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SPOTLIGHT ON GENETICS
Expanding the Technology

Primary immunodeficiency and immune dysregulation disorders (PIDDs) are a large, complex, and rapidly growing group of disorders. In the World Health Organization's initial report on PIDDs in 1970, 16 disorders were described.[1] Recent advances in genetic testing have contributed greatly to the rapid expansion of PIDDs. The International Union of Immunological Societies (IUIS) identified approximately 175 PIDDs in 2010; by 2017, this number had doubled to 354 distinct PIDDs (see Figure 1).[2]

Figure 1: Approximate number of recognized PIDDs over time.[2]

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Early types of genetic testing required a targeted approach: test the most likely gene based on the patient's symptoms, using what you know about symptoms associated with PIDD genes. This approach is limited by the high cost and lengthy turnaround times of individually testing multiple genes. It is also limited by our knowledge of the symptoms associated with specific genes. Since many genes involved in PIDDs were first reported in single patients, our understanding of the symptoms associated with a gene is often incomplete.[3] Previous studies showed the limitations of targeted genetic testing, including a study in 2017 reporting that 4% of their patients had symptoms not previously associated with the gene identified, and 5% had mutations in more than one gene.[4] With newer technologies, it is possible to test for multiple genes at once in patients with symptoms that cannot be narrowed down to a single gene or small group of genes. Broad tests are now available to examine hundreds of genes associated with PIDDs all at once. Their diagnostic rates reportedly range from 15-70%, depending on the patient population.[5]

Even with these broad tests, a significant number of patients (30-80%) are still undiagnosed. With the list of genes involved in PIDDs rapidly growing, tests with defined gene lists quickly become outdated. For example, in a study involving a large cohort of PIDDs, approximately 25% of the genetic diagnoses they made were in genes that were discovered within the past 5 years.[4] Clearly, broader and more flexible genetic testing is still needed. Genomic tests like exome (ES) and genome sequencing (GS) meet this need, however they face several limitations. These include high costs, lengthy turnaround times, the need for parental samples for analysis, and the risk of unexpected (secondary) findings.

Regardless of the challenges of genetic testing, it is very important to find the genetic diagnosis causing a patient's PIDD since it can substantially guide treatment and counseling. Finding the genetic diagnosis may allow for targeted therapies, like gene therapy to fix the underlying defect or therapies targeted at the specific disease mechanism.

Previous studies on genetic testing in PIDD patients showed that genetic testing directly impacted the patient's treatment in 25-37% of patients.[4,5] The genetic diagnosis also allows for accurate counseling about the prognosis, which includes whether to expect other major symptoms in the future, whether these symptoms can be prevented, and accurate recurrence risk counseling.

Given the importance of genetic testing for patients and the limitations of current testing methods, the Laboratory of Genetics and Genomics at Cincinnati Children's Hospital developed the **Immunology Exome**, a genetic test that uses ES technology to analyze a defined list of genes involved in PIDD. It currently analyzes 394 genes involved in PIDD, making it one of the largest genetic tests for immune dysfunction. The list of genes was carefully selected based on the genes identified by the IUIS[2] and in collaboration with clinical immunologists and researchers. The flexibility of the Immunology Exome allows the gene list to undergo regular updates as new literature and guidelines are available regarding PIDD. And while it is ES-based, the Immunology Exome uses a proband-only approach, meaning ordering providers do not need to coordinate parental samples for each order as they do with ES/GS orders (see Figure 2).

Figure 2: Immunology Exome quick facts.

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Each result is reviewed by a diverse and specialized team that includes genetic technologists, bioinformaticians, molecular geneticists, clinical immunologists, and genetic counselors (see Figure 3). This special collaboration allows us to offer an unparralelled level of expertise.

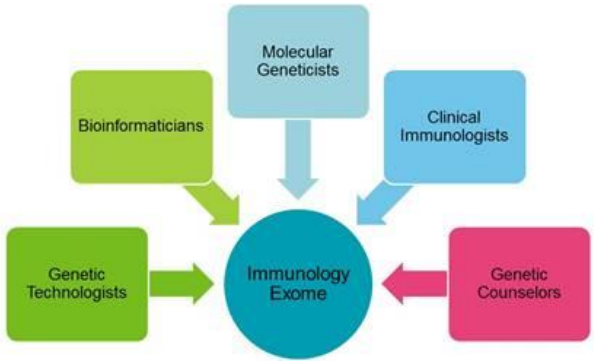

Figure 3: Immunology Exome team.

For more information about the Immunology Exome, please visit the website for the Diagnostic Center for Heritable Immunodeficiencies at the DCHI Webpage.

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