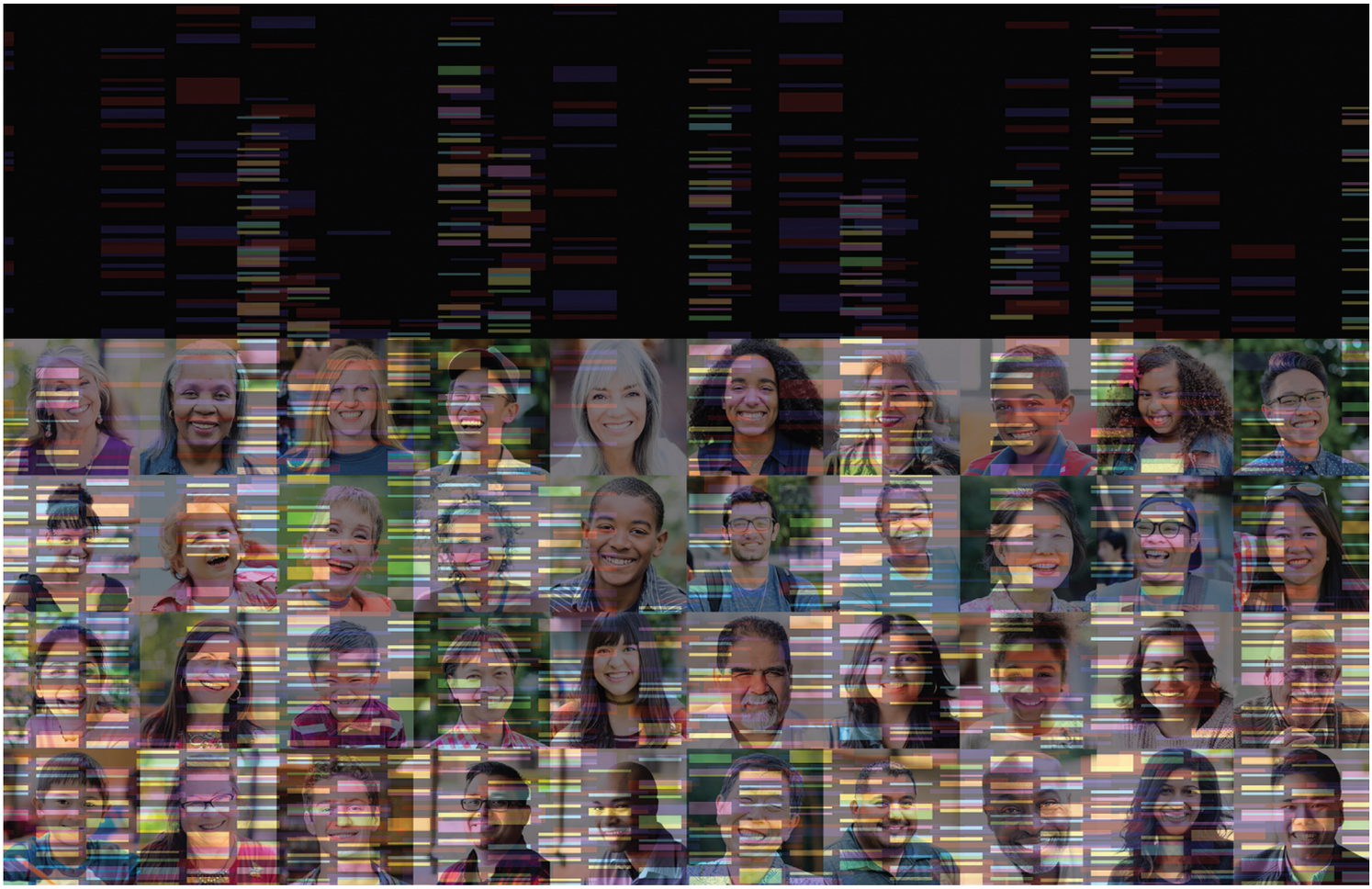

MOUNT SINAI AIMS TO SCALE ONE-MILLION-GENOME PEAK

A progressive project linking hospital patients' genes to their symptoms and treatments could REVOLUTIONIZE PRECISION MEDICINE.

In late 2019, researchers identified an underdiagnosed genetic mutation in people of African descent that carries an increased risk of heart failure. The finding was thanks to people like William Gibson, a 65-year-old heart transplant patient who agreed to share his genetic information with scientists at the Icahn School of Medicine at Mount Sinai in New York.

This approach offers a glimpse into the future of medicine. If enough people like Gibson agree to let experts analyse their genomes, the previously unknown links between genetics and health can be brought to light and translated into new therapies and preventive measures. Eventually, every treatment decision made by clinicians around the world will refer to individual genetic data.

Mount Sinai researchers are stepping up their efforts to reach this future. Over the next five years, one million people treated at its hospitals who consent are to have their exomes sequenced to help discover new genetic links to disease. The Mount Sinai Million Health Discoveries Program aims eventually to enrol every interested patient who walks through the doors of the metropolitan region's eight Mount Sinai hospitals, hugely expanding the genetic information available to researchers and clinicians.

By signing up people with any disease that affects any part of the body, the genome sequencing effort will provide more diverse coverage than existing similar projects, which focus on specific conditions,

▲ **The Millions project aims to offer genome sequencing to every patient treated at the eight Mount Sinai hospitals in the New York metropolitan area.**

individual organs, or healthy people.

"We are on the precipice of a genetic revolution in medicine where we will know every individual's risk for every disease that is caused by their genes," says Eric J. Nestler, chief scientific officer of the Mount Sinai Health System. "And Mount Sinai wants to be at the forefront of this revolution."

Working with the Regeneron Genetics Center, the programme plans to share the data with researchers around the world.

"What excites me about this project is the scale of it," says Alexander Charney, an Icahn Mount Sinai associate professor of psychiatry and of genetics and genomic sciences, who came up with the study along with professor of medicine Girish N. Nadkarni. "This has the potential to become the largest single-centre genetic study of its kind, and the only one where all the people enrolled will already be within the hospital setting and most will have a known disease."

TO ONE MILLION AND BEYOND

While other genomic biobanks gather data from both healthy and unhealthy individuals, this project aims to have a higher proportion of patients with known medical conditions, which should be more useful when linking genes and disease.

"While genetics has proved a powerful tool for understanding rare disorders, we still do not have enough data to know how effective it may be in helping to treat and diagnose most patients," says Charney. The intent of the project is to "provide researchers with the massive, clinically focused, real-world data needed to truly determine the effectiveness of precision medicine and hopefully improve patient care", he adds.

The new study builds on an existing project at Mount Sinai called BioMe – an electronic biobank linked to patient medical records. Roughly 60,000 patient genomes have already been sequenced and stored via BioMe, providing researchers access to clinical specimens and medical records.

It was this project that – with the help of William Gibson – identified the genetic mutation in some people of African descent that increases heart failure risk (Damrauer, S.M. *et al. JAMA* **322**, 2191-2202; 2019). To make this connection, researchers analysed the relationship between a genetic variant in the gene *transthyretin* and heart failure in 9,694 people of African and Latin ancestry. The study also revealed that a disease caused by this genetic variant, called hereditary transthyretin amyloid cardiomyopathy, is significantly under-recognized and underdiagnosed.

Collecting the genome information of so many more people will give the expanded project added reach and scope.

"The goal is to double this number of sequenced genomes in the first year of the Millions project, then ramp up the efforts to reach our goal of one million in the next four years," says Nadkarni. "Beyond that we could continue to two million, or even more."

David Goldstein, geneticist and former director of the Institute for Genomic Medicine at Columbia University, says learning more about the genetic foundations of disease in this way could help unlock many new treatments.

"Fundamentally, precision medicine is about improving the understanding of the causes of disease and using that understanding to target our treatments as much as possible," he says. "Now we can often find the exact causes of an individual patient's disease, and that's a game-changer."

WE ARE ON THE PRECIPICE OF A GENETIC REVOLUTION IN MEDICINE WHERE WE WILL KNOW EVERY INDIVIDUAL'S RISK FOR EVERY DISEASE THAT IS CAUSED BY THEIR GENES.

Like other biobanks that collect genetic information, the Millions project will sequence exons, those regions of the genome that contain the code to make proteins. Exons contain the most similarities between individuals and are therefore the most useful regions to study for disease-related genomic differences. While exon sequencing is an efficient way to sequence large volumes of genetic material, in the future Nestler anticipates having the infrastructure necessary to sequence whole genomes.

Importantly, the project will add diversity to the current pool of genomic information already gathered worldwide. "About 70% of sequenced genomes in biobanks are from individuals of white European ancestry," says Nestler. The eight hospitals that make up the Mount Sinai Health System are spread around the New York metropolitan area, one of the most ethnically diverse cities in the world. "We employ translators for more than 150 languages at some of our hospitals," he adds.

The Mount Sinai Health System handles about four million patients a year and their health data are stored in Mount Sinai's existing electronic medical records (EMR) system. Patients who enrol in the study will be asked their self-identified race or ethnicity. But the team expects genetic analysis of this magnitude to provide a more accurate picture of ancestral origins, to help determine links between genes and susceptibility to certain diseases.

This is important, Nestler says, because genetic insights from one ancestral origin could lead to medical advances that offer much broader benefits.

"This follows the model of anti-cholesterol drugs," he says. "Rare mutations in families with very high cholesterol levels paved the way for the development of statins and newer medicines to treat high cholesterol – now widely used by people of all different origins and backgrounds".

HANDLE WITH CARE

Collections of genetic information, and scientific findings drawn from it, must be handled with discretion, respect and care. Nestler says Mount Sinai takes patient privacy very seriously.

"The responsibility of collecting, storing and interpreting individual genomic data is very much on our radar and we are carrying out this programme with patient safety, security and privacy at the forefront of our minds," he says.

The Mount Sinai server holding patient data is secure, while the confidential platform to organize consent, data collection and clinical administration will be provided by Vibrent Health, a digital healthcare firm that already handles the technology platform

for the National Institutes of Health's million-person *All of Us* research programme.

All the Mount Sinai genomic information is linked with anonymous, or de-identified, versions of patients' EMR data before being sent to be sequenced or made available for analysis. This means specific personal information that could link patients to their genome or medical records is removed. Dates of clinical encounters that could identify patients are shifted randomly for further confidentiality.

"Almost all the information we need for this study is already embedded in the EMR," Nadkarni points out. "This means we can optimize the interview process. Lengthy interviews and surveys in the past have reduced the chances a patient would consent to being enrolled in a study."

Another possible concern with the prospect of identifying individual genetic profiles is potential discrimination based on inherited mutations and elevated disease risks, particularly when it comes to securing health insurance.

Nestler says: "My job as a scientist is to advance science, and ultimately improve health outcomes, but also to do this while working in concert with ethicists to ensure respect and protection of individual liberties."

"PRECISION MEDICINE IS ABOUT IMPROVING THE UNDERSTANDING OF THE CAUSES OF DISEASE AND USING THAT UNDERSTANDING TO TARGET OUR TREATMENTS AS MUCH AS POSSIBLE."

▲ **Sequencing the exomes of patients with known medical conditions should help researchers discover links between genes and disease, potentially leading to new, targeted treatments.**

ACTION OPTIONS

The project researchers are also prepared to act when their sequencing of patients detects 'actionable' genes: specific mutations known to relate to health conditions. Going forward, the programme expects to return results to patients who are identified as having medically actionable mutations, pointing to potential treatments.

Dozens of these genes have been found, including the well-documented *BRCA1* and *BRCA2* genes that increase the risk of breast and ovarian cancer. Medical guidelines say that if a patient is found to carry an actionable gene, they can be offered increased screening, such as mammography or MRI scans, or discuss preventative options such as surgical removal of the ovaries or breasts.

Mount Sinai patients who enrol in the genome sequencing project will be asked whether they want to know if actionable genes are found. In such cases, patients will receive this information alongside genetic counselling to talk through their options.

Nadkarni says sifting such vast amounts of sequenced genomic data from non-healthy patients of diverse ancestry could help researchers discover hundreds of new actionable genes. "This could give doctors the upper hand in preventative medicine, increase treatment options for patients, and, ultimately, improve public health," he says.

Genetic, epidemiological and molecular studies based on the genome sequences could also accelerate development of precision medicines, tailored to a patient's individual genetic make-up.

Nestler stresses that an overall aim of the programme is to bring genetic-based precision medicine approaches to everyday patient care. "Our vision for the future is that every individual's genetic sequence will be accessible on a smart phone via the cloud," he says. "Giving any doctor, in any healthcare setting, in any part of the world access to that information would give the best possible care and outcomes for that patient." ■

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