Comparison of the diagnostic yield of whole exome sequencing (WES) and targeted panel sequencing for children with idiopathic short stature (ISS)

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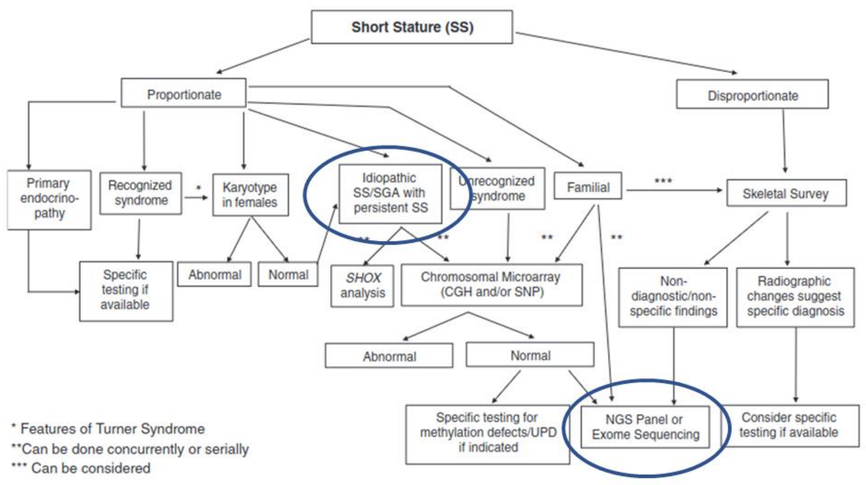
INTRODUCTION

ACMG practice guideline (2021) recommends that children with ISS could be evaluated using targeted panel sequencing or WES.



In commercial laboratories, WES is often performed and the genetic evaluation is offered as a panel, facilitating analysis and interpretation.

There are no studies that directly compare the diagnostic yield between WES and targeted panel analysis for children initially classified as ISS.

OBJETIVE

To compare the diagnostic yield of whole exome sequencing (WES) with panels for the genetic diagnosis of children with ISS;

METHODS

Selected children with phenotype compatible with ISS → **DNA collection (patient and 1st degree relatives)** → **Genetic study of the index case** → **Bioinformatics Franklin Genoox**

WES
- **Single nucleotide variant analysis (SNVs)**
- **Copy number variant analysis (CNVs)**
- **Exonic and intronic regions flanking the exons**

→ **Potentially deleterious rare variants in genes already associated with ISS or growth disorders**

25 targeted panels

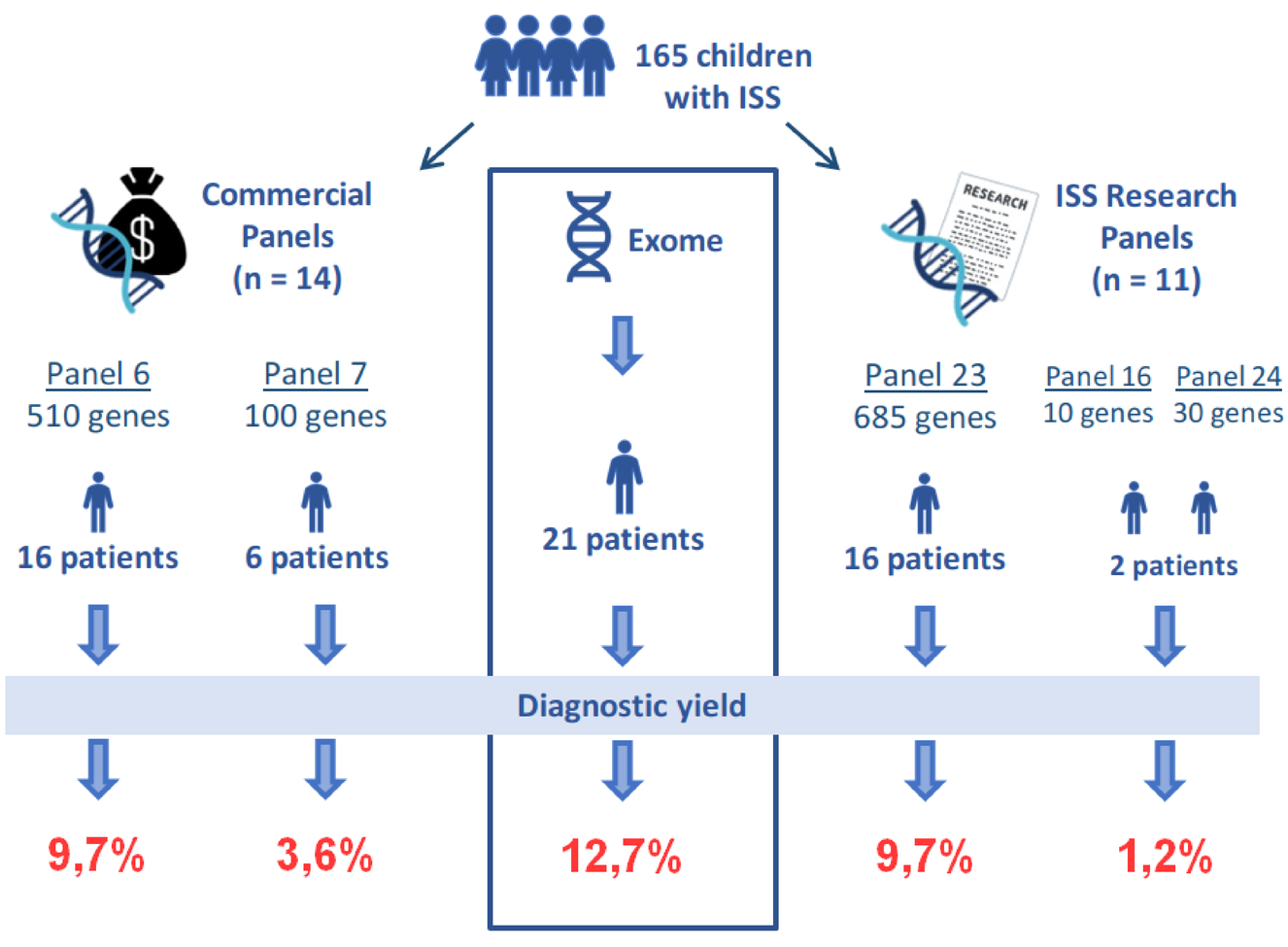
11 research papers

PubMed
- **Search terms: "genetic testing" and "growth disorders" and "short stature" and "idiopathic short stature".**
- **Inclusion criteria were: assessment of growth disorder through panels and availability by the author of the list of genes present in the panel used.**

14 commercials

NCBI – Genetic testing registry; ClinVar and Google
- **Search for websites of Brazilian and international commercial laboratories.**
- **Search terms: "genetic testing" and "growth disorders" and "short stature" and "idiopathic short stature".**

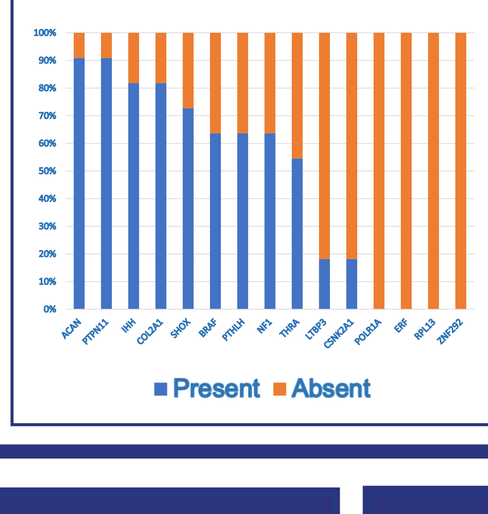
RESULTS

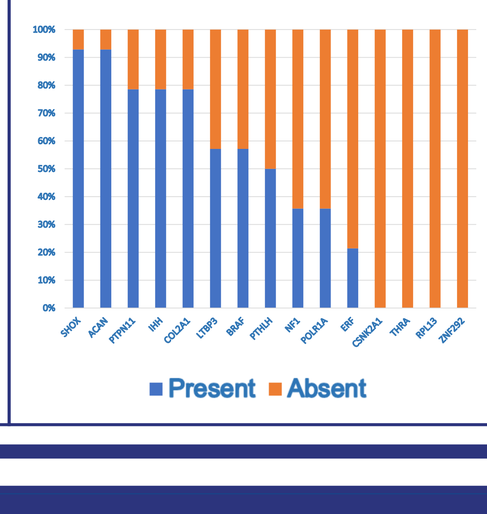


WES – 21 variants P or LP

11 in genes already associated with **ISS**
- ***SHOX*** **(3x)**
- ***ACAN*** **(2x),** ***IHH*** **(2x),** ***COL2A1*** } Growth plate
- ***NF1***, ***PTPN11*** **(2x) –** RASopathies

10 in genes associated with **growth disorders**
- Hormonal resistance: ***THRA***
- Skeletal dysplasias: ***PTHLH***, ***ERF***, ***POLR1A***, ***RPL13***, ***LTBP3***
- RASopathies: ***BRAF***
- Complex genetic syndromes: ***ZNF292***, ***CSNK2A1*** **(2x)**





CONCLUSION

Whole exome sequencing allowed for the identification of a monogenic cause for growth disorder in 12.7% of the evaluated cases (21 out of 165 patients), and it also improved the diagnostic yield compared to panels, providing a better explanation of the genetic basis for the isolated short stature phenotype.

SPONSOR

This study was sponsored by BioMarin which has no influence on data collection, analysis and interpretation

REFERENCES

Turkyilmaz, Ayberk et al. "A Genetic Approach in the Evaluation of Short Stature." The Eurasian journal of medicine vol. 54,Suppl1 (2022): 179-186.

CONTACT INFORMATION

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