# Unraveling Castleman Disease

Dr. David Fajgenbaum was diagnosed with a rare disorder that killed 35% of patients within five years of diagnosis. Dr. Fajgenbaum realised that he would have to lead the charge against his rare condition and we are talking to this young doctor about his incredible journey **unraveling Castleman Disease**. Castleman Disease is a rare disease of lymph nodes and related tissues. This is diagnosed in about 5000 people of all ages each year in the United States. This disorder activates the body's immune system, releasing excess inflammatory proteins that can shut down the liver, kidneys and bone marrow. Dr. David Fajgenbaum, Founding Director of the Castleman Disease Center at the University of Pennsylvania will be discussing the current understanding of the disease that he himself has had nearly for nine years, symptoms, treatment options and explore new trials and research that are in the offing. You can follow Dr. Fajgenbaum's slides **Here**.

**Full Transcript:**

**Priya Menon:** Good morning and welcome to Cure Talks. I am Priya Menon, your host and today we are discussing a rare disease called Castleman disease. February 28th is rare disease day and I think today the discussion is going to be as rare as it can get because we have with us a doctor who is spearheading advances in treatment and research in Castleman disease. He's also treating himself for the condition and earlier this year celebrated his fifth anniversary since he last experienced symptoms of the disease. We welcome Dr. David Fajgenbaum to CureTalks. Dr Fajgenbaum is founding director of the Castleman Disease Center at the University of Pennsylvania. In addition to many other responsibilities that he has at Penn. We will hear his incredible story and unravel Castleman disease in this hour on CureTalks. Welcome Dr Fajgenbaum. Pleasure to have you with us today.

**Dr David Fajgenbaum:** It's a pleasure to be on today. Thank you so much for having me.

**Priya:** The patient caregiver perspective will be discussed by the panel comprising of Mileva Repasky who is mother to Katie who has been diagnosed with Castleman disease. She's patient engagement director for Castleman Warrior program and is director, development for the Castleman disease collaborative network. We also have with us Gary Gravina who is a Castleman disease survivor now in remission and is involved with CDCN's research activities. Welcome to CureTalks Mileva and Gary. We will be addressing questions from the audience towards the end of the discussion. You can send in your questions to priya@trialx.com or you can also post your questions in the comments section. Dr Fajgenbaum has shared slides with us and you can follow them on the link given on the page you are listening to this program on. Dr Fajgenbaum now to the begin with the discussion. I know your story. It's a very compelling and it'd be really great if you could share a little bit more about your diagnosis and journey so far with us.

**Dr David Fajgenbaum:** Absolutely. And thank you for having me on the show and giving me the opportunity to share about Castleman disease and the work that so many people are doing to push forward the science. So I had never heard of Castleman disease, when I started medical school at the University of Pennsylvania. And, for my first two and a half years of medical school, I never had any medical issues and I was planning to become a clinical oncologist. I had lost my mom to cancer a few years before and I knew I wanted to be a doctor to treat cancer patients. And then I went from being this totally healthy third year medical student to being sick in the intensive care unit with night sweats and weight loss, abdominal pain. My liver began to shut down, my kidneys being in a shutdown and my bone marrow stopped functioning properly. And so I was hospitalized in the same intensive care unit at the University of Pennsylvania that I had previously worked in as a medical student and just got sicker and sicker by the day with no diagnosis. And it was absolutely terrifying to really lose grips on life, really without knowing what it was that was making me so sick. Fortunately over the course of several weeks, I eventually began to improve still with an unknown

explanation for what happened before I began to improve. I had a retinal hemorrhage and went blind in my left eye, went in and out of consciousness. But finally I began to regain my vision, regain consciousness, and some of my organs began to work again, but still no diagnosis. We didn't know what it was. Unfortunately, a few weeks later, everything came back. And again, I found myself in critical condition back in the hospital with liver failure, kidney failure, bone marrow failure, in and out of consciousness.

In fact, I was so sick the second time around that my physicians encouraged my family to say their goodbyes and a priest came in to administer my last rights to me. Of course I was unconscious and then I don't remember very much of that episode, but I was clearly very sick. But right before I was administered my last rites, an important diagnostic test was done, a lymph node biopsy was done on me. And a review of my lymph node indicated that I have a disease called idiopathic multicentric Castleman disease which is a rare and deadly inflammatory immune system disorder where your immune system gets out of control and begins to attack your healthy vital organs, and with that diagnosis, my doctors decided to start a form of chemotherapy on me to see if that could help to turn around my disease.

**Dr David Fajgenbaum:** And, that first dose of chemotherapy was enough to keep me alive. Though I was so sick it kept me alive and then I actually began to start to improve. Unfortunately I got sick again just a few weeks later and I was back in the ICU in critical condition again. And this time I needed much more intense chemotherapy. So I ended up getting seven agent combination chemotherapy, and with those multiple agents and chemotherapy, I finally began to improve and improve well enough that I could leave the hospital. After a total of almost six months in and out of the hospital, I was finally able to return home and to begin to improve. Over the course of that time, I learned a number of important lessons mainly and most important among them, just how short and precious life is. And, when I got out of the hospital I was so thankful, I was able to return to medical school and back on my mission, my plan to treat cancer patients. And then really everything came to a halt again. What about one year later I had another relapse of all of my previous symptoms, all of my previous organ failure and I was back in the hospital. But for that fourth one, the fourth hospitalization, I had been previously on a drug that we were hopeful could keep my disease in remission and could prevent a relapse. And clearly, I relapsed while on the drug. And so I had an important conversation with my physician, to understand what was known about Castleman disease and what other drugs were potentially in clinical trials or might be able to help me. And I learned from him just how little was known about the disease.

And I learned that there were no other drugs that were in development for Castleman disease. And, when I found that out, I turned to my wife and my sisters and I told them that I would dedicate the rest of my life however long that may be to trying to cure this disease. And, I was able to, I got multiagent chemotherapy again, so seven different chemotherapies, Adriamycin, Cytoxan, Dex-lenalidomide, Rituxan all combined. And finally, again, I began to improve. But this time when I returned to medical school, I wasn't back on the same track I was on before. This time I returned on a mission to take on Castleman disease. So I began conducting laboratory research in the lab at Penn. And I decided to create a foundation called the Castleman Disease Collaborative Network to try to bring together researchers from around the world to push forward Castleman disease research.

**Dr David Fajgenbaum:** And that was really based on the recognition that there's no way just one lab. My work at one place could make enough progress. We needed to all work together. And, over the course of the next year, I was able to graduate from medical school and I'm actually began business school to hopefully try to develop more skills to be able to advance science for Castleman disease when I had another relapse and this one again was life threatening and again was terrifying and again, I needed multiagent chemotherapy to try to keep me alive. But the difference was that this time, I had some data that I had generated in the lab over the previous year and I had some colleagues through the CDCN and that I'd connected with that I could turn to for some advice on what to do next. And based on a number of experiments I had run on my own samples I identified a pathway that I found was increased and more active in me than in control comparative groups. And there's a drug that targets that pathway. It's called the mTOR signaling pathway and a drug called Sirolimus. So I decided to try it on myself at this stage. I'd recently graduated from medical school and was certainly very early in my career. But I made what was

probably the most important decision of my young life to try this drug that had never been used before to treat Castleman disease. It's FDA approved for patients that experience an organ transplant, a kidney transplant, but it had never been used for Castleman's. And so I tried it and as you shared at the beginning of the show, I just crossed five years that I've been in remission on this drug. And before I started myself on this drug, I had five deadly flares and relapses of this disease in just three and a half years. So I was relapsing almost or little short of every year, leading up to this. So, I've had a really nice long remission. That's been five years. And really importantly, during that time, I was able to get married to my wife, Caitlin. Earlier when I mentioned her, we were just dating at the time. But we were able to get married just a few months after I got out of the hospital for the fifth time. And then just six months ago I had, my wife and I had our first child, Amelia, who has brought us so much happiness in these first six months. And it was something that certainly when I was on my death, but I never thought that I would see.

And, it's been the most amazing experience of my life to be a father. And another milestone that's coming up in September, which I'm also really excited about, is that I've spent my weekend nights working on a book called Chasing My Cure, which documents this crazy journey from the last almost decade battling this disease. And then more recently developing a drug that I'm on myself, that I hope will help to raise awareness about Castleman disease and about the really critical work that the Castleman disease collaborative network which of course Mileva is an important part of and Gary has contributed so many samples towards. But the work that we're doing through the CDCN I really hope we'll be able to be highlighted in a meaningful way through this book.

**Priya:** That's been, that's an actually a very compelling story as I was just mentioning Dr Fajgenbaum and first of all, congratulations, your story definitely needs to be heard and it's so great that you finally put it down and we'll have a book to read about that. And there've been a lot of learnings from your experience so far. And I have a couple of questions on this because I've been thinking about them. First of all, as a medical student and I'm sure you would have realize how bad your test results were, how did you cope with this terror? Because just thinking back, being aware, completely aware of your condition. Was that helpful, emotionally how did you come to terms with it Dr Fajgenbaum?

**Dr David Fajgenbaum:** Yeah, it's a great question. So, as a medical student, I could recognize just how bad the laboratory tests were. I knew that the levels were in ranges far beyond what they should be. But I didn't have enough medical knowledge to really understand what that meant and to piece things together. So you're right. I kind of had all the fear associated with knowing how bad they were, but none of the ability to kind of piece together what was happening. So I think that as you're alluding to, I think it actually in some ways maybe made it more challenging that I knew enough to be terrified. But I didn't know enough to really know what kind of path I was on or where I was headed. And maybe that's a good thing because I was headed on a very severe path. So maybe in some ways the naivety of being a medical student and not yet a practicing physician might have actually, I've been helpful in some ways.

**Priya:** And I believe as you were mentioning, you're treating yourself. So that's another very unique thing here. So how would you say this is different from treating others and how can you remain objective when you are treating their own disease yourself?

**Dr David Fajgenbaum:** So making the decision for any patient to try a drug that has never been used before for that disease is a terrifying proposition for any physician. Obviously we all do our best to help as many patients as possible and to do no harm. And so every drug has to be tried on the first patient. Every procedure has to be done on a first patient. But it's very difficult when you're that physician who's making the decision to try something new on a patient that hasn't been tried before. And so I think some of the same fear that all physicians have and trying to make or not necessarily fear, but concern and apprehension about that first time they try something new. Certainly I had and it happened to be that I was trying it on myself. But I do think that that even further to your point, the fact that it was trying it on myself, I think made it a little bit unique in the sense that, from the patient side, I didn't have the ability to just kind of trust in someone and say, my doctor knows best this is going to work for me because he or she, are in control. This is a case where I was making the decision, I was making it based on data that I generated results that I'd

analyzed. And so I think that may be in some ways made it more tough from the patient perspective that I couldn't just kind of trust that someone else was making the right decision and that maybe they were guided towards that by something. I knew that I made the decision based on work that I had done. And I think maybe that that made it almost a little bit more uncertain and a little bit scary in some ways. And the reality of trying a new drug that's never been used for disease is that you never know if that drug could actually make things worse. Castleman disease, we all have a very fragile immune system and our immune system can get out of control very quickly. And when you try a drug that affects the immune system and it targets one piece of it, you have no idea if things will get better or will get worse. And I hoped based on the data that I had that they would get better. But certainly there were no guarantees.

**Priya:** Incredible. I believe you had a very good support system of your peers and faculty. So how did it further your thinking process of treating yourself, trying out a new drug on yourself? How did it help?

**Dr David Fajgenbaum:** Oh, absolutely. My friends from medical school, faculty at Penn, friends outside of medical school, have played such a vital role in this entire journey. Early on what I really needed was them to just physically be present. It was such a scary time having my friends and my family, my dad and my sisters with me meant so much, having my classmates with me meant so much just I needed them from the supportive angle. It was such a scary time. As time has gone on, they've taken on different roles. So some of those classmates of mine have gotten very involved in Castleman disease research. We do research together, we published papers together. They've played critical roles in advancing the entire field of Castleman disease. So they've gone far above and beyond just simply being good supportive friends. They've actually contributed to the way that we think about research and treat the disease. Other classmates have continued to be important supporters of the CDCN, the Castleman Disease Collaborative Network, helping out as volunteers or donating their time or are financially to the research that's being done. And from a faculty perspective, there are people like John Morris who is the Dean of students, former dean, Arthur Rubinstein, many others like Dan Raider who have played really critical roles in mentoring and advising me as I've gone through this process over the years of transitioning from a medical student to a physician scientist where I'm doing everything in my power to push forward research. And I didn't talk about that too much when I started out with my personal story. My personal story at the beginning was it was really a lot about my battle with Castleman disease as a patient. But that battle fortunately because as a patient who's been in remission for the last five years has really transitioned into a battle against the disease from a scientific level, driving forward research, performing studies, that I think will give us some understanding of the Achilles heel of Castleman disease. So we know what drugs might be even more effective for new patients and what drugs might be able to help the most people who are really struggling with this disease.

**Priya:** I also understand that Dr Fajgenbaum that you went out of medical school to Wharton business and came back with a better way to solve the rare disease research process, to accelerate research on rare diseases. And I would also like to hear about Orphan Disease Center at Penn and the patient impact that you're involved with?

**Dr David Fajgenbaum:** It was a bit unusual that when I finished medical school that I decided that an MBA from Wharton would be the most important next step just because usually you don't think about MBAs related to biomedical research, but it was really clear to me from the very beginning of conducting research that research isn't something that should just be performed in a single lab at a single place. Research that really makes a difference, it needs to work across institutions, it needs to work across countries and needs to be highly strategic. You need to think really critically about what's the most important next step. How do you utilize the resources available to you, whether they're financial or tissue samples or data. And a lot of those sort of decisions and ways to think about things are really not taught to you in either medical school or in PhD programs, those sort of operational decisions and strategic decisions or are really kind of the bread and butter of the business world. And so I felt that it would make sense to focus some time and do an MBA to try to pick up some of those skills. And I really do think that that's had an important impact on the approach to the CDCN has taken to research. We spend a lot of time thinking really critically about how to perform our research studies and how to make sure we're making the most of every dollar that we raise for research. And it really just comes down to the fact that we have a limited amount of money and limited amount of

samples. And how do you make the most of those samples? And the way that we do it is by involving physicians, researchers, and patients all throughout the entire community to contribute ideas and highlight the important needs for research. And then we take those prioritized list and we'd go out and find the best people to do the studies. And that approach is really derived almost directly from a lot of the work that's done in the business world around how do you operationalize innovation and a, and that's what we're trying to do through the CDCN.

**Priya:** What does, can you talk a little bit about the Orphan Disease Center and Patient Impact you are involved with?

**Dr David Fajgenbaum:** Absolutely. So the Orphan Disease Center at Penn was started back in 2012 and has played a really important role for a number of rare diseases to drive forward research. The goal of the Orphan Disease Center is to be a supportive resource for all 7,000 rare diseases, but in particular to really help to push the preclinical. So before drug development, preclinical science for a limited number of rare diseases that we consider the programs of excellence. And we focus on on a limited number of rare diseases where we put significant resources of time and money into pushing forward what is known about these rare diseases, what's not known about them and what drug targets might be potential avenues for future drug development. And so we push forward these programs of excellence. Castleman disease is one of those programs of excellence and as we push them forward, we're always thinking about how do we turn to this preclinical breakthrough into something that could be a future clinical trial that could result in the real impact for patients. So we're not, and this is just something really across the Penn research community. We're not interested in research for research sake. We want to understand the answer to a question so that it can help a patient in as short of a time as possible. And that's really, really important to the Orphan Disease Center.

**Priya:** Oh, that's wonderful Dr Fajgenbaum. I like to ask a few questions regarding Castleman disease, something very basic for the benefit of our listeners. So as basic as it can get, what is Castleman disease and do we know what causes it? I'd also like you to touch upon the symptoms, presentation and the various types that you've seen so far.

**Dr David Fajgenbaum:** Sure. Castleman disease is a rare immune system disorder. There are about 5,000 to 6,000 patients diagnosed each year in the United States, which makes it about as rare as ALS or Lou Gehrig's disease certainly has more awareness of it. But Castleman disease has similarly prevalence, about 5,000 diagnosed each year in the US or similar incidents. Castleman disease really describes a group of disorders that all look the same under the microscope. So if you look at a lymph node from anyone with any form of Castleman disease, they look really, really similar under the microscope. But the disease is very heterogeneous, meaning that depending on what subtype of Castleman disease, you have a very different clinical course, different prognosis, different treatments. And so on one end of the spectrum is unicentric Castleman disease where patients present with a single lymph node or a single region of enlarged lymph nodes. And those patients typically have a more mild symptomatic course. So they may experience flu like symptoms and also may have some abnormal laboratory tests, but they're generally not hospitalized for their Castleman disease. The other worry for patients with the Castleman disease unicentric is that they may go on to develop something called Paraneoplastic pemphigus or another called an FTC sarcoma, there is increased risk of those two complications.

But if the Castleman disease can be controlled by taking out the lymph node, those patients can do really well. Unfortunately, not all patients can have their lymph node resected for various reasons and those patients have a much more challenging and complex clinical course. And then there are three forms of what we call multicentric Castleman disease. One is caused by a virus, Human herpesvirus-eight. That's actually what causes the immune system to get out of control.

And in those patients they get very sick and they typically require hospitalization when they present and also if they relapse. But fortunately because we know what causes HHV-8 associated MCD, you can treat it, because we know exactly how to deplete a particular cell type and those patients actually go on to do quite well with appropriate therapy. And then, the next, the third subtype of Castleman disease, we call it POEMS

associated Castleman MCD. And that's where patients get very, very sick. So again, they end up typically requiring hospitalization. But the difference here is that this is caused by a cancer. It's caused by a malignant cell population and it's the malignant cell population that's causing the immune system to get out of control. Again, there's a fairly clear treatment protocol for poems associated multicentric Castleman disease.

**Dr David Fajgenbaum:** But unfortunately this subtype is a bit more deadly than the previous two subtypes that I mentioned. And then the last is what we call idiopathic multicentric Castleman disease. Idiopathic meaning we don't know what causes it. We don't know why the immune system is getting out of control and the symptoms I mentioned earlier that I had, I had idiopathic multicentric disease, with symptoms like flu like symptoms, liver dysfunction, kidney dysfunction, bone marrow failure. Those are the symptoms and signs that are associated with idiopathic multicentric Castleman disease. But because we don't know what causes it, it makes it more challenging to treat idiopathic MCD than the other subtypes. It's generally, and we recommend first line based on the data to treat it with a drug that targets something called Interleukin-6. So Anti-Interleukin-6, Interleukin-6 is an important protein involved with the immune system uses and so blocking that works for about a third of patients. And the research that I do is very focused on understanding what is it that's really important to idiopathic MCD in the two thirds of patients that don't get better with aisle six blockade. And how can you develop new drugs that can help those patients and importantly apply those drugs to patients with unicentric Castleman disease that cannot get their lymph nodes taken out. And so those are really the two primary areas of research that we push forward.

**Priya:** Thank you very much for that. We have a listener question coming in, he wants to if family history is a risk factor for Castleman's disease. He wants to know if it's genetic?

**Dr David Fajgenbaum:** So we know that a very, very small percentage of Castleman disease patients will have another Castleman disease patient within their family. We are aware of about seven or eight families in the whole world, where there's multiple Castleman disease patients in the same family. In those patients, we think it's highly likely that there is a genetic factor that explains why there would be two patients or more in the same family. We have not yet identified that genetic factor or those genetic factors, what it is in those families. But that's currently an area of intense research where we are performing genetic sequencing to understand what genetic mutations may be associated. Outside of those patients where there are multiple patients in the same family, it's really hard to know the contribution that genetics may be playing to it, to idiopathic MCD or to unicentric Castleman disease. And that's another area of intense research where we are doing a lot of work to understand if there are genetic mutations that are associated with either of those diseases. And if so are there things that we could do to help to identify if maybe it's likely that, that that could be passed on to children. But when we think about idiopathic MCD and also unicentric Castleman disease, it's possible that the genetic mutations could be inherited. It's also possible that they could be what are called acquired mutations. So you get them over the course of your life and you do not pass them on to your children. And actually there was a really important study that was published just two weeks ago in unicentric Castleman disease patients where there were a number of mutations that were found to have occurred over the course of those patients' lives. So they were not mutations. They inherited their mutations that they, um, that occurred over the course of their life. So we hypothesize that there will be other genetic mutations that are found that are acquired or that occur during life that would not be able to be passed on to children.

**Priya:** Thank you Dr. So does Castleman have a defined diagnostic criteria, what is the diagnostic journey of Castleman disease in terms of tests and scans etc?

**Dr David Fajgenbaum:** So one of the first things that the Castleman Disease Collaborative Network wanted to do when we first created the CDCN back in 2012 was to gather all of the data we could on the various subtypes of Castleman disease and then to determine what is the appropriate diagnostic criteria that we can use. And back in 2017 we published the first ever diagnostic criteria for idiopathic multicentric Castleman disease, which clearly defines exactly what features you need in the lymph node, what clinical tests, what laboratory abnormalities you need to have to have idiopathic MCD. Before those diagnostic criteria, it was extremely difficult to diagnose patients because there wasn't a checklist for physicians to use. So now

there's a checklist which makes it easier for physicians to go through and say, yes, this patient has it or this patient doesn't have it. Of course when I was diagnosed, that checklist didn't exist. So it took about 11 weeks for me to be diagnosed. More recently it seems that patients are getting diagnosed more quickly. For unicentric Castleman disease, we have recently over the last few months been working on the first ever diagnostic and treatment guidelines for unicentric Castleman disease. We hope to have those completed over the next few months and hopefully published this year again. Again we think of that will be important to accelerate in the diagnosis of unicentric Castleman disease. Unfortunately the other two forms of multicentric Castleman disease, both POEMS associated and HHV-8 associated are easier to diagnose because there is a very clear blood test that you can do in both cases, that if positive and you have features, it's suggest that they may have MCD, then you can feel quite confident in the diagnosis. So I guess the short answer is to say that the diagnostic journey is still challenging, but it's getting better and it's better than it's ever been in the course of history because there's finally diagnostic criteria, but we still have work that we can do and work that we are doing.

**Priya:** At this point I would like to bring Mileva into the discussion. Mileva, thank you so much for joining. You have a daughter, Katie who has been diagnosed with Castleman disease. So what did her diagnosis journey involve. It would be great if people share any tips for parents with kids who have Castleman disease.

**Mileva Repasky:** Thank you. Katie's diagnosis actually took quite a time but a long time to figure out what was going on. As a baby and young toddler, Katie had low grade fevers and she never really slept well. But it's not something you really worried about because as many parents, know children just have fevers for no reason at times. Sometimes they don't sleep well. It's not something that was a big trigger for us. When she was about 14 months old, we found a large mass under her right arm in her actual armpit when we were changing her clothes. Initially the pediatrician evaluated her and felt that maybe she just had a cold or infection and they put her on 10 days of antibiotics, which I think is pretty normal, pretty standard with children that small and you get lymph nodes, they tend to like look very like they're protruding and bulging. So it wasn't anything that caused us to be concerned yet. After the 10 days of antibiotics, the mass actually had not changed and the doctor, one used to do more antibiotics. We actually pushed him to do a little bit more testing to figure out what was going on. He ran some labs and came back and told us that he was going to refer us to an oncologist because was concerned that she actually might have leukemia which was the heart stopper for us. It took us about two weeks to get an appointment with the oncologist and then over the span of four months, they ran a bunch of tests from everything from non Hodgkin's lymphoma to HIV. We saw multiple people on his team. We saw infectious disease doctors, hematologists. Finally they did a lymph node biopsy, which came back with a diagnosis of Castleman disease. Her oncologist actually had never heard of it before. And when he walked into the room, he said, good news.

Katie does not have leukemia or lymphoma, but she does have something called Castleman's disease. He wasn't very worried. He had never heard of it, but printed off information from Google for us, told us to kind of read over it and then to schedule a follow up appointment so that we can talk about next steps. So that's actually how Katie's journey began and it was a lot of unknowns. We were very scared. It was something that we had never imagined that we'd have to go through with her. And having a child diagnosed with something so rare that hinders them from having a normal childhood is heartbreaking. But through her diagnosis I researched as much as I could and eventually found the CDCN and Dr. David, which was a complete game changer for Katie. I'm very blessed to have her and I love that I'm able to advocate for her and fight alongside her with the CDCN to find a cure. The biggest advice I can give to any other parents who are going through this is to just be your child's advocate. Nobody knows your child better than you do. And so if you know or recognize that things are just not normal, fight for them and push as hard as you can, find the right doctors, ask the right questions and if they have the diagnosis of Castleman disease, coming to the CDCN is probably the best thing I've ever done and something that I would advise anybody to do. When you connect with this organization, it's not just a bunch of doctors who are trying to tell you how to treat your disease. It's the whole entire group of people who are fighting together to try to find a cure. And it's just an amazing organization and I'm very blessed that I was able to come on board with them.

**Priya:** Thank you for that Mileva. Dr Fajgenbaum, treatment mostly involves chemotherapy, correct me if I'm

wrong. So can you elaborate on treatment regimen that a patient can be administered when diagnosed with this disease?

**Dr David Fajgenbaum:** Sure. So, treatment really depends on the subtype of Castleman disease. Patients with unicentric Castleman disease generally can do quite well if the lymph node or regional lymph nodes can be surgically excised. And then with idiopathic multicentric Castleman disease, the recommended first line drug is a drug that targets Interleukin-6, called Tocilizumab. And that drug is not technically chemotherapy. It's really a targeted anti cytokine drug. And so fortunately because it's not chemotherapy, patients actually can tolerate it much better than traditional chemotherapy patients where that drug doesn't work, you're right, that chemotherapy is usually the next line of defense against this disease. And that chemotherapy can range from targeted chemotherapy like Rituximab, all the way through to the more challenging to tolerate chemotherapy like Cytoxan, Adriamycin, Etoposide, drugs that make you feel really sick and her and they're kind of chemotherapies that you think about when most people hear the term chemotherapy. And, and so it really depends on what subtype you have. And then even within your subtype, there may be a drug or a procedure that works really well for you that prevents the need from having to take chemotherapy whereas there's others like myself where chemotherapy's been absolutely necessary to keep me alive and though it was challenging to tolerate, it saved my life and I'm, and it's what I needed to do.

**Priya:** Absolutely. I would like to bring in Gary now, Gary I know you are in remission and thank you so much for being with us today. What did your treatment regimen involve?

**Gary Gravina:** Well, during my flares, a lot of my treatment was while I was unconscious on a ventilator. So actually David may be able to tell you more about what they did in that situation. Once I was conscious my treatment involved, after the first flare, I went on Cetuximab. Now during the ICU stay, I was on radical doses of steroids. We usually talk in terms of milligrams. I was on over a full gram of steroids per day. And basically what happened after the first flare was we tapered off the steroids. And as within two weeks from tapering fully off the steroids, I was back in my second flare. So the Cetuximab did not work for me, that was the first line treatment. So the second player was very bad and they threw a number of things at me while I was unconscious. Once I came through, I went through six rounds of a five day chemo. It was a combination. It would start off with an hour and a half infusion of Rituximab and then followed by four 24 hour infusions of, I believe it was Cytoxan and I believe it was Etoposide.

**Priya:** Yes. So I read that you are on maintenance now?

**Gary:** Yes, so I've been in remission now for 27 months, knock wood. And I've been on Rituxan since the end of those six rounds of chemo. I was going every eight weeks up until December, and we're now stretching that out to 12 weeks. So this past week I was at the point where I would previously have gone for a maintenance infusion and I have another four weeks to go. And I would say I feel about on par with that why, how I felt when it was time to go for treatment.

**Priya:** Dr Fajgenbaum, I still have a couple more questions, but I'm seeing that I'm running out of time so I will ask them at the end after we have a patient perspective discussion as well as so Mileva. I hand it over to now to begin with your questions for Dr Fajgenbaum.

**Mileva:** Wonderful. Thank you. So Dr. David, prior to the formation of the CDCN, I know we discussed a little bit about the diagnosis, but what was it like to be diagnosed with Castleman disease? Was it typically the norm to take over six months or was it longer or shorter?

**Dr David Fajgenbaum:** Yeah, that's a great question. It really depends on or depended on the subtype of Castleman disease that that person may have and the severity of the disease. So some patients that have very severe Castleman disease that maybe you put them in the hospital or the intensive care unit. They typically passed away within a few weeks if the diagnosis was not made that quickly. And whereas other patients that maybe didn't have quite as severe cases that didn't necessarily put them into the hospital, they may have had lingering symptoms for months and sometimes even years, which was obviously incredibly

debilitating, incredibly frustrating. So things are changing and there's progress that we can already see. And I get to see people like Gary who, um, was diagnosed much more quickly than I was. And of course Mileva, you and I get to hear stories of patients daily that are, that are getting diagnosed much more quickly than they typically used to be. So that's a really positive note. But of course, there's also patients where it still does take too long. And that's why you and me and others from the CDCN, we're putting the time into trying to raise awareness about these diagnostic criteria, treatment guidelines. And I'm really excited for us to able to get out the unicentric Castleman these guidelines this year.

**Mileva:** Absolutely. One of the other questions is one of the most amazing things that I see from our organization, our patients and their loved ones wanting to join in the fight. What are some of the ways that our patients can join and do their part to help us find a cure?

**Dr David Fajgenbaum:** Yeah, it's really incredible. I mean, as you know, to Mileva, we wouldn't be able to make any progress if any one of the pieces of the CDCN was taken out. So if physicians weren't part of the CDCN, if researchers weren't patients weren't, and if loved ones were not involved none of this progress will be possible. And so patients and loved ones play a critical and a vital role in many ways. There's loved ones like you who contribute your time as a volunteer. There are Castleman's patients like Gary who contribute samples for research. We can't do research if we don't have samples to do the research on. There are many others who contribute in their ways. And so the best way that Castleman's patients can get involved is by contributing their personal medical data through our accelerate registry which is very easy to learn about and to enroll in if you're interested at cdcn.org/accelerate also contributing samples for research, if patients are currently experiencing symptoms, then we would love to be able to collect a blood sample so we can understand what's going on at a molecular level in the blood of Castleman's patients, so we can start to tease this thing out, figure out how it works. And lastly, contributing funds to Castleman disease research is another way, whether it's through bake sales or fundraisers events that the patients are putting on. Those three ways, data samples and funding, are completely instrumental for the progress that we've made so far in any more progress we want to make.

**Mileva:** Okay. So next question is you have formed this amazing organization, which is comprised of doctors and researchers, volunteers, patients and loved ones. What actually gave me that idea to start it like that?

**Dr David Fajgenbaum:** I think that when I first was looking at the ways that rare disease research is typically done, I noticed that there were a lot of what were called support organizations or patient support organizations and a lot of research institutions and they were always completely separate. And I think that for some reason, sometimes there maybe a good reason to do that. But what I realized and what I thought was that there could be a lot of synergy if the same organization could be both supportive and also be an accelerator of research and treatments. And that you really need a patient perspective to do a really good job with research and you really need researchers to do a really good job with patient support. And so it seemed like if we could get everyone together and we could make sure that everyone knew that they were each valued equivalently that I thought that we could really make a lot of progress. And I should also mention Arthur Rubinstein, my mentor really was fundamental in encouraging that sort of a collaborative model because everything he's accomplished in his life has always been through getting all the right people together and making sure everyone feels heard.

**Mileva:** Yeah, I couldn't agree more. I think what you've done with this organization is amazing and it's very unique to see such a different perspective on trying to find a cure for a disease. Next thing is being the mother of Katie, I have to say one of the things I always worry about her, what chances are it's a scary thing to live in the world of the unknown as you know, and I know that this is a worry for many of our patients. What is the likelihood of recurrence and survival rate across all the subtypes of CD?

**Dr David Fajgenbaum:** Yeah, that's the question that keeps me up at night. And the issue that I think about all the time for so many patients, it's really challenging today to be able to give appropriate and accurate numbers and the likelihood of recurrence and survival mainly because there had been so many really important changes that have occurred over the last few years. So if you look at historical data and you look

at a study that was published in 2012 pre Siltuximab, there was a quite high mortality rate in the first five years after diagnosis. So about a third of patients died within five years and another 25% died within 10 years, and that's really striking and that's quite high even relative to blood cancers like myeloma; it's higher than Myeloma and lymphomas. It's really quite high. The challenge, the good challenges that a lot of progress has been made. And so we've reason to be optimistic that some of these new drugs that have been developed in new drugs that are approved like Siltuximab are having a difference and having an impact on those sort of scary survival rate numbers. At the same time, we know that there are patients like Gary and like myself that have relapsed on drugs that we thought we wouldn't relapse on. And so the good news is that there's been progress and I think that the survival rates are better than they've ever been. The important news that we should all be aware of is that there's still a lot of work to be done and the work that we're currently doing and the work that many people are contributing to will have a major impact and continue to make all of our outlooks in the future a bit more optimistic.

**Mileva:** Wonderful. So obviously, you know Katie's story almost as well as I do. She was diagnosed just like you, it's a very scary time and it's something that I think really shook us and left us with a lot of fear and unknowns and not even knowing where to turn. And then when I found the organization, it was amazing to be able to come on and be able to participate and help and advocate for Katie and advocate for other patients and give all of us a voice to see this through it and walk alongside you to try to find a cure. Final question for you is what does it mean to you when you get to see these patients and loved ones contributing and helping this organization?

**Dr David Fajgenbaum:** It means everything. It means everything to me. It's so special to me because I know how tough it is to battle Castleman disease as a patient. And I know how many demands all of us have on our time and what we do with our time. And I know that all of us have a bit more of a perspective on time and the importance of it then, then maybe others do. And so the fact that people like you and Gary and Gary's wife, Stacey and others put their time and in some cases there they're literal blood towards Castleman's research just means so much because as I said at the onset of this webinar, if it was just me working in a lab by myself, we would have made no progress and we still would have made no progress. But it's because all of us have come together. It's because we're all contributing in the ways that we're able to make progress for all of us. And I know how tough Castleman's is, and I know the demands that are there, which makes it even more special when I hear that someone is taking time out of their busy day to put on a fundraising event or to go out of their way to give a blood sample or to make sure that a piece of their lymph node gets sent for research or to support other patients like you do. It's just incredible.

**Priya:** Thank you, Mileava. Gary, your questions now for Dr Fajgenbaum.

**Gary:** Okay. Dr Dave, as a CD patient and someone in contact with so many other patients, how do you and others live with and take care of your Castleman disease without letting it take over your life?

**Dr David Fajgenbaum:** That's a great question. It's a great question. I think the most important thing and thinking about your personal Castleman disease is to be diligent, but to not let it take over your life. So be diligent meaning always make sure that you get your blood tests when you're supposed to. Always make sure you get your scans done when you're supposed to and make sure you do exactly the things that your doctors are asking for you. Make sure you're aware of your symptoms. are you getting more tired than usual? But know and feel confident that you're doing everything in your power by doing those three things so that you can feel confident doing everything else in your life that you want to do. So make sure that you do your lab tests, you do your scans and you think about your disease or your symptoms, but that you don't, but you don't let there be really much more mental energy that goes towards that and that you can spend time with people you love and to be able to go back to the things you care about, being able to feel confident that you're doing exactly what you can be doing by tracking those things.

**Gary:** Right. So given what you and I both know about the inspiring impact of visits from people in remission to people battling a flare, how can we as patients and caregivers ourselves give the attention and support to others who are just beginning their fight?

**Dr David Fajgenbaum:** I think that it starts with people like Mileva that get on the phone to talk to patients and to loved ones of patients while they're in the hospital being able to even just connect with them virtually or by telephone. But I think maybe the most powerful part, maybe the most powerful weekend of the year for me is when we all get together in person at our patient summit. Most patients that show up to the summit or they're able to travel or are fairly healthy. They've turned the corner against their disease to be able to come to Philadelphia, but not everyone has. And I think that being able to hug people that you've emailed with and to see them doing better, for me, every time I get to see you, Gary, it makes me so happy because of course I have so many images in my head when you were so sick and on a ventilator and I'm just physically being able to see you, just makes me so happy.

**Gary:** Yeah. The summit is a wonderful occasion. It really turned things around for me, seeing, seeing myself as not the only person. Well, I mean, of course I knew. But to see to be in a room with 60 other people who are in this fight is really important. So I'm curious what the life cycle of a research blood sample looks like from the patient's vein through to process the information to the point where you and researchers can visualize and manipulate it to ask questions and draw inferences?

**Dr David Fajgenbaum:** Oh yeah, great question. So, you give blood samples and so when we get your blood samples, those all get processed in our laboratory processing means that we pull out the white blood cells out of your, out of your blood. We get rid of all the red blood cells, which makes up about 99% of what you're providing us. We get rid of the red blood cells, we just honed in on the white blood cells and we pull out the proteinaceous fluid in what's called serum or plasma and we separately store that. So with every blood draw we have a serum sample, a plasma sample and then we have your white blood cells. And our focus recently has been particularly on those white blood cells, and white blood cells are your immune cells. And so what are they doing and how are they different when you're in a flare versus when you're in remission. And the way we probe that is through a technique called flow cytometry. We also do something called single cell RNA sequencing, which is a brand new technology. It's only existed for a couple of years. And when we run these samples through these various technologies or assays and kind of results that we get back from those, we have a team that performs a really in depth data analyses on the data that comes back because you can imagine that you're putting through millions of cells through these techniques, you get back millions of data points and trying to piece together one person, one sample, millions of data points. How do you do that? And that really requires a significant amount of data analysis expertise, but also a significant amount of time. And so a sample you give tomorrow it could be processed that day. But the results from the really in depth experiments we're doing may not be interpretable, at least in the context of other patients samples for maybe even six months after that draw. So the lifecycle is long. And the other thing is that it's not just processing, performing, analyzing, but it's also in the context of other patient samples. We feel more confident in something we find in your blood if we also find it in another patient that had a similar clinical presentation to you, because then that suggests to us that it's not just a secondary finding or it's not just something that maybe is a result of the disease, maybe could be a driver. And so we always like to look at the context or look at every sample in the context of other samples. And of course acquiring other samples also takes time, which means that the timeline's a lot longer than I wish it would be. But of course we have to be really careful with, with the findings we take from research.

**Gary:** Yeah. I noticed you didn't list the mother hen stage of the samples.

**Dr David Fajgenbaum:** Sometimes you have to sit on blood samples when you transport them to keep them warm.

**Gary:** So my next question is, as a patient who's in remission on a drug known to be highly effective on HHV-8 positive multicentric Castleman disease, I wonder if any known HHV-8 research may be helpful to CD research and vice versa or if there are similar symbiosis or commonality between CD and lymphoma or Myeloma research since the specialists in those disorders are the most common to treat Castleman disease patients?

**Dr David Fajgenbaum:** That's a great question. Yes. So we absolutely worked very closely with

researchers in all subtypes of Castleman disease. And importantly, as you said in diseases that are kind of on the periphery like Myeloma and lymphoma. And we're partly lucky as you said that because our clinicians are often treat myeloma and lymphoma, they are some true experts in those fields, which means that when we talked to them about Castleman's data, they can oftentimes think about it in the context of related diseases.

**Gary:** Yeah, I know that doctor Eldritch does a lot of work in particular with the HHV-8, which was exactly wonder. So given that most Castleman disease treatments involve immunosuppressants and/or immunomodulators, what can a patient do to keep their immune system strengthened their condition without counteracting the treatments that keep us from having flares?

**Dr David Fajgenbaum:** I think the number one thing is trying to avoid people around you that you know are sick. Avoiding sick contacts is really important because Castleman's patients, their immune system has been weakened by the drug. I think unfortunately there really isn't enough data and information about alternative sort of things like vitamins and supplements that are known to "boost the immune system". And I generally am a little concerned about anything that could boost to Castleman disease immune system because really the problem with Castleman's is that our immune system is too boosted. So I think that what we needed additional research to understand, if there are things that can be done that could safely "boost the immune system" without causing any sort of issues. But really I think the most important thing is for all of us to avoid sick contact so that way that we aren't exposed to people that could potentially get us quite sick.

**Priya:** Thank you Gary for the questions. Dr we have just two or three minutes left, so I'll quickly go through a couple of listener questions, and then I have one question too before we wrap up for today. The two questions that have come in regarding to relapses, they want to know what are the long term effects multiple relapses has on the body and are there any preventative measures that can be taken to avoid these?

**Dr David Fajgenbaum:** Yeah, so with every relapse there's certainly the potential for organ dysfunction and then organ dysfunction that could be progressive or prolonged organ dysfunction. Fortunately most patients with Castleman disease, Gary and myself included can get very, very sick and then can return to a very, very healthy state. So unlike many diseases where if you get very bad kidney function or liver function, you will not get it back in Castleman disease. There is the prospect that you will have returned to normal of organ dysfunction. But it is important to know that with every one of these assaults on our vital organs, there is the potential for longterm dysfunction. So as far as preventing that, I mean the real key is to make sure you're doing your blood tests when you're supposed to make sure you're getting your scans done and that you're on top of your symptoms so that if you do have a relapse, your doctor can catch that early. And if you do have a relapse, let the CDCN know what my Castleman's research program at Penn know, because we would love to be able to get a blood sample so that we can actually see what's changing with the relapse and, and hopefully you turn around very quickly, you get better right away and we can get another sample when you're better and we can see what changed between when you were sick and when you were healthy.

**Priya:** Thank you. Doctor. The next question is, are there any lifestyle choices in terms of nutrition activity, exercise, diet that can assist in preventing flare ups? Are there any holistic therapies that an individual in CD can benefit from?

**Dr David Fajgenbaum:** I think I would say any holistic solutions, multivitamins and exercise and eating well that anyone does for general health separate from Castleman disease I think is a really good idea if you have Castleman disease. But I don't think there's anything additional for someone who has Castleman disease where it's you should do this because you have Castleman disease and this will be more helpful for you than for anyone who generally wants to do something for their health. So all those things like exercise and eating well and taking multivitamins and things that you would take if you didn't have Castleman disease or that your spouse or a family member would take that doesn't have Castleman disease, I think all those are good, but there isn't anything that we've come across that indicates that based on the way we know the disease works that we think would help to prevent a relapse of Castleman disease. Unfortunately, we need to understand what is occurring at a molecular level in order to be able to make recommendations

like that. And for that we need more samples and more research. And so hopefully, maybe if you guys ask me back on for another call in the future, I'll be able to tell you exactly what's happening in Castleman disease and exactly what sort of supplements may be helpful based on that knowledge, but unfortunately we're not there just yet.

**Priya:** Thank you so much for that. One last question, Dr Fajgenbaum, what does the future say for Castleman disease in terms of research, treatments, clinical trials? What can a patient or the family look towards?

**Dr David Fajgenbaum:** So we're actually getting ready to launch a clinical trial just over the next couple of months here at the University of Pennsylvania and also the University of Arkansas for medical sciences is actually of the drug that I'm on Sirolimus, an mTOR inhibitor. And based on the research that we've done, we believe that this drug may have benefit for a number of other Castleman disease patients that are actually already a few that are benefiting from it. So this trial will test this drug on 14 to 24 patients between Little rock and Philadelphia and patients from all over the country can travel to either place to enroll into the clinical trial. And they'll be on drug for one year. And this will give us the potential to understand how well this drug works in a clinical setting and to see if maybe this is a drug that could help a lot of other patients.

**Priya:** Thank you. That's really exciting. So we have a clinical trial that's going to be recruiting soon, Dr Fajgenbaum. I have to thank you for sharing your story and also for sharing with us and methods we use. So congratulations on the progress you have made for Castleman disease. You've got diagnostic criteria, we found additional markers coming up with collaborative. So we're very pleased to hear that you're in remission now for a sustained period and hopefully this can be share with other patients with Castleman disease. So thank you so very much for your time and for all information that you've shared. Mileva and Gary, thank you so much for participating and bringing the patient's perspective into this discussion. We also thank the University of Pennsylvania and the audience. This talk will be available on curetalks.com and CureTalks@Penn. Visit our website for details on upcoming talks. Dr Fajgenbaum's book titled Chasing My Cure – A Doctor's Race to Turn Hope Into Action is currently available for preorder on Amazon and will be in bookstores on September 10th. So, we have something to follow up on this call when his book is going to be out. So thank you and have a great day, everyone.

CureTalks.com