INTERVIEW

Leukodystrophies: a Patient Advocacy Perspective

MARIA KEFALAS PhD is the co-founder and executive director of the Calliope Joy Foundation, a Philadelphia, PA based charity that advocates for children and families impacted by leukodystrophies. She has published essays about her life caring for her daughter, Callie, who has metachromatic leukodystrophy, in Slate, The Huffington Post, and STAT. Her advocacy for gene therapy was featured on CBS Sunday Morning with Jane Pauley. Ms. Kefalas is writing a memoir titled Investing in Miracles (Beacon Press, forthcoming) about her journey as a parent advocate. Cal is 8 years old and receives hospice care. But thanks to her doctors and nurses, Cal still laughs and smiles every day.

Q Please can you give those of our readers who are unfamiliar with leukodystrophy and with the Calliope Joy Foundation an introduction to both: what is the nature of the diseases in this particular group, and how and why did the Foundation come into being?

MK: The leukodystrophies are a family of inherited white matter diseases – a kind of distant cousin to multiple sclerosis, except that children with leukodystrophy inherit a broken gene that means their bodies have a deficiency of some enzymes that are crucial for healthy development of the brain and central nervous system. All leukodystrophies are characterized by children not being able

to tell their body what to do. Typically, that means that they have trouble speaking, walking, talking, swallowing, very severe GI issues – and all forms of leukodystrophy are fatal. There are some 50 forms of the disease and about 1 in 7,000 people are impacted by one or another of them. The most well-known disease in the group would be either Tay-Sachs (TSD) or adrenoleukodystrophy (ALD, also known as 'Lorenzo's Oil' disease) – those are probably the most common variations.

Our foundation was started in 2013, the year after my daughter's diagnosis with metachromatic leukodystrophy, one of the more common leukodystrophies. As is the case with most patients, she had been a perfectly normal delivery and birth and was absolutely fine until about age 2, when she started to regress – a very typical presentation. We were fortunate to be here in Philadelphia with one of the best children's hospitals in the world on our doorstep – the Children's Hospital of Philadelphia (CHOP). They diagnosed her within 2 days once they saw the MRI. Many families spend years in search of a diagnosis, so we were very fortunate to get it so quickly.

That was in 2012. Then, a year later, gene therapy started to emerge and on the anniversary of Cal's diagnosis, Science published a report by a team in Milan, Italy, led by a very young doctor named Alessandra Biffi, who had tried a gene replacement therapy on my daughter's disease, MLD, and in three of the children, they were not seeing the disease.

That was the moment that changed my life. I remember getting on a phone immediately with a neurologist at CHOP and I just said, "Is this for real?" It was just astounding. The paper showed normal MRIs and these kids should have had an MRI that looked all white from the damage. She confirmed that it was real and that this was a real game-changer.

At the time, we were doing some fund raising and honestly, our fundraising was focused on hospice and palliative care – that was pretty much all anyone could do. The neurologist suggested that I should think differently about fund raising: to try to help families get to this trial. My initial reaction was "You have to be kidding!" I couldn't imagine doing that because Cal was not eligible: the way gene therapy works is it slams the breaks on the disease so you can prevent damage, but you can't undo it.

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DOI: 10.18609/cgti.2018.075

Every single child in the trial had an older sibling with a disease – that's the only way they'd found these pre-symptomatic babies. She said, "You should help these families get to Italy". I said, "You've clearly mistaken me for a brave person!" She said, "No, you have to. Of course you will, because every single one of these families will have sacrificed at least one child to this disease. You have to give them this chance."

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A year later, in 2014, we were given this chance: an American child whose older sister had been diagnosed previously. This family, in Omaha, Nebraska, was quite literally selling firecrackers for 4th of July by the side of the road to get money to get to Milan. I see this beautiful little girl who looks so much like my daughter… It was 4 years ago this week, August 4th. That was it, I packed my bags and said "What do you need?"

So that was kind of the beginning of our journey. Since then, we've helped 12 children get to Milan. Now the oldest children are going to school and playing basketball. It never ceases to amaze me when I see them.

I saw the little girl from Omaha last May, she came to my house. She was running around the place, eating macaroni and playing video games. We just couldn't believe it – she should have been in a wheelchair, needing a feeding tube.

It's been kind of an amazing 4-year journey. When I met the folks at GSK a couple of years back, I said "You've given me a chance to have a front row seat at a medical miracle." I don't even think they knew what they had done: they're looking at papers, looking at MRIs, etc., but I don't know if they understand the actual impact, actually seeing these kids who should be dying, but they're going to school, they're having birthdays. These children reduce seasoned doctors to tears when they meet them – it's astounding! So that's what I do, I support them every way I can.

Q Can you tell us more about some of your current projects and activities relating to gene therapy?

MK: We're a small family foundation so we fundraise as much as we can – we provided over $100,000 in research grants here in

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the USA last year. We try to invest in the next generation of gene therapy researchers through our fundraising, plus we get people overseas to these clinical trials, of course.

Another big part of what we do is simply raising awareness and talking about gene therapy, teaching people about gene therapy: a couple of years ago, I wrote a children's book. I had been speaking to a US Congressman about gene therapy and you could see his eyes glazing over. You're sitting there, you have to support this work, it's actually happening here in Pennsylvania… I went out feeling quite discouraged. A colleague then suggested, half-jokingly, that I should write a children's book explaining gene therapy, so I did. We say it's for the children and families, but it actually came about because of a US Congressman!

I think the biggest challenge for gene therapy will not be about the science (which has of course had many hiccups, to say the least). It will be convincing people to pay for it and figuring out a sustainable business model. We saw with Glybera the failure of the first gene therapy product. I think a lot of people look at Glybera and what happened there and say "We're not going to make those mistakes again", but it's still an uncertain path.

Right now we have a political climate, particularly in the USA that causes me to worry that they won't pay for it. I'm old enough to remember the first heart transplant and the first bone marrow transplant, and nobody ever said in the 1980s "We can't afford a heart transplant, or afford to treat cancer". And yet now that's a very central part of this discussion. When the President of the USA is tweeting about drug pricing, you kind of sit there and think "What's going to happen?"

And it's both political sides make drug pricing a central issue in the USA – the politicization of the pharmaceutical industry and of drug pricing remains a really key challenge for us. So I find myself in this very odd situation where I feel like Cassandra from Greek mythology: I see the future in terms of what gene therapy can deliver, but people either look at me like I'm crazy when I tell them about it, or they tell me it's not worth the money. I'm just sitting there thinking I can't believe I'm having this conversation.

Q Do you have a vision for how this 'who will pay and how?' problem might be overcome? Who needs to step up to make sure there is patient access for future generations?

MK: I don't know if I'm clever enough to answer that question!

DOI: 10.18609/cgti.2018.075

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The pharmaceutical industry has made a lot of enemies over the years and I think that the lack of transparency in pricing feeds the public's frustration. I think that the industry has to be much more willing to discuss the whys and hows of the pricing models that they're using. Of course, industry is going to optimize and maximize profits, but I think it would be amazing to have transparent negotiating systems in the USA and Europe – where just as you have to go to FDA and EMA for approval, you then have to go to another board that reviews your pricing, which negotiates and explains the outcome. I honestly think if there was more transparency there would be more public willingness to support expensive gene therapies.

I think Spark Therapeutics has engaged in some interesting ideas around making payment outcomes based. It was actually the Italians that came up with this idea – only paying for a treatment that works in oncology. The first time I heard about it I thought it was a joke, but it is seems to be catching on here in the USA, especially in relation to the new CAR T cell immunotherapy products. I'm not sure how you would decide if it's working, or working sufficiently – I can imagine a situation where people might say a drug is not working when it actually is... I'm not sure how you would measure efficacy over time because having watched gene therapy, there is fade, of course. But it's not like the children suddenly become very sick – they might have some neuropathy or discomfort, but that pales into insignificance compared to the alternative.

Q Patient advocacy groups are increasingly recognized by pharma and biotech as a critical partner in the successful development and commercialization of novel gene therapies, especially in the rare diseases area – what are some of the keys to initiating and building such partnerships with industry from the patient advocate's point of view?

MK: Well, I do think that it's an increasingly controversial relationship here in the USA. Fairly recently, Senator Gillibrand in New

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York proposed legislation relating to the industry reporting gifts and grants given to patient advocacy groups because apparently, according to some, pharmaceutical companies now give more money to people like me than they do to lobbyists. Not me personally, I hasten to add – I don't get that much money from industry!

The concern within Government is that pharma companies can pump money into patient advocates and basically use them as unregulated lobbyists. So going back again to this point of transparency, I think there have to be more guidelines and best practices relating to the role of industry and these patient advocacy partnerships. I personally do report (on our website) any biotech or pharmaceutical company that gives more than a thousand dollars, because I want people to know exactly what our relationship is.

But it's a wonderful partnership when it's done responsibly and right now, it's up to both the industry, with their history of not being good at self-regulation, and also to patient advocacy groups like the Calliope Joy Foundation – literally, mom and pop operations – to make sure we do things right. So from my point of view, that's about maintaining our independence, our autonomy, and not allowing the possibility of being seen as unregulated lobbyists for industry. If that happens, we lose all our power.

That said, I think we do have a lot to bring to the table in terms of supporting academic and industry research and trials through our philanthropy. Certainly, in the rare disease space, a lot of work wouldn't have happened if families hadn't hosted beer and brats fundraisers or bake sales – some foundations have literally launched clinical trials that way.

I also think we have the power to educate industry about the real impact of what they're doing. We have a critical role to play with keeping patients in clinical trials, too, which has been a big issue – if you have a clinical trial that runs for a decade, you need someone to help keep those patents going back. I'm a big believer in less is more. I think sometimes foundations think they have to raise a million dollars to start a trial, but in fact, it's things like helping patients stay in the trials, or providing feedback to the study team on issues coming up that they can't contact the trial participants about directly, of course.

One of the big issues we have with gene therapy is you treat a child in a trial, then you send them back to Omaha, Nebraska, or Redding, California, or Switzerland, or Dublin, Ireland. You can't really then go to your average pediatrician and say my child received gene therapy – they won't know what to do with them. So follow-up care is a big issue. The Italian

DOI: 10.18609/cgti.2018.041

team we worked with were a transplant team. They had fixed the kids' genes, but they didn't know what to do with long-term care: the follow-up and ongoing management of these very special children. They were literally going back to the regular pediatricians.

How do you figure out whether a child had a speech problem, or fine motor coordination, because of gene therapy, or because it's something the child already had? This is the funny thing: people are fixing genes and giving patients working copies, but we still don't know completely what that means for these children. As patient advocates, we're learning a lot all the time, and we get to teach the study teams and sponsors, which is fun. These kids are teaching us everything, they're amazing, as are their families, to put themselves through it.

Q It was a fantastic achievement for the Calliope Joy Foundation to establish the USA's first Leukodystrophy Center of Excellence at The Children's Hospital of Philadelphia. What further new projects would you like to see the Foundation funding in future?

MK: Our biggest challenge – on top of cost/access, on top of research – is that we now have to find these children in time so that they can benefit from the treatment. There is really a very small window to diagnose these kids and treat them successfully. There was a marvellous piece in the *Wall Street Journal* a couple of months ago pointing out that gene therapies were moving at lightning speed, but diagnostics were still stuck in 1990s.

The go-to strategy has been newborn screening. Well, right now there must be dozens of disease groups that want to have their disease included on these newborn screening panels, and it's a very cumbersome, laborious, bureaucratic process. I don't know how many tests they can put on these little heel prick tests. At some point, of course, it's going to tip over to genomic testing.

The bottom line is these breakthroughs are not getting to patients who need them, so we need to reinvent the diagnostics piece. Maybe diagnostics will involve a direct marketing-to-patients approach? Do you direct market those genetic tests from the likes of 23 And Me? Do we direct market genomic screening to families and newborns? Do we supplement public health with commercial direct-to-patient consumer

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models? Do we train physicians to say "OK, this baby has had seizures, is having feeding issues… I want to do a whole genomic sequence" much sooner? Right now, they only do genomic sequencing when a kid is really sick. But the cost of genomic sequencing is coming down rapidly.

So I think we have to think outside the box. As I said earlier, I used to think the biggest problem was the science of gene therapy, but it turns out after 20-odd years, they've got it. It's very impressive. It's safe. It's efficacious. And now they've cracked the code, there are 160 gene therapy trials ongoing in the USA alone. It's exploding! They want to fix sickle cell anemia, they want to fix cystic fibrosis, they want to fix Duchenne, and I believe, from what I've seen in MLD, they will succeed. But the big problem remains the diagnostics and making sure those who can benefit from these treatments get them.

We've never really thought of medicine in terms of preventing disease outside of vaccinations: you don't treat cancer by preventing cancer, really – you respond to the disease and try to fight it back. But this is a very different model. It will require such a radical paradigm shift in pricing terms, within diagnostics. Forget about the fact you're taking the HIV virus and commercially manufacturing it and turning it into an inert viral vector that you can somehow commercially make available – mass-producing it. When I started working with the team in Milan, they didn't even know if they could freeze the vectors, so they would make them across the street and literally run them over to the children! In fact, right now, Orchard

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Therapeutics are doing a Phase 3 clinical trial that is looking at cryopreservation techniques.

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I feel oddly protective of the companies involved in this. There's something absurd about that, because my advocacy will help make them very wealthy. But that's part of what I'm fighting for, right? I have to work out a way for them to make a lot of money, to make it worth their while. That's the tension. But I don't know what's the right amount of money – I'm not that clever. I just know you can't let this fall apart because we're not making enough money.

Q Do you have a message for all the gene therapy researchers out there?

MK: You are making miracles possible. I'm so fortunate I get to witness this and I can't wait to see where the field is in 10 years. I can't wait to see the amazing things this world will make possible. We just have to figure it out.

Each year, we host a gala and there are a lot of children there who can't speak, who are quietly in wheelchairs with their families. My dream is that in 10 years' time, we will have a room full of healthy children running around and making a mess and driving everyone crazy. That would be amazing!

And one day, diseases like this will be managed as chronic, and kids will get to go to school. I see that future so clearly and I just want to thank them all for giving people like me hope, and to ask them not to give up on that future, on that dream, because it's worth fighting for.

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