For adult patients with inborn errors of immunity

Uncover more insights with exome testing

Inborn errors of immunity (IEI) is a broad term describing over 550 disorders, most of which are single-gene disorders, with new causes being discovered regularly.[1]

The age of onset for IEIs can range from birth onwards, with about half of cases presenting in adulthood.[2] Adults can also experience distinct symptoms.[3]

Exome sequencing looks at ~20,000 genes. This increases the likelihood of finding a genetic cause compared to multi-gene panels that are analyzing a set number of genes.

40%

Diagnostic yield of exome sequencing in the IEI population[4,5]

For about 75% of patients with IEI, genetic testing can change their diagnosis, helping to clarify their medical condition and impacting clinical management[6,7]

Therapies are available for more than 50% of patients with IEI[2]. Identifying an underlying genetic cause can inform treatment decisions, such as[8,9]:

- Bone marrow transplant
- Biologic supportive therapy
- Enzyme replacement therapy
- IgG replacement

The Clinical Immunology Society recommends genetic testing for individuals with IEIs to reach a more precise diagnosis and to help guide treatment[10]

References: 1. Poli CM, Aksentijevich I, Bousfiha AA, et al. *J Hum Immun* 5 May 2025 **2.** Bousfiha AA, Jeddane L, Ailal F, et al. *J Clin Immunol.* 2013;33(1):1–7. **3.** Accessed from Jeffrey Modell Foundation: https://info4pi.org/library/ **4.** Platt CD, Zaman F, Bainter W, et al. *J Allergy Clin Immunol.* Feb 2021;147(2):723-726. **5.** Vorsteveld EE, Hoischen A, van der Made CI. *Clin Rev Allergy Immunol.* Oct 2021;61(2):212-225. **6.** Okano T, Imai K, Naruto T, et al. *J Clin Immunol.* 2020 Jul;40(5):729-740. **7.** Stray-Pedersen A, Sorte HS, Samarakoon P, et al. *J Allergy Clin Immunol.* Jan 2017;139(1):232-245. **8.** Accessed from Jeffrey Modell Foundation: https://info4pi.org/library/ **9.** Nelson CS, Baloh CH. *Allergy Asthma Proc.* 2024 Sep 1;45(5):332-339. **10.** Heimall JR, Hagin D, Hajjar J, et al. *J Clin Immunol.* Apr 2018;38(3):320-329.

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Patient overview

Throughout childhood, Antonio was healthy and active with no major medical concerns. He experienced several throat infections as a kid and regularly had canker sores. He would get quite sick after receiving a vaccine, so his mother stopped taking him for vaccinations.

Clinical history

13 years old

Around 13 years of age, Antonio began to develop skin lesions and boils on both calves, his scalp and torso, as well as intermittent fungal infections on his nails. A dermatologist helped manage his skin conditions.

30 years old

At age 30, Antonio started to experience fatigue after playing soccer and had a yellow tinge to his eyes. He was diagnosed with steroid-responsive leukopenia and thrombocytopenia and an enlarged spleen and lymph nodes. He was prescribed prednisone to help manage his symptoms and was monitored by an oncologist and dermatologist.

39 years old

At age 39, Antonio had a CBC come back abnormal after a routine visit to his primary care doctor. He was referred to Immunology and additional testing identified decreased serum IgG, IgA and IgM and he was diagnosed with common variable immunodeficiency (CVID). Antonio was prescribed Cuvitru.

He developed discomfort in the left side of his body, and it was discovered that he had several enlarged lymph nodes and an enlarged spleen. A bone marrow biopsy, karyotype and FISH studies all came back negative for malignancy. A few months later, Antonio developed a subcutaneous lump on his hand with associated swelling, subcutaneous bleeding and bleeding along his gum lines. After receiving a transfusion for low platelets, his symptoms did not resolve. He was prescribed dexamethasone and responded to the medication but was admitted to the hospital shortly after due to worsening symptoms and lack of response to steroids. While in the hospital he received IVIG and responded well. During his admission, the hematology clinicians expressed concern that Antonio may have autoimmune lymphoproliferative syndrome (ALPS) and referred him to genetics.

Genetic findings and clinical implications

Family history revealed autoimmune and dermatologic conditions: father with chronic skin rashes, an aunt with systemic lupus erythematosus, and an uncle with skin rashes boils.

Genetics ordered an exome trio and a CMA. The CMA was negative.

Exome testing identified a likely pathogenic variant in *NFKB1* associated with *NFKB1*- related CVID. Heterozygous loss-of-function variants in *NFKB1* have been reported in association with CVID and many of the common features match Antonio's symptoms.

- Antonio's diagnosis provides a molecular explanation for his immunologic and hematologic manifestations.
- Early testing and monitoring are recommended for his daughter, who has a 50% risk of inheriting the variant.
- Targeted variant testing is advised for symptomatic paternal relatives.

*Case study is based on GeneDx patient testing, with all identifying information removed.

Photos do not represent actual patients.

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