CASE STUDY: Undiagnosed Hackathon (Global)
PILLAR: 1 (Patient and Family Empowerment)

"Hacking" Undiagnosed Diseases: An Annual Event to Find Answers

Context

Around the world there are an estimated 350 million people living with a rare and undiagnosed disease, and many of them are children.[1] Tools like genome sequencing can provide answers for many. However, despite these technological advances, 80% of people living with genetic conditions still do not receive a diagnosis after genomic testing — prolonging the search to understand their mysterious conditions, with no path forward for care and treatment.[2]

The Undiagnosed Hackathon is an innovative two-year old effort to promote global collaboration and solve — in record time — currently "unsolvable" cases of children and adults with undetermined genetic conditions. The initiative has achieved impressive results — 14 of 52 participants were diagnosed within only 48 hours. Spearheaded by the Wilhelm Foundation, the Undiagnosed Hackathon has created a disruptive model of multidisciplinary partnership that has helped end the diagnostic odyssey for some of the most confounding cases.

Undiagnosed Hackathon

Overview of program

The Wilhelm Foundation is a Swedish-based international foundation dedicated to ensuring that everyone searching for answers about their health condition receives a timely and accurate diagnosis. Founded by Helene and Mikk Cederroth — parents who lost three of their four children to an undiagnosed disease — the Wilhelm Foundation focuses on the critical role that diagnosis plays in helping people living with an undiagnosed disease receive the right care and treatment.

Since it was established, the Wilhelm Foundation has played an important role in influencing the rare disease field with respect to people who have not been diagnosed. From partnering with the National Institutes of Health to help create the Undiagnosed Diseases Network International (UDNI) to launching programs that support diagnostic efforts in low-and middle-income countries, the Wilhelm Foundation has spurred initiatives that have fostered knowledge and collaboration across borders. The idea for the Undiagnosed Hackathon emerged from these earlier efforts and is an outgrowth of the UDNI-Wilhelm Foundation partnership.

What is a Hackathon?

A "hackathon" is a collaborative way to approach complex problem-solving, usually in an intensive, short period of time. With roots in the tech industry, the hackathon model is designed to spark innovation and creativity, making it a useful way to approach intractable problems. The annual Undiagnosed Hackathon convenes multidisciplinary teams — which include experts from academia, health care, industry and patient organizations — to tackle challenging cases from around the world in just 48 hours.

To date, the Wilhelm Foundation has hosted two Hackathons, sharing the costs with the hospital or university partner. The inaugural Hackathon in June 2023 was a joint effort with the Karolinska Undiagnosed Diseases Program at the Karolinska University Hospital, Karolinska Institute in Stockholm, Sweden, and PhenoTips, a medical genetics software startup. The 13 individuals who participated hailed from China, Ghana, India, Pakistan, the Republic of Congo, Sweden, Turkey and the U.S. Four of the 10 families (three families included two affected siblings) received a diagnosis on the first day of the event — and experts continued working on the remaining cases for nine additional months but, unfortunately, could not identify additional diagnoses.

In 2024, the Undiagnosed Hackathon was hosted in partnership with Radboud University. The project team at Radboud University Medical Center in the Netherlands spent hundreds of consultation hours preparing for the event and ensuring that all data samples were collected, analyzed and made available to the experts. As a result of this Hackathon, 10 of 42 participating families received a diagnosis.

How the Hackathon works

Participants and their families at the first Hackathon were nominated by their doctors, who, through the UDNI Diagnostic Working Group, were still not able to make a diagnosis. For the subsequent Hackathons, clinicians apply to have their patients participate; a committee of representatives from the Wilhelm Foundation and the partner organization reviews applications and decides whom to accept.

Those eligible to be considered for the Hackathon are likely to have a monogenetic disease, received genetic testing that has not produced a diagnosis, provided informed consent directly or through their legal guardians, and submitted their raw data for re-analysis. Once selected, the Hackathon arranges for these individuals and their families to work together with the team of experts to solve the puzzle.

Throughout the course of the two-day Hackathon, experts from around the world work intensively in small cross-functional teams to unlock genetic answers, a model that is highly unusual in most health systems where researchers and clinicians tend to operate in siloes and are even less likely to work across borders. More than 200 experts, including doctors, researchers, data analysts, bioinformaticians and AI experts, have participated in the two Hackathons.

To kick off the Hackathon, team members participate in a workshop on innovations in rare disease genetics where they share the latest developments in genetic research from both academia and industry — such as long-read sequencing and optical genome mapping. The tools workshop was introduced at the second Undiagnosed Hackathon after recognizing the need at the first meeting. This knowledge exchange lays the groundwork for important breakthroughs during the event and has grown over time to include additional tools and workshops at each subsequent Hackathon.

Two months before the event, participants provide blood samples and their DNA and RNA are sequenced in different ways, including short-read whole genome sequencing, short-read RNA sequencing, long-read whole genome sequencing, long-read RNA sequencing, methylation EPIC arrays, and optical gene mapping (added during the second Hackathon). When the Hackathon begins, researchers and clinicians have access to extensive phenotype and genotype data to inform their investigatory work. They also retain access to the data to perform re-analyses as they continue to search for a diagnosis for those who did not receive one during the 48-hour event.

Results

The Undiagnosed Hackathon — although operating at a small scale — has proven to be an innovative and effective way to discover genetic answers to challenging questions. At the first Hackathon, four of 10 families received a diagnosis, and six families' conditions remain unsolved. In 2024, the program expanded to include more families and 10 of 42 families received a diagnosis within 48 hours.

Importantly, the Hackathon was successful in making diagnoses that changed the management and treatment options for these children and families. For example, one participant was diagnosed with a neurodevelopmental disorder, after being diagnosed incorrectly with cerebral palsy. Another was diagnosed with spinal muscular atrophy with respiratory distress, a possibility that had been dismissed earlier. A third person was diagnosed with a rare neurogenetic disorder for which there is a recommended treatment.

Technology plays a pivotal role, but careful phenotyping of symptoms is also essential for establishing the correct diagnosis. For example, one child's diagnosis was initially missed because a clinical feature — crossed toes — had not been observed. The parents submitted a photograph showing the child's toes crossed, leading the team to confirm the diagnosis.

Given the importance of phenotyping, the Wilhelm Foundation will organize a virtual phenotyping meeting on Global Undiagnosed Day on April 29, 2025.

Learnings

- **Global collaboration among multidisciplinary teams promotes innovation:** Participants were divided into multidisciplinary teams, often working with people from fields that were completely new to them. This unique collaboration among peers with different areas of expertise fostered creative problem solving that ultimately led to finding diagnoses.
- **People living with an undiagnosed disease provide important clues:** Many people living with an undiagnosed disease and their families participated in the Hackathon in person — and those who could not attend were represented by their physician. Organizers and experts agreed that it was important to understand the whole patient, rather than just their "case." Laboratory specialists and bioinformaticians, who typically do not have contact with people living with undiagnosed diseases, developed a better understanding of the people who benefit from genetic research and advances in technology — which was highly motivating.
- **Utilizing the latest technology unlocks answers:** Applying the latest technological advances, including long and short genome sequencing, RNA sequencing, transcriptomes and optical genome mapping, led to fast answers — providing information to some families right away and giving teams a leg up to search for answers for other families.
- **Access to data and infrastructure for data sharing is critical:** Researchers were able to dive into problem solving because they had access to the information they needed. Consent from participants was critical to ensure that data could be shared and utilized quickly.

Goals & next steps

The Wilhelm Foundation is determined to replicate the innovative collaboration at the heart of the Undiagnosed Hackathon in new settings to improve the lives of more children and adults living with a rare disease and their families. The next Undiagnosed Hackathon will be held at the Mayo Clinic in Minnesota in 2025 with experts and families from around the globe.

The path to scale is establishing local Undiagnosed Hackathons, which is currently happening. The first local Hackathon was held in February 2025 at Karolinska in Sweden, involving 60 experts. A regional Undiagnosed Hackathon is planned for April 2025 in the Netherlands — a collaboration between Radboud University Medical Center and Maastricht University Medical Center.

References

1. Nguengang Wakap, S., Lambert, D.M., Olry, A. et al. Estimating cumulative point prevalence of rare diseases: analysis of the Orphanet database. Eur J Hum Genet 28, 165–173 (2020). https://doi.org/10.1038/s41431-019-0508-0

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