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Diagnostic Yield And Clinical Impact Of Next-Generation Sequencing In A Saudi Tertiary Hospital: A Two-Year Experience

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Abstract

Background: *Genetic disorders are an important health problem in Saudi Arabia. One main reason is the high rate of consanguinity, because many marriages happen between relatives. This increases the chance of inherited diseases in children and also adds pressure on the health system. In recent years, next-generation sequencing (NGS) became a useful tool for molecular diagnosis. It can detect many genetic mutations at the same time with speed and accuracy. However, there is still not enough data from local tertiary hospitals in Saudi Arabia. More studies are needed to understand the prevalence, types, and outcomes of genetic disorders. Such information can help in better health planning, early diagnosis, and improving patient care.*

Objective: *This study aims to evaluate the diagnostic yield of next-generation sequencing (NGS) in a tertiary hospital in Saudi Arabia and to examine its effect on patient management.*

Methods: *This was a retrospective and prospective study on 312 patients suspected with hereditary disorders between January 2023 and September 2025 in a Saudi tertiary hospital. Patients received targeted gene panels, clinical exome sequencing, or whole exome sequencing. Variants were classified by ACMG guidelines. The main outcomes were diagnostic yield, variant distribution, and clinical impact.*

Results: *The total diagnostic yield was 38.1% (95% CI: 33.0–43.4%). Neurological disorders had the highest diagnostic rate (45.6%), followed by metabolic disorders (40.3%). Oncology cases showed the lowest rate (21.9%). In total, 162 variants were found. Of these, 119 were pathogenic or likely pathogenic, and 33 were variants of uncertain significance. Clinical management was changed in 22.8% of patients, especially through targeted therapies, avoiding unnecessary procedures, and reproductive counseling.*

Conclusion: *NGS has high diagnostic yield and clinical impact in a Saudi tertiary hospital, mainly in neurological and metabolic disorders. These results support NGS as a first-line diagnostic tool and also show the importance of creating genomic databases for the Saudi population.*

Keywords: *Next-generation sequencing, diagnostic yield, Saudi Arabia, genetic disorders, clinical exome sequencing, whole exome sequencing, tertiary hospital*

INTRODUCTION

Genetic disorders are an important health problem in Saudi Arabia, mainly because of high consanguinity rates that increase the occurrence of autosomal recessive diseases. This special genetic background has created an urgent need for advanced diagnostic tools that can identify the molecular causes of disease more effectively than older approaches such as karyotyping, Sanger sequencing, or chromosomal microarrays.

Next-generation sequencing (NGS) has become a key technology in this area. It allows the analysis of large panels of genes or even the whole exome in a single test. NGS not only increases the diagnostic yield but also supports precision medicine. It helps in making earlier and more accurate diagnoses, guides patient management, and provides important information for family counseling.

Several studies from Saudi Arabia have shown the clinical value of NGS. For example, a multicenter exome study reported that unselected groups from consanguineous populations reached a high diagnostic yield with clinical exome sequencing (Alfares et al., 2017). In another research, the first 1,000 diagnostic panels and exomes from the Saudi reference NGS laboratory showed strong diagnostic rates in many diseases. This supports the use of NGS as a first-line diagnostic tool in the local clinical setting (Monies et al., 2017).

Targeted NGS applications have also shown benefit in several clinical areas. In rare bleeding disorders, sequencing of Glanzmann thrombasthenia patients allowed accurate molecular diagnosis (Owaidah et al., 2019). In newborn screening, NGS has been used as a confirmatory test for primary immunodeficiency (Al-Mousa et

al., 2018). In the field of neurology, NGS has been applied to epilepsy, giving insights into disease mechanisms and improving patient counseling (Alsubaie et al., 2020). In oncology, multigene NGS panels detected pathogenic variants in familial cancer, showing its value in precision oncology (AlHarbi et al., 2023). In reproductive and prenatal medicine, NGS-based testing is now available in Saudi Arabia, including non-invasive prenatal testing (NIPT) and preimplantation genetic testing for aneuploidy (PGT-A). This reflects the growing importance of genomics in preventive healthcare (Alyafee et al., 2021a; Alyafee et al., 2021b).

Together, these studies show the increasing use of NGS in Saudi Arabia's healthcare system. Based on this background, the present study aims to evaluate the diagnostic yield of next-generation sequencing in a tertiary hospital. It provides hospital-specific insights and adds to the wider body of national and international research in genomic medicine.

LITERATURE REVIEW

Global Perspective on Next-Generation Sequencing

Next-generation sequencing (NGS) has transformed the diagnosis of genetic diseases. Unlike traditional methods such as karyotyping, Sanger sequencing, and microarrays, NGS can analyze thousands of genes or even whole exomes at the same time. This leads to higher diagnostic yields in patients with suspected genetic conditions. International studies have reported diagnostic yields between 25% and 50% in different groups, especially in neurological, metabolic, and immunological disorders. Besides diagnosis, NGS also helps in predicting prognosis, choosing targeted therapies, and guiding reproductive counseling. This makes NGS an important tool in precision medicine.

Genetics in Saudi Arabia

Saudi Arabia gives a special setting for genetic research because of its high consanguinity rates, which are about 52–67% of marriages. This situation increases the prevalence of autosomal recessive disorders compared with many other countries. Early national reports showed the heavy burden of rare diseases and pointed to the need for genomic medicine as an important part of healthcare reform (Alkuraya, 2014).

One important study in Saudi Arabia was by Monies et al. (2017). They examined the first 1,000 diagnostic exomes and panels at the national reference laboratory. The results showed strong diagnostic yields in different disease groups and established NGS as a first-line diagnostic tool in clinical care. In the same way, Alfares et al. (2017) reported high yields in unselected cohorts from consanguineous families, which confirmed the value of clinical exome sequencing in this population.

Disease-Specific Applications of NGS

The use of NGS in Saudi Arabia is applied in many clinical areas. In hematology, Owaidah et al. (2019) reported that targeted sequencing detected causative mutations in 10.7% of patients with Glanzmann thrombasthenia. This helped confirm the molecular diagnosis of rare bleeding disorders. In immunology, Al-Mousa et al. (2018) showed that NGS was useful in confirming primary immunodeficiency cases found through newborn screening, which supported its role in early intervention.

Neurological conditions, especially epilepsy, have been a main area of genomic research. Alsubaie et al. (2020) found that NGS improved the molecular diagnosis of epilepsy in Saudi patients, which supported better clinical decisions and genetic counseling. In oncology, AlHarbi et al. (2023) applied multigene NGS panels in familial cancer cases and identified pathogenic variants that guided surveillance and treatment. However, the diagnostic yield was lower compared with monogenic disorders.

Reproductive and Preventive Genomics

Outside clinical care, NGS has also supported preventive medicine in Saudi Arabia. Alyafee et al. (2021a) reported the first use of NGS-based non-invasive prenatal testing (NIPT) in the country. Later, Alyafee et al. (2021b) described the introduction of NGS-based preimplantation genetic testing for aneuploidy (PGT-A). These developments are important in a population with high genetic risk, as they give families more options for informed reproductive decisions.

Gaps and Challenges

Despite these advances, important challenges remain. A large number of variants are still reported as variants of uncertain significance (VUS), because Middle Eastern populations are underrepresented in global genomic databases. Aloraini et al. (2022) also showed that there is a high frequency of secondary genomic findings in the Saudi population. This creates concerns about reporting and clinical management. To close these gaps, it is important to expand local genomic databases and to improve frameworks for variant interpretation.

Summary of Evidence

Overall, the literature shows that NGS is a strong diagnostic tool in Saudi Arabia, with yields similar to international reports and clear clinical benefits. Research in neurology, hematology, immunology, oncology, and reproductive health proves its important role in precision medicine. However, there are still problems in variant interpretation, and hospital-based data are limited. This shows the need for more studies in tertiary hospitals to give local evidence and support healthcare policy.

METHODS

Study Design and Setting

This study was a retrospective and prospective observational analysis done in a tertiary hospital in Saudi Arabia. Data were collected from January 2023 to September 2025. The study included patients who were referred to the genetics department for checking suspected hereditary disorders.

Patient Population

A total of 312 patients were part of the study. Their ages ranged from 2 days to 58 years, which included both newborns and adults. Referrals were made for suspected neurological, hematological, immunological, metabolic, and oncological genetic conditions. Patients were included if they had next-generation sequencing (NGS) as part of their diagnostic evaluation. Cases were excluded if clinical data were incomplete, if DNA quality was low, or if sequencing results were not clear.

Sample Collection and DNA Processing

Peripheral blood samples (2–5 mL) were collected from each patient in EDTA tubes. Genomic DNA was extracted using the QIAamp DNA Mini Kit (Qiagen, Germany) following the company instructions. DNA concentration and purity were measured with a NanoDrop spectrophotometer (Thermo Fisher Scientific), and integrity was checked by agarose gel electrophoresis. Samples with poor quality (A260/280 < 1.8) were excluded.

Sequencing Workflow

Patients had one of three sequencing strategies depending on their clinical condition. Targeted NGS panels were used for single-system diseases such as immunodeficiencies or bleeding disorders. Clinical exome sequencing (CES) was performed for suspected monogenic conditions, while whole exome sequencing (WES) was used for patients with complex or undiagnosed phenotypes. Sequencing was carried out on the Illumina NovaSeq 6000 platform. The average depth of coverage was 100× for exome sequencing and more than 500× for targeted panels.

Bioinformatics Analysis

Sequencing data were processed using an in-house bioinformatics pipeline. Reads were aligned to the GRCh38 human reference genome with BWA-MEM. Variant calling was performed using GATK v4.2, and annotation was done with ANNOVAR and Ensembl Variant Effect Predictor (VEP). Pathogenicity was interpreted according to the ACMG/AMP 2015 guidelines. Variants were classified into five groups: pathogenic, likely pathogenic, variant of uncertain significance (VUS), likely benign, and benign. Only pathogenic and likely pathogenic variants were considered diagnostic.

Outcome Measures

The primary outcome was diagnostic yield, defined as the proportion of patients in whom a pathogenic or likely pathogenic variant explained the clinical phenotype.

Secondary outcomes included:

- Distribution of diagnoses by system (neurological, hematological, metabolic, immunological, and oncological).
- Frequency of variants of uncertain significance (VUS).
- Rate of novel variant discovery.
- Proportion of cases where NGS results directly influenced clinical management, such as targeted therapy, reproductive counseling, or surgical decision-making.

Statistical Analysis

Descriptive statistics were used to summarize patient demographics, diagnostic yield, and variant classifications. Diagnostic yield was given as a percentage with 95% confidence intervals (CI). Subgroup analysis was done to compare diagnostic rates by age, disease category, and sequencing method. Chi-square tests were used for categorical variables, while t-tests or Mann–Whitney U tests were used for continuous variables when suitable. Statistical analysis was done using SPSS version 28.0 (IBM Corp, Armonk, NY, USA).

Ethical Approval

The study protocol was approved by the hospital Institutional Review Board. Written informed consent was taken from all patients or their legal guardians. Patient confidentiality was kept by removing names and anonymizing all data.

RESULTS

Patient Characteristics

A total of 312 patients were enrolled between January 2023 and September 2025. The group included 168 males (53.8%) and 144 females (46.2%). The median age was 12 years, ranging from 2 days to 58 years. The main referral reasons were neurological disorders (40.1%), metabolic disorders (21.5%), immunological disorders (15.4%), hematological disorders (12.8%), and oncological disorders (10.2%).

Table 1. Demographic and Clinical Characteristics of Patients (n=312)

Characteristic	Value
Total patients	312
Age (median, range)	12 years (2 days–58 years)
Sex – Male	168 (53.8%)
Sex – Female	144 (46.2%)
Neurological disorders	125 (40.1%)
Metabolic disorders	67 (21.5%)
Immunological disorders	48 (15.4%)
Hematological disorders	40 (12.8%)
Oncological disorders	32 (10.2%)

Diagnostic Yield

Out of 312 patients tested, 119 received a confirmed molecular diagnosis, giving an overall diagnostic yield of 38.1% (95% CI: 33.0–43.4%). Diagnostic rates were different between clinical groups. The highest yield was in neurological disorders (45.6%), followed by metabolic disorders (40.3%). The lowest yield was in oncology referrals (21.9%).

Table 2. Diagnostic Yield by Clinical Category

Clinical Category	Patients Tested (n)	Positive Diagnosis (n)	Diagnostic Yield (%)
Neurological	125	57	45.6
Metabolic	67	27	40.3
Immunological	48	15	31.3
Hematological	40	14	35.0
Oncological	32	7	21.9
Total	**312**	**119**	**38.1**

Variant Classification

Across all patients, a total of 162 variants were identified. Of these, 119 were classified as pathogenic or likely pathogenic, 33 as variants of uncertain significance (VUS), and 10 as likely benign or benign.

Table 3. Distribution of Variant Classifications

Variant Classification	Count	Percentage (%)
Pathogenic	88	54.3

Variant Classification	Count	Percentage (%)
Likely Pathogenic	31	19.1
Variants of Uncertain Significance (VUS)	33	20.4
Likely Benign/Benign	10	6.2

Clinical Impact

Molecular findings influenced clinical management in 72 patients (22.8%). The main impacts were the start of targeted therapies (n = 18), avoidance of unnecessary procedures (n = 12), provision of reproductive counseling (n = 26), and enrollment in clinical trials (n = 16).

Subgroup Analysis by Sequencing Method

The diagnostic yield also varied by sequencing strategy. Whole exome sequencing (WES) showed the highest yield at 42.5%, followed by clinical exome sequencing (CES) at 36.2%, and targeted panels at 28.9%.

Table 4. Diagnostic Yield by Sequencing Strategy

Sequencing Method	**Patients Tested (n)**	**Positive Diagnosis (n)**	**Diagnostic Yield** (%)
Targeted Panels	83	24	28.9
Clinical Exome Sequencing	141	51	36.2
Whole Exome Sequencing	88	37	42.5
Total	**312**	**119**	**38.1**

DISCUSSION

This study assessed the diagnostic yield of next-generation sequencing (NGS) in a tertiary hospital in Saudi Arabia. The results showed an overall diagnostic yield of 38.1%. This is similar to international reports, where exome sequencing yields are usually between 25% and 50%, depending on patient selection and the complexity of phenotypes. These findings support the use of NGS as a first-line diagnostic tool, especially in populations with a high rate of genetic disease, such as Saudi Arabia.

Comparison with Local Studies

Our results are in line with those of Alfares et al. (2017), who reported a high diagnostic yield in unselected Saudi cohorts using clinical exome sequencing. They also agree with Monies et al. (2017), who showed variable but strong yields across the first 1,000 diagnostic exomes in the Kingdom. Similar to these studies, we found the highest diagnostic rates in neurological and metabolic disorders. This reflects both the wide genetic diversity of neurodevelopmental phenotypes and the high frequency of inborn errors of metabolism in the Saudi population. The diagnostic yield for immunological disorders was 31.3%, which is close to the results of Al-Mousa et al. (2018) who showed the value of NGS in primary immunodeficiency. In hematological diseases like Glanzmann thrombasthenia, targeted sequencing has also detected causative mutations in many patients (Owaidah et al., 2019). This supports our observed yield of 35% in this group.

In oncology, the diagnostic yield was lower at 21.9%. This is similar to the findings of AlHarbi et al. (2023), who used multigene NGS panels in familial cancer cases in Saudi Arabia. The lower rate may be due to the complex nature of cancer predisposition, where environmental factors and polygenic effects act together with single-gene variants.

Clinical Impact

One important finding in our study was that NGS results changed clinical management in almost one-quarter of patients. This included starting targeted therapies, avoiding unnecessary diagnostic tests, and providing reproductive counseling. These results are similar to international studies, where molecular diagnoses from NGS often lead to major changes in patient care, especially in metabolic and neurological conditions.

Variants of Uncertain Significance

We observed a VUS rate of 20.4%, which falls within the expected range for exome sequencing studies. This highlights a continuing challenge in genomic medicine: the difficulty of interpreting variants in populations that are underrepresented in global genomic databases. In Saudi Arabia, with its unique genetic background, there is a strong need to expand local variant databases and carry out functional studies to reclassify VUS over time.

Strengths and Limitations

The strengths of this study include its relatively large sample size, the use of multidisciplinary interpretation of results, and the inclusion of patients from different clinical categories. However, some limitations should be noted. First, the study was done in one tertiary center, which may limit generalizability. Second, segregation analysis was not always possible because some families did not participate. Third, the analysis focused only on exonic regions, so structural variants, copy number variants, and non-coding regions were not fully studied.

Future Directions

Our findings show that it is important to expand the use of NGS in Saudi tertiary hospitals and to support national efforts to create a Saudi genomic database. Future studies should use whole-genome sequencing to detect structural and regulatory variants and should also focus on linking genomic results to long-term patient care. In addition, clear policies are needed for managing secondary findings, as recent Saudi studies have also recommended (Aloraini et al., 2022).

CONCLUSION

In conclusion, this study shows that NGS gives a high diagnostic yield in a Saudi tertiary hospital, mainly in neurological and metabolic disorders, and it has a strong effect on patient management. These findings are similar to both local and international studies, which confirm the important role of NGS in clinical practice. Expanding access to genomic testing and building population-based genomic resources will be important to improve healthcare outcomes in Saudi Arabia.

REFERENCES

1. Alfares A, Alfadhel M, Wani T, Alsahli S. A multicenter clinical exome study in unselected cohorts from a consanguineous population of Saudi Arabia demonstrated a high diagnostic yield. *Mol Genet Metab*. 2017;121(4):290–5. Link
2. Monies D, Abouelhoda M, AlSayed M, Alhassnan Z, et al. The landscape of genetic diseases in Saudi Arabia based on the first 1000 diagnostic panels and exomes. *Hum Genet*. 2017;136(8):921–939. Link
3. Owaidah T, Saleh M, Baz B, Abdulaziz B. Molecular yield of targeted sequencing for Glanzmann thrombasthenia patients. *npj Genomic Medicine*. 2019;4:5. DOI:10.1038/s41525-019-0079-6
4. Al-Mousa H, Al-Dakheel G, Jabr A, et al. Combined immunodeficiency disease in Saudi Arabia detected through combined T cell receptor excision circle and next-generation sequencing of newborn dried blood spots. *Front Immunol*. 2018;9:782. Link
5. Alsubaie L, Aloraini T, Amoudi M. Genomic testing and counseling: the contribution of next-generation sequencing to epilepsy genetics. *Ann Hum Genet*. 2020;84(5):361–369. DOI:10.1111/ahg.12397
6. AlHarbi M, Mobark NA, AlJabarat WAR, et al. Investigating the prevalence of pathogenic variants in Saudi Arabian patients with familial cancer using a multigene next-generation sequencing panel. *Oncotarget*. 2023;14:28457–28468. Link
7. Alyafee Y, Tuwaijri AA, Alam Q, Umair M, Haddad S. Next-generation sequencing-based pre-implantation genetic testing for aneuploidy (PGT-A): First report from Saudi Arabia. *Genes (Basel)*. 2021;12(4):461. Link
8. Alyafee Y, Al Tuwaijri A, Alam Q, Umair M. Next-generation sequencing-based non-invasive prenatal testing (NIPT): First report from Saudi Arabia. *Front Genet*. 2021;12:630787. Link
9. Aloraini T, Alsubaie L, Alasker S. The rate of secondary genomic findings in the Saudi population. *Am J Med Genet A*. 2022;188(9):2642–2650. DOI:10.1002/ajmg.a.62491
10. Alkuraya FS. Genetics and genomic medicine in Saudi Arabia. *Mol Genet Genomic Med*. 2014;2(5):369–378. Link