IPOPI
INTERNATIONAL
PATIENT ORGANISATION
FOR PRIMARY IMMUNODEFICIENCIES

PRIMARY **IMMUNODEFICIENCIES**

ESSENTIALS OF PID DIAGNOSIS

ABBREVIATIONS

CT	Computed tomography
CVID	Common variable immunodeficiency
DLCO	Carbon monoxide diffusing capacity
Ig	Immunoglobulin
MRI	Magnetic resonance imaging
PID	Primary immunodeficiency
WES	Whole exome sequencing
WGS	Whole genome sequencing

Essentials of PID diagnosis (1st edition).

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INTRODUCTION

This booklet explains how clinical signs and symptoms, family history, tests and genetic analysis can be used in the diagnosis of primary immunodeficiencies.

Primary immunodeficiencies (PIDs) are rare diseases that occur when components of the immune system are either not present or not functioning normally, rendering the patient susceptible to potentially life-threatening infections. PIDs arise due to changes in specific genes that encode proteins involved in the functioning of the immune system.

PIDs can be diagnosed throughout the lifetime of a person, with the most severe forms usually being diagnosed in childhood. Early diagnosis and long-term management with, for example, antibiotic prophylaxis and/or immunoglobulin replacement therapy, are critical to optimise outcomes for patients with PIDs. The following sections provide an overview of the steps required to achieve a diagnosis of PID.

DIAGNOSING PIDs

PIDs can have widely differing presentations, from relatively mild to life-threatening. The presentations of PIDs are often complex with clinical indicators that are suggestive of multiple potential diagnoses. The diagnosis of PIDs often emerges from a picture of recurrent or unusual infections, and also from autoimmune diseases, inflammatory processes, severe allergies and/or cancer.

Once a PID is suspected, clinical and pathological (when relevant) assessments should be conducted. These will include evaluation of the family history with regards to PIDs, repeated severe and/or refractory infections or unusual infections, bronchiectasis, therapy-resistant asthma (or other allergies), autoimmune or inflammatory conditions, and malignancies or even unexplained deaths. In addition, assessments for symptoms of autoimmunity, inflammation and lymphoproliferation will be undertaken and these may indicate a specific PID. Finally, a complete blood count that includes leukocytes and differentiation (including a blood smear) and immunoglobulin (Ig) G, IgA, IgM and IgE plasma levels will be conducted, as well as tetanus and pneumococcus serology whenever possible/available (see Figure 1). A computed tomography (CT) scan may be requested in cases of recurrent pulmonary infections (or any other respiratory symptoms) to assess lung damage as well as CT scans of the head, neck, abdomen and pelvis in order to look for other possible reasons for the symptoms the patient is experiencing such as inflammatory bowel disorder, lymphoproliferation, abscesses of the brain, liver and/or spleen, and sinusitis.

TABLE 1

CLINICAL INDICATORS FOR PIDs [1]
Four or more new ear infections within 1 year
Two or more serious sinus infections within 1 year
Two or more months on antibiotics with little effect
Two of more pneumonias within 1 year
Failure of an infant to gain weight or grow normally
Recurrent, deep skin or organ abscesses
Persistent thrush in the mouth or fungal infection on the skin
Need for intravenous antibiotics to clear infections
Two or more deep-seated infections, including septicaemia
A family history of primary immunodeficiency

As already stated, PIDs can present in diverse ways and approximately 25% of patients with PIDs may not show the above symptoms. Therefore, a PID diagnosis should not be ruled out based on the absence of these signs or symptoms.[2] For children, additional information should be collected, including records of weight and height since birth, as failure to thrive is an important sign of serious disease.

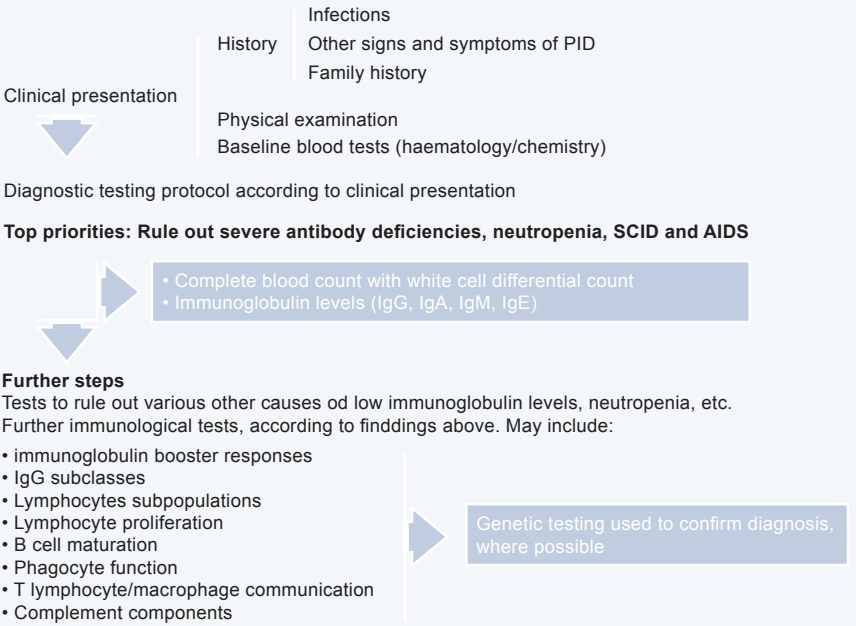
[1] https://esid.org/Working-Parties/Clinical-Working-Party/Resources/10-Warning-Signs-of-PID-General

[2] Thalhammer J, et al. Initial presenting manifestations in 16,486 patients with inborn errors of immunity include infections and noninfectious manifestations. J Allergy Clin Immunol 2021;148(5):1332-1341.e5.

FIGURE 1

A PROTOCOL FOR THE EVALUATION OF A PATIENT WITH SUSPECTED PID

Adapted from the European Society for Immunodeficiencies [ESID] diagnostic protocol [3]



SPECIALIST EVALUATIONS

It is often necessary to involve additional specialists to achieve a diagnosis for some PIDs. Most often this will involve a clinical immunologist but may also include a specialist in infectious disease, an oncologist, a gastroenterologist, a hepatologist and a respiratory specialist. Following diagnosis, this multidisciplinary team will also be critical in the development of a treatment plan.

Specialist evaluations may include respiratory function (spirometry, carbon monoxide diffusing capacity [DLCO], high-resolution CT of the lungs, sputum culture) as well as imaging of the abdomen (endoscopic ultrasound, abdominal CT or magnetic resonance imaging [MRI] scan) and liver (fibroscan) together with liver biopsy and liver function testing. Other evaluations may include the determination of the presence of autoantibodies, vaccination response in case of recurrent infections and microbial diagnosis in case of active infection. Together, this information will provide a complete clinical picture and guide the approach to the management of the particular PID.

GENETIC DIAGNOSIS OF PIDS

PIDs arise due to changes in specific genes that encode proteins involved in the functioning of the immune system, making genetic diagnosis possible in some cases.

Some PIDs arise sporadically (meaning that a de novo mutation randomly occurred during egg formation), while other PIDs already exist in the chromosomes of one or both parents and are inherited. Most of PIDs are inherited in one of two different modes of inheritance: autosomal recessive or X-linked recessive; less frequently is the inheritance autosomal dominant.

As the genetic defect(s) underlying a growing number of PIDs is now known it is becoming increasingly possible to confirm a suspected diagnosis using genetic analyses. Newer techniques, such as whole genome sequencing (WGS; also known as full genome sequencing, complete genome sequencing, or entire genome sequencing, is the process of determining the entire DNA sequence of an organism's genome at a single time) or whole exome sequencing (WES; a technique for sequencing all of the protein-coding regions of genes, known as the exome, in a genome), and also genetic panels can be used to confirm a diagnosis for some PIDs where the precise genetic defect is not known or does not fit a usual pattern. All that is usually required is a sample of blood (of the patient and often of the relatives in order to increase the chance of identifying the defect and/or to study the segregation of the mutation). That said, in PIDs such as common variable immunodeficiency (CVID), several genes may be involved, and as genetic diagnosis is time and resource demanding it should be used appropriately.

While a genetic confirmation may not be required to confirm a diagnosis for all PIDs, this approach may be useful for complex or difficult to diagnose cases or to ensure patients receive appropriate treatments that address the immune-system defect underlying their condition.[4] Prenatal diagnosis may be possible in families where a genetically defined PID has been identified should the parent request it.

More information on the genetic diagnosis of PIDs is available in our leaflet on this topic available through our website at **https://ipopi.org/genetic-diagnosis-of-pids/**.

[3] De Vries E, et al. Patient-centred screening for primary immunodeficiency, a multi-stage diagnostic protocol designed for non-immunologists: 2011 update. Clin Exp Immunol 2012;167:108–19.

FURTHER INFORMATION AND SUPPORT

This booklet has been produced by the International Patient Organisation for Primary Immunodeficiencies (IPOPI). Other booklets are available in this series. For further information and details of PID patient organisations worldwide, please visit **IPOPI.org**.

Provided by

IMMUNO DEFICIENCY UK

Supporting families affected by primary and secondary immunodeficiency

Immunodeficiency UK is a national organisation supporting individuals and families affected by primary and secondary immunodeficiency.

We are the UK national member of IPOPI, an association of national patient organisations dedicated to improving awareness, access to early diagnosis and optimal treatments for PID patients worldwide.

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