AD Manifestations in Inborn Errors of Immunity

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Classification of Primary Immunodeficiency Disorders

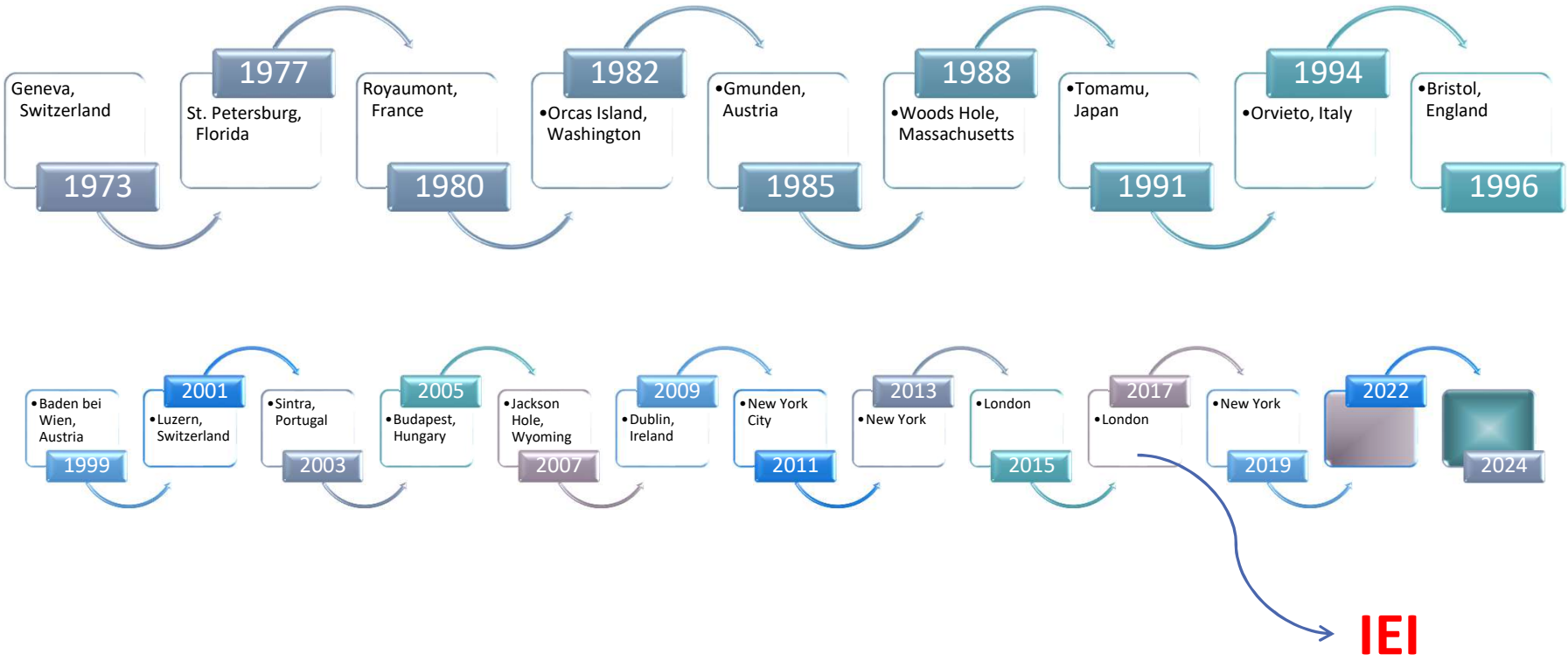
Type	Suggested Cellular Defect		
	B cells	T cells	Stem cells
Infantile X-linked agammaglobulinemia	+		
Selective immunoglobulin deficiency (IgA)	+*		
Transient hypogammaglobulinemia of infancy	+		
X-linked immunodeficiency with hyper-IgM	+*		
Thymic hypoplasia (pharyn. pouch syndrome, DiGeorge)		+	
Episodic lymphopenia with lymphocytotoxin		+	
Immunodeficiency with normal or hyperimmunoglobulinemia	+	+**	
Immunodeficiency with ataxia telangiectasia	+	+	
Immunodeficiency with thrombocytopenia and eczema (Wiskott–Aldrich)	+	+	
Immunodeficiency with thymoma	+	+	
Immunodeficiency with short-limbed dwarfism	+	+	
Immunodeficiency with generalized hematopoietic hypoplasia	+	+	+
Severe combined immunodeficiency			
(a) autosomal recessive	+	+	+
(b) X-linked	+	+	+
(c) sporadic	+	+	+
Variable immunodeficiency (largely unclassified)	+	+**	

*Involve some but not all B cells

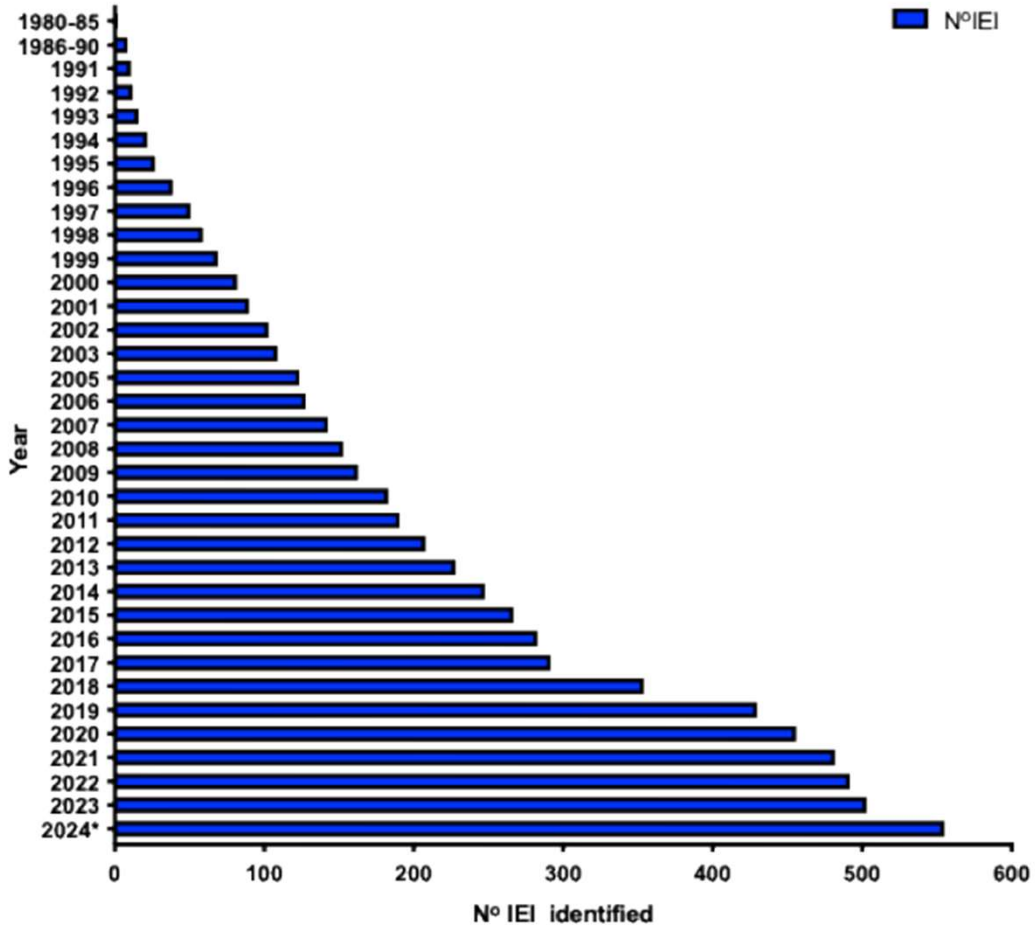
**Encountered in some but not all patients

Fudenberg HH, et al. N Engl J Med 1970;283:656-657

From WHO to IUIS, from PID to IEI



Accumulative discovery of novel inborn errors of immunity: 1980–2024



Poli MC, et al. J. Hum. Immun. 2025 Vol. 1 No. 1 e20250003

Types of IEI

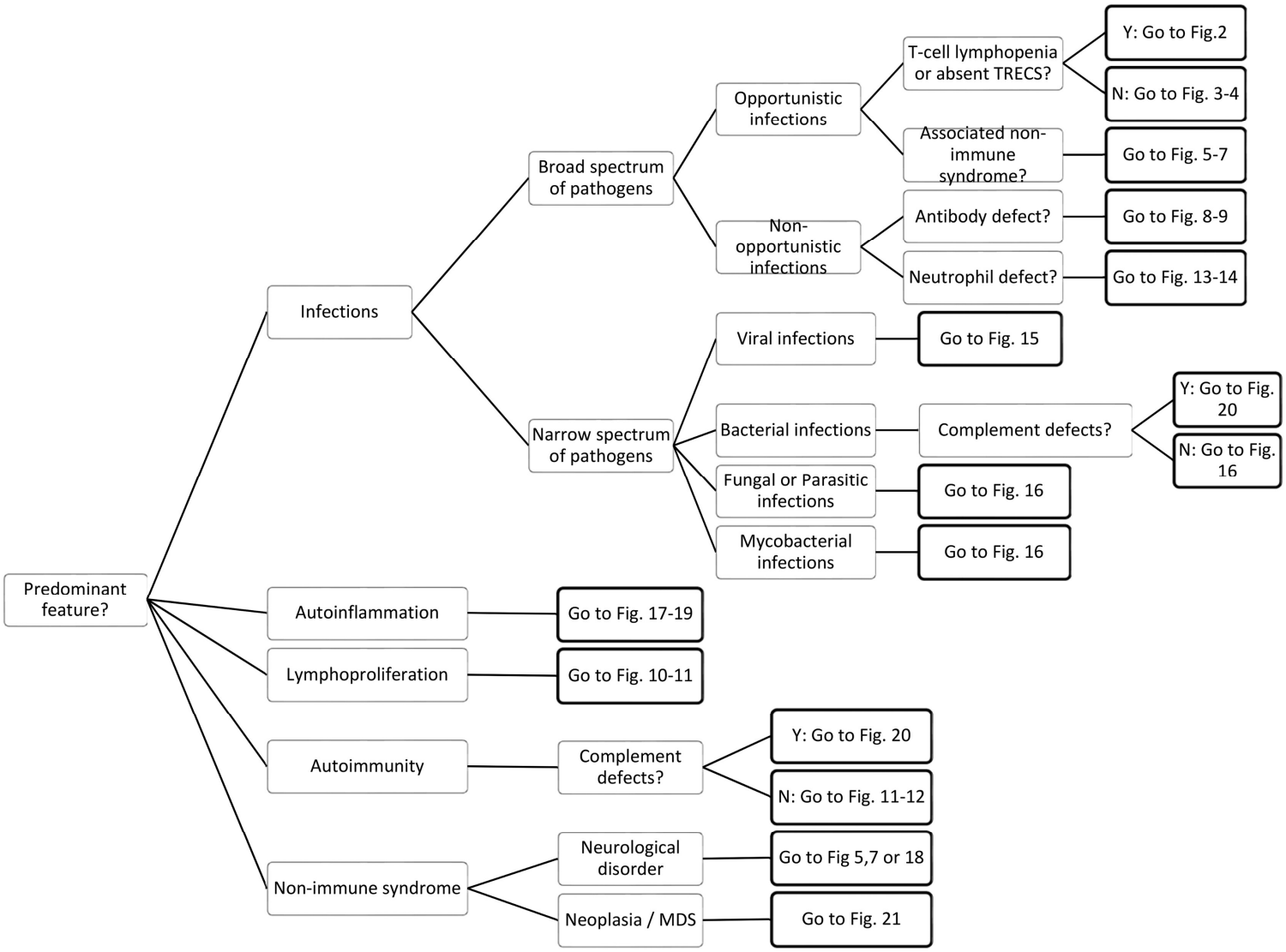
IUIS Classification 2024 – 10 tables **2003**

1. Immunodeficiencies affecting cellular and humoral immunity (3)*
2. Combined immunodeficiencies with associated or syndromic features (9)*
3. Predominantly antibody deficiencies (3)*
4. Diseases of immune dysregulation (7)*
5. Congenital defects of phagocyte number or function (4)*
6. Defects in intrinsic and innate immunity (9)*
7. Autoinflammatory disorders (3)*
8. Complement deficiencies
9. Bone marrow failure **2019**
10. Phenocopies of inborn errors of immunity **2015**

* number of sub-tables

https://iuis.org/committees/iei/

Decision tree orienting through phenotypic IEI classification categories



J Hum Immun. 2025;1(1). doi:10.70962/jhi.20250002

logists have emphasised that it may arise either in patients with active leprosy or, more commonly, in those who have had leprosy (Muir 1948, Browne 1965). Schulz (1965) found normal vitamin-A levels in the blood of leprosy patients with ichthyosiform changes in the skin.

In our patients hydration alone relieved the condition, but dry skin reappeared when daily hydration was discontinued. This suggests strongly that the important factor is the water content of the skin, and that loss of water from the surface of the skin should be prevented, after hydration, by means of a hydrophobic barrier. This suggestion is supported by the observation that dry skin occurs in those situations where there is an irreversible deficiency of endogenous hydration.

Blank (1952) found that human skin becomes brittle when its water content falls below 10 mg. per 100 mg. dry skin. It seems that as long as the relative humidity of the atmosphere is 60% or over, an equilibrium exists between air and skin, and excessive skin drying does not take place. Gaul and Underwood (1952) also found a direct association between air moisture and smoothness and suppleness of the skin. In the patients described by us the dryness of the tropical atmosphere was an important contributory factor in the occurrence of dry skin, in addition to the cutaneous anæsthesia and diminished sweating already referred to.

In leprosy patients, other advantages follow hydration

JOB'S SYNDROME

Recurrent, "Cold", Staphylococcal Abscesses

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INSTRUCTOR

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"So went Satan forth from the presence of the Lord, and smote Job with sore boils from the sole of his foot unto his crown".—*Job*, II, 7.

WE have examined two girls who have had recurrent, "cold", staphylococcal abscesses since birth. The staphylococci do not seem to be unusually virulent, and neither child has diabetes or any other condition known to predispose to infection. Since we are not aware that any similar cases have been described previously, we report these cases in detail.

Case-reports

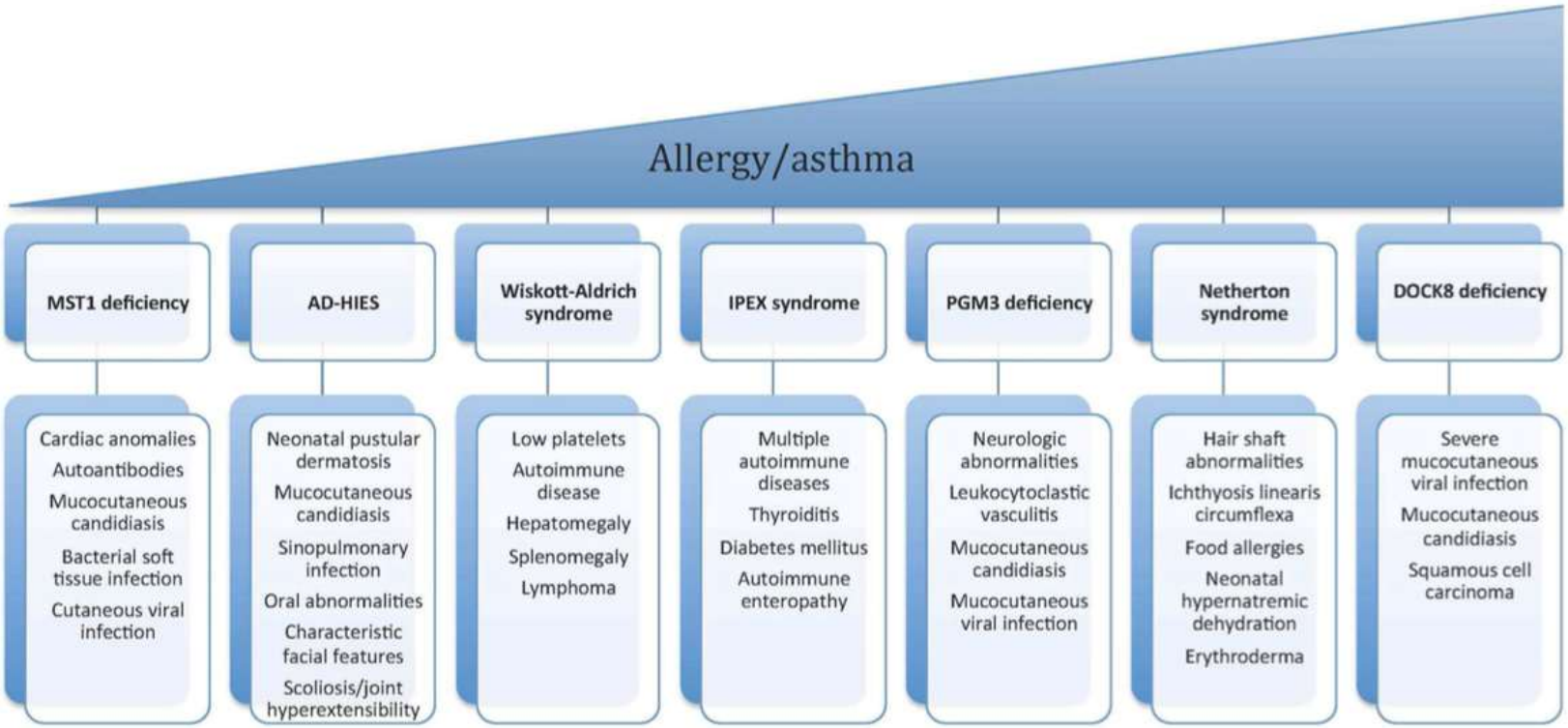
FIRST CASE

The patient is a nine-year-old girl who was originally referred, aged seven, to the University of Washington Hospital. She was normal at birth but at three weeks she had eczema which became infected. She later had recurrent ear, nose, and sinus infections which were treated many times with antibiotics. At three years a tonsillectomy was done because of chronic

6 decades of observation

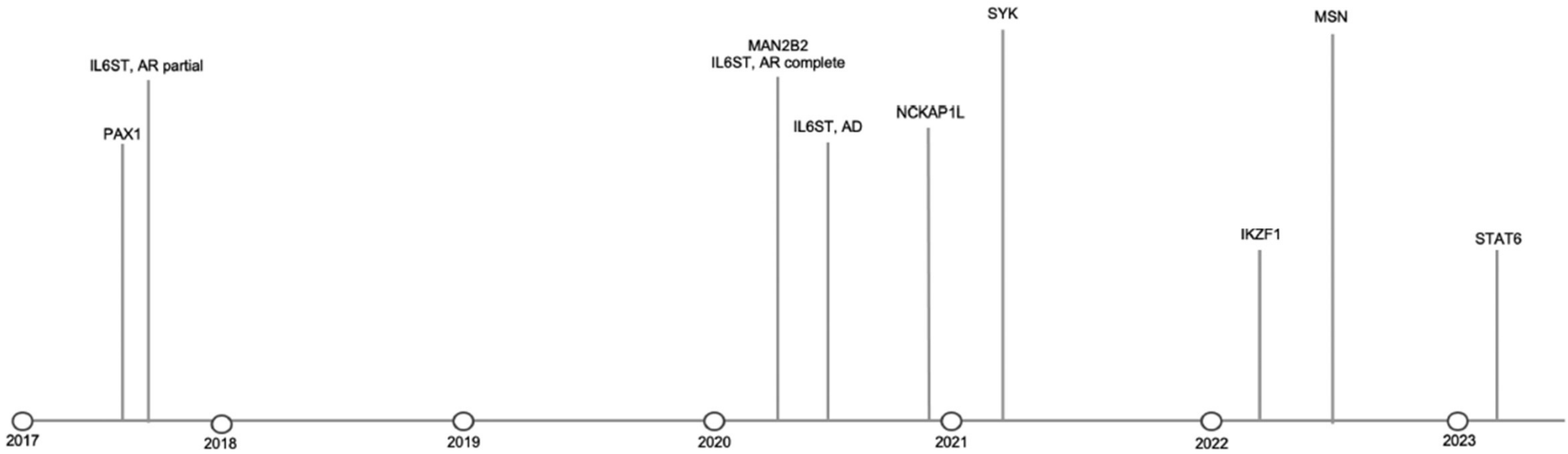
- 1966: Job Syndrome described
- 1972: Syndrome further characterised - elevated IgE, chronic eczema
- 1980: AD-inheritance
- 2004: AR-inheritance
- 2006: Homozygous TYK2 mutation
- 2007: Heterozygous STAT3 mutations in AD-HIES affecting the DNA binding and SH2 domains
- 2009: AR-HIES due to DOCK8 mutation
- *2010 and later: Updates from the last 2 decades*

Syndromes associated with eczematous dermatitis



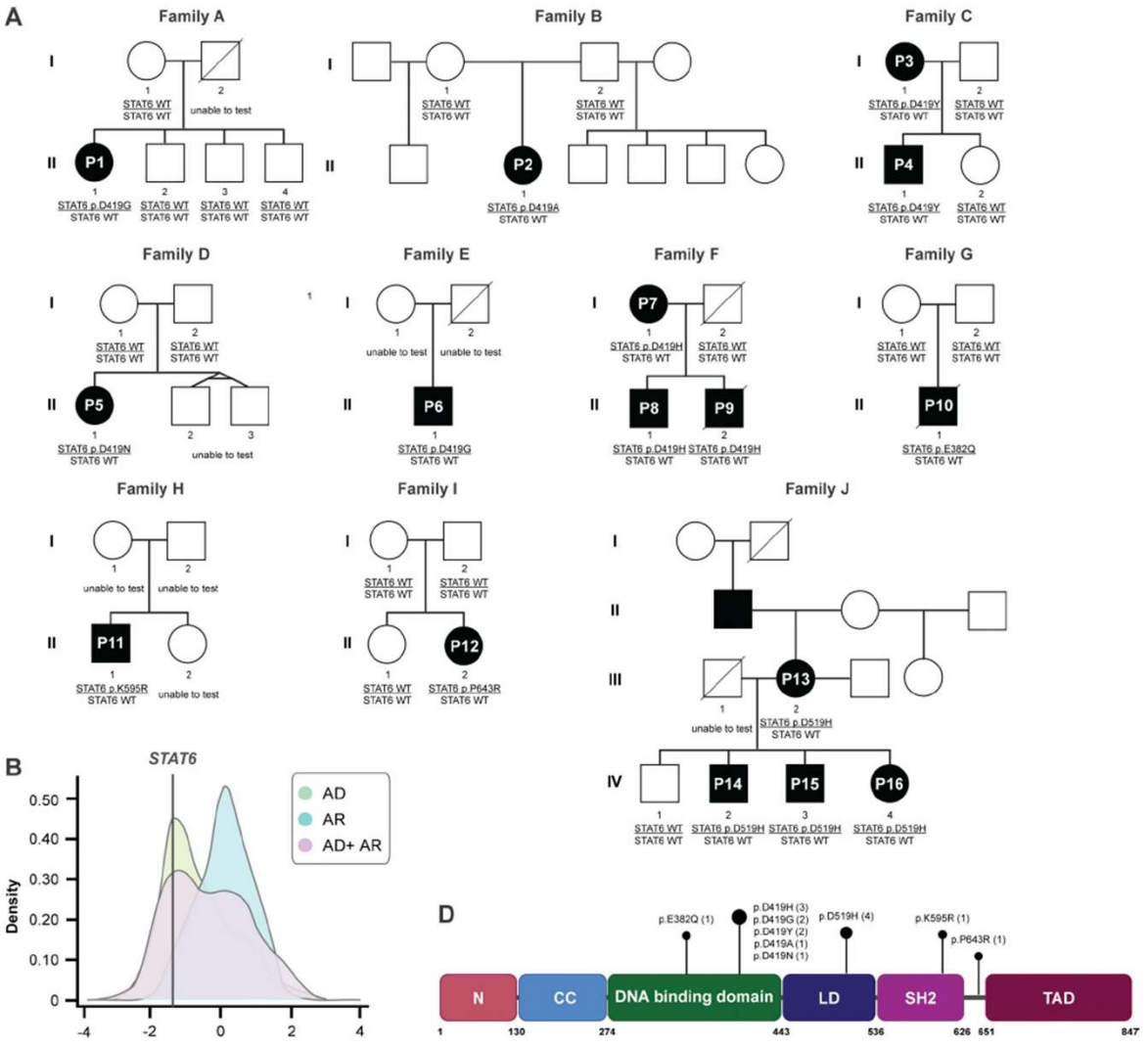
Pichard DC, et al. J Am Acad Dermatol. 2015; 73: 355-364

Updated timeline of genes discovered responsible for IEI associated with atopy



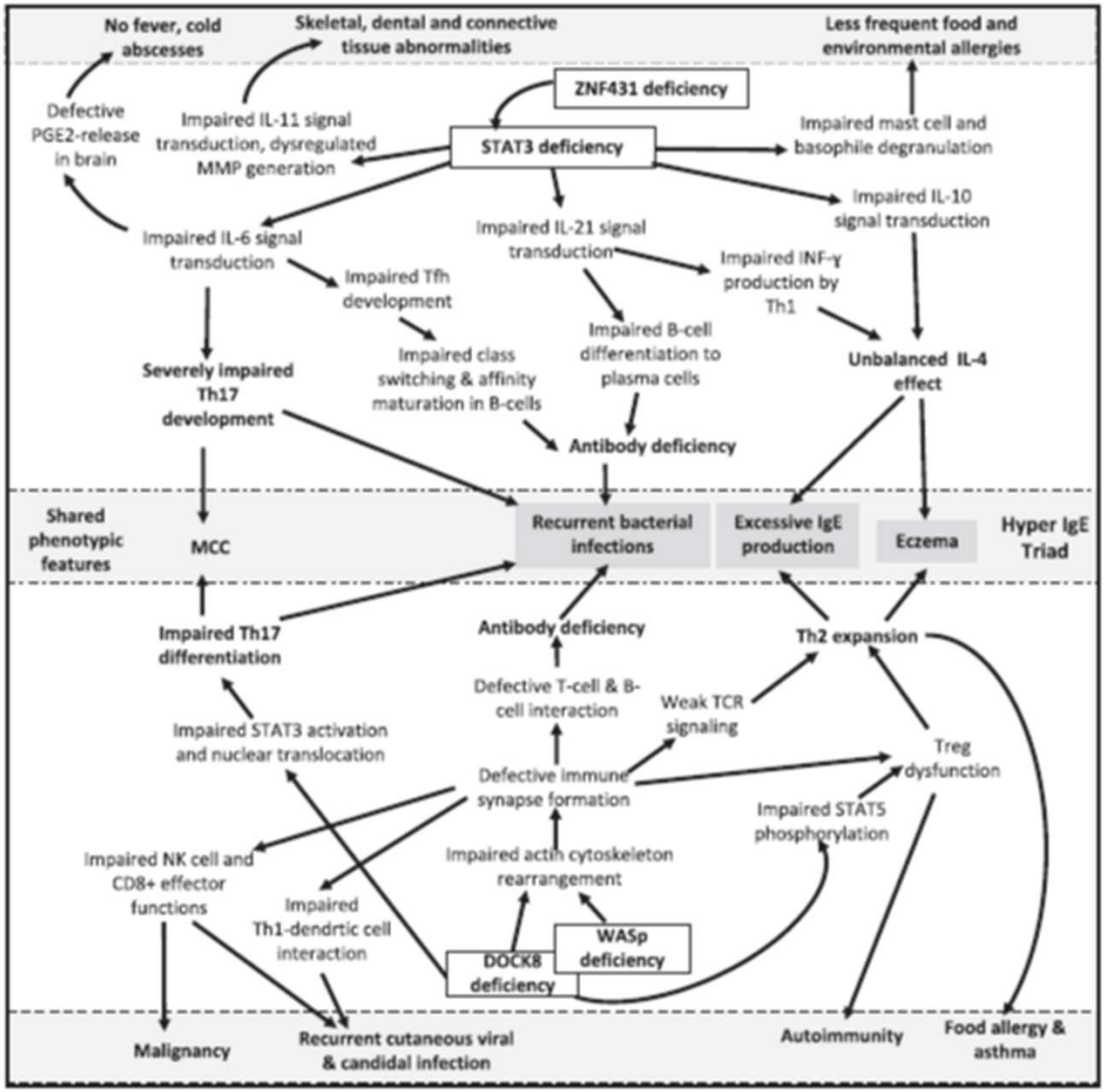
Sams L et al. Curr Opn iAllergy Clin Immunol 2023, 23:478–490

16 patients with severe allergic disease and STAT6 variants in different protein domains



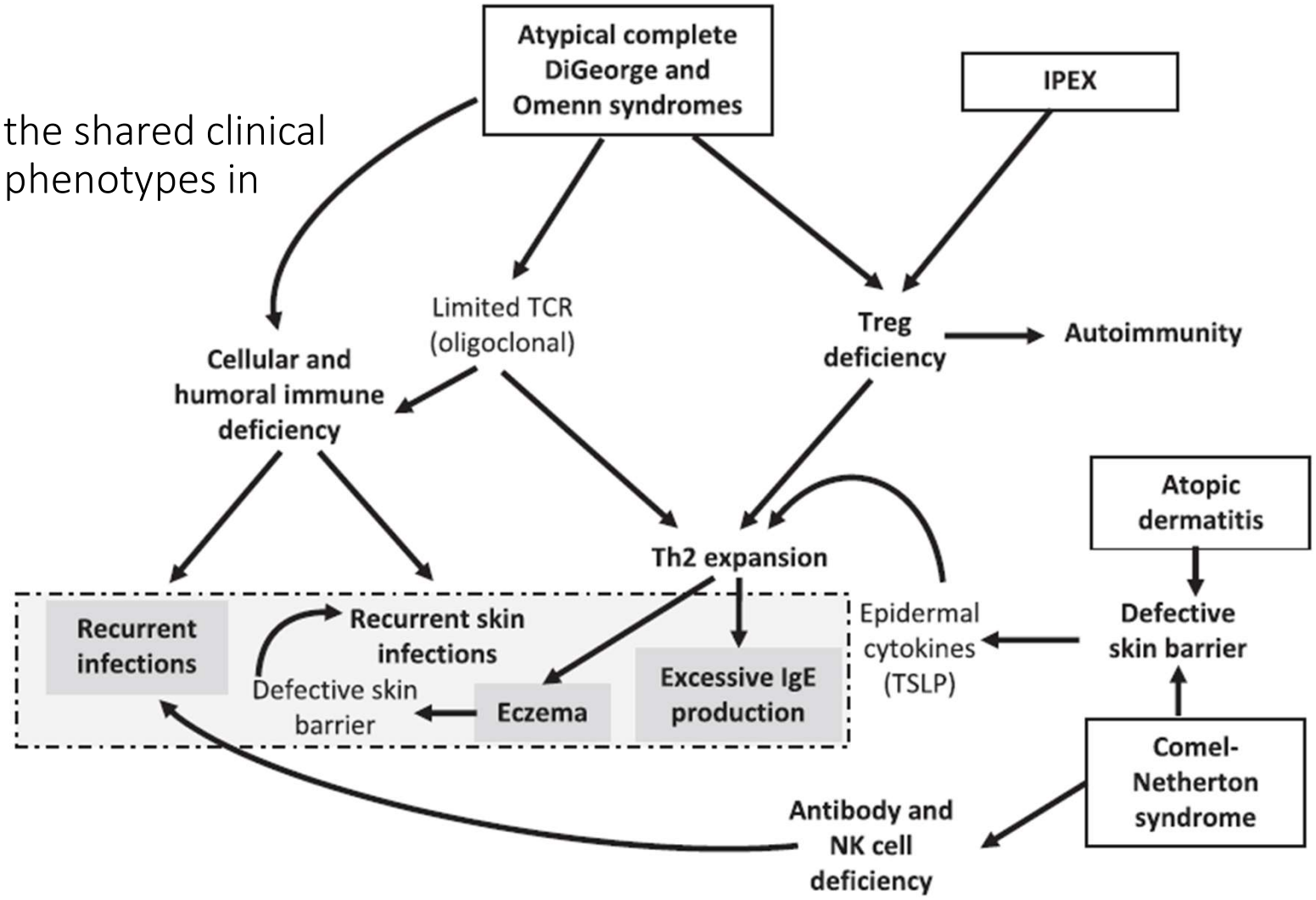
Sharma M, et al. J. Exp. Med. 2023 Vol. 220 No. 5

Molecular basis for the shared clinical and immunological phenotypes in HIES - 1



Al-Shaikhly T, Ochs HD. Immunol Cell Biol 2019; 97: 368–379

Molecular basis for the shared clinical and immunological phenotypes in HIES - 2



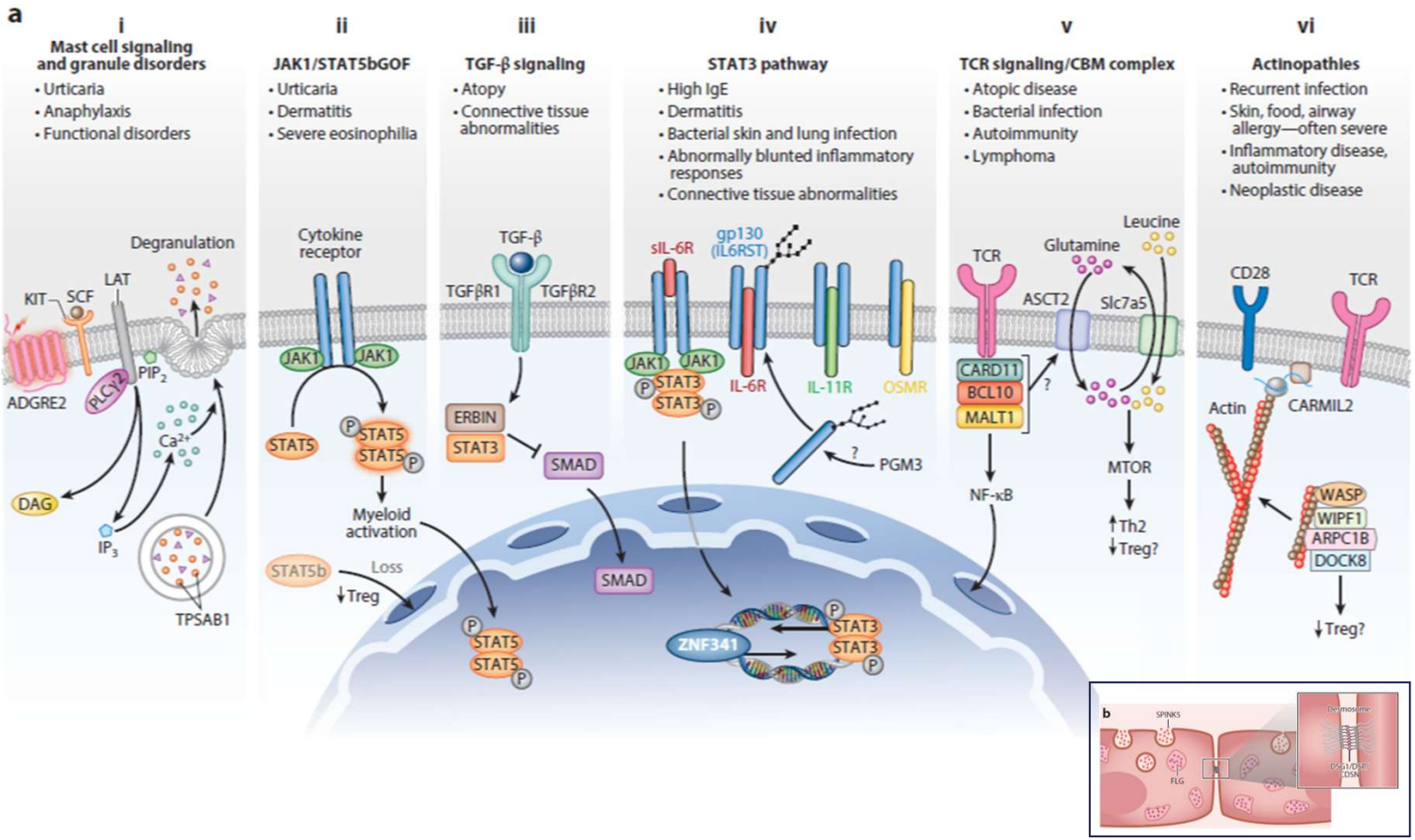
Al-Shaikhly T, Ochs HD. Immunol Cell Biol 2019; 97: 368–379

Genetic mutations associated with primary atopic disorders

Altered process	Genes
Impaired TCR signaling and cytoskeletal remodeling	*ZAP70, CARD11, MALT1, WAS, WIPF1, ARPC1B, DOCK8, CARMIL2*
Altered cytokine signaling	*STAT3^{DN}, STAT1^{GOF}, STAT5B^{LOF}, STAT5B^{GOF}, JAK1^{GOF}, IL4RA^{GOF}, TGFBR1, TGFBR2, ERBB2IP*
T cell repertoire restriction	*RAG1, RAG2, DCLRE1C, ADA, IL2RG, IL7RA, CHD7, LIG4, ZAP70,* 22q11del
Tolerance failure	*FOXP3, IL2RA, STAT5B^{LOF}, TGFBR1, TGF BR2, WAS, CARD11, STAT1^{GOF}*
Metabolic disturbance	*PGM3, CARD11, MALT1*
Skin barrier disruption	*FLG, CDSN, DSG1, DSP, SPINK5*
Mast cell deregulation	*KIT, PLCG2, ADGRE2, TPSAB1*

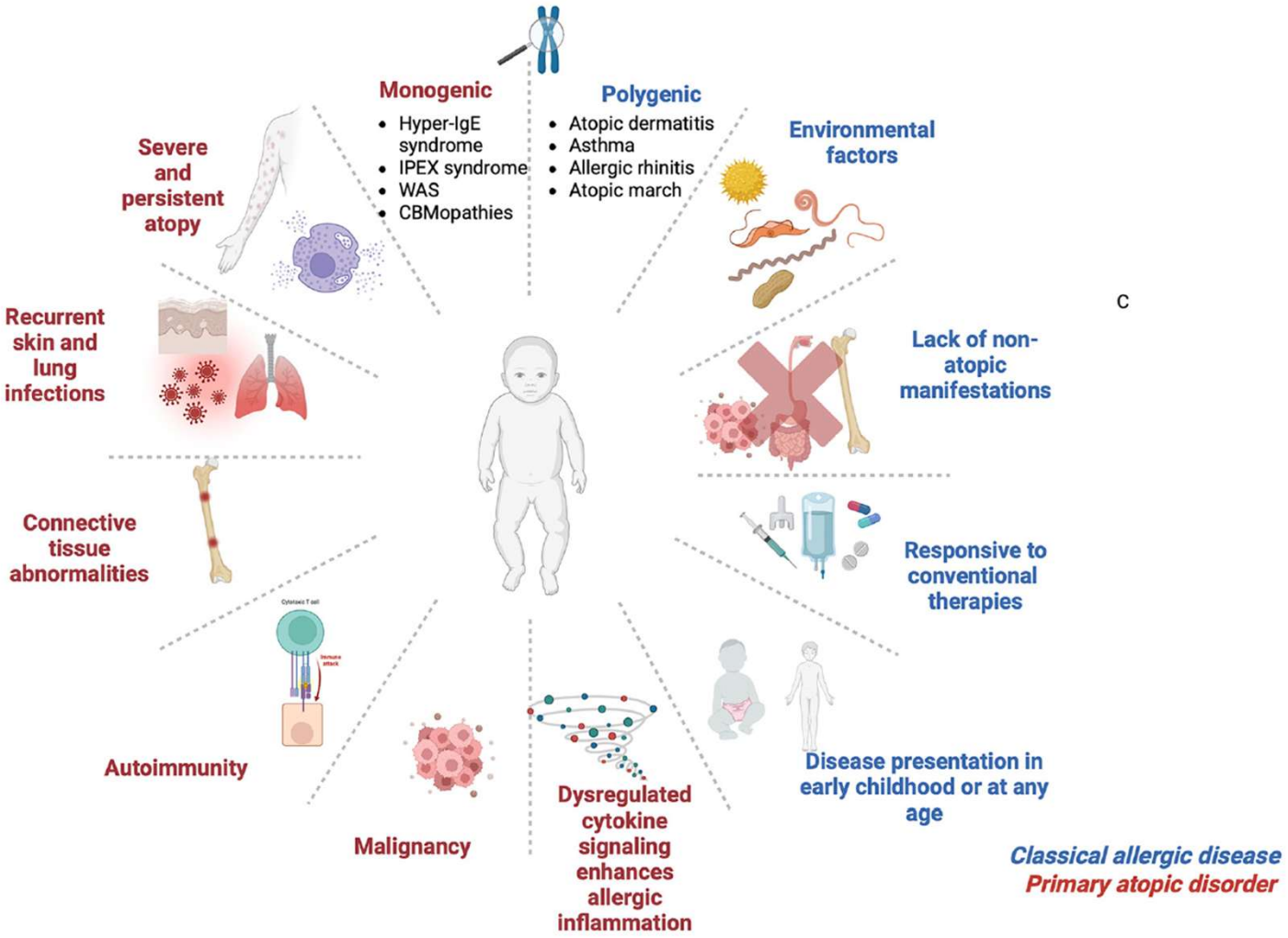
Lyons JJ, Milner JD. J. Exp. Med. 2018 Vol. 215 No. 4 1009–1022

Schematic representation of pathways leading to primary atopic disorders



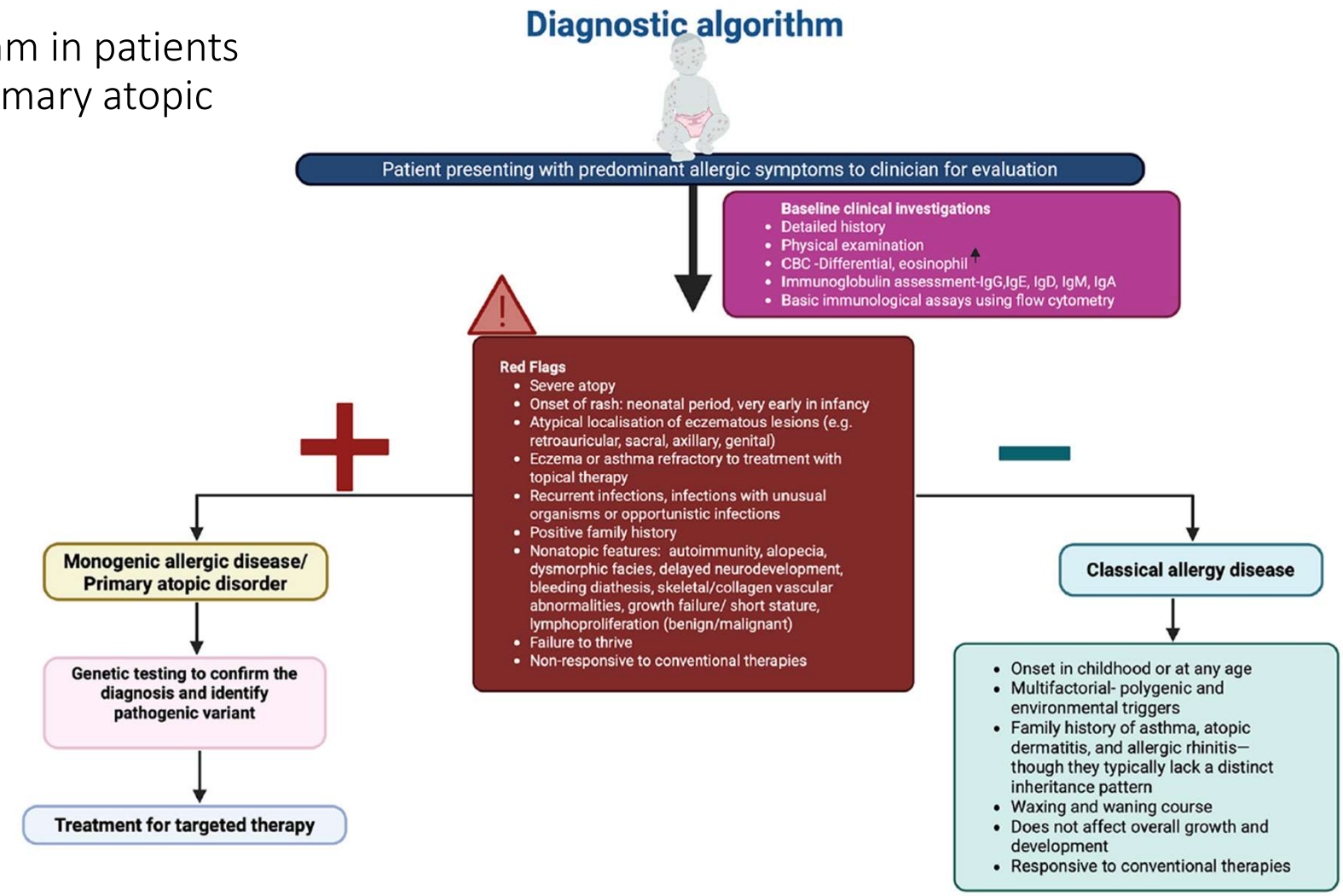
Milner JD. Annu Rev Immunol 2020; 38: 785–808

Clinical characteristics for classical allergic disease and primary atopic disorder



Thakur V, et al. Front. Allergy 6:1617714

Diagnostic algorithm in patients with suspected primary atopic disorder



Thakur V, et al. Front. Allergy 6:1617714