arcensus

Maximizing clinical value with Whole Genome Sequencing (WGS)

The latest evidence demonstrates that WGS has become an essential diagnostic tool in clinical practice, frequently utilized as a first-line test. WGS offers a comprehensive assessment of the entire genome, enabling analysis of a wide range of genetic variants and enhancing diagnostic yield as well as clinical utility.

DIAGNOSTIC YIELD

1. WGS offers a high diagnostic yield for rare diseases.

Supporting Evidence:

Year	Patient Cohort: WGS Patients with Suspected Rare Disease	Diagnostic Yield of WGS
2021 [1]	2183 patients 59% underwent duo, trio, or quad analysis	25.0%
2024 [2]	501 patients	28.3%
2024 [3]	1004 patients 71% underwent trio analysis	41.4%

2. WGS can detect more types of variants than panel tests or Whole Exome Sequencing (WES)

Supporting Evidence:

- In a cohort of 122 rare disease patients and their relatives, structural, splice site and intronic variants made a significant contribution to 20 of the 43 solved cases (16.4% of the cohort) [4, 2023].
- WGS performed after previous first-tier NGS screening was negative, identified structural and deep intronic variants in 33% of 33 suspected inherited retinal disease patients [5, 2024].

- In 822 patients suspected to have a rare monogenic disease, 8.2% had variants that required WGS for identification, including coding variants, intronic variants, small structural variants, copy-neutral inversions, complex rearrangements, and tandem repeat expansions [6, 2024].

3. WGS Increases Diagnostic Yield Compared to WES

Supporting Evidence:

Year	Patient Cohort: WGS patients with a rare disease and previous negative / inconclusive WES	Diagnostic Yield of WGS after negative/ inconclusive WES
2021 [7]	358 patients of all ages	14.5%
2022 [8]	100 children with global developmental delay / intellectual disability	21.0%
2022 [9]	119 patients of all ages	19.3%

CLINICAL UTILITY

WGS has high clinical utility, the likelihood that a test will result in an improved health outcome.

Supporting Evidence:

- In a global cohort of 694 rare disease patients, WGS resulted in a change of management in 41.4% [3, 2024].
- Of the 1165 patients with a genetic diagnosis in the 100,000 Genomes Project Pilot, 25.0% had immediate ramifications for clinical decision making [1, 2021].
- A meta-analysis of 62 studies including 3686 WGS patients found that the clinical utility of WGS was higher than that of WES [10, 2023].

COST-EFFECTIVENESS

WGS has become a cost-effective option as a first-tier test.

Supporting Evidence:

- A study comparing WGS with CMA for patients with neurodevelopmental disorders, showed no significant difference in healthcare costs per patient, suggesting that WGS may be a beneficial first-line genetic test for individuals [11, 2023].

- In a cohort of 870 children with suspected genetic disorders, implementing first-line WGS was a cost-effective strategy for diagnosing outpatient paediatric patients and often provided an earlier and precise diagnosis [12, 2024].

- A meta-analysis of four publications found WGS could be cost-effective in the diagnostic workup of affected infants and children [13, 2022].

RE-ANALYSIS

Re-analysis of WGS data increases diagnostic yield.

Supporting Evidence:

- Within a timeframe of 2 to 2.5 years, 29 of 102 (28.4%) unsolved paediatric WGS patients with neurological disorders obtained molecular diagnoses through reanalysis [14, 2024].

- Reanalysis of WGS data in 323 patients with a neurological rare disease provided a diagnosis for 20.7% of patients [15, 2022]:
  - 50.8% due to recent gene-disease associations
  - 19.7% due to additional or improved bioinformatic analysis
  - 18% due to standardized analysis of phenotyping data

References

1. 100,000 Genomes Project Pilot Investigators, Smedley, D., Smith, K. R., Martin, A., Thomas, E. A., McDonagh, E. M., Cipriani, V., Ellingford, J. M., Arno, G., Tucci, A., Vandrovcova, J., Chan, G., Williams, H. J., Ratnaike, T., Wei, W., Stirrups, K., Ibanez, K., Moutsianas, L., Wielscher, M., Need, A., Caulfield, M. (2021). 100,000 **Genomes Pilot on Rare-Disease Diagnosis in Health Care - Preliminary Report.** The New England journal of medicine, 385(20), 1868–1880. https://doi.org/10.1056/NEJMoa2035790

2. Velasco, H.M., Bertoli-Avella, A., Jaramillo, C.J. et al. **Facing the challenges to shorten the diagnostic odyssey: first Whole Genome Sequencing experience of a Colombian cohort with suspected rare diseases**. Eur J Hum Genet 32, 1327–1337 (2024). https://doi.org/10.1038/s41431-024-01609-8

3. Thorpe, E., Williams, T., Shaw, C., Chekalin, E., Ortega, J., Robinson, K., Button, J., Jones, M. C., Campo, M. D., Basel, D., McCarrier, J., Keppen, L. D., Royer, E., Foster-Bonds, R., Duenas-Roque, M. M., Urraca, N., Bosfield, K., Brown, C. W., Lydigsen, H., Mroczkowski, H. J., ... Taft, R. J. (2024). **The impact of clinical genome sequencing in a global population with suspected rare genetic disease.** American journal of human genetics, 111(7), 1271–1281. https://doi.org/10.1016/j.ajhg.2024.05.006

4. Pagnamenta, A. T., Camps, C., Giacopuzzi, E., Taylor, J. M., Hashim, M., Calpena, E., Kaisaki, P. J., Hashimoto, A., Yu, J., Sanders, E., Schwessinger, R., Hughes, J. R., Lunter, G., Dreau, H., Ferla, M., Lange, L., Kesim, Y., Ragoussis, V., Vavoulis, D. V., Allroggen, H., ... Taylor, J. C. (2023). **Structural and non-coding variants increase the diagnostic yield of clinical whole genome sequencing for rare diseases.** Genome medicine, 15(1), 94. https://doi.org/10.1186/s13073-023-01240-0

5. Zeuli, R., Karali, M., de Bruijn, S. E., Rodenburg, K., Scarpato, M., Capasso, D., Astuti, G. D. N., Gilissen, C., Rodríguez-Hidalgo, M., Ruiz-Ederra, J., Testa, F., Simonelli, F., Cremers, F. P. M., Banfi, S., & Roosing, S. (2024). **Whole genome sequencing identifies elusive variants in genetically unsolved Italian inherited retinal disease patients.** HGG advances, 5(3), 100314. https://doi.org/10.1016/j.xhgg.2024.100314

6. Wojcik, M. H., Lemire, G., Berger, E., Zaki, M. S., Wissmann, M., Win, W., White, S. M., Weisburd, B., Wieczorek, D., Waddell, L. B., Verboon, J. M., VanNoy, G. E., Töpf, A., Tan, T. Y., Syrbe, S., Strehlow, V., Straub, V., Stenton, S. L., Snow, H., Singer-Berk, M., ... O'Donnell-Luria, A. (2024). **Genome Sequencing for Diagnosing Rare Diseases.** The New England journal of medicine, 390(21), 1985–1997. https://doi.org/10.1056/NEJMoa2314761

7. Bertoli-Avella, A. M., Beetz, C., Ameziane, N., Rocha, M. E., Guatibonza, P., Pereira, C., Calvo, M., Herrera-Ordonez, N., Segura-Castel, M., Diego-Alvarez, D., Zawada, M., Kandaswamy, K. K., Werber, M., Paknia, O., Zielske, S., Ugrinovski, D., Warnack, G., Kampe, K., Iurașcu, M. I., Cozma, C., Bauer, P. (2021). **Successful application of genome sequencing in a diagnostic setting: 1007 index cases from a clinically heterogeneous cohort**. European journal of human genetics : EJHG, 29(1), 141–153. https://doi.org/10.1038/s41431-020-00713-9

8. Sun, Y., Peng, J., Liang, D., Ye, X., Xu, N., Chen, L., Yan, D., Zhang, H., Xiao, B., Qiu, W., Shen, Y., Pang, N., Liu, Y., Liang, C., Qin, Z., Luo, J., Chen, F., Wang, J., Zhang, Z., Wei, H., ... Yu, Y. (2022). **Genome sequencing demonstrates high diagnostic yield in children with undiagnosed global developmental delay/intellectual disability: A prospective study.** Human mutation, 43(5), 568–581. https://doi.org/10.1002/humu.24347

9. Velasco, H. M., Bertoli-Avella, A., Jaramillo, C. J., Cardona, D. S., González, L. A., Vanegas, M. N., Arango, J. P. V., Buitrago, C. A., González, J. A. G., Marcello, J., Bauer, P., & Moncada, J. E. (2024). **Facing the challenges to shorten the diagnostic odyssey: first Whole Genome Sequencing experience of a Colombian cohort with suspected rare diseases**. European journal of human genetics : EJHG, 10.1038/s41431-024-01609-8. Advance online publication. https://doi.org/10.1038/s41431-024-01609-8

10. Chung, C. C. Y., Hue, S. P. Y., Ng, N. Y. T., Doong, P. H. L., Hong Kong Genome Project, Chu, A. T. W., & Chung, B. H. Y. (2023). **Meta-analysis of the diagnostic and clinical utility of exome and genome sequencing in pediatric and adult patients with rare diseases across diverse populations.** Genetics in medicine : official journal of the American College of Medical Genetics, 25(9), 100896. https://doi.org/10.1016/j.gim.2023.100896

11. Runheim, H., Pettersson, M., Hammarsjö, A. et al. **The cost-effectiveness of whole genome sequencing in neurodevelopmental disorders.** Sci Rep 13, 6904 (2023). https://doi.org/10.1038/s41598-023-33787-8

12. Nurchis, M. C., Radio, F. C., Salmasi, L., Heidar Alizadeh, A., Raspolini, G. M., Altamura, G., Tartaglia, M., Dallapiccola, B., & Damiani, G. (2024). **Bayesian cost-effectiveness analysis of Whole genome sequencing versus Whole exome sequencing in a pediatric population with suspected genetic disorders.** The European journal of health economics : HEPAC : health economics in prevention and care, 25(6), 999–1011. https://doi.org/10.1007/s10198-023-01644-0

13. Nurchis, M. C., Riccardi, M. T., Radio, F. C., Chillemi, G., Bertini, E. S., Tartaglia, M., Cicchetti, A., Dallapiccola, B., & Damiani, G. (2022). I**ncremental net benefit of whole genome sequencing for newborns and children with suspected genetic disorders: Systematic review and meta-analysis of cost-effectiveness evidence**. Health policy (Amsterdam, Netherlands), 126(4), 337–345. https://doi.org/10.1016/j.healthpol.2022.03.001

14. Chi, C. S., Tsai, C. R., & Lee, H. F. (2024). **Resolving unsolved whole-genome sequencing data in paediatric neurological disorders: a cohort study.** Archives of disease in childhood, 109(9), 730–735. https://doi.org/10.1136/archdischild-2024-326985

15. Bullich, G., Matalonga, L., Pujadas, M., Papakonstantinou, A., Piscia, D., Tonda, R., Artuch, R., Gallano, P., Garrabou, G., González, J. R., Grinberg, D., Guitart, M., Laurie, S., Lázaro, C., Luengo, C., Martí, R., Milà, M., Ovelleiro, D., Parra, G., Pujol, A. Undiagnosed Rare Disease Program of Catalonia (URD-Cat) Consortium (2022). **Systematic Collaborative Reanalysis of Genomic Data Improves Diagnostic Yield in Neurologic Rare Diseases.** The Journal of molecular diagnostics : JMD, 24(5), 529–542. https://doi.org/10.1016/j.jmoldx.2022.02.003