

Proposed algorithm for Primary Immunodeficiency Disorders diagnoses

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Background & Objective: Primary immunodeficiency disorders (PIDD) are genetic defects of the immune system. PIDD comprise a heterogeneous group of phenotypes and genotypes, hence the management of each individual disease is challenging. Immunological workup together with genetic studies is important to establish diagnosis. However, low and middle-income countries might have difficulties to have access to all these studies. Hence, decisions for which and when immunological and genetic studies need to be performed is a paramount for diagnoses of PIDD in low and middle-income countries. We aimed to provide an algorithm for PIDD diagnoses that can be used in low and middle-income countries.

Methods: A systematic search was performed in PIDD diagnoses guidelines and next generation sequencing for suspected PIDD in Web of Science and online tools available for genetic analysis.

Results: We proposed the following algorithm for PIDD diagnoses (**Figure 1**). For PIDD diagnosis,

immunological testing together with clinical manifestations is required to evaluate which cells are affected and this should be correlated with genetic studies to establish molecular diagnoses. Genetic panels for known PIDD-associated genes are available. In most scenarios, next-generation sequencing is considered if panel testing does not result in a diagnosis and a monogenic cause is clinically suspected. After genetic testing, whether no relevant gene is found, diagnosis should be reconsidered. Finally, if genetic tests arise

variants of uncertain significance in a PIDD phenotype-related gene or novel variant, functional studies should be performed in clinical or research setting.

Conclusions: Extensive exome or genome sequencing, functional studies and alternative diagnoses whether no molecular diagnosis is achieved should be considered for PIDD diagnoses.

Conflict of interest disclosure: The authors declare no potential conflicts of interest.

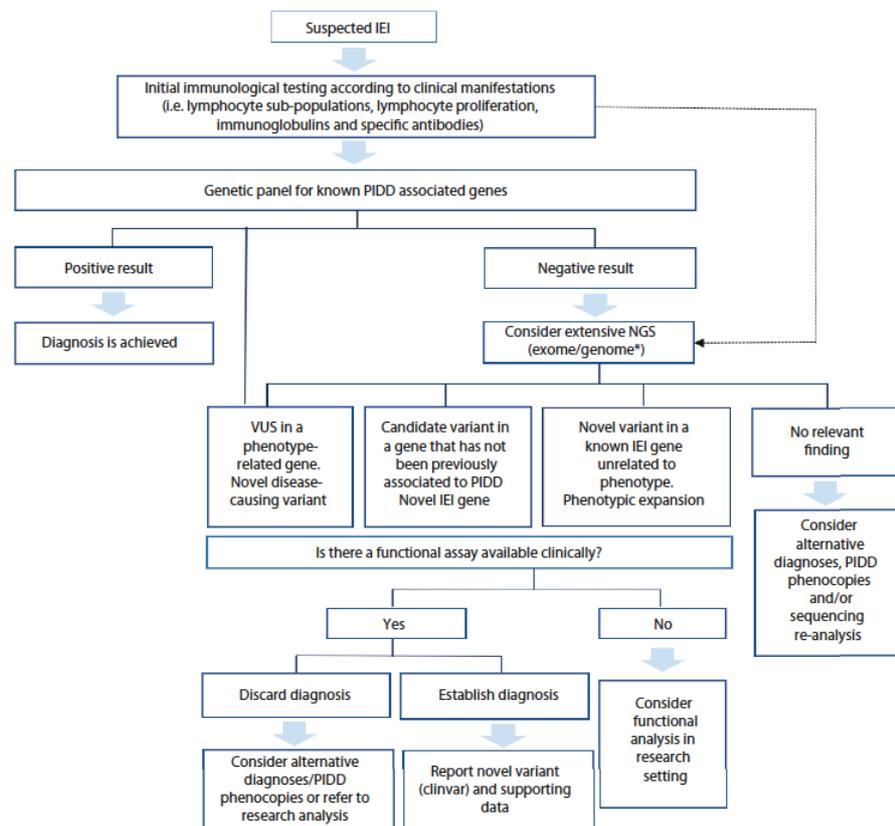


Figure 1. Algorithm for primary immunodeficiency disorders (PIDD).

NGS: Next generation sequencing. VUS: variant of uncertain significance. IEI: inborn errors of immunity.