to essentially create a rank-ordered list of potential targets," says Zhang. One of the top-ranked targets, a phosphoinositide kinase called PIKfyve, is now the focus of Verge's lead clinical program, which is on track to submit an Investigational New Drug application to the US Food and Drug Administration later this year.

To search for new drug targets, BenevolentAI and AstraZeneca comb through experimental and clinical data repositories, as well as the scientific and medical literature. The data harvested in this fashion are then assembled into 'knowledge graphs' that capture the relationships between, for example, genes and pathways. Slavé Petrovski, VP and head of the AstraZeneca Centre for Genomics Research, developed an ML tool that uses insights from dozens of biological databases (including the Human Protein Atlas and various GWAS data catalogs) and disease-specific clinical and genomic resources to decipher potential disease-related genes in large human databases. "It can assign a probability of disease relevance to each of the 20,000 human genes for a particular phenotype," he says. "That's one way that we can sift through all those highly ranked, well-ranked signals that aren't yet slam dunks to pull out those that are potentially true biology."

> "It remains to be seen just how much of a real edge AI and ML confer."

AI can also classify and characterize individual cell subtypes. Celsius's platform analyzes single-cell transcriptomic data from different cohorts of patients to distinguish how certain genes in specific cell types correlate with particular phenotypes. For IBD, says Magram, "one of those cell types is the inflammatory monocyte, which is a key driver of cytokine production, and so we homed in on those cells and asked what receptors might be driving the biology there." This analysis uncovered a protein called TREM1, a cellular receptor that can be selectively inhibited to block inflammation in IBD without broadly compromising immune function, and this protein is now the company's lead target.

Even with the most powerful algorithms, the AI's output is typically only a step along the road to target identification. "Closing the loop is really important," says Su-In Lee, a computer scientist at the University of Washington who has used AI and ML in biomedical research. "You use neural networks to generate this hypothesis, and then you pass that target candidate to experimentalists and do the experiments, and then that can inform the model learning again."

This preclinical work — standard cell culture- and mouse-based assays — will often follow. But a handful of companies, such as Insitro and Verge, are trying to keep this process as human-oriented as possible by performing target characterization in patient-derived induced pluripotent stem cells. "That allows us to take skin cells from patients with ALS and Parkinson's disease and directly convert them into their own brain cells, and then we validate those targets in those human-derived neurons," says Zhang.

It remains to be seen just how much of a real edge AI and ML confer.

"They're a screwdriver and a hammer — they're not going to replace every tool in the toolkit," Zhang says. "There's some things they're really good at; there's some things they're really bad at." The first wave of targets identified with help from AI have yet to be proven in clinical trials.

In addition to Verge, and Celsius, Alchemab expects to submit an Investigation New Drug application by late 2023. And AstraZeneca researchershave unearthed loss-of-function variants in a gene called *MAP3K15* that reducea person's risk of developing diabetes without affecting body mass index. "There's a long way to go," says Petrovski, "but this could truly be a disease modifier, not just looking to treat the symptoms by reducing glucose levels."

Even if AI remains just one tool in drug developers' belts, Osbourn is enthusiastic about its ability to tackle old problems in new ways. "For me, the key is this combination of machine-learning in silico algorithms with some kind of deep interdisciplinary expertise, just to kind make sure that we're learning each time and sort of turning the wheel," she says. "And I just love the opportunity that AI's given us to hopefully do something different." ❐

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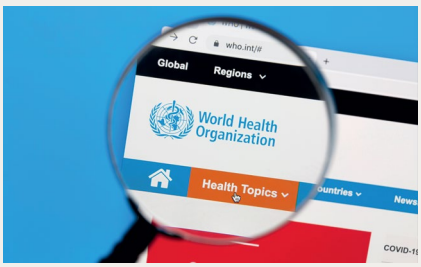
Published online: 1 September 2022
https://doi.org/10.1038/s41587-022-01457-1

WHO tools up for equitable genomics



Credit: IB Photography / Alamy Stock Photo

The World Health Organization (WHO) has called for an equitable expansion of genomics to boost the health and wealth of the population. The benefits of genomics are underappreciated and underutilized, especially in low- and middle-income countries, argues the inaugural report from the WHO Science Council. The council, set up in 2021, chose genomics as the most pressing topic for its first report. It is chaired by Harold Varmus, a Nobel laureate and former director of the US National Institutes of Health, who said in a statement, referring to genomics: "Attention to equity in deploying these technologies is essential for achieving the immense potential benefits to human health."

Among the 15 recommendations is a call for greater advocacy from governments, academics and industry about the benefits of genomics and a new International Genomics Industrial Affiliates Fund to provide training in specialties from medicine and forensics to agriculture. The WHO Academy will provide educational programs on genomics and the WHO Council on the Economics of Health For All will assess the economic case for investment, as well as examining how tax arrangements could promote the sector's growth. Recent investment in sequencing infrastructure for SARS-CoV-2 variant detection provides a blueprint, and potentially a workforce, for the field. "Well-credentialed genomics experts" will be invited to join a new Genomics Committee, reporting to the director general, Tedros Adhanom Ghebreyesus, where topics are likely to include the price of reagents, which are prohibitively expensive in some countries.

Published online: 9 September 2022
https://doi.org/10.1038/s41587-022-01482-0