have to move, too, it's also part of an ethical issue that has been already raised. I mean, only people who have sufficient income to go where PGD can be made, can go there. And those territories are not the richest in France and it's quite difficult for people from the centre of France to go to Strasbourg, Paris or Montpellier. Only three centres for a country like France, it's clearly not enough and I think that the committee has said that. Because, when it comes to the timing, it's very, very long and, as a previous speaker already said, I mean, many people who think of going to PGD are people who have already attempted other things and they are approaching 33, 35, 37 years of age and it's starting to get late. So they have almost a one-shot possibility of doing PGD, which is really also a major ethical issue.

[Slide 11]

So this time is, of course, viable because between the discovery, everything goes through genetic counselling, all the green arrows mean that it's okay. If there is no okay, okay, we go and stop. All this has to be analysed before the PGD demand can go to this place where the advice can be given. And it happens that, because of this long schedule, sometimes, when it comes to here, I mean, people are no longer able to do in vitro fertilisation, so all this process has gone and in the end, we say to the people: it is not possible to go any further.

[Slide 12]

So Stop and Go is at every step. Here, 20 to 30 per cent of the stimulation will go to stop. They won't work. Ovocyte recovery. 4 out of 1000 will go to a stop. Here, 16 out of 1000 if there is no possibility of fertilisation or no mature ovocyte in the biopsy. Embryonic biopsy. If there is no embryo with more than six cells, it goes to a stop. Usually, the average is twelve embryos to go to the further step which is: Can we investigate the quality of the embryo? I said good-looking because it's sort of non, it's not totally, there are criteria, of course. Very strict criteria. But it's also the sight of the doctor who looks through the microscope and says whether it is an embryo which can be re-implanted or not. Or embryos which do not develop. And this goes up to 30 per cent stop. I've heard that there are lists in the UK. This is not a list of conditions which are open to PGD. These are examples of diagnoses which are available in

France in the three centres, Paris, Strasbourg and Montpellier. There is no list in France. And we have, I will tell you that later about the last opinion that we've issued from CCNE. There is no list and we don't want any list to be issued, for several reasons. First, those lists become outdated very quickly. So, there are processes which can help make the list up-to-date. But if there is a list, if I see on the list, or if people, not myself, but if people see that cystic fibrosis is on the list which is open to PGD, it means that cystic fibrosis is something which makes you totally non-normal and non-worth living. And that's something which is a major concern of CCNE. Making a list of conditions which are open to PGD really stigmatises certain conditions. And some of those conditions shouldn't be stigmatised. We have had major problems opening PGD to the detection of Trisomy 21, for instance, and there are major fights in France about Trisomy 21 because people do not want stigmatisation of this condition. They do not want people who carry a Trisomy 21 to be excluded from normal, well-being society. So there is no list, but there are lists of diagnoses which are available and these lists, of course, increase every week, or almost. There are plenty of diagnoses which are possible, but those diagnoses must be approved in every case by this Multidisciplinary Centre for Prenatal Diagnosis. And you see, several conditions are open – neuromuscular, neuro-degenerative and also cancer predisposition syndromes which are open to PGD. The thing is that with the cancer predisposition syndrome, it has already been said by previous speakers, the problem is that there are cures, or we are progressing on the cures of those cancer syndromes. For instance, breast cancer. Breast cancer, much progress is being made and the concern of people in France about including BRCA 1 testing in PGD is really that we are trying to avoid breast cancer instead of trying to cure it. You see what I mean? I don't know if I'm perfectly clear, but it's really that they fear that trying to remove it from the genetic condition of the children being born is really to stop doing research for cures for cancer, breast cancer in this case. So, there are major debates, there are debates also at the National Cancer Institute, at the Biomedicine Agency, in the Ethics Committee, which has been set up by the League Nationale de Contrôle de Cancer, a charity which collects funds to fund research on cancer and to help cancer patients, and we have thought a lot about it and it's very difficult because you cannot say yes for this and no for that because things evolve, so there has been an attempt to make a sort of classification into four groups, which is very difficult.

[Slide 14]

So, very high cancer risk, so, early onset, multiple tumour sites and no or inefficient therapy. This is, for example, for APC, or things like that. Very high cancer risk, only onset localised tumour, not multiple and invalidating therapy constitute group number two. Those two groups are open to PGD relatively simply, I would say. The problems arise when you are here. Which includes BRCA 1, BRCA 2, for instance, with high cancer risk, relatively late onset. Therapy available, which is more or less invalidating. So, this class number three is really a matter of debate and nothing has been set for good in France right now. And the last one, of course, is not open to PGD which is safeguard, I would say.

[Slide 15]

So about history. I told you about the points where we were in 2004, Second Law on Bioethics. Now, we are in the process of revising the bioethics law in France. In this prospect, CCNE has again gone back on prenatal diagnosis and PGD, especially.

[Slide 16]

This opinion was issued in December 2009, or November 2009, so it's quite recent and we went back on all this about PND and PGD.

[Slide 17]

And the questions which were, again, discussed, and I think that all those questions are still open questions, we believe that ethics is more a matter of questions than of answers and I think that, seeing what is under all these questions, we revisited the role of those Multidisciplinary Centres and said that, in fact, the fact that they were multidisciplinary, they were doing quite a good job and the fact that PGD can be authorised only after the agreement of those centres is a good thing. We had, those two questions are really still open questions, and there is no good answer to that. Antenatal diagnosis, so PND and PGD, have been said to be preventive. Preventive of what? In most instances, it's not preventive, because it leads to, for PND, abortion, in most cases, and PGD non-implantation. So we believe that using prevention for PGD or PND is not the appropriate term. We think that we cannot prevent a birth. Prevention doesn't apply to a non-birth. The same question which is still open is: Is PGD eugenic? And there is no good answer to that because we don't, none of us agree on the definition of eugenics. If eugenics is really the result of an ideology, then it is, of course, illegal and cannot be tolerated. If people are trying to have children who will not suffer from major severe genetic diseases which are incurable and this is considered to be eugenics, I open this question, I don't want to answer in front of you because all of the committees have to discuss that. I think that there is no definitive answer to this question. But if we don't address this issue, we are not doing our job, I think. The problem of the assessment of the severity and incurability of the disease is quite difficult because we cannot, and that's why we do not want to have a list of conditions which open to PGD because the same genetic condition can be very severe, dramatic, etc., lead to major suffering of the parents, for instance, in some conditions and will not be that dramatic in other families. So the assessment of the severity has to be in sum, it has to remain human. So, human beings discuss this issue of severity. We have also discussed, and I will not talk about that, whether PGD is an ultra-early form of PND? We say that it is probably not because the grounds on which those two techniques are set up are totally different. In one case, you really don't want the genetic condition to appear. Extending PGD. We have done something which was a major issue in the French journals, etc. with this opinion. Because we said that if people have undergone this process, which is long, which is very difficult, it's not something that you do like that, I mean, it's something which is very difficult for the families, for the women and, okay, you know that you re-implant an embryo which is devoid of genetic diseases which was concerned by the diagnosis. Which was present in the family. You do that, you give hope to the family and in the regular screenings that are done by PND, it happens that the embryo is trisomic. And then you're obliged to propose, to ask the parents: Do you want an abortion or not? And if they say: Yes, I want an abortion. Then, you just kill all their hopes and you send them back to square one and they have to undergo all these processes again. So we have proposed that, considering this suffering, there could be an opening to the diagnosis of Trisomy 21, which is the most frequent case of abortion, medically assisted abortion in France. We opened the possibility for, if the parents want it, screening for Trisomy 21 at the level of the embryo, and that embryo would be re-implanted only if devoid of the genetic condition and of Trisomy 21.

[Slide 18]

Just a few words about PGS, you can read about it, I will not go through all of that. I was asked about PGS, but PGS is really something that addresses many, many ethical issues that need to be rediscussed within CCNE because it's also moving very quickly. Why screening? Screening? Actually, we don't want to screen for anything. Systematic screening would probably mean that we have this fantasy of the perfect baby, or something like that, which is obviously absurd and not feasible. So we are not favourable to screening. We are favourable to diagnosing conditions which do exist in the family, but we don't want to go in search of other conditions which, actually, would be even more difficult because most of the latest genetic screening based on genome sequencing gives you probabilities of having this or that. For this condition or that condition. And those statistics obviously do not apply to the individual. They cannot be taken as certainties and in these conditions, I mean, they should not be performed as part of PGD. The majority of CCNE agrees with this position. And most of the genetic tests proposed, for instance, by private companies, are not fool-proof and there are not really solid indications that there will be a severe genetic condition leading to an illness, a disease which is incurable at the time of diagnosis. So the risk associated with pangenomic investigations is really a concern and I'm not the president of CCNE, fortunately. And, but I'm not the president of CCNE, but I think that there should be major reflection in CCNE about, more generally, about genetic testing and pangenomic genetic testing. So, I hope I've given you, probably in too many words, the current situation in France. It will move with the new law. Probably after the new law within the next months or years, CCNE will again address those issues because, as I told you, we open more than we close questions, and I think that we will have to go back to this subject. Thank you very much for your attention.

(Beifall)

Zweite Fragerunde

Moderation: Wolf-Michael Catenhusen, Mitglied des Deutschen Ethikrates

Prof. Dr. iur. Edzard Schmidt-Jortzig [Vorsitzender des Deutschen Ethikrates]: Ich nehme den Anlass auf, verschiedene Fragen zu beantworten, die während der Pause eben aufkamen, zum Verfahren und zur Terminierung des Deutschen Ethikrates mit seiner geplanten Stellungnahme zur Präimplantationsdiagnostik. Meine Damen und Herren, wir haben uns fest vorgenommen, bis Ende Februar unsere Stellungnahme fertigzubekommen, dann wird es vielleicht dieses und jene technische Stück noch geben, was wir nicht in der Hand haben. Also wir sind zum 1. März auf dem Markt. Das ist deswegen wichtig, weil der Deutsche Bundestag bei seiner ins Auge gefassten Regelung dieser aufgebrochenen Frage – ganz neu ist sie ja nicht – bis dahin ja *nolens volens* noch ein Moratorium hat, so dass auf jeden Fall sichergestellt werden soll (das ist natürlich auch in unserem Interesse), dass der Deutsche Ethikrat mit seiner Argumentation zu diesem Problemkreis noch in die Entscheidungsfindung des Gesetzgebers aufgenommen werden kann. Also noch einmal: Es ist unser fester Plan, bis Ende Februar mit der Stellungnahme durch zu sein. Dass dies unsere Arbeit besonders engagiert und anspannt, braucht nur noch intern hinzugefügt zu werden. Jedenfalls können Sie sich darauf verlassen, dass wir das schaffen werden. Herr Catenhusen, Sie haben jetzt zur Fortführung wieder das Wort.

Wolf-Michael Catenhusen [Mitglied des Deutschen Ethikrates]: Ich habe jetzt schon

einige Wortmeldungen. Zunächst einige aus dem Ethikrat: Herr Wunder, Herr Reich, Frau Kollek, Herr Schmidt-Jortzig, Frau Riedel, Frau Lübbe, Herr Radtke, Herr Schmude und Frau Woopen. Wir sollten drei bis vier Runden machen und dann auch anwesende Mitglieder des Bundestages fragen, ob sie eine Frage einbringen wollen. Herr Wunder, bitte.

Dipl.-Psych. Dr. phil. Michael Wunder [Mitglied des Deutschen Ethikrates]: Thank you. My first question is addressed to Mr. Gaudray from France. You have presented us a lot of numbers of cases for the years from 26 to 28 for PGD assessment and there is an increase in these numbers over these years. My question to you is, what do you know about the reasons for the increase in these numbers of uses? Is it due to the extension of the diagnosis or is it an increasing number inside the groups of diagnosis? Do you understand my question?

Prof. Dr. Patrick Gaudray [Mitglied des Comité Consultatif National d'Ethique (CCNE)]: Yes.

Dipl.-Psych. Dr. phil. Michael Wunder [Mitglied des Deutschen Ethikrates]: I have a second question to all three speakers, but especially to Mrs. Jackson. This is a question of the limits and the limitations of the PGD. You have a very interesting example, but I don't think you've addressed it here. This is the example that you have a decision inside one diagnosis, it's a Neiman-Pick type, and the decision of your institution is that a type 1 is inside the PGD and the type B is not. And it would be very interesting for us to know what is the reasoning of this limitation and what is the reaction of the persons concerned, parents concerned? You know this type here? It's variability of the seriousness within conditions, it's at the end of your presentation. Thank you.

Prof. Dr. med. Jens Reich [Mitglied des Deutschen Ethikrates]: My question, I don't know to whom from the panel I should address it, is about excess information, that is, as we heard, increasingly accruing in future, dynamic information, and so on. How about treating excess information, let me put it into a sort of quiz trap question, if after a PGD diagnosis you have several candidate embryos for transfer and if there are boys and girls amongst them, is it admissible to ask the mother to make a selection?

Prof. Dr. rer. nat. Regine Kollek [Mitglied des Deutschen Ethikrates]: Ich habe drei kurze Fragen an Frau Jackson. Sie haben erwähnt, dass eine Krankheit auch wieder von der Liste entfernt werden kann, wenn eine neue Behandlungsweise vorliegt. Gibt es dafür schon ein Beispiel, ist das schon einmal passiert? Und wenn, können Sie sagen, welche Krankheit das war? Meine zweite Frage ist: Bei Ihrer Fall-zu-Fall-Betrachtung habe ich auf Ihrer Folie gelesen, dass Sie den Grad des Leidens der Familie bewerten. Mich würde interessieren, wie Sie das tun und welche Kriterien Sie dafür anwenden. Die dritte Frage ist: 2008 wurden 182 Patienten oder Paare behandelt. Wie viele sind abgelehnt worden und aus welchen Gründen?

Prof. Dr. iur. Edzard Schmidt-Jortzig [Vorsitzender des Deutschen Ethikrates]: Meine Frage geht an Mrs Jackson und M. Devroey. Frankreich nimmt, so glaube ich, aus deutscher Sicht eine gewisse Zwischenposition ein zwischen dem britischen und dem deutschen Ansatz. Es geht um die Reglementierung. In Deutschland wird gesagt: Dieses und jenes ist unter Strafe verboten. Und was dann möglicherweise nicht strafbar ist, muss unter Umständen das Gericht entscheiden. Bei Ihnen scheint mir es mir – insbesondere bei Ihnen, Mrs Jackson – ein unterschiedlicher Ansatz zu sein, oder es scheint nicht so, sondern ist ja auch, denn Sie sagen: Unter diesen und jenen Voraussetzungen ist es zulässig. Meine Frage also: Welche Erfahrung haben Sie mit der Kontrolle der Ein-

haltung Ihrer Bedingungen, dass nur in lizenzierten Einrichtungen, dass nur nach einem Gutachtenverfahren, dass nur nach einer bestimmten aufgelisteten Krankheit gesucht wird, dass diese Bedingungen eingehalten werden? Gibt es dazu Beobachtungen, ob es auch Umgehungen gibt? Und wie werden die dann unter Umständen, ja, verfolgt? Das Gleiche auch an M. Devroey, denn da scheint mir Ähnliches der Fall zu sein.

Wolf-Michael Catenhusen [Mitglied des Deutschen Ethikrates]: Ja, das waren jetzt die vier Beiträge und, ja, zur Beantwortung, Frau Jackson, wenn Sie anfangen wollen bitte?

Prof. Dr. Emily Jackson [Vizevorsitzende der HFEA]: All of them?

Wolf-Michael Catenhusen [Mitglied des Deutschen Ethikrates]: No, to the questions you were asked but you're free to include information on a question which is not directly to you.

Prof. Dr. Emily Jackson [Vizevorsitzende der HFEA]: Here the Niemann-Pick example. Sorry. The fact that the less severe one is not on the list doesn't mean that a couple with that condition have asked for it to be on the list and have been turned down. The one that's on the list is the one where an application has been made and that application has been approved. That's just an example of how conditions, you may have a name for an umbrella condition but 's lots of variation within that. And where that variation is known and understood, and often, it will be different only in numbers for the different types of variations that the fact that you approve a condition doesn't mean you approve the umbrella. It doesn't mean you approve everything. Where there is variability and that variability is understood, you can confine it. So there are three versions of Niemann-Pick. To my knowledge, two of them have been approved. I don't know whether anybody else has sorted for the less severe one. To my knowledge, they haven't. So I think that's the issue there. In relation to sex selection, no, that's not okay in terms of the law. There is a prohibition on sex selection for non-medical reasons. Now, there is a secondary question about how you can be absolutely sure that sort of saying we have three females and two males, whether or not that ever happens, orally, we would not be able to tell, but it would not be lawful. So if we knew about that, that would be not within the scheme of the legislation.

Prof. Dr. med. Jens Reich [Mitglied des Deutschen Ethikrates]: Would you cast dice, when?

Prof. Dr. Emily Jackson [Vizevorsitzende der HFEA]: Yes. In terms of removing from the list, as far as I know, this hasn't happened yet. But I think it's one of the things I wanted to sort of stress is that we haven't sat down and written a list that is there as some kind of definitive. This is where you can treat for. It's a de facto list that results from transparency. An approval has been given to a condition and we publish that, which de facto leads to a list. It doesn't, there's no sort of getting around the fact that, if you publish what conditions you've licensed, that's there. There is this formal process of review after five years, but there is also the possibility, because we get information from other centres, somebody could say: Actually, I don't think there is a dramatic new treatment breakthrough, this isn't appropriate any more. So, it hasn't actually happened, but it could. It's not set in stone. Severity of suffering, how we make decisions about severity of suffering. Well, that's really, how that's done from the Licence Committee, is part of the process I tried to describe of peer review and of seeking responses to the summaries from the public, from patient groups to the conditions. And what the Licence Committee would have in its papers is a very detailed description from two clinical geneticists of what this condition is like. What it is like to have this condition. What it is like to be born with this condition and what it is like to develop

it. So, it is advice from clinical geneticists as to what the reality of the suffering involved with that condition is. That is where that information comes from. From peer review by geneticists.

Wolf-Michael Catenhusen [Mitglied des Deutschen Ethikrates]: Mr. Devroey, do you want to make a comment on a special point?

Prof. Dr. Paul Devroey [Zentrum für Reproduktionsmedizin am Universitätskrankenhaus Brüssel]: I do want one particular question. The point is, when you do PGD, you are not interested in the sex. You are even, you do not even do a test to find out the sex. You're interested to knowing the disease. It's not even a question, I would say.

Wolf-Michael Catenhusen [Mitglied des Deutschen Ethikrates]: Inevitably learn more than just the diagnosis.

Prof. Dr. Paul Devroey [Zentrum für Reproduktionsmedizin am Universitätskrankenhaus Brüssel]: No, no, no. Absolutely not true.

Wolf-Michael Catenhusen [Mitglied des Deutschen Ethikrates]: In future, if you …

Prof. Dr. Paul Devroey [Zentrum für Reproduktionsmedizin am Universitätskrankenhaus Brüssel]: No. You can do it, but if you have a couple in front of you with a certain risk of a disease, you hope to know the disease, not the sex. Absolutely not. The only way, the only condition where you go for the sex is if you know that this disease only occurs in females.

Wolf-Michael Catenhusen [Mitglied des Deutschen Ethikrates]: That is clear.

Prof. Dr. Paul Devroey [Zentrum für Reproduktionsmedizin am Universitätskrankenhaus Brüssel]: And I think, if I may make a proposal, when I hear the discussion here, why should some of you not pay a visit to a centre, just to realise how it really works. Because then you will really see how it works.

Wolf-Michael Catenhusen [Mitglied des Deutschen Ethikrates]: That was why we invited you because not everybody has time to visit you. But, Mrs Jackson, please continue.

Prof. Dr. Emily Jackson [Vizevorsitzende der HFEA]: I shall carry on. In terms of people being refused treatment for PGD, this a difficult one to answer, basically because of, the situation now is the individual patient. Individual families don't come before the HFEA with their condition. So, what goes on in the centre, if a centre says: You're not appropriate for PGD? That's not something that the HFEA is necessarily going to record. That would be a clinical decision. In terms of conditions coming before the HFEA and being turned down, one of the issues here is that if a condition is very likely to be turned down, that will show up in the peer review process, in which case it's very unlikely to get as far as the Licence Committee. So I think it's important to understand that, by the time a particular application goes before the Licence Committee, there's been a lot of stages before that, including at least two positive peer reviews, including this lay summary that we do. So it will be quite unlikely that something gets as far as the Licence Committee and not be very close to meeting the statutory tests. I think, clearly, the Licence Committee could turn down conditions, it's perfectly possible that they could. It doesn't do so very often. I don't have exact figures. But I think, most of them, by the time they get to the Licence Committee, will have met the criteria. Because, if somebody applies to do something which is not trivial, somebody in the HFEA secretariat will say: That's not going to go through. So there is a whittling out process is what I'm trying to say before it gets to the final stage of the Licence Committee. There was another one, wasn't there?

Wolf-Michael Catenhusen [Mitglied des Deutschen Ethikrates]: But, let me …

Prof. Dr. Emily Jackson [Vizevorsitzende der HFEA]: The final question for me was about how we regulate this. And we regulate this by a process of inspections and monitoring. And so every centre that does PGD has to be inspected and all of their records analysed and there are sanctions that can be taken against centres that breach either the legislation or the Code of Practice. Now, because PGD doesn't happen very often and it happens in very few centres, this hasn't been one of the major areas of enforcement activity for us. So it's not an area where there have been lots of people behaving outside of the law. So, in a sense, regulation is intended to ensure that people comply because they know the Code, the inspectors come in, they look at all of their records, they look at all of their processes to ensure they're appropriate. So it's regulated.

Wolf-Michael Catenhusen [Mitglied des Deutschen Ethikrates]: Why in France do you not follow the British example of licencing not only centres but also new tests? That's a remarkable difference.

Prof. Dr. Patrick Gaudray [Mitglied des Comité Consultatif National d'Ethique (CCNE)]: Actually, we licence the centres because it is really more feasible, I think. The centres are really the places where the tests can be designed and validated from a scientific point of view. Then it goes to the agreement, of course, of the Agence de la Biomédecine, Biomedicine Agency, which is really the government-related agency which has the power to say Yes or No, ultimately. This agency is a kind of ethics committee, which is Conseil d'orientation, and there is a direction, there is a general assembly of this agency. So really, it's a collegial approval or disapproval of a test which has been scientifically grounded in the centre.

Wolf-Michael Catenhusen [Mitglied des Deutschen Ethikrates]: Mrs Jackson, I don't think you've answered all of the questions put to you, or have you?

Prof. Dr. Patrick Gaudray [Mitglied des Comité Consultatif National d'Ethique (CCNE)]: No, I have not answered about the evolution …

Wolf-Michael Catenhusen [Mitglied des Deutschen Ethikrates]: No, no, no. I first want to ask Mrs Jackson if you …

Prof. Dr. Emily Jackson [Vizevorsitzende der HFEA]: Which one am I missing? Could you repeat the one I haven't answered, please?

Wolf-Michael Catenhusen [Mitglied des Deutschen Ethikrates]: Now, the question is: Have you already answered all of the questions put to you?

Prof. Dr. Emily Jackson [Vizevorsitzende der HFEA]: I thought so, but if I, if there's one I've missed, please, if you could repeat this. I think you suppose that one question is missing but you want a questioner to repeat it, isn't it? So, the last one was who? Schmidt-Jortzig.

Wolf-Michael Catenhusen [Mitglied des Deutschen Ethikrates]: Herr Wunder, wenn Sie nochmal wiederholen.

Dipl.-Psych. Dr. phil. Michael Wunder [Mitglied des Deutschen Ethikrates]: My question concerned the numbers of PGD assessments in the years 26 to 28 in France. And what are the reasons for this increase in use?

Prof. Dr. Patrick Gaudray [Mitglied des Comité Consultatif National d'Ethique (CCNE)]: The reasons have not been studied very carefully, I guess. So it's difficult for me to give you a very strong answer to your question. I think that, the fact that the number of tests available is increasing, when a couple comes to a PGD centre asking for a PGD for one particular condition and the test doesn't exist, it takes quite a long time, some, well, depending on the test, but it can take quite a long time to set up the right conditions to have a reliable test.

So once a test is available, as Mrs Jackson said, it's transparent, so everybody knows that this test is available and then, people who didn't dare to ask might ask. The numbers are very small, so it's very difficult to state anything about the evolution of the numbers, although there seems to be an increase in the requests for PGD. But I think, the fact that we are able to do better for very severe conditions makes it easier for people to ask and to be granted the authorisation of going through PGD. So I think it's really a matter of technology more than anything else. And maybe also the fact that more and more people speak about PGD in French society makes people wonder: Why not for me? But this will come to, I think, to a plateau some day and the technological constraints will have a major impact on the numbers, I think.

Wolf-Michael Catenhusen [Mitglied des Deutschen Ethikrates]: M. Devroey?

Prof. Dr. Paul Devroey [Zentrum für Reproduktionsmedizin am Universitätskrankenhaus Brüssel]: Well, I fully agree, I think, many, many negations, you need a lot of time to prepare the test, it takes some time. I think that more and more patients are aware that they could be treated, I think it's quite normal process. So, I think it's the normal process that, when patients are more and more aware that the tests exist and that they ask for the test to be performed, especially when they are infertile.

Wolf-Michael Catenhusen [Mitglied des Deutschen Ethikrates]: Sorry

Dipl.-Psych. Dr. phil. Michael Wunder [Mitglied des Deutschen Ethikrates]: I'm a little bit disappointed about this answer because these numbers are not a natural process. There must be a reason, a reason in society or in the public debate or in the increasing in diagnosis groups or whatever, I don't know, but this is a thing you have to explain. The numbers, you did not present the numbers, but my question to you would be: Do you have numbers about the years? I remember your numbers are aggregated over a lot of years, ten years or eight years, but can you differentiate between the years, is there a development?

Prof. Dr. Paul Devroey [Zentrum für Reproduktionsmedizin am Universitätskrankenhaus Brüssel]: Yes, I fully agree, we have numbers since 1993 where we did one case a week, and now we do one case a day and there are still many patients on the waiting list who have a disease that is not very well developed. You know, for some diseases, once you have mucoviscidosis, for instance, then you can use the probes in the same condition, so it accumulates knowledge, I think.

Wolf-Michael Catenhusen [Mitglied des Deutschen Ethikrates]: M. Gianaroli.

Dr. Luca Gianaroli [Vorsitzender der ESHRE]: Maybe I can help you from this point of view. If you look at the number of cycles of IVF and ICSI that are done in Europe and you see the graph, they show you there is a constant increase. The percentage of PGD done in Europe still remains the same, that is 0.3, 0.4, but of course, the total number increases because it follows the increase of the number of patients treated in the clinic. So, another reason that could help you in the explanation is that the more the technology is used, the higher the percentage of PGD in terms of real numbers. And that could also be part of the explanation. Maybe this also helps you.

Wolf-Michael Catenhusen [Mitglied des Deutschen Ethikrates]: The other question should be the availability of tests. Because, at the beginning, you could only test maybe a few diseases, and expanding the number of diseases you can diagnose could be one of the reasons, too.

N. N.: This is wrong … 2006 …

Wolf-Michael Catenhusen [Mitglied des Deutschen Ethikrates]: Yes, but maybe you should repeat this, the numbers of, erwähnen Sie jetzt die französischen Zahlen? Das ist jetzt ein bisschen das Problem, weil das jetzt durcheinander geht, lieber Herr Wunder. Ich glaube, wir könnten vielleicht in der nächsten Runde nochmal zurückkommen, also ich werde das vielleicht auch nochmal dann nachfragen. Frau Riedel.

Ulrike Riedel [Mitglied des Deutschen Ethikrates]: Ich habe eine Frage an Herrn Prof. Devroey. Sie haben den Cross-Border-Tourismus angesprochen. Den gibt es ja auch, und vor allen Dingen nach Belgien. Meine Frage ist: Aus welchen Staaten kommen die Paare? Kommen die nur aus den Staaten, wo die PID verboten ist, oder kommen sie auch aus Staaten, wo es die PID gibt, aber in einem restriktiveren Umfang als in Belgien? Also zum Beispiel, gibt es Cross-Border-Tourismus von Frankreich nach Belgien?

Prof. Dr. Paul Devroey [Zentrum für Reproduktionsmedizin am Universitätskrankenhaus Brüssel]: Most of the patients come from countries where PGD is forbidden. So most patients come from, for instance, Germany, Norway and Italy. And I think this is the main reason, because it is forbidden, that patients travel to countries where it is allowed. In some countries, of course, for instance, some countries in the Middle East, it's not forbidden, but the science is not there to apply it. So there are two different reasons. But I guess, for Europe, the main reason for cross border is because it is forbidden.

Prof. Dr. phil. Weyma Lübbe [Mitglied des Deutschen Ethikrates]: I'm interested in the phenomenology of borderline cases of such diseases, so perhaps one or some of could you describe a concrete condition which, say, has controversially and explicitly been discussed, whether it should come on the list but in the end has been considered by a majority to be just about not eligible for the list. That would be a borderline case and I would be interested in what sort of disease or condition, to what sort of disease or condition this applies, that it is a borderline case, what it looks like and whether these borderline cases are very different, as far as you know, in the countries where PGD is allowed.

Prof. Dr. Emily Jackson [Vizevorsitzende der HFEA]: I think one is the, sorry, one of the examples of a condition that was for many people thought to raise difficult issues was in relation to later onset lower penetrance, susceptibility genes. So, lower penetrance later onset conditions. So, an obvious example would be (Bracker?) 1 and 2. And before the HFEA made a decision to licence a condition like that, they held public consultation. And a wide ranging public discussion was had about whether and in what circumstances it would be appropriate to do PGD for conditions that don't manifest until later in life and where the penetrance is less than 100 per cent, so it is not guaranteed that a person with the mutation will develop the condition. So, there was public consultation on that and the decision was taken that said: Yes, that could in certain circumstances be acceptable, so, there would be a judgement for the Licence Committee as to whether it met the twin tests of substantial risk and serious condition. Under those conditions, it would still have to be case by case. So a condition like that does not get out into any list, it still has to come before the Licence Committee. So, that's an example of a case seen as borderline.

Wolf-Michael Catenhusen [Mitglied des Deutschen Ethikrates]: Could you give us an example of a disease where this process was, maybe, made in the last two years? Because then we could perhaps compare it with the situation that would happen in this case in France. Mrs Jackson, could you give us an

example of a concrete disease where this decision was made, a process was made, with broad public participation, as you just mentioned.

Prof. Dr. Emily Jackson [Vizevorsitzende der HFEA]: No. Not in, the last one where there was a significant public consultation was what we called our choices and boundaries consultation which was to do with late onsets, susceptibility. There hasn't been, since then, a big public discussion about the acceptability of a specific disease. That hasn't happened.

Wolf-Michael Catenhusen [Mitglied des Deutschen Ethikrates]: But this HLA tissue typing was such a case, hm?

Prof. Dr. Emily Jackson [Vizevorsitzende der HFEA]: That's not a disease, that's a different sort of test. And yes, that was when the 2008 legislation went through Parliament. That was the area of controversy, not what you might call "normal" PGD. So, in the debates in Parliament, if I could just explain, the pushing the criteria for PGD on the face of the Act. That was seen as almost a tidying-up mechanism, putting this on a statutory footing. The question of HNA typing was debated much more extensively, but in the end, and there was a free vote in Parliament, and in the end, that free vote was to allow it, but again on a case by case basis.

Prof. Dr. Patrick Gaudray [Mitglied des Comité Consultatif National d'Ethique (CCNE)]: If I may add a word. I think that the problem is that on every borderline case like BAC 1, predisposition to breast cancer, for instance, you have a late onset, not total penetrance, so not all the women who have the mutation will develop breast cancer, then you have to make choices. I mean, it's always a matter of choice. You have the same with the choice with another condition which is Neurofibromatosis Type 1, which can go from being a very mild disease with just café au lait spots on the skin to major mental retardation and cancer conditions which are really awful. That's a matter, that's why I wanted to bring up the question, every case, when it deals with ethics, is really a matter of choice. What do you do with Huntington Disease? Everybody agrees that it's a very severe, it's an awful disease. But some people consider, even in Huntington families, that the 40 years that you live without the disease are worth living. You have to make a choice. Is this a condition which opens to PGD or not? I'm not taking part in this. I have my opinion but I won't tell you. But you see, every condition, I mean, are very, you can have a debate on most of them. So, the borderline is not a straight line, it's not a line which has the same position for everybody. That's why I think it has to be discussed. Between several people.

Wolf-Michael Catenhusen [Mitglied des Deutschen Ethikrates]: This Huntington question was solved in your country, as I remember, by legislation. Not by the Licence Committee or anything else. That was a legislatory question. Now, in France …

Prof. Dr. Patrick Gaudray [Mitglied des Comité Consultatif National d'Ethique (CCNE)]: In France, there is a Licensing Committee which is this Multidisciplinary Prenatal Diagnosis Centre.

Wolf-Michael Catenhusen [Mitglied des Deutschen Ethikrates]: Yes, but this question regarding Huntington Disease was, as I remember, answered by a legislatory act in 2004 in your country.

Prof. Dr. Patrick Gaudray [Mitglied des Comité Consultatif National d'Ethique (CCNE)]: It has been said that it was one of the severe conditions which were open to PGD. But still, I mean, people are debating on it.

Wolf-Michael Catenhusen [Mitglied des Deutschen Ethikrates]: M. Devroey?

Prof. Dr. Paul Devroey [Zentrum für Reproduktionsmedizin am Universitätskranken-

haus Brüssel]: I think this is one of the most difficult questions about the breast cancer study. Because, depending on the couple or on the family sitting in front of you, if her mother died, she has already had one operation, one mastectomy, it makes sense to help her, of course. So, I think it's a case-by-case decision, I would say.

Dr. phil. Peter Radtke [Mitglied des Deutschen Ethikrates]: Die meisten Themen, die ich hier ansprechen möchte, sind insbesondere von Mrs Jackson und M. Gaudray angesprochen worden, aber sie hinterlassen bei mir eigentlich eher ein Fragezeichen als eine Erklärung. Das eine ist, wir haben gerade von den erst später manifesten Krankheiten gesprochen. Es gibt offensichtlich diese Liste, zum Beispiel in Frankreich, wo Chorea Huntington draufsteht. Die Frage: Ist das hier nur eine medizinische Klassifizierung? Denn das sagt ja überhaupt nichts aus, über – es wurde bereits gesagt – die 40 Jahre bis zum Ausbruch der Krankheit hinsichtlich des Lebenswertes. Und die Frage ist auch: Wie hoch wird dann die Präferenz der Eltern gewertet gegenüber dem Betroffenen, der ja eben 40 Jahre ohne Symptome lebt? Das heißt: Wie weit können die Eltern, die vielleicht in 40 Jahren gar nicht mehr leben, über dieses Leben bestimmen?

Das Zweite ist die Frage des Schweregrades. Wenn ich das richtig sehe, ist es doch enorm schwierig, bereits bei der PID den Schweregrad einer Behinderung festzustellen. Manchmal ist es ganz gut, wenn man aus der Theorie in die Praxis geht. Ich selbst habe die Osteogenesis imperfecta, das ist die Glasknochenkrankheit, und bin eigentlich nach der herkömmlichen Klassifizierung der schwere Fall. Der schwere Fall, der normalerweise nach drei Tagen stirbt. Und ich bin heute über 60 Jahre alt. Die Frage ist also: Inwieweit lässt sich dieser Schweregrad tatsächlich schon bei der PID feststellen? Wir haben Betroffene mit der Glasknochenkrankheit, die kaum Symptome aufweisen.

Und schließlich noch die Frage: Wie weit spielen eigentlich auch die Medien eine Rolle? Wie weit wird den Eltern eigentlich klargemacht, dass eine PID noch nicht garantiert, dass ein gesundes Kind zur Welt kommen wird? Sowohl von der Empfängnis bis zur Geburt ist alles noch möglich, und auch bei der Geburt: Sauerstoffmangel und das Kind ist vielleicht spastisch gelähmt. Also, wie weit wird hier auch eine Illusion geweckt, dass es möglich ist, behinderte Kinder zu vermeiden?

Und schließlich die Frage der Liste. Ich habe ein bisschen das Gefühl, keiner möchte gerne zugeben, dass es eine Liste geben wird, aber es wird doch letztendlich entweder eine schriftliche oder eine mündliche Liste geben. Wir hatten ja in Deutschland eine ähnliche Situation: Es gab – zwar nicht für PID oder Pränataldiagnose – für die Frage, wie weit man noch therapeutisch einwirken soll auf schwerstbehinderte Säuglinge, die sogenannten Einbecker Empfehlungen. Da waren die Krankheiten aufgeführt. Erst nachdem man merkte, dass das also äußerst kompliziert ist, wurde diese Einbecker Empfehlung wieder zurückgezogen. Aber man wird nicht von der Entscheidung entbunden werden, zwischen lebenswertem und lebensunwertem Leben entscheiden zu müssen, auch, wenn man sagt, es gibt keine Liste.

Wolf-Michael Catenhusen [Mitglied des Deutschen Ethikrates]: Frage jetzt an die Ethikratmitglieder: Hat jemand jetzt, der sich zu Wort gemeldet hat, direkt zu demselben Komplex noch eine zusätzliche Frage? Jürgen Schmude.

Dr. iur. Dr. h. c. Jürgen Schmude [Mitglied des Deutschen Ethikrates]: Herr Gaudray, Sie haben uns gesagt, es drohe die Gefahr der Stigmatisierung der Bestimmung bestimmten Lebens als nicht lebenswert, wenn man eine verbindliche Liste hat. Das schließe ich an die

Frage meines Kollegen an. Denn später haben Sie uns gesagt, die Liste der Diagnosen, die Sie uns hier vorgeführt haben, das sei natürlich eine Liste von Fällen, bei denen in jedem Fall die PID genehmigt würde. Da hätte ich gerne etwas gehört über die ethische Beurteilung dieses Problems auch aus Ihrem Ethikrat. Wie gehen Sie damit um? Auf der einen Seite die Gefahr der Stigmatisierung, auf der anderen Seite sehr wohl eine Liste.

Wolf-Michael Catenhusen [Mitglied des Deutschen Ethikrates]: Jetzt zu den Antworten. Zunächst, Sie, Herr Gaudray, sind ja auch direkt angesprochen.

Prof. Dr. Patrick Gaudray [Mitglied des Comité Consultatif National d'Ethique (CCNE)]: Yes, I would like to start because the thing is that the fact that you have a list of available tests doesn't mean that it's a list which automatically gives you access to PGD. It's not, maybe I was not clear when I presented it. It's really a list of examples of available tests, genetic tests. It's not a list, if you are on the list you will be open to PGD right away with no questions. I mean, the questions are issued in every case. I think that, for instance, with Huntington Disease, it's clear that somebody who asks for PGD for Huntington Disease will be granted PGD with no major difficulty. But it's not of use for all the tests which are on the list. I think that Multiple endocrine type 2, for instance, is not, or, as I said, Neurofibromatosis, I mean, some information also has to be given to the parents regarding what this condition really is. What is the spectrum of problems, of health problems which can occur in this particular condition? So I knew that showing you a list of the tests which can be performed in the three PGD centres in France and telling you that we were against the elaboration of a list of diseases open to PGD would be slightly paradoxical and would probably raise some questions. So I'm not surprised by your questions, but really, it's two different things. I think that PGD has to go through this process I tried to describe to you. And the evaluation of this severity, of the condition, of the family, etc. has to be performed in these Multidisciplinary Centres. It's not related to the list. Of course, if no test is available, I mean, there is no possibility to make a diagnosis. That's as simple as that. That's why I think that the evolution of the number of tests which can be performed also explains the number of cases which can be addressed by the, those Multidisciplinary Centres. But it's something which is logical with the evolution of knowledge, of science, of technology. I mean, before PGD was possible in any instance, I mean, there was no request for PGD anywhere in the world. So, because it was simply not possible. If a test is possible, it's okay. If a test is not possible, there is no question. If the test is possible, you have to address the issue, is this a severe disease? The severity, I agree with Mr. Radtke that it's a very difficult issue. That's why it cannot be decided by a single person. It cannot be decided by the parents. The parents have a word in the matter, but that comes second. First, it's a matter of medical evaluation. Then the rest comes, it's as important as a medical evaluation, the medical evaluation comes first. But the severity, I mean, as you said, something can be very severe for somebody and not for somebody else. So you cannot impose that Osteogenesis Imperfecta is a disease which will be open to this or that, to the elimination, to the destruction of embryos. You really have to discuss thi. Well, I think, if somebody else wants to answer this?

Prof. Dr. Emily Jackson [Vizevorsitzende der HFEA]: I mean, just on the last points about the illusion of avoiding disability altogether. I think, two points I'd want to make there which is related to a colleague of mine at the LSC who's an anthropologist. She's did a very large-scale ethnographic study of PGD patients in one of the large London centres. Two points I just

wanted to raise. Many people who come forward to a clinic having been recommended by a genetics counsellor decide against PGD. Once they know what's involved, once they are told how gruelling it is, they decide they don't want to do it. The idea that this is a quick fix is certainly not the case and there is a large number of patients who decide against it. The second thing that her research showed was that quite a few people wanted PGD because they had an existing child with the condition, a child who is often terminally ill, and they would have found a difficult to have a termination for that condition because they had an existing child with that condition, they found that a difficult judgement to make, to terminate in the cases somebody, an existing child who is often terminally ill. So, I think, the second point in relation severity, it's a difficult, difficult judgement. And I think, the process that you are undergoing here is really important. It needs to be a democratic judgement. It needs to be a judgement made by the democratically elected parliament and in the UK, there is, the decision was taken there by a regulator that is directly accountable to Parliament. So different countries will reach different decisions, of course they will. But that has to be a judgement which has been formed by a democratic judgement.

Dr. Luca Gianaroli [Vorsitzender der ESHRE]: I just wanted to briefly expand on the concept of the test. If a test is not technically available, no exam can be done. I mean, no amniocentesis, no CVS, no PGD. So the point is, the non-availability of a test limits, all in all, all genetic activity. First point. The second point is that each test can be developed so it's almost impossible to think about, because we are talking very much about this list, it's almost impossible to generate a list that is a fixed list, because it could vary every three months, every six months. If I understand correctly, the concept of the list is to reduce the risk of using this technology for something that is not considered important. So if you have to start, why don't you go the other way around? Why don't you make a list of the things that are not allowed? And that's probably easier than going the other way around to make a list of the potentiality of each single disorder. Because it will probably be a shorter list.

Wolf-Michael Catenhusen [Mitglied des Deutschen Ethikrates]: Aber ein Indikator wäre doch, wenn es für bestimmte Krankheiten, die diagnostiziert werden, auf einmal einen starken Rückgang gibt der Diagnosen, weil offenkundig die Abwägung unterschiedlich ist. Denn in Deutschland wird immer die Frage gestellt, gibt es auch eine Krankheit, die aufgrund der Verbesserung der Therapie auf einmal nicht mehr relevant für PGD ist? Gibt es solche Beispiel? Das wäre für uns ganz wichtig. Kennen Sie ein Beispiel, wo eine PID seit Jahren praktiziert wird und auf einmal durch einen Fortschritt im Therapiebereich der Bedarf an PGD deutlich sinkt? Gibt es so etwas? Ist Muskoviszidose ein solcher Fall? Wir reden jetzt nicht pränatal, sondern über PGD.

Dr. Luca Gianaroli [Vorsitzender der ESHRE]: No, because again I would like to go back to the concept of the severity. To have a treatment for a disease with a very light symptom has nothing to do with the same disease with extremely severe symptoms. So, again, the treatment applies only to some circumstances of the same disease. And this applies to any area of medicine.

Frau Prof. Dr. med. Christiane Woopen [Mitglied des Deutschen Ethikrates]: Ich habe drei Fragen an Frau Jackson und eine an Herrn Gaudray. Frau Jackson, Sie sagten, dass eine Lizenz für eine Krankheit bisher noch nie zurückgenommen wurde. Wurde denn schon mal eine Lizenz für ein Zentrum zurückgenommen, das ein paar Jahre hat PGD durchführen können und dem dann die Lizenz wieder entzogen wurde? Zweite Frage: Sie sprachen davon,

dass bei manchen Lizenzierungen von Krankheiten Patientengruppen angehört werden. In Deutschland wären das vor allen Dingen Selbsthilfeorganisationen und Behindertenverbände beispielsweise. Wir haben in Deutschland eine intensive Diskussion um diese Diskriminierungsfrage dahingehend, dass sie sich verletzt fühlen, gedemütigt fühlen, dass sie es als ein Lebenswerturteil empfinden. Ist es schon einmal vorgekommen, dass so eine Patientengruppe durch ihre Äußerungen tatsächlich auch dazu beigetragen hat, dass eine solche Lizenzierung einer Krankheit nicht stattgefunden hat? Dass es aufgrund dieses Einspruches tatsächlich nicht zu einer Lizenzierung kam.

Die dritte Frage ist eher zahlenorientiert, nicht weil ich sie für ethisch ausschlaggebend halte, aber weil es mich trotzdem wundert, wenn man das so gegenüberstellt. Die Frage richtet sich eben an Frau Jackson und Herrn Gaudray. England kommt in Deutschland eher als sehr liberal rüber im europäischen Vergleich, hat von der Embryonenregelung her – Gleichzeitigkeit von HFEA und unserem Embryonenschutzgesetz – einen sehr liberalen Charakter, während Frankreich in Deutschland eher als etwas konservativ wahrgenommen wird. Wenn man sich jetzt die Zahlen ansieht, ist es so, dass 2007 in Frankreich an drei Zentren 228 Patienten PID erhalten haben und in England an neun Zentren 169 Paare bei ungefähr gleichen Bevölkerungszahlen. Wie erklärt man sich vor diesem Hintergrund den Unterschied?

Wolf-Michael Catenhusen [Mitglied des Deutschen Ethikrates]: Eine gute Frage, auf die dann die Kollegin aus Großbritannien und der Kollege aus Frankreich antworten können. Ich nehme jetzt aber noch Frau Holzheid in diese Frage rein und dann können Sie wieder antworten.

Hildegrund Holzheid [Mitglied des Deutschen Ethikrates]: Wird bei der Zulassung nicht von Zentren, sondern vom konkreten Fall für eine PID denn auch bei den betroffenen Müttern oder Eltern nachgeprüft, in welcher Weise sie mit der Abweichung umgehen können, die ihnen bevorsteht, wenn das Kind mit dem entsprechenden genetischen Merkmal zur Welt kommt? Also in anderen Worten: Wird die konkrete Situation der betroffenen Eltern oder Mütter berücksichtigt?

Wolf-Michael Catenhusen [Mitglied des Deutschen Ethikrates]: Es gibt ja zumindest in Großbritannien auch konkrete Regelungen, Handlungsanleitung zum Thema Beratung. Vielleicht könnten Sie uns da noch ein paar Informationen geben, auch in Frankreich, welche Gesichtspunkte bei einer Beratung eine Rolle spielen, weil das für uns wirklich sehr wichtig ist. Frau Jackson?

Prof. Dr. Emily Jackson [Vizevorsitzende der HFEA]: On both. Okay. Well, have Centers have lost their licence? Yes, but not in relation to PGD. There are very few centres that are very specialised. There has never been a license removed from a centre because of a breach in relation to PGD. So wrongdoing in relation to fertility treatment has not been in this particular area. In terms that patient groups contributing to not approving a condition, I'm afraid I don't have that information on me, but all of the Licence Committee minutes are published on the website. So anybody in Germany who wants to see the decision-making process can find those minutes on the website and see what happened. So, yes, the patient group will be considered in the same way as other sorts of decisions that License Committees have to take in the UK. You get representation from groups you perhaps disapprove of the decision you want to take of course, you consider all of those, but you are making a decision. In terms of explaining the difference between, or apparent difference or not difference between the UK and France process, I think it's hard to say. I think the image of… maybe this is an important point to make, that there is an image of the UK of being

fantastically liberal here but, you can see from the statistics, that doesn't mean we have an endless train of people doing this. That, in a sense, that this is what I'd want to say to you, we have quite a strictly regulated system. The rules may permit PGD in a wide range of circumstances, but it is quite heavily regulated. I can't say what the differences are between England and France, maybe my colleague can. In terms of taking into account individual circumstances, in the UK because, apart from HLA typing and the susceptibility of later onset they, the family, circumstances are anonymised so we can sit it by the Licence Committee. But for the vast majority cases it's for the clinic which must make a judgement based of upon all sorts of things to do with the family circumstances and genetic counsellors and other counsellors will be involved in that process.

Prof. Dr. Patrick Gaudray [Mitglied des Comité Consultatif National d'Ethique (CCNE)]: About the numbers between the UK and France, I think I agree with my colleague on the fact that is not because in the international mind the country seems to be more liberal, I don't think that liberalism can really apply to bioethics, to me it's a bit paradoxical. So I don't think that France is very conservative, it is, sort of, yes, of course. As every country, I think, but the UK, too. So the numbers are not the same, it means that the way you regulate doesn't affect the number, it might affect the case-by-case situation, but not the general numbers. The fact that groups of patients can influence things, I think that in France groups of patients, disabled people and Down syndrome affected families have had a major impact on the refusal, the present refusal of PGS screening. Because trisomy 21 cannot be present in a family, it's not a familial condition which can opened to PGD. But if it was opened to PGS, we know how to diagnose trisomy on an embryo, and here the association of patients are really very active to block the system at this level, because they don't want these conditions to be granted screening, which is not again, it's not diagnosis, it's a screening, that would be proposing those conditions which are not hereditary, in the usual sense of the term. The fact that, the way parents cope with the disease and the disability, the handicap, is taken into account in those multidisciplinary councils. And, in fact, we have, I don't have the examples in mind to tell you precisely, but we have discussed that the committee at the Center we have discussed some conditions for which, for some people it was really considered as a severe conditions in the family, in this particular family, and it was not in another one. The same was also done for the predisposition to breast cancer, for instance, we speak about that because it has been authorised in the UK and when the first girl was born with, after PGD 4, BAC 1 mutation it was really in a family where the severity of the predesposition to breast cancer was incredible. I mean at every generation there were several sisters who where affected who died at a very early age, it was really something which was – confronted with this condition, I think that many people would say: Yes, go for PGD. Although we do not agree, on a general basis, that it would open PGD for every BAC 1 mutation. So the condition to severity, the way the family can cope with this condition, is really a major issue which has to be put forward, it's really one of the main concerns that people should have when deciding it is okay or not okay.

Wolf-Michael Catenhusen [Mitglied des Deutschen Ethikrates]: Jetzt sind die beiden Abgeordneten, bitte.

N. N. (weiblich): Ich habe eine Frage zu der französischen Praxis. Ich hab das so verstanden, dass die Zentren stark einzelfallorientiert entscheiden. Sie haben ja nicht eine Liste von Krankheiten. Ist es denn denkbar, dass sich in den verschiedenen Zentren auch eine völlig unterschiedliche Bewertungspraxis herausbildet?

Dass ähnlich gelagerte Fälle in dem einen Ort anders bewertet werden als in dem anderen Ort? Und wie gehen Sie damit um? Versuchen Sie da eine Standardisierung? Wie bewerten Sie die Arbeit der Zentren? Und wirken Sie auf diese Frage irgendwie ein?

Frau Sitte: Ich hab zwei Fragen, die eine bezieht sich auf eine Debatte, die wir gerade unlängst geführt haben bei der Antragserstellung. Da ging es um die Frage Chromosomenanomalien und die Korrespondenz zu Fehlgeburten. Ich bin keine Medizinerin und ich bräuchte einfach einmal Ihre Auskunft, wie mit dieser Frage umgegangen wird. Es ist uns natürlich bewusst, dass es keine verlässliche Auskunft gibt, aber inwieweit das in Ihrer Praxis eine Rolle spielt.

Das Zweite bezieht sich auf ein bisschen auf den Kontext der Familien, aber eben auch auf den Kontext der Gesundheitssysteme. Können Sie irgendetwas dazu sagen, ob es eine Korrelation gibt zwischen dem Wunsch auf PID und Qualität beziehungsweise dem Ausbau des jeweiligen Gesundheitssystems? Denn man muss ja schon sagen, dass die Perspektive, mit einer Krankheit leben zu müssen, nicht nur die Familien vollkommen in ihrem Zusammenleben verändert, sondern man ja das auch bewertet unter der Option, was ist innerhalb dieses Gesundheitswesens für mich später und mein Kind sozusagen zu erlangen. Und kann ich therapeutische Angebote unabhängig von meinem sozialen Kontext, also eine Bestversorgung für das Kind beziehungsweisen den Heranwachsenden erlangen? Selbst wenn es sich nicht genau belegen lässt, hätte ich gern aus Ihrer Sicht eine Meinung dazu.

Herr Henke: Mein Name ist Henke, ich bin Mitglied im Gesundheitsausschuss des Bundestages und bin an der Formulierung der Initiative beteiligt, die sich für ein – jedenfalls jetzt, zu dieser Zeit – komplettes Verbot der PID ausspricht, um eine Situation wiederherzustellen, von der wir meinten, dass wir sie hatten. Ich habe in aller Diplomatie eine kleine Antwort auf Herrn Devroey …

Wolf-Michael Catenhusen [Mitglied des Deutschen Ethikrates]: Aber seien Sie jetzt nicht böse, wir wollen Fragen stellen. Da muss ich jetzt darauf bestehen, egal wer, was woher kommt, bitte fragen Sie, aber jetzt keine Kommentare. Das würde ich auch den Mitgliedern des Ethikrates genauso sagen. Bitte.

Herr Henke: Ich möchte Herrn Devroey fragen, ob die Auflösung seiner Abneigung gegen grenzüberschreitende Inanspruchnahme der PID nach seiner Auffassung nur darin bestehen kann, dass wir Deutschen unser Recht dem belgischen anpassen, oder ob auch andere Auflösungen für dieses Problem des Gesundheitstourismus in dieser Frage denkbar sind. Die zweite Frage, die ich habe, richtet sich an Frau Jackson. Sie habe ja von der demokratischen Legitimation gesprochen, auf die sich die Entscheidung beziehen muss. Ist die demokratische Legitimation in jeder Weise ausreichend für die Wahrung der individuellen Rechte des am stärksten selbst Betroffenen? Also dessen, der die genetischen Eigenschaften aufweist. Oder kann man sich denken, dass der kollektiven demokratischen Entscheidung auch bestimmte zu definierende Grenzen gesetzt sind? Ich meine, dass Sie in England seit 1679 mit dem Habeas Corpus Amendment Act eine Tradition solcher Rechte haben.

Wolf-Michael Catenhusen [Mitglied des Deutschen Ethikrates]: Damit sind wir dann schon auch an den Fragen des moralischen Status des Embryos bald angekommen. Aber bitte, wenn Sie jetzt, ich glaube, Herr Devroey, Sie sind vorhin angesprochen worden, wenn Sie vielleicht anfangen?

Prof. Dr. Paul Devroey [Zentrum für Reproduktionsmedizin am Universitätskrankenhaus Brüssel]: First of all, I think that we should

have the greatest respect for human embryos, (2), if we think about PGD, most of the couples have a long history of failure, abortions, (3) if this serious disease is confirmed by medical geneticists after counselling, after advice, it is decided to do PGD. So I would like to say that this practice does not give the greatest respect to the couples and the child to be born.

Prof. Dr. Patrick Gaudray [Mitglied des Comité Consultatif National d'Ethique (CCNE)]: Maybe I can answer the question related to abortions and to repeated abortion. It's quite clear from the medical point of view that there are situations in which embryos will never develop to term. That means if we have one extra chromosome in 16 or if we have an extra chromosome in 22, this always ends in an abortion. There is no living individual with three chromosome 16 or three chromosome 22. Like there are no abortions because they never implant if they have one missing chromosome in some of the chromosomes that we are talking about. That means, that the concept to apply this technique to reduce the risk of abortion is there, up to now has been applied to a stage of the embryo in which, as mentioned before, the risk of misdiagnosis, so the risk of not making the correct diagnosis is there, and that slightly changes the accuracy of the technique. Once we move to a different embryo stage and once we move to microarray, this technical problem could be or should be solved. And that is the technical answer to the problem that has been posed.

Prof. Dr. Paul Devroey [Zentrum für Reproduktionsmedizin am Universitätskrankenhaus Brüssel]: I think there is big concern in Europe about cross border, not only for PGD, but also for sperm donation, for oocyte donation.

Wolf-Michael Catenhusen [Mitglied des Deutschen Ethikrates]: Please, you should speak more directly in the microphone.

Prof. Dr. Paul Devroey [Zentrum für Reproduktionsmedizin am Universitätskrankenhaus Brüssel]: So I think that for cross border, I think there is great concern that there is this cross border, because it is done for PGD, it is done for egg donation, it is done for sperm donation. And then the patients fall pregnant and return home. And then the home country has to take care of these pregnacies. And sometimes the conditions are not ideal. So I think there is a lot to say against cross border.

Prof. Dr. Patrick Gaudray [Mitglied des Comité Consultatif National d'Ethique (CCNE)]: I wanted to answer the question about the differences between those centres. I told you there were approximately, there are 47 centres in mainland France, and they don't react exactly the same regarding file cases. Some of those centres are more restrictive than others. And this is perfectly acceptable to me. We are not in a factory, we are not creating babies on a conveyor belt, we are human beings with emotions, and the emotions are also part of the consideration that has been to be given to a special case, to the suffering of the family. I mean, this cannot be put in a question. It is something which is a human decision. And if people are not granted by the centre closest to their home, nothing forbids them in France to go elsewhere to get advice and maybe to receive permission to go to a PGD centre. So it is not something, you are not constrained, stuck to a particular committee, you can address your file to others, and of course there is no equality because some people can move more easily than others. It's true. We know that. But I think that removing humanity from decisions concerning humanity, it's to meet something that I am not totally ready to accept now. Although I know that those centres have to be evaluated for what they have said, for their refusal statistics, and their grounds, etc. etc. This job is done by the biomedicine agency. So there is an evaluation of the way the centres decide. But

really the cases in which they don't agree are once more borderline, I mean it's one out of a few tens or hundreds of cases. And, but it means that, to me the fact that they could disagree on one particular case makes it more human. That's my personal point of view, I don't say that it is the opinion up there …

Wolf-Michael Catenhusen [Mitglied des Deutschen Ethikrates]: Thank you very much. Ih habe jetzt noch ungefähr sechs bis sieben Wortmeldungen aus unseren Reihen. Bitte konzentrieren Sie sich, wenn es irgendwie geht, auf eine Frage, dann haben wir noch eine faire Chance, durchzukommen.

Prof. Dr. theol. Eberhard Schockenhoff [Mitglied des Deutschen Ethikrates]: Ich habe an Herrn Devroey zwei Fragen. Sie haben von der Mukoviszidose gesprochen. Gibt es bei Ihnen Fälle, wo Mukoviszidose auch nicht akzeptiert wird als Indikation für eine PID angesichts der Tatsache, dass die Behandlungsmöglichkeiten sich doch deutlich erhöht haben? Und die zweite Frage bezieht sich auf den höchsten Respekt. Sie haben gesagt, Sie haben höchsten Respekt für das zu produzierende Leben. Bezieht sich dieser höchste Respekt auf das gesunde Kind, das am Ende des Verfahrens dann das Licht der Welt erblicken soll? Oder bezieht sich dieser höchste Respekt auf die Embryonen, die Sie alle erzeugen, um unter ihnen auszuwählen? Und wenn sich der höchste Respekt auf diese Embryonen bezieht, dann lautet meine Frage: Wie äußert sich dieser höchste Respekt gegenüber den Embryonen, die Sie verwerfen? Die Sie erzeugen, testen und anschließend nicht weiterbehandeln.

Dr. theol. Dr. rer. pol. Anton Herr Losinger [Mitglied des Deutschen Ethikrates]: Ich bin sehr dankbar, dass die Diskussion beim Status embryonis als zentrale ethische Frage gelandet ist. Meine erste Frage: Wenn die Zulassung einer Familie zu einer PID genehmigt ist durch eine solche Verfahrensweise, wie Sie es geschildert haben, muss man dann nicht in den Konsequenzen denken? Wenn, Herr Gianaroli, klar ist, dass ein aus wissenschaftlichen Gründen nicht lebensfähiger Embryo entstehen würde, sind die Dinge klar. Aber wenn – da ja Wissenschaft immer auch ergebnisoffen ist – ein Embryo entsteht, bei dem man sich nicht sicher ist und der in der Tat lebensfähig wäre, dann haben wir es ja mit einer Frage zu tun, wo ein Mensch tatsächlich nach seiner genetischen Qualität eingestuft und ethisch bewertet wird. Und die daran anschließende Frage: Unsere Bundeskanzlerin sagte auf dem Parteitag als Naturwissenschaftlerin, sie ist gegen die Zulassung von PID, weil sie eine Begrenzung auf Einzelfälle nicht für möglich hält. Ist das jemals schon eine realistische Option gewesen, dass, wenn man angefangen hat, tatsächlich das Ganze in den Grenzen gehalten werden kann?

Wolf-Michael Catenhusen [Mitglied des Deutschen Ethikrates]: Die Frage könnte man auch so sagen: Können Sie in Ihrer, zum Beispiel in der französischen Regulierung sagen, wir haben Grenzen gezogen? Das heißt, bestimmte Grenzen können nur durch den Gesetzgeber überschritten werden, und Sie haben ja bisher PGS in Frankreich verboten, untersagt. So kann man in den internationalen Statistiken nachlesen, dass Norwegen und Frankreich PGS verboten haben, nicht erlaubt haben. Jetzt sind direkt angesprochen Herr Gianaroli und Sie, Herr Gaudray, und dann würde ich weitere Fragen hier noch einmal reinnehmen und dann die anderen auch noch einbeziehen.

Dr. Luca Gianaroli [Vorsitzender der ESHRE]: Yes, if I have understood correctly, the question is, the question is, there is always a chance that what has been studied or said in the scientific area could be wrong and it could be possible that an embryo escapes the rules. This is only potentially true for some disease or some disorders. For instance, for the chromosomal disorder that they mentioned, there are no

doubts, it's in the literature around the world that you can have a human living individual with one missing chromosome. That's it. And this is finished as that from the technical point of view. You are now asking me something that is slightly different and it goes inside the concept of the embryo, and the respect of the embryo, it sounds as if it was being asked to Paul Devroey. I can only give my own personal opinion, which has nothing to do with the ESHRE opinion. It is my personal opinion that a fertilised egg is always a project, it's only a project of life, but they can not consider all these projects at the same level when I understand that one of these projects can create one of the most destructive cancers for a woman, that is the (corean?) carcinoma. I can't see that fertilised egg to be a project of life. I see that fertilised egg as a project of death. So, to the best of my knowledge, when there is a need I'll try to avoid the project of life entering a project of death on a project of suffering for the patients who, for me, are the most important individuals that I have in front of me. That is my answer to you.

Wolf-Michael Catenhusen [Mitglied des Deutschen Ethikrates]: Herr Gaudray, bitte.

Prof. Dr. Patrick Gaudray [Mitglied des Comité Consultatif National d'Ethique (CCNE)]: Yes, personally I would totally agree with Mr. Gianaroli on this particular topic. In France, you know, in the French law, you can be an object of law or subject of law, you cannot be in between, and that's why the legislators have decided not to give any status to the embryo. They don't want it as a sort of enigma, it's actually addressed as an enigma, it's, there is no possibility to define it, so it's clearly in the human lineage, it's not a thing, and it deserves respect. And I think that respect doesn't mean that you have to consider only the embryo. The embryo is part of the history of humanity, so the embryo also has to be considered in the family history, it has to be considered as having or not having a link in what we call a parental project which is a, I don't like that at all, but since I have no better word, the embryo is nothing by itself. Okay? The embryo, well, to me, I should add it's not the opinion of the committee. Therefore, I think that respect has to be considered as respect for one particular embryo in a family of embryos and in a family. Full stop. You cannot, the fact that you have respect for a family history, respect for the born, the child to be born, I think we very often forget this dimension. We are also speaking of a child who will be born and will have a life in a family, etc., etc. We also have this respect. So that conditions, actually the balance that we have to make, which is never good, when you make a decision, is it a good decision, a bad decision? I mean, it can be good or bad, depending on the time it has to be made and depending on the family it will be made in. So I think there is no good answer to your question, and I am totally convinced that I haven't answered you question. I want people to open their minds to questions, you cannot just remove a question by saying, well, what do you do with that and close the debate. The debate on the embryo will never be closed to me.

Wolf-Michael Catenhusen [Mitglied des Deutschen Ethikrates]: We have an interesting interdisciplinary dialogue about ethical questions even with the scientists active in this field. Wir haben jetzt noch 12 Minuten Zeit, deshalb jetzt noch bitte kurz noch mal mit Nachfragen, Frau Kollek, Herr Radtke, und dann hab ich noch eine kleine Frage selbst.

Prof. Dr. rer. nat. Regine Kollek [Mitglied des Deutschen Ethikrates]: Ich habe eine Nachfrage an Mr. Gaudray. Als Sie den Prozess der Präimplantationsdiagnostik beschrieben haben, haben Sie erwähnt, dass Sie diesen Prozess nicht weiterführen, wenn weniger als sechs Eizellen vorliegen, und nur dann weiterführen, wenn mehr als acht vorliegen, die befruchtet und kultiviert werden können. Meine Frage ist

nur, ist das richtig? Habe ich das richtig verstanden? Offensichtlich ja.

Meine zweite Frage richtet sich an alle Beteiligten. Ich habe noch nie Informationen darüber bekommen, was mit den heterozygoten Embryonen passiert, wenn man eine rezessive Erbkrankheit diagnostiziert. Dann hat man ja homozygote, die möglicherweise erkranken, und heterozygote und Embryonen ohne jedwede Mutation. Werden heterozygote Embryonen mit der gleichen Wahrscheinlichkeit übertragen wie Embryonen ohne Mutation, ohne Heterozygotie?

Dr. phil. Peter Radtke [Mitglied des Deutschen Ethikrates]: Wir haben eine ganze Zeit nur von den Fällen gesprochen, wo Behinderung durch die PID verhindert werden soll. Gibt es aber eine Möglichkeit, wo es ein Grenzfall ist, und ich wüsste gerne, ob da ein Meinungsbild in Ihren Ländern besteht, und zwar die sogenannten Rettungskinder. Das sind Geburten von Geschwistern, wo das Geschwisterkind behindert ist und man hofft, dass durch zum Beispiel Nabelblutspende das behinderte Kind geheilt werden kann. Wie sieht es damit aus? Da wird ja dann ein Embryo beziehungsweise ein Mensch produziert als Ersatzteillager, also nicht um seiner selbst willen, sondern für einen anderen Zweck.

Wolf-Michael Catenhusen [Mitglied des Deutschen Ethikrates]: Ich wollte dazu auch noch vielleicht noch einmal die Nachfrage stellen, dieses *tissue typing*, ist das eigentlich schon mal evaluiert worden, inwieweit tatsächlich auch dieses Gewebe des neugeborenen Kindes dann auch in das kranke Geschwister – es geht, glaube ich, nicht so sehr um behinderte, sondern um kranke Geschwister – tatsächlich vorgenommen wird? Und eine letzte Frage noch an Herrn Gianaroli. Vielleicht noch mal kurz und prägnant von Ihrer Seite aus: Wie schätzen Sie die Perspektiven der Verwendbarkeit von Blastozystenbiopsie in den nächsten vier Jahren für die PID ein? Jetzt fangen Sie an, Herr Gianaroli.

Dr. Luca Gianaroli [Vorsitzender der ESHRE]: Well, I would like to go for the last one, of the blastocyst. Why? I think that for HLA maybe (Polish?) well they have the largest centre in Europe so I think that should go for his answer. So what is going to happen to blastocysts use and cryopreservation? This is the question. What I foresee and the data really shows trend, so a trend usually in our field becomes reality, it is for a certain number of years because, don't forget that, when we have half a million cycles every year at our registry, it means that we have millions of fertilised eggs that are followed and registered. So the trend is in the direction of blastocysts, both, for routine IVF and ICSI with the aim of reduccing the number of twin and triplet pregnancies with the aim of, of course, keeping the pregnancy rate as high as possible. Using this technique and having this technique more and more available, PGD will probably have the best place in terms of the stage of the embryo, the development at the blastocyst stage. So I can foresee an increase in this technology, in this technique. The only limitation was, and I insist in saying was, until last year on cryopreserve blastocystes, but now it seems that this problem is overcome via vitrification. So if the technology goes in the direction I showed you, I can see that blastocysts would be the stage at which embryo biopsy will usually be carried out. Also because it is the only stage at which a part of cleaving embryo you can reassess also, the male derived problem. That you cannot do on polar bodies.

Wolf-Michael Catenhusen [Mitglied des Deutschen Ethikrates]: Thank you. Herr Devroey.

Prof. Dr. Paul Devroey [Zentrum für Reproduktionsmedizin am Universitätskrankenhaus Brüssel]: So in fact if you think about HLA typing, this is probably one of the most difficult questions which is not really related to PGD. We

had a very long discussion in our department before we started because it was an argument against instrumentalisation. I think that is a very important point. But after seeing different patients, we decided to go for it after each individual approach. Because the point is that women convince us that if you take care of a sick child you would also take care of the newborn child. Where fetal cord serum is used to cure the sick child. In fact if you think about it, it's having no child because it will die or having two children, one which will be cured and another one which will be healthy, that's the reason why we do it. We have transplanted a lot of fetal cord cells.

Prof. Dr. Emily Jackson [Vizevorsitzende der HFEA]: In relation to HLA typing, yes, there are cases in the UK where the umbilical cord has saved existing siblings' lives, so there are cases where that has worked. And in relation to allowing it, obviously, lots of people want more than one child anyway. And you can continue to have children in the hope that there will be a tissue match with a one in four chance of success. This just enables you to get that decision right. And so people have children for lots of different reasons, commonly, in the cases that we have had, people want more children anyway and there is every evidence, that they are, they fall in love with a new baby as soon it is born and love that child tremendously?. We have no cases in which that is not the case. And just in relation to harm, as I think my colleague is implying, the harm of being born into a family which has just experienced the death of a child, if a child is born naturally and not a good tissue match, is a harm that we know a great deal about. It's horrible to have a dead sibling and it's horrible for parents to have a dead child.

Prof. Dr. Patrick Gaudray [Mitglied des Comité Consultatif National d'Ethique (CCNE)]: In France we have in fact also the possibility of the saviour baby but it is only secondary to the diagnosis PGD for the illness which was there in the first place. So it can only come second, you cannot only test for a child if you have not tested first for the mutation which was present in the family. So it's also open. Concerning heterozygotes, I think it is a very important question, but I must confess that I am not totally clear because it refers to a previous opinion of the committee which did not deal with PGD but with the status for cystic fibrosis a heterozygote person who are carriers, and can we say that. So I think that heterozygotes, since it doesn't affect the condition of the baby to be born, the egg should be reimplanted, with no problem. The problem comes when the baby is born, what are we entitled to say to this new person about his genetic status and the fact that he is among the people who transmit this disease? So it is not something which is totally closed once more, but for the reimplantation of the embryos and it doesn't affect the embryo, it should be possible to be reimplanted.

Prof. Dr. iur. Edzard Schmidt-Jortzig [Vorsitzender des Deutschen Ethikrates]: Herzlichen Dank Ihnen, Frau Jackson, Mrs. Jackson und Ihnen, meine Herren Kollegen, für Ihre Hilfe, die Sie uns geboten haben, Erfahrungen aus Ihrer Regulierungssituation, aus Ihrer gesellschaftlichen Diskussion heraus uns weitergegeben haben. Herzlichen Dank.

(Beifall)

Wir haben hoffentlich viel Bereicherung für unsere eigene Meinungsfindung da herausgezogen und wünschen Ihnen ein gutes Nachhausekommen, insbesondere gilt natürlich der Wunsch, dass Sie nicht von irgendwelchen Schneekatastrophen am pünktlichen Weiterkommen und Nachhausegelangen gehindert sind. Herzlichen Dank und gute Heimfahrt.

Im Übrigen danke ich Herrn Catenhusen für die souveräne Leitung unserer Anhörung. Er hat eine Punktlandung hingesetzt, um Punkt halb

sechs sind wir fertig. Herzlichen Dank, Herr Catenhusen. Damit ist unsere öffentliche Anhörung zur Praxis der PID in anderen Ländern beendet. Vielen Dank und guten Heimweg.