So just a general overview of metabolic liver disease and you know this is a little bit - talking about metabolic liver disease and particularly about transplantation for metabolic liver disease in Pittsburgh is a little bit - in the UK we'd have called it selling coal in New Castle you know because they know quite a bit about it here already. And now why metabolic liver disease as opposed to any other form of liver disease? There is a couple of things that are unique about it naturally. First of all if you happen to establish a diagnosis it's likely that for a family you'd be able to offer a significant prognosis. These are inherited genetic diseases, and for all of these families we would be able to provide genetic counseling.

But a very important part, particularly of the acute early present diseases is that often the first child is to some extent sacrificed to the severity of the disease. A child who is born with urea cycle disorder whose is undiagnosed and presents symptomatically with hyperammonemia will not escape unscathed. The child will have neurological sequelae of that initial illness. Now we can do things to make that child's illness better and we can provide them with ongoing care, but a very important duty is that if the next child in that family is affected the parents can make decisions before the child is born, or if the child is born and is affected we can start preemptive treatment and completely transform the outlook. For children with tyrosinemia we can prevent them getting liver disease altogether. So there is a duty to this child but there is also a duty to the next child if the family are continuing to have children.

Also for metabolic liver disease there is some treatment for all of these disorders that may be rather generic treatment but increasingly for a number of disorders, and I'll talk to some examples of this,

there is specific treatment. And obviously where there is specific treatment this is particularly important to introduce as early as possible.

What forms of liver disease? Liver disease sounds quite complicated but it's not really, there is only about 5 things that can happen to you as a result of liver disease and all of these clinical presentations can be caused by metabolic disease. And the point, I'm not trying to make long lists of conditions, but for example hydrops, not the only cause of hydrops foetalis is metabolic disorders. If you don't do tests on a hydropic infant to identify the cause then you won't recognize that small proportion who have metabolic liver disease, and hence their next child may or may not benefit from any intervention that you can make.

Similarly for children who present with neonatal cholestasis we have a very important duty to recognize surgery correctable conditions like biliary atresia as quickly as possible. But we also have a duty to recognize disorders that have a metabolic cause. So again we recognize that there are a number of disorders that may present with neonatal cholestasis and some are easier to diagnose than others. For example a 1 Antitrypsin deficiency, the one at the top, this is our commonest metabolic cause of neonatal cholestasis and the way to diagnose it is not clinical, although you can have clinical predictors, you know children with a 1 Antitrypsin deficiency tend to not grow quite as well as children with biliary atresia and they tend to have a high incidence of vitamin K deficiency and a high risk of bleeding, so there is some clinical parameters. But the way you diagnose a 1 Antitrypsin deficiency is do the test for a 1 Antitrypsin deficiency. It's not a marker of our clinical acumen, it's a marker of how good. So you need structured protocols for investigation of children with hydrops,

for the investigation of children with neonatal cholestasis so that you make a specific diagnosis, so that you may be able to offer specific treatment.

Increasingly DNA is becoming an important part of the diagnostic group. As I've mentioned and as you know many of these disorders are genetic and they present as a phenotype. There is relatively few clinical features that we can take to distinguish between one or another. So traditionally we've characterized the children with neonatal cholestasis where we don't know the diagnosis into two groups, those with low ggt and those with high ggt. And that's the best we can do with simple tests. Now we may know the family or the area of Pennsylvania that these families come from and that gives you significant diagnostic clues, but largely what we want to know is the specific genetic diagnosis. And this of course used to take years, you do a skin biopsy and these children grew up themselves and 10 years later somebody would ring you up and oh we've got an answer. But things have moved on now. You know with next generation screening now for our children with neonatal cholestasis - I've just taken - this is the recommended local next generation screening panel, screening for 20 genes associated with neonatal cholestasis, and the turnaround is here in 3 to 4 weeks. So a blood sample sent off quickly, we should be able to get the diagnosis in a high proportion of cases, not 100% because of the exegesis of the thing, but in a significant number and we'll be able to get that diagnosis quickly. So the availability of rapid turnaround genetic tests have transformed our diagnostic practice and have moved us much more away and I'll come back to this from doing invasive investigations. We reserve invasive investigations really increasingly for where you really need to do an invasive investigation. And for example liver biopsy for diagnostic purposes is becoming less necessary. And I'll come back to that.

A really very dramatic presentation of liver disease is acute liver failure, you know a true genuine medical emergency. And for a significant number of these children the only treatment they will require that will benefit for them is liver transplantation done in a timely fashion before the disease is recognized. But again there are some children in whom there are specific treatments that might rescue them from liver transplantation. And on the other side, there are some children who will not benefit from liver transplantation because they have progressive systemic disease. So as much information as we can get to help the team make the right decision for this family, the more information we can get before transplantation or at the time of presentation the better.

Now we all recognize there a couple of new disorders which we hadn't recognized before. And again the rapid new genetic techniques are really helping us in this. This for me was a child who was very important as a learning exercise, 19 month old child, he seemed relatively normal up to this, came from the east part of England. Came in with vomiting, cries, a little fever, just general vague malaise, he bruised a little so somebody did a coagulation profile and you can see below he had a significant coagulopathy and very high transaminases and 12 hours later he had really high transaminases and a huge encephalopathy, he was hyperammonemic, he was encephalopathic and he came across to us. With no obvious precipitant we actually listed this young man for a liver transplantation because we thought his chances of recovery were very low. And in fact instigating this list is he must have been listening because he suddenly started to turn around and he started to get better. So we reassessed the situation, took him off the list and a few days later ironically he was jumping around saying I want to go home, and antics.

And then a month later he did the same thing again. Now I think we were a little wiser this time because we knew what happened the last time. So we didn't list him for transplantation but I have to say it was quite scary, his INR went up to 6 and he was encephalopathic and hyperammonemic again. I have to say I was sweating a little. But he got better. And then he kept doing this, he kept doing this a few times. This is not normal, this is not normal. We are nastily suspicious people and you know he did, he wasn't receiving Paracetamol or Tylenol, for you guys you know. He was not being poisoned by his parents because you know obviously that was one of the differential diagnosis that we had. And in fact he is not what we call - he has a mutation in the protein NBAS which is very interesting, it's a heat sensitive protein and it seems to be involved in vesicle transport.

Now traditionally we dealt with children who presented with almost this recurrent Reye-like illness for those of you who remember Reye syndrome, if you are old enough to remember Reye syndrome. And we always thought that these might be disorders in fatty acid oxidation, but in fact this has nothing to do with fatty oxidation and it's involved in vesicle transport and yet it can present in a very similar way with a stereotypical recurrent acute liver failure.

The first presentation is exactly like our young man, was less than 2 years old and again this is very temperature sensitive and it presents with a fever, chills and they get better. Now we know that some children have had liver transplantation for this and it's been very successful, but also many of these children don't require, or escape without liver transplantation. I'm sorry this is what the NBAS protein is involved with, it's involved in retrograde transfer from the endoplastic reticulum to the

Golgi apparatus. So it was a completely unexpected defect to cause recurrent acute liver failure. And I'd have said well liver transplantation be done. But in fact the local team in Heidelberg have seen a number of these children over the years and had recognized the phenotype before the genotype and they were quite cool about managing these patients, and said oh just cool them down and give them Paracetamol, not we didn't give them Paracetamol, but cool them down and give them IV fluids and what we found is interesting is giving this group intralipid and there is no doubt - now this is not randomized controlled data but when this young man came back to us the next time we gave him some intravenous lipid, his recurrence, his recovery was much, much quicker.

And interestingly what tends to happen with this disease is that with age your admissions with recurrent acute liver failure get less. So I think with our young man he hadn't been admitted for a year the last time I was in Birmingham so I think with time his disease will get better. And when he is at risk throughout this life and it's very interesting that it's a whole new group of diseases that can cause recurrent liver failure and again with the new genetic mutations, our huge genetic technology we are recognizing more of these. Within the traveling Irish community in Dublin there was recognized a different group of recurrent liver failure and interestingly this seemed to require a high protein emergency regime and then they seemed to recover without requiring transplantation.

This is another rare disease of which I have no personal experience but again this seems to be very - this is another Golgi transport defect and again the recurrent team of fever sensitivity. These tend to be very sensitive to recurrent fever to precipitate their illness. And many of these diseases probably have a good natural history and in general we should probably, and I say probably, be avoiding

transplantation for this group because of their natural history. However I do know for the Ralph patients some children have had transplantation and I think in the context these are families who have lost 2 children with acute liver failure before the diagnosis was established. And I think in that setting when the next child comes through with recurrent liver failure I can understand that transplantation seems an attractive option if you've lost 2 children to this defect in the past. So I think in general we can avoid transplantation but for some families transplantation might be an advantage. And again that's I think with metabolic liver disease just because you've got one diagnosis does not necessarily mean the following treatment is right for you, there are individual and family and local circumstances that might determine different things.

The other area which we changed in the investigation of children with hepatomegaly, those in whom we require - we think they might have storage diseases, particular glycogen storage disease. Some of you, not many of you after looking around here, may look - remember how we diagnosed glycogen storage disease, we had to take a liver biopsy, you had to spend 3 weeks talking to the laboratory because of how you kept the sample. You had to keep a little bit frozen and a little bit not frozen, had to send it out. And you did a liver biopsy on these otherwise well children. I don't think I've done a liver biopsy on a child with glycogen storage disease for more than 10 years now because increasingly with the blood tests or increasingly with the DNA panels you can establish the diagnosis genetically in greater than 90% of the children. The management doesn't require histology to make the diagnosis and largely this is an outpatient diagnosis, an outpatient management of children with glycogen storage disease compared to 50 years ago where it was a liver biopsy, skin biopsy, etc, etc.

And again another good example of where we can be more selective about our invasive investigation.

So when we have diagnosed a child or a family with metabolic disease what options do we have? And certainly the first option is to be always the best one because of course I don't have to do anything, you have the dietetic and the nutritionist to manage this, and that seems to be always a good philosophy. For most disorders where there is a recurrent metabolic instability they should have an emergency regime to use at home. These children become sick when they start to become catabolic, so it's reversing that cycle or preventing that cycle that's key. So it's very important they continue to have a calorie intake, fasting is deadly to many of these children. So when they develop an undercurrent in this it's important we do not stop their feeds, in fact we keep them drinking, ideally a sugary mixture or a high carbohydrate intake, even if they can only sip that every 10 minutes so that we can keep some calorie and some carbohydrate intake to prevent catabolism.

And most children with glycogen storage disease, hyperammonemia, methylmalonic acidemia, etc., etc. they should have their own individualized emergency regimen so that their families or carers know what to do when they get an intra-recurrent illness. And that should be something that they take home with them at the time of diagnosis. And again that can be individualized and titrated to the individual.

The other thing is of course that we are treating children so whatever crazy diet we put them on it has to be enough to allow them grow. We can't completely restrict their protein because they need

protein to grow, they need protein to develop new muscles. But in some ways it's easier to treat children because they are anabolic, they are growing, so generally we can get away with a little bit of calorie excess, we can get away with a little bit of protein excess. Treating adults with metabolic disease is a little more difficult because you can't easily get away with calorie excess because they will just get fat in the circumstance.

Now we treat the defect depends on what the problem is. In something like fetal ketonuria, tyrosinemia the problem is accumulation of a toxin in the blood. So the dietary treatment is to restrict that toxic. If they've got fetal ketonuria then you just give them a diet that contains less phenylamine But it mustn't be a protein restricted diet because they need protein to grow. /So as well as cutting back on phenylamine or methylmalonic or whatever it is, the rest of the diet must contain enough protein make up for the amino acids hat are not phenylamine or precursors of methylmalonic acid so they are getting a normal protein intake, it's just restricted in the amino acids that are toxic to that child. The problem with this is of course that the restricted amino acid, there are amino acid mixtures that are restricted in some amino acids are horrible, and they are really quite, really they smell bad, they taste bad and they are really difficult to give to children. But that's the philosophy of treatment.

The other treatment is if they can't make something. And I'll use the example of the glycogen storage disease children in this case. Then your philosophy is to replace that. Children with glycogen storage type I have a problem - sorry obviously when we eat we don't become hypoglycemic because we synthesize glycogen immediately, 2 hours later I hope you don't become

hypoglycemic because we start to break down our glycogen and we've got a very rapid flux from the liver becoming a synthetic organ to the liver becoming a catabolic organ. And the liver exports glucose 2 hours after fast to maintain a normal glucose and it completely depends on this enzyme glucose 6 phosphatase, because this is the only way you can get the glucose out of the liver again. So in glycogen storage disease type I we don't have any of this, so when you eat you take up all your glucose, make glycogen, the problem is 2 hours later when you go to break that glycogen down you can't do that and you become hypoglycemic. Your liver becomes huge because it's distended with all this fat and glycogen.

So the treatment for this then is to avoid fasting, is to provide continuous feeds, breast fed for newborn babies because it's a really good way of providing continuous feeds, and then after the newborn period to continuous feeds with a gastrostomy feed through the night and frequent feeds during the daytime. So actually it's quite simple really, you know those first 2 hours are safe but after that they need to have some calories going in. And as they are babies we tend to use feed, but as they become older we just tend to use a glucose infusion at the slowest rate to prevent them becoming hypoglycemic through the night and you can achieve normal growth. There is a risk of making these children fat because you do tend to give them a lot of carbohydrate, but in general we should have them growing up relatively normal.

And the other treatment that we use, I don't know whether they use it here, but we use cornstarch, I'm just checking that things are the same here. And we used uncooked cornstarch, which is another thing that's absolutely horrible. You know I don't know if you've ever tasted cold corn flour, it really

is horrible, that's why we heat it. But it has the advantage of providing this slow release form of glucose. And what we hope is for many of these children after at some stage they might be able to come off overnight feeds by providing long term control through the night with cornstarch, if they can tolerate it. And traditionally we've used only modified cornstarch, and this is the sort of fasting profile that we get with unmodified cornstarch in young people with glycogen storage disease. Now there are have been some new forms of uncooked cornstarch which will act for a little bit longer, and that I have to say looks quite unimpressive, you know this new starch lasts for a bit longer. But in fact this is the absolute time that you need it, it provides 1 or 2 hours that might make the difference between a 6 hour sleep and an 8 hour sleep. And for how we live our life that hour is terribly important. So although it doesn't look that impressive it might be enough to improve the quality of life significantly. And do you use the new cornstarch here? Yeah, so this is still in use right. I just need to check what's in use here. So again for individual patients small iterative examples like that have made a significant improvement to a much better balance in the management of children with glycogen storage disease.

The other thing we used to have terrible difficulty with is how do you monitor a child who is at home on overnight, overnight tube feeds on 2 hour, 3 hour feeds during the day? And how do you monitor their metabolic control? I'm embarrassed to admit it but we used to do was admit these children to hospital to provide profiles during the day. Now how unphysiological is that? You know you take them to the most you know abnormal place they can be and you say oh well they'll be safe in hospital, therefore they are gong to be safe when they go to school you know. It is completely unrepresentative of real life. And it was always a dilemma how to monitor children's glucose

control through the day, and this is where these new subcutaneous glucose monitors have absolutely transformed the management of children. You know you can monitor their glucose profile for 3, 4 days at a time, and while they are going about their normal life. They can go to school stay at home the weekend and you can see what their control is like, and you can make some dietary interventions and you can monitor at home. And simple technical solutions have made such a difference to how we manage children and younger people with glycogen storage disease.

This is type III glycogen storage disease, Debrancher deficiency and they tend to present similarly to type I glycogen storage disease in the newborn period, or in the area of life with hypoglycemia. But they have much less severe hypoglycemia and many of these young people can come off overnight tube feeds by the time they are 5 or 6. So it's particularly important to monitor them. Whereas many of the type I glycogen storage disease will probably need overnight tube feeds until they stop growing with some caveats. They'll need it generally for a lot longer.

The other philosophy of treating metabolic liver disease as I've mentioned these are autosomal digestive conditions, it's usually a single enzyme defect. That enzyme calls for a protein, the protein is missing, dysfunctional, etc. So in theory a very good way to treat the metabolic disease is just to give them their protein back, and we have a very elegant model of that with the infusions of glucose - of glucocerebrosidase, which I can't pronounce, for the treatment of Gaucher disease. And again the initial enzyme replacements for Gaucher disease were a complete failure because the enzyme was taking up by the liver cells rather than the lysosome where it was actually needed. And by finding some simple biochemical trickery by putting mannose moiety onto the protein this was taken

up by the lysosome and completely recapitulates the effect of glucocerebrosidase. It's taken up into the lysosome and it's reconstituted. And this has transformed the management of patients with Gaucher disease that turn up for their infusions every 2 weeks. It really has transformed and that came in the 1990s and that was a pioneer for that treatment. And now you see the long list of conditions that are available in which the protein is available given by infusion. Extraordinarily effective.

And the most recent one that's become available is one that I was just going to talk about, the one for lysosome acid lipase deficiency, which we traditionally call Wolman disease when it presents in the newborn period and cholesterol ester storage disease when it prevents in older children. Well the underlying defect is lysosomal acid lipase and there is now a protein replacement for that, Sebelipase alfa.

This is an overview of the pathology in lysosomal acid lipase deficiency, cholesteryl esters are taken up into the lysosome and then they are broken down into free cholesterol, which is an important substrate for the cell itself. And in acid lipase deficiency these esters accumulate so you get gross distention of the lysosomes, gross distention of the liver and you get cellular deficiency of cholesterol, so you get a toxicity. And as I've mentioned two phenotypes, the Wolman disease, very sick children who died in front of your eyes really, rapidly fatal disease, and then the more variable cholesterol ester storage disease, and this has really been where it's from.

This is the natural history study of children with Wolman disease and personally I'd never seen a child more than 6 months old with Wolman disease because they are all dead by that stage historically. Efforts at liver transplantation, bone marrow transplantation a disaster. Now with this protein replacement this is a life saver. You can see it hasn't saved all of these children's lives because of course by the time the diagnosis was made many of them had already suffered sequelae. But now I had the amazing opportunity of seeing a child with Wolman disease who was 3 years old. It just didn't occur beforehand. So the enzyme replacement has completely provided a life threatening, sorry a lifesaving option for these children. Now whether that should be continued lifelong for these children or whether they should have something like bone marrow transplantation, etc. you know there are some long term decisions to be made about the thing. But at least they are there to have these long term decisions made about it, because historically they didn't have any long term decisions made about them.

The more complex issue is that in later onset disease the cholesterol ester storage disease, which is a very variable disease, tends to present with hepatic fibrosis, GI symptoms, abdominal pain. And may of these children are fibrotic/cirrhotic, and in our experience one of these children had come to liver transplantation because of hepatopulmonary syndrome. But a very variable disease and a much more difficult decision as to whether enzyme replacement would be appropriate because we don't know the natural history of this disease quite as well. But there has been a study of Sebelipase alfa and it does show that you get a significant decrease in liver volume and you get a significant decrease in liver fat and like many of these protein replacements it does reconstitute and replicate the function of the protein in the body. Of course it's extraordinarily expensive and whether it makes

enough of a difference to a variable disease like cholesterol ester storage disease I think the jury is still open on that. But obviously there is significant commercial factors suggesting that we should use this for all of our children with cholesterol ester storage disease but for Wolman disease it really has been life transforming and lifesaving for that group of diseases.

Moving on, obviously as particularly as physicians we like to have drugs to treat our diseases and we have a few examples but the most dramatic example has been in the treatment of tyrosinemia type I. This is a rare metabolic disease in the metabolism of tyrosine as the name might suggest and the defect is in the last step of tyrosine metabolism. And as a result of the defect these toxic metabolites accumulate, which accumulate in the liver, cause liver fibrosis, liver cirrhosis, liver malignancy and porphyria.

Traditional our treatment was to restrict dietary tyrosine and that was singularly ineffective. This was the natural history survival of children with tyrosinemia with dietary treatment. Those who presented in the first 2 months of life essentially 3/4 of them died in the first year of life. Those who had the milder defect who only presented after 6 months did fairly well until they were 9 or 10 and then they started dying of liver cancer. So horrible disease, dietary treatment didn't work, liver transplantation was a lifesaver. So every child with tyrosinemia the question was when would they have a liver transplantation rather than if.

And then the Swedish and the English through ICI invented this product Nitisinone which inhibited the enzyme 3 steps above the metabolic defect and as a result you didn't produce the toxin

metabolites. And this - this was given to a child in Gothenburg in 1991, it was this white powder, it was produced under completely non-commercial circumstances. Lynchstead who was probably smoking while he did this, there was probably cigarette ash in it and they gave it, and it was just amazing you know. Our first patient we got an envelope of white powder you know. This was pretty good. But it was amazingly effective. And this is the effect on the coagulation of children with liver failure with tyrosinemia, within days of giving them NTBC they start to get better. And all but one of the children that we treated with liver failure responded to NTBC. So a remarkably effective treatment. And over the years we treated 35 children in Birmingham with NTBC or Nitisinone, it is non-commercially available, very sterile production facilities and very professionally produced. And 11 of the children with acute liver failure responded, so it was extraordinarily effective. But the problem is and again even those who presented with chronic liver disease they all improved, okay, so it benefitted these children. But all of these children were sick beforehand so although they improved they were left with residual liver disease and some risk of liver cancer. And I'll come back to that. So although we did very well for these children in their acute management you can see that those who presented with chronic liver disease in fact we transplanted 5 of those and one of them got a cancer and died before we could protect them. So it stabilizes the children but it does not remove the risk of cancer. So we can get them into better shape but the children who presented clinically with tyrosinemia are probably still candidates for transplant.

But where we did remarkably well I think is those who we picked up at birth, either because they had siblings who presented or because they were picked up on the newborn screening. To my intense frustration we do not screen, we did not screen for this in the UK, I know that you do screen

for this here in Pennsylvania, but the children who were treated from birth are clinically normal, and we can probably prevent them ever getting liver cancer. And so I think we do a big duty to them, to the others I think they will always require long term monitoring because of their risk of cancer.

But I think as a protection against arrogance and complacency you know we think okay tyrosinemia is sorted, and now what do we find? These children have significant neurological difficulties. Our children with tyrosinemia are growing up, their IQ is not normal and they have some executive function abnormalities that are akin and probably a little more severe than children with fetal ketonuria. So what's doing this? Why did we not notice this before? Was it because all the children died or because they required liver transplantation? So there was a little bit of a cloud about the medical management of tyrosinemia because of these children's neurological difficulty and the mechanism of this we do not know. I suspect it's due to pure metabolic control and that if we had been tougher with their amino acid control we might have prevented this. But although we almost abandoned liver transplantation for this it may be that when we get more information that we will have to consider using liver transplantation again. So I think it is you know a message for me, don't be complacent just because you think you've got a new treatment. You know there are unintended consequences. I don't think this is due to the drug itself, I think it's probably due to pure amino acid control I suspect, but we don't know. And it's something that we - that's our next duty in the management of tyrosinemia is to try and understand why they don't do so well neurologically.

And again the last part I want to finish of course the very dramatic treatment for metabolic liver disease is liver transplantation. I was just comparing rough figures for Birmingham and Pittsburgh

for those who have transplantation for metabolic disease. And I think overall the balance is very, very similar. Again interestingly much more alpha 1 antitrypsin deficiency transplanted here and things, and obviously the huge difference is you know the very effective treatment for the treatment of maple syrup urine disease which was a disease we didn't see much of in the United Kingdom.

And in thinking about liver transplantation for metabolic liver disease there is a couple of things to think about. And I think this is a 2 by 2 rate to see what effect of the metabolic disease is. These children to the left have liver disease due to the metabolic defect, and they've got alpha 1 antitrypsin deficiency. And we do a liver transplant on these children because they have liver disease, not because they have alpha 1 antitrypsin deficiency and our criterion for a child with alpha 1 antitrypsin deficiency is pretty much the same as it is for a child with biliary atresia. So it's a bit of a swiz really for us to talk about treating - you know doing liver transplantation for metabolic disease. We do transplantations for liver disease in this situation. The other part of the 2 by 2 is whether the defect is completely confined to the liver or not, because the impact of that is will you have a residual defect after liver transplantation. So those are the two ways of thinking about the efficacy of transplant.

Now these are the really important group, because this is where we have to make significant decisions based on the severity of the metabolic defect about transplantation. Sorry that's our normal indication for transplantation for liver disease and so for alpha 1 antitrypsin deficiency the metabolic defect is irrelevant in that situation. The more difficult decision as I say is what to do about the metabolic defect, what to do about Crigler-Najjar syndrome, what to do about OTC deficiency, what

to do about metabolic acidemia? They do not have liver disease which is causing their problem where they get a liver transplantation to correct a metabolic defect and to improve their quality of life. And you have to have take a number of facts, you have to have a good transplant team. You know if transplantation has a 50% survival you don't do this, you know. So transplant you have to have a successful transplant team, you have to know the prognosis of the metabolic disease and you have to know that the next NTBC isn't around the corner. You know they are working on something that will absolutely wipe out the problem with the OTC deficiency, so you need to be aware of that as well, although you can't predict all of that. And it's weighing up those risks, the risk of the defect, the quality of life and particularly with the urea cycle disorders, what's the risk of them having irreversible brain injury beforehand? I think you want to do your transplant before that happens. You know you really do want to do the transplant before that happens, so it's a very complex group of measures to make an elective decision for the long term.

From the point of view of success of transplantation this slide is from George and Pittsburgh's figures and you can see that with time it gets better. And now elective liver transplantation is an extraordinarily effective treatment with a low risk and an excellent long term prognosis. So as a result you can offer it to a wider range of metabolic defects confidently because you know it can do that. And we know that when you correct the metabolic defect that is a lifelong correction for the metabolic defect if it's confined to the liver, and it is an extraordinarily effective treatment.

One of the things of treating metabolic disease which we were unsure as to whether or not live related transplantation would be appropriate because most of these parents are obligate

heterozygotes. And in general the very reassuring thing, it doesn't seem to make a button of difference. There are a few defects that we might take but in general life related transplantation is entirely appropriate for most metabolic defects despite the fact that their parents are heterozygotes with a couple of exceptions and question marks that can be done.

The other question is of course these beautiful livers which look very well in the operating theater and I think is a trauma for surgeons to have to remove a normal looking liver from somebody's abdomen is what do we do with this, and do we throw it away afterwards? And one of the first groups to look at this was maple syrup urine disease where an adult who was undergoing a transplantation, his liver was given to a man who had a very poor prognosis, hepatocellular cancer due to hep C and he received that liver as a domino and in fact it was very effective. The child shoed an improvement, or the young person showed an improvement in their metabolic control because they got - this is their reducing oxidation went from 0 to about half of normal; and the man who got the MSU disorder, his leucine oxidation went from normal to about half, but had no functional sequelae for him. He became a long term survivor and it was very effective. And here there have been an institution here of the children with maple syrup urine disease, 15 of those livers have been dominoed on to somebody else. And in an area of organ shortage this is an excellent resource to use. A beautiful liver which is very well preserved, the timing of transplant can be perfect, the recipient can really benefit from this. And so far in all the survival is up to 10 years here in the local program. This has been very successful. You can detect some minor metabolic abnormalities but there is no functional defect and it looks as if these livers will be very effective in the long run. And this is a

very important contributor to the donor organ program. The shortage of cadaveric transplantation is a national issue.

And this has been done in a number of metabolic defects including homozygous hypercholesterolemia and familial amyloid polyneuropathy which is a disease of adults really rather than of children. There are some diseases you can't give. Oxalosis is one because if you give it to an adult with oxalosis, a liver with oxalosis they get oxalosis very, very quickly and become symptomatic. But there are some metabolic diseases in which that liver can work in somebody else who has got the extrahepatic - doesn't have an extrahepatic problem and it can be a very effective control of liver disease for them. So that's an interesting way of improving the organ pool.

Who can't have transplant? That's becoming less and less with time. I think the ones we worry about really are those who have mitochondrial disease, progressive systemic disease, those who have valproate associated liver failure, they almost always have an underlying defect of energy metabolism and transplantation tends to correct the liver problem but not the body problem. And they have progressive systemic disease so in general that's a group that we avoid. Niemann-Pick disease is a controversial group but in general it's probably a contraindication of transplantation. But in individual cases it's worth a consideration. We had in Birmingham accidentally transplanted a child with Niemann-Pick C who I have to say 5 years after transplantation is looking very well indeed, so it's you know - that's a complex area.

The other thing of course is that although liver transplantation is very successful there are some problems with it. There is surgical morbidity, this is not keyhole surgery, it's a big operation, it requires a long time to recover and there is a significant donor organ shortage. So we want to also consider alternatives to liver transplantation and evolutions of this. And one does - one condition which is very a good example is Crigler-Najjar syndrome, an inherited disorder of bilirubin metabolism. You can treat this with phototherapy. You know phototherapy is really good for newborn children but phototherapy becomes a bit of a drag when you become 10. You know you can use it in bed, you can use it - you can get these ingenious machines that provide phototherapy all day but you have to spend 13 hours in it. And it's not a great life. And you have to be in the nude. It doesn't work well for sleepovers really if you are 13 and you want to bring your friends over for a sleepover and you sleep in this, so you know it's not. And we do liver transplantation for this and it's extraordinarily effective. But you don't need a liver transplantation for this, 5% of the liver is enough in this situation.

So one very successful treatment was an auxiliary transplant for Crigler-Najjar syndrome. You kept your liver there as a failsafe and then you took a little bit of it out and then surgically put a part of somebody else's in so you'd have two livers in combination and yet you had your own to fall back on if there was a problem. Technical problems associated with this, but the idea is very interesting and again very effective treatment for Crigler-Najjar syndrome. Maybe that's the only condition it's very effective for because you don't need so much defect. But again you have to take a whole piece of liver that then can't be used for someone else.

A new more exciting thing is combining the concept of domino and auxiliary so that you have less damage to the organ pool. This is a child who had Crigler-Najjar syndrome who was given the liver of somebody who had propionic acidemia who had been transplanted. So the propionic acidemia's liver was taken out, half of it was split and put into the child with Crigler-Najjar syndrome. That was not enough to give the child propionic acidemia but it was enough to cure his Crigler-Najjar syndrome. So you can see the potential of doing exchanges between people with different metabolic defects in a very complex way without damage to the organ pool, so that you are not using a liver that could be used for somebody who is dying of end stage liver disease. So it opens up a different combination of metabolic defects and might challenge the diagnostic laboratories as this child with propionic acidemia, but functionally this is a very interesting concept.

And of course we want to take that a little bit further, and a very attractive way is of course not doing surgery is doing noninvasive providing cells for treatment, and this has been very important. And this is a slide that Arry recognize from some years ago of a child treated, a young woman and treated with hepatocyte transplantation for Crigler-Najjar syndrome. And you can see that this had an effect. It showed the proof of principle giving liver cells by an infusion not surgical treatment. It was taken up by the liver and provided some effectiveness. Now it wasn't dramatic, you know it didn't change completely and this young woman got away with maybe less phototherapy. It didn't cure her in the normal sense, but it had an effect.

And since then there have been a number of experiments with hepatocyte transplantation and again the same thing applies, it seems to be safe if you monitor the portal pressure, you don't seem to do

much damage to the liver itself, but the engraftment in the liver is relatively small and what happens to the cells in the long term is rather unclear and the effect tends to be temporary and doesn't tend to be longstanding using current technology. So that was the only form of hepatocyte transplantation, so there has to be options to do something to make this better, either give more cells or do something to the liver so that the cells that you give can then be taken better of. A work in progress.

Something that I had been involved in had the concept of using stem cells, and the concept here was that these would be better than hepatocytes if you infuse these, these are stem cells, they might grow better than hematocytes and they might have a more long term effect. And we were involved in this study using these hepastem cells and the theory was that they were stem cells, what better? And again this is amazingly noninvasive. Percutaneous infusion into the liver, infuse cells over a few hours, you know you can take - you can see when the ultrasound, when you take the catheter out you don't generally cause a portal vein thrombosis, an outpatient procedure and very common. You know it is very, very noninvasive.

And this was a representative patient with OTC deficiency and to measure OTC isn't so easy but this is a measure of C13 urea production. And you can see it was very low at baseline. At 3 months significantly improved, at 6 months well improved, starting to feel good. But in fact it has behaved very similar to hepatocyte transplant, the effect was temporary and it wasn't obvious had a clinical effect. So again it showing the perfect principle, this can be done but the experiments to decide to make this into clinical standards where you can change a clinical phenotype have yet to be done and

this is work in progress, but it's a noble aim because it is so noninvasive and as I say it has a potential in the long run to protect the donor pool, which is important.

The other very important method to correct metabolic disease is somatic gene therapy, which has been thought about for a long time. Obviously gene therapy took a step backwards after the tragic death of one young man after a viral vector problem. But in fact gene therapy programs for metabolic liver disease are now active and there is one in Europe for Crigler-Najjar syndrome and there is likely to be one in North America for Crigler-Najjar syndrome, so this era is back and being visited again and it's likely to develop with time. But it's not in our clinic, we can't do this for our patients with Crigler-Najjar today but who knows in 5 years time what will happen.

So I think overall metabolic liver disease it's an important cause of liver disease, I think for public health point of view we do need to think about screening for more disease. I think you are already doing this here. This is aimed at where I come from in the UK. We had tried to persuade them to screen for more diseases.

Treatment options change rapidly, so the decision we might make today might be different in 5 years because we have different options. You can only give your advice to families on the knowledge you have at the minute. We give patients now different advice than we would have done 5 years ago because things are different. And things will continue to change and we need to be adaptive.

Liver transplantation is the very effective form of gene therapy and after that it's a lifelong effective gene therapy. There is a lifelong correct of the defect and it is a low risk, highly effective treatment. Cell treatment which we are working towards and I think has still a great potential has shown proof of principle but it's not yet at the clinically impeccable stage.

Obviously I'd like to thank our cohorts in Birmingham and being there for 25 years and I worked with the inherited metabolic team. I've been working here for the last 3 months and everybody has made me extraordinarily welcome and I'd like to take and thank everybody in the GI and liver and liver transplant team and particularly Rob and George and Mark for asking me to come here in the first place. Thank you.