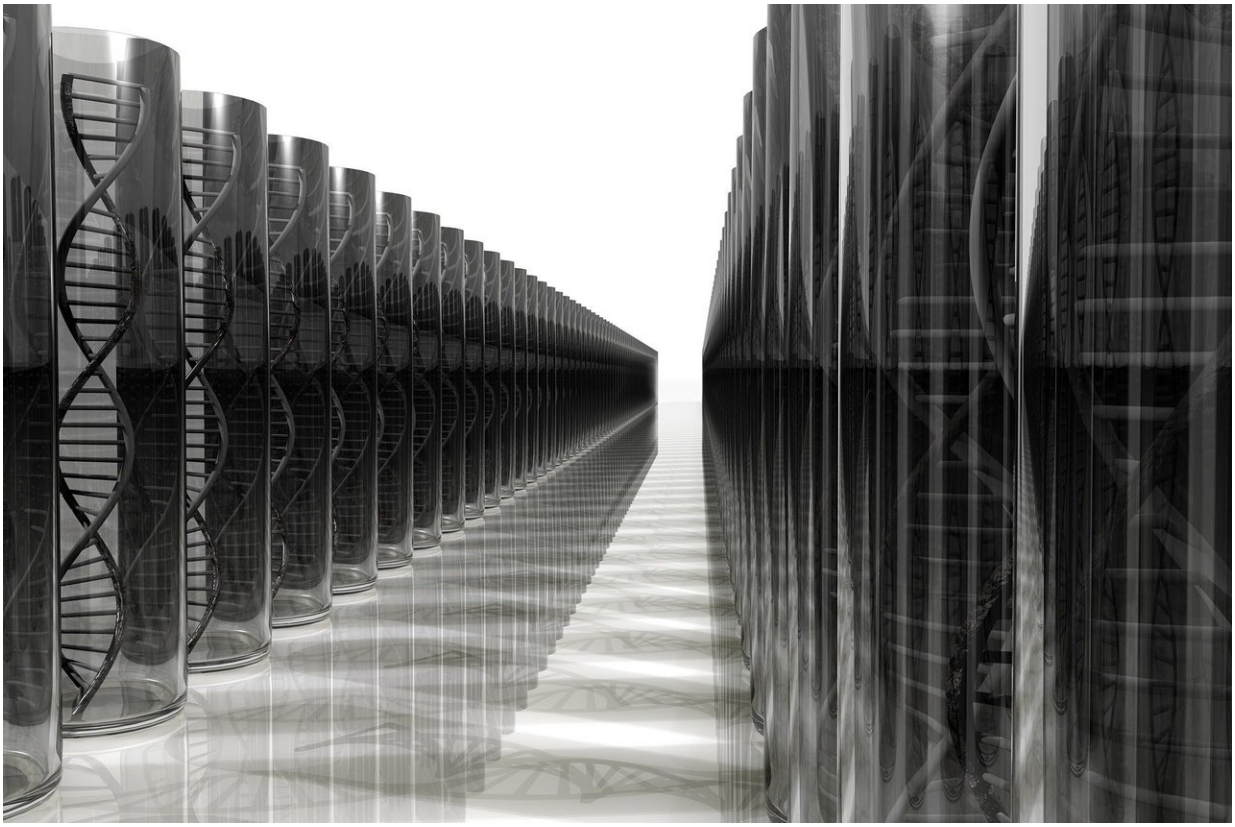
Genomic autopsy can help solve unexplained cardiac death

August 15 2018, by Will Doss



Credit: CC0 Public Domain

Molecular autopsies can reveal genetic risk factors in young people who unexpectedly die, but proper interpretation of the results can be challenging, according to a recent study published in *Circulation*.

Following guidelines set by the American College of Medical Genetics and Genomics (ACMG) can help assess the risk of certain genetic variants, enabling proper counseling of surviving family members, according to the study co-authored by Steven White, MD, Ph.D., adjunct assistant professor of Pathology and assistant medical examiner at the Cook County Medical Examiner's Office.

"While genetic testing may help in understanding the underlying pathology in sudden, unexpected death, the greatest benefit is to surviving family members with the hope of preventing future deaths, further highlighting that autopsies, whether conventional or molecular, are performed to benefit the living," White said.

Sudden cardiac death is a major health burden, killing as many as 450,000 people annually in the United States. According to the study, the majority of these deaths are caused by coronary artery disease or related conditions. However, up to 5,000 young people every year die suddenly, and about 40 percent of these cases remain unexplained after autopsy.

Lethal and inheritable cardiomyopathies or channelopathies, diseases that affect the heart muscles or heart rhythm, may be responsible for a substantial portion of these unexplained cases. A whole-exome or whole genome molecular autopsy can reveal genetic variants that can potentially cause sudden cardiac death.

However, erroneously judging variants as pathogenic has the potential to harm patients and their families. According to the authors, as much as 10 percent of the variants associated with long-QT syndrome, a common arrhythmia disorder, may be classified incorrectly in literature, emphasizing the importance of corroborating evidence when determining pathogenicity.

In the new study, investigators examined 25 cases of sudden unexplained

death in young adults from Cook County, IL, analyzing 99 gene variants thought to be associated with sudden cardiac death. They found 27 ultra-rare variants present among 16 of the victims, meriting further investigation.

Following the ACMG framework, the investigators next used weighted factors to determine clinical relevance. Whether the gene was major or minor, whether its phenotype matched the patient's presentation at autopsy, and any resemblance to previously established pathogenic gene variants are all factors that have point values, which are combined to establish classification.

In the end, four of the 25 patients examined in this study were found to have clinically actionable genetic variants, warranting genetic testing of surviving family members.

Notably, several more patients would have been classified as clinically actionable based on genetic data alone, but their autopsy presentation didn't match the genetic phenotype. These cases underline the importance of following ACMG guidelines to avoid alarming surviving family members in a time of grief, according to the study authors.

"In addition to the cost reductions in genetic testing, clinicians and pathologists are seeing the benefits of postmortem genetic testing," White said. "These benefits include counseling and treating surviving family members and gaining a better understanding of the causes of sudden, unexpected death in cases where a conventional autopsy fails to reveal an anatomic cause of death."

The study was supported by the Mayo Clinic Windland Smith Rice Comprehensive Sudden Cardiac Death Program.

White continues to investigate sudden, unexpected death in children and

young adults. A multidisciplinary group led by White and Robert Gregory Webster, MD, assistant professor of Pediatrics in the Division of Cardiology, conducts genetic testing on the deceased and surviving family members, coupling that data with clinical testing to counsel surviving family.

More information: Garrett W. Shanks et al. Importance of Variant Interpretation in Whole-Exome Molecular Autopsy, *Circulation* (2018). DOI: 10.1161/CIRCULATIONAHA.117.031053