Podcast 7. Cynthia Morton & Eliot Shearer "Genetic Newborn Hearing Screening: Time for a Paradigm Shift?"

This text is an edited transcript of a recorded podcast.

Hello and welcome once again to a ManCAD / British Academy of Audiology podcast. You might well know that ManCAD stands for Manchester Centre for Audiology and Deafness and that we are located at the University of Manchester in the UK.

I am Gabrielle (Gaby) Saunders. I'm a Senior Research Fellow at ManCAD and I moderate these podcasts.

We always try to address the topics pertinent to the practise of audiology but also want to make sure that they are relevant to researchers and anyone interested in hearing and hearing loss. Some of them are specific COVID related issues and others are more general considerations in audiology.

We will record a new podcast each month each one will be about 20-30 minutes long and we will post the audio recording along with a transcript on our University of Manchester webpages.

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http://research.bmh.manchester.ac.uk/ManCAD/Podcast/

Gaby: Today we have a double bill; I am going to be chatting to Cynthia Morton & Eliot Shearer both from Harvard Medical School in the US. Cynthia also has a part-time faculty position at ManCAD. Cynthia is a Medical Geneticist and Eliot is a Paediatric Otolaryngologist. They share an understanding interest in the genetics of deafness. They have a particular interest in comprehensive newborn hearing screening to improve identification of deaf and hard of hearing children. That is what they will be discussing today but specifically genetic newborn hearing screening.

Before we start Q&A lets say a bit about yourselves. Cynthia why don't you go ahead.

Cynthia: First of all I would like to say Hi to all my ManCAD colleagues, missing you dearly, but hope to see you perhaps early in 2021. So proud to be part of that group. This topic has been a great interest to me since the mid 2000's when I published a paper with the Chairman of my Graduate School, Walter Nance, in the New England Journal of Medicine entitled "Newborn Hearing Screening: A Silent Revolution". Since that time have really thought that we needed to advocate for genetic etiologies incorporated into newborn hearing screening. This is something that has really resonated with me for a long time.

Eliot: Thanks a lot for having me, am really excited to be here and talk to you. I always love talking with Cynthia and have been working on this project for a few years now. I am a Paediatric Otolaryngologist, attending physician at Boston Children's Hospital and have an appointment at Harvard Medical School. I have been interesting in genetic hearing loss since I started my PhD. I worked on development of a comprehensive genetic testing platform using massively parallel sequencing, which we launched on a clinical basis in 2011. My research is focussed on genetic hearing loss and ways to improve genetic testing and genetic screening for hearing loss as a way to directly impact my patients. Happy to be here.

Gaby: Thank you. You titled this podcast "Genetic Newborn Hearing Screening: Time for a Paradigm "Shift?" which implies then that you are proposing a change to the status quo of newborn hearing screening. Before we get onto what you are proposing, I think it would help our listeners if you tell us a bit more about the current model of screening and what takes place in the standard newborn hearing screening. Eliot why don't you tell us about that.

Eliot: A couple of important points, before we criticise anything we have to talk about how successful it's been. Universal newborn hearing screening has dramatically changed care of children with hearing loss

and individuals with hearing loss. Also, I would like to point out that what Cynthia and I know about is the US newborn hearing screening protocols and so this may differ somewhat in other parts of the world. But really the newborn hearing screening as we know it developed as a result of a lot of research in the 1990's and that research showed that early identification of hearing loss in children is key to best outcomes from a speech and language perspective. So based on this research the universal newborn hearing screening was proposed in the late 90's and then adopted in the early 2000's in the US and now it's mandated in 43 States by Law and in the rest of the states they have a newborn hearing screening programme without a law. Newborn hearing screening is just one step of the process. The Joint Committee on Infant Hearing (JCIH) in the US has a guideline called the 1-3-6 guideline. Screening is the first part of that and is supposed to be done by one month of age and diagnosis by 3 months and intervention by 6 months; so that's where the 1-3-6 comes from. When we think about newborn hearing screening, it's good to differentiate it and delineate it as a physiological screen. What I mean by that is that we are testing the auditory system function in response to sound, so we are playing a sound and evaluating the response to that sound.

There are two methods that are widely used as a screening test. It can vary by in the US by state and sometimes by institution. The two different tests are otoacoustic emission (OAE). I think of OAE as a reflex, it's kind of like hitting your knee or patella tendon with a reflex hammer, the sound goes into the ear and the ear actually plays the sound back and you're not actually watching the sound go to the brainstem. Whereas with the auditory brainstem response also called ABR or automated ABR or AABR or VAER is what a lot of people call it. That's kind of like an EEG for hearing. A sound is played and an electrical stimulus is followed towards the brain. So really the physiologic newborn hearing screening which is what most people talk as a hearing screen is composed of one of those 2 tests. Here in Massachusetts and lots of places in the US, you have an initial screen in the hospital followed by a re-screen if the patient fails that. That's done on an outpatient basis. After screening comes diagnosis, everything according to the guidelines hopefully.

Gaby: That seems pretty sensible. What are the advantages and ultimately if you are proposing a change what are the limitations of this?

Eliot: Like I said it's been enormously successful and we don't want to discount that. When it was first implemented, there was only a couple of hundred children with hearing loss in the US identified per year before the age of 1. Now it's 6 or 7 thousand a year so it's been very successful. It's been widely adopted, most recent data in the US at least, shows that 98.3% of newborns are screened at least once by newborn hearing screening. Other thing is that it's really easy to train people to do this test. So most people at least in the US who are doing this screening are trained providers, so they are going into a room soon after a baby is born and performing a screening test. So it's not a complicated test and doesn't take a lot of time so those are big advantages of it. The disadvantages that Cynthia and I and others focus on in the paper where we propose this comprehensive newborn hearing screening is that there are 4 primary disadvantages that think of:

One is that newborn hearing screening as it stands in the US has a high false positive rate. What I mean by that is that if you look at all the kids who are screened using the newborn hearing screening; at the end of the day only 16% of them are actually found to have permanent hearing loss - which is the goal of this screening. There is a lot of debate about semantics and the math behind this and everything. When I think about a false positive rate and most other clinicians think about it, the goal of hearing screening is to identify permanent hearing loss in children and 83.7% of kids that fail the newborn hearing screening actually have normal hearing. That's a missed opportunity and that leads into this second big disadvantage of newborn hearing screening which is loss to follow up. So a huge percentage, about 30% of kids who fail on their newborn hearing screening don't come back and aren't evaluated again. The main reason for this is because the screeners and the paediatricians who interact with these families say well it's most likely they have normal hearing. Which is true, absolutely true, but at the same time we don't want to lose patients and we are losing kids who have hearing loss because they don't return to

follow up. The third reason that current newborn hearing screening could be improved is that we are not identifying certain types of hearing loss, so mild or moderate hearing loss for instance is often not picked up by the current physiological newborn hearing screening. Any hearing loss that occurs right after the newborn period is not identified. Specific types of hearing loss like autosomal or auditory neuropathy spectrum disorder (ANSD) is not evaluated at all if you just perform an OAE test. There are several different types of deafness that are not identified by the physiologic screen.

Finally, the result you get from the screen is either pass or fail. You don't get any other etiology or diagnosis. It just says you passed or failed. We think that probably underlies some of the loss to follow up as well because we are not providing solid information to families at a crucial juncture for them to follow up.

Gaby: I guess the issue about the false positives is a) the cost of the programmes is higher than it need be and b) that you are also adding to the stress of the parents who needn't be worrying. Is that what the main concerns about false positives are?

Eliot: Exactly. It's a huge source of stress for parents and actually my daughter failed in one ear so I know exactly what it feels like. You have to hand it to these screeners. They work hard to go and screen these kids and it's a huge difficult topic to broach with a family with a beautiful newborn baby to say well they just failed this test. No-one wants to hear that they failed. Screeners and paediatricians are probably trying to help by saying that it's probably normal but we think that leads to a loss of follow up.

Gaby: Makes a lot of sense. So what are you proposing then?

Eliot: So, and Cynthia you can chime in if you have any comments so far. What we are proposing really is to make a comprehensive newborn hearing screen. Right now, the paradigm is, you fail the screen and you go onto diagnosis. Really our idea is to combine the physiologic screen with genetic screening at the same time as well as with screening for or testing for congenital cytomegalovirus (congenital CMV) which we haven't talked about. As Cynthia puts so nicely in her paper in New England Journal of Medicine it's about 20% of congenital hearing loss is due to congenital CMV. We won't talk about more about it on this podcast but it's a treatable form of hearing loss so very important to diagnose early. So if we can combine a physiological test, the genetic screening of at least some common genetic variants and congenital CMV at the same time. We think we would be able to improve our ability to provide etiologic information or diagnostic information and we would also be able to pick up other forms of hearing loss which are otherwise missed by the current newborn hearing screen.

Gaby: So the advantages of genetic screening are clearly picking up the CMV. What else is there to add?

Cynthia: That you can make compelling arguments for a few clear advantages. One is that it would allow us to optimise current and future management. For example, it could impact the choice of facilitation based on the underlying genetic cause. The underlying genetic cause that might have other systems involved later on such as usher syndrome. So in the newborn just screened, a child might not pass their newborn screening test, but there would be no way to distinguish that child from a child who didn't have usher syndrome at that point. Certainly might influence whether the parents would choose sign language as a means of facilitation versus cochlear implant or hearing aids. That's one advantage. Also, it turns out we are more aware now. We have known for a while that there was an increase from the birth rate of deafness to school age and we didn't have a really good idea about that. I think there were definitely some cases that some individuals, some babies, who have well respected genes and variants within them that are responsible for deafness are simply not penetrating in that newborn period. So they pass their newborn hearing screening test and yet later before school age they are diagnosed with hearing loss and in some ways those kids are like the ones before we even had newborn hearing screening. Their parents and their paediatrician know they passed their hearing screening so they don't think that would be a

problem so that's been something that has been more well known now through these big screens that have occurred in Asia.

There is potentially some savings in the way children are worked up here in that there could be a reduction in other testing. If you knew that the genetic etiology of the hearing loss, you might not have to worry about some others things. You might not need to do an EKG to rule out Jervell Lange-Nielsen syndrome. You might not need a CT because you just know that that's not a finding that's associated with that particular genetic etiology that's defined. Our Healthcare systems and Governments really love to find ways that we can potentially use our medical healthcare dollars in the best possible way and this way really could potentially reduce some of that follow up testing. Other thing that's really heartening as a geneticist is that families in Asia who received information that their child had genetic variants that were well recognised to cause hearing loss were more likely than not to come in for the follow testing. The fact that the functional testing does have a false positive rate that alone wasn't the driver in coming up for follow up. Once they got that report that there was a genetic variant, they were really much more likely to show up for their follow up exams.

Gaby: Just for my own clarity then. If you do this genetic testing, it would seem that you are being more specific and could you potential rule out some of those false positives from the physiological testing by saying well also there are no genetic signs so would you be comfortable in saying there's fewer people we need to follow up?

Cynthia: I don't think we would want to do that and especially there could have been some birth trauma or some other etiology of other hearing loss so I think we really would want those children to continue to be followed in the regular system.

Gaby: Could you apply some of this genetic testing in other non-hearing newborn screening?

Cynthia: I think this is the future of newborn hearing screening. I think that hearing and deafness are maybe perhaps an easy place to engage the public. Many of the things that are screened for, on a newborn screening programmes, are metabolic diseases; many of them rare disorders that maybe have scary names and you've never heard of them before and there's not a general discussion of what is on every newborn screening panel. I feel that the public has a better understanding and less fear perhaps of deafness as a finding from a newborn screening. We have therapies; we have hearing aids, we have sign language, we have cochlear implants. There is really something that they are also probably more familiar with than some diets that children would have to be put on to prevent disorders occurring that are related to their genetic findings. Another thing that I think is quite true is that most kids with hearing loss are born to parents who have normal hearing. This is not something that these families are knowledgeable about how to negotiate the system. I think it would be good for them to be facilitated by having some genetic etiology and following a path of care for that. I will just say that the newborn screening is typically a heel-stick for a blood sample so it differs from the current newborn hearing screening because it's a functional test.

Gaby: But because you take blood sample anyway, you could use it for genetic analysis.

Cynthia: I think that lays into something else that we maybe wanted to address. The implications in screening during times like we are living right now through a pandemic. We can talk about that as we talk about the Covid survey that we have done.

Gaby: Which is a great segway into the Covid survey. Being the world we are in, we keep talking about covid and I know that you have recently completed a study about newborn hearing screening during the pandemic. Will you tell us a bit about that?

Eliot: Cynthia and I started talking about this over the summer as something we were concerned about when we saw rationing of care and changes in standard clinical care at least in the United States during the covid pandemic. We wanted to look at the effect on newborn hearing screening in the US during the

pandemic and the way we did this was two different ways. We looked at State level data. Actual objective date for the number of newborn's that came in for newborn hearing screening. It's surprisingly difficult to get this data in the US because of the patchwork of States and different rules for access to the data but we did get data from 5 different states across the US. Then we did a nationwide survey of audiologists and newborn hearing screeners to see what they thought the effect of the pandemic was on newborn hearing screening.

What we found was a significant drop in the newborn hearing screening. Initial in-hospital screening in the US decreased 11 per 1000 births which is pretty significant but then the secondary outpatient follow up screen that we talked about dropped by 26% just in this study period so a lot less kids are showing back up again for that follow up. What we were able to calculate is that if you extrapolated that the current covid period data that we have is some 7 months past March to the entire US over the course of a year we would be missing 660 children with permanent hearing loss in the US per year. We are not through the pandemic yet and we expect that this trend will continue and get worse unfortunately.

The audiologists and newborn hearing screeners that we surveyed ¾ of them saw a significant change to their clinical care for these kids and newborn hearing screening. Nearly half of them actually were deferring newborn hearing screening because of the pandemic and because of staffing issues. What was frightening to us was that in 40% of cases the respondents said they were not tracking the kids that were being lost. We are having the experience now where kids will be disappearing until they show up later and are found to have hearing loss and we know this has significant effects on their speech and language development later. This represents another opportunity where we can improve the screen. If we are only able to contact these patients at one point, typically when they are in the hospital after the baby is born, that's the time to get all the data that we need, that's the time to do all the testing that we can do, at the same time. If we are only able to get one time period to get access to them, then doing genetic testing or genetic screening as well as congenital CMV testing at the same time would be most beneficial, we think.

Gaby: That's shocking that 40% of people are not being tracked.

Eliot: We are going to do a follow up survey of course to see this but we are hypothesising that this is just because everybody in all walks of life are scrambling to sort this out. We found out from many survey responders that many people were being just immediately furloughed from their jobs and so there just weren't staff available to track. They just didn't have the manpower to do it.

Gaby: The naïve ones amongst us would have thought there would be electronic chart notes that you can look back into easily enough to find out what's going on.

Eliot: You would hope so, but in the US, it's a patchwork every hospital has a electronic different medical record. Even in Boston; there's 3 hospitals within 200 feet of each other and each one has a different medical record to access and it takes time to access. I am sure, everyone wants what's best for these kids and I am sure people are going to try and go back after but it is disturbing to hear that we may be missing some of these kids.

Gaby: If we had already had genetic testing set up do you think it would have been different. How do you see that process would have been happening?

Cynthia: I mentioned the traditional newborn screening test is the heel-stick blood test and I think there was probably much less disruption in that testing that occurred. If there was genetic testing for hearing on that same panel, I think we would be able to at least pick up those cases that we know have genetic etiologies that lead to take hearing impairment. Certainly, that doesn't mean that that testing also doesn't get interrupted because there was a loss of newborn screening that occurred in this country following hurricane Catrina in New Orleans. Kids were born and were not tracked. There was a big scramble after the hurricane to try to track down all those kids and get newborn screening performed. I still think had this been in the routine panel of tests it would have been more likely to have taken place.

Gaby: What proportion of newborns, born deaf, would the deafness be due to something that you would pick up with a genetic screening versus other forms of deafness?

Eliot: In newborns congenital hearing loss that's profound upto 60% is genetic and so it's a significant proportion. The issue which Cynthia and I and other people are working on is what sort of genetic screen you would actually do. What genes you would test for, what mutations in those genes. That varies by how severe the hearing loss is and ethnicity of the individuals. There is a lot of work to be done but a couple of papers now from Asia have looked a testing a handful of genetic mutations that are most common and their results are promising.

Gaby: What is the process to try and get this happening and what might a timeline look like?

Cynthia: I would say that we are excited to welcome a new administration to the US that values science. To put it a little bit in context for you, although I am sure you are bombarded with the news from our country for the past four years. I have to say that I was taken back by an article published by Politico Oct 20th, which was indicating that the Trump administration would consider, in essence, sort of punishing Cities/States whose Democratic governors were not controlling lawlessness etc. The Dept of Health and Human Services was asked to provide some lists. Newborn hearing screening was on the list for being unfunded in Washington DC. The Mayor in Washington and our President have not seen the same on various issues and so they indicated that that could be 423,000 for universal hearing screening for newborns in the District of Columbia. I still find many things hard to believe when I hear about them but then things I have seen happen, I don't know. Somebody has put this on a piece of paper as a possible somewhat punishment.

Gaby: So it seems that in terms of this, there is a way forward as you see it now.

Cynthia: Absolutely. President Elect Biden has made it clear that he values science on many occasions and so I believe that this is part of that science that would have more attention and possibility at this time.

Gaby: Before we end, is there anything else either of you would like to add about this topic?

Cynthia: Maybe we should just focus a second about what happens in England. There is a goal for genomic medicine laboratories to actually test for over 100 variants for newborns who don't pass their hearing testing, they are confirmed to be deaf. Obviously, everything is delayed because of covid but it really is putting that in place whereas that's not always possible for us because of insurance concerns that Americans have.

Gaby: The UK is probably further ahead in establishing this than the US?

Cynthia: We still would miss the kids that are not in the directly newborn period.

Gaby: Eliot do you have anything to add

Eliot: Lots of work to be done. Everyone who looks a newborn hearing screening is kind of united in the idea that we need to improve it in order to identify these children early. Lots of different approaches to looking at this, using different sequencing techniques, looking at different genes and mutations and ultimately I think doing a comprehensive genetic screen is going to help us identify infants with hearing loss.

Gaby: I think it is really exciting, to be on the forefront of this kind of research that can have such a dramatic impact that I think that's wonderful.

All it remains for me to do is say thank you for your time and sharing your thoughts. Thank you both for this.

If the audience have any follow up questions, feedback or share ideas for future topics please contact me. You can send me an email. Gabrielle.Saunders@manchester.ac.uk

I hope you enjoyed this discussion and are going to come back to the next podcast. Until then farewell and stay well.

References:

Ehley B, Roubein R: White House looks at cutting Covid funds, newborn screening in 'anarchist' cities. https://www.politico.com/news/2020/10/20/white-house-cuts-city-funds-coronavirus-430498

Howell RR: We must now put in place an updated, comprehensive newborn screening program for deaf and hard-of-hearing infants. Genet. Med., 2019; 21:2439-2441. https://doi.org/10.1038/s41436-019-0638-3

Morton CC, Nance WE: Newborn hearing screening: A silent revolution. N. Engl. J. Med. 2006; 354:2151-2164. doi: 10.1056/NEJMra050700
https://www.nejm.org/doi/full/10.1056/nejmra050700?casa_token=YImtp6eghw8AAAAA:e-TFxz48hWjeJdIZnvkEvTvo_LvcrSWYw9JJr3p5W9tUjqt_YjeaKQGVFTHZ1FEkeYe3OcKrvHP3EA

Shearer AE, Shen J, Amr S, Morton CC, Smith RJ on behalf of the Newborn Hearing Screening Working Group of the National Coordinating Center for the Regional Genetics Networks: A proposal for comprehensive newborn hearing screening to improve identification of deaf and hard of hearing children. Genet. Med., 2019; 21:2614-2630. https://doi.org/10.1038/s41436-019-0563-5

Wang Q, Xiang J, Sun J, Yang Y, Guan J, Wang D, Song C, Guo L, Wang H, Chen Y, Leng J, Wang X, Zhang J, Han B, Zou J, Yan C, Zhao L, Luo H, Han Y, Yuan W, Zhang H, Wang W, Wang J, Yang H, Xu X, Yin Y, Morton CC, Zhao L, Zhu S, Shen J, Peng Z: Nationwide population genetic screening improves outcomes of newborn screening for hearing loss in China. Genet. Med., 2019; 21:2231-2238. https://doi.org/10.1038/s41436-019-0481-6