

Families for Families Day 2016

Medical Advisory Group Q&A Session

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Q: My son is six years old. If you'd asked me before if he had any traits of Autism, I'd have said no – he has lots of eye contact, you can tell if he's sad or happy, has great emotional awareness but he's totally fixated on cars and is very stubborn and I wondered if we should investigate this further, to make sure his medical practitioners and his school [are aware] that he might be on a spectrum of Autism despite the fact it's not the normal spectrum everyone thinks about when they think about Autism.

JG: Well you're right that autism is a spectrum and in my talk I did talk about what we call "partial features". So really autism is a behavioural syndrome. It's defined and assessed through understanding a pattern of child behaviour through development and that's really what it is and we know that those patterns of behaviour tend to co-occur together over development and be quite persistent. Some children do have some bits of it and not others as it were but on the other hand there are also other reasons why a child might be interested in cars or might be struggling. So you shouldn't inevitably assume that one little bit of the collection of symptoms actually means it's part of autism. Generally in child behaviour, there are lots of different causes for a fairly limited range of behavioural presentations – there are lots of different causes generally speaking so that's where you need someone to make an assessment. So if it's a problem for you or you think it's a significant issue, then yes, it is worth having an assessment to look at the range of potential options which might include that it's just a normal variation of things – you know, children are different and have different interests - or it might indeed be a representative of an underlying difficulty. So I can't answer your question directly except to say it's not necessarily part of the ASD but it might need looking at if you think it's a big problem.

Q: OK, thank you. It's not really a big problem but he is, I would say, more than another child, very fixated on certain things, very stubborn but he's lovely at the same time.

Delegate: It's quite common nowadays, as somebody who's 29 and currently waiting to have an Asperger's assessment, [that] people often assume that because I can pick up a mike and speak up that I don't come under the Autism spectrum. But I very much struggle to maintain established relationships with people. So please bear in mind that as an adult, it can be very very difficult to get assessed on the Autism spectrum and if you really believe [there's] something, then there's no harm in investigating whilst your child is younger so that you could get them support younger rather than having to wait until their adult life when they've had difficult

circumstances and got into trouble in life because they did in fact have autism but nobody cared to look into it. I just wanted to share that with you. Thank you.

MP: At lunchtime, we had a number of people asking about getting referrals for psychiatric help – what is the best way of getting the right resources for a medical referral?

JG: It is a sad fact at the moment that there aren't the resources to give people proper psychiatric assessments throughout the country. It's very patchy – there are some excellent services and there are some areas of the country where the services are very thin on the ground. I do think it's a scandal. The Government do accept this in principle and have allocated quite a wad of extra money; at least it seems a lot and it is a lot but as a proportion it's perhaps worth bearing in mind that the resources devoted to child health and child mental health specifically are a very small proportion of general health resources; much smaller than you'd expect from then proportion of children in the population. It is disproportionately small. Why is that? It's historical - children don't have a voice; advocacy hasn't traditionally been as strong; small people, small problems; It's the sort of, you know, latent assumption. None of these things of course are true. Children are at the beginning of their lives and a lot of the things which happen in childhood have long-reaching effects. We in the profession try to advocate as much as we can about this. In the end it's a political thing – this is about resource allocation. And there have been more resources that the Government has put in recently but this will by no means make up the deficit. It's going to need to be just big sustained effort to get more money allocated for this sort of area.

VD: So I would say, if you're looking for that and you're not getting the support you need, the most valuable thing you can have is a good GP or a good general paediatrician who can advocate for you and knows their way round the system. Now I was lucky enough – I've just moved to Great Ormond Street so until last year I worked in Birmingham. Birmingham has a child psychiatry service that's run by the Children's Hospital in Birmingham and it's run for the whole city. And so I was lucky enough because I was working in the Children's Hospital I knew all the child psychiatrists and I could pick up the phone and speak to them. So I knew my way around the system. I've now moved to London and quite frankly, child psychiatry in London's a mess and nobody knows who's delivering it and there's all sorts of gaps in the service and I know there's other parts of the country - South West and so on - where the provision's very poor. But at least having a general paediatrician who knows you, knows your family and who can pick up the phone to the service and argue your case, is the most valuable thing you can have.

IL: We have some written questions on Lymphoedema: How common is Lymphoedema in children with Noonan Syndrome? Is watching and waiting the best treatment for a mild Lymphoedema or is it worth using compression garments early on to prevent it getting worse?

SM: Lymphatic problems are very common – hydrops, swelling of the feet at birth, web neck, they're all lymphatic, so they're all very common but the sort of thing I described is very rare and I suspect under diagnosed as well. I think some children with Noonans and adults may have lymphoedema and not realised that that might be

the problem or even their intestinal problems. If there's some Lymphoedema, once it starts there is the possibility of it increasing and, I am biased, but we tend to treat people at an early stage with light garments – we don't want to make life unbearable so they should be comfortable and easy to put on and we work with the patient to try to optimise that because if they don't like wearing it, especially a child, they won't comply so there is an in-between round for it but we would advocate early use of compression garments. It doesn't cure it; it doesn't stop it progressing but it may slow down and stabilise it. And there are quite a lot of centres throughout the UK who can provide these garments and do the measurements so it doesn't have to be at our centre, although we tend to start the treatment at St George's and then make recommendations locally.

MP: We have another question from someone whose son gets leg and foot pain in bed which is relieved by Calpol and hot water bottles, and asks if this could be connected to problems in the lymphatics?

SM: Lymphoedema is not usually painful – you may get a bit of discomfort particularly if you're on your feet all the time, but as a general rule it's not going to cause pain so if there's no swelling, it's just pain so I don't think so.

MP: We do get quite a number of children who seem to get joint pains in the teenage years and we've often puzzled about that. There are various theories but it doesn't seem to be progressive and damaging arthritis and it does seem to improve with time and to be resolved with local treatments and with things like Calpol and paracetamol.

BK: At the American meeting in Seattle in July, support groups - CFC, Costello, NS – made presentations and all raised this issue of pain so I think it's very common and I think it's very poorly understood but an American research group has recently got a small amount of funding to start looking at it. But it does seem to be very common across the pathway.

JDVM: I'm also suffering especially when I'm laying in bed from pains but also I can't keep my legs still so I have restless leg and for me it helped to take magnesia. You can just get it at the pharmacy and just try it. I don't say it cures everything but for me it helps. I feel it immediately if I don't take my magnesium.

Q: This is a question on the future of genetics. With the advent of cell and gene therapies that's started to emerge – we see more and more about on the media – is there any prospect for genetic disorders to be treated per se rather than treatments being focused on the ailments that result from the syndromes themselves?

BK: I think that there is some interest in whether certain classes of mutation might be amenable to treatments that might modify the expression of the abnormal gene, but I think we really are a long way from gene-based therapy in developmental disorders because the diagnosis isn't made until many of the manifestations are present so I think in the short term we are looking at treatments that might be directed at manifestations of the condition.

JDVM: I spoke to a professor who was interested in gene therapy and he looked into Noonans and because it's very heterogeneous and he's not completely understanding what the proteins are doing so he's not really sure what kind of gene therapies are doing and he's also – if you look at NS it's not really deadly – it's not that severe so they're first of all looking for gene therapies that are very deadly at a young age so probably it will be in the future but as I understand now at the moment it is not a focus of interest

JK: I guess the comments that BK made are applicable to the heart itself. One possible exception is the study that BK mentioned earlier – the Novartis Study which is looking at targeting in particular proteins within the pathway and I think it's still very early days but it's possible for these sorts of drugs might potentially halt the progression of the thickening of the muscle in the heart and potentially in some cases may even reverse it. There's animal data on this and some anecdotal reports of these drugs being used in children with disorders of the RAS pathway so it's possible there might be some progress – it's not gene therapy as such but it's gene-guided therapy that might improve some of the features we see in the heart but I think we're still some way from this being seen as a routine treatment.

BK: Because this is a pathway which is so important in cancer – this pathway was first recognised in 1982 and there's been tremendous work done on modifiers of this pathway but the difficulties when you realise changes in this gene causes developmental disorders is that the side effect profile of what you would accept with someone with cancer is completely different to the side effect profile of someone – a child – with developmental disorder. We're still very much at the stage of understanding the inter-relationships of the pathway and there's a lot to be learned about just how it functions in the cell normally but then of course you have on top of that, mutational genes but people are very positive about this group of disorders that there will be treatments and the work that's going on is directed at that but it's just that it's going to take some time.

PO: I just wanted to say that it took 13 years to get that first genome covered but now technology's moved on but gene therapy is still in its infancy so it will take a another few years before we can really understand and make gene therapy general available but there's also various problems depending on where this error is happening so it could be decades before there's any solutions.

Q: On social media, there's a lot of discussion about sensory issues in children with Noonans. Is there any link to those sensory issues and behaviour and have there been any studies done on that?

JG: What people usually mean by sensory issues are some atypicalities or unusualness in processing sensory information of all kinds – incoming visual, auditory or touch but also sensations from inside our own bodies, what we think of as proprioceptions. Children do vary on this and it is true that as part of the Autism spectrum complex, these kinds of sensory processing problems are often intrinsic to the difficulty. They also though occur outside autism as part of particular developmental difficulties. But they're very real and they can be associated with behavioural difficulties for sure. The assessment of these is not as advanced as for some other areas of behaviour and development in the professional literature –

there's not as much assessment and research work on this area. But I think it's a growing one and yes often these things are related to behavioural difficulty and managing them can have really tremendous benefits on behaviour.

MP: Re Social Media – we've learnt a lot from listening to families' problems and maybe we should be looking at social media where these sort of issues come up.

Q: You mentioned about Hydrops being quite common in Noonans children. Our daughter's 5 and had hydrops when I was pregnant. I just wondered if there's a high chance of those that did suffer with hydrops of developing lymphoedema problems later in life?

SM: We don't know! We've only seen about 15 people with Noonans and lymphoedema and some of those had hydrops but not all – and then I've seen many children with hydrops who haven't developed lymphoedema so there's no clear correlation at the moment so I wouldn't worry too much.

Q: We've got three kids, all grown up now but we also have a grandson who's been diagnosed with Noonans. "J", my youngest daughter, is one of the 30% for whom they don't know what caused the Noonans but our grandson who is J's nephew, he's under the 3D scheme which I think is being run by Cambridge University and the geneticist at Middlesbrough who saw J is waiting for the results of the 3D study to see whether there's any links. How do we make sure all these studies are linked together and the results are correlated and we get the best benefit out of them?

BK: The 3D Study was set up to look at 12,000 children that was later extended to adults across the UK who display intellectual disability. Enrolment has been really through genetic services. The study only stopped recruiting in April 2015 and it was actually a much bigger task than people thought it was going to be to just deal with the sheer volume of samples in terms of new technology so the first few years – it lasted 5 years – were actually very much about getting the actual experimental processes to work. And we really only started to get a lot of results in the last 12 months. As part of that process, people can express an interest in research into particular genes and our intention is to take forward the rasopathy genes and to look at those patients who were identified through the 3D study as having one rasopathy disorder which would most commonly be Noonan Syndrome to see what we can learn because they would presumably be people who are less typical. We've already seen some people in Manchester through 3D and other studies who have been found to have Noonan Syndrome

MP: We started looking at this in 1986 so we've been trying for some time but the technology's moved on and I'm sure with the family structure you've got you'll be able to identify this gene in due course

Q Have you found patients with more than one mutation on the RAS pathway?

MP: Yes. But sometimes we only look for one gene like PTPN11; we weren't systematically looking at all but now we run a panel of maybe 10 or 12 genes and we occasionally find one that's got more than one gene fault. I spoke to one parent at lunchtime who had a child with both the Noonan gene and another genetic condition

causing short stature. It's going to happen by chance occasionally but probably relatively rarely but with increasingly accurate testing, there will be more identified. It does seem to be a chance event rather than any biological principle underlying it.

Q: Can partial ASD (Autistic Spectrum Disorder) be explained by the way other children treat them as a result of their differences and by their medicalised experience?

JG: The simple answer would be no. ASD caused purely by the way a child is treated or by the way their peers treat them is not something that we see. ASD is a different kind of problem to that. Of course the way a child is treated can exacerbate an underlying vulnerability and that can bring things out or make them worse. But as a primary cause we don't see that, no.

Q: Do a lot of children with Noonan Syndrome suffer from stomach pain and bowel problems?

BK: I haven't experienced stomach pains specifically apart from the fact that recurrent abdominal pain without an obvious cause is not uncommon in childhood in general terms. I haven't seen it in Noonan Syndrome as different to that I don't think.

VD: Recurrent stomach pain and cramps is quite common and I always describe it as a bit like headaches – just as some people get a lot of headaches it doesn't mean that they've got an underlying disease or problem in their head. Stomach pains and stomach cramps are quite common in children and they do have a genuine experience of pain – some people say it's attention seeking but I certainly don't think it's that. But for the overwhelming majority – 90-95% - you look after it with reassurance, simple painkillers, rubbing their tummy and usually you tend to find that it gets better. If a child's severely unwell, has got diarrhoea or is losing weight or is becoming paler than you should, then you should definitely get medical help.

SM: It's rare but intestinal lymphangiectasia may present with bloating, abdominal pain particularly with fatty foods and chronic diarrhoea – greasy, floating, smelly so it's just something to bear in mind.

MP: I think one of the points coming out of that is that of course you can have things coincidentally to Noonans and one of the questions we had was if Gilbert's Syndrome part of Noonan Syndrome. It's a cause of jaundice and it's relatively common and I think the answer to that is it's likely to have been coincidental. And I'm sure some of the other things we're hearing about may be coincidental rather than part of the syndrome.

Q: We have a little girl who's nearly 3 and she often complains she gets very hot. She's always fanning herself and I've read a few of the things on temperature regulation. Is there any research on this? Is it related to the lymphatic system or could it be dealt with by diet. I've noticed she often gets this and she sweats a lot at night and we often feed her by tube when she's in bed and she really sweats. I wondered whether that's to do with fat in the diet? Is there any research?

BK: I don't know of any research but sweating at night is very common. I saw a child with Noonan Syndrome aged 10 yesterday and he sweats a lot and pyjamas changed. I think it's common but we don't know what causes it.

Colin Stone confirmed this was extremely common in children with Costello Syndrome and in his experience it tended to improve with age.

Q: My 9 year old son has ASD/ADHD. Other than medication, what other routes are there?

JG: I mentioned some of the treatment options in my talk so it depends upon the age of your child and other circumstances. In general terms, there are some really interesting new treatments in early life so a bit younger than your child in pre-school and early school years, but really focusing on improving social communication, usually in a family or parent-child context; and they're proving pretty effective, more than a lot of people thought they'd be. This has opened up some really interesting thinking about the flexibility of Autism symptoms. It's not a magic cure but there's significant evidence of improvements that are sustained. Those are the options. Psycho-social therapies going through parent-child communication and then there are a whole raft of other things that can be done to really aid social skills, social adaptation both from the child in relation to the environment but also from the environment in relation to the child – that can easily be forgotten – so the lives of these children can be made hugely better if the environment can be adapted round them and understands them. And that is one of the big things that can be done, to improve the environment but the child can learn techniques and coping strategies - so-called social stories are very popular these days and are really quite effective. So ways of managing and working out strategies for social situations when you find it difficult. So there are a range of psychological therapies of that kind – that's for ASD. For ADHD, it's a slightly different picture, mainly through parents' support and advice but also environmental adaptation can be useful.

JVDM: I was diagnosed with ADHD in adulthood and was put on medication but unfortunately I developed cardiac arrhythmia and I just want to warn parents about it because of course a lot of people with Noonans also have cardiac problems and ADHD medication can give cardiac arrhythmias. I know about one medicine which is prescribed in the States for children with cardiac problems. It's also now allowed in Europe and I know it will be distributed in the UK.

JK: I know your experience is very helpful and valuable but as a general rule though, it's unusual for us to see cardiac arrhythmia in childhood with ADHD medication. Clearly it needs to be monitored and I know we are all aware of the possibility of arrhythmias developing but it's not something we see very frequently and often it's a balance that needs to be struck between the clear benefits of the ADHD medication and often a small risk of arrhythmia. The key thing is adequate and appropriate monitoring. We shouldn't ignore the possibility of using ADHD medication in a situation as long as the cardiac follow up is in place.

Q: A Cardiology question. What are the chances of a child who had open heart surgery in the past having more surgery as she gets older – this is a child with pulmonary stenosis.

JK: It's very variable. It depends on the initial condition and the initial procedure performed. It's not unusual for individuals who've had particularly surgery to the pulmonary valve for that valve in time to become leaky and often that does require further procedure. It's not universal by any means and it depends on the shape and the look of the valve – the morphology of the valve and the procedure that was performed.

MP: Could I just ask about follow-up because often children with pulmonary stenosis are seen at the paediatric cardiology clinic. Things seem to be stable and they are dismissed and they don't attend the clinic. But you're saying sometimes later in life, they may run into problems. What's the best way in dealing with this?

JK: Certainly anyone who's had an intervention to their pulmonary valve should have lifelong follow up, I think that's well established. There are adult congenital heart services around the country which would provide that sort of follow up. There's a slightly different situation with a person with mild pulmonary stenosis who haven't had an intervention; and I think you're right that often these children as they get into their late teenage years, they often do get lost to follow up or discharged from services. I think pulmonary stenosis outside the setting of Noonan Syndrome is relatively common and usually very very benign and actually I think current practice still would be that if the stenosis was very very mild they would be discharged during adolescence. It's a slightly different situation in Noonan Syndrome and related disorders because there is the potential for the development of narrowing stenosis or leakiness developing, at later stages so I'm sure Guidelines will continue to recommend ongoing screening in that setting.

IL: This is another one on the leg pains which we've heard mentioned at meetings and we've heard mentioned again here - leg pains at night. Last year we mentioned that vitamin D deficiency could be associated with this. Is there any more evidence that this is correct? Is it advisable to supplement vitamin D? What are the other possible treatments, for example massage, Calpol?

MP: I did follow this up and I did find problems with calcium but I'm going to pass this on to Vin.

VD: Low vitamin D levels are very common in the UK mainly because you need to spend at least 8 hours a day out in bright sunshine in order to have adequate vitamin D levels. Vitamin D levels are even lower as you go north, to Sweden and places like that. So if your child is under the age of 5, they should really be taking some sort of vitamin supplement if they're fussy and not eating well. Leg pains are very common in childhood so what I always recommend is that you go and try just going onto normal vitamin supplements. If leg pains persist, particularly if leg bones start looking bowed or bent, that sort of thing, then it's worth getting Vitamin D levels checked. But your vitamin D levels really have to be quite low to get a high dose of vitamin D to bring them up again – it's better in childhood to make sure you take your childhood vitamins. And then the other thing is to try to spend some time outside and then have a diet that's got plenty of vitamin D in it – things like eggs, fish, vegetables – all those things that children like eating!

Q: Just going onto the feeding issues with children with Noonans, do we know what it is about the Noonans that causes feeding issues? Is it because of the small stature that they don't need as much to eat or is it because they don't eat as much and they're bad eaters generally speaking and then that's why they have a short stature? Do we know much on that?

MP: We did originally start looking at the feeding difficulties and it's almost like a neuro-muscular inco-ordination – small children can't chew and that's later sometimes in children with Noonans where there's a delayed maturation. There's also sometimes a problem with the sensation of food in the mouth and the children will sort of "tongue-thrust" and push the food out. But I think it's basically a neurological control of the feeding; it's not because they're small and eat less, and they tend in most cases to get enough nutrition in but will be cases where you need to tube feed children with Noonans to begin with and that group needs quite careful follow up from the nutritional point of view .

Q: To be really unscientific, I think from my personal experience that my son doesn't actually get hungry. I think there might be a problem associated with Noonans about feeling hunger. So my question is around my son – he's got a peg, he's 6 so all he has is his nutrient, his pectorin milk, and water that we give him. Now should we be thinking of supplementing that with anything else now he's getting older and older and there doesn't seem to be any coming future in actually eating different food, fresh fruit and vegetables. Should we be thinking about supplementing his diet with anything else other than this milk and water?

VD: I probably don't know enough to say how common not feeling hungry is although you definitely see that in some children because just like adults we have variable appetites. I think the most important thing with regard to diet and calories and vitamins is to be under a good dietician who can add up the number of calories and know what vitamins and things to take. The other thing I would say is once you've got a good dietician who's making sure your son or daughter's getting the right amount of calories is to not actually make the food too much of an issue. What you don't want is for food to become a battle every mealtime because once you know they've got good calories in, you want to make food a pleasurable experience and that's what you focus on. I think the other thing is they say that most children will need to taste a new flavour at least 15 to 17 times before even thinking about liking it so [when you] introduce anything new into the diet, I wouldn't expect too much too fast. That would be my main advice – not to make it too much of a battle and ensure you've got a good dietician who can help you.

Q: His calorie intake apart from his peg is about zero so nothing else is introduced into his diet – are we missing out on anything?

VD: Calorie milk should have the full range of nutrients your child needs going in through the peg so you shouldn't have to worry.

Parent: Have you thought about tube feeding with a blended diet. Our daughter is orally very averse and we were feeding her with a gastroscopy tube and we were feeding her milk but we switched to a blended diet and we blend with a bit of nutrition and milk as well but she has completely transformed and thrived with the blended

diet. It's not sanctioned by the British Dietetics Association but it's very widespread. If you go on social media, you'll see lots of parents who do it and it makes a massive difference in our opinion. It's quite widespread in America.

BK: Some of the Costello mums have done just that – you've probably seen it on social media – but they have found it very beneficial to replace complete milk with a blended diet.

MP: The research we did on feeding was very much on the very small babies with just 6 months of life but later in childhood wasn't part of the research we did so there may be a research issue here.

IL: It sounds like there are opportunities for families to talk to each other – there's a family over here with feeding issues and developing strategies for that:

Parent: My son is 12 and a half and he's been tube fed since 6 months and had a gastrostomy at 16 months. We switched to a blended diet when he was 3 because he was vomiting everything. The doctors were fine actually and thought it was a good idea. The dietitians are another matter. It's been a very big uphill battle to get the dietitians on board but they are slowly kind of getting there. He is medically much much healthier, his colour is better and his energy is much better. It's a difficult one because those of us who do it almost all of us find real health benefits but the medical profession struggles because all of the NICE Guidelines say "don't do it" but if you find an old dietitian who was working 30-40 years ago, they say that's what we needed to do, that's fine.

Q: *When are the revised Noonan Syndrome Guidelines likely to be published in the UK and can you tell us some idea of the group working on them?*

BK: Well, we've started the process. There's a whole industry around Guidelines in general and the best methodology for developing Guidelines, and then if you add in Guidelines for rare diseases, that introduces a whole new complexity. So the European approach to Guidelines is now very well delineated and there's a website for Guidelines for Rare Diseases and they use a methodology called AGREE II. And so in December I had a medical student come and she looked at our existing Guidelines from the point of view of AGREE II so that we can make sure the new Guidelines are compliant with that because that's best practice. So we started with that process and in fact, apart from the area of patient involvement, our existing Guidelines scored very well on AGREE II measure even though it wasn't in existence at the time we did them. It's very labour intensive – [there are] many publications a year on Noonan Syndrome and we're talking about all publications since probably 2009 so we're probably looking at evaluating 700 publications in terms of whether or not they have anything useful to say about the Guidelines. So it's not something you can just sit down and write tonight or next week and ideally what we'd have is someone who's actually resourced to do the literature search and so on. Having said all that, there's a big EU programme currently which is setting up European reference networks and Manchester is leading one application on congenital malformations and intellectual disability and there will be a Guideline theme for that and if we are successful there will be some funding for that and we will probably make the Noonans Guidelines the first one that we did. When we meet on the Friday

morning in Barcelona, we're going to hear first of all from Ineke van der Burgt who was the person who came up with the diagnostic criteria for Noonan Syndrome originally. So she's going to talk about whether they are appropriate and I think that's quite a challenging question actually. And the other thing we're going to do earlier in the day is hear from the French who have just developed some guidelines for Noonan Syndrome because the French have very bureaucratic, very labour-intensive approach to guideline development and it may well be actually that a lot of the work we need to do they've already been done. So until this has got a bit further down the track, I can't give you a timescale but I'm hoping what we'll have it done within the next 12 months.

MP: I know you have other questions which have been sent in but maybe we should look at these afterwards and maybe email people if it's appropriate because I don't think we're going to be able to take any more questions if that's the time in the programme.

IL: I think we do have to draw it to a conclusion. Obviously we do want to get you on the road at a decent time but I have got some more questions which we haven't got to but what we'll do is try to get answers to those and either email people individually or possibly put them up on the website so you can see the answers to those questions on the website. It will take a little while but we can't cover everything obviously and we have got some questions from people who can't be here today so we'll try to bring them together on one section, probably on the website as I think that's a good place to put it and it's available to everyone which is what we've done before. I think I'm right in saying the existing guidelines are on the website and what would help us, because we are going to a part of that meeting in Barcelona – Bronwyn mentioned it earlier - is to ask you to look at those guidelines and flag up with us any areas that you think might need to be looked at and also the way in which they are presented from a family point of view – do you have any thoughts on that. So it's an opportunity. Feed that into Peter Clarke and then Peter will be feeding stuff to me as well so that when we go to Barcelona, we'll be going armed with your thoughts and suggestions and we can make a good contribution to the changes.

I would really like to thank the panel. I think there are always aspects when you come to these meetings and I've come to a few over the years – a couple of families said to me earlier on that they'd had quite a late diagnosis of Noonans and you sort of think "are we making progress here?" because my own son was diagnosed 30 years ago and there are still families in the room where diagnosis was really made quite late. Then you hear what we've heard today in terms of the work that is going on and you also see very visibly the commitment of this group of people who've given up their Saturdays to come here – to make the effort and come here – they don't need to do that and they've done that today and I think you'll join me in saying they've absolutely handled all the questions both individually from families and in the session with great patience and great knowledge and great understanding. I hope everyone is walking out of here with a much better understanding and knowledge they can use to help their families. So I think they deserve a fantastic round of applause from all of us.