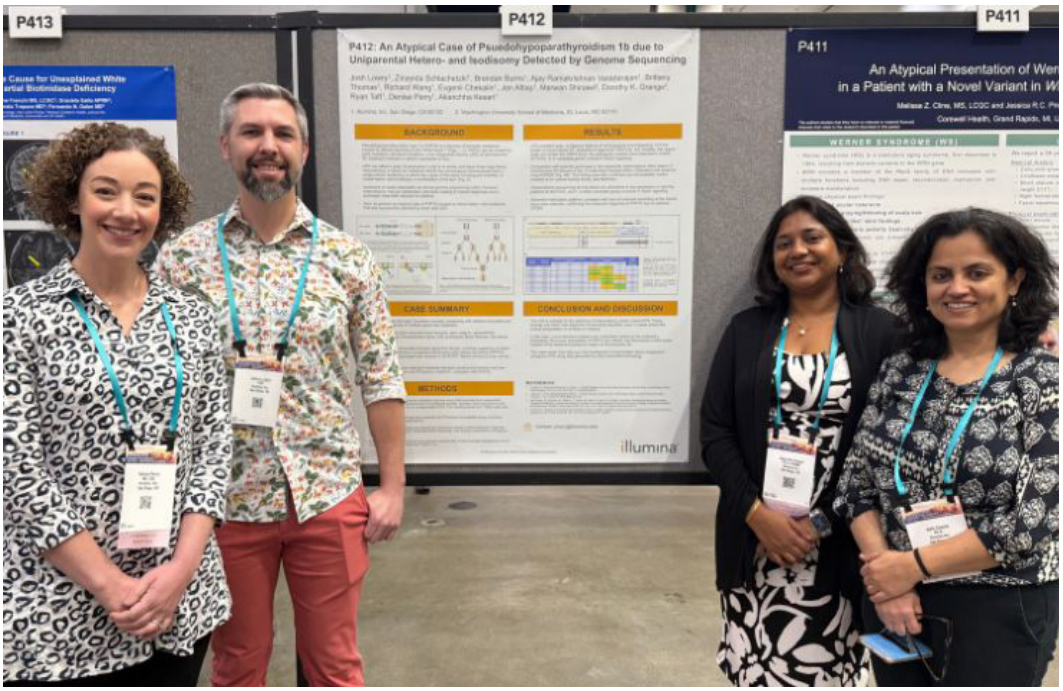

Illumina colleagues Denise Perry, Joshua Lowry, Akanchha Kesari, and Aditi Chawla in front of one of their posters at ACMG 2025. Photo by Illumina

Interrogating challenging genomic regions provides new answers for patients

At ACMG 2025, Illumina demonstrates how whole-genome sequencing and improved bioinformatics has solved cases of rare genetic disease

AT THE ANNUAL American College of Medical Genetics and Genomics[1] (ACMG) conference in Los Angeles this month, Illumina presented three posters.

The posters highlighted the power of clinical whole-genome sequencing (WGS) and advanced bioinformatic software to diagnose rare genetic diseases. The results were generated through Illumina Laboratory Services, or ILS—the company's own CLIA-certified, CAP-accredited, and New York state–approved clinical laboratory that serves to drive adoption of genomics solutions by translating Illumina products for clinical laboratory use.

"Clinical whole-genome sequencing is useful in the diagnosis of rare genetic disease," says Illumina Senior Director of Medical Genomics Laboratory Services Denise Perry, who coauthored all three posters. "You can broadly and efficiently interrogate medically relevant regions of the genome to look for changes in the DNA that could cause a patient's clinical features. We have to have sophisticated bioinformatic and software tools that help us figure out where we need to look to find the answer." Some regions are medically important but are difficult to sequence for a variety of reasons. It might be that a region is repeated several times, a piece of one chromosome is missing, or a string of nucleotides is duplicated and disrupting a gene that is important for the human body's development and function.

"The first two posters show examples of DNA variants we were able to see in a genome and demonstrate that they were actually causing the patient's clinical presentation, or phenotype," Perry says. "And both of these variants are types that have been historically difficult to sequence and interpret from clinical whole-genome sequencing data."

For the first poster, "Genome Sequencing Detects Transposable Element Insertions in Two Diagnostic Challenging Cases," Illumina partnered with the University of Washington, Sanford Children's Specialty Clinic, and Le Bonheur Children's Hospital.

A transposable element is a type of variant that has been historically tricky to detect by short-read sequencing. In both cases from the study, an outside lab had looked at the gene of interest and found only one variant—but the suspected disease in these patients was an autosomal recessive condition, requiring two

1. acmg.net

disease-causing variants. ILS found the second causal variant with WGS. "With advanced bioinformatics and focused interpretation, this type of variant can be easily detected by the short- read technology. This will help us to provide diagnoses to more patients who are still searching for an answer," says Akanchha Kesari, PhD, clinical laboratory director for Illumina Laboratory Services.

The second poster, "An Atypical Case of Pseudohypo-parathyroidism 1b due to Uniparental Hetero- and Isodisomy Detected by Genome Sequencing," was authored in collaboration with the Washington University School of Medicine in St. Louis, Missouri. Humans typically have 23 pairs of chromosomes, one copy from each parent. Uniparental disomy is a genetic abnormality when part of or an entire chromosome is inherited from just one parent, which can cause certain genes on that chromosome to not work properly. In this case study, the WGS data provided strong evidence for uniparental hetero- and isodisomy on the patient's chromosome number 20. This was confirmed by a separate test at an outside laboratory, resulting in a firm molecular diagnosis for the patient.

The third poster, "Systematic reanalysis of clinical genome sequencing data in a cohort of acute care patients results in increased diagnostic yield," reexamined 350 samples from the NICUSeq Randomized Time-Delayed Trial.[2] Perry explains: "We reran the entire cohort through an updated DRAGEN pipeline and the Emedgene software and demonstrated that we could find the same diagnostic variants we'd found before. Additionally, due to technology advancement and information changes over time, we were able to find diagnoses for 14 more patients than we did in the initial testing."

The power of progress

Perry is a board-certified and licensed genetic counselor who joined Illumina 10 years ago. During her time at the company, she says she has seen "just how far the field has advanced and how mature clinical genomics testing has become." These three posters illustrate specific areas of progress, and Perry is proud that Illumina scientists and engineers have been working systematically to improve the company's products to increase diagnostic yield from clinical WGS testing. "We remain firm in our mission to continually improve our products and solutions so that we can provide answers to patients about the cause of their rare disease and to their physicians to provide the best care." ◆

2. illumina.com/company/news-center/press-releases/press-release-details.html?newsid=22054f20-61c4-4b1c-8427-e30d8bbacf05