BMS101 Forum on preimplantation genetic diagnosis and preimplantation genetic screening: Murdoch University May 16, 2013, ECL1.

Dr Jim Cummins – Good afternoon everybody. Thanks to all the students and guests and University people who have turned up to watch this forum. We've been running these forums for about twelve years now in BMS101. We've had a diversity of topics ranging from surrogacy to inter-country adoption, to stem cell research, to same sex marriage. The same- sex marriage one was a real doozy. This (on screen) is the program that's going to be running today. It is going to be available on Lectopia, hopefully both as screen capture and video capture so you can see what's going on in the theatre as well as just what's on the screens. Before I say anything more I'll hand you over to Dr Anne Jequier who is going to be chairing the session and you can see the program up here on screen.

Dr Ann Jequier – Well hello everybody. It's lovely to see such a large turnout. Genetic disease of course is becoming an increasing problem that we face in infertility clinics and its management is not only problematic technically but also ethically. We've got a program this afternoon of a number of experts in this field who are going to talk about genetic disease, particularly in relation to infertility. Our first speaker is Dr Itziar Rebollar-Lazaro who is the Senior Embryology scientist at Hollywood Hospital at their infertility clinic. Itziar has worked in all sorts of different places including Mexico and must have had a wonderful life. I look forward to her talk entitled "Overview of how PGD fits within a fertility clinic: techniques available for PGD/PGS, possibilities and ethical limitations."

Itziar Rebollar-Lazaro – Hello everybody. Thanks for the introduction and thank you Jim for the invitation today and for letting us share our experience in the IVF clinic with PGD. First of all I'm going to start with a little bit of a reminder or refresher of human genetics, just some basic DNA stuff to get you started which should help you with the rest of the forum today. Human DNA as you know is arranged in 22 pairs of autosomes plus one sex chromosomes which you can see here in this beautiful fluorescent colour image of the 22 autosomes plus the X and Y chromosomes here. We know that the human genome has approximately 3.3 billion base pairs, the base pairs are represented here as well, the ATCG which we are all familiar with and they are the building blocks of our DNA. There are more than 20,000 human genes. These genes are like the words of all of the information that we require to have all our cells function, how to make a human beings. It would be like all of the text encoded like an instruction manual of how to have a life. These genes are surrounded with non-coding DNA which can be remaining from evolution or it can be different sizes, it can be quite variable between people and it's not informative but it can have it's uses as well. There can be multiple variations of the same gene, so as we were saying, we have an instruction manual to produce human life, well if we all had the same information to make

a whole body, why are we all different? Well because there are different variations within the words, even if it still has the same content to have the information to make a human being, there can be variations between the genes. These are the alleles. And there are different patterns of allelomorphism so if we add up all of the variability between the different genes like tall, short, blonde, brown plus all of the differences between the non-coding sections of the DNA, all of these different sizes and styles, we have the different haplotypes. And we also know that genes are susceptible to mutations. Machinery within the cell should be able to repair any mutation so every time there is a cell division the DNA is susceptible to actually being altered or there can be mistakes. These kinds of mistakes should be able to be fixed or sometimes they are not. Most of the time the mutations that do actually stay because they are not repaired will be lethal, especially if they are in any genes that are encoded for anything that is of vital function, anything for the most basic cellular functions, these will not be compatible with life and it will be self limited and it will be lethal. However some will be beneficial and that is the basis of evolution as you all know, the changes in genes can give us more variability and it also gives us knew characteristics as well. And some will be non-lethal so they will stay, they will be able to be transmitted but they might be detrimental such as the case of oncogenes where we have the development of cancer for instance or regulation of the cell cycle which can be effected, and also the single gene disorders and we will be talking today a little bit today about conditions that are caused by a mutation in a specific gene.

A single gene disorder is a condition that is caused by a mutation in one specific gene. In humans there are more than 4000. They are usually congenital so they are present from birth and in some cases they can be developed in a late onset kind of fashion but the person carried that mutation from birth. They are usually rare and that means that one person will be affected out of several thousands or millions, depending on the kind of disease. And they are heritable so if the parents have it there is a possibility that it will be transmitted to the next generation. There is also a possibility of the mutation being spontaneous so if the parent is not carrying it there will be mutation that takes place either in the germ cell or once the embryo has been formed and the mutation will be apparent at the first generation in that child. Mutations can be dominant, recessive, they can be carried on the sex chromosomes, some can be related to unique parental disomies and errors of imprinting, I won't go into too much depth about this, I'll just give you a brief outlook of what I mean.

So if we start with a autosomal dominant and sex linked conditions and a couple wants to have a child but one of the couple suffers with a disease. In this case it can be the female or the male that is effected with the condition and they have a fifty percent chance of having an effected child. So the kinds of diseases we are talking about are usually debilitating conditions, as we said, they are compatible with life so this child can be born but they will be developing some sort of phenotype sooner or later in their life. There are metabolic diseases, neurological, muscular, and intellectual disabilities. It does affect the quality of life and sometimes it is associated with shorter

lifespan. It is important to remember that one of the couple will be affected with that condition. As we said there are thousands of them but here is just a short examples of some names that represent some of the diseases.

Then we have the autosomal recessive conditions. In this case both the parents are carriers of the condition and they have a twenty five percent chance of transmitting this condition to a child. So both parents are carriers but they usually do not have any phenotype so there is no symptoms of a condition. So how do they know that there is this chance of having a child with the condition? Well usually they have already had a child and they have discovered that they were carrying this mutated gene and that in combination when they have a child there is a chance of it having this condition. Sometimes they can also figure it out with routine screening, especially for cystic fibrosis because that is the most frequent one so there can be routine tests for some members of the population, or in general there are thousands as we said and not everyone having a child gets screened for everything because it's not what we do. So there's this group of people who have a chance of having an effected child. Then if we leave behind so a second the genetic level we can talk about things that can go wrong with the whole chromosomes, what we call chromosomal aberrations.

So we can have mistakes in the chromosome, numeric or structural. Numeric means that we have the wrong number of chromosomes, which is an aneuploidy, or structural when the shape of the chromosome is mixed and matched instead of what it should be and we have what's called a translocation. So in this case we would have a couple who is trying to have a child and for some reason they keep having miscarriages or they are just taking much longer than the regular population – they don't know what's going on. So in this case we know that usually their biological clock of the female's ovary is quite strict so as women age, their ovaries age as well and when ovaries age they lose the capability of doing the splitting of chromosomes of the daughter cells efficiently so they can lead to an aneuploidy cell. So we can have more eggs that are aneuploidy so they have the wrong number of chromosomes, which will be leading to aneuploidy embryos. This can also happen in meiosis or even in the first round of mitosis. In this case we will have an aneuploidy pregnancy. For most of the chromosomes, for instance, if we have three chromosomes that are only this large or ones up here, that will be self limited and will not be compatible with life, but there are some aneuploidy's that are actually compatible with life such as trisomy 21 and 13, some wrong numbers of sex chromosomes, some of them will lead to late miscarriages or even live births.

We also have another kind of couple when they struggle to have a child, they keep having miscarriages and they don't have a child. In many cases a doctor will recommend to have a karyotype. So normally, a normal karyotype would look something like this with two chromosomes or each plus a sex chromosome, but in some cases we can see that even if the whole information is complete, here there is something funny. So instead of having a short one and another short one here, we have a long one and there is something missing. Well this chromosome got stuck to this one and even if

that person actually has all of the information that she needs to actually… like the book is complete, lets say that we have as we were talking about, an information manual for how to make a human being. So it has all of the chapters, however chapter 9 is before chapter 8, so you just have to read it upside down and it is a bit confusing but it is fine to make a human. However when they are trying to make these gametes, that means eggs or sperm, we have a problem because I might be passing on two chapter 9's and no chapter 8. So there is no information that is correct to actually be able to make a human being anymore and that's why this woman keeps having miscarriages because the information in not complete, even if she had it all complete because it was misplaced, it doesn't go on to the next generation complete. So they have quite a big chance of continuing to have miscarriages instead of having a normal pregnancy sooner. In this case it can be both the male or female that can be affected with a translocation. So for all of these group of patients that are carriers of a specific condition, the patients that have a higher risk of having an aneuploidy pregnancy or patients who carry a translocation, their only option of what's available traditionally is prenatal testing. So a couple who doesn't want to transmit any of this genetic situation to their offspring can have the pregnancy tested through CBS or with an amniocentesis a bit later, where we're taking a sample of the placenta or amniotic fluid and that is tested so they can do a genetic analysis of those cells and see what's going on. But of course if that pregnancy is abnormal or effected with a condition then the only option that this couple would have is to have a termination of the pregnancy. So even if a termination is legal, for a couplet that is trying to conceive or very keen to have a baby because that's what they are together trying to achieve, it can be a heartbreaking and ethical dilemma. In many cases, having a termination because the possible child will have a disease that you already have can be quite an emotional struggle. So this is less than ideal for most couples.

We're going to leave the genetic issues just for a second and we're going to talk about what we normally do in a fertility clinic. So we have the same kind of couple, they're just trying to have a child just like the previous ones we had in the images and in some cases the way of actually getting to have a baby can be a bit harder than expected, it can be quite bumpy, and so they have to come to the fertility clinic to get some help. There can be some less invasive options for couples such as ovulation induction or IUI's where we only bypass some of the problems they might have when it's just like a mild case of infertility. We have other more invasive and more reduced currently, which are the combination of retrieving the eggs from the ovaries, doing the fertilization outside of the body and then putting the embryo back. Ideally we should put one or at tops two back, but also as you know there is also the possibility of the octomums and this kind of thing that is very popular in the news. And we also have the technique that allows us to freeze both gametes, eggs or sperms, and also embryos. So with all of these techniques, we know that we are getting quite good at retrieving the eggs, inseminating the eggs, creating the embryos, growing the embryos for up to six days, so keeping the embryos alive and happy outside of the body. We also have learned a lot about embryos, how resilient they are, how they can be biopsied, they can be

frozen and they do survive. So we have lots of knowledge about human embryology and what we can do with the embryos.

So if we mix these two together, all of this technology that we have already developed with the need of these couples that do not want to have insemination but they don't want to have a child affected by a specific disease or with an abnormal pregnancy, then this gives rise to PGD and PGS. So these are the genetic testing of an embryo before it is put into the uterus. So we just need to create the embryo outside of the body and culture it for a few days so that we can take a sample from the embryo. So this is what human embryos look like on day 1, day 2 they have divided a couple of times to a four cell stage. Day 3 to eight cells, a blastocyst where it jumps a lot with a quick cell division between day 3 and day 5 when they reach around one hundred cells or more. Hatching blastocyst is the shell is being left behind and here are some cells coming out, more cells coming out until it leaves the shell behind. So usually this is the stage when we would want the embryo back in the uterus because it is time to implant. So traditionally we have been putting embryos back in the womb on day 3 or day 5 and it is also possible to take a small sample of the DNA of the embryo at those stages. Something that is not that informative but can be done is to obtain the complimentary information from an egg by removing the polar body, that is after meiosis this structure which is the polar body will contain half of the chromosomes from the mother which will be complementary to the one which will be forming the embryo. So if we remove that and we know that this is normal then this should be normal as well, however this is quite limited, we are only looking at the version from the female and not from the male and it is before they started dividing so if there are any mistakes that happen later they will not be accounted for. The same thing with a zygote, we can take the first and the second polar body after meiosis too, but again it's quite limited. However if we wait for a bit longer, like I said we're good at growing embryos, so why not wait? We can do a biopsy and remove one or two cells of an egg cell embryo but we prefer to do a biopsy on day 5 or 6 when we can take up to five or six cells. So we have six copies of DNA and the remain of the embryo will be left behind and we can freeze it, transfer it and it survives the biopsy. It's just like biopsying yourself when you take just a little sample from you but the rest is fine. This is the video, which hopefully will work.

This is a video showing how we do our biopsies at Hollywood, we do them on day 5. So we have micro-manipulation tools that allow us to handle the embryo. They have around five cells being held. We use a laser, which you cannot really see, but you will see just little movement here. So pretty much we're just like helping to stretch the cells in a way that we can remove them from the rest of the embryo. You can see that there is a small hole there and this is the tissue that we removed and one hour later the embryo has healed. Pretty much you should not be able to tell that there was a biopsy, as long as it's a strong embryo it would be like surgery; if you have someone very sick and you do surgery on them they might not survive. But if you have a strong person there shouldn't be a problem to actually go and have a procedure, well same thing here. If an embryo is strong it should survive a biopsy and the freezing and following processes.

So now we have a sample from the embryo, what do we do with them? Well we do our genetic testing. We can test for genetic conditions or for chromosomal aberrations. So when we're looking at the gene level we do what we call PGD and when we're looking at the whole chromosome it can be both for a ? translocation, we do nowadays, mostly CGH. So if find that the embryos are effected with a condition of they are abnormal, as in the number of chromosomes then they will not be transferred and if possible they can be donated for research, if anything.

So what is PGD? It is a PCR based technique where we are looking at one specific point of our DNA so we're just focusing with lots of detail into one specific region that contains this mutation. As we said, it is only for couples that we know that carry a specific condition so that we know exactly where it is coded. We know if it was a protein that had shrunk, we know if it has been mutated and we can look at the detail just there. So we have to build a family tree and we can create the test from that specific family once we know exactly where it is. So we need to also look at the flanking areas of the gene. So lets say that this is the mutation, this is the gene, a healthy one and the mutated one. As we said, we're working with a very limited amount of DNA, we're just using around five or six at tops, so there might be some problems with amplification with the DNA and it might not be very reliable just to trust… to find or not, the mutation. So for that reason what we would do is also use the flanking areas. As we said, every gene is surrounded by non-informative DNA that can be different between people, so we would use that characteristic to actually make our linkage test and we would be able to determine whether we have the affected or non-affected alleles within the embryo. So only the embryos that are healthy will be transferred into the mother.

Then we have PGS and the screening for translocations. A few years ago we were still doing this technique which at lease in our clinic we don't do anymore, which is called FISH – Fluorescence In Situ Hybridisation and it is a limited test that looks at some of the chromosomes and it is limited because we use fluorescence and fluorescent colours and we can only see so many colours in one single slide. So here is how it would work; here we have the DNA of our embryo and we have a fluorescent complementary sequence that we add to our cells – our biopsied cells that we separated from our embryo. So this red DNA will match complementary to our embryos DNA, it will just be like one flag saying that here's where the chromosome is, and then when we look under the fluorescence microscope we can count the number of signals that we have of each of the colours and we know which colour means which chromosome and we know if we have two or more or less. And in that way we can know if the embryo is aneuploidy or not. We can also design specific probes for translocations. So we said that in translocation we have bits and pieces of the chromosome missing, we can count how many tops and bottoms we have of each and then we can see if the translocation is present or not. So this technology was good and was used for many years but it was limited, for example we were not looking at all of the chromosomes and second because there was a sense that we might be having a bit of a high

false positive rate so for that reason, a new technology has been looked for a while and what we're currently using which is much more reliable is what CGH.

CGH stands for Comparative Genome Hybridisation and it involves us to have a whole ?genome amplification where we have the DNA of the embryo and also a normal control DNA and we amplify. Imagine that we have the DNA of the embryo, which is my little book where we have the instruction pamphlet, and also the instruction pamphlet of a normal reference sample. So I know that this is the correct size. The number of pages that we have in a normal sample, this is how big my embryo should be. So because my sample is so tiny I need to amplify it so I can actually see. So I put both of them into a photocopying machine – one has green paper, one has red paper and I copy and copy and copy them so at the end of the day I should have a pile that's red and a pile that's green of the same size, because if a normal red is this size the green one should be the same size as well. If for any reason we have too much green or not enough green then we know that we have either too much information or some of the information is missing in the embryo. So this is grossly how it works at the molecular level. These are my copied pages and when I mix them and I put them in a specific slide called a microarray which looks like something like that – thousands of dots that represent each of the red sections for each of the chromosomes. Our machine can read this fluorescent that it is ?metred by the slide, and I can actually see the number of chromosomes and if there are any abnormalities, if there are any bits in excess or in defect. And I can see if my embryo is ok or not. So this is what we are currently doing but there is always the possibility in science of what is more or what is next and there's always science fictions as well hitting the customer's head around and making them think that we can do more things than we can actually do.

So what is currently available already, not for embryos but for humans in general, is DNA testing to get your risk factor for specific conditions. So I just need to send my saliva to our lab in America and in Australia and they can tell me that you have this chance and this chance of having high blood pressure when you grow old, you may have as high as 85% chance, you will die of a stroke before you are 50… they can tell all of these risks which are just percentages but because of the more information that we have about diseases and how they are encoded in the different haplotypes they can tell me which is my relative risk, and this is currently available. So if you combine that with a need or how people are eager to know what will happen in their lives, we have this commercial testing where the patients or clients will be determined as having a higher risk of a determined disease. For a few conditions it can actually be diagnostic, for example, you do have this gene that always lead to this kind of condition, but in most cases it will just be a relative risk. For most conditions as we know, it is not just genes, it is also their environment that determines if you will develop it or not. So they are advertising this kind of thing as a preventative measure so if you know that you have a risk of high blood pressure, then start not having salt right now you will avoid this risk. So that's a good idea in theory but the more information we have, of course insurance companies could have access to this

information so if you have a higher risk of something you will be having to pay a higher premium for if you were to have a condition that you already that you might develop. Also employers, why would I train someone that I know will be developing a debilitating condition in the next ten years, so that could lead to discrimination.

So if you combine this with the embryology and then PGD that we were talking about then we have the famous designer babies that people ask if that is what we do when we do the genetic testing of embryos and if we can choose more traits and can we make a taller baby or can we fix them, can we improve them? So as I was saying, we don't improve the embryos, we don't change anything, we just have a number of embryos and we don't use the ones that are affected and we do use the ones that are healthy. But it sounds very fashionable and sexy to have this designer baby thing. This could be leading to eugenics, we only have a specific trait that we think is better. If we actually googled eugenics or designer babies there are thousands and millions of entries that you can find out about what it should do or opinions. We also have blogs that say what is going to happen when they start doing it. Well it's not really happening but we are very concerned about it. And there's lots of science fiction about it.

So it's really not that simple for us to get to that stage. Many of these things that we are talking about are multifactorial, they are polygenic and there are many diseases that are very complex. So if people wanted to select for specific traits like height or hair colour, strength or intelligence, they may want to do that but it's not very easy. For example, with height, we all know that it is something that is inheritable, we all know that tall parents would usually have tall children, but even in that case, there are more than fifty genes that have been associated with height. Even with the variability within families, it hasn't been found that there is high variation, just like two or three percent within the genes. So really, traits like that that are already well defined it's not that clear about how it could work.

However with better understanding of the genes and the haplotypes and with more informative tools like better microarrays or something like that, it would be technically possible to do it, or to just increase the chance of having that specific trait. So if you are just increasing the chance, what do you want to choose? Then if I ordered a baby that was tall and smart and I don't get it, what happens to this baby? I don't want that. What's my return policy? And what is really a desirable trait? Why would brown be better than white? Or would tall be better than short? What's so desirable about that? What about evolution when all that variability is actually beneficial for any species. So if we start getting more uniform we might be losing some traits that would actually be better adapted in the future, so do we really want to lose traits that as a species would help us in the long term. And maybe by just selecting towards one end we might be losing some other traits that are not so obvious and we are being quite susceptible in case of any chaotic situation. At the end of the day this is not really what we're doing – it has nothing to do with what is currently available but this mostly the idea that people have a bout designer babies.

Dr Anne Jequier – We've got time for just one very quick question. Does anybody have anything they would like to ask? I would like to ask one question if I may? What do you consider to be the minimum number of genetic abnormalities we ought to exclude in an infertility clinic first visit?

Itziar Rebollar-Lazaro - So what kinds of diseases we should be looking for? Well the Reproductive Technology Council (RTC) makes it very easy for us because they will decide if if we can actually screen for that or not. In our case in WA it's quite regulated, however you could have an unlimited number of conditions that you could test. In my personal opinion I think you should have something that is quite debilitating and obvious condition that will definitely be present, that it's not just a chance. But I guess as a parent they might want to ensure the healthiest possible life for their child.

Dr Anne Jequier- Thank you very much indeed. Our next speaker is Sarah O'Sullivan who is a Genetic Counselling and Works at the Genetic Services in WA. She provides information to the patient and is probably therefore one of the most important people in the team. She graduated from UWA but has worked in New Castle, New South Wales as well as the UK and the USA.

Sarah O'Sullivan – Thank you Anne for the introduction. As Anne said, my name is Sarah O'Sullivan, I'm one of the genetic counsellors at Genetic Services of Western Australia, which is one of WA's only genetic service. So I'm going to talk to you today about genetic counselling generally, about the services in which I work, and then via a hypothetical case example I'm going to talk about preimplantation genetic diagnosis. So what is genetic counselling? It's one of those questions that when I tell people that I'm a genetic counsellor as my profession it's like ooh, how do I describe exactly what I do because it is quite a variable thing and there are different areas of genetic counselling. I've got a definition here that comes from the Australian Society of Genetic Counsellors Code of Ethics, which is quite wordy but also does give a pretty good overall description of what the process is. So "genetic counselling is a communication process which aims to help individuals, couples and families understand and adapt to the medical, psychological, familial and reproductive implications of the genetic contribution to specific health conditions." As I said it's quite wordy and quite variable in terms of what's it's all about and what we do for different patients can differ from patient to patient depending on the nature of the condition that they have and why it is that they're coming to us in the first place.

So to expand upon that definition a little bit further. The process integrates the following components; there's interpretation of family and medical histories to assess the chance of disease, occurrence or recurrence. So we might see someone who they themselves are unaffected by the condition that they know is in the family but they want to know what's my chance in the future of developing this condition, or if I were to have children what's the likelihood that I' might have an affected child? We provide education about the natural history of the conditions, their inheritance pattern, testing, management, prevention, support, resources and research. So there's a lot

of information that we provide to people. Often it can be a bit overwhelming and one appointment is not enough because we can throw so much information at them and it can take quite a while for that to sink in and be processed and become meaningful for them. So sometimes we will see people or families on more than one occasion. Other times it's a one off meeting. We talk about the inheritance pattern of whatever the condition is as Itziar was talking about earlier, there are different ways and hopefully at least some of you would have covered this if you've done genetics units, there are different types of inheritance patterns and they can have different implications in terms of passing on that genetic condition. We talk about, offer and facilitate genetic testing in some situations. I couldn't off the top of my head what proportion of people we do actually offer genetic testing to, but it's not necessarily everyone who comes in our door will be offered or proceed with testing; in some cases it's just not available. We know that a condition is genetic but we don't what gene or genes causes that condition, or technology s not to a point where we are able to test for a particular gene or genes. And for various reasons they decide that they don't want to have it. But for others they do want to have it so we work closely with diagnostic laboratories to offer that service where indicated.

We talk about management and prevention to some extent but we are usually or often one part of a multidisciplinary team that manages a patient or a family. We often find ourselves talking globally if you like or generically, but then patients often linked in with a specialist, so whether that's a neurologist, and endocrinologist, whatever 'ologist' that's appropriate to their condition. Support resources, that's often something that we will direct patients to, so again it's part of the information provision side of our work. We do some research but it's important to highlight here that research is not the main things that we do. The clinical service is our focus and often people o come thinking that research is what we do, they hear about genetic research in the media, genetics is a relatively new field of medicine and there is a lot of research that's going on and people often think that if they're offered testing it's to help our research and people often say "yes I'm happy to have that testing if it's helpful for your research" but really the main focus of what we do is to provide the clinical service to the individuals or families that we see.

Counselling is about promoting informed choices in view of risk assessment and family goals, ethical and religious values. People often think of counselling in the psychological setting, so sometimes people will say "I don't need counselling" but it's not about providing psychological support, a lot of the time it's about providing information and helping them to make decisions and make that information meaningful to the patient or their family. Then support where we encourage the best possible adjustment to the disorder in an effected family member or to the risk of recurrence in that disorder. So helping people to cope with a new diagnosis or the potential of a diagnosis, the potential of having an affected child, they don't have control over their genetics so how do you gain back some of that control? So we help them to work out their best coping strategies for dealing with the impact of whatever their genetic condition is.

As I mentioned, in WA there is just the single clinical genetic service. In different states there are multiple services that provide regional services to the population, but in WA if you need clinical genetics you are stuck with us. We are based in Perth but we have outreach clinics in various locations around the state, which I will move onto in just a second, but to name the main players in our organisation we have Clinical Geneticists, they are doctors who are trained in medical genetics; Genetic Counsellors like myself we come from a variety of backgrounds. I think it's fair to say that most people have some kind of science background but technically you need an undergraduate degree. If you have done a music degree technically you can become a genetic counsellor, I suspect you would struggle with the training that you then need to go on and do because after you've done your undergraduate degree you go on to do what is now a Masters in Genetic Counselling, a postgrad Masters degree. As I mentioned before we have laboratory scientists who we work with very closely but we are separate in that we are not behind the lab doing the hard yards to some extent, we're not doing the wet work if you like. As I mentioned we do have some research going on, we work wit researchers and of course we've got our Admin staff who make our day to day go more smoothly.

This is a map showing where we offer outreach services. As I said, we're based in Perth. The main location for us is at King Edward Memorial Hospital in Subiaco which yes is the main women's and babies hospital in Perth but as a clinical genetics service we are seeing everyone and anyone including men who sometimes think it's a bit strange to be coming to the baby hospital but that is an historic thing more than anything where we're based, but also the paediatric clinic is at Princess Margaret Hospital. Then we go as far as north as Port Headland, Geraldton, Kalgoorlie, Bunbury, Albany and the Perth Clinic also provides a service in Rockingham and Joondalup.

So why would someone come for genetic counselling? There are various areas of genetic counselling if you like and our service is divided quite discretely into three separate area, those being paediatric, familial cancer and prenatal which we call prenatal/general because general kind of encompasses anything that doesn't fall into the other categories and they tend to be the adult onset disorders. At the top left of the picture we've got an ultrasound picture and one of the things we do in the prenatal service is talk to people who have abnormal prenatal screening or diagnostic results. You've got a colon probably with lots of polyps happening on the bottom left there and that's about one of the familial cancer syndromes. Top right you have four people with achondroplasia, which is a dominant condition. And a little cartoon of what it looks like when we're in practice, sitting down and talking; talking really is the main thing that we do. So a bit more specifically, a very limited list of why people would come to us, I've got a list here of some common reasons for referral and I've mentioned probably most of those already and the one down the bottom there the preimplantation genetic diagnosis is the one that we're all here for today and that I'm going to focus on. I'm going to talk about it in the context of as I said earlier, a hypothetical case example. I know that when I was going to the lectures like this it was always the case examples that made things fall into place and make sense of

what it is that someone is talking to you about. And just to explain those pictures – you probably recognise Julia Roberts up the top. She is an ambassador for Rhett's Syndrome, which is a genetic condition, and we do see a number of children effected by Rhett's syndrome. You've seen a karyotype thanks to Itziar's presentation and this one you can see the red arrow down the bottom there pointing to the three copies of chromosome 21 and that is what a karyotype of someone who has Down's Syndrome usually looks like. If you're anything like me you might have to do a double take of that bottom picture to look closely and see that there's actually six fingers there which is polydactyly and can go as a part of numerous genetic conditions. When I first look at it, it looks quite normal to me.

So the case example, I'm going to run you through a hypothetical case of a couple who come to us and are wanting to access preimplantation genetic diagnosis. So I'm going to call them A and B, or we could call them Angelina and Brad, and they're wanting to have children. Angelina has a strong family history of cancer. You can see from the pedigree there that the arrow down the bottom here is pointing to Angelina. So just as a refresher, the circles are for the females and the squares are for men. If you see any black areas that probably means that someone has something genetic going on or they've got some kind of health condition. So in this family history, the coloured in bits refer to cancers. So the one person there with the bottom left quadrant coloured in, that refers to ovarian cancer and the ones with the top right coloured in, they are breast cancer. So before coming along for preimplantation genetic diagnosis and genetic counselling, Angelina's family was seen in the context of familial cancer genetic counselling. So her mum was diagnosed quite young with ovarian cancer, she passed away quite young. Her maternal aunt had breast cancer which was also diagnosed quite young and their mother also had breast cancer. We were able to provide genetic testing to this family because they fulfilled the criteria for us being able to offer that. We're not able to offer it to everyone, there are very strict criteria particularly in the context of familial cancer for who can or can't have the testing. But in Angelina's family it was possible and we were able to find that there is a breast cancer gene fault running in the family. You might have heard recently some news about BRACA I in the media, so in Angelina's family this was the gene change that was found, a BRACA I gene fault or a BRACA I mutation.

I'm putting aside everything that would have happened in the context of the genetic counselling for the BRACA I mutation because we are here today to focus on PGD. Because the gene fault was found in the first person, Angelina's mum, we were able to offer what we call predictive testing to Angelina. This is where you know that there is a gene fault running in the family, you know that you're at risk. You yourself are unaffected, healthy, asymptomatic but there is a chance that you could have inherited this and therefore and could go on at some point in the future and develop the condition yourself. So Angelina went through the process of predictive genetic counselling for the BRACA I mutation and it was found that it was positive, so she carries it. She then would have had a whole lot of information and support given surrounding that and the implications of that. One of the

things that would have been discussed with her is the option of a prophylactic mastectomy which possibly she would have gone ahead with.

So back to focusing on the PGD side of this. The picture here is similar to the one that Itziar presented earlier. It's showing the inheritance possibility of a dominant genetic condition. You can see that the female, depicted by the skirt and half coloured in, she is the mutation carrier. It is dominant which means that there is a fifty percent chance that any children she has, she would pass that gene fault on to and along with it, the predisposition to the increased risk of cancer. This is something that Angelina and Brad have thought long and hard about and have decided that this is something that they don't want to pass onto any children they might have in the future. So they're referred along and we talk to them about the issues surrounding that and what the options are.

The first question is to have children or not to have children? This is something where they have obviously made their decision already and in their situation they have decided that yes they do want to have children. But other people who have inherited a genetic fault or mutation they might decide that because of that they're not going to have any children. But that's not the case for Angelina and Brad. So the next question is would they have biological children or non-biological children? Non-biological children would include adoption, donor egg, donor sperm, donor embryo, but Angelina and Brad have decided that no we want to have our own biological children. So what are our options now? They could fall pregnant themselves naturally, as my boss would say, the old fashioned fun way. Or they could choose to have preimplantation genetic diagnosis which does involve going through IVF program which is usually something that infertile couples undertake. But in the context of preimplantation genetic diagnosis it is one for couples who are usually fertile but it is necessary for the procedure to occur. If they were to go down the prenatal diagnosis path you saw earlier in Itziar's presentation, prenatal diagnosis options of chorionic villi sampling (CVS) and amniocentesis to refresh your memories. They were the pictures of the woman lying down and the needle going into the stomach. So they would be conceiving naturally but taking that 50/50 risk that the child would be affected. As Itziar covered, if the pregnancy was found to be affected, knowing that they don't want to have an affected child, their option then is to consider stopping the pregnancy.

So for various reasons people can decide that that is not the pathway that they'd like to take. They still want to have biological children but they don't want to have an affected child and they don't want to have a prenatal diagnosis. So that's where PGD comes in, and that's what they have decided to go with. So the process itself is that they are referred along for genetic counselling to us. They are then seen at a fertility clinic and have consultations there. A feasibility study is done and this was touched on again earlier; is it possible to do the testing on just the one single cell for the condition that's in the family. I think the next talk from Kathy who is from the Reproductive Technology Council will talk more about this, but the next step in the process is for an application for them to go ahead with PGD is presented to the RTC and a decision is made as to whether or not it can go

ahead. I'm just skimming the surface there because Kathy is going to discuss it in more detail. Assuming that it's approved, PGD, the process that was described earlier, goes ahead, a pregnancy is achieved and a baby is born. Done. Easy, right? Seems straight forward. It's not Hollywood and there can be difficulties, challenges, hurdles to be overcome. So just to run through a few of those. In the first instance the familial mutation must be known, Itziar was talking about that earlier. A lot of people I think are under the impression that they can have PGD because there's something in the family. But we need to know in the first instance what, at a genetic molecular, what the fault is that causes whatever the condition is in the family. If that's not been done, then PGD can't be done.

There's a lot of uncertainty that goes along with the process; can the feasibility study be done? Is the RTC going to approve the application? Are there going to be embryos available for implantation? Because what if they're all affected. You've got a 50/50 chance of having an affected or unaffected embryo – what if it turns out that they're all affected? Then you're not going to have any to implant. What about the accuracy of the test? It's not one hundred percent, it's not perfect. And what is often recommended after a PGD pregnancy has been achieved, to ensure the accuracy of the result, prenatal diagnosis with is the CVS or the amniocentesis procedure is often recommended to be done to increase the accuracy of the result. Then what about safety? There is not a lot of long term data out there about what's the effect down the track on children and adults who are conceived and born after PGD. There have been a lot of studies that have looked into this and so far the risks tend to be associated with the procedure itself, so the IVF or ICCI, which I believe you have spoken about in other lectures, that process itself rather than the PGD as a package. The risks, although they may be increased on an individual level, or the absolute risk if you like, aren't enormous but it is something to be taken into consideration. There's no guarantee of having the perfect baby and I have put there that there are always going to be environmental influences. We are testing for one particular genetic condition; it's not a guarantee. I think Itziar said there are 20, 500 different genes that could possibly have a fault in them. That number's a bit fluid. We actually go with a higher number, around 30,000 genes, so there's possibility that there's something else in another gene that you don't necessarily know about and certainly hasn't tested for. And what about the likelihood of success? Different fertility clinics are going to quote different success rates, but what we talk about, because we're not talking from the perspective of a particular fertility clinic, we can only talk globally and we base our advise on a large study that was undertaken in Europe, we talk about take home baby rates. So often people talk about success rates in terms of a chemical pregnancy or a heart rate being identified on ultrasound, but the people who come to us, they really want to know what's the likelihood of me having, holding, taking home a live born unaffected baby? And the statistics are indicating that per cycle there is about an eighteen percent chance that that's going to happen. The flow on effects of that are that often more than one cycle is going to be necessary in order to achieve that and for some couples, they might go through cycle after cycle after cycle and it never happens.

So uncertainty and stress are highly linked and there are some other sources of stress associated with PGD including the physical impact on the woman, psychological, financial. It is a costly procedure, and of course ethical as Itziar was talking about earlier. I am going to end by saying that for most people, for a lo of people I should say, that even bearing in mind all those challenges that they will face if they decide to proceed down the PGD pathway, the thought of having and the hope of having their unaffected healthy baby is what can get them through and decide to go down this pathway. Thank you.

Dr Anne Jequier – We've got time for just a few questions. Has anybody got anything they are bursting to ask? No?

Dr Jim Cummins – we have a roaming microphone and we'll have time for general discussion at the very end. So if you've got questions save them up but make sure you shout them out so that we can hear them.

Dr Anne Jequier – Our third speaker in this session is Dr Kathy Sanders who is the Chair of the Reproductive Technology Council PGD Committee. Kathy got her PhD and her degree at UWA and is now an Assistant Professor in the School of Anatomy, Physiology and Human Biology. It's a great pleasure to have her come and talk to us this afternoon.

Dr Kathy Sanders – Thanks very much Anne and Jim for the invitation to speak and I also teach human biology, so the equivalent of what you guys do but from the UWA perspective. So it's nice to be talking to a different audience for a change. My job today is to talk about how and why preimplantation genetic testing is regulated in Western Australia. And to think about this we need to think about it in the context that it is used, IVF. So a lot of the regulation to do with PGT is to do with the regulation of reproductive technologies in general. I'm going to start with a brief history of preimplantation genetic testing and how it fits in with the discoveries of IVF.

So way back in 1968 rabbit blastocysts were first sexed, and in 1978 after a lot of work, by Steptoe and Edwards the first IVF baby, Louise Brown, was born. The advent of IVF led to the ability to do preimplantation genetic testing of embryos. Initially this was to look for sex linked conditions and it was an aside, as an alternative, to the prenatal testing that both Itziar and Sarah talked about. Instead of having to terminate, or potentially having the dilemma of whether to terminate, an established pregnancy, since embryos can be generated through IVF, why not test these embryos? Initially it was to avoid sex linked conditions, as Itziar described, particularly recessive sex linked conditions where the male is more likely to be affected because he only has one X chromosome, and if he's got the condition he will express that condition. So by testing the each embryo and looking to see whether it was a male or a female, specifically in this case they looked for the Y chromosome that identified it as being a male embryo, then they didn't transplant that embryo. However this technique at this time wasn't able to distinguish between normal female embryos and carrier embryos and also normal male embryos. Around about the same time Western Australia had legislation

written to regulate the use of Assisted Reproductive Technologies and at this point in time PGD was not allowed in Western Australia. Over the next ten or so years, the use of PGD extended from this initial testing of the sex of the embryo to include single gene disorders, to include late onset disorders like the BRCA mutation that Sarah has just talked about, to include HLA typing - that's tissue matching where a couple try to achieve a pregnancy where that embryo has a matching tissue type to an affected offspring such that they can use cord blood at the time that the baby is born for a stem cell transplant in the hope of treating a condition in the affected child.

Also during this time, in some cases, there was sex testing not for the purposes of avoiding a sex linked transmitted disease but for family balancing reasons. So, for example, you might have four boys and you want a girl or four girls and you might want a boy. By 2002, about a thousand babies had been born worldwide by preimplantation genetic testing. As I mentioned, the initial Western Australian Act that was written in 1991 and was enacted in 1993 did not allow preimplantation genetic testing in Western Australia. That meant that couples who wanted to make use of this technology had to go to another state where it was allowed, or at least it wasn't regulated. As a consequence of that so-called reproductive tourism, amendments to the HRT Act were permitted in 2004. Now lots of developments have taken place in the last eight or so years, and particularly the ability to screen, as Itziar was talking about, for more than a set number of chromosomes. So now with array CGH we can screen for all 22 autosomes and the X and Y chromosome and potentially with other array technologies you can screen for more than one gene, the single gene defect, so potentially multiple single gene defects.

How is PGD regulated in Australia? There are various layers of regulation within Australia. The first is at a professional level, where the Fertility Society of Australia which is a body of individuals who work in Assisted Reproductive Technology labs together with obstetricians, gynaecologists, andrologists and scientists develop clinical protocols and laboratory protocols for those who work within that area through a system known as the Reproductive Technology Accreditation Committee (RTAC). There is also NATA and they are the body that regulates diagnostic testing. So for example PGS and PGD are diagnostic tests, so if a laboratory was going to carry that out they need to be NATA accredited. The Australian Government also has a system, The National Health and Medical Research Council (NHMRC) who have a set of guidelines for a number of different things, particularly to do with ethical issues. With Assisted Reproductive Technology, there are ethical guidelines on the use of Assisted Reproductive Technology in clinical practice and research.

There is also some national legislation but that's primarily to do with regulating the research on excess embryos, so embryos that have been generated through IVF but are not going to be used for the couple to achieve a pregnancy. For example they might have already had one or two pregnancies, their family is complete and they don't want to use the rest of those embryos. Potentially they could be donated for research and there's national legislation regulating that. It also impacts on whether or not you can

generate an embryo for the purpose of research. For example research into therapeutic cloning, the generation of stem cells that are tissue matched to that individual who has a disease, for example.

In some states, Western Australia being an example, there is also state legislation. As I mentioned, in 1991 the Western Australian Human Reproductive Technology Act came about. This was enacted in April 1993 and the Act established the Western Australian Reproductive Technology Council. One of the Council's roles was to establish a code of practice governing the use of human reproductive technology including the practices, the procedures and the ethics involved, and to continually review and update those practices and procedures. It set in place a system of licensing for those individuals, the professionals involved in assisted reproductive technology, and systems to license storage of eggs and sperms and embryos and also the carrying out of various procedures like IVF, PGD and ICSI. It also made certain practices prohibited for example, you can't make a chimera embryo, so an embryo that's comprised of genetic information from a human and an animal, or an embryo that is comprised of genetic information from more than two parents. You can't commercially trade in gametes or embryos. At the time this legislation was enacted in 1993 PGD also was illegal.

This led to, as I mentioned before, some reproductive tourism to other states, particularly Victoria which allowed the use of PGD and New South Wales which didn't have any legislation and allowed the use of PGD. That of course lends itself to an additional cost and an additional emotional burden on those couples. It was somewhat ironic because the government of Western Australia would subsidise the cost of travel under an assistance scheme which allowed travel to be subsidised when you could not access particular medical technologies within this state. So in 2004 there were amendments to the WA Reproductive Technology Act. Under this amendment it permits diagnostic testing of embryos in Western Australia where the embryo is intended for use in treatment of a woman and the procedure is unlikely to leave the embryo unfit for implantation and there is a significant risk, and the word significant is important, of a serious, again the word serious is important, abnormality or disease being present in the embryo.

We can consider preimplantation genetic testing in two different ways; we can consider it as preimplantation genetic screening where the aim is to identify an aneuploidy, and Itziar has already described what an aneuploidy is where you've got too few or too many chromosomes. The issue with aneuploidies is that it increases the risk of miscarriage because the vast majority of aneuploidies are not compatible with life; there are only a few that are compatible with life. Under the current policy, for preimplantation genetic screening, Council approval is not required for eligible women. These are women who are at high risk of having an aneuploid embryo: so women who are over the age of 35 - as Itziar described the risk of aneuploidy increases with age and it becomes exponential after the age of 35; women who have had more than two miscarriages because the risk of miscarriages is associated with aneuploidy; where there's been more than two unsuccessful IVF attempts where embryos have been transferred, again, because the

likelihood of a failed IVF cycle is due to aneuploidy in the embryo; and where a couple or a woman may have been referred to the clinic by a clinical geneticist because they have a family history of aneuploidy but it wasn't caused by any translocations and other chromosomal rearrangements. So, PGS does not require specific Council approval providing the couple meet these eligibility criteria. If couples don't meet these eligibility criteria it would need to be referred to the Council to be considered.

Preimplantation genetic diagnosis is primarily aimed at looking at single gene defects as we've discussed and also translocations. There's an example of a translocation here where the chromosome 21 has been joined to the chromosome 13, we saw nice images of that earlier. Also sex linked conditions, particularly X linked conditions, so we can have sex testing where there is a medical reason for it. Council approval is required for each of these cases, so the clinic must apply to the Council and I'll talk about that approval process on the next slide. By the end of June last year there had been more than one hundred and ten cases approved for PGD in Western Australia since its implementation in 2004.

So how does the Council approval work? As Sarah discussed there is discussion with the genetic counsellor and a clinical geneticist and, after discussing the inheritance of the condition and talking about the various options, if PGD is decided upon then there is referral to a fertility clinic and discussion with the clinic counsellor who covers the implications of what actually undergoing IVF involves, because IVF itself is a fairly invasive and stressful procedure. The clinic will then undertake feasibility tests or refer the samples off to another clinic that is able to undertake the feasibility tests. Providing the feasibility test comes back as positive the clinic then applies to Council together with the clinical geneticist's report and the results of the feasibility test. The application is then considered by the PGD subcommittee which comprises an experienced embryologist, an experienced clinical geneticist, other scientists with relevant knowledge a consumer representative and members of the Health Department. That group consider all the evidence and they make the decision on the basis that there is a significant risk of the embryo having a serious genetic disorder and that that is going to impact on the quality of life of that individual and also the family. They then make a recommendation to the Council and the Council also consider this and potentially approves it. I highlighted the significant risk of being affected with a serious genetic condition. So the question is what is regarded as a serious genetic condition? There is variability in how individuals experience a genetic problem and their perceptions of disability is going to vary. All of that is taken into account in the Geneticist's report and the Council's decision making.

So that's how it is regulated in Western Australia, let's think about why it is regulated. And I guess the most cynical answer is because it can be. It's very hard to regulate reproduction the old fashioned way as Sarah put it, the fun way, when two people just get together and make a baby. We can't regulate that very well, but in the case of IVF and PGD we have a couple and a doctor effectively in a contract to make a new individual. As a consequence of that we have a duty to consider the consequences of the process to the

welfare and the interests of the person born and the men and women who are involved in the process. If we think back to the history of IVF, the use of IVF and PGD, it came about with very little animal testing. Most other medical procedures, drug procedures, undergo a much more rigorous testing procedure before they are started. We don't really know what some of the long term consequences of IVF and PGD can be which is one of the reasons why it is regulated so that there is accurate data collecting taking place so we can look to see what the future consequences may be. It is also to prevent the exploitation of the reproductive capabilities of men and women and any children born and to avoid the so called 'slippery slope' to avoid the production of children for the satisfaction of parents' desires for certain characteristics, athletic ability, height, music ability, IQ, for example. The risk of the so-called 'new eugenics' is that we decrease our tolerance of difference and disability and this can be a concern and an ethical issue to think about. There is variation in opinion and lack of consensus on many issues. One of the purposes, I think, of forums like today is that actually having good regulation depends on having well informed public discussion about what are the benefits of having a particular procedure, what are the risks of having that procedure and what are the potential concerns for the future.

I'm just going to cover a couple of concerns and controversies that surround the use of preimplantation genetic testing. We've said that in Western Australia there has to be a significant risk of the embryo inheriting a serious genetic disorder, so what conditions should be actually screened for? Well we've said a serious genetic condition, but how do you define what is serious? With the advent of new medications, people's life expectancy increases, so for example twenty years ago the life expectancy of an individual with cystic fibrosis was into their early teens, now an individual with cystic fibrosis because of medication can live into their thirties or forties. So how do you define serious? It changes over time. What about conditions that increase the risk of late onset diseases, so Sarah gave the example of the BRCA-I gene. That is a tumour suppressor gene, having a mutation increases your susceptibility to develop breast cancer by the age of seventy. So you might get it at 69 or you may get it at 30, so it increases your risk, but you may not get it at all. With the advent of new technology to potentially screen for more than one defect at a time, how much information should be available to parents versus the child's right to make up their own mind, especially for late onset diseases. So there's concern that a parent having too much information changes the child's right to an open future, to determine for themselves whether they want to know their risk of a particular disease in the future, for example.

Sex selection, I've mentioned that a couple of times. Under Western Australian legislation and under NHMRC guidelines, sex selection is acceptable for the purposes of avoiding sex linked diseases, so for example haemophilia. What about conditions that may have a genetic basis but may also have a strong environmental impact and/or the genetic basis isn't really understood at the moment, for example things like Autism, but we know that there is unequal sex incidence, for example males have about four times the incidence of Autism than females. Is it acceptable to screen on the basis of

sex to avoid conditions like Autism? That has been accepted and has been done. But what about family balancing where there might be four boys and you want a girl or four girls and you want a boy? Is that acceptable? At the moment under Western Australian legislation sex selecting on the basis of social reasons is not accepted. It is not accepted for the following reasons: that admission to life shouldn't be conditional on being a specific sex, that potentially it contributes to bias particularly against women, and that gender imbalance particularly in certain societal groups can lead to a shortage of women which impacts on men and causes an increase in conflict amongst men in access to women for marriage, for example.

The last thing I want to raise as a concern and controversy links to designer babies, and again we've heard a little bit about this. The issue I want to raise first is savour siblings. A savour sibling is a child that has been conceived such that they are a tissue match to a sick sibling and when they're born their cord blood will be taken to provide stem cells to hopefully provide a transplant to the sick sibling. Consideration here is the welfare and the interest of the child to be born. The likelihood that the medical condition is actually life threatening, so the sibling is likely to die and that there aren't other means to treat that child, and that the new child to be conceived through PGD is wanted in it's own right to be a child as a welcome addition to the family and not just as a source of tissue. Under the NHMRC Guidelines, savour sibling technology using PGD is accepted. I don't actually think it's been used in Western Australia and it's a bit iffy with our legislation, we can talk about that later if you'd like to. But another controversy with savour siblings is, that to an extent, it is designing a baby and the opponents to it suggests that it leads us onto that slippery slope where "well if you can match for these characteristics why not match for eye colour, IQ or athletic ability". As we've heard from Itziar, it's not possible to do that yet but at some point in time it could be. So these are the consideration that you as informed members of the public will need to be considering in future years.

In summary, we've discussed how preimplantation genetic testing is carried out in Western Australia, how it's regulated by the Reproductive Technology Council, that it's primary use is for avoiding transmission of serious genetic diseases and reducing the risk of aneuploidy in at-risk groups, that sex selection for non-medical reasons is not permitted and that we've talked about what new technologies and some of the concerns and implications of new technologies could mean, also what diseases and traits to screen for and how much information to reveal and to whom that information should be revealed. I've got some references if anyone is interested in finding out a little bit more. Thank you. Does anyone have any questions?

Question from the audience – not audible

So the legislation regulates clinics, people could potentially do things in their own backyard. You would never get it published because universities and publishing houses require any type of research to be published to have undergone Human Research Ethics Committee evaluation and approvals. So potentially these things could be done, we wouldn't necessarily know about it

but I don't know what the value of it would be and it requires huge amounts of technology.

Dr Jim Cummins – Thank you Kathy, I think we're going to move on. Anne has asked me to introduce our next speaker. You've probably realised that we've got company here – Damien, Briony his wife and Charlotte have come along to show you the outcomes of PGD.

Damien – I see the university are still using Apple Macs thirty years after they're out of fashion. Hello everyone, you've probably all met Charlie by now, this is Charlie or Charlotte. I'm Damien and this is Briony. It's getting towards the end of the day so we're going to try and get through this fairly quickly and keep it fairly light. Just as a side story, I was at a seminar the other day where the presenter talked for seventy five minutes non-stop, forty nine PowerPoint slides and I think for those students who have planned to do public speaking in the future I think one of the things to avoid is sitting down when you're doing a presentation which this guy was. So I always recommend standing and if you're worried that you're going to talk for a long time, I can babble on a bit, just get some Deep Heat and rub it around your groin area and within about ten minutes you'll be wanting to finish your presentation pretty quick.

Charlotte is almost two years old, so we started the whole IVF/PGD thing in the end of 2010, that's just the background. So kicking off. A brief introduction to my disability… I'm the one with the defective gene, Laing Distal Myopathy, it's a very rare form of muscular dystrophy, it's autosomal dominant and that's the gene. If anyone knows which chromosomal area that's in I'm impressed because I've got no idea. It's so rare and when we were first diagnosed with the disorder in the early 90's it was considered an orphan disease, it may still be. There were seven members of my extended family alive at the time, unfortunately two have passed since then that have had the disease. Around the world since then there has been more diagnosis I think in North America and Europe. More recently I discovered a whole branch of the family in South Australia through Ancestry.com a common ancestor who had the gene, so they've all just been going through the screening process and we just found out that my third cousin once removed has just got pregnant, we presume it's through PGD/IVF process in the Eastern States, so that's wonderful news.

So diagnosed in the early 90's and they weren't quite sure what to call it. I think at one stage it had been called Viking's disease but it was the wrong gene. In about 2003/4 Professors Laing, Lamont et al, there's a string of about twenty names on the paper if you're interested, rediscovered exactly what gene it was on, what chromosome it was on. It was named after Professor Nigel Laing himself, it was named after his brother and I think I have this right but I might have got this wrong, I think his brother passed away some time ago, it may have been from a muscular or neuro disease. So that's where it gets it's name from.

The disease is hereditary and autosomal dominant but it could be much worse than that; it's not life threatening in itself but it is progressively degenerative and also what we've discovered amongst our individuals in our family, it manifests itself quite differently across different individuals. So some of my family have problems with their hips and shoulders, I don't and my father doesn't. So people have problems with their feet and hands, my Dad and I do. Some of us are calf muscles, some are more or less ?mobile, some of us are looking progressively towards a wheelchair; certainly my father and I've got a second cousin who is in a gofer quite a lot. So mobility is different for different people. We're not quite sure what that is, whether its different expressions of the gene mixing with other genes from other parents, whether it's environmental, you know what we did as kids and what we raised or a combination or even if it's some epigenetic factors that are going on, we can't really tell. The reality is, as most of you would know as students, modern genetics is telling us that genes don't just switch things on and off, the whole process is a bit more complicated than that. SO basically part of our decision in the IVF and PGD process was that we could get a more mild form like my grandmother and my father, or more medium form like myself, or it could be a much more degenerative form like my cousins have unfortunately got.

In my particular experience with the disorder is that I've been clumsy all my life. It started expressing itself when I was about ten years old. I can remember walking home at about ten or eleven years old from the train and he noticed my gait which was very much what I call a Frankenstein gait, you can hear me coming down the corridor. I do tend to scare young women and children when I'm walking around the office. He noticed that I had the same gait as himself but this was in the 1980's and we had no idea, so he was trying to teach me to walk heal to toe "You've got to practice walking heal to toe Damien" which we now laugh at because it's actually an expression of the gene, it's actually nothing to do with learned behaviour. I suppose like many children I just couldn't get running. I couldn't understand why other people could go fast and I just couldn't seem to get it. But then once again, in terms of those combinations of genes it could have been that I was also an unco-ordinated child as well so you never know. For my Dad and myself the disease expresses itself in type I muscle atrophy in our claves so if you like, a tightening of the structural muscles which gives me really sexy legs actually. I had a girlfriend in university who said that I had the legs of a porn star which was pretty cool until twenty years later when I discovered that it was because of muscular dystrophy. Achilles tendon tightens, I have what I like to call manky feet which is a medical term, which is high arches, clawed toes and real lack of flex in our feet. It's kind of like spending your life in high heeled shoes without the heels. It leaves time to see a lot more tripping and falling on our asses, Dad and I trip and fall quite a bit. I avoid all stairs going down. If they can just make stairs going up I'm set, but I haven't discovered that yet so going down stairs I try to avoid or go very slowly. Also there's a weakness in the hands and that expressed in my father, he's not actually able to grip with those two fingers at all anymore.

The actual disease itself has been manageable for me, it's been the knock-on effects for me limiting my physical ability, I used to kayak and canoe a lot

when I was younger and do a lot of bush walking. A lot of that stuff now is out for me. I my late thirties and forties I started to stack on the weight. Also the other issue for me is the pressure on my toes, I've got orthotics and I'm getting some custom made shoes – picking them up tomorrow. Last year for example a blister that I got when we were doing a bit of bush walking in Victoria ended up turning into an ulcer, unbeknownst to me, and it took me about nine months to have that treated – back and forth to podiatry clinics.

So here's some more information about Laing Distal Myopathy – you can Google it yourself .com. I do actually have some links to leave behind if anyone is interested.

I just wanted to quickly go through my journey in PGD. So my journey as a man through PGD went basically something like this; find a willing partner, spend some intimate time in a quiet room with a cup, pay the bill, wait nine months and voilà. So that's really the process from the bloke's perspective, but seriously, the first challenge is obviously finding a special person. Even when you have a genetic disease and you're a mega nerd who can't get enough of Dr Who and Star Trek, now they're two huge challenges there alone. But I was lucky enough to find the right person that wanted to be with me and have children with me. So after that the process for us, even finding out that PGD was an option and our GP certainly wasn't aware about it and I was very lucky that I regularly see my neurogeneticist at Royal Perth, Professor Lamont and I said to her "I've met this wonderful person, we want to have kids. You know all about the disease, what are our options?" And she went through a bunch including amniocentesis and termination if we didn't want the child if it had the disease, rolling the dice and going fifty/fifty, sperm donation was another one to find another donor other than myself, and then she said "by the way there's just this relatively new technology, it's only been approved a couple of years ago called PGD. Maybe you want to go and talk to someone about that." So just knowing there's an option is your first step. I think the other speakers have already discussed this, the health screening process, we went to see Genex WA I think is the right term at King Edward and then of course speaking extensively to our GP. Explaining to the family exactly what PGD is "they do what with what?" so going through with our parents and extended family why we were looking at this as a choice. Finding the right IVF clinic; we were referred and decided to go with Fertility WA at Bethesda and the reason we got that recommendation was because of the Embryologist there Steve ?Jung and we're glad we did. He was awesome. He's not there anymore unfortunately but he's already done his job.

Then of course you have to go through the IVF screening and counselling process itself, so that takes some time and I'll come back to that issue because we did have some issues with that part of the process. Then of course there's WA Reproductive Technology Council approval that was just talked about. The IVF clinic handled that for us. We were a little bit surprised; we expected that we would actually have to front up in front of the Council with our cap in hand to explain why we needed approval but the IVF clinic all did that behind the scenes which was good but surprising for us. Then of course starting to build to genetic picture, design the PGD that was specific to

my gene and that involved our parents having blood samples, I think my sister went in and got a sample because she doesn't have the gene, it was all sent over to Monash. From my perspective being a bit of a science nerd, I certainly would have liked to understand that process a bit more and engage a bit more with Monash. Monash was across the other side of the Nullarbor and we didn't even speak to anyone from there but the IVF clinic probably thought that that was a good thing.

So once we'd done all that, that was the easy stuff in some ways, then it was letting the actual IVF begin itself. So as someone just explained, we said "we'll have IVF with the lot please" because this is what primarily what Briony went through; cycle control, first stop, hormone city, follicle stimulation, egg extraction, ouch for Briony, sperm extraction less ouch for me, the ICSI process was there – exhausted yet? Because Briony was. Then the blastocyst – take off two cells, send it over to Monash, couriered over on a flight two cells of each the embryos, we got eight in total that were viable sent over to Melbourne where they ran the tests. I presume you're familiar with ICSI, I've just put that up there, that's what I call one sperm only please process. Anyway, PGD was done, we got back the results which out of the eight viable embryos, four had tested positive for Laing's which is about right, 50/50, autosomal dominant. One had come back inconclusive which is one of the possibilities always in PGD so they just couldn't tell us conclusively, or with a degree of certainty is probably a better way to say that and three came back testing negative for the gene. But we were counselling all the way along the process. The test still has a percentage error in it and that ranged depending who we talked to from one percent to five percent, so there was still that minor chance that we got a false negative. But that was a fairly good result out of eight that we got three, we were delighted. And that ended up with what I refer to as "Ploppy Mark I" I get to name the unborn children, she gets to name the born children, it's a good deal. Ploppy Mark I, it was the best of the three embryos so we went with that and the other two went into frozen storage. Then, as there is with all IVF couples there was the nervous wait until we could test and come back and be absolutely sure that we were pregnant. So when I said "we're pregnant…with an alien!" I thought it was really cool but Briony didn't so… So after that we were handballed over to the obstetricians. So there's Charlie, still Ploppy at that stage, Charlie at that stage, because we decided to know what the sex was. Everything was going fine… I'll just say one thing though, we were a little surprised that there wasn't any follow up from the IVF clinic, almost as soon as we got from there we said goodbye and we didn't see them again until number two which I'll talk about later. So we were a bit surprised at that, we thought given that it was such an extensive process, ICSI, IVF, PHD that they'd want to do some sort of debrief with us about the process from out end and how things went emotionally and how things went physically and so on, but we just sort of ended up at the obstetricians and he was fantastic, Michael Brent who is at Murdoch.

So everything is going fine, until someone decides to show up seven and a half weeks early to surprise us. My wife was sitting calmly at work in Midland and (sounds of waters breaking) – the dam broke, they're still not using that chair to this day. My wife was working for WA Police, which is one really cool

thing about working for the Police is that you get driven in a police car, with sirens flashing etcetera all the way to the maternity ward. The funny story was that I got the phone call, I was at home, "I'm on my way" – I got all my bags, I'd read all my books, she'll need extra nighties… Zoomed in the car, go up to Roe Highway and saw a Police car with sirens going in the right hand lane going about 130ks. Zipped into the slip stream of this police car, zoomed all the way out, got to the turn off where the hospital was and that police car kept going and I hopped off. It wasn't my wife's police car it was some other police car going to an emergency, so I was a bit naughty but I'm sure they would have understood.

That was Charlie I think about twelve hours later in the NICU at King Eddies so that was all a bit nerve wracking for us. She got her first two nicknames in the first five hours; from me she got called Genghis Khan because I loved her little red Genghis hat, and then the first night she was in the NICU, the nurse called her party girl because she kept wriggling all night and she hasn't stopped since. That's her taking some rays…man. But we'll never know why she was early, there's a lot of speculation, some indication that IVF can have a causal effect in terms of premature babies but also Briony had a LEEP procedure and there is some recent research showing also that that is linked to premature births but also there was a lot of stress going on both in terms of Briony at work as well as some stuff going on my side of the family, the less we talk about the better. So we're never going to be sure what the reason was. Anyway, after a period of getting used to this… oh I expected more ooooh's there. That's all right, you're all still in your 20's so babies aren't cute yet.

We decided to go back for more, so introducing the competition, Ploppy Mark II coming to a maternity ward near you. So as I said, we still had two viable embryos without Laing's and obviously we found this side of the process a lot easier and smoother because there was no extraction, no ICSI, no PGD, there was just the cycle control and then the implantation. So far things are going smoothly, we at 18 weeks now. So we've got our 21 week scan and sexing scan on Monday week.

Some things we struggled with through the process; we struggled a bit with the IVF clinic's what we call infertility culture. By that we mean, understandably IVF clinics have a long history in dealing with couples with infertility. We didn't have infertility, that wasn't our issue. Randy buggers and both fertile as ? empire, we didn't have infertility issues but every step of the way we kept feeling like we were being treated like an infertile couple. So that was some frustration. As I used to say to them, "we're not an infertile couple I just have dodgy genes". The other issue that we had was that the IVF clinic wanted us to get the amniocentesis done so it could be tested for the gene and as you may know there's a small risk associated with amniocentesis in terms of miscarriage – we weren't going to terminate if Charlie had my genes so we didn't see the risk as worth taking. However unfortunately since Charlie's been born we can't seem to get her tested. So it's funny that we were encouraged to test her when there was a risk of miscarriage but we

haven't been able to get her tested since she's been born. So that's a slight issue for us.

Medicare – we were both in a financial position and obviously willing to pay for the PGD, some reasonably expensive but not ridiculous, but I suppose we were surprised to find out that Medicare didn't cover any of the PGD side of stuff, they covered all the IVF side of stuff and our question was my wife has done an estimate just in the last five years of both the health costs of both my father and I dealing with our muscular dystrophy and the equipment costs, a couple of hospital stays for both of us, orthotics, I regularly go to podiatry clinics in Freo Hospital, the list goes on and on, she estimates about one hundred thousand dollars between the two of us just in five years. The tax payer is primarily picking up wither through Medicare or through the rebate on private health. So the logic seemed a bit reversed to us, you're going to spend about six thousand dollars and we have a child as I think the previous speaker said, we could have had a child in the back of a panel van, and it could have had muscular dystrophy and it would have cost society hundreds of thousands of dollars potentially in the long term. So we found that a bit funny but as I said we were in a financial position for that not to be an issue for us.

The little not so quiet room, I'd just like to tell this to everyone because I've heard many men say it but no-one wants to speak about it. I can't understand why the IVF clinic sends you down to a room where you can hear everything going on and it's not just the IVF clinic we were going to but we've heard it with many IVF clinics. The walls are paper thin and you're meant to do your job into a cup and you can hear the ladies at the front desk having a chat and the two colleagues outside talking about how their golf went on the weekend and I'm supposed to get in the mood while my wife is sitting down having a ten foot needle stuck into her to get the eggs and I know that it's got to be fresh and warm and the swimmers have got to go and so… yeah, one of the things I've said to the IVF clinic is do something about your not so quiet room because it's an issue. And of course we have struggled with the issue of having a premi baby as everyone who has a premi baby does.

The things that have amazed and excited us; obviously that it worked. We still look at each other in wonderment sometimes that we had the lucky timing that the incredible technology and the policy settings have come together, it seemed to be made for us. If we had met even five years before it wouldn't have been a possibility so we just think we're so lucky. Obviously having a supportive family all the way through, extended family. That was fantastic for us, but most of all it was that the science and a fantastic bunch of committed scientists and health professionals and our pluralistic community allowed us to produce this miracle and of course the next miracle that's on it's way. Thank you. Any questions?

Dr Jim Cummins – we do have time for a few questions but there is somebody here who might like to say a few words. Julie Gilmore do you want to talk to the audience about your experience and Mitchel's?

Julie – for those of you that are stuck with me every week, you know who I am. And for those of you who aren't stuck with me you get the joy of me now. We have had some excellent presentations today on why we need to do PGD and as you've just seen the bashful one leave, I just wanted to stand up and explain what your options are if you don't go down that path. If you're sitting here now and you've heard all of this about genetic mutations and how we can test for genes that might make us susceptible to diseases, and you're wondering what happens if you say "No, not for me. I don't like needles, I like to take chances." My son has Duchenne muscular dystrophy. It's a genetic condition that occurs randomly in one in every ten and a half thousand boys. That is, you don't need it in your family, you don't need it in your germline, it just happens. PGD couldn't save us. PGD couldn't predict it. Probably half the really good gypsies in this world did not see that chid in their little crystal ball. But he's mine. If you had've asked me sixteen years ago when I looked like this, and I walked like this, how I would have gone with a child with a disability I would have told you that I probably would have been curled up in the foetal position on the floor and I would not get out of that until it was over. And that is what a lot of us think because that is what the media tells us. All we ever hear is bad news stories. Parent crying because their child needs equipment and they can't afford it. Parents crying because their chid is going to die. That's a harsh reality and unfortunately what PGD can' guarantee is that your healthy child wont die. That sounds harsh but that's the truth. I pick my son up from school every day and watch all of these high school students that are packed with hormones and chasing females run out in front of cars. My son is safer at that point from death than they are. So if you go into PGD and you look at this as an easy option to buy you an easy parenting route, think again. Because no matter whether your chid has a perfect genome or a genetic mutation, that will eventually break my heart, don't think I'm in denial, there is no guarantee that you will be a perfect mother, that you will have a happy family and that you will not outlive your children.

I have been blessed with fifteen of the most incredible years with my son. We have done things that probably we would not have done had he not had Duchenne. And I have learned things about life that I wouldn't have learned if he didn't have Duchenne. Most of those when the alarm goes off in the morning, go "God, one more hour." That child wakes up every morning and says "thank God I'm alive". So what he has taught me is that we can exist in this world, we can get up every morning and we can suffer through the week until Friday or you can all walk out of here today and you can squeeze every ounce of fun and enjoyment out of today because that's all every one of us has. If I had known about this condition, if I had been given the option to select for this mutation I would have missed out on knowing the most incredible kid I have ever had the pleasure of knowing. And with Angelina in the news at the moment, hen we look at things like the BRCA I gene, for all of those boys that grew up having wonderful dreams about Lara Croft, if her parents had been offered PGD would the world have been a better place without her? So that's what I'd like to encourage you to think about because this technology is fantastic. but you watch Damien give an amazing presentation too. Having a genetic mutation does not make you imperfect it just makes you different. And in some cases, Mitchel's mutation, and they

actually run it through the database, is the only child in the world with a deletion insertion non-coding inversion. If he was a Monet he'd be worth millions because he is so unique. So I don't think we as a society should write our fellow human beings off based on the fact that they're not all like us.

D Jim Cummins - it's pretty hard to do anything after that. I think all we do is thank Julie, thank Mitchell, thank all the speakers specifically Charlie who has left us to go running around outside and I thank all of you attending for coming along, giving up your time, giving up your classes, sometimes having to miss work. Thanks all of you. This is the last forum I'll be running, as you might know I'm retiring at the end of semester. Bye.