Building Genetic Diversity Into Cancer Research

NCI awards Fred Hutch $3.5M to create a colorectal cancer risk calculator based on data from multiethnic populations.

June 23, 2020 By Diane Mapes

Scientists at Fred Hutchinson Cancer Research Center have long sought to correct the "Eurocentric bias" in research, particularly when it comes to cancer prevention.

"We currently have a cancer risk prediction score that works in people of European descent," said Ulrike "Riki" Peters, PhD, MPH, a molecular and genetic epidemiologist who's been focused on this issue for more than a decade. "But it doesn't predict cancer risk well in Latinx populations or Asians or African Americans or Native populations or others."

Current prevention tools like risk calculators don't work well in racially or ethnically diverse populations because they're based primarily on the genetic data of whites — about 80% of the DNA sequenced by the Human Genome Project was from people of European ancestry. As a result, they're missing the full range of genetic variants that are possible in the human genome.

"Genetic research is predominantly conducted in European-descent populations — that leads to a bias in the genetic risk variants that have been identified," Peters said.

And that's bad for everybody.

Without the DNA of Black and Latinx populations, Native Americans, and other racial and ethnic minorities, you can't get a *full* understanding of the human genome. You can't truly tell which genes are linked to cancer and other common diseases.

"For genetics, it's key to have racial and ethnic diversity," said Li Hsu, PhD, a Hutch biostatistician. "We are missing opportunities to identify important risk factors in these populations. Plus, it will teach us about biology overall and point us to new drug targets that can benefit anyone."

Now, with a $3.5 million award from the National Cancer Institute, Peters, Hsu and others are launching an ambitious effort to build more equity into cancer risk prediction. Their aim: creating and disseminating colorectal cancer risk-prediction models — also known polygenic risk scores — for the multiethnic populations that need them.

Eventually, these nuanced models will be used to inform screening and prevention strategies in colorectal cancers — and, they hope, beyond.

Strength in Numbers

The five-year study will be conducted through the GECCO research collaboration, which Peters launched more than 10 years ago.

The Genetics and Epidemiology of Colorectal Cancer Consortium manages the genetic and epidemiological data of over 130,000 study participants from 70 studies across North America, Australia, Asia and Europe. Fred Hutch acts as GECCO's data coordinating center; Peters is the consortium's principal investigator as well as the PI of the new study, along with co-investigator Hsu.

GECCO's strength lies in its numbers. By running genome-wide association studies, or GWAS, of very large cohorts, they've been able to identify a number of new germline, or inherited, mutations that either help or hinder the development of colorectal cancer. They've also accumulated extensive data on mutations that happen as a result of environmental or lifestyle exposures.

By adding up and weighing all the tiny genetic variants that can accumulate to produce a cancer, then folding in mutations or interactions that occur as a result of other exposures (think body weight, red meat consumption, alcohol and tobacco use), GECCO's researchers can create polygenic risk scores that can help pinpoint who needs to be screened early and who doesn't.

Current guidelines recommend people of average risk get a colonoscopy, sigmoidoscopy or other test starting at age 50. But for three decades, colorectal cancer has been steadily increasing in people *under* 50. These early-onset cancers disproportionately affect minority populations, and both incidence *and* mortality of colorectal cancer are highest in Black populations.

One option would be to lower the screening age, but that could put a "huge burden" on the health care system, said genetic epidemiologist Tabitha Harrison, who manages GECCO's coordinating center at the Hutch.

"You'd have an additional 21 million people eligible for screening and that would increase health disparities since more people would be competing for limited resources," she said.

A better solution is to take the time and fix the bias now, the researchers said.

Currently, the accuracy rate of GECCO's risk-prediction model is about 64% in people under 50 and about 81% for people over 50. That's if you're white. In nonwhites, their tool is much less effective.

The GECCO researchers believe they can do better.

"There's a lot of hype about precision medicine, about using people's genetic risk scores to define

people's risk for disease," said Jeroen Huyghe, PhD, a statistical geneticist on the project. "We can't just apply a precision model to white people. We have to apply it to all racial groups. It's important to do this now."

Harrison said using biased polygenic risk scores to inform prevention in people of color has "major scientific and ethical limitations."

"GWAS studies have so far been overwhelmingly Eurocentric," she said.

Personalized Cancer Prevention

For this study, the GECCO team will amass a new cohort of 121,000 colorectal cancer patients of different ethnic backgrounds from patient registries, studies and even commercial entities around the world — everything from the Black Women's Health Study to the Japan Public Health Study to the Hispanic Colorectal Cancer Study to 23andMe.

By analyzing these participants' existing genome-wide and epidemiological data, they'll create a risk-prediction model or risk score (or scores) for a racially and ethnically diverse population.

"It would be nice to develop one score that would work across all racial and ethnic groups but we don't know if that will work," Peters said. "So, we'll explore. Our research goal is to develop the *best* risk-prediction model. If that means we have to develop one for each racial/ethnic group, there will be multiple scores."

Once developed, these scores will help personalize the screening recommendations for various types of patients, each with different environmental exposures and inherited risks, to pinpoint those most at risk. These individuals would be tapped for an early screening, even if they don't meet the current age and family history requirements.

They'll then use a microsimulation model developed by investigators from Erasmus University in the Netherlands to see how this screening strategy translates into clinical practice.

"These types of models provide a relatively inexpensive way to estimate population-level effects — including costs and benefits — of policy change," Hsu said. "Based on observational and experimental results and expert opinions, the model will simulate the cancer development process in a large number of individuals, from adenoma formation to colorectal cancer and mortality."

Bringing It to the Community

After validation and testing, the GECCO team will work with research partners at Moffitt Cancer Center in Florida to create a culturally appropriate, web-based risk communication tool — i.e., a precision prevention app of sorts — to disseminate information to patients and their health care providers.

Throughout the study, the GECCO team will work with a multiethnic community advisory board, or CAB, to ensure the results of the study as well as the new app communicate the information in a

racially and ethnically sensitive way.

“At each stage, we will review findings and seek guidance from our community advisory board,” Peters said.

Though ambitious, Peters said the project is of great importance, especially as biased polygenic risk scores continue to be pushed out to consumers.

“The limitations haven’t stopped a growing number of companies from commercializing European-derived polygenic risk scores,” she said.

And that’s a huge problem, colleagues agreed.

“Using risk scores prematurely to inform colorectal cancer screening guidelines could exacerbate existing disparities in screening and survival rates,” Huyghe said. “It’s critically important that we increase racial/ethnic diversity in genetic studies.”

This article was originally published on June 18, 2020, by Hutch News. It is republished with permission.
