Exome sequencing identifies those with cancer predisposition syndromes missed by current screening guidelines

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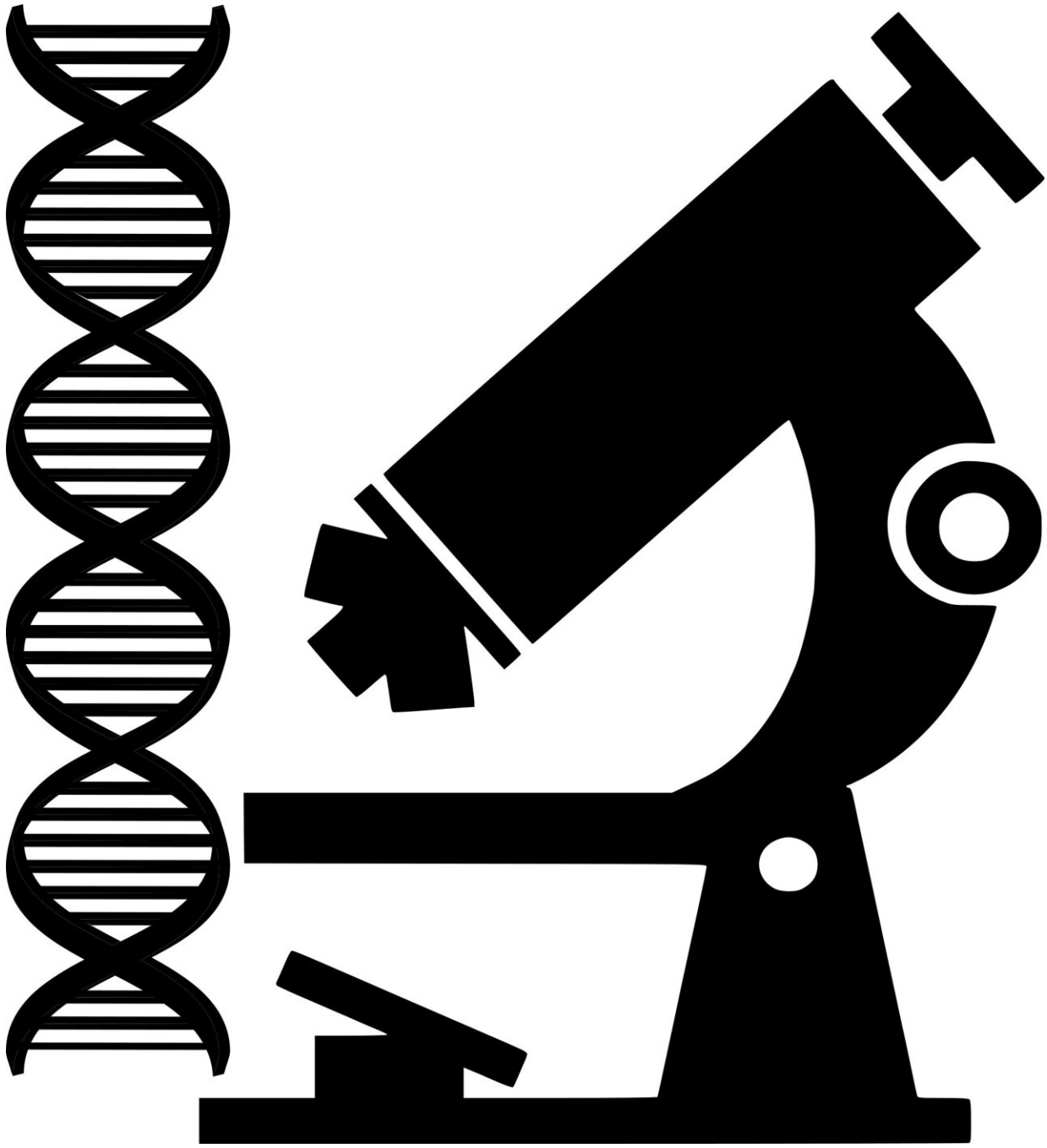

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Among individuals who consented to whole-exome sequencing and were identified as carriers of predisposition genes for hereditary breast and

ovarian cancer (HBOC) or Lynch syndrome, 39.2% would not have qualified for genetic screening under current guidelines, according to results from the Tapestry clinical trial presented at the AACR Annual Meeting 2023, held April 14–19.

Patients with HBOC have up to an 80% lifetime risk of developing breast cancer and a markedly increased risk, relative to the general population, of developing ovarian cancer, pancreatic cancer, prostate cancer, and melanoma, Samadder said. Patients with Lynch syndrome have up to an 80% and 60% lifetime risk of colorectal and endometrial cancer, respectively, with additional increased risks of upper gastrointestinal, urinary tract, skin, and other cancers.

Both of these conditions are classified by the Centers for Disease Control and Prevention as Tier 1 genetic conditions (CDCT1), meaning that early detection of these conditions and proactive intervention could significantly improve public health. The National Cancer Control Network (NCCN) has established a set of guidelines based on an individual's family and personal history of cancer to identify individuals who should undergo genetic testing for these conditions.

If individuals know about their genetic risk for certain cancers, they can undergo enhanced screening and consider prophylactic surgeries, explained N. Jewel Samadder, MD, a professor of medicine at the Mayo Clinic College of Medicine and co-leader of the precision oncology program at the Mayo Clinic Comprehensive Cancer Center, who co-led the study. For patients with Lynch syndrome, this can include regular colonoscopies, blood and urine screening, and prophylactic hysterectomy. For patients with HBOC, this can include advanced breast imaging and prophylactic mastectomy and/or oophorectomy.

Despite the potential benefits, these criteria are not always adequately applied, and even when used appropriately, they do not catch everyone

who should be screened, Samadder explained.

"These criteria were created at a time when genetic testing was cost-prohibitive and thus aimed to identify those at the greatest chance of being a mutation carrier in the absence of population-wide whole-exome sequencing," Samadder said. "However, these conditions are poorly identified in current practice, and many patients are not aware of their cancer risk."

As whole-exome sequencing becomes cheaper and more accessible, Samadder and colleagues hypothesized that the benefits of screening a broader population may outweigh the costs. They initiated the Tapestry study to investigate whether whole-exome sequencing could provide individuals with more robust information about their genetic predisposition for certain diseases.

At the time of data cut-off, 44,306 patients from Mayo Clinic sites in Minnesota, Arizona, and Florida had enrolled in the study. Each individual provided a saliva sample that was subjected to whole-exome sequencing. For this portion of the study, researchers evaluated samples for pathogenic mutations in BRCA1 and BRCA2, denoting HBOC, and MLH1, MSH2, MSH6, PMS2, and EPCAM, denoting Lynch syndrome.

Samadder and colleagues identified 550 carriers of pathogenic mutations in these genes, comprising 387 individuals with HBOC and 163 with Lynch syndrome. Of these individuals, 52.1% did not know prior to this study that they had a cancer predisposition condition and 39.2% did not satisfy the existing NCCN criteria for genetic testing. Among the patients who were newly diagnosed with Lynch syndrome or HBOC during this study, 60% were ineligible for genetic testing per the current guidelines.

Patients with HBOC or Lynch syndrome from racial and ethnic minority

groups were significantly more likely than white patients to not meet NCCN screening criteria (49% versus 32%, respectively). Samadder suggested that this may indicate a systemic bias in the current guidelines that could potentially be overcome by universal genetic testing.

The study aims to enroll a total of 100,000 patients before completing its final analyses, which will include a sub-study that follows patients for 10 years to observe how the information gained from whole exome sequencing impacts their health.

"The knowledge that comes from genetics can empower patients to take control of their disease risk and increase their likelihood of avoiding a deadly cancer diagnosis or catching it at an early stage when it is highly curable," Samadder said. "This study shows the feasibility of providing whole-exome sequencing to large populations of patients within an integrated health system and diagnosing individuals who have an inherited susceptibility to cancer."

Limitations of this study include the exclusivity of the patient population to individuals enrolled in the Mayo Clinic system, a tertiary and quaternary care system that may not reflect the demographics of the general population. This includes an enrollment of 10% underrepresented minorities, a number Samadder and colleagues intend to increase as the study continues recruitment.

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