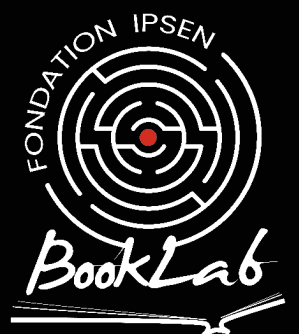


The Rare Disease Gazette

*Conversations with
the world's experts
about rare disease*

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DIAGNOSIS



Editorial

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Rare Disease Detection: Rare But Not Alone



The plight of patients with rare diseases is a critical unmet need of patients in health-care. The statistics are frightening; there are 7000 rare diseases in the world that affect 350,000,000 people. One in eleven Americans has a rare disease. Three-quarters of patients with rare diseases are children and only half of patients receive an accurate diagnosis. The average delay for a patient to receive a diagnosis with a rare disease is 1 1/2 years. It is deeply concerning that one in four patients with a rare disease waits four years for an accurate diagnosis. There is an urgent need to communicate knowledge and expertise in the field of rare disease detection.

The journal *Science*, (American Association for the Advancement of Science) in collaboration with Fondation Ipsen delivers international science webinars for the general public. In 2021 these webinars focused on improving the detection of rare diseases. *The Rare Disease Gazette* is a magazine that broadcasts these discussions.

James Levine



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The Conversation

Experts of the month

Helena Kääriäinen (MD, PhD)
Sean Sanders (PhD)
Marshall Summar (MD)
Jimeng Sun (PhD)
Cynthia Tiftt (MD, PhD)

Sean Sanders (host):

Hello, and a very warm welcome to this third installment of the New Science and Life Webinar series on rare diseases. My name is Sean Sanders, and I am the Director and Senior Editor for Custom Publishing at Science, as well as the moderator for today's discussion. In this nine-part series that will run through the remainder of 2021, we are unpacking many different aspects of this important topic of rare diseases.

If you missed our first two webinars in the series, you can find archived recordings at webinar.sciencemag.org. These webinars as well as recordings of future events will be posted right there. Our first webinar in this series was a broad overview of this topic, while the second focused on the challenges of diagnosing rare diseases. Today, we have taken a slightly different tack, investigating the detection of rare diseases.

Thank you to Fondation Ipsen for sponsoring today's event and this series. Now that we have those details out of the way, I am honored and delighted to introduce our exceptional panel of experts to you now.

Marshall Summar:

Alright, my name's Marshall Summar, I run the Rare Disease Institute at Children's National Hospital here in Washington, DC.

Cynthia Tiftt:

Good morning, I am Cynthia Tiftt, and I am the deputy clinical director of the National Human Genome Research Institute at the National Institutes of Health.

Jimeng Sun:

Hi everyone. This is Jimeng Sun, I am a professor at Computer Science Department, and also at Carle Illinois College of medicine at the University of Illinois Urbana-Champaign. My research focus mostly on AI for healthcare. I am a computer scientist working very closely with many clinicians and leveraging electronic health record to build predictive models. Great to be here.

Helena Kääriäinen:

Hello everybody, I am Helena Kääriäinen. I live in Helsinki, Finland, and I am a clinical geneticist. I have been working with rare diseases all my professional life.

Sean Sanders (host):

Today we are going to talk about the detection of rare diseases. Marshall, I am going to put it on you first to see if you can explain to our audience the difference between detection and diagnosis.

Marshall Summar:

Well, I am going to substitute the word "detection" also with the word "suspicion" of a rare disease diagnosis. From where we are sitting in the clinic, and we obviously got a great group here, there is kind of three ways that we detect rare disease. One is what I would call population-based screening. Obviously, a good example is the newborn screening programs that are available.

The other one is in the hands of a clinician seeing a patient, the detection is they have a suspicion that this patient is no longer falling in the normal range of disease, but is actually falling into that rare disease category. And I think one of the exciting things about having Jimeng on here is, there is another way we can detect, which is scanning data pools, and trying to sift through patient data to try to identify those patients with a rare disease. So I am thinking of detection, those are kind of the ways I would line that out.

Cynthia Tiftt:

I think of detection as confirmation of a suspicion of a diagnosis. As Marshall said, I think once a child or an adult leaves that spectrum of what one would consider more common diseases and begins to look a little different, you may have a variety of things that you think perhaps could be going on in that individual, and detection is really the diagnostic testing. And that could be metabolic, that could

be genetic sequencing, that could be a number of things that would help you actually pinpoint the particular diagnosis out of maybe three or four rare potential conditions.

Jimeng Sun:

My background is building predictive models with a large amount of patient data, usually electronic health records, or other type of patient data, even medical claims data and so on. So a rare disease detection is very tricky in that regard, mainly because it is just the number of samples is very limited. So most of those AI algorithm, machine-learning algorithm require a large amount of high quality training data in order to build the algorithms.

But for rare disease, we have worked on a few, but it is just very few high quality patient dataset that we can use to build those predictive models. So I think it is not much different from detecting other diseases other than it is just much harder because of the sample size, and also data quality issues and all kind of challenges with what the input feature should be included there. So it is just a harder version of disease detection in general, from patient database.

Sean Sanders (host):

One of the topics that came up a number of times in our previous two webinars was the use of databases or the importance of databases. So Jimeng, you mentioned that one of the challenges is that you have very few cases in these databases. So is this improving our doctors, hospitals, getting better at putting information into databases that you can use?

Jimeng Sun:

Well, I think that definitely these days data are digitized. So one thing, at least in most of the developed countries, electronic health records are widely used. So they are at least in a digitized form that can potentially be used for building models. The challenge with rare disease is they are rare and they are distributed, right? So it is hard to take one hospital's data and then build a predictive model for any of those rare disease, just the case count is very small.

Also predicting rare disease probably requires non-traditional input features, like genetic tests and other type of data, that just not common. So we have done a lot of common disease, you just use comor-

bidity and age, a lot of other factors, you can build a very accurate model. But for rare disease, you need some specialized features that require a very special test, and also the case count is small. So that is made this very, very hard.

Marshall Summar:

Let me throw something on top of that. I think one of the things we went across in the modern electronic medical record is the physical exam or the phenotype description is not always as in-depth or as well... We do not have great coding on those. I wonder if the rest would like to comment on how can we use imagery data? So in other words, how might photography, radiography, things like that, that do provide depth to that?

Helena Kääriäinen:

The problem with rare diseases is that they are so rare. So that is the sort of main problem, and I can understand that collecting big data for something that is very rare is always difficult, so there remains also the alert clinician and his or her role. It doesn't disappear even though we are hoping for the big data.

Where big data is very useful, is the gene diagnostics, because for gene diagnostics, we need a lot of normal data. Otherwise, we do not recognize what is normal and what is abnormal. But yes, in Europe, we try to join forces and so that the small countries like my country would add their cases to the other countries. But always, there will be rare patients who are so rare that there may be is not another case in the world.

Cynthia Tift:

But what the advantage to being in a small European country like Finland is that you have data on each patient in a very consistent way going back from childhood. Our issue in the United States is that many people are in multiple health systems and move from one health system to another over their lifespan, so there is not that continuity of data that one would have if they were living in a place like Finland where there is just really nice retrospective data.

Helena Kääriäinen:

We also have registers, a lot of registers in all Nordic countries, and this collects useful data for healthcare. For the patient more important are privacy issues, which we also try to keep safe. But anyway, there is not such a conflict between private issues and using registered data.

Marshall Summar:

There is a flipside to this that I do not think a lot of folks think about. So, we show the graphic we use for rare diseases, you'll see this huge population of figures and then there is one that is a different shade or a different look, and the goal is to pick that one out. One thing we must keep in mind too, if we start picking out ones who do not have rare disease, there is a consequence for that as well too.

So the false positive rate in rare disease is something we pay a lot of attention to, make sure we are not overly stressing families who may not have anything else to worry about, that we have either picked them up through a screening tool or things like that. And there is some data showing in newborn screening that the false positives can have long-term impacts as well too.

So while we want to be incredibly sensitive to pick up those patients, we got to be careful too that we do not have a lot of side effects on other folks who do not really have anything to worry about otherwise.

Sean Sanders (host):

So about 70% of rare diseases are caused by genetic factors, and about 30% are other factors, and we are going to get to the others in a minute. But Cynthia, I'd like to come to you to explain to us what does it mean to have a genetic defect or a mutation that causes a rare disease?

Cynthia Tift:

In the genetics world, we do not like to call them defects, genetic changes perhaps, because all of us have a certain number, six to eight rare recessive lethal genes that we all carry. And if you do not happen to have children by someone who is carrying a mutation in the same gene, you may go generations without ever seeing that.

"In terms of trying to not point out defects.... you want to make sure that the language you use is non-stigmatizing"

In terms of trying to not point out defects, I guess you would say, or you want to make sure that the language you use is non-stigmatizing, I guess would be the

best way to say that. We know that there are many factors that can lead to these genetic diseases, some of them you inherit the gene from your families, and some of them are what we'd call new spontaneous mutations that occur just in that person. They are hereditary in some cases, and they are spontaneous in others, but They are all genetically based.

Sean Sanders (host):

Do you have an idea of the breakdown, the percentage that are hereditary and the percentage that are de novo and new mutations?

Helena Kääriäinen:

There are more the de novo than we expected in the old times, I think we all probably thought that it could be recessive and it could be inherited from the both parents, but today we know that really, really many cases, mistakes in one egg cell or one stem cell, and of course, from that person on, they might be hereditary in the coming generation if the person has children at one time.

But I remember so many families, where you have to be prepared to the fact that it may be hereditary and it may come in another child, and today, knowing the variant, we know that very many of the cases will not recur in the family.

Marshall Summar:

Helena, would you say 50-50 is a reasonable number?

Helena Kääriäinen:

Might be, yes.

Marshall Summar:

Yes, that is a guess, but just from what we have seen clinically, I do not know.

Cynthia Tift:

I think many of these ultra-rare diseases have gone undiagnosed for such a long time; they tend to be these new dominant mutations, which in a sense, is reassuring for the family, because the chance it would happen again is exceedingly small, as opposed to a recessive disease where they would be looking at a one-in-four recurrence risk -- that is really useful information for the families.

As part of my role here at the NIH, I run the pediatric portion of the Undiagnosed Diseases Program, and so not only are we dealing with rare and ultra-rare diseases, we are dealing with diseases that

are brand new, that have never been seen before, that maybe there is only one or two other cases. And I would say, often it is the case that these are new dominant mutations. They are not rare recessives that we once assumed them to be.

Marshall Summar:

When you find a genetic change in a patient, unless it is something really straightforward -- Downs Syndrome would be really straightforward -- the most common answer a lot of times after doing sequencing is, "Maybe." And that may be a maybe with a high degree of certainty, but we are discovering so many things at such a rapid rate.

I think when all of us started, you could diagnose a couple of dozen things accurately with molecular testing, which used to be chromosomes. Now, it is every week, there are several new links between a genetic change and a clinical phenotype or clinical disease. And that is going to, I think part of the pace of that means that some of that is going to change, we are going to go back and say, "Oh, we thought this one did it, now we are not for sure." So "maybe" is a word we use a lot.

Helena Kääriäinen:

Yes, and that is the part of genetics diagnostics where we seriously need big data to accumulate. It is so sad that we say that "Yes, there is a gene and there is a variant in the gene, but we do not know if it means anything. Maybe, maybe not."

Cynthia Tift:

And in the Undiagnosed Diseases Program we come across this all the time, and in order to really sort it out, even if you find a change in a gene that is quite compelling in terms of its function, but it is not been described before.

Cynthia Tift:

You can either find another family or two families that have the same change or a similar change in that gene and similar symptoms, and based on that, you can invoke that as a diagnosis. Or in the absence of second or third cases, you are left then with trying to model genetic changes of that gene in a model organism like a fruit fly or a mouse or a zebrafish and looking at the phenotype in that animal model. And if that is similar, then you can invoke that gene change as being causative in the patient. But that is a long process. Having to go to the modeling stage is a three or four-year process that you might be coming direct to a patient in four or five years saying, "Oh yes, now

we know what you have." But it is a long process.

Marshall Summar:

I was doing some back of the envelope math the other day, and the pace of linking new genetic changes to disease, I think is something like five to 10 a week. Which also means trying to figure out what those diseases are. Is it truly a disease or a variation? I think this is where the big data comes into, we have got to get some great ways to store those genetic changes in patients, realizing we are going to have to re-evaluate a lot and we are going to have to build those systems into it.

Marshall Summar:

So that we can come back and actually, we are going to occasionally have to be wrong, because those changes later on are going to show that either be benign or the different one. I think there was a New York Times... I know it was Times or Wall Street Journal article on that last year, or year before, about how a family gone through two or three iterations of this.

Cynthia Tift:

I think one of the ways that we are wrong in some cases is to have very rare publications or case reports of very rare diagnoses in families that are consanguineous or related to each other by blood. And so in those cases, you are not usually looking at one or two genetic, what we call candidate genes or genetic changes, you may be looking at a whole series of those.

Cynthia Tift:

And you may be looking at a person that doesn't just have one rare disease, they actually have more than one rare disease, and the clinical presentation kind of gets mixed together, so it is much more difficult to try and sort that, drag that apart.

Helena Kääriäinen:

Well, this all reflects that. There was a time when we thought that when we can read the genome, then we can solve everything, but it seems that new questions are popping up all the time.

Sean Sanders (host):

And actually to that point...

Marshall Summar:

We have a colleague who shall remain nameless who back in the late '90s said once the human genome was finished,

we'd never need to examine patients anymore, and couldn't be further from where we are.

Sean Sanders (host):

Now that is, I think it is an important point that both you and Helena make. And I wanted to also mention, so we have talked about sequencing but there are different types of sequencing. There is sequencing individual genes to look for a defect, there is sequencing exomes, and there is sequencing entire genomes.

So the question I wanted to ask is, if we were able to sequence people's genomes or if the rates of full genome, whole genome sequencing increased, do you think we would identify more rare diseases?

Helena Kääriäinen:

Yes, but at present, we are quite unable to analyze all the data that we get from the whole genome, because we do not have enough of the background data, so the normal data yet. But we will find new diseases or new variants in the same genes that are not in the area that we used to sequence before.

Cynthia Tift:

There is a very interesting project that has been going on. One of the lead people on this is Stephen Kingsmore (<https://www.rchsd.org/doctors/stephen-kingsmore-md-dsc/>), who is looking at babies in the Intensive Care Unit, newborns, and doing very rapid genome sequencing on these very ill newborns to come up with the diagnosis. And really asking the question, if we can do very rapid, genomics, can we identify the cause of the child's problem and change our therapy rapidly, within a day or so, and look at the outcome of these infants?

And it has been very interesting to find that if you can do that, you can change outcomes because you can change your therapy. And there have been several instances that this whole team of experts reports as being helpful, and therefore advocating for sick newborns, that may be something that we want to do, do this rapid genome sequencing to arrive at a very rare diagnosis.

Marshall Summar:

I'll throw a little word of caution in here because I think if I do a whole genome sequence on any of us or anyone else, you know, and I am looking to see if there

are changes that might predict disease, the answer is probably going to almost always be yes. The problem is that doesn't always manifest in that patient's actual physical appearance and their physical behavior.

"I look at as though we have all the puzzle pieces spread out on the table... we do not know what the picture is .. or where the pieces necessarily fit."

There are some that are so extreme, they always do, but coming back to Cynthia's point earlier, we are all carrying several lethal or at least severe mutations in there. I look at as though we have all the puzzle pieces spread out on the table. Some of them, we do not know what the picture is on the puzzle or where the pieces necessarily fit. Eventually this technology will become more and more useful. It is going to be a process that evolves with time.

Cynthia Tifft:

It is going to require big data analysis, so in that sense, Jimeng's approach to big data may give us some answers we didn't have before.

Jimeng Sun:

I want to point out the challenge has now become more on the phenotype side as opposed to on the genotype side. The genetic data are standardized but if you do not have the phenotypes, you do not have the disease labels – you need the symptoms, and very detailed characterization on each individual. It can be very hard to find what really that the link between the genetic features to the phenotypic features.

That is, I think, is the challenge. The genetic data get better and more plentiful. We need a better algorithm to process that huge amount of data, but on the phenotypic side, we do not even have a very reliable phenotypes a lot of times -- especially for those who do not have the disease. Because to predict, to classify the disease, you need both the cases, confirmed cases and the confirmed negatives.

The negative side is even worse. A lot of those phenotypes have not been documented, so you just must assume they do not have the gene. It is very hard to build a classifier when you only have some con-

firmed positive cases and no negative. It is a very challenging situation.

Helena Kääriäinen:

Also there are challenges in a normal diagnostic laboratory. I am for instance working as a clinical geneticist in a diagnostic laboratory, and the problem we have is that the clinicians send such poor phenotypic data that it becomes difficult to build patient profiles. For instance, a phenotype can be reported as, "Developmental delay," without telling us what is normal. "Growing normally, and eyes are normal, ears are normal," things like that. But this is not mentioned. Hence there are big problems with all the variants that I have found, because there are a many variants in every individual case.

Marshall Summar:

Consider comparing the old hand-written notes to the electronic notes, as far as how rich they were for the phenotype. We found the old hand-written notes had more depth as far as describing the patient. The electronic EMR (Electronic Medical Record) has a lot of check box items in it.

We have actually been doing detection of rare disease for a very long time, going back to in the '60s, but it is what I would call functional detection, such as the newborn screening card for PKU (phenylketonuria), which will detect the genetic rare disease, but detects it by the actual end functional phenotype. In some ways, that is a very powerful tool often not thought about enough.

I think everyone has become very enamored with sequencing, myself as well as others, but there are functional tests you can do. I think, Jimeng, probably looking in the EMR, we can start to find patterns of either everything from radiographic to EEG, EKG and electrolytes that may be functional markers for some of these rare diseases.

"Part of the problem is, we have lacked a common terminology in genetics for describing what we see... If we are all seeing the same thing, we want to be able to describe it in the same way."

Cynthia Tifft:

Going back to the phenotyping idea just for a second, part of the problem is, we have lacked a common terminology in genetics for describing what we see. I think with the expansion, of what we call the human phenotype ontology that contains very descriptive detailed terms to describe something. If we are all seeing the same thing, we want to be able to describe it in the same way.

In this fashion, hypotelorism, narrow spaced eyes, will be called the same thing by everyone, and it will be much more easily identified. Having very specific language for phenotyping is going to be also helpful.

Marshall Summar:

We are all using image analysis, where you can codify recognition and measurements. Even phones now are so powerful, you can perform with millimeter precision, many of those measurements. I wonder if that more objective capture might be something that will power those phenotyping systems more.

Cynthia Tifft:

There even are now some databases that take a standardized image of a particular syndrome, and you can feed your patient's picture into the computer to see how they match and what the most likely diagnosis would be. They are crude at best at this point, but I think over time, they are going to get more refined.

Marshall Summar:

We worked with the NIH to do that with what I would call the common syndromes. The reason being in parts of the world, you can't get genetic testing, but you can find a smartphone just about anywhere. We found that for things like Downs Syndrome, it is about 98% accurate. So, this is another way to performing detection.

"Whenever you must introduce a human in the loop to assign some judgement, then it becomes unreliable in my mind, or oftentimes, unstandardized."

Jimeng Sun:

I want to summarize one important observation here that is, whenever you must

introduce a human in the loop to assign some judgement, then it becomes unreliable in my mind, or oftentimes, unstandardized. I really like the idea of an alternative way of documenting phenotypes. Maybe imaging, can do that, more efficiently, and more reliably.

At least standardization is moving forward. Also, incentivization becomes a problem and also how you standardize across hospitals. There are many issues regarding human documentation of phenotype, which is today's practice. But if this can be done more reliably, such as like a lab test or an imaging test, then phenotyping will get better.

Marshall Summar:

We found that facial geometry is quite predictive on those things, and aspects that you do not normally recognize as a person are taken into consideration. A computer analysis of an image will pick up things that we do not see.

Sean Sanders (host):

The next part of the discussion I want to come to is detection of known and unknown rare diseases, but before we get to that, I did want to touch on, very quickly, the non-genetic side of rare diseases, and I know that several of you are geneticists and Marshall, as you said, you've been enamored with genome sequencing. I think we all have been.

But there is those 30% of rare diseases that are non-genetic, so how are those detected? And we are talking bacterial infections, environmental issues like mercury poisoning, nutritional deficiencies. Marshall, maybe you can start us off.

Marshall Summar:

When you get out of the non-genetic area of rare disease, what you are doing is statistics. How often does a particular event happen, how often does a particular bacterial or tropical infection happen in the population you are looking at. In the United States if it falls below 200,000, then technically it is a rare disease. In the European Union, they use one in 2000. Japan, Taiwan, and some of the other countries use a set list but then will also use that one in 2000. It is therefore how commonly does something happen. For certain fungal infections that are very rare, you can make the argument, sometimes,

that there is a genetic predisposition for getting that very unusual condition. So being geneticists, we are always going to drag it back there, but it is really, for me, it is a numbers game.

Sean Sanders (host):

Jimeng, coming back to your work, can you just talk briefly about how you use your databases especially to detect non-genetic rare diseases? Because you are looking at phenotypes and you are looking across raw broad databases?

Jimeng Sun:

Most of the work we are doing is with data sets or electronic medical records, such as disease diagnosis, medication procedure. All the historical information has been documented during patient encounters, so we are just using that information as a longitudinal record. Eventually, maybe some rare disease will be diagnosed, then for now we are just looking backwards using historical data as input features, trying to find correlations.

Can we maybe predict this diagnosis earlier? It can take quite some time to confirm the diagnosis if the disease is already active. The approach can be used for non-genetic disease as well. Because most of the data is not genetic.

Cynthia Tift:

Even non-genetic rare disorders have a signature, whether it is environmental or infectious. There are ways to diagnose some of these things. Metabolites, for example would show up in the electronic medical record. I think of lead poisoning in children, which unfortunately in Baltimore is not considered a rare disease, but in the world generally, it probably is. Or some very rare central nervous system infections caused by micro-organisms, often viruses. There are still intricate ways of making those diagnoses and they also involve genetic sequencing, but sequencing in this case of the virus itself, not the person. Some of these we consider non-genetic diseases, and you can see that they have a characteristic signature.

Sean Sanders (host):

We talked briefly about neonatal testing, and I wanted to ask, could you lay out the standard tests for diseases, for rare diseases, and specifically genetic diseases? I know these vary by country. Maybe you can just run us through a few examples.

Helena Kääriäinen:

Phenylketonuria, PKU, was the disease that started this because if you diagnose or detect this disease early enough in the first weeks of life, the child becomes a healthy adult person. And if not, there will be severe developmental problems. For instance, in Finland, PKU is now extremely rare.

"It is not only screening, but also what happens to the baby afterwards. There must be a sound healthcare system, and good pathways for the detected babies and families. It is not just screening, but the whole process."

Other diseases have now been added to the panel, but you need to be careful to avoid screening for diseases you cannot very efficiently treat. There is the whole spectrum: there are countries that are very ambitious and screen a lot of diseases. It is not only screening, but also what happens to the baby afterwards. There must be a sound healthcare system, and good pathways for the detected babies and families. It is not just screening, but the whole process.

Marshall Summar:

Helena's got a great point there. Should you screen for things that you can't necessarily do anything about? There is a set of criteria worked out by the World Health Organization that was based on some earlier publications and I still think those hold true. (1) Can you detect it early? (2) Can you do something about it? (3) Is the disease present in the population you are looking at? And it is a more detailed than that, but I those are not necessarily bad guidelines.

Cynthia Tift:

In the United States, there is a whole committee that has come up with a recommended screening profile of diseases, and there is a whole long process. It takes years and years to get something added to this profile. And their criteria for doing that include: (1) Is there a therapy? (2) How common is the disease in the population? (3) How accurate is the testing?

Whether it is recommendations of the World Health Organization or this RUSP group in the United States, that there

needs to be some rhyme and reason about what goes on a newborn screening panel. I think Helena brings up a most important point: once you find something, that is the easy part! But then you must have a healthcare system on the backend that is able to support families, provide the treatment to the child, and follow the child over time, and support the family. Therefore it is not just putting blood on the heel card. There is a big process that follows. We need to be careful about what we decide to screen for and then have the ability to follow up on – that is the real key.

Marshall Summar:

There was some great data from New South Wales a few years back, where they looked at the return on investment in newborn screening. Interestingly, the biggest payoff was in thyroid. Hyperthyroidism in the newborn had something like a 50 to 1 payback to the state. And I guess legislators, have to look at these things. Also, PKU screening does well. But as we are getting into these more and more rare and more uncommon and very difficult to treat diseases, it is going to be an interesting process to figure out how that balances out.

Sean Sanders (host):

From a clinical perspective, what is the impact on the patient having the knowledge of what causes their disease? Do you find that this is useful? Or is it not of any use to the patient if it is not actionable?

Cynthia Tifft:

No. We found this through the Undiagnosed Diseases Program and reported it widely. I call it, “What’s in a name?” And I say everything. Because a family looking for a diagnosis may spend years and years trying to find a diagnosis. They do not really belong. They do not belong to a group of other people with the same condition. There is stigma attached. “Why doesn’t your child have a diagnosis? You must not be seeing the right doctors.”

In the population, one thinks that all diseases should all be able to be diagnosed. And for these ultra-rare diseases, that is not the case. The anxiety attached as a parent to having a child with a rare disease that is undiagnosed is substantial. And once the family receives a diagnosis, even if there is no treatment, they will say to you, “Now I know what this is.” “I perhaps have a community that I can belong to, an advocacy group to share best practices. Even if all I am providing to my

child is supportive care.” There is a lot in a name, a lot. Even if there is no therapy.

Helena Kääriäinen:

But it is also very important for the healthcare, because otherwise, we as doctors cannot concentrate on treating the patient. Because we are looking for the diagnosis for years and taking new tests, and not concentrating to what is important in the everyday life for the child and family. I said child, and of course, there are also adult patients. But for most of the genetic diseases we see them first in childhood.

Marshall Summar:

I think that closure seems to be very important. There are also a couple of publications out there showing the expenditures go down after you make a diagnosis. There is a health systems reason to do it as well. It is not all about that, but it is an important thing that I think it is lost sometimes. That closure is important for the families. What Cynthia and Helena said is spot on.

Sean Sanders (host):

This brings me to a question I wanted to ask Jimeng, and that is the broad database analysis that you are doing, how can that information be brought back to the individual patient level that will aid in disease detection and diagnosis?

Jimeng Sun:

I think that those algorithms require a lot of data, as we have discussed again and again, which is very tricky in rare diseases. I do agree with the other panelists. The patients and the families are very eager to participate, probably to help this line of research as well.

There is one time even my computer science paper got read by a mother of a child. I do not know how they found it, although I had, “rare disease detection” in the title. She called me and asked, “Okay, are you doing more of this research?” and so on. I was surprised to see patients and families that are really, really interested pushing this forward.

“patients and families that are really, really interested pushing this forward.”

One possible idea is if patients start to collect or gather their own data, there is a mechanism for them to share their data as well and directly for research. And then there is a lot of benefit to bypass privacy concerns if the patient consent. And we probably will discuss that topic, but if a patient owns their own data and are eager to participate, it can help research. It can help to build this database.

It is unlike common disease. Even if you access a single hospital, you can probably get enough patients to build a detection algorithm for a common disease. For a rare disease, you need to gather all types of patients from the entire nation or beyond. So patient engagement will be key to building such a database.

Marshall Summar:

I must blow the horn for both the NIH and Finland on this. The NIH has a robust rare disease clinical research program: National Organization for Rare Disorders does this well. Finland has been a world leader in collecting this natural history data. As long as I have been in the field since the 1980s, they had this world class data. Without that information, you can’t reverse engineer what a patient looks like before they have been detected or have a diagnosis. Those efforts are not necessarily the sexiest science you can do, but they are some of the most important science you can do.

Cynthia Tifft:

I deal with an ultra-rare disease called GM1 gangliosidosis, and it is rare enough that we do not understand the natural history of it. One way of doing that is to see a number of patients over a long period of time, but another way that has turned out to be very effective is to allow patients who own their data to contribute it into a registry. There are organizations out there now who are collecting this data and putting it through the types of artificial intelligence, to come up with a natural history. That is turning out to be very useful for companies who are developing or have developed therapies for the disease, to understand what the milestones are in the history of that disease, to look for outcome measures.

The next question is, what are you going to call success? If you do not know how people fall apart over time, you do not know what to call success. But using this artificial intelligence of patients’ medical records, it has been successful in pinpointing things they should be looking at in their therapies.

Sean Sanders (host):

Should the patients be concerned about privacy? And Jimeng, you mentioned this in your previous comment. I guess if they are sharing their own data, that is okay, but are there any privacy issues that we should be thinking about? Jimeng, maybe you can start us off.

Jimeng Sun:

I think from the computer science point of view, privacy is defined as if you re-identify the individual from a dataset, that is you generally consider not very good. And for various reasons, maybe because the diagnosis is maybe sensitive. The records contain sensitive information. In the United States, there is a law, HIPAA, where it is illegal to gather or share such a data without patient consent.

A lot of research has focused on the privacy aspect. Most of the ideas are about removing patient identifiers and add noise to the data so the data become less re-identifiable to a specific individual. But in the rare disease case, it is very tricky because of the sample size issue, and so it is almost always re-identifiable.

Others can say more about patients' and their families' motivations as opposed to a patient saying, "Oh, you used my data, I do not want you to do that."

Helena Kääriäinen:

But also, I had the feeling that rare disease patients usually are not very worried about the privacy. Instead, they very much want that their data used, because they know that too little is known about their disease. So of course, the ones who collect the data must take care of that, that it is properly protected. I do not think that the patients as a rule are against this.

Marshall Summar:

It is harder to find the controls than it is the patients, as far as getting them to agree to participate.

Cynthia Tiff:

The patients that I had deal with rare disease, want their stories known, and tend to know each other. And so as much time as I spend trying to not talk about other patients to a particular patient, they all know each other. They are all sharing their medical information anyway.

The other point I would make is, in some of these registries, families are able even to contribute information on their deceased children or their deceased family members, who have succumbed to a very

serious genetic disease. I can tell you, in some cases, the parents are grateful for the opportunity to have their children's information used so that something positive could come out of something that was so negative for them. And I have heard that many, many times among families.

In the rare disease community, families do not seem so worried about data privacy as they do, in general

Sean Sanders (host):

I wanted to touch on something related to this discussion, and that is cultural considerations when doing testing. Could you talk to that?

Marshall Summar:

Well, there is a couple of things. One is biologic, and one is what I would call more social. The biologic is that when we are starting to do sequencing, we have to remember that different groups are going to have a lot of different variations. So any time we go into a population that hasn't had a lot of sequencing done in it before, or genetic testing done in it before, we have to be very careful that we do not call things abnormal that are actually normal for that population, vice versa. So there is the context of the genetic sequencing.

The other is what I would say, the understanding of the implication of genetic testing. Genetic testing is different from getting a set of electrolytes or getting a throat swab for an infection, things like that. The data is more permanent. When you come in and you test someone's DNA, you are giving them lasting information and it is pretty much going to be the life of that patient. And particularly in families. If they do not have a good understanding of that, you can create a lot of problems.

There are a couple of good examples. They are what are called ancillary findings or findings beyond what you were looking for. A lot of testing labs now will ask if you want to know you have a risk for Huntington's disease or some of the other diseases that might be detected. There are unintended consequences to genetic testing that can happen.

And then sometimes the family may learn something about the family that they did not expect or want to know. This can be quite upsetting or quite troubling; everything from parentage to other issues. So when you go into different cultures, different parts of the world, DNA testing can have some very serious implications that you have got to think through very carefully.

I use the term "cultural competencies", as one of the things we must think about when we are looking at other groups.

Helena Kääriäinen:

Well, one thing is that if there is a hereditary disease in the family and you find the mutation or mutations that cause it, then suddenly prenatal diagnosis becomes possible. Or maybe predicting a disease in a young family member comes possible. And this raise very difficult questions, which may be very much culture related.

There may be cultures where you cannot discuss about prenatal diagnosis, and there may be other cultures like most Western cultures, where it is one option and families are of course different, but it can at least be discussed.

Sean Sanders (host):

Great. The other topic that I wanted to talk about was how the medical workforce can make proper use of genetic testing. What sort of education do you feel that they need to really understand how to use that data? And also, how to share that information with the patient in a culturally respectful way as well as a personal, personally respectful way?

Cynthia Tiff:

It is clear there are not enough geneticists worldwide to fill the need, so we are going to have to rely on other practitioners to basically give those results. It would be wonderful if medical schools provided that kind of curriculum. Genetic counseling programs certainly do, not only what the results are that you are delivering, but how to, as you say, culturally sensitively deliver those results.

I realize that there is a lot to learn in medical school, but competencies and how to talk to patients about how to have difficult conversations with families, and how to interpret genetic information, would be extremely helpful. And I can tell you that there are situations where physicians have ordered laboratory genetic testing, the results have come back, and it has not been clear to that physician that this is a positive result. It can get filed in the medical record sometimes for years before someone goes back and looks and says, "Well, the answer is right here, you ordered it two years ago." One, we need to educate practitioners. Genetics impacts every specialty in medicine, there is no question about that, and we need to educate people to be able to read those

reports and deliver sensitive information in a really clear way.

Marshall Summar:

People like binary answers, it is yes or no, you have it or you do not. And with the way genetic sits right now, still, as we are evolving our understanding about the results of these things, that just simply doesn't happen. A lot of physicians have not been trained that way. We have to get back into training and start to get medical personnel used to doing and dealing with that level of uncertainty.

Helena Kääriäinen:

Yes, and there is again, the problem that rare diseases are so rare. It doesn't happen every day to another doctor, an ophthalmologist or dermatologist, that he or she is supposed to explain a genetic result, and so the words do not easily come.

Marshall Summar:

It is kind of a paradigm shift. I think historically, physicians were expected to be masters of all the knowledge in their field. In genetics, that is impossible. With the addition of new diseases every week or every day, there is no way to be absolutely encyclopedic in what you know, when for many of these diseases, they are brand new, we do not have a good understanding yet. It is a different way of thinking about human disease.

Cynthia Tiff:

And that is when we rely on large databases and compendia of disease variants to tell us how to interpret the results.

Marshall Summar:

I would say genetics is more digitally dependent than any field of medicine.

Helena Kääriäinen:

But in addition to having doctors who can discuss these things with their patients, we also need, something written. We should have information on the internet. And it is maybe not practical that every university hospital creates its own, but it could be that the genetics community creates good information that would support both the doctor and the patient to better understand the results.

Sean Sanders (host):

Well, I think all of you are doing fantastic things to support the rare disease research community. I did want to thank you so much for your input, for

your research, everything you do. So many thanks to our fantastic panel for generously sharing your knowledge and your insights today.

As I mentioned earlier, this webinar is just the third in a year-long series, so please do look out for more, for future events that will be coming soon, and you can find them at webinar.science-mag.org. If you would like to sign up to receive alerts about future events, you can use a link in the "resources" tab to the right of the video window. If you'd like to send us your thoughts on this webinar, you can email webinar@aaaas.org. Thank you so much to our panel and to Fondation Ipsen for enabling this conversation through their kind sponsorship. Goodbye, everyone.



Journal Club

Article of the month

Katsanis SH, Katsanis N (2013) Molecular genetic testing and the future of clinical genomics. *Nat Rev Genet.* Jun;14(6):415-26. doi: 10.1038/nrg3493. PMID: 23681062; PMCID: PMC4461364.

It's free at: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4461364/>

It is now possible to measure the DNA of any person. The entire DNA sequence of a human can be analyzed in hours. How will new DNA testing revolutionize medicine?

Today's journal club article tells us about the different methods of genetic testing and how they will be used to help people.

There are six ways that genetic tests can be used;

1. Screening newborns. Certain genetic disorders when they are identified at birth can allow treatment to prevent a child becoming ill. One example is phenylketonuria. Genetic testing of newborns can help prevent children with certain disorders becoming sick.

2. Diagnostic testing. This is where a patient comes to a doctor with a complaint and a genetic test is performed. The genetic test helps the doctor identify the illness that the person has.
3. Carrier testing. A healthy person has a genetic test to determine whether they are carrying a hidden genetic mutation that could be passed on to the person's offspring.
4. Predictive testing. A genetic test is used to predict whether a patient will develop a disorder later in life. This includes cardiovascular disease diabetes and some types of cancer. A genetic test conducted early on could allow prevention and early treatment of certain illnesses.
5. Presymptomatic testing. A genetic test is used in specific families where a genetic disorder is known to affect that family. DNA testing can identify people who are prone to develop a disease before symptoms occur. One example is hemochromatosis, and another could be Alzheimer's disease
6. Pharmacogenetics. Genetic tests can predict how a medication is metabolized by the body. This enables doctors to give a patient the correct dose of the medication.

As you can see genetic testing has a huge variety of applications in medicine.



History of Science

Lou Gehrig's disease - Amyotrophic Lateral Sclerosis
by Florian Delval

[https://www.mayoclinic.org/diseases-conditions/amyotrophic-lateral-sclerosis/symptoms-causes/syc-20354022#:~:text=Amyotrophic%20lateral%20sclerosis%20\(a%2Dmy,who%20was%20diagnosed%20with%20it](https://www.mayoclinic.org/diseases-conditions/amyotrophic-lateral-sclerosis/symptoms-causes/syc-20354022#:~:text=Amyotrophic%20lateral%20sclerosis%20(a%2Dmy,who%20was%20diagnosed%20with%20it)

Often described as the least rare of rare diseases, which is a counter truth, Amyotrophic Lateral Sclerosis is a neurodegenerative disease that, according to the rare diseases portal Orphanet, is characterized by:

“A weakening and then paralysis of the muscles of the legs and arms, the respiratory muscles, as well as the muscles of swallowing and speech. Intellectual and sensory functions are not affected. It is a serious progressive disease resulting from the destruction of nerve cells (neurons), which reduces the life expectancy of people affected by it. »

Amyotrophic Lateral Sclerosis (ALS) is a highly disabling and life-threatening disease. While there is currently no cure for ALS, ways have been found to increase life expectancy and improve the quality of life of patients. It breaks out quite late in life, with the average age of diagnosis at 60, and affects men slightly more than women (the ratio of men to women is 1.5 to 1). It is estimated that ALS affects about 1 in 25,000 people and, in France, nearly 800 people are diagnosed each year. As a reminder, in Europe, a disease is considered rare when it affects one person in 2,000. Many other characteristics define the disease, and to find out more I invite you to listen to my colleague Yannick's excellent podcast channel: *Our Health!*

If we all know ALS, at least by name, it's mainly for two reasons. The first is the famous 2014 viral campaign on social networks: the ice bucket challenge. The premise was very simple: encourage named participants to have a bucket of ice water dumped on their heads, while being filmed, and nominate others to do the same. Often, the nominated participants had 24 hours to complete the challenge or not and therefore commit to donating to research or a charity. The second is that ALS has affected public figures such as theoretical physicist and cosmologist Stephen Hawking (who suffered from a very rare form of ALS), and baseball player Lou Gehrig. In fact, as we will see in this episode, Lou Gehrig's story has touched the American people so much that the disease is now commonly referred to, in North America, as Lou Gehrig's disease. ALS has indeed different names in different parts of the world. It is widely known as Charcot's disease in French-speaking countries, Lou Gehrig's disease in North America, and motoneuron disease in the United Kingdom and in other countries such as Ireland, Australia or New Zealand. As we'll see, the motoneurons, which are the nerve cells that control movement, will be fundamental in understanding the disease.

In this podcast we will focus on the advances and work that led to the identification of the disease by Jean-Martin Charcot and discuss the touching story of the man who became the face of the disease, Lou Gehrig.

Progress before identification

As its name in France suggests, the first true clinical description is now largely attributed to Jean-Martin Charcot, in 1865. The name Amyotrophic Lateral Sclerosis was used for the first time in 1874. However, many other scientists contributed to the understanding of the disease and, in part, facilitated this formal identification. One example is the Scottish anatomist and surgeon Charles Bell, who lived from 1774 to 1842. In 1824, he published a work that is fundamental for our purpose: *Exposition of the natural system of the nerve*. In this paper, Bell was the first to distinguish between two types of root within the spinal cord: the anterior roots, which have a motor function and therefore concern movement, and the posterior roots, which have a sensory function. This discovery was essential since it allowed to reach the conclusion that certain neurological pathologies can be distinguished according to the type of spinal cord roots concerned. The idea that diseases can be purely motor was thus advanced for the first time. A first step had been taken.

Amyotrophic Lateral Sclerosis was first described in 1850 by the French physician François-Amilcar Aran. At that time, many French scientists were interested in these neurodegenerative diseases that affect motor functions but were not yet able to distinguish them completely. Why? Because the motoneurons, which are the cells that control the body's voluntary muscles, and whose death leads to these neurodegenerative disorders, were not yet fully understood. Guillaume Duchenne de Boulogne, who gave his name to a disease similar to ALS, thought, for example, that the latter was due to a purely muscular condition. It was Duchenne in particular who made it possible to separate progressive muscular atrophy from other paralyses, since he was the first to note that certain paralyses “were accompanied by a fatty degeneration of the muscles”. But in 1853, real progress in the understanding of the disease was made by Jean Cruveilhier, a prominent scientist at the time, notably a member of the French Academy of Medicine. During an autopsy, Cruveilhier was able to demonstrate that the disease first materialized through damage to the spinal cord and, more precisely, through atrophy of the anterior roots.

Although the clinical identification is rightly attributed to Jean-Martin Charcot, it is also important to mention the remarkable

work of Augustus Jacob Lockhart Clarke, who accurately described the disease in the early 1860s. Now best known for his descriptions of the spinal cord, this British scientist wrote two detailed case reports following post-mortem neuro-pathological studies of what we now think are cases of Amyotrophic Lateral Sclerosis. Lockhart Clarke is one of those scientists who have been somewhat forgotten by history, despite his remarkable contributions. Unambitious and above all devoted to his work, he did not hold any prestigious or even academic positions and was hardly recognized by his peers during his lifetime. In an article published in *The Lancet* in 2000, entitled *Lockhart Clarke, his role in the early history of muscular dystrophy. Neuromuscular Disorder*, the Emery authors tell us that he was “a unique man, of noble independence and honesty, without any ambition... he will be remembered, not as the popular physician, but because of his patient and painstaking researches, so fruitful for medical science.”

Lockhart Clarke's descriptions: the case of patient F.P.

As mentioned, Lockhart Clarke published two reports. For the purpose of our discussion, we will focus on the case of patient F.P., who Clarke worked on in collaboration with Charles Bland Radcliffe. This case study will also help us understand the pathogenesis of the disease. F.P. was a 40-year-old male, which suggests that he had an early onset of ALS. In this patient, the progression of the disease was rapid. Prior to the onset of symptoms, F.P. was visibly healthy and, according to the report, “never had [...] a sick day”. Clarke's acolyte in this case, Radcliffe, described his first encounter with the patient, and his observations were as follows:

“Looking at the clinical facts, it was obvious that there was no material lesion in the seat of intelligence, and it was probable that there was a serious lesion in the parts which govern the movements of the tongue and pharynx, and the respiratory movements in general. Without this latter lesion, indeed, it was difficult to account for the state of paralysis and decay of the tongue, the difficult swallowing, the occasional disturbance of breathing.”

Eight months later, the patient's symptoms had spread to both arms, and more generally to the upper body. There was no

increase in leg tone either, and the patient was constantly weak and tired, making it impossible for him to stand. Our two scientists did not notice any change in the face, and I quote: “the eyes were intelligent, and the features not inexpressive”. The patient therefore seemed to have retained his cerebral and cognitive capacities, which was also confirmed by the patient’s wife, Mrs. P., who told our two scientists that her husband was “never tired of hearing her read books to him, requiring attention and reflection”.

F.P. eventually died, suddenly, six days after being admitted to hospital. According to Martin Turner, Michael Swash and George Ebers, author of the article *Lockhart Clarke’s contribution to the description of amyotrophic lateral sclerosis*, this type of death is common in ALS patients and is usually due to respiratory failure, pulmonary embolism or cardiac arrhythmia.

It was Lockhart Clarke himself who did the post-mortem examination of the patient, and he immediately noted that there was something remarkable about this case. I quote:

“All the most important symptoms of the disease - the extensive paralysis and muscular atrophy described in the patient’s history, are so clearly and satisfactorily explained by the structural lesions discovered on examination of the nerve centres, that the case before us must be regarded as one of the most remarkable and interesting ever recorded.”

Using techniques that were at the cutting edge of science at the time, Clarke carefully studied the patient’s lumbar canal, cervical canal and brain stem. In each of these areas he noted anomalies, such as cells that looked completely different from what they should have. I quote: “the cells were wonderfully altered from their natural appearance ... looked like aggregated granules ... all more or less atrophied and shriveled”. He also noted that, in addition to their irregular shape, the number of nerve cells was small and that some had no nuclei.

What also leads us to understand and believe that the patient had ALS is that a signature characteristic of the disease as we know it today was present: degeneration of the cells of the anterior root and lateral corticospinal tract which, simply put, is the direct link between the motor cortex and the motoneurons of the spinal cord. As Turner, Swash and Ebers tell us, it was clear from Clarke’s report that he had studied the patient with thoroughness, brilliance and a certain fascina-

tion. He ended his report by stating that he was unable to draw any “firm conclusions” from the case, again quoting Clarke: “some important facts ... may be more safely or advantageously examined after some other cases of a similar nature have been similarly carefully considered”. And this is precisely where Jean-Martin Charcot comes in, as it’s exactly what he would do a few years later. Clarke’s contribution to Charcot’s work was recognized by Charcot himself, who mentioned it in his *Lectures on Diseases of the Nervous System*, published in 1881.

The official identification by Jean-Martin Charcot

The life of Jean-Martin Charcot is a classic example of an unstoppable social ascent. Born into a family of the Parisian *petite bourgeoisie*, he quickly decided to devote himself to medicine and passed the highly competitive examinations for an internship at Paris hospitals in December 1848. In 1851, he joined Pierre Rayer’s team at the *Hôpital de la Charité*. The latter, a very prominent doctor at the time, was appointed ordinary doctor to Napoleon III in 1852. Rayer quickly grasped Charcot’s potential and eventually became a support and mentor for him. After brilliant studies, Charcot was appointed family physician in 1854, on Rayer’s recommendation, and he passed the competitive examination to become a Paris hospital doctor in 1856. Charcot was then 31 years old and assigned to the Salpêtrière Hospital, a hospital where he would make his greatest discoveries. Once again recommended by Rayer, he was appointed an officer of the Legion of Honor in 1858 for his work, and two years later received the *agrégation* of medicine, where one of the most eminent members of the jury was... Pierre Rayer. Now a lecturer, Charcot quickly became a popular teacher. In the first half of the 1860s, he began to take a serious interest in neurological disorders.

In 1865, the case of a female patient who died at the Salpêtrière Hospital changed the course of history for the disease. Like many others, she was considered hysterical by a large part of the medical staff because of her permanent muscular stiffening, which they considered exaggerated. At the time, the lack of knowledge and understanding of unidentified diseases led some medical staff to draw hasty conclusions, to the detriment of the health and wellbeing of certain patients who were considered ‘comedians’ even though their suffering was very real. It was Char-

cot himself who performed the autopsy of the patient and he quickly understood that she was far from hysterical. He noted the sclerosis of an entire cord of neurons on the lateral bundle of the spinal cord and the presence of lesions on the anterior roots of the latter. The study of another patient with similar characteristics led him to publish, in 1869, *Two cases of progressive muscular atrophy with lesions of the grey matter and the anterolateral beams of the spinal cord*.

Through these two cases, Charcot understood that several diseases concerned the motor system. Having worked with Duchenne in the past, his ambition was, from that point on, to distinguish these neurodegenerative diseases which seemed, at first sight, very similar. In one of his lessons he stated that in the period 1858-1867 “the role of alterations in the nerve cells themselves had not yet been elucidated”. In 1870, a new patient with the same characteristics as those already examined made him observe a bulbar impairment linked to the disease. This characteristic, which was also present in Lockhart Clarke’s F.P. patient, affected the tongue, soft palate and perioral muscles. In 1874, after studying 20 cases and performing 5 autopsies, Charcot was now certain that all these patients suffered from a rare and unique disorder. He decided to give to the disease the name of Amyotrophic Lateral Sclerosis.

In 1881, in his *Lectures XI, XII and XIII*, he mentioned two forms of degeneration of the motor system that lead to muscle atrophy and weakness. He called these forms “protopathic” and “deuteropathic”. What does this mean? The first, protopathic, is characterized by muscle atrophy and degeneration of the anterior root of the spinal cord. The second, deuteropathic, describes degeneration of the anterior root of the spinal cord, associated with degeneration of the lateral beams of the spinal cord. Charcot based his conclusions not only on the cases examined at the Salpêtrière, but also on other cases already recorded at the time, such as the two patients reported by Lockhart Clarke.

Jean-Martin Charcot examined not only the signature features of the disease, but also observed its slow evolution. He was the first to do this, since he knew that it was a single and unique disease. He recognized it as progressive, and as a condition that starts in adulthood, at a fairly advanced age. He also noted that the disease sometimes runs in families and suggested that the disease may have a hereditary form. He also understood that the disease can develop more or less gradually, and that some patients may survive

for up to 20 years after the first symptoms appear, while others will succumb within five years. In both cases, the progression of the disease is slow, and according to him, is characterized by progressive muscle weakness in one arm, which eventually spreads to the other. The disease, in its early stages, rarely affects the legs, and he doesn't note any stiffness in the muscles.

A prolific scientist, Charcot didn't focus solely on ALS and made important contributions to the identification and understanding of many other disorders. A true medical "superstar" in the 1880s, and a famous figure in French society, he was celebrated not only in France but also abroad, where he embodied the excellence and influence of French science, along with the no less famous Louis Pasteur. In 1882, the first chair in the world to focus on diseases of the nervous system was created for him, on the initiative of the then President of the Council of Ministers: Léon Gambetta. The following year, he was elected member of the Academy of Medicine. Charcot died of pulmonary edema on 16 August 1893 and was granted a national funeral three days later, along with military honors.

After Charcot: a better understanding but few advancements

As mentioned above, Jean-Martin Charcot had suggested that hereditary forms of the disease might exist. Although he was unable to confirm his hypothesis, another scientist did so 15 years later. The scientist was William Osler, another iconic figure in the history of medicine. In 1880, he was the first to report a typical ALS with autosomal dominant inheritance in a family in Vermont, (U.S.). Again, what does this mean? Well, an autosome is a non-sexual chromosome, which is likely to carry a gene with an abnormality. According to AFM Telethon, and I quote: "In these so-called autosomal dominant diseases, an abnormality affecting only one copy of the gene is sufficient for the disease to develop. This anomaly is transmitted by one of the parents, the father or the mother. The latter is himself ill: he has the genetic anomaly in one copy on one of his chromosomes." The family studied was the Farr family, and Osler published a paper in 1880 dealing with their particular case: *Heredity in Progressive Muscular Atrophy as illustrated in the Farr family of Vermont*. In this article, he focused on Erastus Farr,

whose father, uncle, aunt and four cousins died at an early age from a form of ALS that is now known as Familial Amyotrophic Lateral Sclerosis. The Farr family represented a very rare case of a disease that is now considered rare (today, we know that 5-10% of ALS is hereditary). It took more than 100 years to find one of the genes involved, SOD1, which was identified in 1993. As the Orphanet portal for rare diseases and orphan drugs tells us: "the majority of cases [of ALS] are sporadic, but 5-10% are familial and 20% of them have mutations in the SOD1 gene (21q22.11)." According to Dr. Robert H. Brown, Professor and Chair of Neurology at the University of Massachusetts Medical School, I quote:

"This family [Farr] has been of immense importance to ALS studies. Thanks to this family, and others like it, it was possible to discover the first genes for the disease. These genes have made it possible to create cell models of the disease that have been essential in the search for treatments for ALS. It is possible that the first treatable types of ALS will be those that have been so devastating to this wonderful family."

After Charcot's work, there were very few advances, and attempts at treatment were even less frequent. Worth mentioning is the identification of a variant form of ALS, pseudopolyneuropathy, in 1918 by Pierre Marie and his student Patrikios. If you recall, we had already mentioned Pierre Marie in our two episodes on Acromegaly, another rare disease. Pierre Marie was the one who definitively named the disease and went to meet patients in the 1880s at the request of... Jean-Martin Charcot. This variant form of ALS discovered by these two men is characterized by an involvement of the legs, whereas the vast majority of forms of ALS first affect the arms, by a slow progression due to a slow death of the upper motoneurons, and by a life expectancy estimated at five years from the appearance of the first symptoms. Until advances were made in modern molecular biology, there would be little change in the understanding of the disease or in the prospects for its treatment. There is still no cure for ALS, but several public figures that have been affected by it in the 20th century have helped bring it to light, and it is now one of the most well-known rare diseases in the world. Let's focus on one of these public figures.

Lou Gehrig, the face of ALS

If the name Lou Gehrig doesn't ring a bell, it's because, like the vast majority of Europeans, you have very little interest in baseball. However, the sport is extremely popular in the United States and, according to a 2017 study by the American polling institute Gallup, it's neck and neck in the ranking with basketball as Americans' favorite sport, American football. Lou Gehrig is a legendary figure across the Atlantic. In 2019, *Eurosport* focused on the story of Lou Gehrig in its series *The Great Tales*, and this is how journalist Maxime Dupuis began his article:

"Lou Gehrig, it is the story of one of the greatest players in the history of baseball. An athlete that America cherished for his modesty and humility. And whom it imagined to be invincible. At the age of 36, illness unjustly took him. It took his life; he gave it his name."

Lou Gehrig was born on June 19th, 1903, in New York City, a city he would never really leave. Coming from a very modest background, he began to play American football before focusing on baseball, where he was quickly recognized on the youth teams for his impressive technical and physical qualities. As an adult, he was 1.83 meters tall and weighed 91 kilos. Very quickly upon entering the professional circuit, he was given the nickname of *Iron Horse*. Powerful and enduring, Lou Gehrig was a modern athlete. After a stint in the minor league to familiarize himself with the top ranks of the sport, he quickly joined the first team of the legendary *New York Yankees* franchise, where he would wear the legendary white jersey throughout his entire career. His association with Babe Ruth, considered today to be the greatest player in the history of the sport, was working wonders. In 1927, he was one of the strongmen of the team that many consider to be the best in history, culminating in a landslide *World Series* final victory over the *Pittsburgh Pirates*. Maxime Dupuis tells us about his career:

"We could pour a flood of statistics to sum up his immense career, tell you that he won the World Series 6 times, was elected MVP twice, 7 times All Star and remains to this day among the 18 players in history to have hit 4 home runs in a single game. But a number better sums up the man that Gehrig was: 2130. As the number of matches played in a row by the New Yorker with his franchise of always. A record that lasted fifty-six years."

After 2130 matches, Lou was forced to stop playing. Accidents he had known, but he always continued playing, never flinching. But in April 1933, when wearing a helmet was not yet compulsory, he was hit in the head during training. Later, an x-ray would show that he had suffered from 17 fractures during his career, without taking the time to treat them. He could play an entire game with lumbago. Lou knew how to take it. He was a tough guy. But no matter how big a superhero he was, the disease forced him to stop. In 1938, Gehrig saw his performance drop, and he had the very unpleasant feeling that his physique was starting to fail him. A top athlete, he was 34 years old at the time, and one could think that it was just that his golden years were over. But Lou could tell that the loss of his physical capacities was too brutal. He sometimes lost consciousness. It wasn't normal, and he knew it. In June 1939, after a rough season with the *Yankees*, he visited the Mayo Clinic in Rochester, Minnesota, on the advice of his wife, Eleanor. A few days later, on June 19th, he emerged from the clinic, probably with a heavy heart. Under his arm, a file including a letter from Dr. Harold C. Habein. The diagnosis was official. Lou suffered from Amyotrophic Lateral Sclerosis, Charcot's disease. Dr. Habein's letter stated that "the nature of this disorder is such that Mr. Gehrig will be unable to continue his active participation as a baseball player to the extent that it is desirable that he retain his muscle energy". Optimistic by nature, Lou Gehrig tried to reassure his close ones, telling them that he had a one in two chance of being able to continue living a normal life, despite the illness. In truth, he probably knew he was condemned. The announcement of the end of his athletic career loomed, and the time for farewells arrived, only two weeks after the diagnosis. It happened on a symbolic date for the United States, July 4th, Independence Day. Before a game against the Washington Senators, Lou Gehrig was celebrated for representing, as Maxime Dupuis describes, the "legend next door", a simple, humble and approachable man, adored by his teammates and fans. Already very weakened, he found it difficult to carry the many gifts that he was showered with on the short path leading to the center of the field. He put down the gifts, one by one, before taking the microphone in front of the 62,000 fans present at Yankee Stadium. 4 minutes of a legendary speech marked by the total silence of the crowd. A rare moment suspended in time. Lou Gehrig told them:

"For the past two weeks you have been reading about a bad break. Yet today I consider myself the luckiest

man on the face of the earth. I have been in ballparks for seventeen years and have never received anything but kindness and encouragement from you fans. When you look around, wouldn't you consider it a privilege to associate yourself with such a fine-looking men as they're standing in uniform in this ballpark today? Sure, I'm lucky. [...] When everybody down to the groundskeepers and those boys in white coats remember you with trophies - that's something. When you have a wonderful mother-in-law who takes sides with you in squabbles with her own daughter - that's something. When you have a father and a mother who work all their lives so you can have an education and build your body - it's a blessing. When you have a wife who has been a tower of strength and shown more courage than you dreamed existed - that's the finest I know. So I close in saying that I might have been given a bad break, but I've got an awful lot to live for. Thank you."

His health gradually declining as the disease progressed, Gehrig wanted to stay active, but he eventually succumbed to the disease on June 2nd, 1941, sixteen years to the day after his debut as a starter with his long-standing team, the *Yankees*. One of America's most famous and beloved men had passed. Since then, Amyotrophic Lateral Sclerosis has been commonly referred to as Lou Gehrig's Disease in the United States. This baseball player, this incredible human being, through his touching story, managed to put the human before the disease. He who preferred to leave megalomania to others and who sometimes seemed almost embarrassed by his immense popularity, had become, paradoxically, eternal.

And it is with this beautiful and tragic story that we end the History of Amyotrophic Lateral Sclerosis, of Charcot disease or, of course, Lou Gehrig disease. This history is marked by a late discovery and identification, but a remarkable one. As Turner, Swash, and Ebers tell us, we should take the time, and I quote:

"To salute the remarkable progress made in our knowledge of motor neuron diseases in the 19th century. Reading these reports, one cannot help but be impressed by the clarity of the clinical and scientific questions formulated so many years ago. They are as relevant today as they were then; indeed, it is sobering to note that many of these questions are still the subject of current debates."

Although little progress followed the remarkable work of Lockhart Clarke and Jean-Martin Charcot until the era of modern molecular biology, the disease was embodied, as it has

rarely been the case in history, by famous scientists and patients, making it possible to highlight it and attract the attention of the general public. Research continues and represents the best hope for existing patients and the 800 new people diagnosed with this disease each year in France. We all hope that treatments will be found to help them. With that, let me once again redirect you to my friend and colleague Yannick's channel, who offers on his program *Our Health!* an interview with Dr. Maria Grazia Biferi, heading a research team at the Institute of Myology in Paris, and dedicated to the preclinical development of gene therapy for motor neuron-related diseases such as ALS.

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What's up?

Highlights of the month

Movies to move you by Emilia Guarrigues

Awareness about Amyotrophic Lateral Sclerosis (ALS) went viral through the famous Ice Bucket Challenge (website???). We've all heard of several public figures with ALS. The film industry has highlighted these challenges through films and documentaries. A few of my recommendations are:

1. **The Pride of the Yankees:** A 1942 biographical film about the baseball legend Lou Gehrig. It's the first movie on ALS.
2. **Hawking:** The 2013 documentary film of one of the world's most famous scientists, Steven Hawking, told for the first time in his own words and by those closest to him.
3. **The Theory of Everything:** A 2014 biographical romantic drama film also about Steven Hawking, winner of multiple awards.
4. **The Luckiest Man:** The John Paine Story: A 2015 documentary film featuring a successful entrepreneur, adventurer and family man's inspiring story of hope and transformation in the midst of his 15-year journey with ALS.
5. **Getting Up:** The Tempt One Story: A 2012 documentary film about the legendary, fully paralyzed ALS sufferer and graffiti artist "Tempt One", who gets his creative voice back through an unlikely friendship with a perfect stranger.

Fondation Ipsen-OECD program: Neurotechnology in and for society

Neurotechnology has great potential for improving societal health and well-being. Yet, just as with many other emerging technologies, it faces ethical, legal, and social implications (ELSI). In the absence of international instruments in this field, the OECD Council adopted a Recommendation on Responsible Innovation in Neurotechnology in December 2019.

This two-day virtual workshop on 19-20 May 2021 is hosted by the Swiss Delegation in Zurich and focuses on issues of societal deliberation, stewardship and trust that are vital in the notion of Neurotechnology in and for society. It focuses on Principle 5 (Enable societal deliberation on neurotechnology) and Principle 8 (Promote cultures of stewardship and trust in neurotechnology across the public and private sector) in the Recommendation.

Workshop objectives

1. Share initiatives, good practices and experiences related to Principles 5 and 8 of the Recommendation;
2. Engage stakeholders in a critical discussion on what worked and what needs to be improved to implement the Recommendation;
3. Explore how the Recommendation fits with and could be implemented in national and transnational activities in the future;

4. Generate insights which inform guidance resources for adherents and fuel future discussions.

[See the full agenda: here](#)

Children's program: Oki and the DNA code by Dr Yannick Tanguy, PhD

Oki is a very curious raccoon! He has just gone in search of the DNA code that will allow him to understand why he is so unique! However, Oki can't read this information without you. You have to help him to find the DNA code. Thanks to this code, we can decode the information contained in all the chromosomes in the world.

[Play the game: here](#)

History of Amyotrophic Lateral Sclerosis

Listen to our podcasts series on
the history of science



(podcast in French - verbatim in English)

Treating ALS by gene therapy : a true hope

Listen to our podcasts series
series on health



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Detecting rare disease

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