The magazine of the
Center for Molecular Fingerprinting

WAVES

PATH TO A HEALTHIER FUTURE

2024

Impressum

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Dear Reader,

Welcome to the second issue of Waves, the magazine of the Center for Molecular Fingerprinting!

The year 2024 was a transformative period for us at the Center for Molecular Fingerprinting (CMF). Over the past five years, we have been committed to advancing health monitoring and early disease detection with the objective of developing cutting-edge diagnostic tools capable of identifying diseases such as cancer at their earliest stages, even before clinical symptoms manifest.

At CMF, we continue to advocate for a paradigm shift in healthcare, transitioning from a reactive to a preventive model. The current medical landscape predominantly focuses on treating illnesses after they have developed, with individuals often seeking medical attention only upon experiencing severe symptoms. Our mission is to contribute to the advancement of preventive medicine, offering significant benefits not only at the individual level but also in reducing the burden on healthcare systems and enhancing economic sustainability in Hungary and elsewhere.

A cornerstone of our efforts is the Health for Hungary, Hungary for Health Program (H4H), which has garnered the support of more than 10,000 people in Hungary. Through this initiative, participants can monitor their health status at affiliated medical centers while supporting our research endeavors. In 2024, we expanded our national network, which now includes over 20 locations across Hungary. We are preparing to grow even furher to make the H4H Program more conveniently accessible to everyone in the country.

In the summer of 2024, CMF relocated its state-of-the-art laser equipment to its laboratory at the ELI-ALPS Research Institute in Szeged, representing a considerable advancement, allowing us to conduct high-precision laser measurements in Hungary. To mark this achievement, we hosted our first scientific conference – CMF Summit 2024: At the Forefront of Disease Profiling. This landmark event featured esteemed speakers, including Nobel Laureates Katalin Karikó and Gérard Mourou, who provided invaluable insights into their respective fields.

Collaborations also remain integral to our progress. Our long-standing strategic partnership with the Ludwig-Maximilians-Universität München has been extended to the Max-Planck-Institute of Quantum Optics, the Max Planck Institute of Biochemistry, and the Bavarian NMR Center, all in Munich, aiming to complement our infrared fingerprinting approach with mass spectrometry(MS)-based proteomics and MS/NMR-based metabolomics for enhancing the extraction of molecular information from human blood. Additionally, our collaboration with Semmelweis University in Budapest has been raised to a new level by jointly establishing a new data science institute focusing on the integration and exploitation of disparate datasets for probing human health.

While pursuing our ambitious scientific objectives, our team is also working on creating CMF's new home, a world-class research complex encompassing our laser- and biological laboratories, biobank, medical center, research exhibition space, and offices in Budapest.

The following pages present an overview of our recent activities and pursuit of grand goals. As we set ambitious goals for 2025 and beyond, we extend our profound gratitude to the volunteers of the H4H Program, our esteemed healthcare partners, and the numerous dedicated supporters of our research. Their unwavering support – along with the dedication of our CMF team – is the key to our pursuit of shaping the future of healthcare.

Sincerely yours,
Prof. Dr. Ferenc Krausz

Center for Molecular Fingerprinting
Budapest, Garching, Szeged

CMF Summit 2024 – At the Forefront of Disease Profiling

A Nobel Symposium with Ferenc Krausz, Katalin Karikó and Gérard Mourou

Pálma Bruder

Ferenc Krausz's laser technology has arrived in Hungary, marking a significant milestone in CMF's mission and work.

On June 17, 2024, CMF inaugurated its new laser laboratory at the ELI-ALPS Research Institute in Szeged. This advancement brings innovative laser testing technology, foundational to CMF's research in Germany, to Hungary for the first time. Celebrating the conclusion of a long preparation process called for a fitting event. True to the forward-looking mission of our research center, a day-long scientific symposium replaced a traditional opening ceremony.

The CMF Summit 2024 – At the Forefront of Disease Profiling was a particularly unique event for several reasons. The opening of the new laser laboratory in Szeged, Hungary, represents a major milestone for our organization and advancements in disease detection. Having several Nobel Prize-winning scientists share insights into their recent work in one venue was a rare opportunity. The presence of two Hungarian Nobel Laureates was especially significant. As CMF is also committed to inspiring young generations to pursue research, we shared this experience with a broad audience by live streaming the Summit online.

"The transfer of our laser instruments from the Munich laboratory to Hungary will allow us to begin the world's first systematic molecular fingerprinting analysis of tens of thousands of plasma samples already collected," said Prof. Dr. Ferenc Krausz in his opening speech. He added that this partnership exemplifies how international collaboration drives scientific progress and can potentially lead to groundbreaking discoveries.

János Csák, former Minister of Culture and Innovation, delivered a brief yet inspiring speech, emphasizing that the government's priority is to create knowledge platforms in Hungary and support scientific research through funding and infrastructure. He encouraged Hungarian researchers to promote valuable programs and mentor young talent.

Dr. Mihaela Žigman, CMF's Former Research Director hosted the Summit, introducing speakers and moderating Q&A sessions between presentations. She said, "...we have three distinguished speakers whom I am honored to introduce. Our first speaker of the day is Dr. Ferenc Krausz... his work has truly opened the door to a new world, a world within molecules and atoms."

In his lecture, Ferenc Krausz, the 2023 Nobel Prize winner in Physics, presented CMF's research objectives explained the significance and applications of attosecond physics. Prof. Dr. Katalin Karikó, who received the Nobel Prize in Physiology or Medicine in 2023 for her groundbreaking discoveries that led to mRNA-based vaccines, shared the history of her scientific journey, beginning in Szeged in 1978. Prof. Dr. Gérard Mourou, awarded the Nobel Prize in Physics in 2018 for his work on phase-modulated pulse amplification, presented the fundamentals of this technology and its wide-ranging applications.

"I believe the conclusions were far-reaching and have a broad societal impact... I hope this motivates you as much as it does me," said Mihaela Žigman in her closing remarks, bringing the day's events to a close.

CMF's first Summit was a resounding success, setting a promising precedent for future professional and educational events.

A Year of Unprecedented Intensity

How Receiving the Nobel Prize Transformed the Life of Ferenc Krausz

Dr. Veit Ziegelmaier

Few moments have the power to reshape a person's life overnight, and receiving a Nobel Prize is undoubtedly one of them. Ferenc Krausz, one of the three Laureates of the 2023 Nobel Prize in Physics, is living proof of this. Already renowned as a leading figure in attosecond physics, Krausz's announcement in October 2023 propelled him into the global spotlight. The subsequent months were marked by a whirlwind of media interviews, conference invitations, congratulatory messages, and even requests for autographs and video greetings from all over the world. With only 24 hours in a day, his time for rest became a rare luxury.

Krausz's groundbreaking research, which was once the domain of specialized scientific circles, has now captivated the public imagination. His pioneering work on attosecond pulses – ultrafast bursts of light that measure electrons' motion, the fastest phenomena outside the atomic nucleus – became widely celebrated. This recognition extends beyond fundamental research, as Krausz's work has significant potential for early disease detection, a focus of the Center for Molecular Fingerprinting (CMF) in Hungary, where he serves as CEO and Scientific Director.

His international engagements continued into 2024, with appearances in North America, including prestigious institutions like the University of Southern California, Stanford, and Berkeley.

Having dual citizenship in Hungary and Austria and conducting research in Bavaria, Germany, Krausz's achievements were honored on multiple fronts. Even before the official Nobel ceremony in December 2023, he delivered lectures in cities such as Belfast, Warsaw, and Berlin. Following the award ceremony in Stockholm, where he received the prize from the Swedish Royal Family, Krausz embarked on a lecture tour across Sweden, visiting Uppsala, Umeå, Gothenburg, and Lund. His international engagements continued into 2024, with appearances in North America, including prestigious institutions like the University of Southern California, Stanford, and Berkeley, as well as a series of talks in major Chinese cities such as Shanghai, Beijing, Wuhan, and Changsha, aimed at fostering scientific collaboration.

The accolades for Krausz have been abundant. In Bavaria, where he conducts research at the Max Planck Institute for Quantum Optics and the Ludwig-Maximilians-Universität München, he received the Maximilian Order for Science and Art, the state's highest honor. Austria recognized him with the Grand Decoration of Honour in Gold with Sash, presented by President Alexander Van der Bellen, while Hungary bestowed its highest state honor, the Hungarian Order of Saint Stephen.

In Hungary, Krausz holds a special place alongside Katalin Karikó, the 2023 Nobel Laureate in Physiology and Medicine. Both have become national icons, with Budapest lighting its iconic Chain Bridge in the national colors to celebrate their achievements on December 10, 2023 – the day they received their Nobel Prizes. To further honor their success, Hungary's National Bank issued a commemorative silver coin featuring their portraits, and a mural of the two scientists now graces a prominent wall in downtown Budapest.

Under Krausz's leadership, CMF has achieved remarkable milestones. In early 2024, Hungary's first ultra-short pulse laser system and biolaboratory was established at ELI-ALPS in Szeged, where blood samples from the H4H Program are being analyzed. This groundbreaking development was celebrated at the CMF Summit 2024 – At the Forefront of Disease Profiling, featuring lectures from Nobel Laureates Katalin Karikó, Gérard Mourou, and Ferenc Krausz himself.

Among the many accolades and honors, one personal gesture stood out: Krausz's research team collaborated with U.S. sportswear brand Newton to create a custom running shoe for him. A passionate runner, Krausz now owns a one-of-a-kind pair featuring the iconic attosecond streaking trace and a reference to the 91-attosecond light pulse, the shortest ever recorded by his group in Vienna. These bespoke shoes, like the winged sandals of Hermes, symbolize his drive to forge his own path and achieve new heights in his scientific journey.

Hungarian Nobel Laureate Works Tirelessly for the Health of the Hungarian Population

Katalin Karikó in conversation with Pálma Bruder

The year 2023 marked a dual success for the Hungarian scientific community and the Hungarian people, with Katalin Karikó and Ferenc Krausz each winning the Nobel Prize in their respective fields. In the 123-year history of the prestigious award, this was only the fourth time two professionals of Hungarian descent or nationality were recognized in the same year.

When Prof. Dr. Katalin Karikó honored CMF by presenting at our scientific symposium in June 2024, we couldn't miss the opportunity to ask her about her work and future aspirations.

Since its establishment by Alfred Nobel in 1901, the Nobel Prize has been awarded to 227 scientists. Katalin Karikó became the 16th Hungarian, the 13th woman, and the first Hungarian woman to receive this immense recognition.

How did sharing the stage at the CMF Summit with two other Nobel Laureates and a fellow Hungarian feel?

It was a wonderful feeling, already back in Stockholm, to receive the Nobel Prize together with Ferenc Krausz.

The Research Center, founded by Ferenc Krausz, aims to revolutionize early diagnostics of diseases. How do you see science in general, and especially your field, contributing to the health of Hungarian citizens?

The protein-coding messenger RNAs with a therapeutic effect will be healing for certain patients with acquired or genetically inherited diseases. The antibody-coding messenger mRNAs will help in the treatment of patients with cancer.

What do you believe is the key to your success? What drives you forward with determination despite the obstacles you faced early in your career?

During all my research, I concentrated on solving the tasks that were in front of me, and I did not pay much attention to whether I looked "successful" or not. It was already a good ten years ago, at the age of 58, when I was last sent away from a workplace – when the difficulties did not only characterize the initial period. It was a small startup running on an e-campus.

What research or projects are you currently working on?

I have read a lot about the processes of RNA formation and degradation in our bodies, and it has become clear to me what the cause of certain neurodegenerative diseases might be and what therapies could be used to treat them. This is now the big task ahead of me and and what I am concentrating on.

Introducing CMF's Scientific Advisory Board

Leading Experts Guiding the Future of Healthcare

In 2024, CMF welcomed the establishment of its Scientific Advisory Board (SAB), comprising many globally acclaimed experts. This multidisciplinary, international board was created to guide CMF's ambitious mission, assess its research progress, offer strategic insights, and suggest innovative improvements. Through their expertise, the SAB will play an essential role in CMF's journey towards pioneering advancements in healthcare diagnostics.

Meet the distinguished members of CMF's Scientific Advisory Board, who are committed to redefining healthcare diagnostics through cutting-edge research and global collaboration:

Rohit Bhargava

Photo: University of Illinois Urbana-Champaign

Rohit Bhargava is the Director of the Cancer Center at Illinois and the Associate Director of the NSF Science and Technology Center for Quantitative Cell Biology. Bhargava's research focuses on creating advanced imaging methods to study complex biological systems, such as the microenvironments of cancer cells, which is crucial for improving cancer diagnosis and understanding disease progression. He has translated chemical imaging to clinical settings and developed new approaches to manufacture tumor-mimicking systems in the laboratory. He is a leading proponent of the emerging field of cancer engineering.

He is a pioneer in developing infrared spectroscopic imaging and has earned numerous accolades for his groundbreaking work, including the Ellis R. Lippincott Award (2021), the Pittsburgh Spectroscopy Award (2022), and the Society for Applied Spectroscopy Gold Medal, SAS NY/NJ Section (2022).

Steven Chu

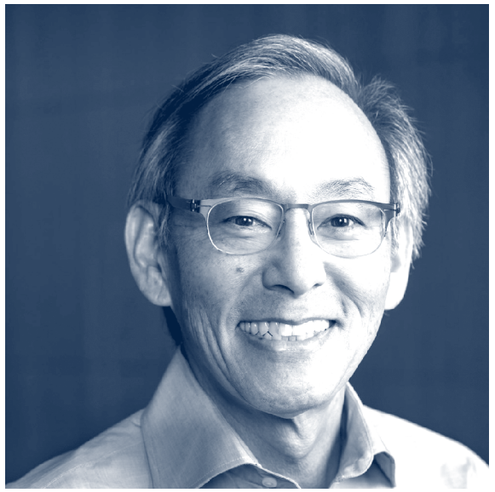


Photo: Stanford University

Steven Chu is a physicist, energy scientist, and Nobel Laureate renowned for his pioneering work in laser cooling and trapping of atoms, for which he was awarded the Nobel Prize in Physics in 1997 alongside Claude Cohen-Tannoudji and William D. Phillips. His career is marked by interdisciplinary achievements, bridging physics, biology, and environmental science, and he remains active in energy innovation and climate policy. He is a Professor of Physics, Molecular and Cellular Physiology, and Energy Science and Engineering at Stanford University.

Chu is a member of several prestigious academies and societies, including the National Academy of Sciences, the American Philosophical Society, the American Academy of Arts and Sciences, and the National Academy of Inventors. He is also a foreign member of the Royal Society, in the United Kingdom, the Royal Academy of Engineering, the Chinese Academy of Sciences, Academia Sinica, the Korean Academy of Science and Technology, and the Pontifical Academy of Sciences.

Bernhard Lendl

Photo: Ludwig Schedl

Bernhard Lendl is a chemist and researcher known for his pioneering work in analytical chemistry, particularly in mid-IR laser-based spectroscopy. His research interests include infrared and Raman spectroscopy, lab-on-a-chip systems, and integrated photonics. Lendl currently holds a professorship at TU Wien in Vienna, Austria, where he leads a research group focusing on the development and application of novel sensing schemes for gases, liquids, and nanoscale imaging. His work spans various fields, including process analytical chemistry, material characterization, and life sciences. He is an Honorary Professor at the University of Nottingham and co-founded QuantaRed Technologies GmbH. He has served as a member of editorial boards for scientific journals and was part of the Governing Board of the Society of Applied Spectroscopy (2016–2018). Lendl has received several prestigious awards, including the Robert Kellner Lecture Award (2015), the Agilent Thought Leader Award (2021), and the Norman Sheppard Award (2022). He holds granted patents in Austria, Europe, the United States, Canada, China, Russia, and Japan.

Béla Merkely

Photo: Balint Barta/Semmelweis University

Béla Merkely is a cardiologist and professor widely recognized for his expertise in interventional cardiology and electrophysiology. As a leading figure in Hungarian and European cardiology, Merkely has contributed significantly to research and practice in heart disease treatment, including advanced techniques for heart failure management, arrhythmia treatment. His work has garnered international recognition and published extensively in cardiology research.

He currently serves as the Rector of Semmelweis University in Budapest, one of the leading medical universities in Hungary and Central Europe, where he is also the Director of the Heart and Vascular Center of Budapest. He serves as the Chair of the Department of Aviation and Space Medicine and the Chair of the Department of Sports Medicine. He is the President of the cardiology section of the medical professional college and the honorary President of the Hungarian Society of Cardiology, and he also acts as the honorary President of the Hungarian Heart Rhythm Association. He served as the President of the Hungarian Society of Cardiology (2010-2013), Councilor (2014-2016), and Vice-President of the European Society of Cardiology (2016-2018). Among many honors, he received the Order of Merit of the Republic of Hungary (Commander Cross) in 2016 and the prestigious Széchenyi Prize in 2021.

Judit Sándor

Photo: Kinga Lakner

Judit Sándor is a bioethicist, legal scholar, and professor renowned for her contributions to bioethics, health law, and biotechnology regulation. She is a professor in the Departments of Political Science, Legal and Gender Studies and founding Director of the Center for Ethics and Law in Biomedicine (CELAB) at Central European University (CEU). She also serves as a Governor of the World Association of Medical Law (WAML). She is a former Head of the Bioethics Unit of The United Nations Educational, Scientific and Cultural Organization (UNESCO, 2004-2005) and the author of numerous books and articles on human rights and bioethics, covering topics of medical negligence and biobanks.

She is also known for her interdisciplinary approach to topics at the intersection of law, ethics, and biomedical science, focusing on patients' rights, genetic privacy, and reproductive health. Her research and advocacy work has often centered on human rights issues in healthcare and research ethics, making her a notable voice on ethical and legal challenges posed by new biomedical technologies.

Jürgen Popp

Photo: Sven Döring/Leibniz-IPHT

Jürgen Popp is a physical chemist specializing in biophotonics and optical health technology research covering the complete range from photonic basic research towards translation into clinically applicable methods. He is well known for his pioneering work in applying Raman spectroscopic approaches to biomedical diagnostics with a clinical focus on infectious diseases and cancer. Popp's research focuses on developing non-invasive optical methods for analyzing biological samples, aiming to improve diagnostics by providing rapid, precise, and label-free imaging techniques. He has contributed significantly to innovations in biomedical optics, pushing forward translational methods that allow for real-time, in situ diagnostics in healthcare settings.

He serves as the Chair of Physical Chemistry at Friedrich Schiller University Jena and Scientific Director of Leibniz Institute of Photonic Technologies. Juergen Popp is Founding Editor and Editor-in-Chief of the Journal of Biophotonics and a Photonics21 Executive Board member. He has many awards, including the Pittsburgh Spectroscopy Award and the Charles Mann Award from the Federation of Analytical Chemistry and Spectroscopy Societies. He received an honorary doctorate from the University at Albany (USA).

Karine Sargsyan

Photo: Laura Schaffelhofer/MedUni Graz

Karine Sargsyan is a prominent researcher and expert in the field of healthcare, particularly known for her work related to health informatics and biostatistics; a pioneer in biobanking. She serves as the Scientific Director of the Cedars-Sinai Cancer Biobank. She was the Managing Director of Biobank Graz at the Medical University of Graz, Austria. She is an innovator in biobanking, dealing with quality measures and regulation requirements, and serving as an advisor at various institutions in many countries.

Sargsyan has an outstanding academic background and has contributed significantly to research on healthcare systems, and medical data analysis. Her research often focuses on using data analytics to improve health outcomes and optimize healthcare delivery. Additionally, Sargsyan is involved in various projects and collaborations aimed at enhancing healthcare practices and policies through the application of informatics and statistical methods.

The Laser Laboratory in Szeged

Operations have begun in Hungary

Dr. Alexander Weigel

In 2024, CMF achieved a significant milestone in its mission to shape the future of healthcare through health monitoring based on infrared fingerprinting of blood samples by opening its first laser laboratory at the ELI-ALPS Research Institute in Szeged. Establishing this laboratory for laser-based measurements complements the highly successful H4H Program (Health for Hungary – Hungary for Health), which focuses on collecting human blood plasma samples. The H4H Program aims to track 15,000 individuals over 10 years through regular health check-ups and dedicated blood sample collections. This provides a unique opportunity to monitor the development of diseases statistically and correlate them with characteristic changes in the infrared molecular fingerprint of blood plasma. With this new laser laboratory, CMF can measure samples directly in Hungary using the latest laser-based molecular fingerprinting technology.

ELI-ALPS, home to the new laser systems, offers ideal conditions for our infrared fingerprinting laboratories, featuring vibration-isolated clean rooms and advanced facilities for operating state-of-the-art laser systems. Preparations for our field-resolved infrared spectrometers began years ago, equipping the laboratory with unique laser tables for stability and vibration dampening to enable ultra-sensitive spectroscopic measurements. In addition, vacuum lines, clean-room equipment, and instruments like oscilloscopes and spectrometers were installed to monitor and control critical parameters of the infrasampler system. A functional laser laboratory requires various optics, optomechanics, and other tools for daily research and maintenance. The experience gained from operating laser laboratories at MPQ and the Light Extreme Infrastructure (LEX) laboratories of LMU was invaluable during this preparation.

Simultaneously with laboratory preparations, the infrared fingerprinting instrument, INFRASAMPLER 1.5, entered its final development stage in the autumn of 2023. To optimize performance for blood-sample measurements, it was upgraded with a new compressor stage that enables shorter laser pulses, approaching durations as brief as 14 femtoseconds. This improvement enhanced fingerprinting performance, granting access to protein signatures previously undetectable by the instrument. The laser beam layout was redesigned and adapted to accommodate the shorter laser pulses. Engineering approaches complemented scientific efforts to ensure maximum stability for upcoming measurement campaigns. INFRASAMPLER 1.5 is now equipped with

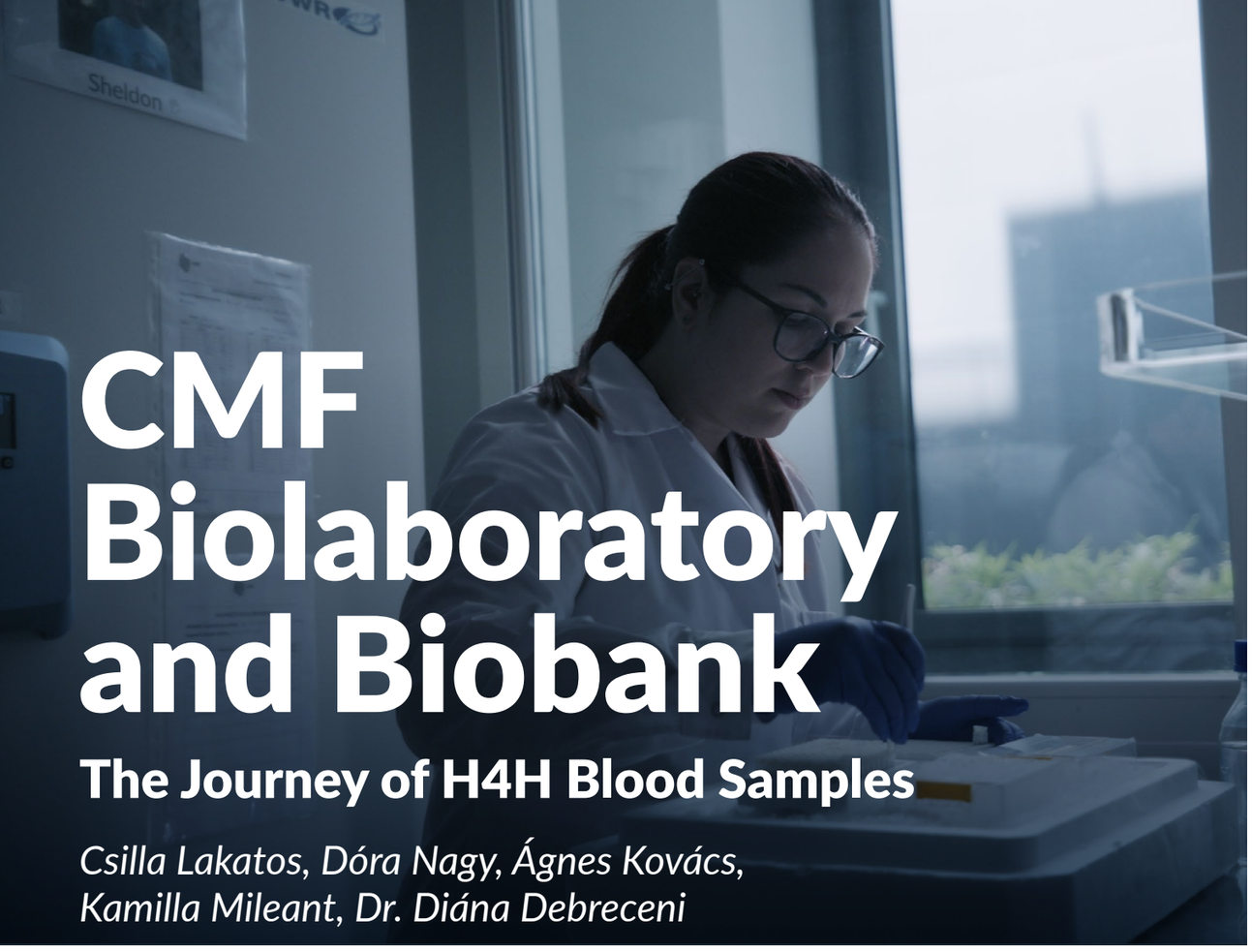
ultra-stable, temperature-controlled vacuum chambers, incorporating next-generation technologies. The final laser instrument for infrared molecular fingerprinting comprises four individual laser chambers with dedicated electronics for synchronization and high-speed detection.

Special care was taken to prepare the complex system for the move to Hungary without disturbing the sensitive optics. During the first two weeks of 2024, the instrument was meticulously disassembled and prepared for transport.

By early 2024, the instrument was packed and transported to its new home in Hungary. The laser chambers and accessories filled an entire truck, transporting the system overnight. In the following weeks, the system was reassembled on the laser table, connected to the cooling circuit, and integrated into the institute's laser safety system before being brought back to life. "After some initial alignment, we were excited and relieved to see the heart of the instrument, the high-power laser oscillator, working again," explained Dr. Abhijit Maity, who is responsible for the instrument and its development. Each module was carefully initiated, and the entire system was characterized to ensure optimal performance. The CMF laboratory was officially inaugurated on June 17, 2024. It was a special moment as distinguished guests gathered in the new laboratory to observe the first live measurements of field-resolved infrared signals using an infrasampler in Hungary.

In our continuous efforts to advance infrared molecular fingerprinting, CMF's laser development team is already working on the next-generation instrument, INFRASAMPLER 3.0. The new system will measure twice as many infrared frequencies as INFRASAMPLER 1.5, providing more detailed information on the molecular status of a blood plasma sample. Preparations are underway to transport these new research systems from the laboratories in Garching to Hungary in 2025. The CMF laboratory will also house unique infrared fingerprinting instruments and serve as a hub for active research. In September 2024, Dr. Sanchi Maithani joined the Szeged team and is now working with Dr. Abhijit Maity on innovative approaches to isolate delicate infrared fingerprinting signals from the background of strong laser pulses.

Overall, with the new laboratory in Hungary, CMF has established a unique facility for molecular fingerprinting and laser research.



CMF Biolaboratory and Biobank

The Journey of H4H Blood Samples

Csilla Lakatos, Dóra Nagy, Ágnes Kovács, Kamilla Mileant, Dr. Diána Debreceni

During the multicentric medical research conducted by CMF, over 50,000 blood samples have been collected across 21 study sites, each involving 10 storage tubes per collection resulting in the collection and storage of more than 500,000 tubes. The goal is to increase the collection rate significantly in 2025.

How do the samples travel from the study sites to storage?

The plasma samples, centrifuged at the study sites upon collection, are stored in 0.75ml Micronic tubes arranged in SBS racks. Each site has a dedicated Clinical Research Associate (CRA) responsible for coordinating with the CMF Biolaboratory team once a sufficient number of samples has been gathered for shipment. When ready, a shipment is arranged to the Biobank of the University of Szeged (SZTE Biobank), where samples are stored in a Liconic semi-automated system at -80°C.

How do we ensure that clinical data corresponds to the correct sample?

Samples are identified with unique 1D alphanumeric codes, and each storage tube is marked with a 2D data matrix code. This system facilitates seamless cataloging of samples during both the collection and biobanking phases. The clinical data for subjects who undergo sampling is stored in a centralized pseudonymized electronic database (eCRF platform) alongside the identifier codes of the tubes, ensuring precise linkage of clinical data to corresponding sample identifiers.
The CMF interim laboratory, in its bioanalytical function, is equipped with advanced automated tools and next-generation technologies – such as a liquid handling robot, an FTIR spectroscope (Fourier Transform Infrared Spectroscopy), and an absorbance reader – for performing various pre-analytical tests, quality control measurements, and method validations.

Preparing the samples for testing and measurements

The experimental workflow begins with retrieving samples from the biobank and transporting them to the CMF interim laboratory at the ELI-ALPS Research Center in Szeged. Upon receiving samples from the SZTE Biobank, the initial step is to scan both the plasma tube racks and the 2D codes to verify the integrity and accuracy of the shipment. All processes are meticulously documented in our Laboratory Information Management System (LIMS) platform, ensuring traceability at every stage. The samples are stored at -80°C in Ultra-Low Temperature (ULT) freezers.
Once received and stored, the samples undergo aliquoting. This process begins by thawing the tubes overnight at +4°C. Four sets of 96 tubes are prepared, each labeled appropriately. After thawing, the samples are gently shaken, centrifuged, decapped, and aliquoted using a liquid handling robot dispensing 4 x 90 µL of plasma from each tube into labeled empty tubes. These aliquots are used as follows: one for FTIR measurement, one for laser measurement, and two reserved as backups. Upon completion, special lids – called thermoplastic elastomer (TPE) – are placed on each tube, and the samples are scanned and stored again at -80°C in their dedicated freezers. The scanned tube identifiers are then uploaded to the LIMS, which precisely tracks each aliquot's source tube and storage location.

What are the necessary steps for a successful measurement?

Each day begins with powering on the FTIR machine's detector, followed by a 20-minute wait before conducting the performance qualification test. If the test is successful, measurements can begin. Each batch selected for measurement consists of 28 plasma samples, along with water, a special solution (dimethyl sulfoxide – DMSO2), and quality control (QC) serum. As in aliquoting, samples must be thawed, gently shaken, and centrifuged before measurement. After completing each batch, cleaning protocols are followed to maintain the machine's smooth operation. Post-measurement, each spectrum is reviewed to ensure successful data acquisition, and all results – successful and failed – are documented in the LIMS. If a measurement fails, the corresponding backup sample undergoes the same process. The resulting data files are then provided to the Data Science Division of CMF for further analysis. Daily operations also include tracking the materials required for aliquoting and FTIR measurements. This is managed through detailed Excel sheets, enabling timely inventory management and ensuring supplies are available.

Future development plans to keep up with technological advances

Original sample tubes and aliquoted samples are currently stored in -80°C freezers. Compared to traditional storage at this temperature, cryogenic storage using liquid nitrogen at -150°C or lower offers unparalleled longevity for preserving biological sample integrity and ensures exceptional operational reliability. Consequently, CMF is working on acquiring a state-of-the-art liquid nitrogen (LN2) cooling system with an associated workstation. The automated cryogenic units are expected to have capacity storage of up to 500,000 sample tubes each. Most of the transfer of these tubes will be automated using robotic arms. Storage units will also connect to an automated, temperature-controlled workstation via a rail system, enabling complete automation of sample selection, handling, and storage processes and, most importantly, maintaining the quality of the sample by preventing thawing above -130°C during manipulation.

From Innovation to Impact

How Technologies Shape Society

Dr. Mihaela Zigman, Dr. Veit Ziegelmaier

Throughout history, technological advancements have driven breakthroughs that transformed healthcare, saved millions of lives, and elevated our quality of life. From early surgical tools to today's advanced diagnostic techniques, these innovations reflect humanity's enduring quest to better understand the human body and conquer disease. Among the pivotal figures in this journey is Hungarian physician Ignác Semmelweis (1818–1865), whose discovery of antiseptic practices laid the groundwork for modern medicine and paved the way for the latest advancements in personalized medicine.

The Germs on Our Hands

In the mid-19th century, hospitals were perilous places. Mortality rates were alarmingly high, especially among mothers giving birth. In some clinics, as many as one in three new mothers succumbed to puerperal fever, a deadly infection. Many causes were theorized, from "bad air" to bodily fluid imbalances. However, Ignác Semmelweis, a physician with a sharp eye for observation, noted that doctors moving directly from autopsies to childbirth wards – without washing their hands – were unknowingly spreading harmful infections. His simple but revolutionary solution was to wash hands in a chlorinated lime solution before treating patients.

The results were extraordinary: puerperal fever cases drastically declined, saving numerous lives. However, Semmelweis faced immense resistance from his peers, who found it hard to accept that such a simple act could yield profound effects. It wasn't until years after his death that his ideas were widely accepted, thanks to the rise of germ theory, pioneered by Louis Pasteur and Joseph Lister.

Semmelweis' insight extended beyond saving lives – it established modern hygiene practices in healthcare and marked the beginning of infection control, a cornerstone of medical care that continues to evolve with advances in technology.

The Antibiotic Breakthrough

The 20th century saw an explosion of medical innovations built on the foundations laid by pioneers like Semmelweis. One of the earliest breakthroughs was Wilhelm Conrad Roentgen's discovery of X-ray imaging in 1895, which allowed doctors to peek inside the body without surgery, revolutionizing diagnostics and enabling countless life-saving interventions. Later technologies, such as MRI and CT scans, offered even more detailed glimpses of the body's inner workings, significantly improving diagnostics for complex conditions like cancer, heart disease, and neurological disorders. Simultaneously, groundbreaking advances in surgical techniques and the development of artificial organs have redefined the limits of modern medicine. Innovations like pacemakers, kidney dialysis machines, and, ultimately, artificial hearts have made it possible to replace damaged tissues and organs, often granting patients not just years but entire decades of extended meaningful life.

While physical and technical discoveries often received the most attention, one of the most profound breakthroughs was the development of antibiotics. In 1928, Alexander Fleming discovered that mold (Penicillium notatum) produced a substance capable of killing a wide range of bacteria. However, it took the combined efforts of Ernst Boris Chain, who figured out ways to isolate and concentrate the germ-killing agent, and Howard Florey, who developed new methods, to make penicillin medically available. Yet, even these advances were built upon the early work of Ernest Duchesne, who, in 1896, demonstrated that Penicillium glaucum inhibited bacterial growth.

Among humankind's most significant discoveries, antibiotics stand out as a triumph that transformed medicine, yet, they introduced a profound new challenge: antibiotic resistance. This unintended consequence compromised patient care, increased mortality rates, and escalated healthcare costs. Antibiotics reshaped contemporary biomedicine, as well as its potential and limitations. Today, we continuously need to develop new generations of antibiotics to combat this resistance and sustain their effectiveness. More fundamentally, this issue underscores how scientific discoveries, when viewed in isolation, may not achieve their full societal impact. Knowing about a specific mold wouldn't have saved lives during World War II, just as stabilizing a molecule alone wouldn't have revolutionized medicine.

The scientists who pioneered these breakthroughs couldn't have anticipated the extent to which their discoveries would shape societal "evolution." Similarly, as we innovate today, we often lack full awareness of the long-term social or ethical implications. The key is understanding our limitations, embracing responsible innovation, and acknowledging that even the most groundbreaking achievements may carry consequences we must be prepared to address.

While physical and technical discoveries often received the most attention, one of the most profound breakthroughs was the development of antibiotics.

The Legacy of Genomics

Was the new era of genomics in the 21st century any different? In this phase, medical technology again shifted its focus – this time toward the molecular secrets of the human body. A pivotal moment in this transformation was the completion of the Human Genome Project (HGP), a monumental international collaboration that spanned over 13 years. Involving more than 20 research centers and thousands of scientists worldwide, the project aimed to map the entire human genetic code – a staggering 3 billion DNA base pairs. Did they achieve a perfect completion? Not quite. HGP researchers faced limitations in decoding specific stretches of human DNA, particularly in highly complex or repetitive regions. However, by April 2003, they had produced a map accounting for 92% of the human genome. This significant achievement laid the groundwork for understanding the genetic basis of various disorders and opened the door to personalized medicine, where treatments can be tailored to an individual's genetic makeup.

However, the impact of the HGP extended far beyond medical treatments. One of its most transformative legacies was its influence on how scientists share data. Prior to the project, large-scale biological research initiatives were often met with skepticism, and research typically focused on specific, hypothesis-driven questions. The HGP demonstrated the power of open data-sharing and international collaboration, reshaping research practices and providing a foundation for the establishment of new fields.

The HGP in another way also highlighted that genes alone do not tell the whole story of human health. While it identified 20,000-25,000 genes that provide a crucial foundation, we now understand that many diseases and traits are influenced by factors beyond genetic coding. The regulation of genes, their interaction with non-coding DNA, and environmental factors – such as lifestyle and exposure to chemicals – are equally important in understanding health and disease.

What else did the Human Genome Project map beyond our genes? It revolutionized our approach to science, healthcare, and our understanding of human identity, growth, and aging. As we continue to explore how DNA interacts with the surrounding environment, the next significant breakthroughs may build upon this extraordinary legacy. It is clear that while gene-centric considerations remain vital, they should not constrain our perspectives; embracing a more holistic view is essential.

Could Phenotyping Improve Our Understanding of Health?

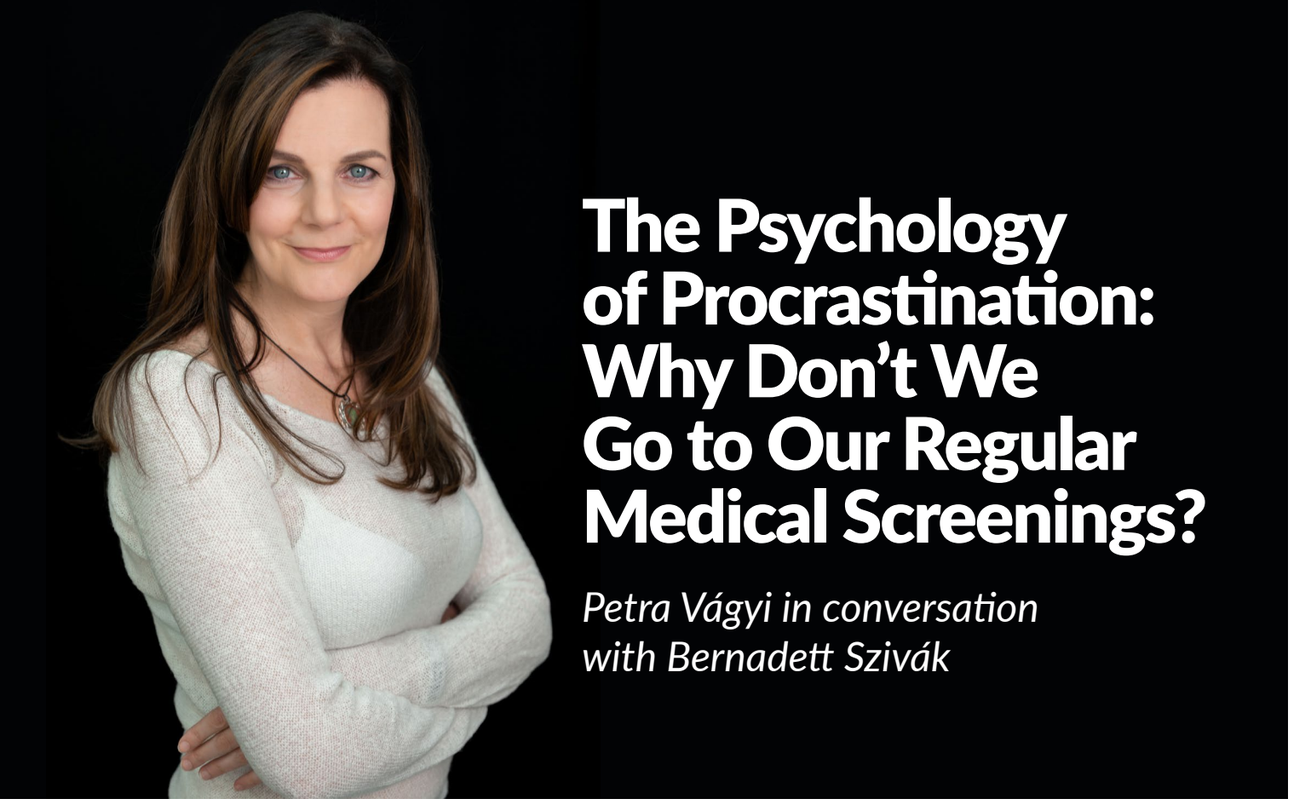
Biological systems are inherently complex and exhibit emergent properties – characteristics that cannot be explained by the functions of single components of the system but only by their interactions. Similarly, human diseases display non-linear dynamics, where small changes can lead to significant and unexpected effects over time. Traditional medicine, which relies on population-based observations and clinicopathological classifications, is effective when diseases have clear, singular causes (e.g., infectious diseases). However, this approach struggles to address the new chronic conditions prevalent in Western populations, which often have multifactorial causes.

So, how can we best grasp this complexity? One method is to quantitatively phenotype human systems by non-invasively studying tissues that reflect internal bodily processes – such as blood. This approach does not directly identify causes but comprehensively describes a person's health status. At CMF, in partnership with LMU and MPQ, we aim to better characterize what we call a "phenotype" – a combined state of health resulting from the combination of genome, lifestyle, environment, and their intricate interactions.

Whether analyzing the cell-free component of our blood will yield insights to improve our understanding of phenotypes and health states and guide personalized therapies remains to be seen. This is a substantial effort. Rather than merely decoding a single human genome, we are now striving to understand the diversity of human phenotypes and define what it means to be healthy throughout our lives. This effort is vast because each of us is unique, leading lives shaped by a combination of genetics, lifestyle, and environmental factors. Consequently, health becomes an individualized concept, and no two people share the same phenotype; what constitutes "healthy" varies for each person.

In this exciting future, the legacies of pioneers like Ignác Semmelweis continue to inspire advancements in prevention, early disease detection, and personalized care, ultimately enhancing and safeguarding human health.

Today, we face challenges that, although different, still echo those of past centuries. We remain engaged with nature's evolving responses to our scientific advancements and developments in environmental and computational realms. Such ongoing interactions highlight the dynamic relationship between nature, science, and society. In the case of penicillin, its transformation from a scientific curiosity to a medical revolution was not the result of a grand collective vision. Rather, it stemmed from scientists diligently focusing on the details – such as improving molecular stability to enhance antibiotic effectiveness and refining our understanding of DNA. Without this attention to fundamentals, the transformation of medical practices might never have occurred. As we expand our technological toolkit to explore the intricacies of molecular phenotypes, we strive to gain deeper insights into the signatures of individual phenotypes, thereby advancing our understanding of the uniqueness of human health.



The Psychology of Procrastination: Why Don't We Go to Our Regular Medical Screenings?

Petra Vágyi in conversation with Bernadett Szivák

According to a recent study[1], over half of Hungarians fear developing some form of cancer, yet only one in five would take all possible steps to prevent it. Astonishingly, 49% of the population does not even attend regular cancer screening appointments. So, why do we avoid screenings when we know that skipping them could harm us in the long run? The psychological reasons behind this procrastination are at the heart of our inquiry, and clinical psychologist and schema therapist Petra Vágyi shares her insights on this issue.

Many people tend to delay their medical check-ups, but what's really behind this procrastination?

According to schema therapy, procrastination is often an avoidance strategy. This means the person tries to avoid situations that could potentially lead to negative emotions. However, there are several problems with this behavior. First, it's not guaranteed that the situation will actually result in bad feelings. When we fear something, we tend to view unknown situations as potentially threatening. This mindset can narrow our scope of living, as we stick to things that are part of our everyday routines and preventing us from discovering what the delayed or postponed situation might have been like. Interestingly, this avoidance strategy is learned in childhood, when it may have been useful in frightening situations. Over time, people unconsciously carry this behavior into adulthood.

Some people explicitly say they would prefer not to go for screenings to avoid being diagnosed with something. What's the psychological reasoning behind this mindset?

Several factors could contribute to this belief. Following the previous line of thought, this mindset may develop as a coping mechanism. As children, individuals may have had a frightening experience that they couldn't process. In response, they may have developed this belief to shield themselves from the discomfort of facing unknown, unsettling situations.

Additionally, it's possible that this behavior was learned from influential figures, such as parents or other important adults. If a child witnessed these figures avoiding unpleasant situations, they may have internalized the behavior as normal or acceptable for dealing with things that are feared or unknown. As adults, they may then carry this avoidance pattern with them, especially when confronted with new and uncertain experiences like medical screenings.

Why do we persist in using coping strategies that may not serve us well in the long run?

When a coping strategy successfully protected a child during emotionally overwhelming or distressing situations, it becomes registered as a helpful and effective tactic. As children, we are focused on short-term solutions, considering only the immediate relief a strategy provides. The long-term consequences of this approach, however, are not considered, as children are unable to see the bigger picture. This means that future problems stemming from these coping mechanisms are often unrecognized. As a result, the individual continues to rely on the same strategies, unconsciously believing they will help.

Can we be rational when fear of a negative outcome is so overwhelming?

The issue at hand is that, in these situations, we are often not rational. When a person is functioning in a healthy adult mode, even if their fears are triggered, they can recognize that they are afraid but remain grounded. They can see clearly that their fear or sense of hopelessness is not entirely based on the current situation.

However, this distortion of perception can make rational, mature thinking impossible. As a result, automatic reactions take over, such as procrastination, making excuses, secrecy, or pretending that a situation does not exist. Ultimately, these are unconscious automatisms that can only be resolved once the individual becomes aware of them.

How can we overcome this fear and see screenings as beneficial?

As with all symptomatic fears, I believe that lasting change in these negative feelings and coping strategies can be achieved through therapy. In therapy, the individual learns to reconnect with their wounded child and confront the beliefs shaped by fear-inducing parenting. When one begins to work on these fears and understands that the root causes lie in past experiences, it becomes easier to see that the current fears are often a reenactment of old, painful, or even fearful stories. Recognizing that these past patterns are being replayed in the present allows individuals to unburden themselves. This newfound awareness helps them see things as they truly are – no more, no less, and certainly not more frightening.

What does the individual need to work on in this situation?

It can be valuable for the individual to explore when avoidance was a logical and understandable choice of behavior, given their childhood circumstances and the options available at the time. By identifying the root cause of the avoidance behavior, they can begin to understand its origin and eventually release it. Recognizing that avoidance is only understandable within the limited capabilities of a child allows the individual to see it for what it is: a short-term mitigation that leads to long-term complications. As an adult, the individual has far more choices and opportunities to respond to fear in healthier ways. This newfound awareness allows the childhood fear to be reframed and seen in a new light.

Moreover, if avoidance was a learned strategy, shaped by an influential role model, the individual can reflect on how much that behavior truly helped them. After ten or twenty years, it becomes clearer whether the life of the role model, who may have also followed this pattern, was genuinely better or happier. This reflection can help the individual move forward and break free from old patterns.

About Petra Vágyi

Petra Vágyi is a clinical psychologist, schema therapist, supervisor, and trainer. She completed her university studies at the University of Debrecen. Alongside her clinical and teaching work, she has maintained a private practice since 2007, including a period in Munich between 2012 and 2019.

Vágyi is also an accomplished author, having published two books on schema therapy: In the Captivity of Our Schemas and Our Schemas in Pairs.

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[1]*Representative study conducted by Affidea Magyarország, 2024*

Progress Report on the H4H Program

The First 16,000 Person-Years

Dr. Domokos Gerő

The Health for Hungary – Hungary for Health (H4H) Program is a prospective study aimed at promoting the clinical translation of a novel health monitoring approach. This research program focuses on the study of health–to–disease transitions. Participants are healthy at baseline, meaning they are free from significant clinical diseases, but may develop new conditions over the course of the decade–long observation period. This enables us to investigate disease trajectories. As new conditions develop, changes in the blood will be directly compared to the healthy baseline state, represented by plasma samples collected prior to the onset of disease. This approach allows us to trace the true origin of a disease and uncover its earliest detectable signs in the blood. If new biomarkers are discovered, they will be validated by testing additional samples collected within the context of CMF's current study or by running new clinical trials, to support the future clinical use of these blood tests.

Middle-aged individuals who are apparently healthy often have risk factors for cardiovascular disease or suffer from milder conditions that require long–term drug therapy (e.g., antihypertensive and lipid-lowering drugs). Medications alone introduce variations in plasma, and whenever changes occur in drug therapy – such as the initiation of a new drug, a dosage modification, or the discontinuation of a drug – novel alterations may appear in the blood. Thus, all blood tests are influenced by pharmacological interventions, and effective health monitoring requires relevant information on these changes. Tracking drug use will allow us to document medication trajectories in association with corresponding changes in plasma composition, providing essential information for future health monitoring.

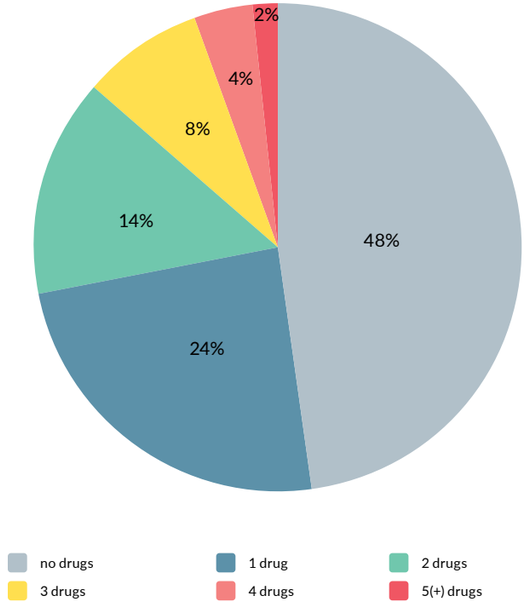
In our approach, four pre–disease samples are assumed to represent an individual's healthy state, and any minor differences detected at this early stage are believed to correspond to normal biological variation. On the other hand, any changes that occur thereafter may be associated with new-onset conditions, such as the emergence of a disease precursor or the presentation of a true clinical disease. Therefore, it is essential to understand what the "apparently healthy state" of subjects means, and to identify any risk factors or underlying conditions present at the study's onset.

Medication Use at Study Onset

At study onset, 52% of participants were taking prescription drugs (48% of men and 54% of women), while 48% of subjects were not receiving any pharmacological treatment at enrollment *(Figure 1)*. Overall, 24% of participants took only a single tablet, 14% took two prescription drugs, and another 14% took more than two drugs on a daily basis. Fewer than 2% of participants were prescribed five or more prescription drugs. Drug consumption increased considerably with age: fewer than 50% of participants aged 40-59 years took any medication, whereas 70% of those aged over 60 years were on prescription drugs.

In the apparently healthy population, cardiovascular risk reduction is, as expected, the primary reason for pharmacological therapy. Hypertension was the leading indication for drug therapy: the highest proportion of medication use was associated with high blood pressure, with 62% of participants on medication taking antihypertensive drugs. The second most commonly used drug was levothyroxine (synthetic thyroid hormone), prescribed for the treatment of hypothyroidism. The relatively high incidence of hypothyroidism can be attributed to the female predominance in the study population. As a result, a larger proportion of women were on drug therapy compared to men, not only due to thyroid hormone supplementation but also because of contraceptive use. However, little difference was observed in the use of other drug classes between genders. Antidiabetics were the third most prescribed drug class, while lipid-lowering therapeutics ranked fourth in the study population.

Medication use in subjects



Shares of medications in subject

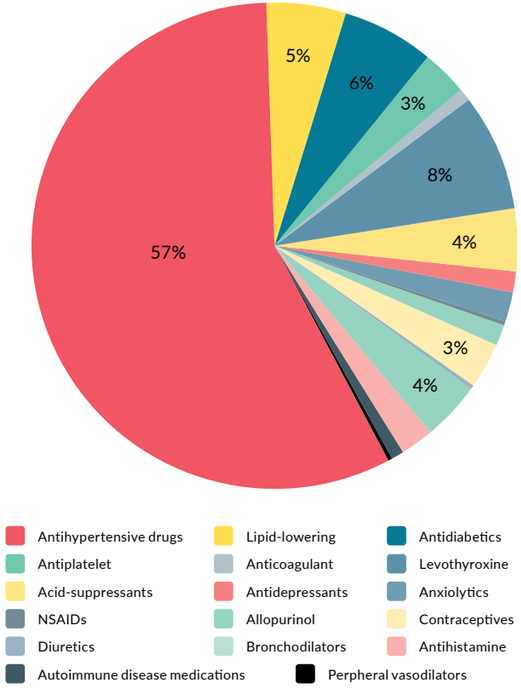


Figure 1

New-Onset Diseases in the Study

The development of new diseases is of great importance because disease–specific molecular signals can only be discovered through relevant cases, once a given condition is recognized and medically documented. These cases are also prerequisites for future tests to detect subclinical disorders: molecular fingerprint patterns specific to precursor states may be identified after diseases are clinically recognized, by re–analyzing prior samples from affected individuals. Thus, following up with subjects and tracking any new diseases diagnosed during the observation period is essential for the future use of molecular fingerprinting.

Diseases recorded shortly after enrollment (i.e., within 1 year) may not represent new–onset conditions but rather pre–existing conditions that were noticed and documented with a delay. However, conditions identified after more than 1 year (i.e., after the 4th visit of participants) may indicate truly new–onset diseases.

In the H4H Program, CMF has several hundred subjects with diseases indicated after the first year, but many of these represent minor abnormalities (e.g., allergies, hypertension), which may not require a blood test at all *(Figure 2)*. For other cases, CMF is collecting further data on the disease specifics to confirm that the indicated conditions belong to the group of targeted non–communicable diseases (NCDs).

While CMF is still in the early phases of the study, these cases are invaluable as they help guide our next steps in the investigation. The sooner we recognize specific signals for clinical diseases, the better, as this enables us to begin our search for signals specific to preclinical conditions. This process could contribute to the foundation of a new era in medicine, where precursor conditions are clearly defined by validated markers of pre-symptomatic stages of disorders, rather than relying solely on risk factors to avoid or treat them in hopes of preventing the development of clinical diseases.

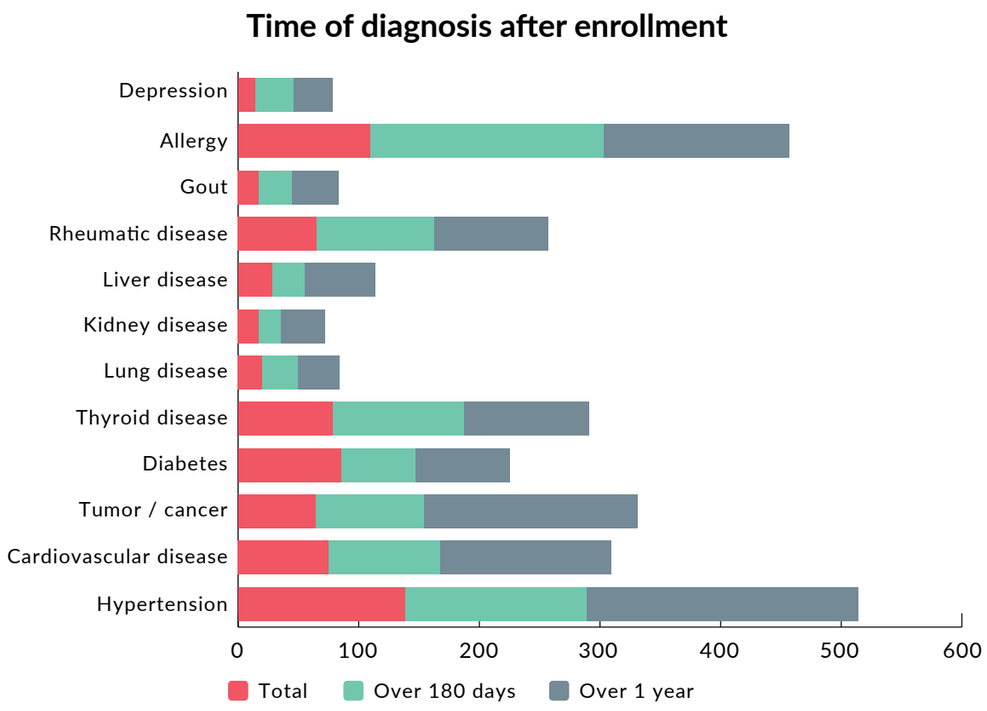


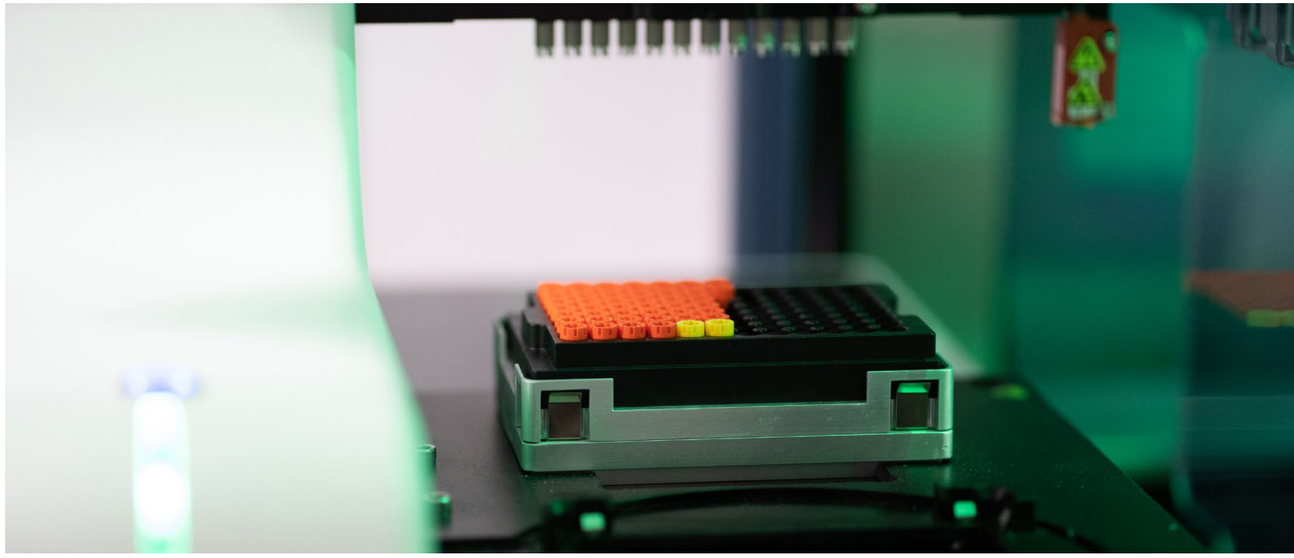
Figure 2

High-Risk Arm of the H4H Program: A New Approach to Early Disease Detection

Dr. Domokos Gerő

The H4H Program is a pioneering effort to develop cutting-edge, reliable tools that detect diseases earlier than ever, promoting timely treatment and extending healthy lifespans. With non-communicable diseases (NCDs) like heart disease, cancer, chronic respiratory disease, and diabetes responsible for over 90% of mortality in developed countries, including Hungary, the Program focuses on these life-threatening conditions.[1] Cardiovascular disease alone accounts for over 40% of annual deaths in Hungary.[2] Since these conditions typically develop over decades, often with subtle precursors, the H4H Program seeks innovative ways to identify them during the earliest, most treatable stages.

The Program's first stage involves primarily middle-aged individuals, with a minimum age of 40 at entry. Given this demographic, the annual rate of new diagnoses is expected to be low, especially in the study's early years.



[1] *Monitoring noncommunicable disease commitments in Europe 2021: are we on track to reach targets 10 years after the Moscow Declaration and First United Nations High-Level Meeting? Copenhagen: WHO Regional Office for Europe; 2021. Licence: CC BY-NC-SA 3.0 IGO.*

[2] *OECD/European Observatory on Health Systems and Policies (2023), Hungary: Country Health Profile 2023, State of Health in the EU, OECD Publishing, Paris/European Observatory on Health Systems and Policies, Brussels. ISBN 9789264657779 (PDF), Series: State of Health in the EU, SSN 25227041 (online)*

This population, termed the “low- and moderate-risk arm”, will yield fewer cases over time, but each diagnosis will likely occur in its purest form (without other health complications), with detailed, pre-disease blood samples available for study. This unique dataset will allow researchers to trace disease trajectories from their earliest indicators, though case collection will be gradual.

To accelerate the discovery of new disease markers, a high-risk stratum was initiated within the Program: individuals with increased susceptibility to cardiovascular disease and lung cancer. This high-risk cohort is essential, as studying them can speed up our understanding of disease onset and lead to new, early-detection methods for the broader population.

Identifying High-Risk Participants: Targeting Key Health Factors

Participants in the high-risk arm have been selected based on significant risk factors for cardiovascular disease and lung cancer. These factors fall into two main categories: modifiable and non-modifiable. Modifiable factors include lifestyle and health conditions like hypertension, high cholesterol, smoking, obesity, and diet. Non-modifiable factors, such as age, gender, and family history, are those we cannot control but still significantly impact risk levels.

In the high-risk arm of the H4H Program, CMF focuses on individuals over 50 years of age who are more likely to develop certain clinical diseases. These participants are older than those in the low-risk group and possess three major modifiable risk factors: hypertension, high cholesterol, and a significant history of tobacco use.

The risk of lung cancer rises with both age and cumulative smoking exposure. The study initially defined the high-risk population as those over 50 with at least a 20 pack-years smoking history. As the years of smoking or the number of packs smoked per day increases, the pack per year count multiplies. This high-risk group is thus not only more susceptible to cardiovascular disease but also faces an increased risk of lung cancer.

While participants in this high-risk group are more likely to develop overt disease, some may already have underlying subclinical or precursor conditions at the study entry or may develop them soon after. By monitoring this group, the H4H Program aims to advance early detection methods, offering a proactive approach to managing and potentially preventing life-threatening diseases.

Health Monitoring and Proactive Disease Detection in High-Risk Subjects

To minimize potential risks and confirm that participants in the high-risk arm start the study free from certain subclinical conditions, the H4H Program employs a comprehensive assessment process at enrollment and shortly afterward. To keep disease detection precise, the first four visits for high-risk participants occur close together, allowing for rapid baseline sampling in a pre-disease state. This short period for initial visits mirrors the interval between two regular visits in the low-risk arm. Additionally, high-risk participants complete a more detailed self-report questionnaire and routine bloodwork to capture comorbidity details.

Participants undergo blood pressure measurement and resting electrocardiography (ECG) for a closer look at cardiovascular health. Bioimpedance analysis (BIA) is also conducted during the initial visit to gather additional insights into metabolic health. Although these tests are not highly sensitive to coronary disease, they help screen out more severe abnormalities early. After these first four samplings, a medical check-up verifies each participant’s health status, while two critical imaging tests are performed first: a low-dose computed tomography (LDCT) scan of the chest and a coronary artery calcium (CAC) score assessment. LDCT screens for lung abnormalities, including nodules, while the CAC score reveals calcification in coronary arteries – a marker of atherosclerosis.

A thorough medical review assesses participants’ health using these imaging results, repeated blood tests, a fresh physical exam, and a cross-check of electronic health records via the National eHealth Infrastructure (EESZT). This step ensures all baseline data are accurate and verified, so any future conditions recorded in the study genuinely represent new disease onset.

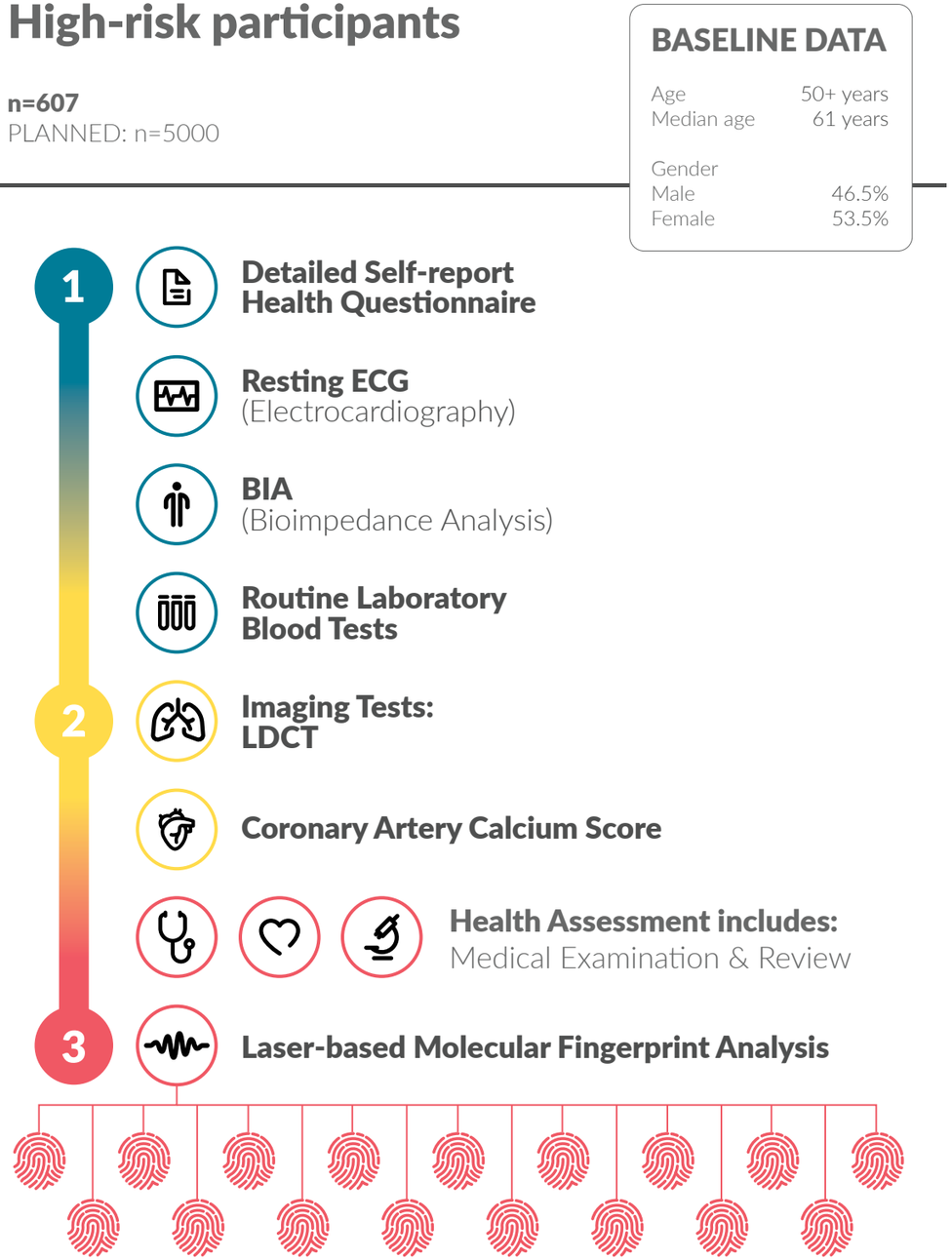


Figure 3

Lasers4Life

Cross Sectional Study to Investigate Lung Cancer

Dr. Domokos Gerő

Cancer remains a global health challenge, with 51% of men and 43% of women developing malignant neoplasms during their lifetime. Lung cancer, one of the most prevalent tumors, is the leading cause of cancer mortality in Hungary. In 2022 alone, 9,911 new lung cancer cases were registered[1, 2], accounting for 14.7% of the annual cancer incidence, while 8,462 deaths were reported, representing 26.1% of yearly cancer mortality. Alarmingly, five-year survival rates remain dismally low – 21% for men and 16% for women – primarily due to the late diagnosis of the disease.

Reducing lung cancer mortality hinges on early diagnosis. Efficient screening programs are critical to detecting tumors early and improving survival outcomes. Radiographic imaging methods, such as computed tomography (CT) scans, have been widely utilized for this purpose. However, their population-wide application is often constrained by limited availability and high costs. Currently, low-dose CT (LDCT) screening is reserved for the "high-risk" population – adults aged 50 to 75 years with a smoking history of at least 20 pack-years. Broader implementation of this screening tool remains controversial due to its expense, the high rate of false-positive results, and the relatively low incidence of true positives. Furthermore, a considerable number of lung cancer cases occur in individuals outside the high-risk category, who, therefore, remain untested in LDCT-based screening programs.

Given these limitations, the development of novel biomarkers and methodologies is urgently needed. These innovations aim to support ongoing and future lung cancer screening campaigns with two critical objectives:

- Enhanced Risk Identification: To better identify individuals at high risk of developing lung cancer.
- Verification of True Positives: To aid in confirming true lung cancer cases among individuals flagged as positive by imaging methods, ensuring more accurate diagnosis and reducing unnecessary interventions.

By addressing these challenges, the integration of new biomarkers and advanced methodologies has the potential to revolutionize lung cancer screening efforts, paving the way for improved early detection and, ultimately, better patient outcomes.

Aims and Design of the Study

The Lasers4Life (L4L) study aims to identify and validate novel biomarkers to improve lung cancer diagnosis and treatment. A key focus of the study is the use of molecular fingerprints, which have the potential to meet the demands of modern screening and diagnostic approaches. These advancements are expected to facilitate the clinical translation of a novel blood test that could serve two main purposes:

- Risk Assessment Tool: The blood test could be used as a preliminary screening method at the forefront of screening campaigns, helping to assess individuals' risk before performing radiographic imaging.
- Complementing LDCT Examinations: The blood test could act as an additional diagnostic tool alongside low-dose CT scans to improve accuracy and reduce false positives.

The overarching goal of these diagnostic strategies is to enable earlier detection of lung cancer, which can significantly improve survival rates and therapeutic outcomes. Moreover, the study aims to explore another promising application of molecular fingerprinting: predicting therapeutic outcomes. By analyzing the first blood sample taken at the time of diagnosis, researchers hope to anticipate the efficacy of different anticancer medications for individual patients.

While this predictive approach may seem ambitious, it holds immense promise for optimizing treatment delivery. By tailoring therapies based on predictive insights, the study seeks to enhance treatment effectiveness and improve overall patient care.

The L4L study employs a cross-sectional approach, distinguishing it from programs like the H4H. In this design, a single blood sample is collected from participants with positive imaging test results before tissue biopsies are performed. These blood samples are analyzed for potential markers of lung cancer. Following this, the underlying disorders – whether lung cancer or benign lung disease – are confirmed as part of the routine care through histological analysis of tissue samples. Based on the results, participants will be categorized into two primary groups: those with and without malignancy. Lung cancer patients will undergo further subclassification based on the stage and histological subtype of their disease. Since the detection of early-stage lung cancer (stages I-IIIa) is of particular interest, these cases must be compared to samples from healthy subjects instead of individuals with benign lung diseases. To achieve this, a third group of participants, comprising individuals free of lung disease, will be enrolled to establish a baseline for the normal molecular fingerprinting pattern (i.e., the "healthy phenotype").

The study aims to enroll approximately 10,000 participants over a 5-year period, with a predominance of subjects presenting with lung diseases. Among those with positive imaging tests, it is anticipated that the number of benign and malignant cases will be comparable. Notably, around 10% of cancer patients are expected to present with stage I disease, with a larger proportion having other early-stage cancers. One key challenge is the unpredictability of group sizes, as participants are enrolled before a final diagnosis is made. Additionally, a shift toward earlier cancer detection is expected over the study's duration, reflecting advancements in diagnostic technologies and screening practices compared to trends observed in prior decades.

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[1]*Bray F, Laversanne M, Sung H, et al. Global cancer statistics 2022: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2024; 74(3): 229-263. doi:10.3322/caac.21834*

[2]*Ferlay J, Ervik M, Lam F, Laversanne M, Colombet M, Merz L, Pineros M, Ynaor A, Soerjomataram I, Bray F (2024) Glocal Cancer Observatory: Cancer Today, Lyon, France: International Agency for Research on Cancer. Available from: https://gco.iarc.who.int/today accessed on 13 October 2024.*

Clinical Centers: A Close Collaboration to Follow-Up on Clinical Outcomes in Patients

In cancer care, diagnostic investigations, such as tumor staging and grading, are essential for selecting the most effective therapeutic interventions. These interventions aim to induce remission, extend relapse-free survival, and improve overall survival rates in patients. While longer remission and better survival outcomes are generally associated with early-stage disease, numerous factors can influence these measures, making the outcomes unpredictable in many cases. To address this unpredictability, companion diagnostic tests have been developed for certain therapies. These tests often involve the mutation analysis of tumor cells or the investigation of expression profiles (i.e., specific oncogene) at the translational level. By providing insights into tumor biology, these tools help estimate the efficacy of specific anticancer agents and tailor treatments to individual patients. Molecular fingerprinting of plasma may offer a promising alternative for predicting therapeutic success. This technique is highly sensitive and provides broad coverage, capturing a wide range of molecular changes. Unlike traditional methods, it has the potential to offer a more comprehensive picture of the disease and treatment response. However, this application of molecular fingerprinting remains untested in clinical settings. Future studies will be necessary to explore its ability to predict therapeutic outcomes and guide personalized treatment plans.

To determine whether molecular fingerprinting can meet the challenge of predicting therapeutic efficacy and identifying circulating molecules that indicate treatment success, the study will gather information on subsequent therapeutic interventions and clinical events. Clinical outcomes will be recorded in a longitudinal manner over a 2-year follow-up period for cancer patients. A thorough and close monitoring process is required, which can only be achieved through specialized care in pulmonology wards and oncology centers. To ensure such a comprehensive follow-up, the project involves collaboration with three distinguished clinical centers from the outset: National Korányi Institute of Pulmonology; Department of Pulmonology, Semmelweis University Medical School, and Department of Pulmonology, University of Szeged, Albert Szent-Györgyi Medical School.

These centers will provide the necessary expertise and resources to monitor patients closely and assess the therapeutic outcomes, ensuring the success of the study's objectives. They will diagnose, treat, and manage cancer patients, recording relevant outcomes in electronic case report forms (eCRFs), which will be correlated with patients' molecular fingerprints.

Once complete or relapse-free partial remission is suspected based on clinical evaluation and adjuvant chemotherapy is discontinued, a second plasma sample will be collected from the patient. This sample will be analyzed to identify differential fingerprinting signals, which reflect the difference between pre-treatment and post-treatment molecular profiles. These signals will help confirm the cancer-specificity of the fingerprinting method and detect early signs of relapse, which is often difficult to identify at early stages in clinical practice.

The goal of the L4L study is to find novel tools that can offer:

- Higher sensitivity for earlier disease detection
- Greater specificity to cancer, ensuring more accurate diagnostics
- Cost savings by reducing the need for expensive diagnostic tests
- Better predictions of therapeutic response, particularly for costly medications

Building on these efforts, CMF anticipates extending the study to include other types of cancer, such as pancreatic and prostate cancer, which also require more advanced diagnostic approaches in the general population.

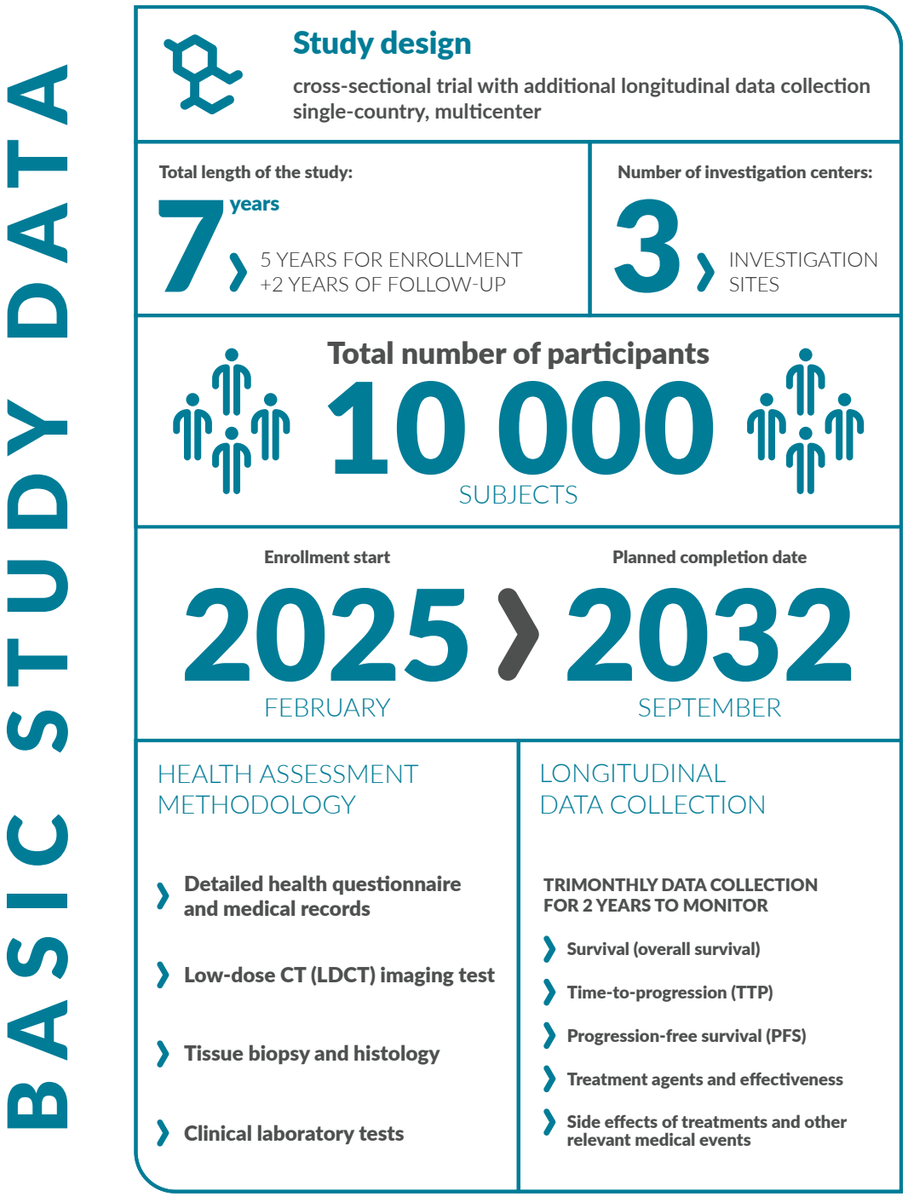


Figure 4

A New Path to Better Diagnostics

Dr. Frank Fleischmann

CMF aims to pave new avenues for improved health diagnostics and healthcare. This mission has been set in motion through the H4H Program, in which up to 15,000 participants are donating blood samples for research purposes over several years. Recently, CMF has joined forces with two outstanding German research institutes: the Max Planck Institute for Biochemistry and Helmholtz Munich. Together, they are combining CMF's infrared molecular fingerprinting (IMF) technology with mass spectrometry of proteins and nuclear magnetic resonance spectroscopy of small metabolites. Their shared vision is to develop a groundbreaking blood diagnostic method for early disease detection, utilizing samples collected through CMF's H4H Program.

CMF is taking its diagnostic efforts a step further by integrating infrared molecular fingerprinting with two advanced techniques that provide detailed insights into molecular changes in blood plasma. Blood plasma, the cell-free liquid component of our blood, consists predominantly of proteins, which make up approximately 80 percent of the plasma's dry matter. In addition to these proteins, plasma contains a vast array of small molecular weight metabolites, including sugars, amino acids, and lipids.

CMF utilizes unique, in-house-developed laser-based infrared spectroscopy systems to analyze the collected blood samples. This process creates a fingerprint of the blood plasma's composition within minutes, encoding information from all classes of molecules – whether proteins, lipids, carbohydrates, or other metabolic products. By monitoring changes in these fingerprints over time, disease-related alterations can be identified.

Using nuclear magnetic resonance (NMR) spectroscopy, the most abundant proteins, along with small metabolites and lipids, can be analyzed in detail. For these investigations, CMF collaborates with Prof. Dr. Michael Sattler and his team at Helmholtz Munich, renowned experts in the field. The process involves exposing samples to a strong static magnetic field and measuring their response to a rapidly changing magnetic field. This generates unique fingerprints of the sample, offering insights into its composition and enabling the identification of numerous individual metabolites in plasma. While this method might provide more detailed information on plasma composition and disease-related changes compared to infrared molecular fingerprinting, it definitely requires more time and comes with higher costs.

To gain deeper insights into the composition of plasma proteins, researchers employ a method called proteomics. This approach involves digesting proteins into smaller fragments at first, known as peptides, which are then analyzed using a mass spectrometer. These proteins are then reconstructed from the numerous individual pieces of information on the fragments. While the process is as complex as it sounds, requiring significant expertise, CMF collaborates with Prof. Dr. Matthias Mann and his team at the Max Planck Institute of Biochemistry in Martinsried near Munich, Germany. A leading authority in plasma proteomics, Mann uses cutting-edge technology to analyze samples from the H4H Program. This method enables the identification of thousands of proteins in blood plasma. Although more complex and expensive than infrared fingerprinting or NMR spectroscopy, proteomics offers unparalleled insight into plasma composition.

Ferenc Krausz, in collaboration with the teams led by Matthias Mann and Michael Sattler, has envisioned groundbreaking ways to detect diseases at their earliest stages by integrating their three advanced techniques. Infrared fingerprinting, as a cost-effective and rapid method, could be employed routinely for every sample from a subject. Through repeated longitudinal sampling, disease-related changes in plasma composition can be detected by comparing a new sample with the subject's previous samples. If abnormalities are identified, one or both of the more specific yet costly methods – NMR spectroscopy or proteomics – can then be utilized to provide detailed insights into the individual's health. The H4H Program represents the first study to test this innovative approach, laying the groundwork for a potential revolution in healthcare diagnostics.

Causal Inference in Medicine and Clinical Practice: Unlocking the Power of Cause and Effect

Dr. Kosmas Kepesidis

In modern statistics and data science, causal inference is crucial in unraveling cause-and-effect relationships between variables, especially in medicine. In clinical practice, understanding these relationships is essential for grasping disease mechanisms, predicting treatment success, and designing targeted interventions. While traditional statistical methods reveal associations and correlations, causal inference digs deeper to answer pivotal questions: what causes specific health outcomes, and how might changing one factor directly influence another? The primary aim is to estimate the true impact of one variable – such as a treatment or lifestyle change – on another, like disease progression or recovery. This distinction is vital in healthcare, where treatment decisions must rely on clear cause-and-effect connections rather than simple correlations.

The Basics of Causal Inference

Causal inference hinges on a fundamental distinction: correlation does not imply causation. Correlation signals that two variables are related, but we can only say that one influences the other by establishing causality. Determining causality requires meeting specific conditions, such as confirming that the cause precedes the effect, that a plausible mechanism links them, and that other influencing factors are controlled.

One core idea in causal inference is the concept of a counterfactual: imagining what might have happened if a different action or treatment had been taken. In medicine, this means comparing actual outcomes with hypothetical ones, offering a lens into alternative scenarios. For example, in clinical research, investigators compare treated and untreated patients or, more abstractly, assess the "same patient" under different treatment conditions.

Various approaches identify causal relationships in medical research. Randomized controlled trials (RCTs) are the gold standard, as they eliminate confounding factors by randomly assigning participants to treatment or control groups. However, when RCTs are unfeasible, researchers turn to observational data and advanced techniques like propensity score matching (PSM), which mimics randomization by matching patients with similar characteristics across groups. Instrumental variables (IV) methods allow researchers to control for unmeasured confounding by identifying external factors that affect treatment but not the outcome. In longitudinal studies, difference-in-differences (DiD) compares outcome changes over time between groups that did and didn't receive an intervention. Additionally, directed acyclic graphs (DAGs) help visualize relationships and identify potential confounders.

Applications in Medicine and Public Health

Causal inference has profound applications in clinical and medical research. Identifying disease risk factors is one of its most impactful uses. Understanding causal links between lifestyle factors – like smoking or diet – and health outcomes enables preventive strategies. For instance, while correlations between smoking and lung cancer were initially observed, causal inference confirmed smoking as a direct cause of lung cancer, ruling out confounders such as age or genetics.

Evaluating treatment efficacy is another critical area. RCTs are ideal for determining treatment effects, but many therapies are evaluated using observational data due to ethical or practical limitations. In such cases, PSM and other techniques allow researchers to adjust for differences between groups, enabling a more precise assessment of a treatment's impact. For example, suppose a study aims to assess whether a diabetes medication reduces cardiovascular risk. In that case, causal inference methods can help isolate the medication's effect by balancing confounding factors like age and existing conditions.

Public health policies also benefit immensely from causal inference. When analyzing the impact of interventions like vaccination campaigns, causal inference techniques reveal the actual effect. In the case of COVID-19 vaccines, researchers applied these methods to assess correlations with infection rates and measure whether vaccines directly reduced transmission, hospitalizations, and mortality. By comparing health data before and after a vaccination

rollout and adjusting for external factors, researchers clarified the causal impact of vaccines.

In personalized medicine, causal inference is increasingly applied to real-world data from large health records and genomic databases. Integrating these data sources helps researchers derive causal relationships that guide personalized treatment decisions. For instance, causal inference techniques help pinpoint which cancer therapies are most effective for patients with specific genetic mutations or determine the optimal treatments for chronic conditions like hypertension based on their unique health profiles. This tailored approach improves outcomes while reducing unnecessary treatments.

Healthcare Monitoring and Patient Management

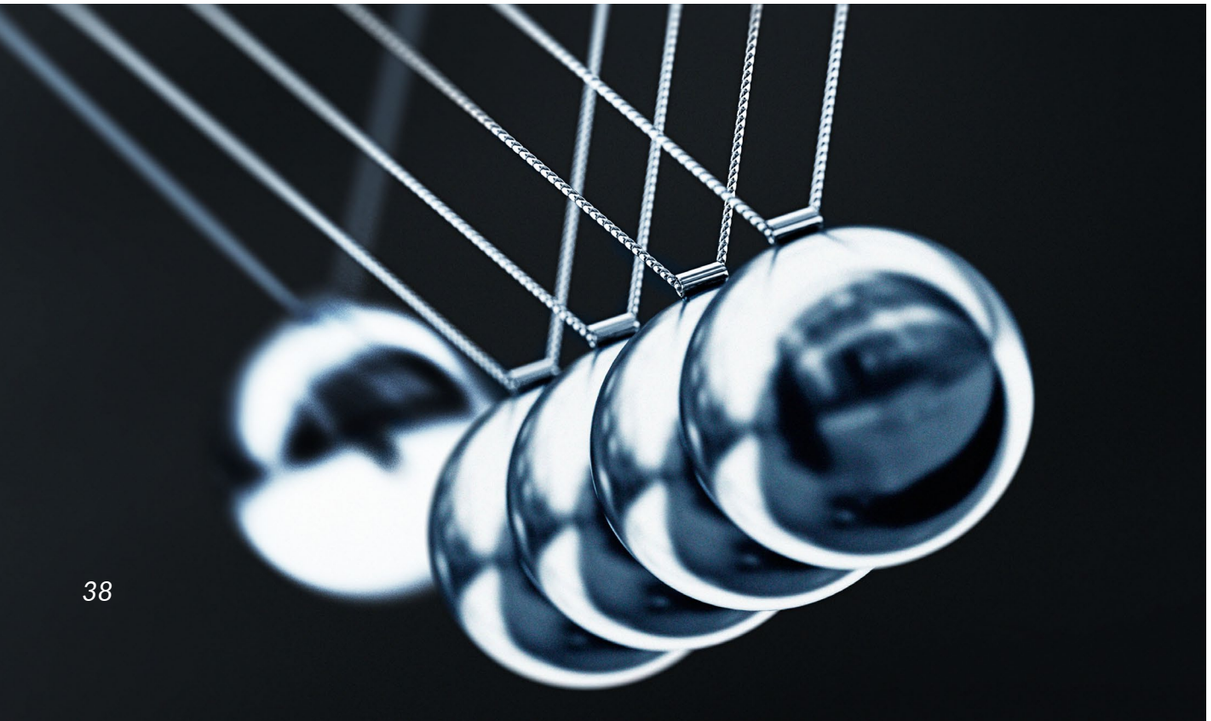
The importance of causal inference extends beyond research, playing an expanding role in healthcare monitoring and management. Hospitals and healthcare systems are incorporating causal models into patient outcome predictions based on treatment patterns, helping clinicians make more informed decisions. For instance, machine learning algorithms that integrate causal inference can predict adverse events, hospital readmissions, or chronic disease progression, enabling proactive and personalized patient care.

In managing chronic conditions like heart disease or diabetes, causal inference helps identify lifestyle changes or treatments most likely to reduce the risk of complications. By continuously monitoring patient data, healthcare providers can use causal models to adjust care plans in real time, ensuring patients receive the most effective interventions.

Challenges and Future Prospects

While causal inference offers significant advantages, it comes with challenges. Many methods depend on assumptions that don't always hold in real-world conditions, such as the absence of unmeasured confounders. Observational data can also be prone to biases, like selection bias or measurement error, complicating causal estimates. Yet advances in machine learning and artificial intelligence are refining causal inference techniques, enhancing accuracy and reliability in large datasets.

As big data, including electronic health records and genomic information become integral to healthcare, causal inference will drive further innovation. These data-driven methods promise more precise, actionable insights that can enhance personalized medicine and population health, ultimately leading to better, more informed outcomes in healthcare.



The Symbiosis Between AI and Medical Professionals

Márton Görög in conversation with Bernadett Szivák

Over the past two years, artificial intelligence has become one of the most talked-about topics, sparking widespread interest across various fields. According to AI expert Márton Görög, developments in AI, including new models and capabilities, are emerging at such a rapid pace that even the professional community is often surprised. We sat down with the expert to discuss the latest AI advancements and their potential healthcare applications.

What is the impact of artificial intelligence on healthcare developments in Hungary?

In Hungary, artificial intelligence (AI) is already making significant strides in various areas. One notable example is its use in medical image diagnostics, including PET, CT, and MRI scans within radiology. AI technology has been under development in this field for many years, and it is now being employed for tasks such as image quality enhancement and tumor detection. However, the development of AI is only one part of the equation. Full integration into healthcare systems requires several additional steps. It will take time for the technology to gain approval from relevant authorities, for hospitals to acquire the necessary infrastructure, and for doctors to learn how to effectively use these AI tools.

Hungary has made strong progress in development, but there may still be a need to catch up in terms of hospital adaptation. The country's size plays a significant role in this, as larger nations with bigger populations have a more significant market demand and a higher number of patients, which can drive faster adoption of new technologies. Many of the AI developments in Hungary are designed with the U.S. market in mind. This is not only due to the available financial resources but also the larger patient population, which provides a more substantial market for new technologies.

Another important factor influencing the adoption of AI in healthcare is the speed of return on investment. Most pharmaceutical companies operate on a market-driven basis and have been leveraging AI transformations for years. For example, AI is used to simulate the effects of new drugs and to model the spatial structure of proteins and molecules. However, the exact methods and processes behind these AI-driven research activities are not always straightforward. Much of the research conducted by pharmaceutical companies remains confidential, leaving us to make informed guesses about how these studies are being carried out.

Can AI be involved as a supplementary workforce, for example, in diagnosis? And could this be a threat or some help for doctors?

From an attitude perspective, it is essential to view AI as an assistive tool rather than a replacement. In many developed countries, there is a shortage of healthcare workers. Therefore, the real issue is not about AI replacing humans but rather how AI can help address the workforce shortage. Ideally, doctors would use AI tools as assistants, incorporating their recommendations without entirely relying on them. The responsibility for decision-making would still lie with the doctor since AI is particularly effective in handling repetitive tasks. Automating tiring, exhausting, and time-consuming tasks can greatly benefit not only doctors but also patients by allowing healthcare professionals to focus on more complex aspects of care. This creates a symbiotic relationship where both AI and healthcare workers collaborate to enhance the overall efficiency and quality of care.

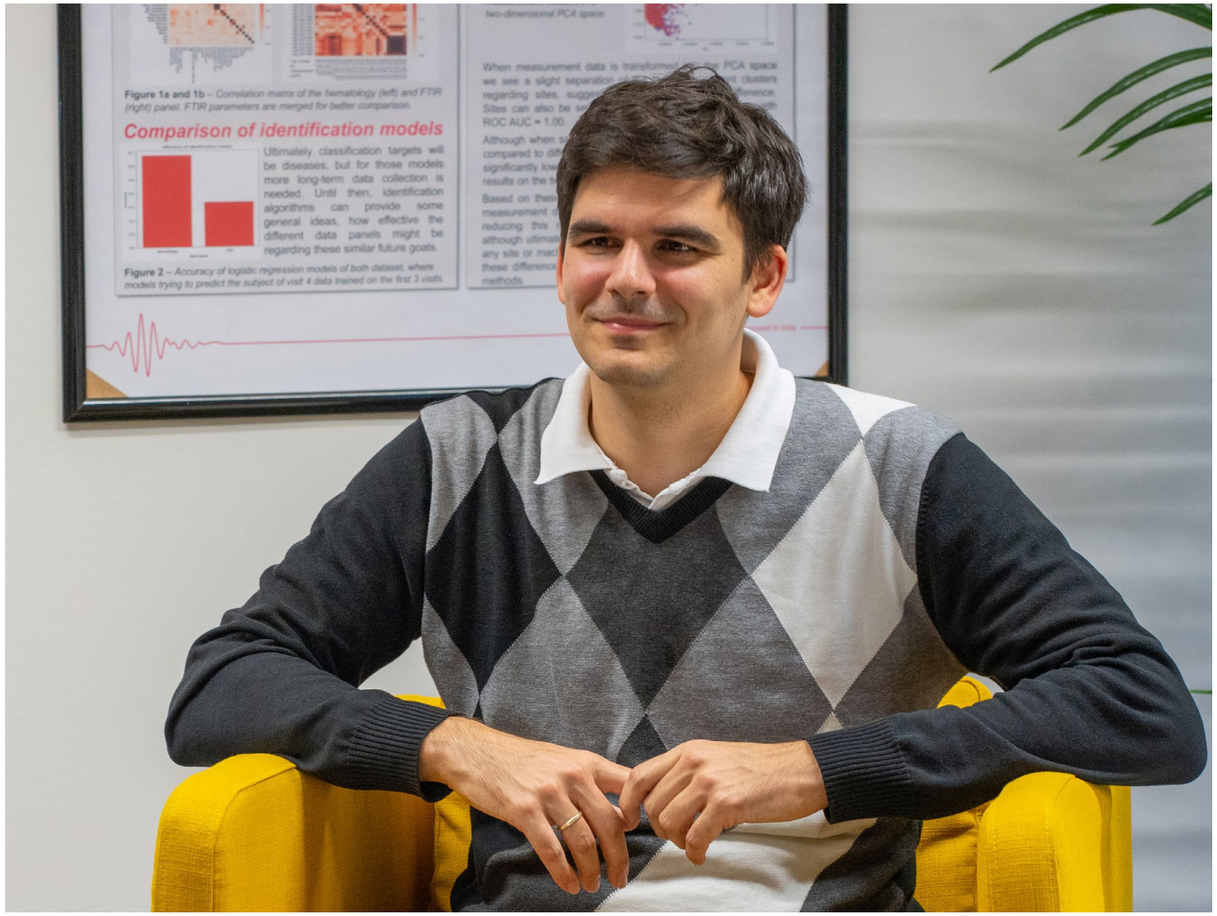
For AI to be as accurate and useful as possible, large amounts of data are required. Are there issues surrounding data protection and storage that must be addressed?

There are stringent regulations in place worldwide to protect sensitive data. While these regulations are crucial for ensuring privacy, they can also pose challenges for AI development. As an AI developer, these regulations are disadvantageous, significantly limiting data sharing. For instance, sharing data for scientific purposes between hospitals is often either legally too complex or entirely impossible. This can slow down the pace of development and experimentation in AI research. While these legal constraints are necessary to protect personal rights and data protection, they present a dilemma. Europe, for example, stipulates that certain health data cannot leave the continent, and similar regulations exist in the U.S. as well. While it is possible to collect data in regions with fewer restrictions, doing so is often more expensive, slower, and more cumbersome.

Anonymization or the use of pseudonyms, as seen in the H4H Program, is a crucial strategy in addressing privacy concerns. In many cases, it is essential to determine whether we can record data without directly identifying individuals, ensuring that other characteristics do not make the person identifiable. However, the more data is available, the better AI can be trained. A larger dataset enables AI to provide more accurate insights and improves its ability to cover a broader population. Thus, balancing privacy through anonymization or pseudonymization while collecting extensive data is key to enhancing the effectiveness of AI technologies.

Where is AI development headed? What can we expect in the future?

Artificial intelligence continues to evolve rapidly, and I remain optimistic about its future potential. AI has already demonstrated its ability to assist with many tasks, and we are only scratching the surface of what is possible. A decade ago, AI development was primarily focused on tasks related to imaging. However, with the recent explosion of large language models, AI has become increasingly adept at processing textual data



and solving related problems. Voice-based speech generation and understanding are also growing areas of AI development.

In healthcare, every visit and diagnosis produce a textual outcome – data that AI could not previously process. In the future, we can expect many innovations based on written diagnoses and medical histories. AI will likely be able to detect or suggest insights by interpreting data collected over the course of a person's life, looking at patterns across years of medical history. For instance, while a single visit might not reveal much, analyzing all entries for a person could uncover trends – such as a steady increase or decrease in certain values – helping doctors identify changes that may not be immediately noticeable. AI can quickly scan through these trends, providing valuable insights.

In Hungary, the National eHealth Infrastructure (EESZT) is an example of success, as it houses a wealth of data and functions more efficiently than similar systems in many other countries. With this foundation in place, I anticipate clever developments in the system over the next five years, further enhancing the role of AI in healthcare.

From the perspective of the average person, how wise is it to turn to ChatGPT for medical questions or issues in the mid-2020s?

As a patient, I would not rely solely on AI for important medical matters. At best, I would consider the information provided by AI and then discuss it with a doctor. However, when dealing with a relatively common problem that has substantial data available – such as the treatment of an insect bite – I might feel comfortable relying on AI for advice. This is not only because there's a lot of data on the issue but also because it is a minor problem, and there's little risk of causing harm by following AI's suggestions.

For more complex or emerging health issues, however, I would hesitate to rely on AI. Those models, such as big language models, take weeks or even months to train, meaning they may not have the freshest data, especially concerning recent outbreaks or newly discovered conditions. On the other hand, for diseases that have been around for decades, AI might provide more reliable and up-to-date information, as there is a wealth of data to draw from.

While AI systems, like ChatGPT, often provide very convincing answers, it's important to approach their responses with caution. AI systems are designed to give an answer – whether they truly know the correct information. One of the key limitations of AI is that it does not know what it is uncertain about. AI systems do not offer answers like "I don't know," "I'm not sure," or "I have no idea." Instead, they provide a confident answer, even when they lack certainty. This behavior is known as hallucination among professionals. It's important to note that AI is not intentionally misleading – it simply cannot express its uncertainty. If you ask the same question multiple times, you may receive contradictory answers, further highlighting the system's limitations.

Even though AI is advancing rapidly, I believe we will still seek out doctors in the future for our health concerns. Trust, accountability, and the ability to communicate with a human are qualities that a robot cannot replicate. The value of having a long-term relationship with a doctor – someone you know, trust, and who shows empathy – adds significantly to the quality of healthcare. These human qualities are irreplaceable, even in a world where AI plays an increasingly prominent role.

About Márton Görög

Márton Görög is a software developer and artificial intelligence researcher. He studied at Pázmány Péter Catholic University and shifted his professional focus from self-driving cars to the use of AI in the medical field. In 2019, he won the prestigious Pommerman Competition at NeurIPS, one of the most important AI conferences in the world. He has also worked as a data scientist at CMF and is currently in a similar role at an EEG startup.

Building on the Scientific Legacy of Hungary: The CMF Complex

Interview with Markó Madaras

Hungary has long been a cradle of scientific innovation, home to world-renowned researchers and groundbreaking discoveries. The country's history is rich with contributions that have shaped modern science, as it has produced many Nobel Laureates whose work continues to resonate globally.

Continuing this proud tradition, Budapest will soon host the new building of CMF, a cutting-edge research facility designed to advance multidisciplinary science. The CMF Complex is a natural evolution of Hungary's rich scientific heritage, combining modern infrastructure with a legacy of excellence in research.

How would you describe the new CMF Complex to be built?

The new CMF Complex is set to become a landmark for scientific research and innovation in Budapest, representing a next-generation facility designed to advance multidisciplinary scientific endeavors. The state-of-the-art building will include laser laboratories for measurements and development, biological laboratories, medical examination rooms for blood draws, modern offices, and operational units essential for long-term success.

A standout feature of the Complex will be the National Biobank, incorporating cryogenic biological sample storage as its cornerstone. Unlike common (-80)°C storage systems used by many academic institutions, this facility will preserve samples at an ultra-low temperature below (-150)°C. Automated reception and retrieval systems will enhance efficiency, making the biorepository a unique resource in the region.

By integrating diverse complementary facilities, the CMF Complex will foster collaboration and innovation, enabling researchers to achieve breakthroughs in science and technology.

What is CMF's aim with the new building infrastructure?

CMF aims to establish the building as a leading hub for innovation and science, not only in Hungary but on a European scale. By providing cutting-edge infrastructure and fostering interdisciplinary collaboration, the facility will support researchers in tackling some of the most pressing challenges. Among our goals is positioning Hungary as a destination for world-class scientific talent and investment. Additionally, the building reflects CMF's commitment to creating a collaborative ecosystem where academia, industry, and government come together to drive impactful research and translate it into real-world applications.

When and how was the idea for the new CMF Complex conceived?

The idea for the CMF Complex was born from the need to centralize CMF's diverse operations, which are currently spread across Budapest & Szeged (Hungary), and Garching (Germany). We recognized that consolidating these activities into a single, modern facility would boost efficiency and create a hub for outstanding research. The concept was further inspired by the potential to elevate Hungary's scientific capabilities. Early planning highlighted the importance of incorporating advanced laboratories and a state-of-the-art biorepository, paving the way for a facility that promotes long-term innovation. The early concepts gained momentum, solidifying the vision for a project that would shape Hungary's scientific landscape for decades to come.

At what stage are the preparations currently?

Preparations for the CMF Complex are making steady progress. The architectural designs and the first stage of technical blueprints for the laboratories and biorepository are nearing completion, ensuring that the facility meets the specific needs of researchers. Simultaneously, CMF's project team is optimizing the construction process to maintain alignment with the proposed timeline. Site preparations, including substructure engineering, are scheduled to begin in 2025, marking a significant step forward in the project's development. These efforts underscore CMF's commitment to turning its ambitious vision into reality.

Future of CMF

Interview with CEO and Scientific Director Ferenc Krausz and Managing Director László Vastag

Why was CMF born, and what are the goals of the research center?

László Vastag: CMF was born in 2019 and declared by the Hungarian Government to create the optimal framework for performing the research and development activities related to the medical applications of the attosecond pulse laser technology: the great discovery of our CEO, Ferenc, which was recognized by the Nobel Prize in 2023. Our main goal is to move this research forward, encompassing medical research, laser physics, data analysis, and biobanking. Hungary is an appropriate candidate for this research, having a particularly strong knowledge base of biomedical research coupled with an available population at risk. The epidemiological data and low willingness to regular screening attendance provide the potential for significant health benefits. Biobanking is another crucial element in our long-term plans, as Hungary – and the region – lacks the substantial storage capacity of cutting-edge liquid nitrogen storage, which is expected to put Hungary at the forefront in the world of biobanks. In addition, as laser development moves forward, the redundant sample collection and cryogenic storage conditions ensure that can re-test the same samples at a more evolved stage. Our ultimate goal is to start the new age of proactive healthcare – where

a simple, easy, and affordable procedure (i.e., blood draw) may provide significant information on the health status of an individual and set the alarm off at an early stage of certain conditions when the range of available medical interventions is broad and the chance of fully recovering from the disease is very high. This approach would create value not only on a personal but also on a societal level.

How would you describe the year 2024 for CMF in one sentence? And in one word - if possible?

Ferenc Krausz: The formation of a world-class research institution is taking shape. In three words (instead of one): Coming of age.

László Vastag: 2024 was a milestone in the life of CMF as the relocation of an Infrasampler to Hungary took place, enabling the team in Hungary to get the measurements up and running, which opened a new chapter for all of us. It is a giant leap forward, a remarkable 'advancement' in our many-decade-long journey.

What are the biggest challenges for CMF in 2025?

F. K.: Completing the first comprehensive infrared fingerprinting and – in cooperation with partners in Munich – molecular profiling measurements on more than 10,000 blood plasma samples from our H4H Program upon using our next-generation instrumentation currently under development. Equally challenging will be recruiting 5,000 high-risk individuals for the H4H Program and the structured digitization of the health data of our 15,000 study participants.

L. V.: Besides the scientific questions yet to be answered, in 2024, we started the building design phase for CMF's new research center, which requires extensive engineering and project management work, so our focus shifted toward planning and building the new infrastructure. This process will result in several months of cooperation between the engineers and other CMF divisions, meaning that we face a very intense period with a long-term goal: to create a future-proof building infrastructure that will serve all our current and potential future needs. I expect this to be a period of creativity seasoned with tensions. At the same time, the result of the final infrastructure shall strongly represent our values and be considered a tribute to innovation and science.

What is the most important milestone set to be reached in 2025?

L. V.: While most of 2025 will still be affected by the planning of CMF's new research center, some underground construction is already expected to start. The completion date of the final building is yet to be determined, but our current estimate is the end of 2027. Besides these grand milestones, we have significant other ones ahead of us in the near future, i.e., deployment of the first liquid nitrogen tank in our interim biobank, getting several research studies up and running, recruitment to be completed while also making essential steps forward in laser technology development and at the same time completing the measurements and data analysis of an ever-growing database.

As of today, what are the five major milestones planned for CMF in the next five years?

F. K.: Maturing to a well-organized, internationally renowned research institution in a new home accommodating a world-class team and cutting-edge research infrastructure for biobanking and next-generation in-vitro diagnostics. Building a reputation as one of the world's leading research institutions in blood-based molecular phenotyping and medical data science.

Performing infrared electric-field molecular fingerprinting (EMF) measurements and – with collaborators – proteomic and metabolic profiling of tens of thousands of H4H plasma samples to address the overriding question: can we extract sufficient molecular information from human blood with EMF and complementary molecular profiling to provide an early alert for prevalent non-communicable diseases and predisposition to them?

Developing a fully automated EMF instrument suitable for high-throughput, low-cost cross-molecular analysis of blood plasma samples along with a preprocessing

and data analysis pipeline for maximizing the extraction of medically useful molecular information from the samples.
Building an international, inter-continental network of strategic collaborators for testing and validating the novel blood-based molecular phenotyping approaches in different ethnic groups and cultures, which – at a later stage – may also foster the proliferation of the new technology worldwide.

Where would you like to see CMF 10 years from now? Is this even a measurable timeframe to consider for a research center?

F. K.: It is inherent to scientific research that it cannot be planned in detail for a period reaching into the distant future. This is simply because we constantly acquire new knowledge, which may force us to adjust our plans. The more efficient we are in acquiring new knowledge, the more frequently we may need to ask if – given the latest findings – the approach we initially chose still appears to be the best one for achieving our goal. The grand goal that we derive from our big, bold vision of preventive medicine is robust and future-proof – answering the Grand Question: how can we most cost-effectively access health data that are comprehensive enough and respond sensitively enough to major prevalent non-communicable diseases to allow capturing them reliably at an early stage of their development or even before? Can human blood provide the required information, and can we access it cost-effectively to allow populational screening in low- and middle-income countries?

Suppose we can provide an answer to these grand questions. In that case, CMF will have managed to make a significant contribution to creating the basis for the individualized preventive medicine of the future, which will not only save millions of lives but – equally significantly – also extend healthy life years, particularly in low- and middle-income countries, and thereby provide an essential contribution to the economic development and to improving the living conditions in these countries accommodating almost half of our planet's population.

In 10 years, I would like to see CMF as one of the leading institutions of worldwide research efforts aiming to create the basis for transforming healthcare to a dominantly preventive mode of operation – an affordable basis also in low- and middle-income countries.

L. V.: CMF shall be the flagship research institution of the future. Once the building is completed and technology is deployed, it will act as our headquarters for our research purposes. We aim to facilitate Hungarian innovations and spark the higher education ecosystem by providing research opportunities and space for local and international partners. At the same time, CMF shall grow into the role of becoming the Hungarian National Biobank. There is a long way to go, but we are already making small steps in this direction. I am entirely determined and convinced that our team is the only one that can make this happen eventually!

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