

## **Advancements in Rare Disorder Diagnosis: Six Years of Experience with Auragen's Genomic Diagnostic Pipeline**

**Background:** As part of the 2025 French Genomic Medicine Initiative, AURAGEN is a large-scale genome sequencing laboratory delivering diagnostics for rare diseases (RD), oncogenetics, and oncology. Since 2018, the platform has processed over 50,000 genomes (17757 index cases) at 30× coverage, reaching a throughput of 360 genomes per week, and 700 medical reports per month. Technological upgrades have improved diagnostic yield and variant prioritization.

**Materials and Methods:** SNV, CNV, SV and STR detection is integrated into a phenotype-driven prioritized shortlist (Aurapport), supported by an industrial variant browser, SeqOne SAS. In 2025, major improvements included detection and annotation of mitochondrial DNA and UTR variants, uniparental disomy, and aneuploidies, including mosaics. Biological interpretation was enhanced through semi-automated literature searches and report drafting. Diagnostic performance increased with Auramatcher, enabling gene-based cross-querying within the AURAGEN database for variant reinterpretation.

**Results:** Diagnostic yield in rare diseases reached 32%, distributed across SNV (84%), CNV (12%), SV (2%), and other variants including mtDNA and STRs (2%). Over 99.77% of diagnoses originated from Aurapport shortlists. Semi-automated reanalyses produced more than 300 clinical reports, including ~50 new disease-causing genes, notably the non-coding RNU genes.

**Conclusion:** After six years, AURAGEN demonstrates that industrial-scale genome sequencing combined with clinician-driven analysis sustains diagnostic innovation. Future efforts target automation of reanalysis processes, international collaboration for VUS reclassification, and coordinated scientific dissemination to further enhance genomic medicine impact.