Introduction

Dr Richard Finkel: Hello, and welcome to this CMA webcast on the update of the standard of care recommendations for spinal muscular atrophy (SMA). My name is Dr Richard Finkel, and I am the Chief of the Division of Neurology in the Department of Pediatrics at the Nemours Children's Hospital in Orlando, Florida. I am joined today by Dr Tom Crawford, who’s the Director of the neuromuscular program in the Department of Neurology at the Johns Hopkins Hospital in Baltimore, Maryland.

Educational Objectives

Dr Tom Crawford: Following this activity the participants should be able to implement the currently recommended algorithm for SMA diagnosis in daily clinical practice; to apply a multidisciplinary approach to the management of SMA according to current best practices; to develop a comprehensive care plan in close cooperation with neurologists, physical therapists, respiratory therapists, and all the other medical specialties of the multidisciplinary team; and to describe the key benefits of the first treatment approval for the management of SMA.

Purpose of the Spinal Muscular Atrophy Standard of Care

One of the important questions is why is there a standard of care? What is the purpose of a standard of care? I see four reasons why a standard of care is important.

First, and most obvious, is that it supplies an aspirational or an optimal care guideline of what things can be accomplished, what things we should all try to accomplish, knowing, of course, that there are substantial difficulties with availability and resources available at any one place.

Another important thing is to have it as a justification for resource allocation. Every country, every city, has constraints of what’s available, what’s possibly there
financially or in the institution available, and a standard of care provides the opportunity to say this is what is thought by experts around the world to be important.

It is also important to note that multidisciplinary care is important, and this is a document that identifies how multidisciplinary care can make a difference and that will come through in later discussions here.

A third reason for the standard of care is to help the experts know where the gaps are, to figure out where it is that we haven’t moved from expert opinion, to data, to multidisciplinary proof at higher and higher levels of standards.

The final one is important for research protocols for new therapies. We require that patients be treated according to the standard of care in order to minimise the amount of variation that you would see and improve the accuracy and the efficiency of clinical trials.

Dr Finkel: Tom, I think those are all really important points. Let me talk now about some of the goals of the new standard of care consensus, and I think it is important to remember that these are guidelines. It is not a formal practice parameter because this was largely derived by expert opinion and is not so much data driven. We wish we had a lot of randomized controlled-type data from trials on which to base these opinions, but largely, we got together people in a room to see where we could agree upon certain topics and also identify, as you said, the gaps. What do we not know, and what do we need to focus on going forward?

Dr Crawford: One of the things is, we even debated about whether to call it a standard or a practice parameter, but there is this issue about whether or not it’s a consensus. It’s the considerations that we wanted to have, and one of the debates we had was exactly what to call it. We did agree upon standard of care.

Dr Finkel: Exactly, and I think it is important for those that read the documents and are listening to this webinar to recognize that these are guidelines. They are not written in stone, and, in fact, these are evolving over time as well, as we learn more about SMA. In particular, now that we have treatments for SMA, we are going to see a changing phenotype, and we are going to see changes in how we care for these patients with SMA.

So I think these will be an important basis for the evaluation and the management of patients with SMA going forward.

The need for the care is going to continue. It is not going to go away in the face of these new treatments.
Practice goals of the Spinal Muscular Atrophy Standard of Care

How is this really going to be helpful to the patient and the parents of a child with SMA? Hopefully, these standards of care will reduce the diagnostic odyssey of what we call the whole process of taking a child who has some hypotonia, some motor delays, and a suspicion of SMA, and trying to move forward. How do we make that diagnosis most efficiently, with the least burden on the patient and the family? You are going to talk about that in a moment.

I think also we want to make the point that it is really important to identify patients with SMA as early as possible so that we can discuss different treatment options now that those are available.

A third point is that having these care guidelines allows us to have some anticipatory guidance. We know with a child with type 1 or type 2 SMA what the natural history course is likely to be. We know that we need to pay attention to their pulmonary care, nutritional aspects, orthopedic concerns. To get on top of these aspects early in their course, shortly after diagnosis, we feel is important, and these guidelines can be quite helpful in that regard.

In that same sense, we are now focusing more on what we would call proactive care as opposed to reactive care. Not waiting for there to be a problem, but saying we can anticipate this. How can we get going with proactive management?

Standards of Care and the Changing Natural History of Spinal Muscular Atrophy

We also have to keep in mind that the natural history of SMA is changing now that we have better supportive care and with drugs being approved for SMA. Of course that’s going to change the whole phenotype. So how we use these care guidelines is certainly going to change over time.

**Dr Crawford:** One of the things that is interesting is that the meetings for this were before the approval of the most recent SMA-enhancing therapy, but everyone in the room knew that it was coming. The guidelines reflect the optimum clinical care at that time, but they actually aren't undermined by any of the new developments. We still care about caring. We still care about managing all the complications of SMA exactly as it was before. Nothing has changed, but we have added the new opportunities, and so while things are changing, they are also always the same.

**Dr Finkel:** Right, I think it emphasizes the point that we are going to need to be on our toes. We are going to need to keep in mind these care guidelines because
The phenotype is going to change, but the basic issues are still there and will need to be addressed.

Adaptation of Spinal Muscular Atrophy Subtype Classification to Functional Status

Dr Finkel: Maybe a third point to mention here is that when we think about SMA, these children are characterized as type 1, meaning babies who never achieve independent sitting; or type 2, sit but don’t walk; and type 3, walkers. However, when we actually see them in the clinic we look at them more at their current functional level, so the care guidelines really address the child from are they a non-sitter, a sitter, or a walker, independent of whether they may have been a sitter at one point, a type 2, but they may have lost that skill so now we are going to functionally look at them as a non-sitter.

Dr Crawford: That was one of the changes from the previous guidelines.

Further Changes from 2007 Guidelines

Dr Finkel: Exactly, and if you compare the original guidelines from 2007 with these updated guidelines from 2017, several of the topics are the same but have been updated. So the pulmonary management, GI, nutrition, and orthopedic topics really underwent quite a bit of revision, which we will talk about in a moment.

I think also there has been some evolution in how we look at the physical therapy and the rehabilitation, and, importantly, you led the ethics and palliative care topic, and I think it is important that those issues should be kept in mind when we are treating a patient with SMA – that having these new treatments does not remove the need for these ethical considerations.

Dr Crawford: Palliative care, doing good, is timeless. It hasn’t changed from before or after new therapies or from 2007 to 2017.

Further Changes from 2007 Guidelines

Dr Finkel: The new guidelines did add a couple of new topics. There’s a focus now on acute care management. What do we do for the patient who’s in the hospital, who might have an acute illness like acute respiratory distress? Or a post-operative patient – how do we manage those patients better?

In addition, we are starting to focus more on other organ systems. Having a deficiency of this SMN protein, what does it mean for muscle? What does it mean for the GI system or other parts of the body? We are trying to recognize that while we
have these treatments, they may be restoring SMN protein in motor neurons, but not necessarily in other tissues of the body. So we have to consider these in children.

Diagnosis

Important Factors in the Diagnostic Processes

Dr Finkel: Tom, let me ask you now to discuss some of the issues regarding the diagnosis and the importance of the genetics of SMA. How has this changed, and what are some of the challenges that the clinician needs to keep in mind?

Dr Crawford: One of the biggest changes, and one of the things that I think we are going to have to really push, is that the evaluation of a hypotonic child is different now. In the past I think most pediatricians were schooled appropriately that a “floppy” baby more often than not is going to get better. Just see it along, see him back in a month or two, and see how things are going, because if he gets better, you didn’t venture, you didn’t lose anything.

Nowadays, of course, that month or 2 is critical to the efficacy of the therapies we have, so we need to change practice across the entire spectrum of medical specialties. Pediatricians need to send the “floppy” baby to a neurologist immediately with a tag that this is important.

Simple Diagnostic Signs for Pediatricians

Dr Finkel: What should the pediatrician look for at that well-child visit?

Dr Crawford: We have together developed these ideas of what babies are supposed to do. Certainly any baby, when you put them on the table and support their weight, should extend their legs and support their weight. They are not going to stand, of course, but at least they can support their weight when you are holding them under the axilla.

Most babies, by the time they are a month or 2 old, are going to have reasonably good head control and we want to see that head control is improving. Any time we have a story of a baby where a mother says, “He could do this before, but not now. There’s a change” – that is going to be one of the important tells, and we want pediatricians to be paying attention to that. Because in the past they would say, “Yes, but I don’t see anything abnormal. Let’s just kick this along for a little while and see”, but that loss of something is one of the most important tells for SMA.
I am fond of another one, which I call the de-rotary (actually, it has been called de-rotary for decades) where you put the child on the table and rotate the pelvis, and if the shoulder girdle stays behind, or the other way around that when you rotate the shoulder girdle and the pelvis stays behind, that tells you there is weakness of the axial muscles.

It is interesting to me that we call type 1 a baby that never sits, that was diagnosed before 6 months of age, but in fact most of us when we see a 2-month old know this child is never going to sit. They are not supposed to sit at 2 or 3 months of age, but we know they are not going to because of that weakness of the trunk.

Those are the tells that should get a pediatrician to a neurologist, and certainly a neurologist sees that bright face and the axial weakness with relatively better power in the arms and legs, and knows that’s SMA, that could easily be SMA.

Now we have this new urgency. The pediatrician needs to send the hypotonic baby right away. The neurologist has to have a way of bringing patients in and seeing those that are hypotonic quickly. It is a little bit like what child neurologists know for possible infantile spasms. You see that baby in days. Not necessarily that day, but in a few days. Certainly not in the rotation of 6 weeks from now.

**Diagnostic Algorithm**

The third thing is that the neurologists have to have a means to be able to send a test quickly.

**Dr Finkel:** What test is that? Where do we start, Tom?

**Dr Crawford:** Funny you should ask! It used to be that a hypotonic infant would get MRI, or EMG, or organic acids, or any number of other sorts of valuations to try to see what was wrong, and those are certainly meaningful in some of the children, but we have this genetic test. The gene test for SMA is both sensitive and specific. 95/96% of patients are going to have an abnormal test, and when the test is abnormal it is correct 100% of the time.

There aren’t very many tests that are that sensitive and that specific, and most of the commercial labs that do it will turn it around in a matter of a week, or not much more. We certainly don’t want to be sending it to a lab that is going to send it, and it holds in abeyance for a month before you finally get that test back.
Other Testing and Screening Considerations

That is one of the things that I want child neurologists and geneticists to know in advance – what’s the turnaround time? Because getting that answer back, literally the difference of a week or 2 can make a lot of difference in the newborn or the several-month old infant in terms of how much they can get back.

When you send the test, you want to send the test for the SMA gene test, and nowadays most labs will give you both the copy number of SMN1 and SMN2.

**Dr Finkel:** Let me talk a moment about the importance of this SMN2 copy number. I think you are absolutely right that you not only want to get that diagnosis established by confirming that there’s the deletion of the SMN1 gene on both alleles, the homozygous deletion, but it is important to try to get the lab to also give you the copy number of the back-up of this SMN2 gene.

I think we appreciate now that that’s a very strong prognostic biomarker. We can predict what the course is going to be for this child. If you have a little symptomatic baby, you can look at that child and say this is a type 1 infant, but knowing that the copy number is 2 or 3 does give you some advantage as well. And I think now that newborn screening is starting to come on the horizon, what we are going to have to do is think about how does the genotype, meaning the copy number, predict the phenotype? How good are we going to be at being able to predict how this apparently normal-looking newborn is going to actually evolve over time?

**Dr Crawford:** The interesting thing about newborn screening, it has achieved an acceptance but there are still regulatory issues about where it is going to be applied, commercial, how much it is going to pay, and which states and what nations are going to do it. I think we are both enthusiastic about the study and feel that it will be gaining acceptance in different places rather rapidly.

There is still going to be a place for diagnosing children with clinical features, and so we don’t want to put that aside completely.

**Dr Finkel:** Right, and I think that algorithm is very helpful because it guides you through the pathway. There is still a role for doing EMG, particularly if that genetic test is negative.

**Dr Crawford:** If the first test is negative. If you have one copy of the SMN1 you probably want to get a specialist who can say, “Does this really look like SMA, or does it look like something else other than SMA?” But if it really looks like SMA then we are going to be doing an additional genetic test to say is that one copy broken in
some novel way that wasn’t seen by the initial test. But that’s the 4% of children that aren’t cut by the initial screening.

**Dr Finkel:** That requires a different technology, is that right?

**Dr Crawford:** Yes, it does.

**Dr Finkel:** Therefore, the test that we would send for the initial diagnosis, really, is only good for the deletion. If you still suspect SMA you have to order a second type of test for sequencing, is that right?

**Dr Crawford:** And I would expect that’s the providence of neuromuscular specialists, to take the ball and roll after that. But if you have a child who you thought had SMA and has one copy of SMN1, that’s the one you want to refer to the specialist to do that process.

**Dr Finkel:** Right, so there is really still a role for, let’s say, EMG, but not as a first line. That’s sort of moved to a second tier.

**Dr Crawford:** We, EMG-ers have been demoted once again! There is still a role for EMG, but it’s after the genetic test has been returned.