to bias and had some limitations. Historic vaccine uptake is low, which may diminish the impact of maternal vaccination.

This study demonstrates meaningful benefit of COVID-19 vaccination during pregnancy, which has moderately waned over time, but still supports the need to reconsider the decision to remove vaccine eligibility during pregnancy. Continued studies on the COVID-19 risk and vaccine effectiveness in this population are important.

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Correction: This article was corrected on October 27, 2025, to correct the panel label of Figure 2B.

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Clinical Long-Read Sequencing Test for Genetic Disease Diagnosis

Recent work in genome sequencing (GS) shows a 4% to 8% increase in diagnostic yield over exome sequencing (ES) alone, albeit the overall diagnostic gain (<1%) is marginal if GS is compared to combinations of ES with other standard tests.[1]

Supplemental content

Recently, we reported undiagnosed cases following GS could be recovered by long-read sequencing (LRS), due in part to the simultaneous detection of clinically relevant repeat expansions,[2-4] methylation abnormalities,[5] and improved structural variant detection.[6] However, no study has assessed the implementation of LRS as a first-line clinical test. Herein, we report the comparative diagnostic yield and turnaround time and evaluate the ability to consolidate standard-of-care (SOC) approaches using a single clinical LRS test.

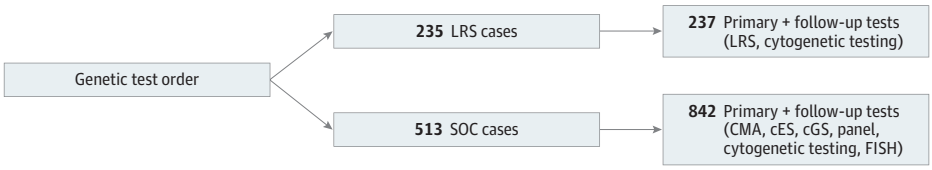
Methods | Clinical high-fidelity (HiFi) LRS was performed on 235 patients aged 0 to 18 years compared to an age- and phenotype-matched control cohort of 513 patients. Patients selected for the control group underwent SOC inpatient genetic testing, including expedited ES/GS, karyotype, fluorescence in situ hybridization (FISH), chromosomal microarray (CMA), and targeted panels. The eMethods in Supplement 1 provide further details. The Standards for Reporting of Diagnostic Accuracy (STARD) reporting guidelines were followed.

Results | LRS case results were compared to controls (**Figure 1**), with the true diagnostic rate determined by counting diagnoses explaining the primary signs and symptoms. Variants of uncertain significance, carrier status, incidental findings, or pathogenic changes associated with late-onset or variable phenotypes not directly linked to presenting complaint were excluded.

The LRS cases yielded a significantly higher (P = .004, 2-2 χ^2 test) diagnostic rate compared to the SOC group (**Figure 2**). The mean length of time from test order to diagnostic report (27 days) was significantly (P = .048, t test) shorter among LRS cases (Figure 2) compared to controls (62 days). Similarly, if a negative result was returned, the average time to report was significantly (P < .001, t test) shorter among LRS cases (29 days) compared to controls (91 days).

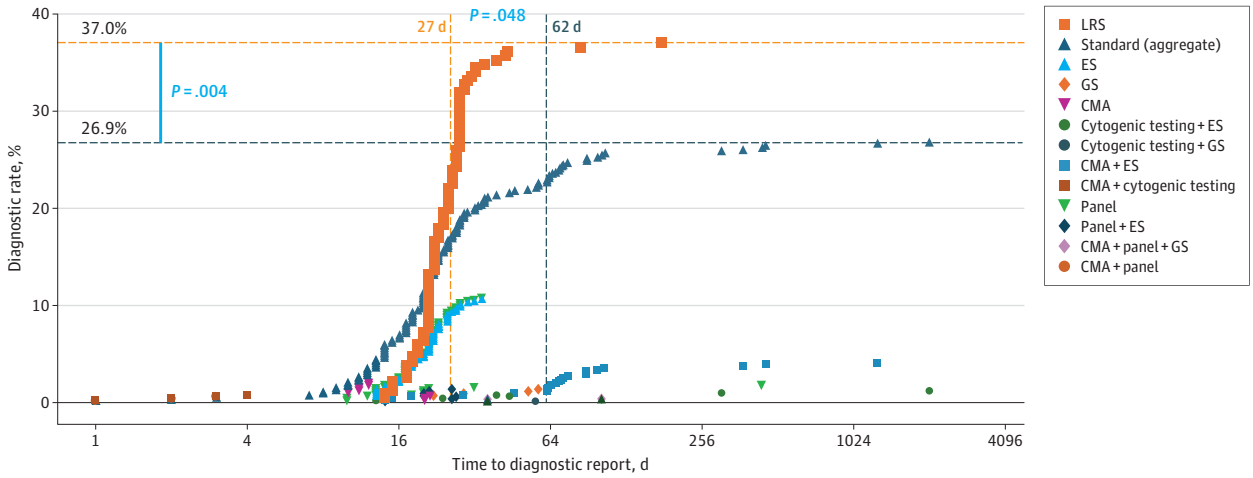
Factors negatively impacting the time to diagnosis specific to LRS were low sequencing yields requiring reloading and technical limitations of tertiary analysis software. Among the SOC group, the primary cause for delayed diagnosis was mul-

Figure 1. Diagram Reporting Flow of Probands and Number of Test Orders in Long-Read Sequencing (LRS) and Standard-of-Care (SOC) Cohorts



cES indicates clinical exome sequencing; cGS, clinical genome sequencing; CMA, chromosomal microarray analysis; FISH, fluorescence in situ hybridization.

Figure 2. Long-Read Sequencing (LRS) Compared to Standard Genetic Testing Among Matched Pediatric Cases



P values calculated using Fisher exact test. CMA indicates chromosomal microarray analysis; ES, exome sequencing; GS, genome sequencing.

tiple test orders required to reach a diagnosis, with an average of 6.1 tests required in the SOC group compared to 2.7 tests in LRS cases. When limited to diagnostic cases, SOC controls had an average of 1.6 test orders for each diagnostic finding (n = 138), compared to 1.01 among LRS cases (n = 87, with 1 diagnosis requiring follow-up cytogenetic testing). If the first test was positive in controls, the mean time to diagnosis was comparable to LRS. However, 57 SOC cases required multiple tests to reach a diagnosis in which the average turnaround time was more than 4 months.

A large fraction of variation in LRS originated from complex structural variants (SVs) and copy number variants, repeat expansions, and methylation variation. Specifically, 16 of 87 reported diagnostic variants in the LRS group (18.3%) benefited from the integrated capability of LRS, which included aberrant methylation, rare expansion disorders, phasing of single-nucleotide variation in a singleton, and detection or refinement of SVs. Note that the availability of standard clinical testing is limited, such as *GNAS* methylation and newly described repeat expansions (eg, in *DIP2B*), which were diagnostic findings captured by LRS. As expected, 71 of 87 diagnostic genotypes (81.6%) without previous standard genetic testing would have been detected by ES, GS, or CMA.

Discussion | Clinical LRS offers a single, comprehensive genomic assay for diagnosing genetic disease. The advantage of LRS was explained by its expanded variant detection. While the framework used to interpret LRS variation relies on changes also detected by combinations of standard tests, the difference is that in clinical practice, all testing modalities are not typically deployed, and some tests, such as repeat expansions, may not be included in the differential if a presentation is atypical. Due to the sequential nature of SOC testing, there are significant delays in reaching diagnoses compared to LRS. These benefits of clinical LRS are likely only the beginnings of what may be uncovered through expanded testing and further understanding of noncoding regions.[5,6]

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Cannabis and Alcohol Use to Initiate Sleep Among Young Adults

More than 20% of US young adults struggle to fall or stay asleep.[1] Cannabis and alcohol can help initiate sleep,[2,3] but regular use may be problematic.[4] Increasing tolerance can lead to greater use to produce consistent sleep outcomes, potentially contributing to use disorder and sleep problems.[2] Young adulthood is a critical developmental period for both substance use risk and sleep problems, underscoring the need for national data on cannabis and alcohol use for sleep.[5,6]

Supplemental content

Methods | Data were from the 2022-2023 Monitoring the Future (MTF) Panel Study collected from US young adults aged 19 to 30 years (from 2010-2022 12th-grade cohorts).[6] MTF annually surveys nationally representative samples of 12th-grade students (modal age, 18 years); a subsample from each cohort is selected for the MTF Panel, with participation starting at age 19 or 20 years and then biennially through age 29 or 30 years.[6] The response rate was 51.5% of active participants and 34.5% of all selected 12th graders (eFigure in Supplement 1). Written informed consent was provided by all respondents. Analysis weights accounted for sample selection and attrition. A University of Michigan Institutional Review Board approved the study. We followed the STROBE reporting guideline.

Substance use measures included past-12-month use of cannabis, alcohol, and both substances (yes or no); past 30-day daily or near-daily use (≥20 occasions), nondaily use (1-19 occasions), or no use; and past 2-week binge drinking (yes or no). Respondents reporting past 12-month use were asked to select all applicable answers about the primary reasons for use, including "To get to sleep."

Covariates included gender identity (man, woman, another gender), race and ethnicity (Hispanic, non-Hispanic Black [hereafter Black], non-Hispanic White [hereafter White], non-Hispanic other [Asian, Middle Eastern, multiracial, and other not specified]), age (range, 19-30 years), and college-level education (currently attending, graduated from 4-year college, other). Two-sided $P < .05$ indicated statistical significance. Data analysis was performed using SAS 9.4 (SAS Institute).

Results | Of the 1473 respondents (mean [SE] age, 24.5 [0.09] years), 51.0% identified as female, 44.7% as male, and 4.2% as another gender. Of these respondents, 11.2% identified as Black, 25.4% as Hispanic, 54.8% as White, and 8.5% as other race and ethnicity.