

Science AMA Series: Hi! We're William Gahl and Cyndi Tifft, NIH researchers in the Undiagnosed Diseases Network, a program to solve medical mysteries. Ask us anything about rare diseases, genomic medicine, or the Undiagnosed Diseases Network!

UndiagnosedDiseases¹and/ScienceAMAs¹

¹Affiliation not available

April 17, 2023

Abstract

The doctors involved in the Undiagnosed Diseases Network (UDN) are real-life House M.D.s. We're using genome sequencing along with a network of specialists from numerous medical disciplines at seven clinical sites around the country to diagnose the most challenging and rare genetic diseases. But rare genetic diseases aren't so rare. The National Organization for Rare Disorders (NORD), as well as the Rare Diseases Act of 1983, defines a rare disease as one that affects fewer than 200,000 people in the United States. And even despite the impressive state of medical technology today, the causes of many rare genetic diseases remain mysteries. Since accepting its first patient in 2015, the UDN – an NIH-funded program – has been trying to find the causes and treatments for patients with unknown disorders and to help provide answers for families that have nowhere else to turn. The UDN is an expansion of an Undiagnosed Diseases Program initiated in 2008 within the Intramural Research Program of the National Human Genome Research Institute (NHGRI). This week at NIH and around the world, we celebrated Rare Disease Day. To help raise awareness in the science community and share info about rare diseases and their impact on patients' lives, we're here today to answer your questions about rare diseases, how the UDN is using genomic techniques to find cures, or just how to find support if you or a loved one is suffering from a rare, undiagnosed condition. Today's AMA brings together us – two UDN investigators at the NIH Clinical Center – along with Chad Smith, the father of a young boy with a rare, unidentified condition whom we evaluated at the Clinical Center in June 2016. A bit more about us. We are: Dr. William Gahl: Clinical Director, and Head of the Undiagnosed Diseases Program (UDP) at NHGRI, one of seven clinical sites within the UDN. Dr. Cyndi Tifft: Deputy Clinical Director, and Head of the Pediatric portion of the UDP at NHGRI. Mr. Chad Smith (aka "Chad the Dad"): Father of Blake, an 8-year old undiagnosed child who is currently being researched by the UDN. We will be answering your questions at 1 p.m. ET – Ask Us Anything! Update: We're signing off for now, but thanks to the Reddit community for such thoughtful and engaging questions! We had a blast and hope to do it again sometime to share more stories from the Undiagnosed Diseases Network. (More info here: <https://undiagnosed.hms.harvard.edu/>)

[REDDIT](#)

Science AMA Series: Hi! We're William Gahl and Cyndi Tifft, NIH researchers in the Undiagnosed Diseases Network, a program to solve medical mysteries. Ask us anything about rare diseases, genomic medicine, or the Undiagnosed Diseases Network!

UNDIAGNOSED_DISEASES [R/SCIENCE](#)

The doctors involved in the Undiagnosed Diseases Network (UDN) are real-life House M.D.s. We're using genome sequencing along with a network of specialists from numerous medical disciplines at seven clinical sites around the country to diagnose the most challenging and rare genetic diseases.

But rare genetic diseases aren't so rare.

The National Organization for Rare Disorders (NORD), as well as the Rare Diseases Act of 1983, defines a rare disease as one that affects fewer than 200,000 people in the United States. And even despite the impressive state of medical technology today, the causes of many rare genetic diseases remain mysteries.

Since accepting its first patient in 2015, the UDN – an NIH-funded program – has been trying to find the causes and treatments for patients with unknown disorders and to help provide answers for families that have nowhere else to turn. The UDN is an expansion of an Undiagnosed Diseases Program initiated in 2008 within the Intramural Research Program of the National Human Genome Research Institute (NHGRI).

This week at NIH and around the world, we celebrated Rare Disease Day. To help raise awareness in the science community and share info about rare diseases and their impact on patients' lives, we're here today to answer your questions about rare diseases, how the UDN is using genomic techniques to find cures, or just how to find support if you or a loved one is suffering from a rare, undiagnosed condition.

Today's AMA brings together us – two UDN investigators at the NIH Clinical Center – along with Chad Smith, the father of a young boy with a rare, unidentified condition whom we evaluated at the Clinical Center in June 2016.

A bit more about us. We are:

Dr. William Gahl: Clinical Director, and Head of the Undiagnosed Diseases Program (UDP) at NHGRI, one of seven clinical sites within the UDN. Dr. Cyndi Tifft: Deputy Clinical Director, and Head of the Pediatric portion of the UDP at NHGRI. Mr. Chad Smith (aka "Chad the Dad"): Father of Blake, an 8-year old undiagnosed child who is currently being researched by the UDN.

We will be answering your questions at 1 p.m. ET – Ask Us Anything!

Update: We're signing off for now, but thanks to the Reddit community for such thoughtful and engaging questions! We had a blast and hope to do it again sometime to share more stories from the Undiagnosed Diseases Network. (More info here:

<https://undiagnosed.hms.harvard.edu/>)

[◊ READ REVIEWS](#)

[✍ WRITE A REVIEW](#)

CORRESPONDENCE:

DATE RECEIVED:

What is an example of one of the more elusive diseases you've diagnosed?

Why did it take so long to determine? How is this compared to your average "turn-around" time?

[Richara9](#)

March 04, 2017

DOI:
10.15200/winn.148854.49077

ARCHIVED:
March 03, 2017

CITATION:
Undiagnosed_Diseases ,
r/Science , Science AMA
Series: Hi! We're William Gahl
and Cyndi Tift, NIH
researchers in the
Undiagnosed Diseases
Network, a program to solve
medical mysteries. Ask us
anything about rare diseases,
genomic medicine, or the
Undiagnosed Diseases
Network!, *The Winnower*
4:e148854.49077 , 2017 , DOI:
[10.15200/winn.148854.49077](https://doi.org/10.15200/winn.148854.49077)

© et al. This article is
distributed under the terms of
the [Creative Commons
Attribution 4.0 International
License](https://creativecommons.org/licenses/by/4.0/), which permits
unrestricted use, distribution,
and redistribution in any
medium, provided that the
original author and source are
credited.



We had a 22 year old woman with dystonia, an abnormal and involuntary contraction of muscles. In her case, it involved the tongue, and she was unable to eat so she needed a feeding tube. We were stumped, but put her genetic information on a website, along with a brief description of her symptoms, in a de-identified fashion. Well, a neurologist in London called me up and told me she had 19 patients with a variant in the gene we suspected in our patient! So we had a diagnosis after 2-3 years. And not only that, but the paper describing this new disease is now published, and there appears to be a treatment: deep brain stimulation. Our average turn-around time is only slightly faster, and reflects the fact that we more often make a diagnosis of a known, rare disease. -William Gahl

Hi

Thanks for helping out with this AMA. This is a very interesting topic indeed!

I have two questions:

1. What has been the most unusual case your team has had to solve?
2. What is the role of artificial intelligence in this space? I am aware that IBM Watson has just been launched in Germany in a similar area of unknown diseases with apparently some success. Are there plans for your team to do something similar?

Thanks in advance!

[mvea](#)

We had a case of five adult siblings with enormous calcification of the arteries of their lower extremities, along with poor circulation. Their parents were third cousins, so we looked for a homozygous variant (potential mutation) and, in collaboration with our National Heart Lung and Blood Institute (NHLBI) colleagues, found one! This turned out to be a gene that encodes an enzyme that converts adenosine monophosphate (AMP) to adenosine and inorganic phosphate. New disease; 9 patients from 3 families in the world. We do not use artificial intelligence; hoping that we have enough natural intelligence. But we do share information across the globe, and this is absolutely essential. - William Gahl

If a single known person has a disease/abnormality does it classify it as a disease?

[daveed2001](#)

Yes, in the Undiagnosed Diseases Program we have diagnosed the first case of a number of diseases and only later found second or third cases of the same disease. There are about 7,000 rare genetic diseases known and about 22,000 genes. That means there are many more rare diseases still to be discovered. - Cyndi Tift

If you have a "difficult to diagnose" condition how do you get the medical community to keep working with you? I find that many doctors give up intellectually on you if your problem isn't solved immediately or after the first review of blood tests, x-rays, etc.

[Stairwayscaredandare](#)

Be persistent! Try to find a healthcare professional who can be your advocate. Find a medical home. Keep track of all your tests and records -- don't expect that your doctors will have all the medical records. Be a "binder mom, dad, or patient." - Cyndi Tift

Dr. Tifft! I was one of your and Sandra Yang's adult Fabry's Disease patients at Children's National Medical Center years ago. Thank you for dedicating your career to us "orphans."

Question 1: Those of us with rare diseases are often put in the awkward position of educating our own doctors on our diseases, which can be met with resistance. What do you feel is a good approach for educating doctors so that we will be heard? Should we print out studies or bring references?

Question 2: You mentioned being "real life House M.D.s" The Fabry's Disease episode of House was laughably inaccurate. Do you at UDN find your work inhibited by the misinformation spread by Hollywood's misrepresentations of rare diseases?

Chad, I feel for you and your family and hope you find the answers you need.

[defanged_destroyer](#)

Patients with rare diseases often have this issue. You WILL know more about your disease than most if not all of your physicians. Be concise, but yes, supply articles on your disease if you have them. You can do it in a way that is non-confrontational by saying things like, "I know I have a very rare disease that you might not be familiar with and I brought you some information that may be helpful." Most physicians will welcome information and will be willing to work with you in managing your disease. I tell my patients that I deal in many rare diseases, but that they only have one of them. I fully expect that they will know more about their disease than I do within 6 months of diagnosis. If your physician is threatened by your involvement, you may need to find another physician. - Cyndi Tifft

Dr. Tifft! I was one of your and Sandra Yang's adult Fabry's Disease patients at Children's National Medical Center years ago. Thank you for dedicating your career to us "orphans."

Question 1: Those of us with rare diseases are often put in the awkward position of educating our own doctors on our diseases, which can be met with resistance. What do you feel is a good approach for educating doctors so that we will be heard? Should we print out studies or bring references?

Question 2: You mentioned being "real life House M.D.s" The Fabry's Disease episode of House was laughably inaccurate. Do you at UDN find your work inhibited by the misinformation spread by Hollywood's misrepresentations of rare diseases?

Chad, I feel for you and your family and hope you find the answers you need.

[defanged_destroyer](#)

Patients with rare diseases often have this issue. You WILL know more about your disease than most if not all of your physicians. Be concise, but yes, supply articles on your disease if you have them. You can do it in a way that is non-confrontational by saying things like, "I know I have a very rare disease that you might not be familiar with and I brought you some information that may be helpful." Most physicians will welcome information and will be willing to work with you in managing your disease. I tell my patients that I deal in many rare diseases, but that they only have one of them. I fully expect that they will know more about their disease than I do within 6 months of diagnosis. If your physician is threatened by your involvement, you may need to find another physician. - Cyndi Tifft

As a patient... thank you for your work!

I have been diagnosed with a couple rare conditions already and have been given a tentative diagnosis for a rare type of migraine.

I'm seeing a new neurologist soon and am worried that they won't know much about that migraine type (the last neurologist basically laughed off the diagnosis and said I just needed therapy). What's the best way to approach the appointment to ensure I get the most out of it?

I'm also concerned because doctors don't always understand my other conditions and this just seems to frustrate them because I'm complicated. What can I, as a patient, do to help make this easier for all of us?

[yellowwalks](#)

Realize that most doctors are under a time crunch to see as many patients as they can in a day. (Unfortunately, reimbursement drives the healthcare system so more patients means more revenue.) Be as concise as you can be and organized with your issues when you see your doctor. Do your homework...you may well know more about your disease than your doctors, especially if your condition is rare. Provide them articles from the medical literature if you have them so you can educate them. Most physicians will welcome learning from their patients and working together as a team in optimizing your health. If not, perhaps you need to search for a different physician. - Cyndi Tift

Hi! Thank you for taking your time to do this AMA! My 20 month old daughter Maggie has a dup on 15q13.3 including CHRNA7 (very rare) and a dup on Xq28 near (but not encompassing) MecP2 (she's the only one on record with this specific dup). We have used the genetic services at the NIH to gather information (shout out to Sarah!) and we are doing the rounds of specialists at our local Children's hospital now. NORD and others like Unique have been invaluable to us on our journey. My question is, where should we go next in terms of working with someone who could maybe introduce us to a cure, or even what our future will look like? So far, we her parents know a lot more than her doctors. Also, when people ask to donate money in her name, which avenue do you think would do the most good?

[Idem22](#)

In our life we have found our selves associated with several non-profits. A family member wanted to donate money and wanted to know where best to send the funds. I took the time to explain the different organizations we are involved with and then let them choose where to send the funds. Chad the Dad

I was recently listening to a podcast in which they talked about Hickam's dictum, which states "Patients can have as many diseases as they damn well please". How often does a patient with with a mystery diagnosis turn out to be a combination of separate issues throwing doctors off the trail?

[iregretjumping](#)

It does happen, but it is difficult to tell how often because we cannot predict how one gene will affect the action of another. Said differently, it is more productive to hypothesize that a single gene mutation causes a disease than to try to find two gene changes and determine the effect of the combination of those changes. Probably many of our unsolved cases represent two gene mutations combining to cause detriment. - William Gahl

Thank you all for doing this AMA!

Chad the Dad: How has it felt as a parent as your son is dealing with something doctors are unable to diagnose? How did you hear about UDN, and were you apprehensive at all about bringing Blake there?

Dr. Gahl and Dr. Tift: What kind of academic path would you suggest for college students who want to

be involved in this type of work as a career goal?

[supergyration](#)

Throughout our medical journey many doctors, nurses and medical facilities have done what I have termed, "Tapping Out". Tapping out is when medical professional express their limitations and tell us there is nothing more they can do for our son. We respect people when they share their limits but mourn the loss of yet another possible avenue for help. Ultimately, we started asking where else can we go and who else can help provide answers, we were told about the NIH, an Undiagnosed program at Duke University and the UDP. So, I hit the internet and began looking into these options. The UDN has promised to never "Tap Out" and never give up. For this we are eternally grateful and know that our son is well worth the research. We don't know what the future has in store for Blake; what he can achieve, and where life will take him. Unfortunately, he is still undiagnosed. But, we take great comfort in the knowledge that, not only are the UDN and it's associates working to finding a diagnosis/cure/treatment for Blake, but that Blake will provide answers for children with rare neuromuscular conditions. - Chad

What is an example of disease that, at the moment (or previously), is(was) just absolutely baffling to you?

[Richara9](#)

We have many baffling diseases, but we also continue to solve disorders of patients who came to us years ago. We have 3 different patients with (likely) 3 different genetic causes, who have terrible inflammatory skin lesions, causing ulceration and great pain. Two of the 3 have passed away due to infections because of the lost skin barrier. But we do not have a genetic basis for any of them. We are still working on it. Incidentally, two of the main ways in which we solve these baffling cases are:

A. A similar case, with the genetic cause, is published by another group that has a series of such cases. B. We find a second or third case ourselves, and that helps us find the genetic cause. -William Gahl

What was your most exciting/fulfilling diagnosis? Why?

[Forgotmyfknpassword2](#)

Of course we have cases that are intellectually stimulating, and solving them offers great satisfaction. But our most exciting and fulfilling are diagnoses that have meaning to the patient. Sometimes that can involve knowing what to expect of the disease in the future. Sometimes it involves counseling for other family members. And sometimes it involves actual treatment. We recently diagnosed a very difficult case of a young man with painful bone lesions who turned out to have an unusual presentation of lymphoma; he is now being treated, probably in time to have a good outcome. A few years back we diagnosed a woman with huge muscles; the hypertrophy involved her heart, and would have been fatal in a few months without treatment. We made the diagnosis of multiple myeloma with muscle involvement, i.e., amyloid myopathy. This patient received a stem cell transplant in 2009, with no recurrence. - William Gahl

From a sequencing perspective, do many of these rare diseases have converging genetic profiles, or are they generally caused by a spectrum of different mutations that result in similar phenotypes?

Have any of you worked on FPIES or similar food protein related digestive disorders? It seems these

can be classified in a similar way but have highly variant levels of severity depending on the patient, so I am curious as to whether any genetic profiles are known.

[whiteknight521](#)

One disease, ascertained by a set of signs and symptoms that patients have in common, is generally caused by mutations in a single gene - but those mutations differ from one patient to another. So, yes, a spectrum of different disorders. Occasionally patients may be related to each other, and then a single disease-causing mutation could be responsible. We have not worked on FPIES. It seems to be based upon an allergic response, and those responses could have, in part, a genetic basis. I know of no genetic profiles for FPIES. - William Gahl

What can be done to educate MDs about the existence of rare diseases?

It took me three years to be diagnosed with myalgic encephalomyelitis, (which affects 1 million Americans and 20 million people worldwide, so not rare at all) and I other sufferers have been insulted, abused and told "all the blood tests are normal so there's nothing wrong with you." I am bedridden now, with no treatment.

It seems strange to me that doctors are not aware that some diseases are difficult or impossible to diagnose with standard medical test.

If doctors were made aware of this, maybe they would be more accepting of patients who can't be diagnosed easily.

[Soktee](#)

We do our best to spread the word about rare diseases. We do this by publishing papers on new and rare diseases, by giving talks around the world, and by doing AMA's frequently, at least once every 500 years or so (we hope to do more AMAs in the future, though!). I think that we physicians feel uncomfortable if we do not know about a disease; we have to continue to learn and, as you say, be aware of our limitations. Thank you for bringing up this important issue. It is said that "All men live lives of quiet desperation." - William Gahl

At what level are you looking at the diseases? Metabolomic, transcriptomic, single cell?

How do you decide where to start given the dearth of information on these diseases?

How big is your team?

[ThisWanderer](#)

Actually, all of the above and more. First we gather all the medical records for review, invite the patient to the NIH for a one-week inpatient evaluation tailored to their symptoms and findings and based on what we find we proceed with genetic and metabolic testing. This often involves genome or exome sequencing to identify candidate genes that may be causing the patient's disease. Based on the genes and mutations we identify we move on to transcriptome, metabolome, or making model organisms with the mutation in question. The team at the NIH includes about 20 people but we have about 50 physician consultants who offer their services to evaluate our patients and also provide valuable insights. The UDN is much larger and involves 7 clinical sites, two sequencing centers, a metabolomics core, a model organisms core, a biorepository, and a coordinating center. There were more than 100 people sitting around the table at the last steering committee meeting and that did not include many folks back home. - Cyndi Tiff

Hi Drs. Gahl and Tifft! My sister works for you and a few years ago, she lost her daughter for unknown reasons. I want to say thank you from our whole family for taking the time to figure out what happened and why she passed. It really means a lot to us to have an answer other than "SIDS," especially as many of us relatives are still producing babies.

I cannot imagine having a job where many patients are lost. What have each of you found as the best coping mechanisms?

[furrylittlebeast](#)

Our lives are filled with failure that is devastating and successes that are inspirational. To deal with this situation, I have to concentrate on the good outcomes, and understand the limits of a system that requires triage. A Native American story relates how a mother told her son about the wolf of peace and the wolf of worry or unrest. The boy asked, "Which wolf survives?" And the answer is, "The one you feed." - William Gahl

Why are so many doctors willing to just throw their hands up and leave their patient's issues unresolved? What is the best way a patient can get a doctor to take them seriously?

[sweng123](#)

The truth is that most Doctors are regular humans who may not always have the answers. I know we have put pressure to have a label or an answer to my son's issues, which can often be unfair, as Blake is known to be rare. We have gained a level of respect with the honesty of family doctors and others telling us that Blake has exceeded their medical knowledge. We truly do mourn this lost resource and information. But celebrate those who are willing to continue and support us. Please do not give up and continue with more appointments and move on with your own journey.- Chad the Dad

Could you give an example of a tangential application that arose from a rare disease diagnosis and/or treatment?

[Richara9](#)

We discovered a new pathway involving calcification where it did not belong. That pathway might be targeted to develop treatment for other calcification disorders, including perhaps the vessel calcification that occurs in some people on dialysis. Just potential right now, though. -William Gahl

My child has an unknown (assumed to be rare) disease. We have searched for years now for a diagnosis. Still have none.

What is the right way to get her into your program? Is there a referral process, are there insurance hurdles? Thanks!

[Strings to be pulled](#)

Here is the link for applying <https://undiagnosed.hms.harvard.edu/apply/> There is an attachment with instruction. They have prepared a sheet of information for you to share with your provider , as well as a set of example study recommendation letters. - Chad the Dad

Have you been utterly stumped? Had a debilitating or deadly disease that you weren't able to diagnose until after the patient died?

[WRCousCous](#)

Yes, we have had that situation more than once, unfortunately. Sometimes the patient has been undiagnosed for so long by the time they get to the UDP that they are in very fragile condition. Diagnosing rare diseases is unfortunately time-consuming and sometimes we just can't work fast enough. That said, just having an answer even after the patient has died is comforting and a source of closure for the family.

What advice can you give to a person who suspects that they have been misdiagnosed?

[blahblahwordvomit](#)

This sadly has been a reality for my family, we often pressure the medical community for answers that may not have been identified yet. We have found other with similar symptoms and issues. Although not the same we still share stories, problems and can relate to each other. - Chad the Dad

Thanks for doing this AMA! I'm curious about the dynamics of the network:

How does the Undiagnosed Disease Network work together to solve cases? What do you think are the most important aspects of the Network? How can the Network improve to increase diagnosis rates?

Also, Dr. Gahl, do you have any good jokes?

[SmithingGold](#)

The UDN shares cases at meetings and over the phone. We also have cores that study model systems for evaluating gene changes that potentially cause the disorder. I do think that the most important parts of the UDN are: Sharing, expansion from the UDP, and funding the investigation of gene function to define new disorders. To improve diagnosis, we can share more broadly, i.e., with sequencing centers and other countries. As far as your question about the joke, happy to oblige: A couple goes to a marriage counselor. The wife says, "There is no excitement, no passion in our marriage." The counselor gets up and hugs her passionately, kissing her full on the lips. He tells the husband, "This is what your wife needs 3 times a week." The husband says, "Well, I can bring her in on Monday and Wednesday, but I go fishing on Fridays." - William Gahl

Thank you for taking the time to do this AMA! I have two questions:

- 1) Could you speak a bit about CRISPR-Cas9 gene editing and how it may (if it doesn't already) affect your work?
- 2) Do you see the development of gene editing technology like CRISPR changing how your team tackles rare genetic diseases?

[hahniel](#)

We use CRISPR-Cas9 regularly to produce organisms (mice, zebrafish, fruit flies) that model a candidate gene mutation that we have found in an undiagnosed patient after genome sequencing. We then evaluate the organism in the laboratory to see how closely the model organism mirrors the patient's phenotype. If they are very similar, then that is good evidence that the genetic change is actually causing the disorder in the patient. We call these functional studies. We can then use these

models of the human disease to test potential therapies. - Cyndi Tifft

What's the "rarest" disease you have found to date?

[notyourfish](#)

Congenital Disorder of Glycosylation IIb, a disorder of the gene that encodes glucosidase I. There are 3 patients known in the world. Complicated disorder; maybe need to look it up. - William Gahl