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NEWS

ACMG clarifies recent statement on use of secondary findings recommendations for general population screening

On 25 April 2019, the American College of Medical Genetics and Genomics (ACMG) issued a policy statement (https://www.nature.com/articles/s41436-019-0502-5) on the use of secondary findings recommendations for general population screening. The statement referred to previous policies ACMG SF v1.0 and ACMG SF v2.0, also known as the ACMG 56 and ACMG 59, respectively. The recommendations asserted that "reporting some incidental findings would likely have medical benefit for patients and families of patients undergoing clinical sequencing." The original policy statement indicates that the ACMG SF v2.0 list of genes was not validated for general population screening. Many of the genes have uncertain penetrance. As such, the policy statement seeks to mitigate untested interventions based on genotyping information alone. ACMG does not endorse the use of ACMG SF 2.0 for purposes other than to report secondary findings after clinical sequencing. However, some genetics professionals raised questions and concerns about the policy statement on social media and via other avenues. To address these concerns, ACMG leadership has issued a clarification (https://www.acmg.net/PDFLibrary/Secondary%20Findings%20Clarifications%20to%20ACMG%E2%80%99s%20recent%20statement%20on%20Secondary%20Findings%20-%20Final.pdf). The clarification makes nine points, the key points reiterated here: (1) secondary findings are reportable when identified from sequencing already being performed and risk–benefit analysis suggests that present variants should be reported to care providers, (2) additional factors must be taken into account when screening the general population, and (3) ACMG does not currently sanction the use of the list of genes for population screening until penetrance is better understood in asymptomatic individuals and appropriate follow-up care approaches can be assured. In conclusion, ACMG makes three recommendations. First, ACMG discourages any reference to the term ACMG SF2.0 or ACMG59 except in the case of reporting incidental findings after clinical sequencing. Second, ACMG SF™, ACMG 59™, ACMG 56™, and related words or designs that use "ACMG™" are trademarks and may not be used for any commercial purposes. Finally, ACMG supports continued research into genotype–phenotype correlation to determine appropriate interventions for asymptomatic patients with pathogenic and likely pathogenic variants in genes known to be associated with disease. —*V. L. Dengler, News Editor*

Artificial intelligence helps speed diagnosis of genetic diseases

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Genetic diseases are a leading cause of infant mortality, especially in the 15% of newborns admitted to intensive care units. In infants, many genetic diseases present with similar signs and symptoms, making diagnosis and subsequent treatment difficult. Genome sequencing offers a powerful diagnostic tool, but can take weeks to yield a potential diagnosis, meaning precious time escapes for ill newborns. Furthermore, professionals with the skills to analyze the prodigious amount of data are in short supply. In a recent article in *Science Translational Medicine* (https://stm.sciencemag.org/content/11/489/eaat6177), Clark et al. report the use of an automated platform to diagnose genetic diseases in children in a median time of just over 22 hours. The diagnostic platform uses a form of artificial intelligence called clinical natural language processing (CNLP) to collect medical information from electronic health records (EHRs). The program extracts phenotypic features directly from the records without human intervention. This deep-phenome analysis is then linked with genome or exome sequencing data from patient blood samples. To determine a provisional diagnosis, the automated diagnosis platform then matches the CNLP phenome results with possibly pathogenic variants identified in the patient's genome; phenotypic and genotypic rankings are correlated to suggest the most likely diagnoses. The researchers first trained the CNLP artificial intelligence on EHRs from children previously tested for genetic diseases by genome sequencing. Then they tested the performance of the CNLP with EHRs from children who had genetic diseases previously diagnosed by genome sequencing. Next, the scientists assessed the entire autonomous diagnostic system for retrospective diagnosis of children with genetic diseases. The automated diagnosis was compared with experts' manual interpretation of patient EHRs and genome sequencing results. CNLP identified 27-fold more phenotypic features from EHRs compared with manual interpretation by experts. Additionally, the phenotypic features that experts selected showed lower diagnostic utility than the CNLP-derived features when used as part of the autonomous system. The automated diagnoses matched experts' assessment with 97% recall and 99% precision. Finally, DNA and EHRs from seven gravely ill children with suspected genetic disease were used to test the diagnostic capability of the autonomous diagnostic system prospectively. The platform correctly diagnosed three of the children with 100% precision and recall and a 22-hour time savings. The researchers emphasize that the automated platform will not replace medical experts. They call the new platform "augmented intelligence" rather than "artificial intelligence," adding that, while the technology can expedite accurate diagnosis of genetic disease, patient care will always begin and end with the doctor. —*V. L. Dengler, News Editor*

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