Approach to an adult with recurrent infections

Dr Elaine Au

Disclosure

- No disclosure related to this presentation

Warning signs

Table 1 European Society for Immunodeficiency (ESID) and the Jeffrey Modell Foundation (JMF) warning signs for primary immunodeficiency in adults

The 6 ESID warning signs (≥ 1 criterion)	The Jeffrey Model Foundation warning signs (≥ 2 criteria)
1. Four or more infections requiring antibiotics within one year (otitis, bronchitis, sinusitis, pneumonia)	1. Two or more new ear infections within one year
2. Recurring infections or infections requiring prolonged antibiotic therapy	2. Two or more new sinus infections within one year, in the absence of allergy
3. Two or more severe bacterial infections (osteomyelitis, meningitis, septicemia, cellulitis)	3. One pneumonia per year for > 1 year
4. Two or more radiologically proven pneumonia within 3 years	4. Chronic diarrhea with weight loss
5. Infection with unusual localization or unusual pathogen	5. Recurrent viral infections (colds, herpes, warts, condyloma)
6. A family history of primary immunodeficiency	6. Recurrent need for intravenous antibiotics to clear infections
	7. Recurrent, deep abscesses of the skin or internal organs
	8. Persistent thrush or fungal infection on skin or elsewhere
	9. Infection with normally harmless tuberculosis-like bacteria
	10. A family history of primary immunodeficiency

Red Flags

- Aspects of Infections:
  - Unusual frequency
  - Unusual severity : complicated, in multiple locations
  - Unusual duration
  - Unusual complications
  - Refractory to standard treatment, ie, require multiple courses of oral antibiotics or any need for IV antibiotics to resolve
  - Unusual organisms
- Noninfectious Clues
  - Chronic diarrhea or malabsorption
  - Autoimmunity, especially if more than one (eg, hypothyroidism and alopecia or vitiligo)
  - Hematologic disorders (hemolytic anemia, neutropenia, thrombocytopenia)
  - “Failure to thrive”
  - Lymphoproliferative conditions
- Family History

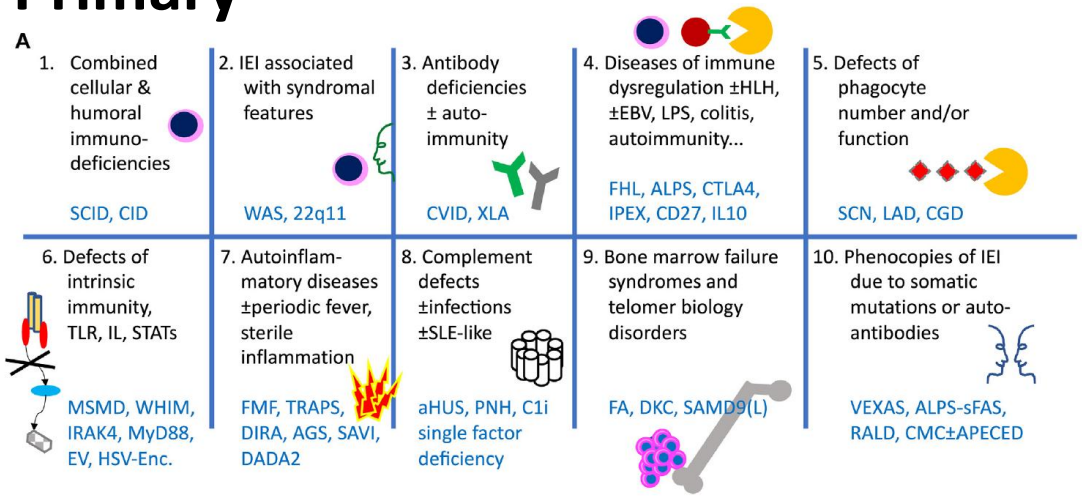
S- Severe: can the presenting complaint/recurring infection be life-threatening if untreated?

P- Persistent: does not respond appropriately to conventional treatment?

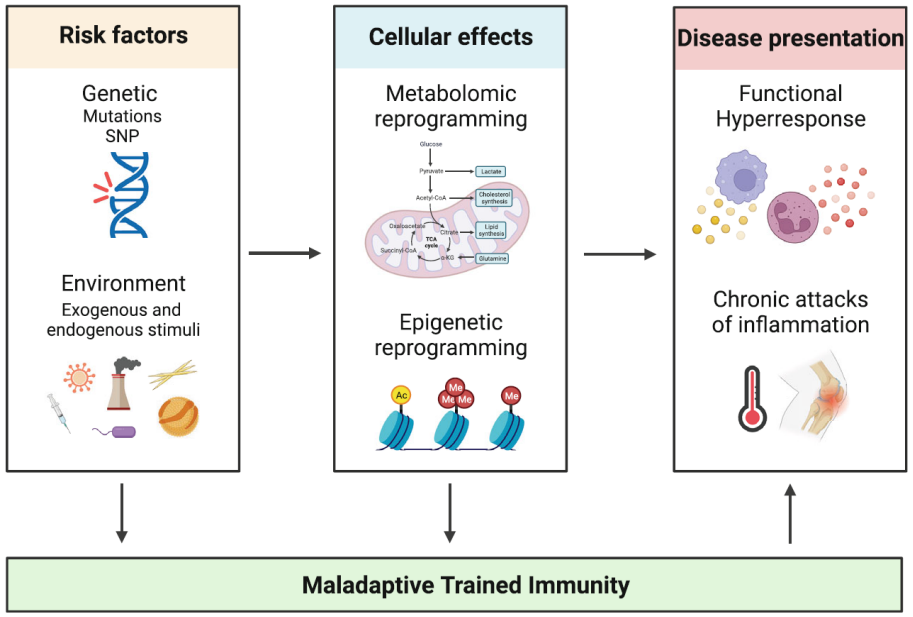
U- Unusual: is the site of infection and type of microbe unusual? E.g. deep tissue infection, opportunistic microbe

R- Recurrent: does the patient have more frequent infections than the average for a person without any immunocompromised features?

Primary



J ALLERGY CLIN IMMUNOL VOLUME 153, NUMBER 6



The FEBS Journal 291 (2024) 4414–4432

Secondary

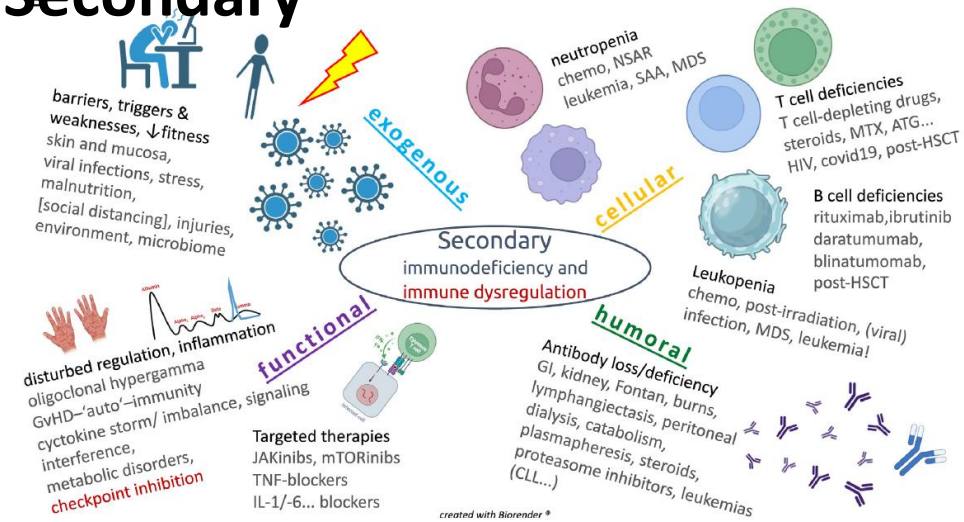
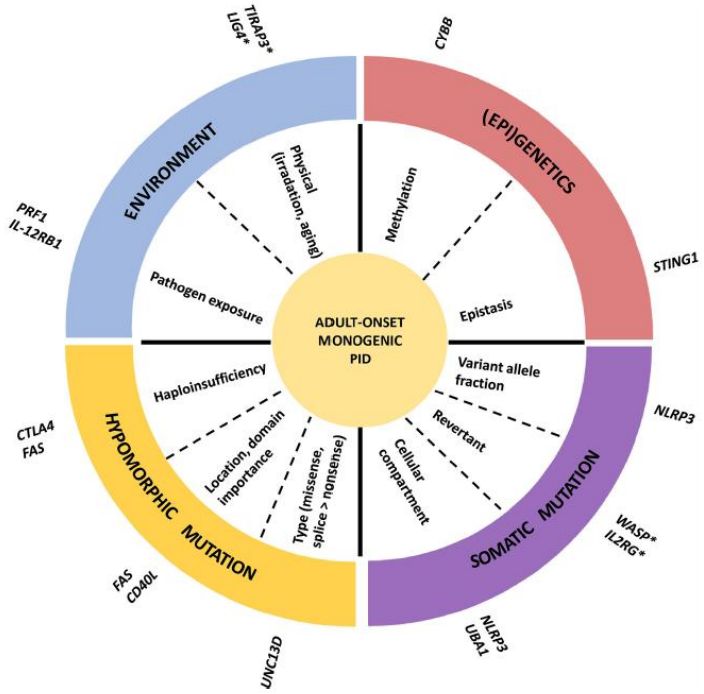


FIG 1. Examples of PIDs and SIDs, respectively. **A**, PID_{new} modified from the 2022 IUIS classification of IEIs. **B**, Spectrum of SID_{new}.



Front. Immunol. 12:753978.

secondary causes & Infection risk stratification

Secondary Causes:

- Iatrogenic: Corticosteroids, immunosuppressants (methotrexate, rituximab), splenectomy
- Malignancy: Hematologic (myeloma, lymphoma), thymoma (Good's syndrome)
- Infections: HIV (CD4 lymphopenia), chronic viral (CMV, EBV)
- Metabolic/Nutritional: Diabetes (phagocyte dysfunction), malnutrition, nephrotic syndrome (protein loss)
- Other: Cirrhosis, uremia, aging

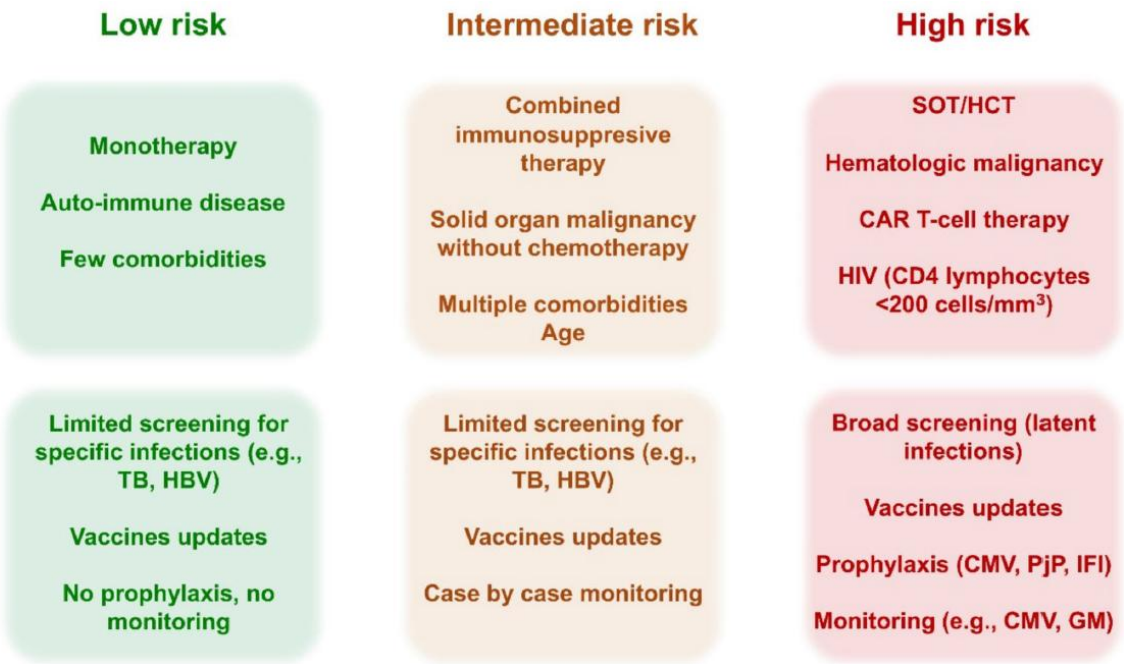
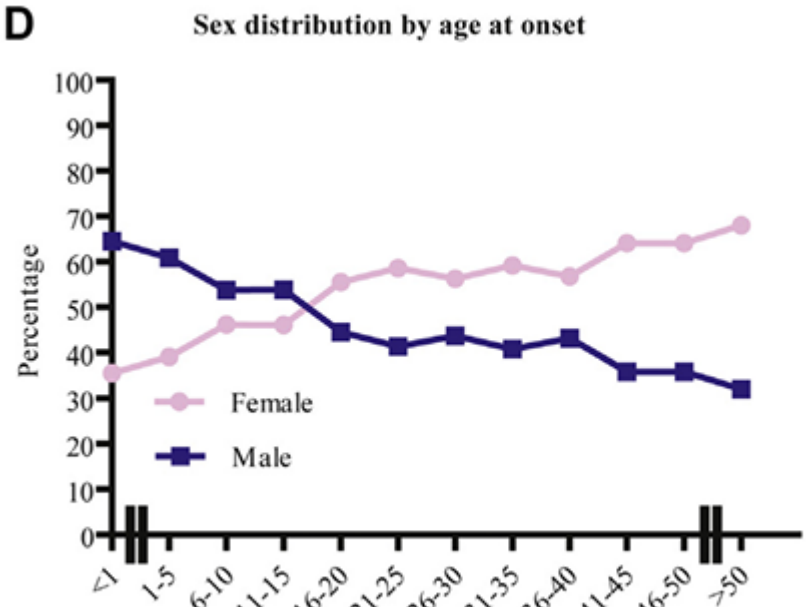


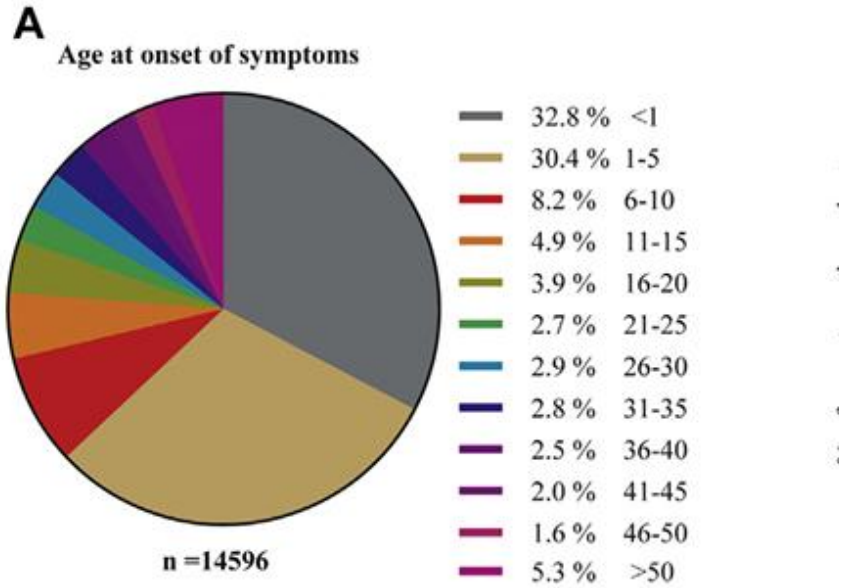
Table 2 Most common medications causing secondary immune deficiency

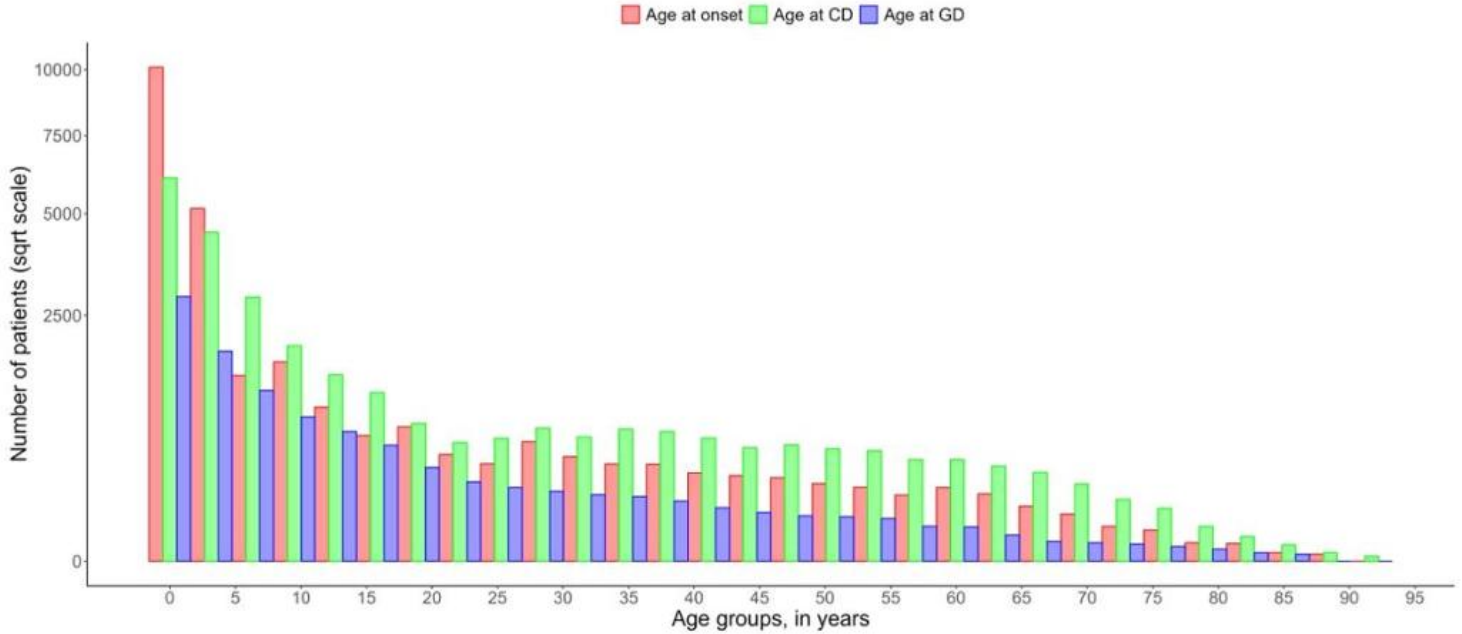
Medication family	Examples
B cell targeting monoclonal antibodies [21]	Rituximab, daratumumab, belimumab
Immunosuppressants and cytotoxic agents [22–24]	Prednisone and derivates, methotrexate, cyclophosphamide, mycophenolate mofetil, cyclosporin, calcineurin inhibitors, purine analogs
Tumor necrosis factor alpha inhibitors [25]	Infliximab, etanercept
Tyrosine kinase inhibitors [26]	Ruxolitinib, tofacitinib, baricitinib
Others [27–30]	Anticonvulsivants: carbamazepine, phenytoin, lamotrigine Antipsychotics: clozapine Antimalarials: chloroquine and hydroxychloroquine

Clinical Reviews in Allergy & Immunology (2025) 68:92

IEI: Age of onset





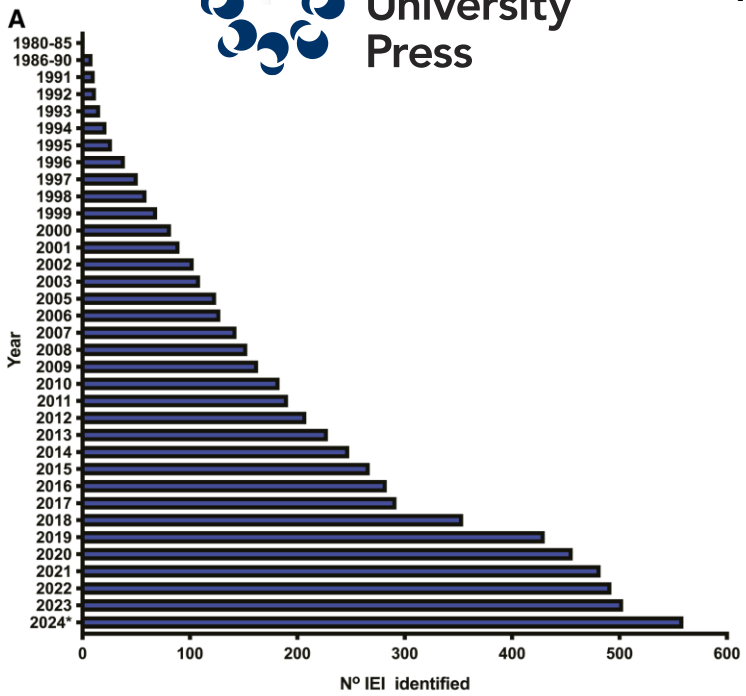


J Allergy Clin Immunol 2021;148:1332-41

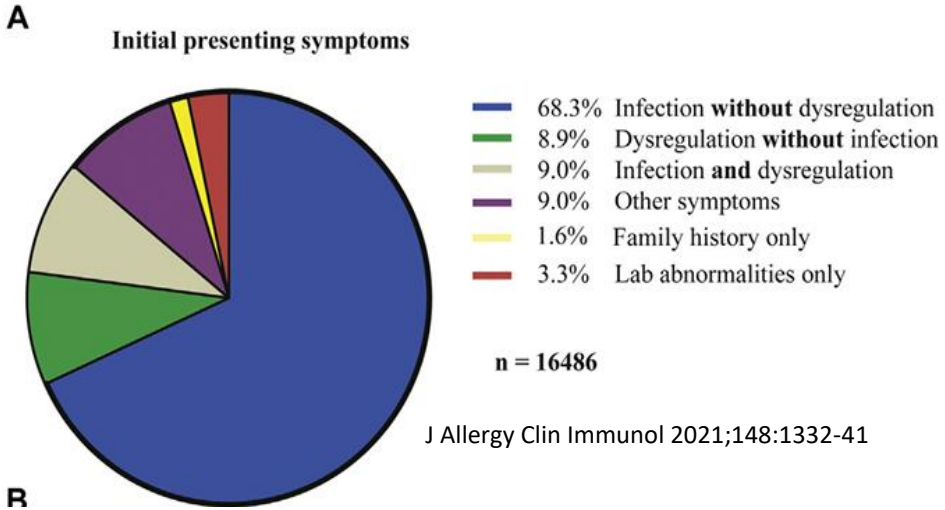
J Hum Immun. 2025 Sep;1(3):e20250007

Rockefeller University Press

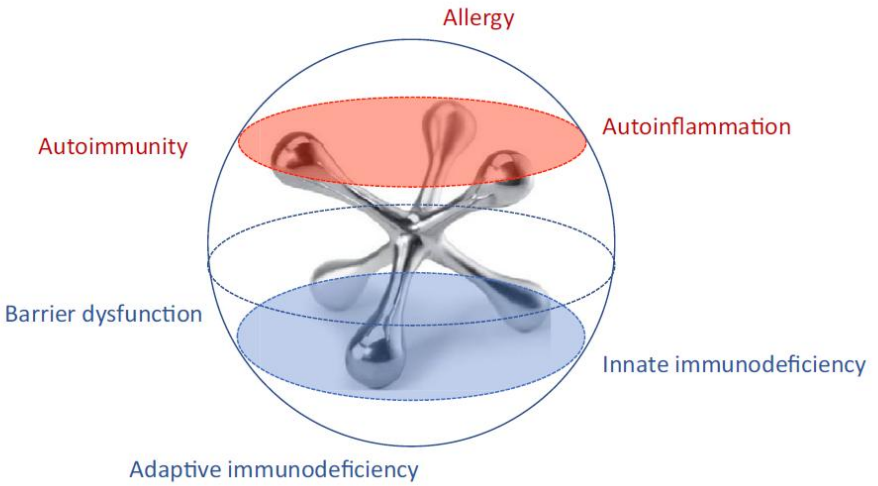
Human inborn errors of immunity: 2024 update on the classification from the International Union of Immunological Societies Expert Committee



- Combined immunodeficiencies
- Combined immunodeficiencies with syndromic features
- Predominantly antibody deficiencies
- Diseases of immune dysregulation
- Congenital defects of phagocytes
- Defects in intrinsic and innate immunity
- Autoinflammatory diseases
- Complement deficiencies
- Bone marrow failure
- Phenocopies of inborn errors of immunity



J Allergy Clin Immunol 2021;148:1332-41



J Allergy Clin Immunol 2020;146:960-6.

J Hum Immun. 2025;1(1). doi:10.70962/jhi.20250003
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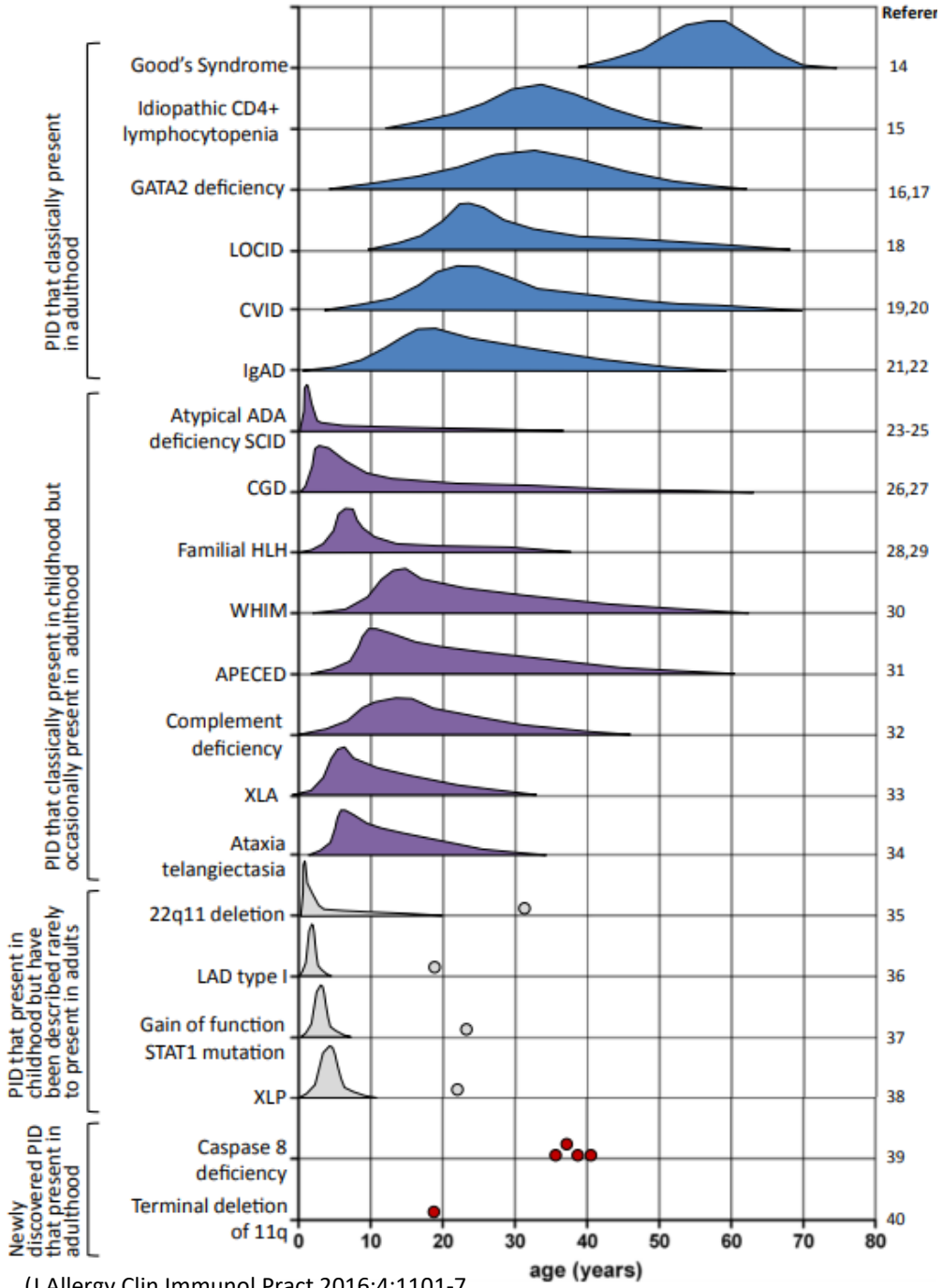


(J Allergy Clin Immunol Pract 2016;4:1101-7

TABLE IV. Age at initial presentation for selected immunodeficiencies

Immunodeficiency	Total patients	<1 y	Age 1-5 y	Age range (y) at which >70% had symptoms	Age range (y) at which >90% had symptoms
All IEI	14,677	33	30	6-10	36-40
SCID	833	87	12	<1	1-5
APDS	122	36	53	1-5	6-10
WAS	254	82	15	<1	1-5
AT	631	12	78	1-5	1-5
DGS	579	81	15	<1	1-5
HIES	333	50	32	1-5	11-15
CVID	3,663	6	18	31-35	> 50
ALPS	195	25	43	6-10	11-15
FHL	169	68	17	1-5	6-10
CGD	844	45	39	1-5	6-10

Table of age at onset of presenting manifestations for specific IEI. Presentations within the first year of life and at age 1-5 y are shown in percent. The age range at which 70% and 90% of patients had their initial presenting manifestations is shown in the right columns. SCID includes SCID, atypical/leaky SCID, and Omenn syndrome. HIES contains STAT3-associated HIES only. See Table I for disease abbreviations.

J Allergy Clin Immunol 2021;148:1332-41.

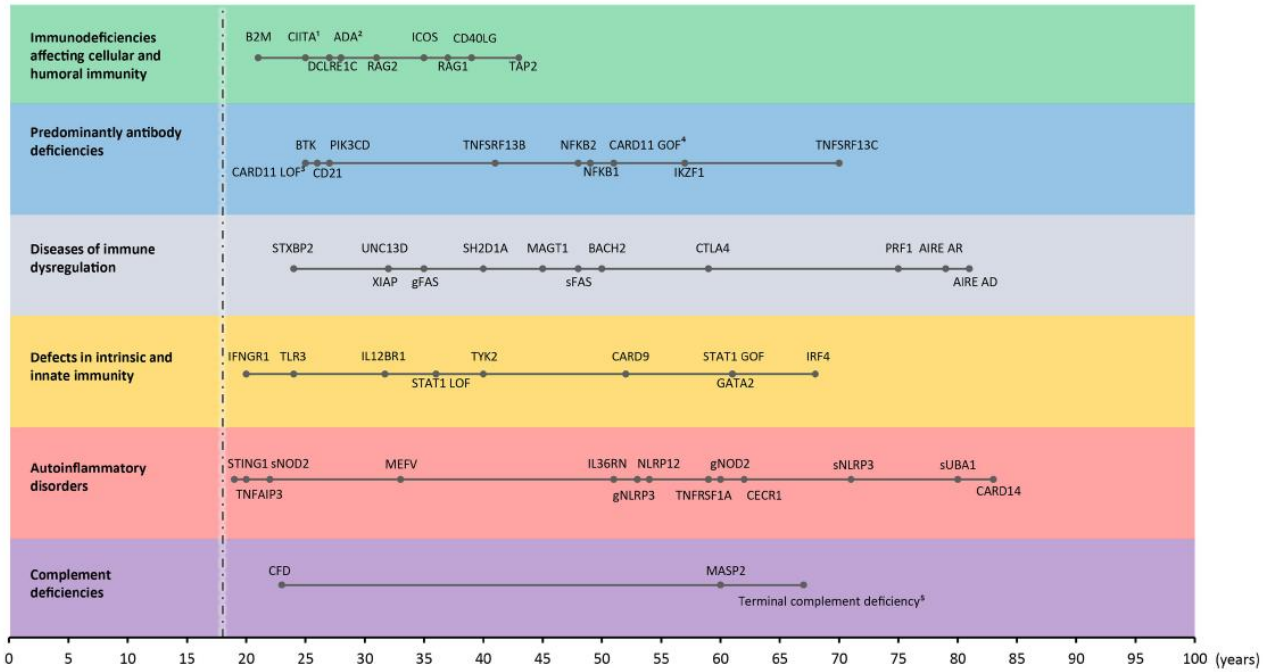


FIGURE 3 | Time of onset in adult IEI. Adult-onset IEI genes with oldest age-of-onset patient reported for every gene (from all reviewed manuscripts) in each category. s: somatic. g: germline. [1]onset between 20-30 years, [2]immunological abnormalities, [3]onset in mid-twenties, [4]asymptomatic, 51 years old, [5]genetic defect in C5/6/7/8 or 9, mean age of oldest presentations. Dashed line indicates threshold for adult-onset (18-years-old).

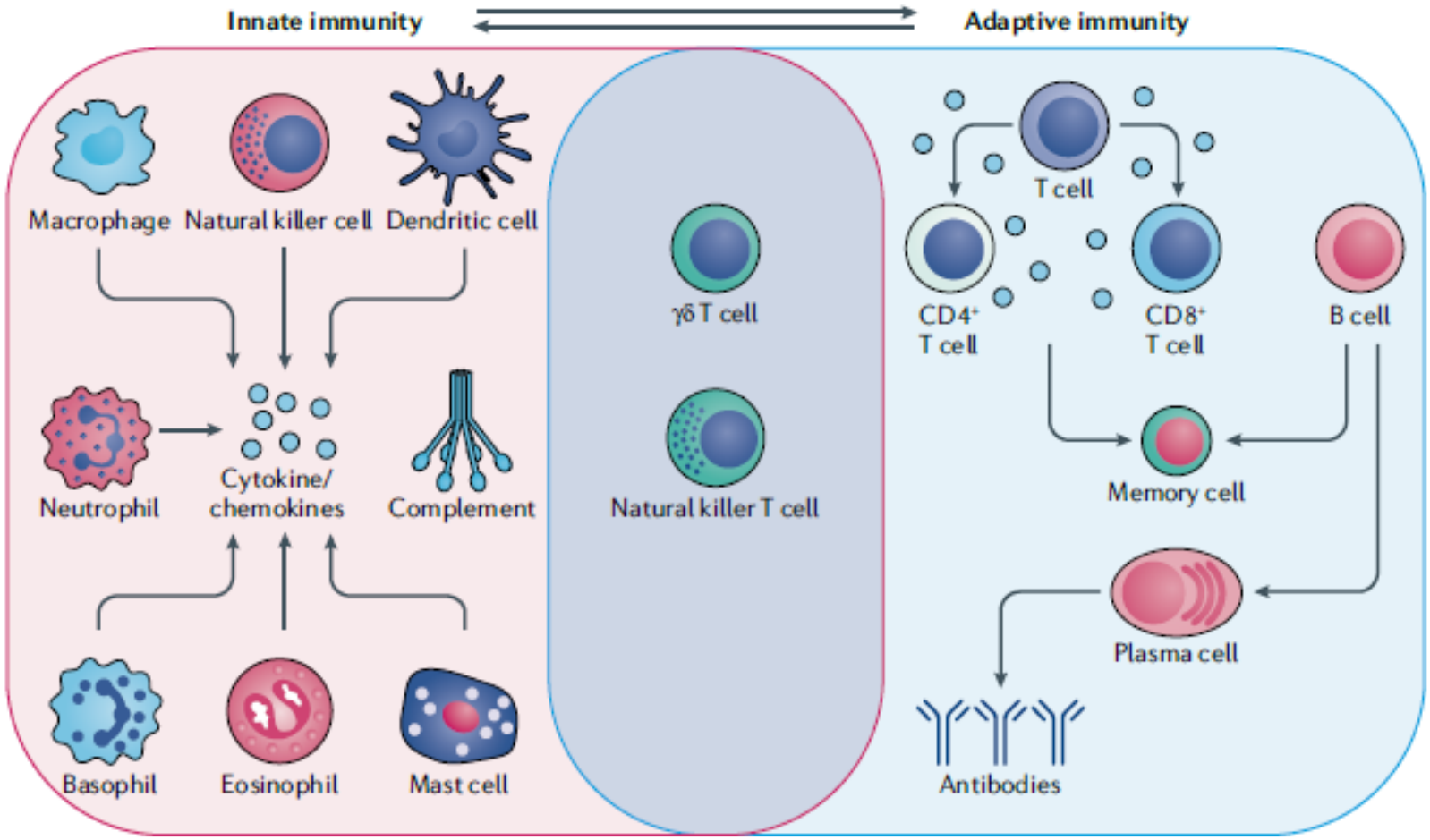
Front. Immunol. 12:753978.

History

- Details of the infective episodes (SPUR)
  - Sites/ microbes involved
  - Frequency
  - Clinical course/ response to treatment
- Age of onset
- Non-infective conditions
  - Autoimmunity
  - Atopy
  - Lymphoproliferative conditions
- Vaccination History
- Family History
- Potential secondary causes /Medication history/ underlying medical conditions

Initial Laboratory Evaluation

- CBC with differential (lymphopenia? neutropenia? eosinophilia?)
- Comprehensive metabolic panel (albumin, renal/liver function)
- HIV test
- Immunoglobulins: IgG, IgA, IgM, Ig E
- (+/- IgG subclasses in some cases)
- Serum/urine protein electrophoresis (SPEP) / immunofixation
- CRP / ESR



Immunodeficiency vs immunodysregulation

Nature Reviews Rheumatology volume 17, pages585–595 (2021)

Affected immunity arm	Typical site of infection	Common pathogens
T cells	Sepsis, lung, GI tract, skin	Viruses: CMV, adenovirus, measles, molluscum Fungi: *Candida, Aspergillus, Pneumocystis jirovecii* Protozoa: Cryptosporidium
NK cells	Skin, lung, GI tract, disseminated infections	Viruses: EBV, CMV, VZV, HSV, HPV
Phagocytes	Skin infections, lymphadenitis, liver, lung, bone, GI tract, gingivitis/periodontitis	Bacteria: Staphylococci, *Serratia marcescens, Burkholderia cepacia, Klebsiella, E. coli, Salmonella, Proteus* Fungi: *Candida, Aspergillus, Nocardia*
Complement	Systemic infections, meningitis	Pyogenic bacteria: Streptococci, *Haemophilus influenzae, Neisseria*
B cells/ antibody	Sinopulmonary tract, GI tract, joints, CNS	Pyogenic bacteria: Streptococci, staphylococci, *Haemophilus influenzae* Enteroviruses: ECHO, polio Mycoplasma

Stiehm's Immune Deficiencies: Inborn Errors in Immunity

Pattern of Infection	Most Likely Immune Defect Category	Classic Examples
Recurrent bacterial sinopulmonary	Humoral (antibody) deficiency	CVID, specific Ab deficiency
Recurrent / invasive herpesviruses, opportunists	T-cell / combined defect	Late HIV, idiopathic CD4 lymphopenia
Recurrent staphylococcal abscesses / granulomas	Phagocytic defect	Chronic granulomatous disease (rare in adults)
Recurrent meningococcal / disseminated Neisseria	Complement deficiency	C5–C9 deficiency
Recurrent fungal / mycobacterial	IFN-γ / IL-12 pathway	Adult-onset immunodeficiency (autoAbs)

	Initial Test	Further Investigations
Humoral immunity deficiency	IgG, IgM, IgA, and IgE levels	B-cell phenotyping
	Isohemagglutinin titers	Flow assessment of protein components
	Antibody response to vaccine antigens (eg, Haemophilus influenzae type b, tetanus, diphtheria, conjugated and nonconjugated pneumococcal, and meningococcal antigens)	Molecular diagnostics: single gene/ Gene Panel/WES/ WGS
	Lymphocyte subset	
Cellular immunity deficiency	Absolute lymphocyte count	T-cell phenotyping
	Delayed hypersensitivity skin tests (eg, using Candida)	T-cell proliferative response to mitogens/ Antigens
	HIV testing	Cytokine production assessment
	TRECS	T cell repertoires study
		Molecular diagnostics: single gene/ Gene Panel/WES/ WGS
Phagocytic cell defects	Phagocytic cell count and morphology	Flow cytometry for CD18 and CD15
	Flow cytometric oxidative burst measurement using dihydrorhodamine 123 (DHR) or nitroblue tetrazolium (NBT)	Neutrophil chemotaxis, phagocytosis , killing
		Molecular diagnostics: single gene/ Gene Panel/WES/ WGS
Complement deficiency	C3 level	Specific component / activation products assays
	C4 level	Molecular diagnostics: single gene/ Gene Panel/WES/ WGS
	CH50 activity (for total activity of the classical pathway) and AH50 activity (for total activity of the alternate complement pathways)	

Approach of Workup for IEI

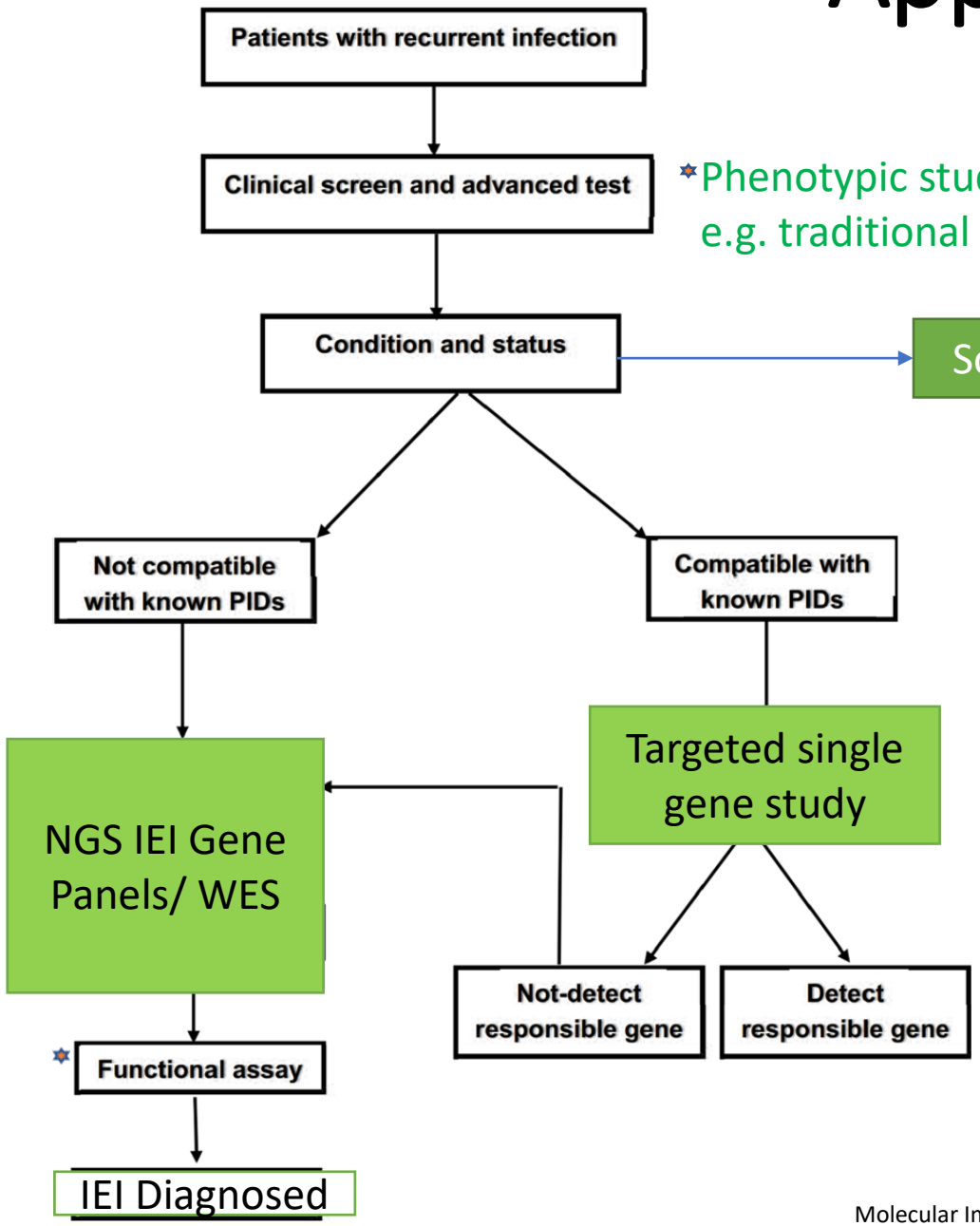


Fig. 1. A schematic view of proposed stepwise approach to the diagnosis of IEI gene mutations.

Molecular Immunology 137 (2021) 57–66

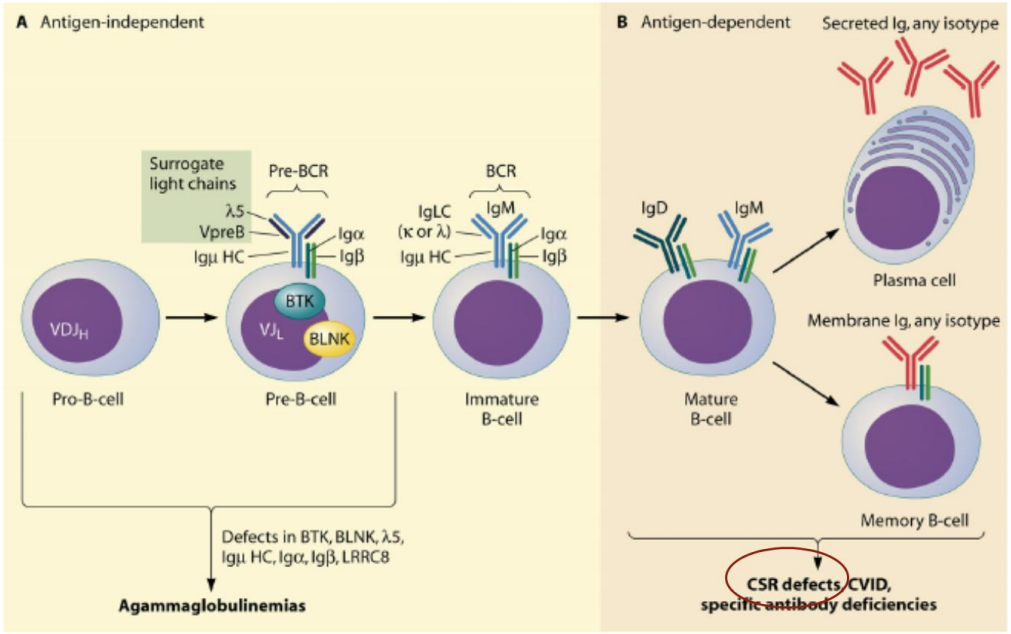
*Phenotypic studies
e.g. traditional functional assays

Targeted Gene Sanger Sequencing Should Remain the First-Tier Genetic Test for Children Suspected to Have the Five Common X-Linked Inborn Errors of Immunity
Chan et al. Frontiers in Immunology 2022

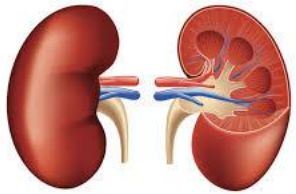
Recurrent sinopulmonary Infections

Antibody Deficiency

Conditions associated with humoral immunodeficiency



Other genetic disorders
- Monogenic
- Chromosomal



Systemic
- Malignancies/ catabolic state
- Renal/ GI loss

Drug-induced
- Antiepileptic
- GC, SSZ, penicillamine, gold salts

Infectious diseases
- HIV
- Congenital rubella/ CMV/ gondii

Ig pattern evaluation

IgA	IgM	IgG	Likely or possible diagnoses	Next steps of immunologic evaluation
Absent	Normal	Normal	IgA deficiency; other humoral deficiencies; combined immune deficiencies	Evaluation of antibody and/or vaccine titer responses; B-cell enumeration and phenotyping
Absent	Absent	Absent	Agammaglobulinemia; other humoral deficiencies; combined immune deficiencies	B-cell enumeration
Low	Normal or elevated	Low	Hyper-IgM syndromes; other humoral deficiencies; combined immune deficiencies	Evaluation of antibody and/or vaccine titer responses; B-cell enumeration and phenotyping
Normal	Normal	Low	Humoral deficiency; transient hypogammaglobulinemia of infancy; combined immune deficiencies	Evaluation of antibody and/or vaccine titer responses; B-cell enumeration and phenotyping
Any combination of low and normal			Many humoral deficiencies, including common variable immune deficiency; combined immune deficiencies	Evaluation of antibody and/or vaccine titer responses; B-cell enumeration and phenotyping
Normal	Normal	Normal	Specific antibody deficiency vs normal individual; other humoral or combined deficiencies still possible; other primary immune deficiencies	Evaluation of antibody and/or vaccine titer responses; B-cell enumeration and phenotyping

Ann Allergy Asthma Immunol 123 (2019) 444–453

Assessment of suspected antibody Deficiency

Level 1	Primary screening tests	CBC with differential counts
		Serum Ig levels, complements, ESR
Level 2	B cell function evaluation	Naturally acquired antibodies: isohaemagglutinins
		Commonly acquired antibodies: TdP, MMR
		Vaccine challenge (protein or polysaccharide Ag)
	Others	Quantitative IgG subclasses
	T- and B-cell subpopulation	Characterizing B cell subset useful in evaluating patients with CVID
Level 3	Disease specific analysis	Gene expression, gene sequencing

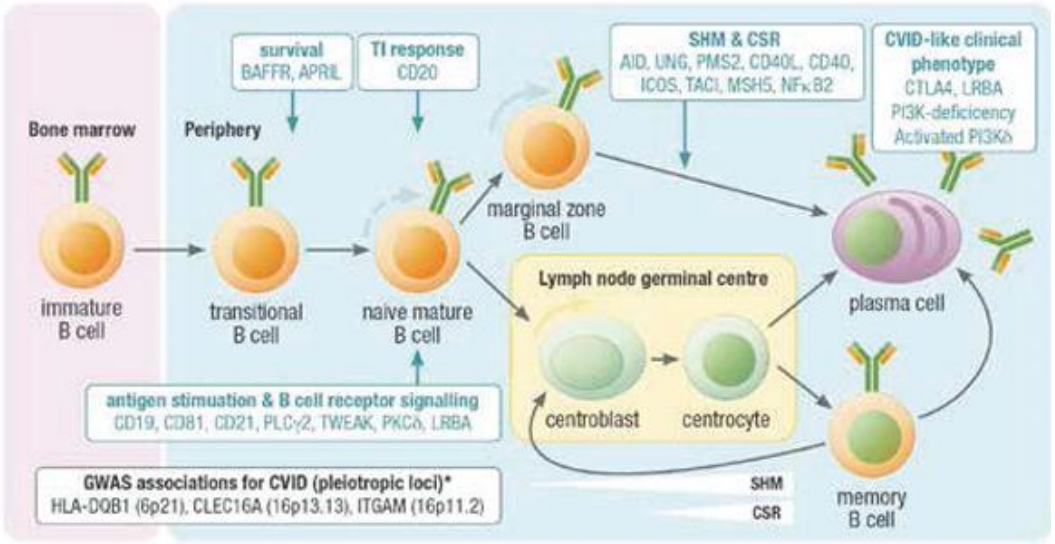
Tests to exclude rare and secondary causes:

- Thoracic computed tomography to exclude thymoma (particularly useful if patient is >50 years old with low B-cell numbers)
- To exclude gastrointestinal or urinary protein loss or lymphatic loss
- Paraprotein workup

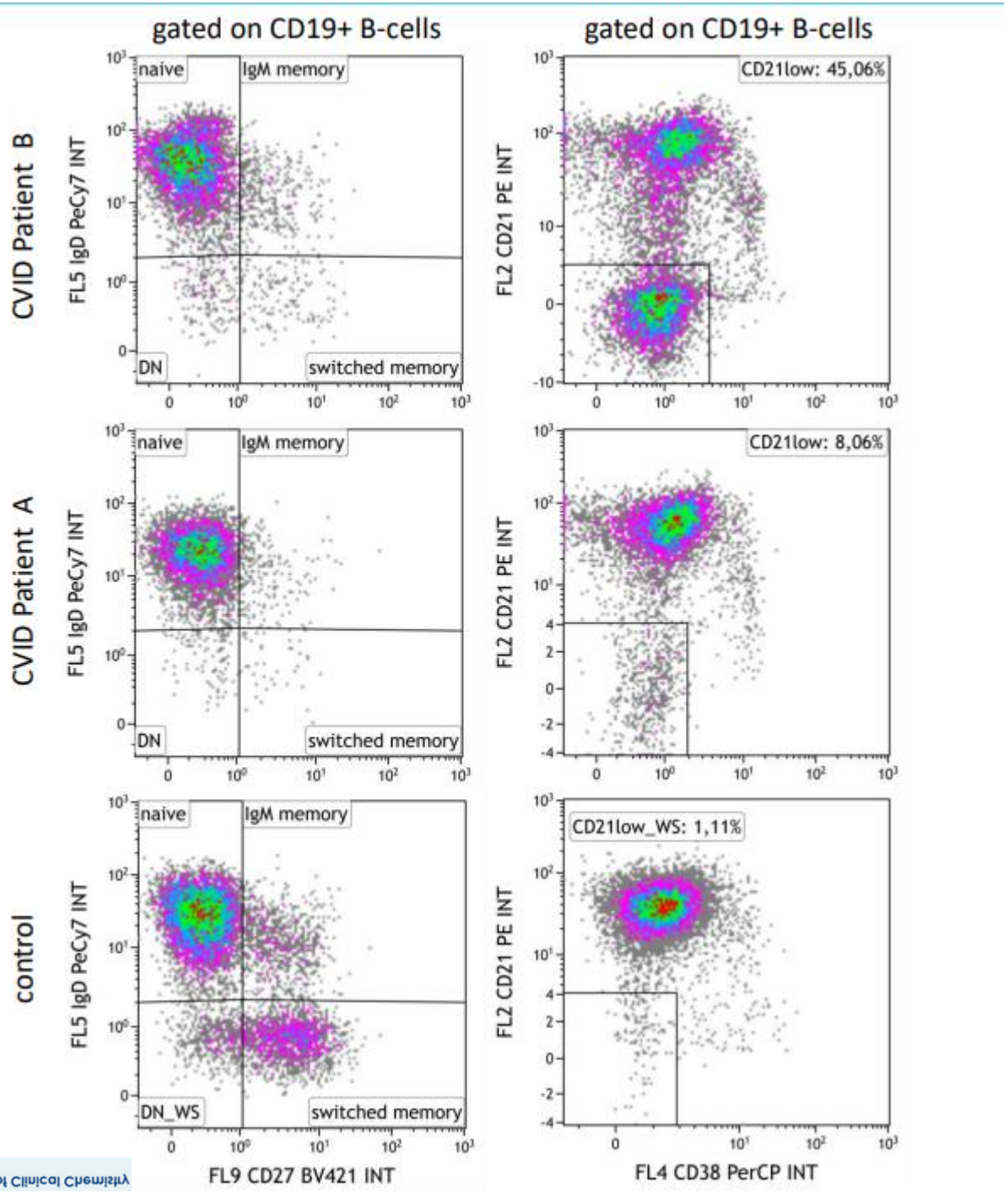
Screening for complications:

- USG abdomen
- Lung Function/ CT thorax

B cell Immunophenotyping



Current Allergy & Clinical Immunology | September 2015



the Journal of the International Federation of Clinical Chemistry
and Laboratory Medicine

Vaccine response

T-dependent B cell response		T-independent B cell response	Laboratory findings support the following alternative diagnoses
Tetanus (Strong antigen)	**Diphtheria (Weak antigen)**	**Pneumococcal polysaccharides**	
+	+	+	No immunodeficiency
+	+	-	Primary antibody deficiency secondary immunodeficiency
+	-	-	Primary antibody deficiency mild form of combined immunodeficiency secondary immunodeficiency
-	-	-	Combined immunodeficiency Secondary immunodeficiency

CVID

TNFRSF13B (TACI)
TNFRSF13C MSH5
TNFSF12 TNFSF10

CVID-like

CD27 CD81 CD19 CR2
PIK3CD TCF3 LRBA
ICOS PIK3R1 IKFZ1
MS4A1 NFKB1 CTLA4

?? Multigenic disorders ??
?? Epigenetic changes ??

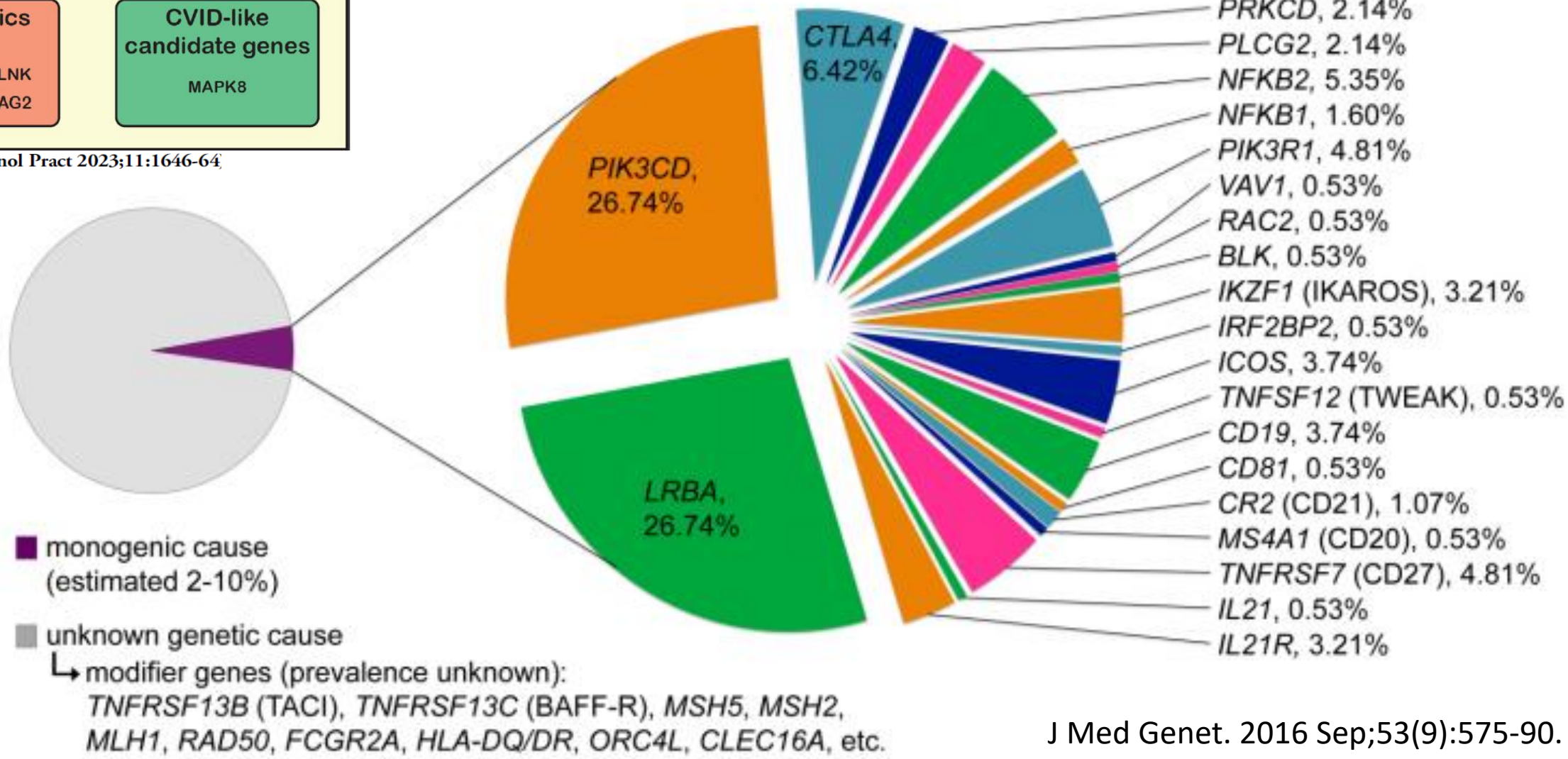
CVID-mimics

SH2D1A
BTK BLNK
RAG1 RAG2

CVID-like candidate genes

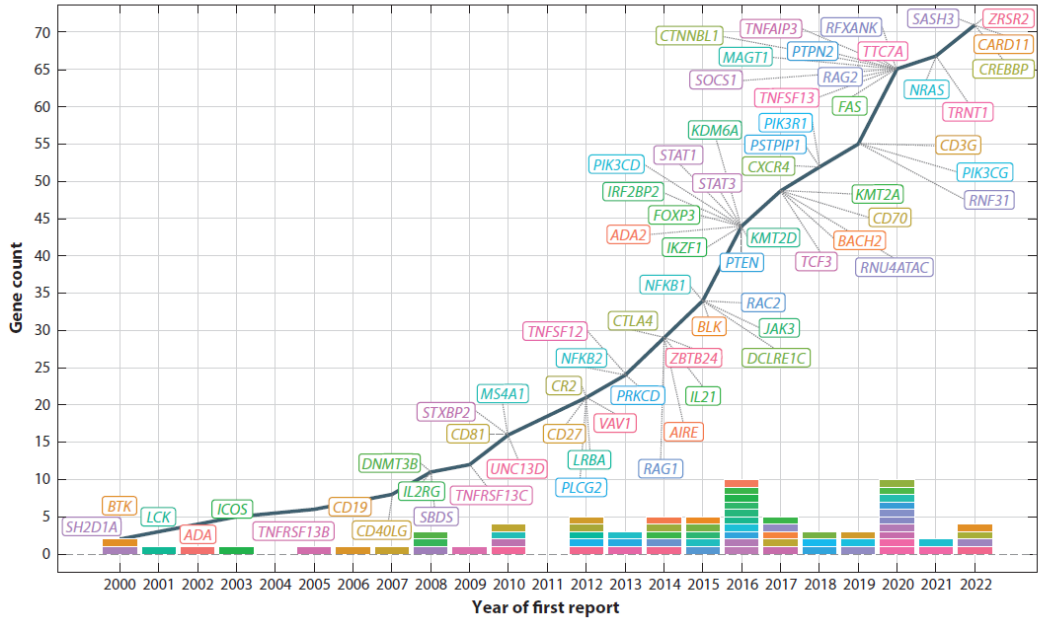
MAPK8

J Allergy Clin Immunol Pract 2023;11:1646-64



J Med Genet. 2016 Sep;53(9):575-90.

Monogenic causes identified in CVID-like presentations



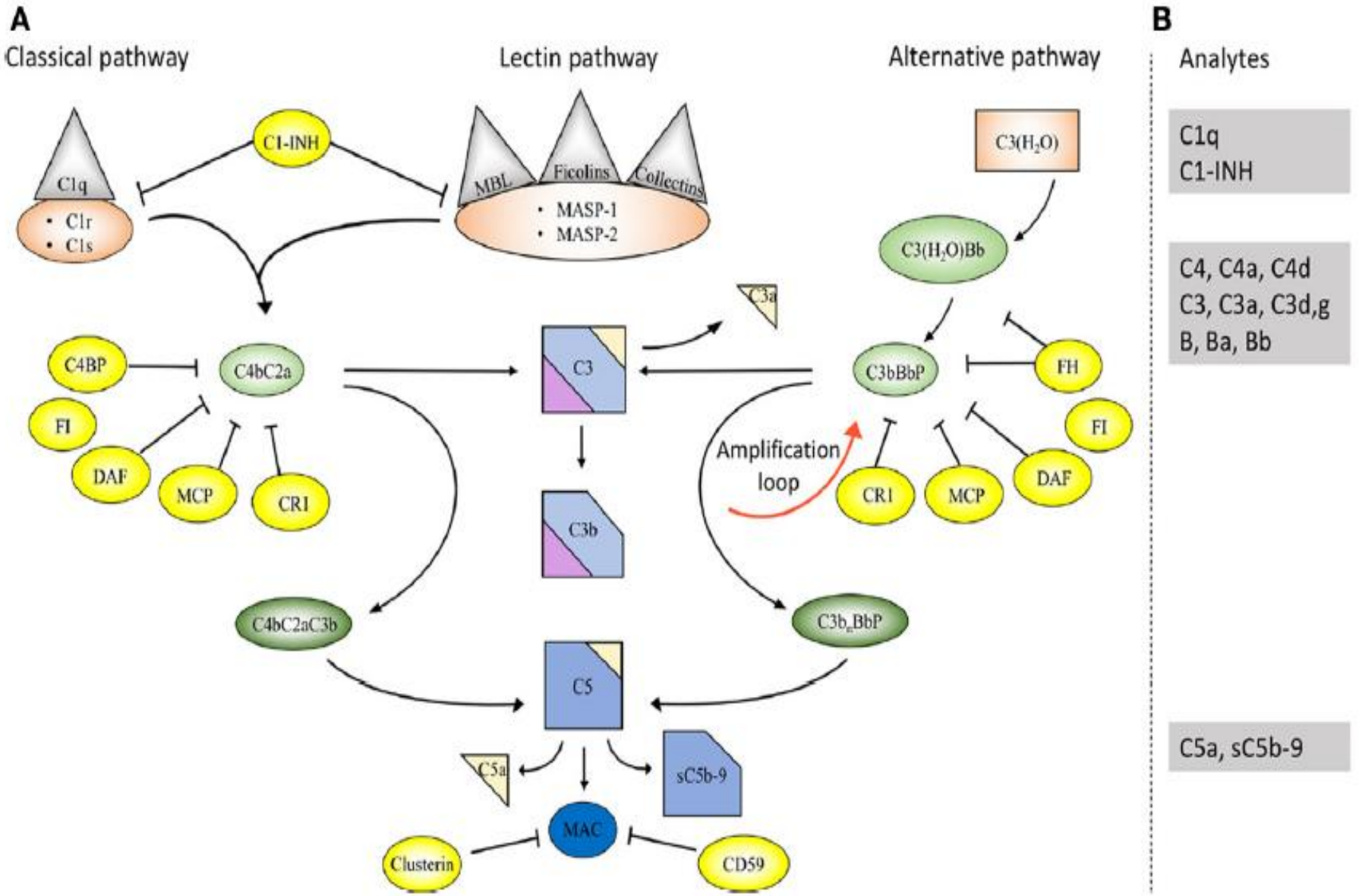
Ann Rev. Pathol. Mech.Dis.2023.18:283-310

Table 1 Monogenic causes of CVID reported in original publications, organized by IUIS classification (159)

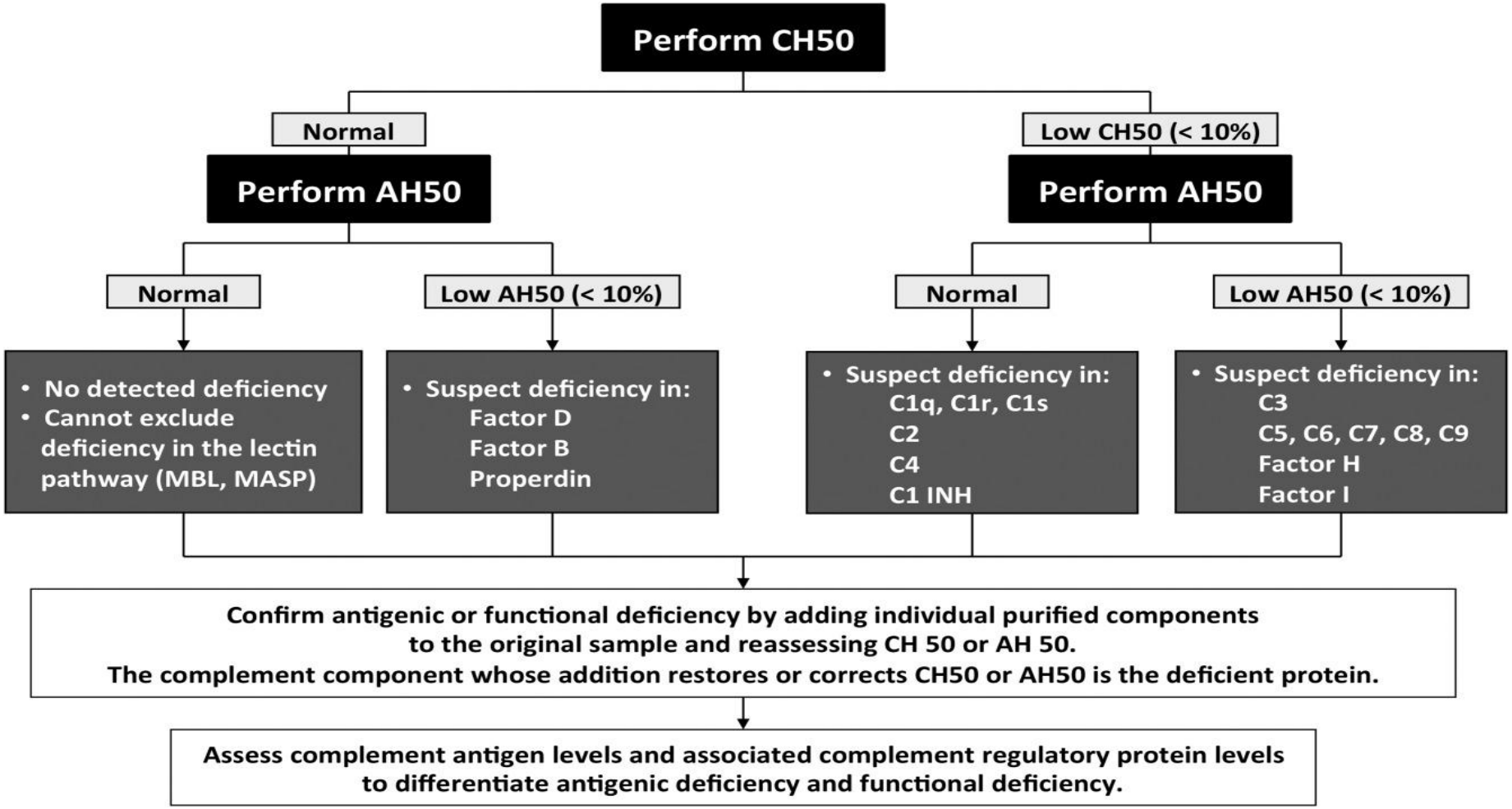
IUIS classification	Cause	Gene(s)
Table 1	Immunodeficiencies affecting cellular and humoral immunity	*CD3G*, *CD40LG*, *DCLRE1C*, *ICOS*, *IL21*, *IL21R*[a], *IL2RG*, *JAK3*, *LCK*, *RAG1*, *RAG2*, *RFXANK*, *SASH3*
Table 2	Combined immunodeficiencies with associated or syndromic features	*CARD11* [DN], *DNMT3B*, *KDM6A*, *KMT2A*, *KMT2D*, *PMS2*[a], *RNF31* (HOIP), *RNU4ATAC*, *TTC7A*, *ZBTB24*
Table 3	Predominantly antibody deficiencies	*ARHGEF1*[a], *ATP6AP1*[a], *BTK*, *CD19*, *CD81*, *CR2* (CD21), *CTNNBL1*, *FNIP1*[a], *IKZF1*, *IRF2BP2*, *MOGS*[a], *MS4A1* (CD20), *NFKB1*, *NFKB2*, *PIK3CD*, *PIK3CG*, *PIK3R1*, *PTEN*, *RAC2*, *SEC61A1*[a], *SH3KBP1*[a], *TCF3*, *TNFRSF13B* (TACI), *TNFRSF13C* (BAFFR), *TNFSF12* (TWEAK), *TNFSF13* (APRIL), *TRNT1*
Table 4	Diseases of immune dysregulation	*AIRE*, *BACH2*, *CD27*, *CD70*, *CTLA4*, *DEF6*[a], *FAS*, *FOXP3*, *LRBA*, *MAGT1*, *PRKCD*, *SH2D1A* (*SAP*), *SOCS1*, *STAT3* [GOF], *STXBP2*, *UNC13D*
Table 5	Congenital defects of phagocyte number or function	*SBDS*
Table 6	Defects in intrinsic and innate immunity	*CXCR4*, *STAT1* [GOF]
Table 7	Autoinflammatory disorders	*ADA2*, *PLCG2*, *PSTPIP1*, *SYK* [GOF][a], *TNFAIP3* (A20)
Table 9	Bone marrow failure	*SAMD9*[a]
Table 10	Phenocopies of inborn errors of immunity	*NRAS*
NA	Other primary adaptive immune defects not found in IUIS classification tables	*BLK*, *PTPN2*, *VAV1*

Ann Rev. Pathol. Mech.Dis.2023.18:283-310

Complement Deficiency


A
Classical pathway
Lectin pathway
Alternative pathway
C1q
C1r
C1s
C1-INH
MBL
Ficolins
Collectins
MASP-1
MASP-2
C3(H2O)
C3(H2O)Bb
C3a
C4BP
C4bC2a
C3
C3bBbP
FH
FI
DAF
MCP
CR1
Amplification loop
C3b
C4bC2aC3b
C3b2BbP
C5
C5a
sC5b-9
MAC
Clusterin
CD59
B
Analytes
C1q
C1-INH
C4, C4a, C4d
C3, C3a, C3d,g
B, Ba, Bb
C5a, sC5b-9

Screening assays for complement pathway



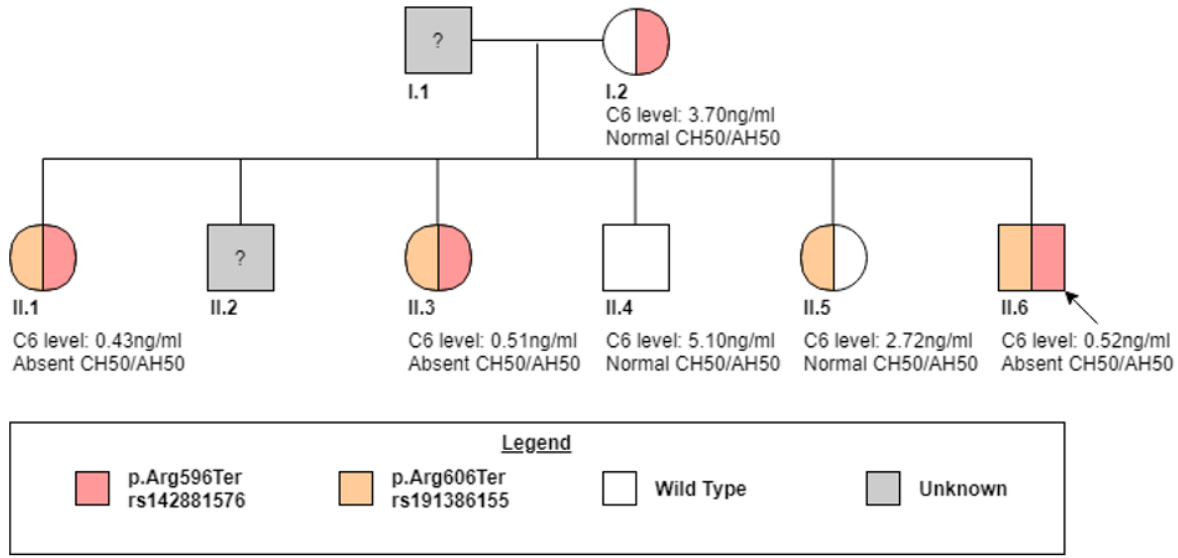
American J Hematol, Volume: 90, Issue: 12, Pages: 1180-1186, First published: 06 October 2015, DOI: (10.1002/ajh.24209)

Diagnosis: C6 deficiency

	Patient		Genotype	Phenotype	
				C6 level (ng/mL)*	CH50/AH50
Compound heterozygous	II.1	F/35	p.Arg596Ter / p.Arg606Ter	0.43	Absent
	II.3	F/29	p.Arg596Ter / p.Arg606Ter	0.51	Absent
	II.6	M/23	p.Arg596Ter / p.Arg606Ter	0.52	Absent
Single heterozygous	I.2	F/62	p.Arg596Ter / WT	3.70	Normal
	II.5	F/26	p.Arg606Ter / WT	2.72	Normal
Wild Type	II.4	M/28	WT / WT	5.10	Normal

* C6 levels also performed in 8 healthy individuals, with a mean (range) level of 4.3-7.3 ng/mL.

Figure 1: Family tree and summary of C6 genotypes

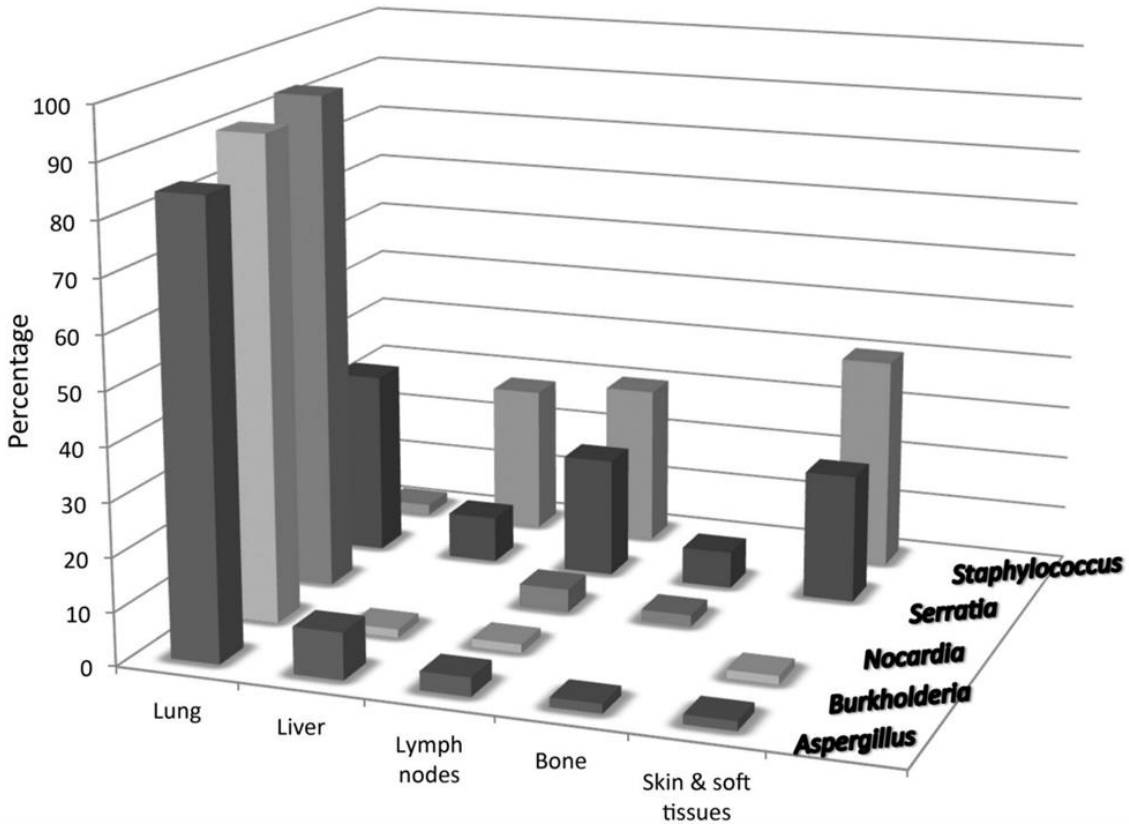


Phagocytic Defects

Phagocytes

- Recurrent soft tissue infection/ abscess
- Deep seated infections with bacterial/ fungi
- Poor wound healing
- Chronic gingivitis/ periodontal disease
- In CGD, susceptibility to Catalase + organisms:
  - Fungi → Aspergillus spp. (most common cause of death), other molds
  - Bacteria → Burkholderia cepacia complex, Serratia, Nocardia, Staphylococcus aureus, Klebsiella
  - Others → rare mycobacteria, Paecilomyces, Sporothrix

Common Severe Infections in CGD



From: Common Severe Infections in Chronic Granulomatous Disease
Clin Infect Dis. 2014;60(8):1176-1183. doi:10.1093/cid/ciu1154
Clin Infect Dis | Published by Oxford University Press on behalf of the Infectious Diseases Society of America 2014.
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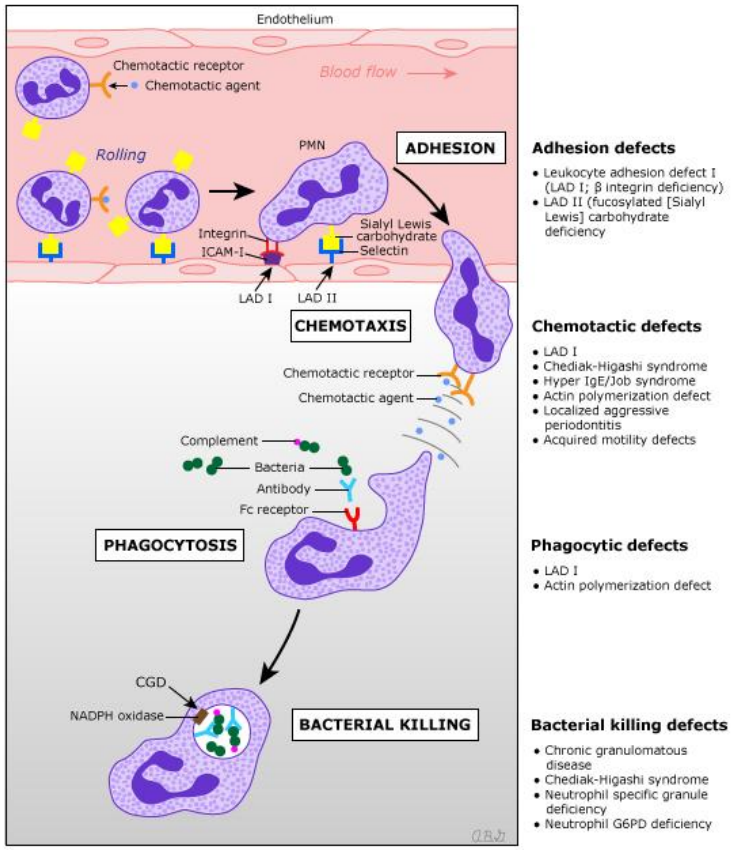
Polymorphonuclear neutrophil (PMN) defects



Normal neutrophil functions in the circulation (pink background) and the tissues (gray background) are illustrated, along with inherited defects in each of the stages in response to pathogens (adhesion, chemotaxis, phagocytosis, and killing). Refer to UpToDate topics on individual syndromes and laboratory testing for these defects for additional information.

LAD: Leukocyte adhesion defect; CGD: chronic granulomatous disease.

Courtesy of Thomas Coates, MD

UpToDate®

Lab investigations

CBP
Flow cytometry for markers, e.g. CD11b/CD18

Chemotaxis assay

Phagocytosis and Killing assays

Neutrophil oxidative bursts activity assessment: e.g. DHR/ NBT assays
NADPH oxidase components measurement

Molecular genetics

Copyrights apply

Adult onset CGD

Vast majority CGD diagnosed <5 years → but 5–15% present/diagnosed in adolescence or adulthood

Adult cases:

- •Median age at diagnosis: 38–40 years (range 19–74)
- •More common in AR forms (especially NCF1/p47phox – most frequent adult presentations)
- •Rare X-linked cases in adulthood (usually hypomorphic or mosaicism in females)
- •consider in adults with:
  - •Recurrent unusual catalase-positive infections
  - •Refractory granulomatous/inflammatory conditions
  - •Poor response to standard antimicrobials

•In general, less fulminant than pediatric cases

Common presentations:

•Refractory/recurrent pneumonia (Aspergillus, Burkholderia, Nocardia)
•Deep abscesses (liver, brain, perianal)
•Granulomatous colitis mimicking Crohn's disease
•Recurrent skin/soft tissue infections or cellulitis
•Osteomyelitis, lymphadenitis

Atypical / late clues:

•Inflammatory bowel disease-like symptoms as first/only feature
•Refractory "TB-like" pneumonia
•Spinal cord infection, brain abscess, or unusual fungal infections
•Misdiagnosed as sarcoidosis, IBD, malignancy

Phenocopies of IEI

Phenocopies of IEI-anticytokine antibodies

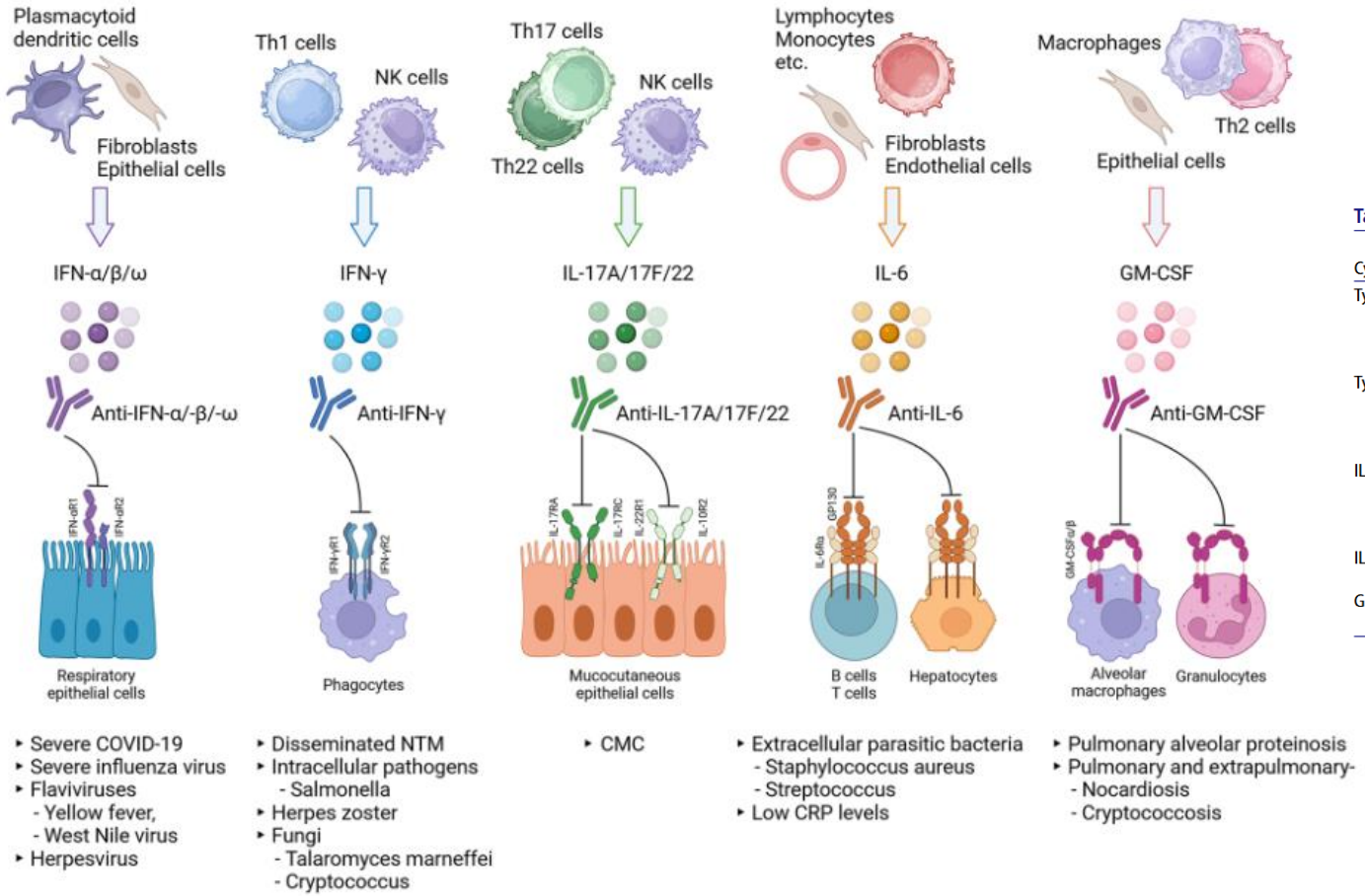


Table 1. Overview of phenocopies of IEI associated anti-cytokine Autoantibodies.

Cytokines	Cytokine receptors	Anti-cytokine autoantibodies	Infections and findings associated with autoantibodies
Type I IFN (IFN-α, β, ω)	IFNAR1 IFNAR2	Anti-IFN-α2, other IFN-α, IFN-β and IFN-ω	• Severe COVID-19 pneumonia • Severe influenza virus pneumonia • Infection with flaviviruses (Yellow fever, West Nile virus encephalitis) • Infection with herpesvirus (herpes simplex, herpes zoster virus)
Type II IFN (IFN-γ)	IFNγR1 IFNγR2	Anti-IFN-γ	• Disseminated nontuberculous mycobacterial disease • Infection with intracellular pathogens (Salmonellosis) • Herpes zoster caused by varicella-zoster virus • Fungal infections (Talaromyces marneffeiya, Cryptococcus)
IL-17A, IL-17F, IL-22	IL-17RA IL-17RC IL-22R1 IL-10R2	Anti-IL-17A,IL-17F and IL-22	• Chronic mucocutaneous candidiasis (CMC)
IL-6	IL-6Rα GP130	Anti-IL-6	• Infection with extracellular parasitic bacteria (Staphylococcus aureus, Streptococcus) • Low CRP levels
GM-CSF	GM-CSFRα GM-CSFRβ	Anti-GM-CSF	• Pulmonary alveolar proteinosis • Pulmonary and extrapulmonary, nocardiosis, cryptococcosis

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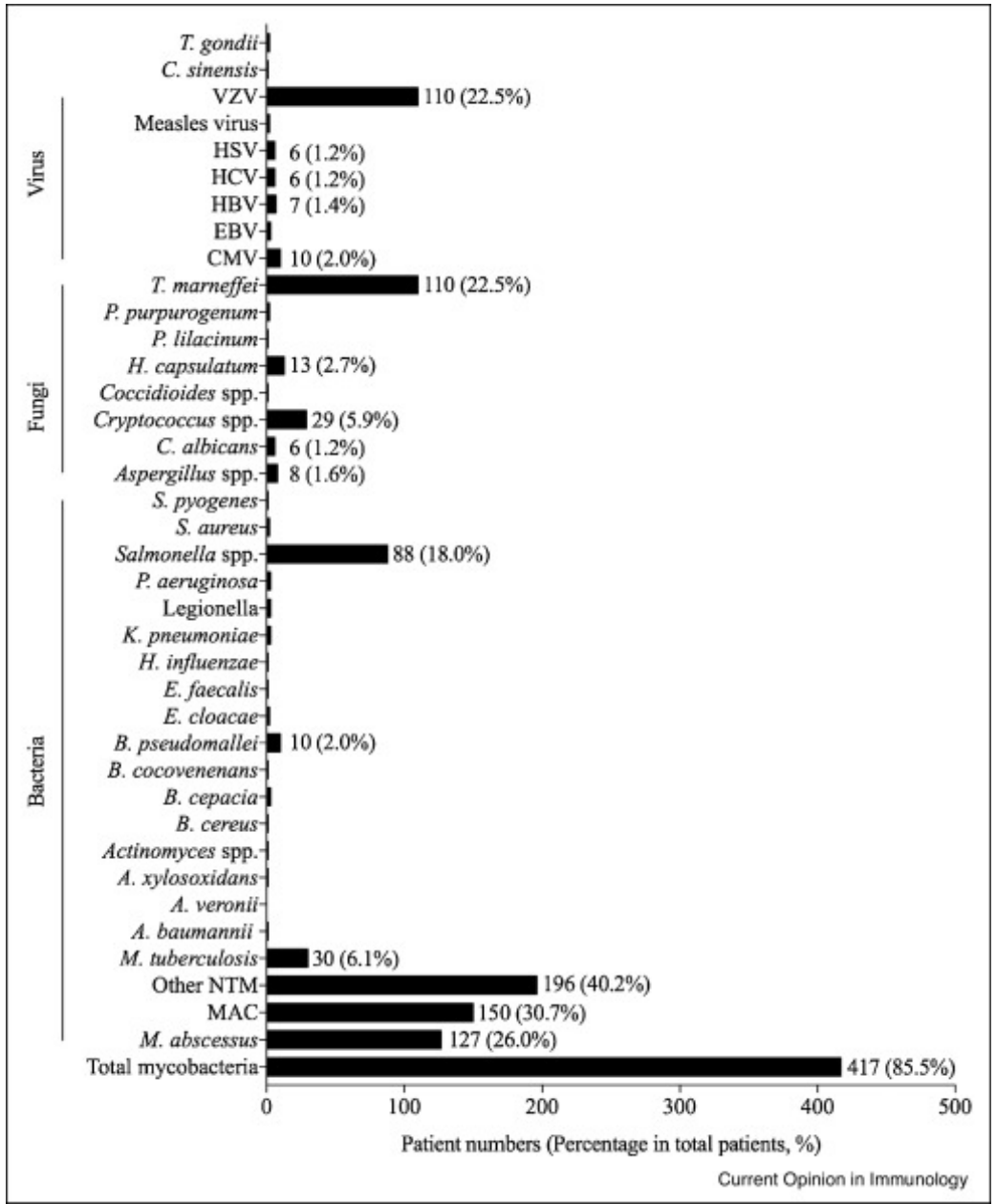
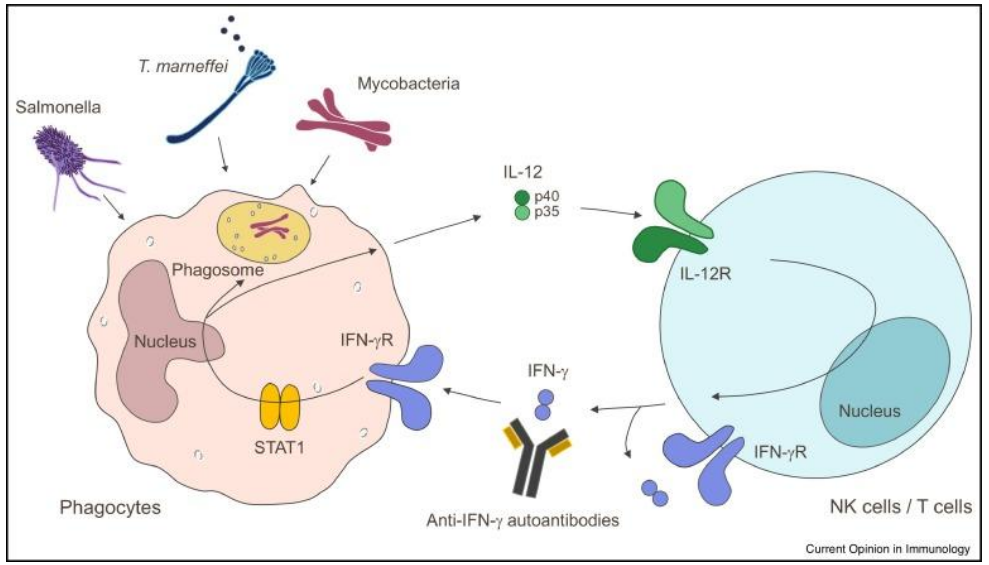
IEI vs phenocopies in AIGA

Analysis of pathogens in infected patients with AIGAs.



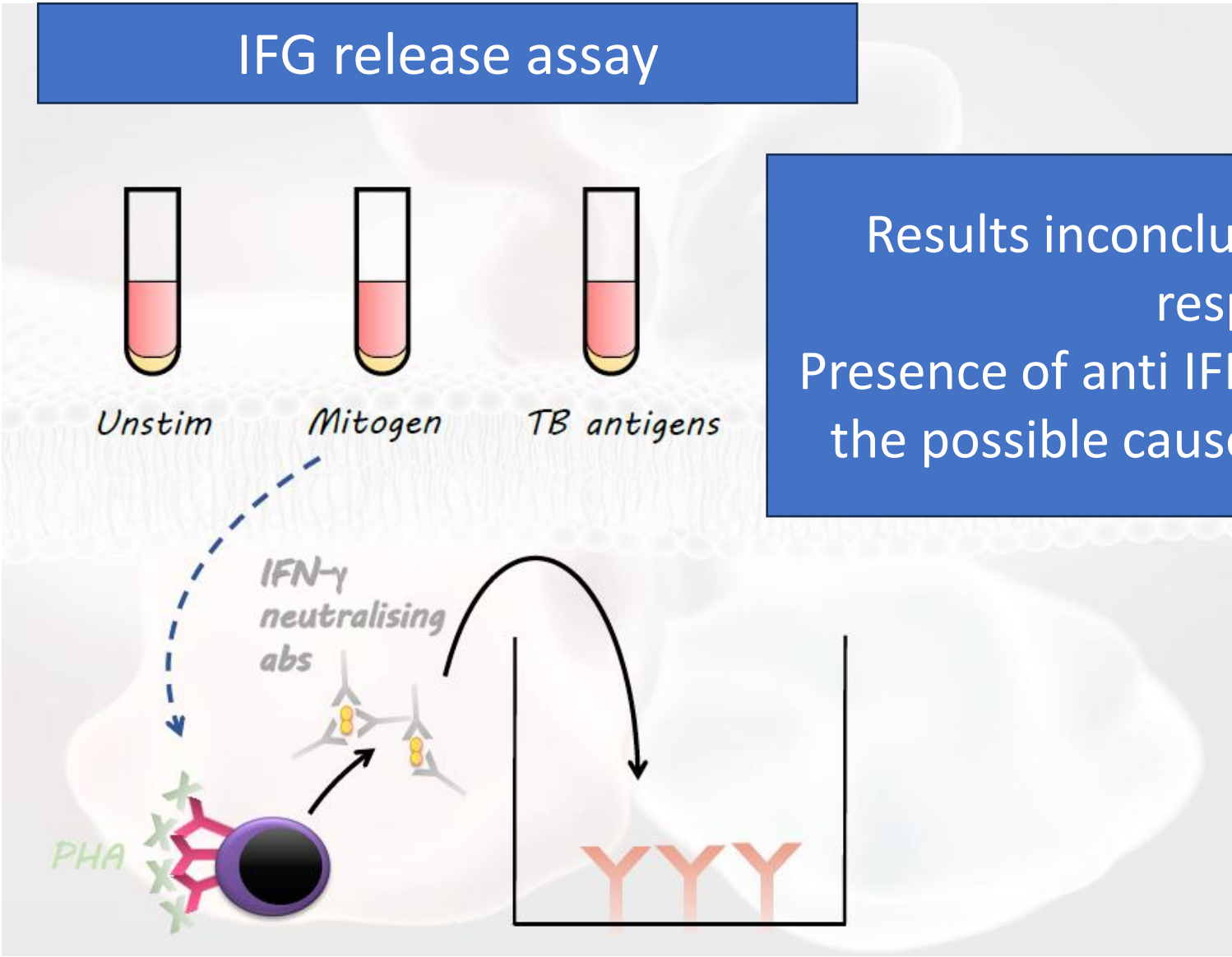


Gene symbol	Gene full name	Signaling affected	Inheritance	Functional impairment	OMIM ID	Chromosomal position
IFNGR1	Interferon-gamma receptor-1	IFN-γ	AR/AD	C/P	107470	6q23-q24
IFNGR2	Interferon-gamma receptor-2	IFN-γ	AR/AD	C/P	147569	21q22.11
IL12B	Interleukin 12B	IL-12/IL-23	AR	C	161561	5q31.1-31.1
IL12RB1	Interleukin 12 receptor subunit beta 1	IL-12/IL-23	AR	C	601604	19p13.1
STAT1	Signal transducer and activator of transcription 1	IFN-γ, IFN-α/β	AR/AD	C/P	600555	2q32.2
NEMO/ IKBKG	NF-κB essential modulator/Inhibitor of NF-κB kinase subunit gamma	IL-12	XR	P	300248	Xq28
TYK2	Tyrosine kinase 2	IL-12/IL-23	AR	C	176941	19p13.2
IRF8	Interferon regulatory factor 8	IFN-γ	AD	P	601565	16q24.1
CYBB	Cytochrome b-245 beta chain	NADPH oxidase activity	XR	P	300645	Xp21.1-p11.4
ISG15	Interferon-stimulated gene product 15	IFN-γ	AR	C	616126	1p36.33
RORC	RAR related orphan receptor C	IFN-γ/IL-17	AR	C	602943	1q21.3
JAK1	Janus kinase 1	IFN-γ	AR	P	147795	1p31.3
IL12RB2	Interleukin 12 receptor subunit beta 2	IL-12	AR	C	601642	1p31.3
IL23R	Interleukin 23 receptor	IL-23	AR	C	607562	1p31.3
SPPL2A	Signal peptide peptidase-like 2A	IL-12/IL-23	AR	C	608238	15q21.2
IFNG	Interferon-gamma	IFN-γ	AR	C	147570	12q15
TBX21	T-box transcription factor 21	IFN-γ	AR	C	604895	17q21.32
ZNFX1	Zinc finger NFX1-type-containing 1	Stress granules recruiting	AR	C	618931	20q13.13
PDCD1	Programmed cell death 1	IFN-γ	AR	C	600244	2q37.3

AR, autosomal recessive; AD, autosomal dominant; XR, X-linked recessive; C, Complete; P, Partial.

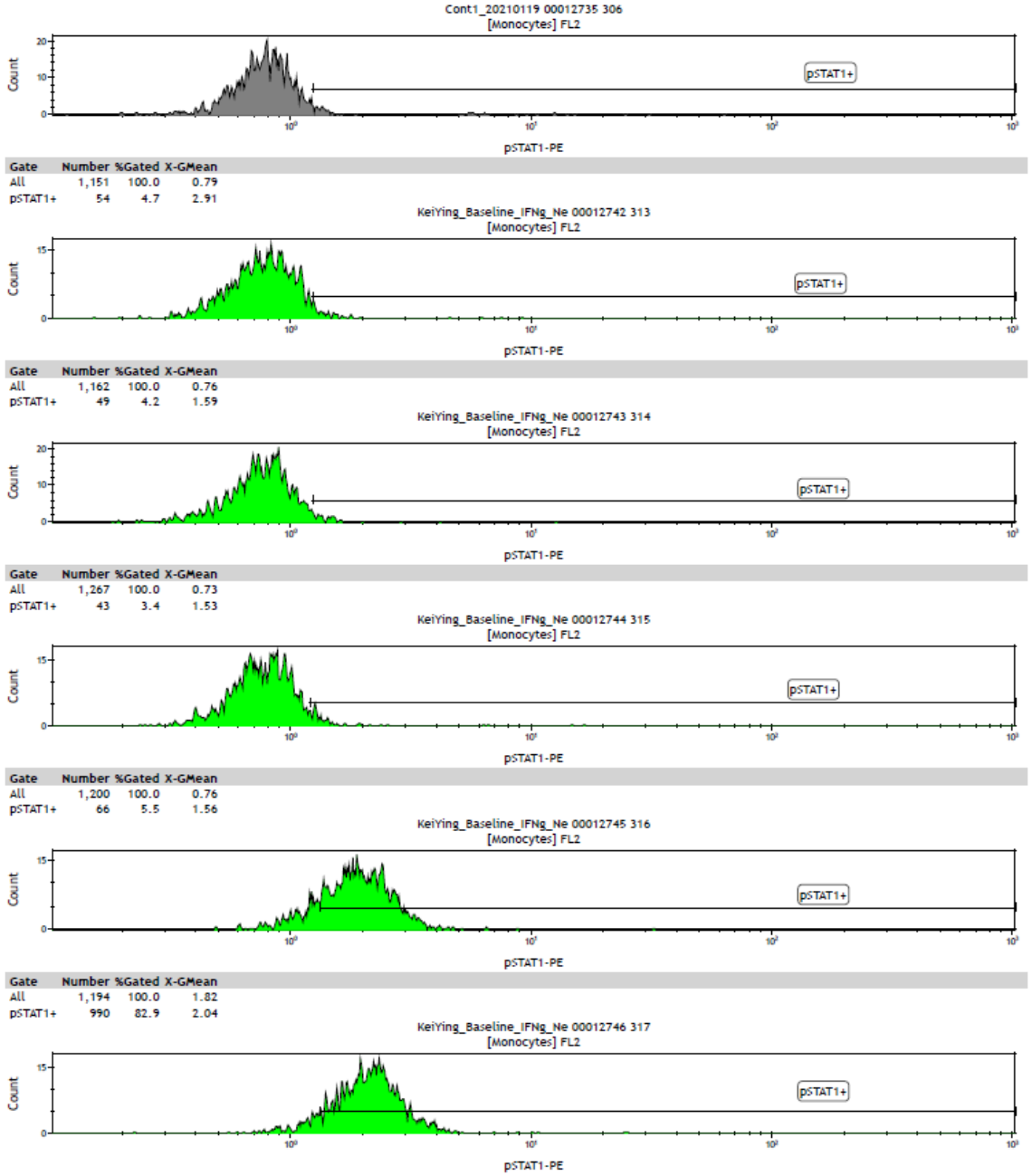
Quantiferon Gold assay

IFG release assay



Results inconclusive if fail mitogen response

Presence of anti IFNG antibody is one of the possible causes of fail pos control

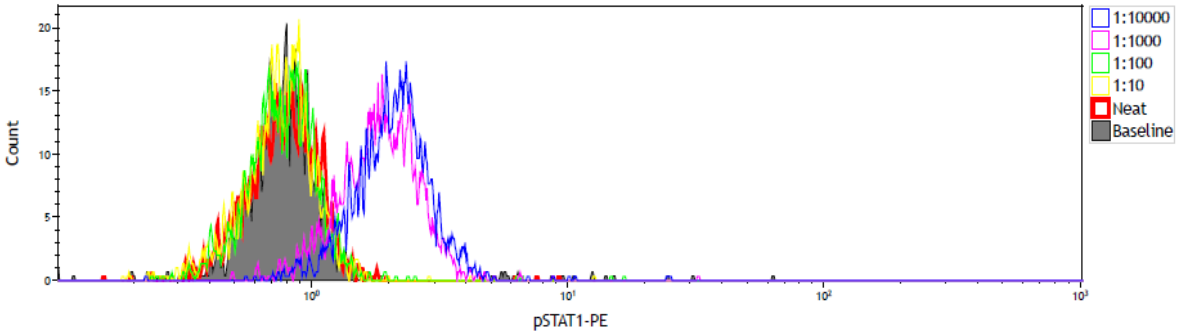


Anti-IFN g Ab

Anti-IFN Gamma Neutralizing Antibody

	pSTAT1 respond cells (%)	Stimulation Index
Neutralizing Ab Positive Control	2.5 %	0.99
Blank Control	91.9 %	3.07

Patient Serum Dilution	pSTAT1 respond cells (%)	Stimulation Index
Neat	2.8 %	1.05
1:10	2.5 %	0.90
1:100	2.6 %	0.89
1:1000	78.8 %	2.24
1:10000	88.5 %	2.51



Case: 62/F

- MG with thymoma
- Smear positive M abscessus chest infection, treatment refractory with smear positive sputum after 6-7 weeks Tx
- Vision threatening left CMV retinitis
- Ig pattern normal
- Normal T cells number
- HIV Neg
- Anti-IFNg Neg

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

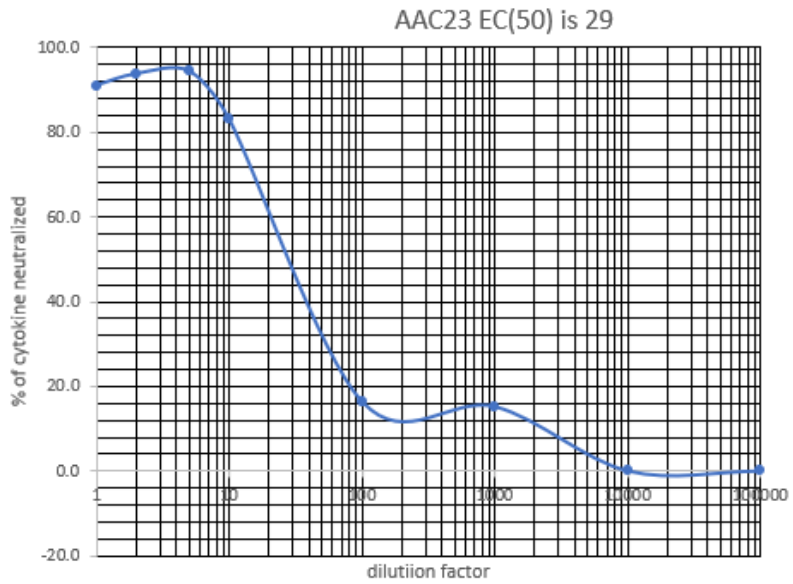
Anti–Interleukin-23 Autoantibodies in Adult-Onset Immunodeficiency

Aristine Cheng, M.D., Anuj Kashyap, B.A., Helene Salvator, M.D., Ph.D., Lindsey B. Rosen, Ph.D., Devon Colby, B.S., Fatemeh Ardeshir-Larijani, M.D., Patrick J. Loehrer, M.D., Li Ding, M.D., Saul O. Lugo Reyes, M.D., Sean Riminton, M.D., Ph.D., Madison Ballman, B.A., Joseph M. Rocco, M.D., Beatriz E. Marciano, M.D., Alexandra F. Freeman, M.D., Sarah K. Browne, M.D., Amy P. Hsu, Ph.D., Adrian Zelazny, Ph.D., Arun Rajan, M.D., Irini Sereti, M.D., Christa S. Zerbe, M.D., Michail S. Lionakis, M.D., Sc.D., and Steven M. Holland, M.D.

Sample ID	AAC23	Reference Range#
Patient Name (sex/age)	Zhang, R Y (F/62)	Adult (Male and Female)
Anti-IL-12P40	13343.5 (MFI)	2112 (MFI)

#Note:
The prelimary reference range was calculated from the 99% CI of 108 controls.

	only cytokine O.D.		
	3.358		
Dilution factor	O.D. AAC23	O.D. - only cytokine O.D.	% of cytokine neutralized
1	0.303	3.055	91.0
2	0.211	3.147	93.7
5	0.1895	3.1685	94.4
10	0.572	2.786	83.0
100	2.809	0.549	16.3
1000	2.8485	0.5095	15.2
10000	3.358	0	0.0
100000	3.358	0	0.0
The EC(50) of AAC23 is 29			



Take Home:

- Alert to red flag S/S, for early referral to specialist for assessment
- Recurrent infections in adults:
  - Always exclude common non-immune & secondary causes first
  - CVID remains the most common treatable primary immunodeficiency in adult
- Start with history + basic labs
- Try categorize the type of immune defects and the severity
- Immunology workup helps in the prognostication/management
- Phenocopies of IEI is increasingly recognized as an important entity in adult-onset immunodeficiency

Thank You