Clinical Immunology of Primary & Secondary ImmunoDeficiencies

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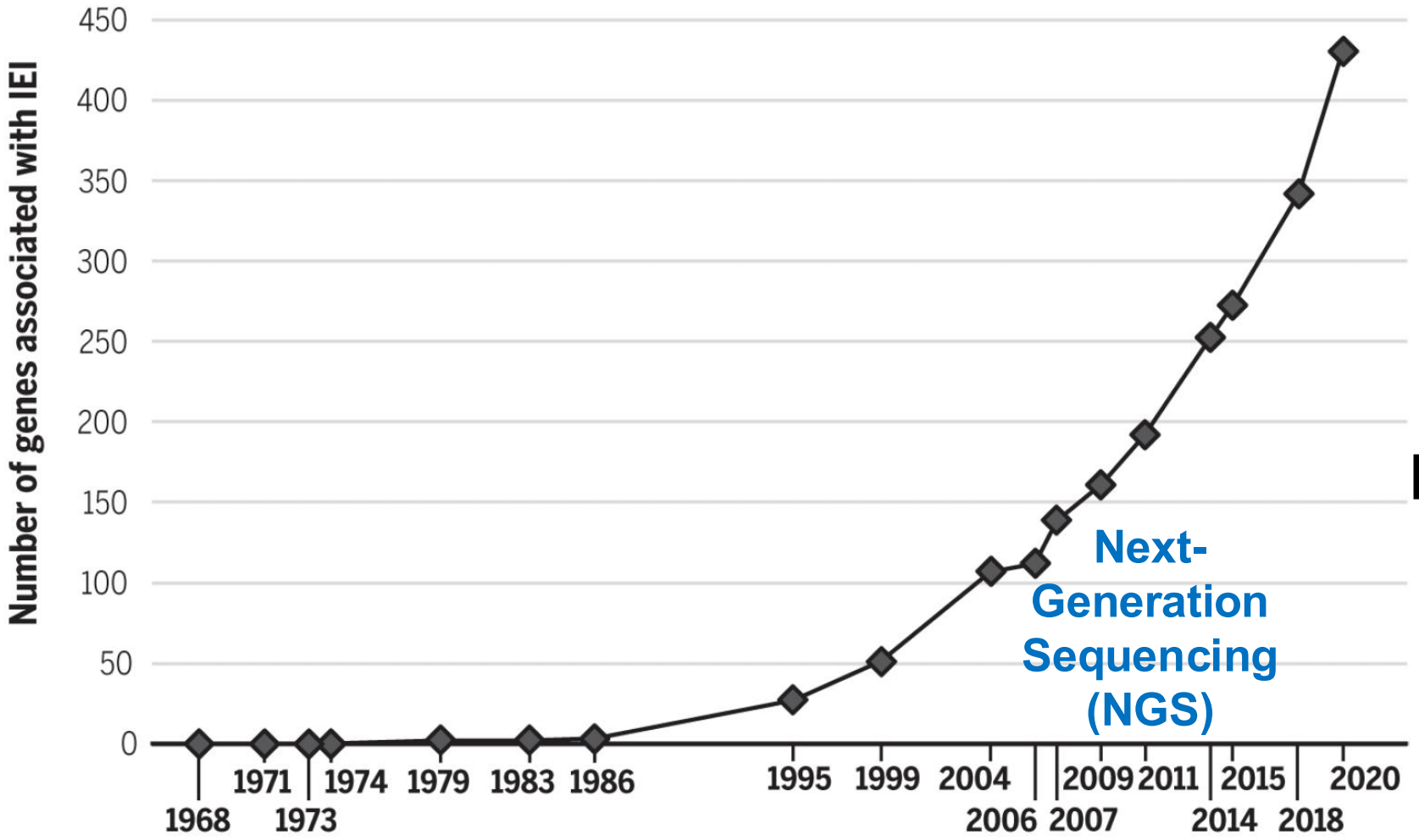
June 8, 2026

What are Inborn Errors of Immunity (IEI)?

Rare Monogenic (Single-Gene) Disorders of the Immune System



555
Genetically-Distinct IEI,
63 Novel since 2023

How Rare?

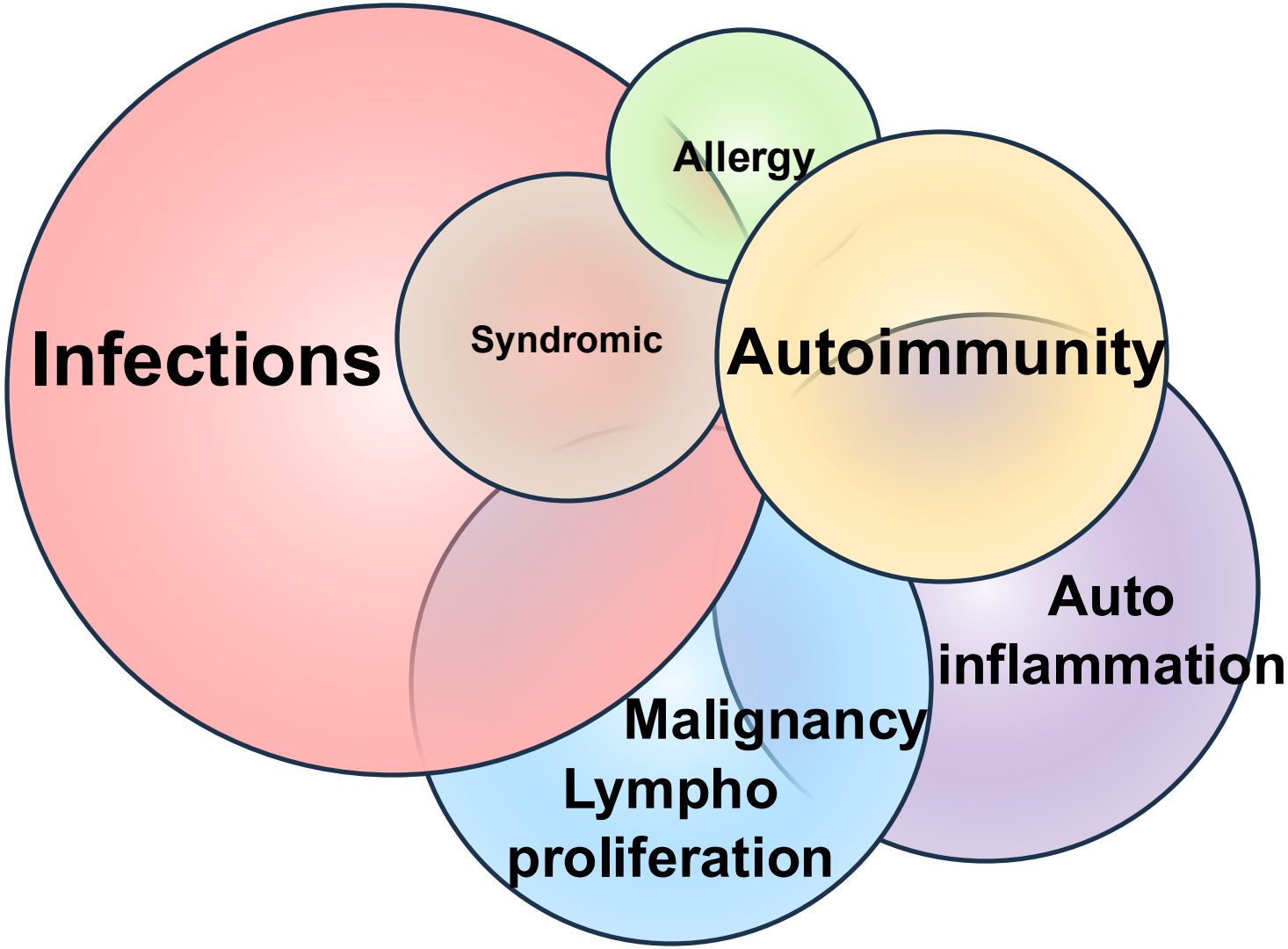
Estimated: 1:1,000-5,000

?

True Prevalence: ~1:500

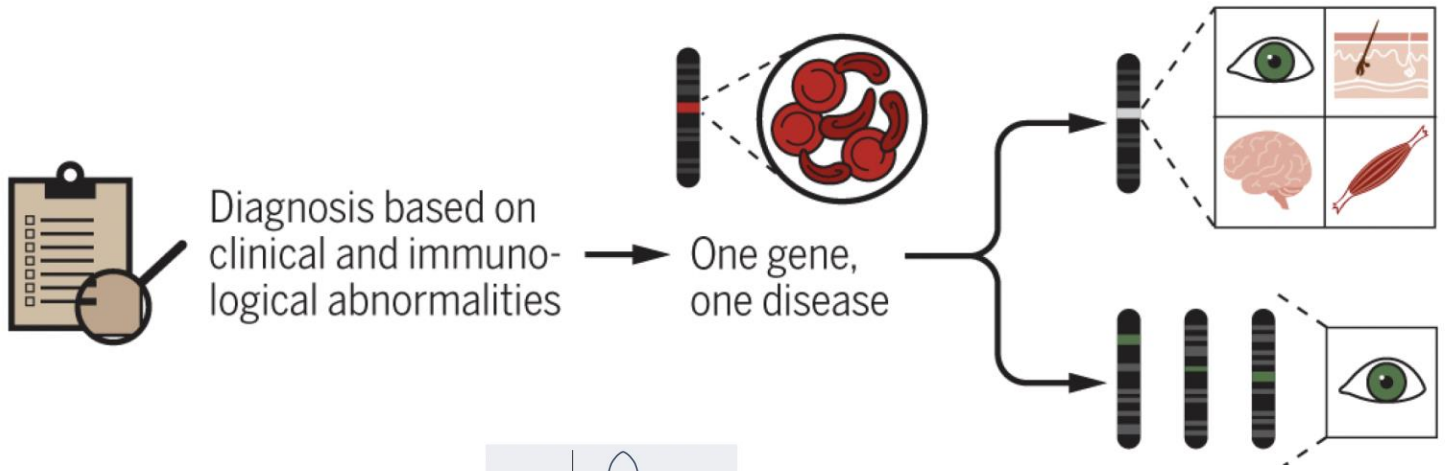
Poli et al., IUIS Classification, 2024

Inborn Errors of Immunity (IEI): Clinical Heterogeneity
Diverse Spectrum of Clinical Phenotypes



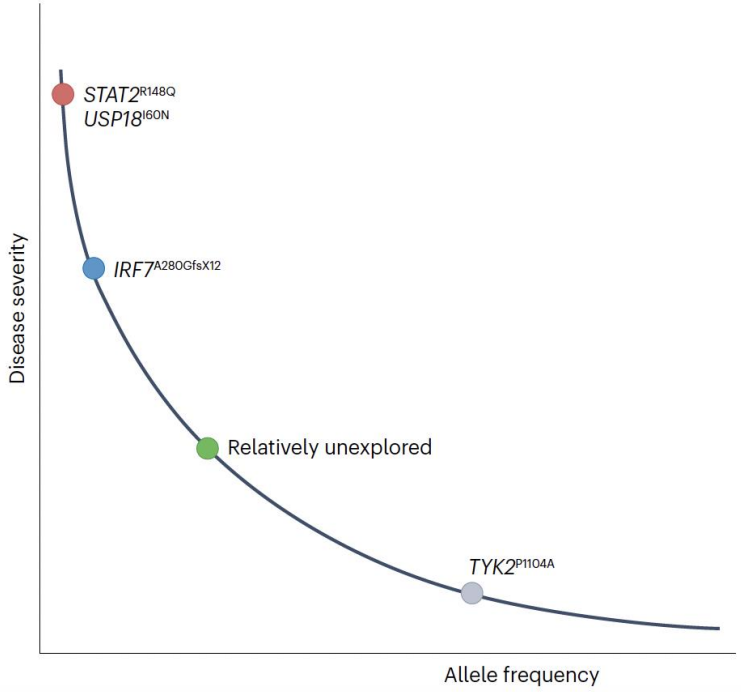
Adapted from Ng et al., 2023

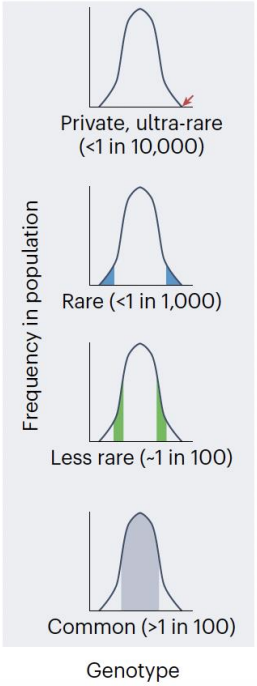
IEI: Genetic and Molecular Heterogeneity

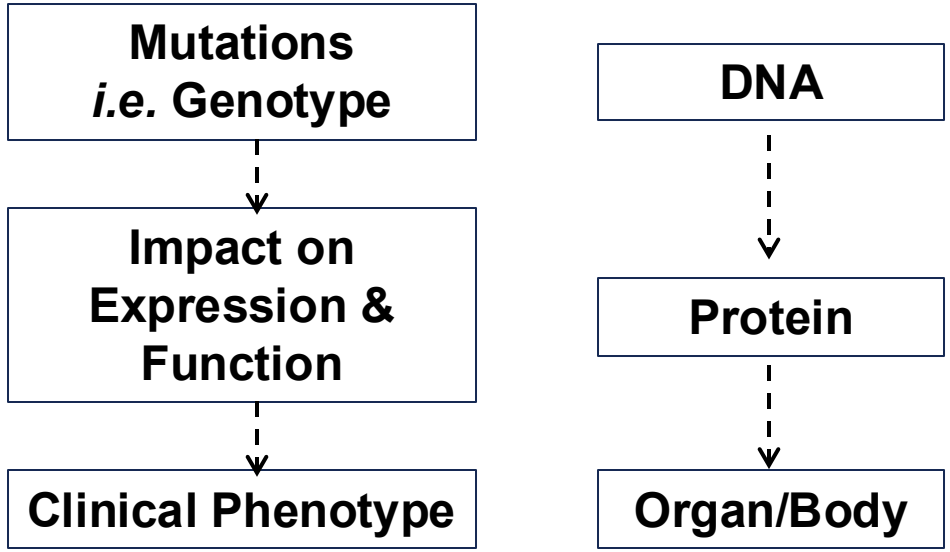


Allelic Heterogeneity

Genetic Heterogeneity







Akalu & Bogunovic, 2024

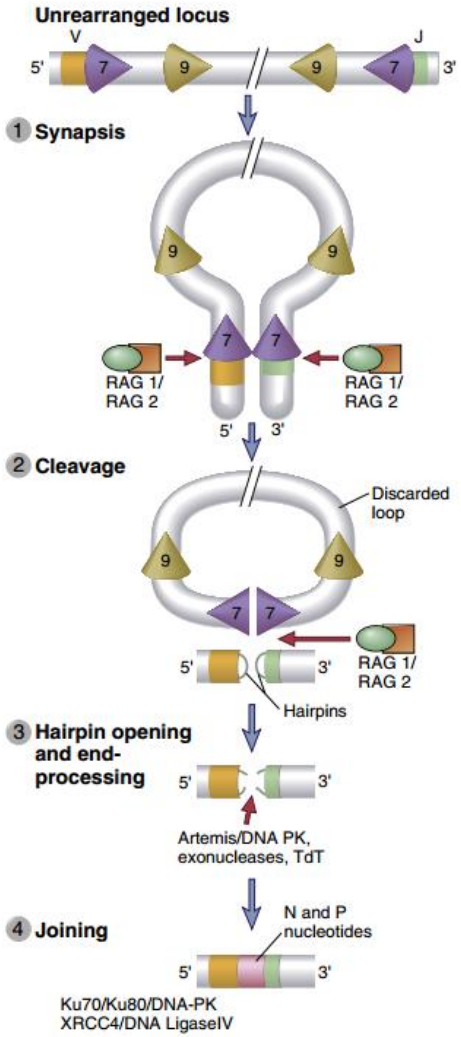
Notarangelo et al., 2020

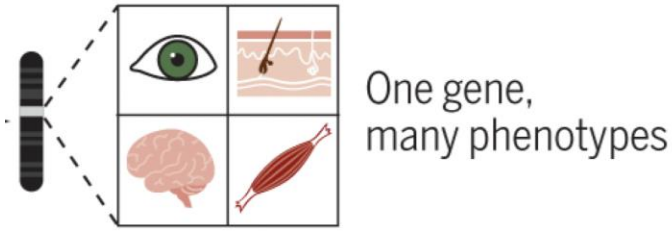
Inborn Errors of Immunity (IEI): Different Functional Outcomes One Gene, Many Phenotypes

Severe Combined ImmunoDeficiency (SCID)

due to

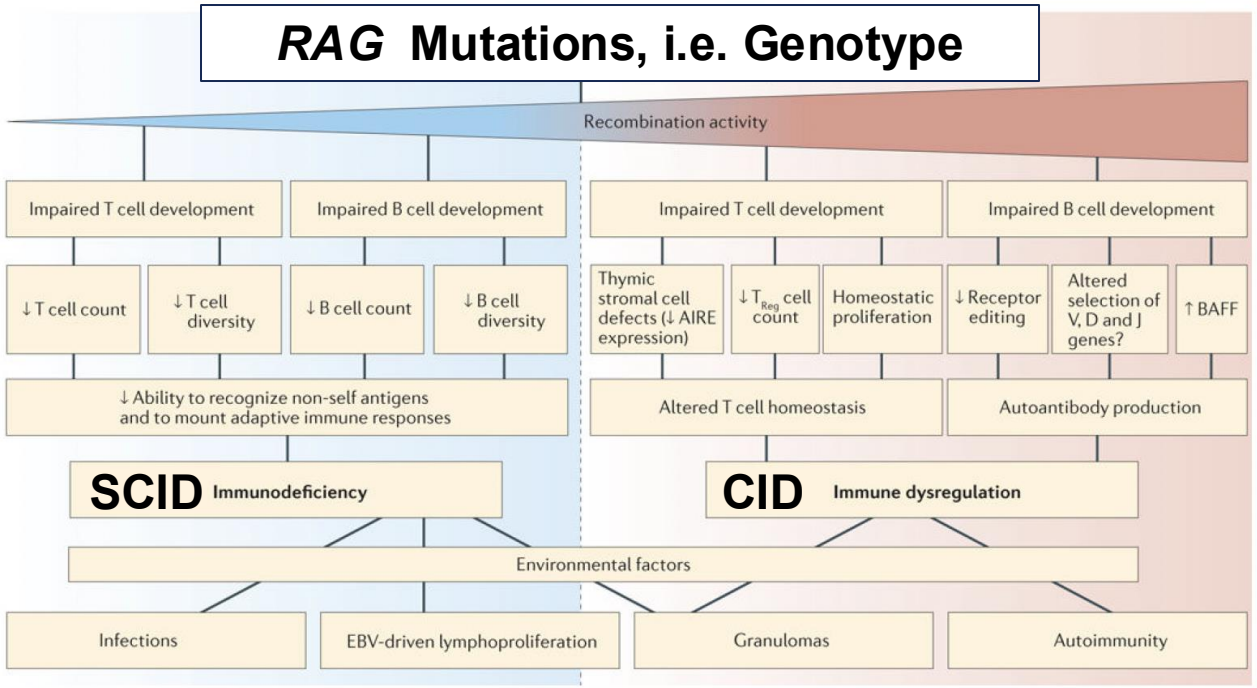
RAG Mutations





Protein Expression & Functional Impact

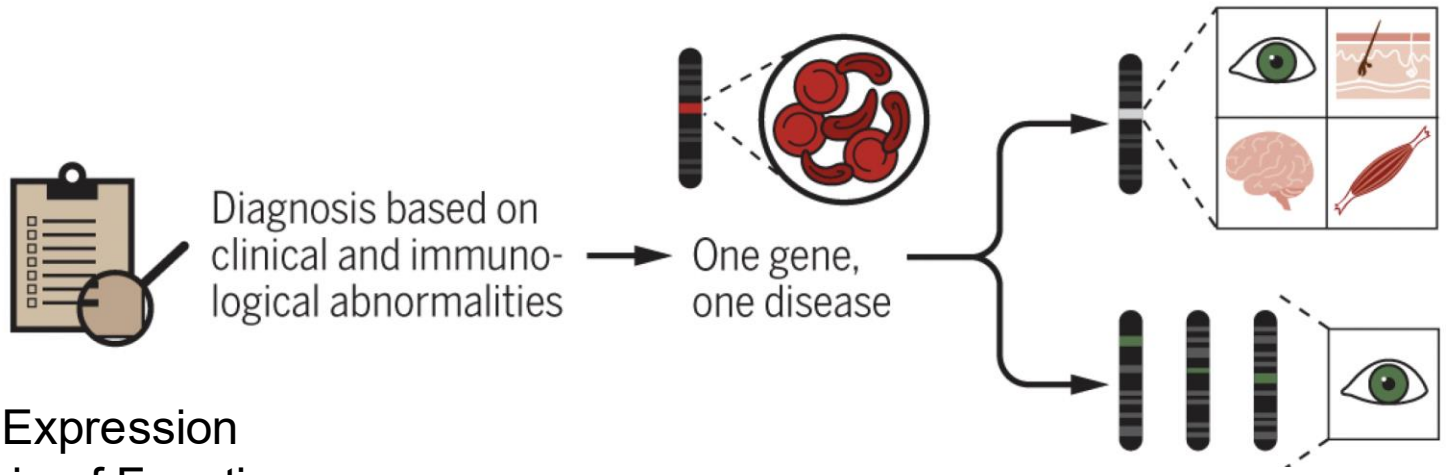
Clinical Phenotype



Notarangelo et al., 2016

Abbas, Litchman & Pillai; Cellular & Molecular Immunology 10th edition

IEI: Genetic and Molecular Heterogeneity



Allelic Heterogeneity

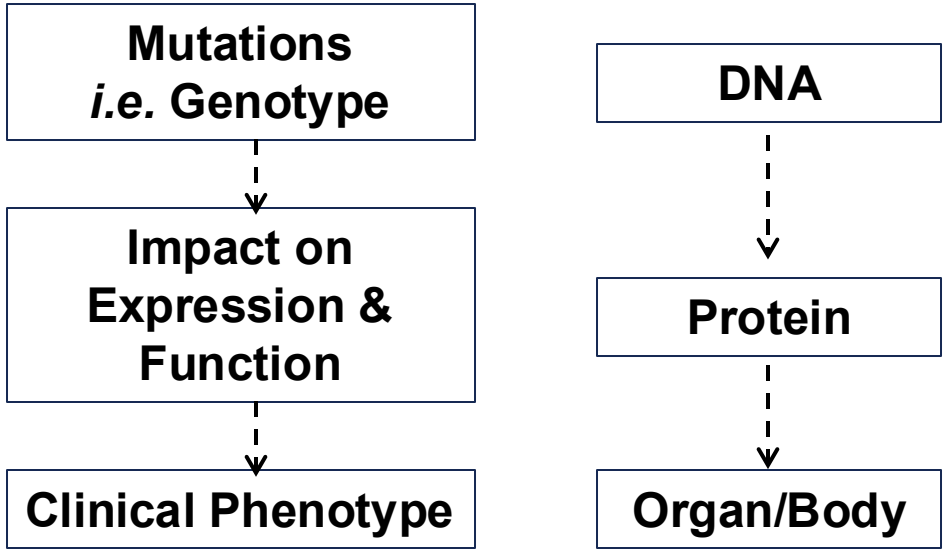
Genetic Heterogeneity

- Loss of Expression
- Loss/Gain of Function

- Haploinsufficiency
- Dominant Negative

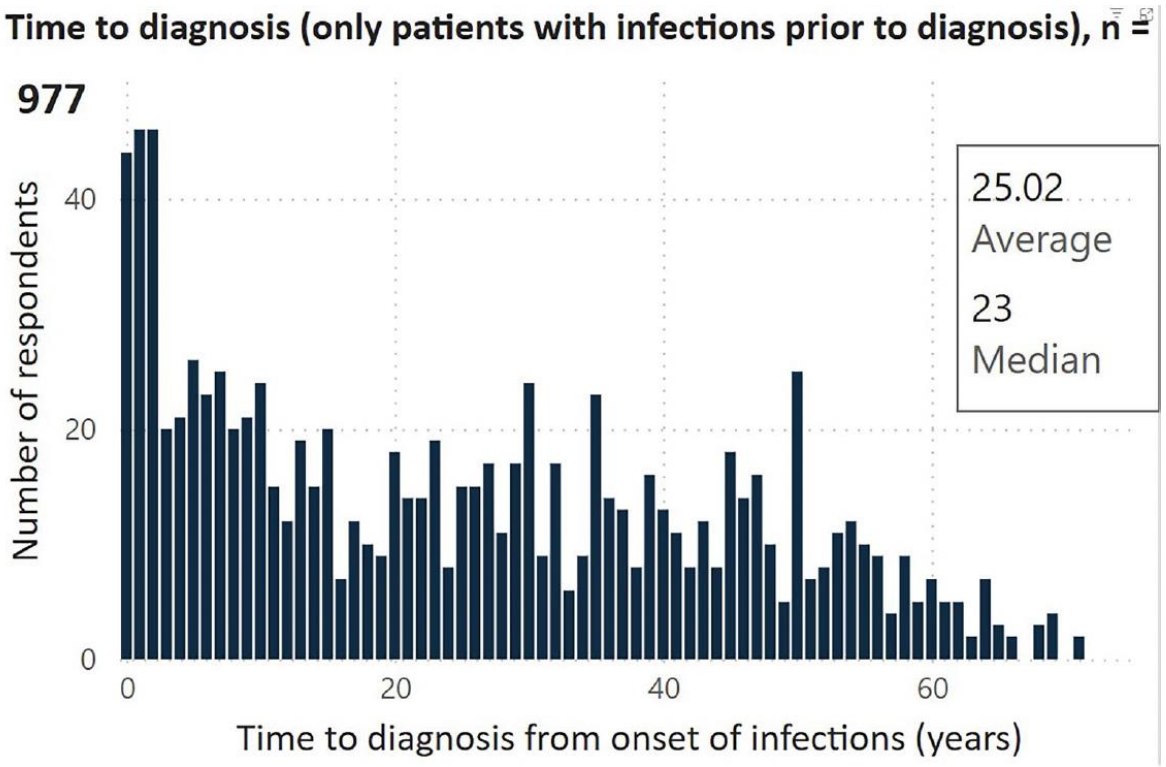
- Hypomorphic
- Neomorphic

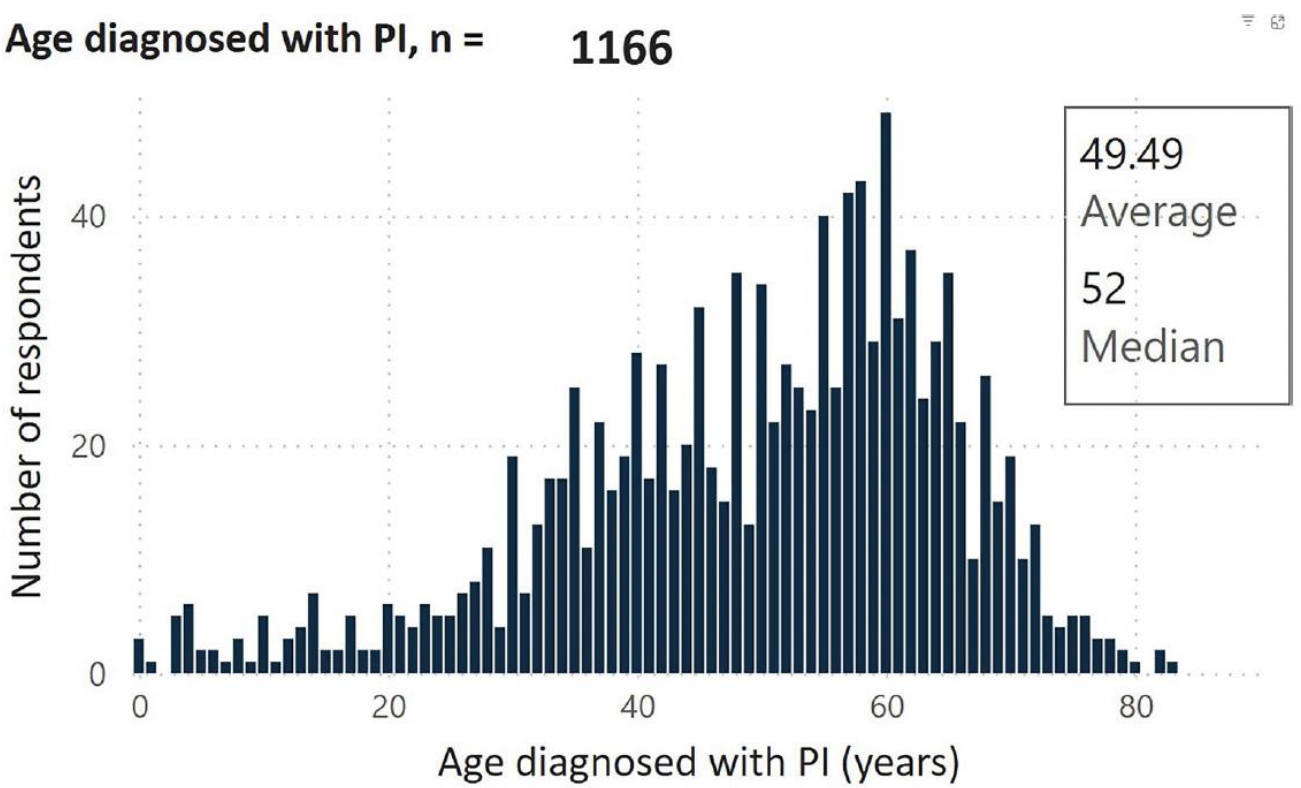
- Somatic Mutations
- Random Monoallelic Expression



Notarangelo et al., 2020

What is the Problem that we want to Solve in IEI?
From Scientists Perspective: Dissect Mechanism
From Patients Perspective:
Shorten the Long Diagnostic Odyssey …



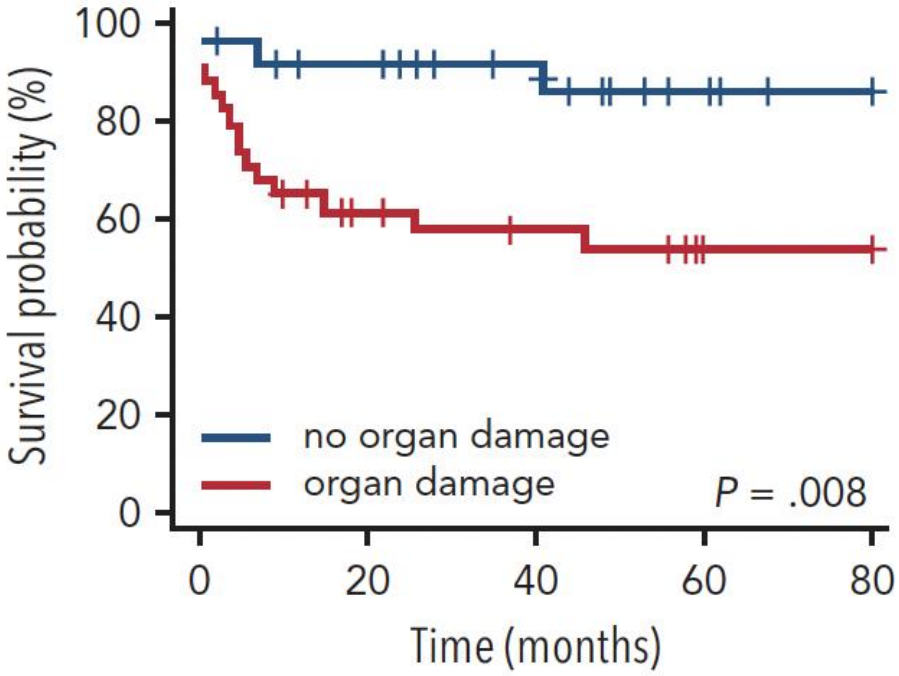


Kim et al., 2024

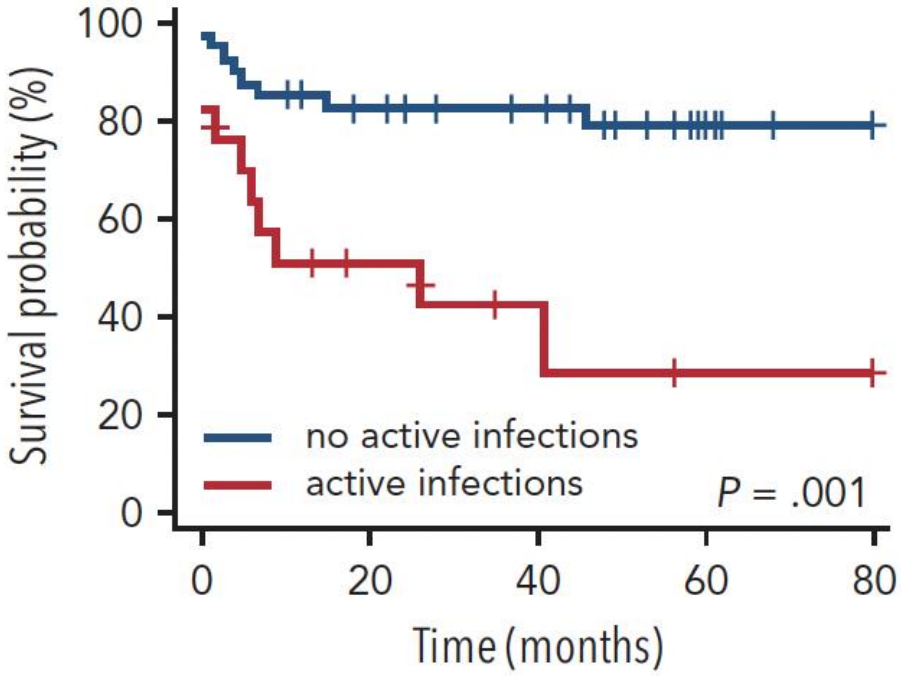
Why Do We Need & Care To Solve This Problem in IEI?

Efficiency of Diagnosis = Improved Survival

Organ Damage prior to Hematopoietic Stem Cell Transplant (HSCT)



Uncontrolled Infections prior to Hematopoietic Stem Cell Transplant (HSCT)



Schuetz et al., 2023

Why Do We Need & Care To Solve This Problem in IEI?

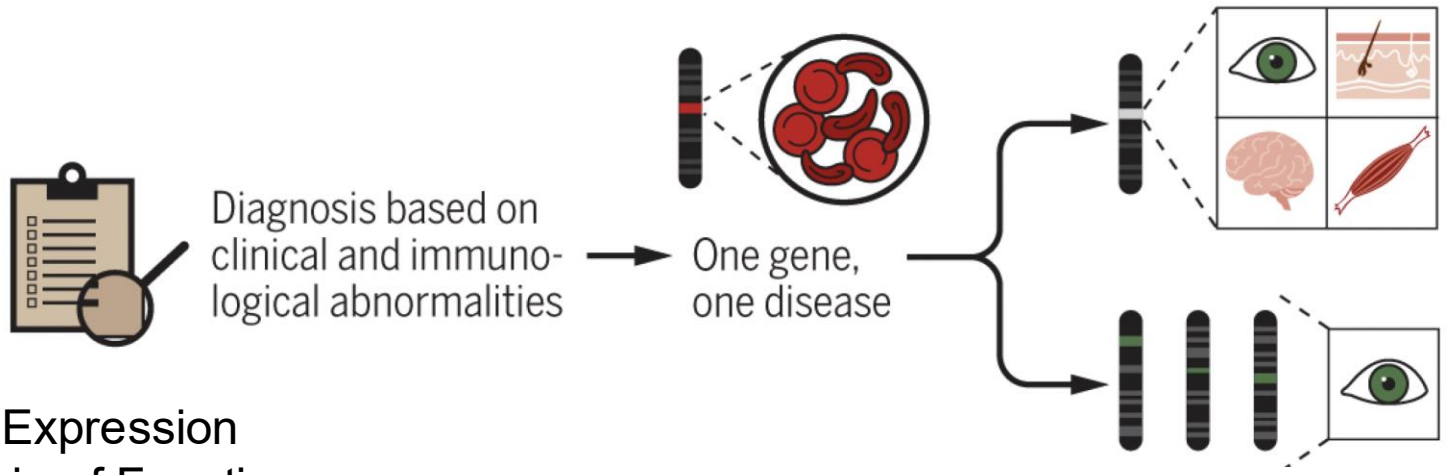
We don't just want our Patients to Survive …
We Want them to Thrive

Efficiency of Diagnosis + Precise Therapy =
Improved Survival & Quality of Life

Precision Medicine = Personalized Pathway-Specific Therapy

The goal of precision medicine is to treat the ***right patient*** with the ***right treatment*** to at the ***right time***

IEI: Genetic and Molecular Heterogeneity



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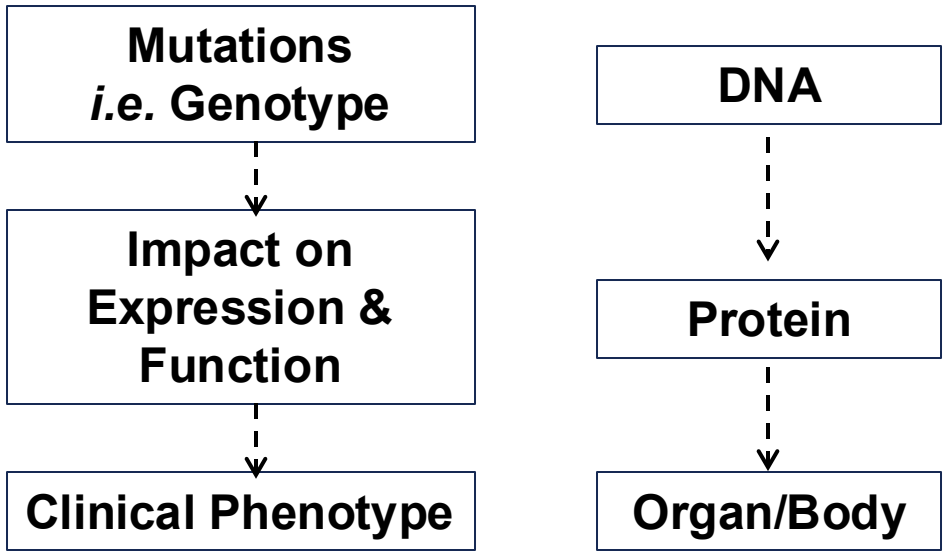
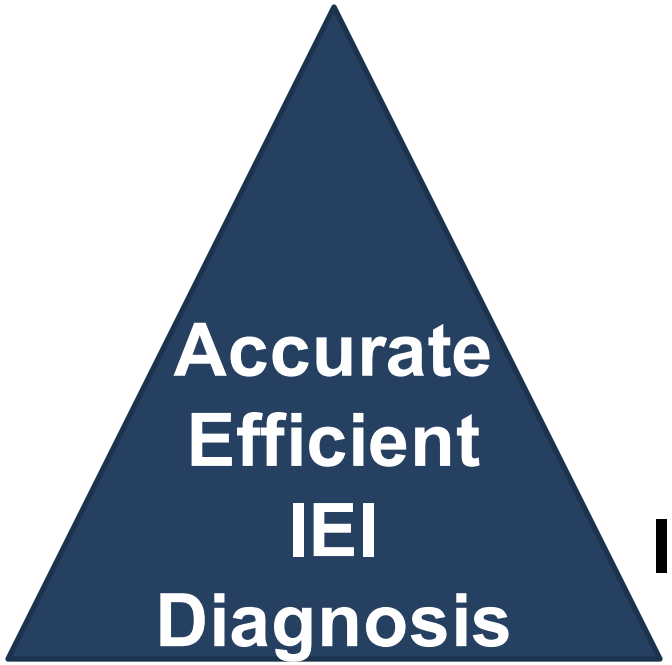


How do We Solve this Problem … Faster while keeping our Patients Well?

Notarangelo et al., 2020

How do we Find "The Right Patient:" The Traditional "Wholly Trinity" of IEI Diagnosis

Clinical Presentation & Family History

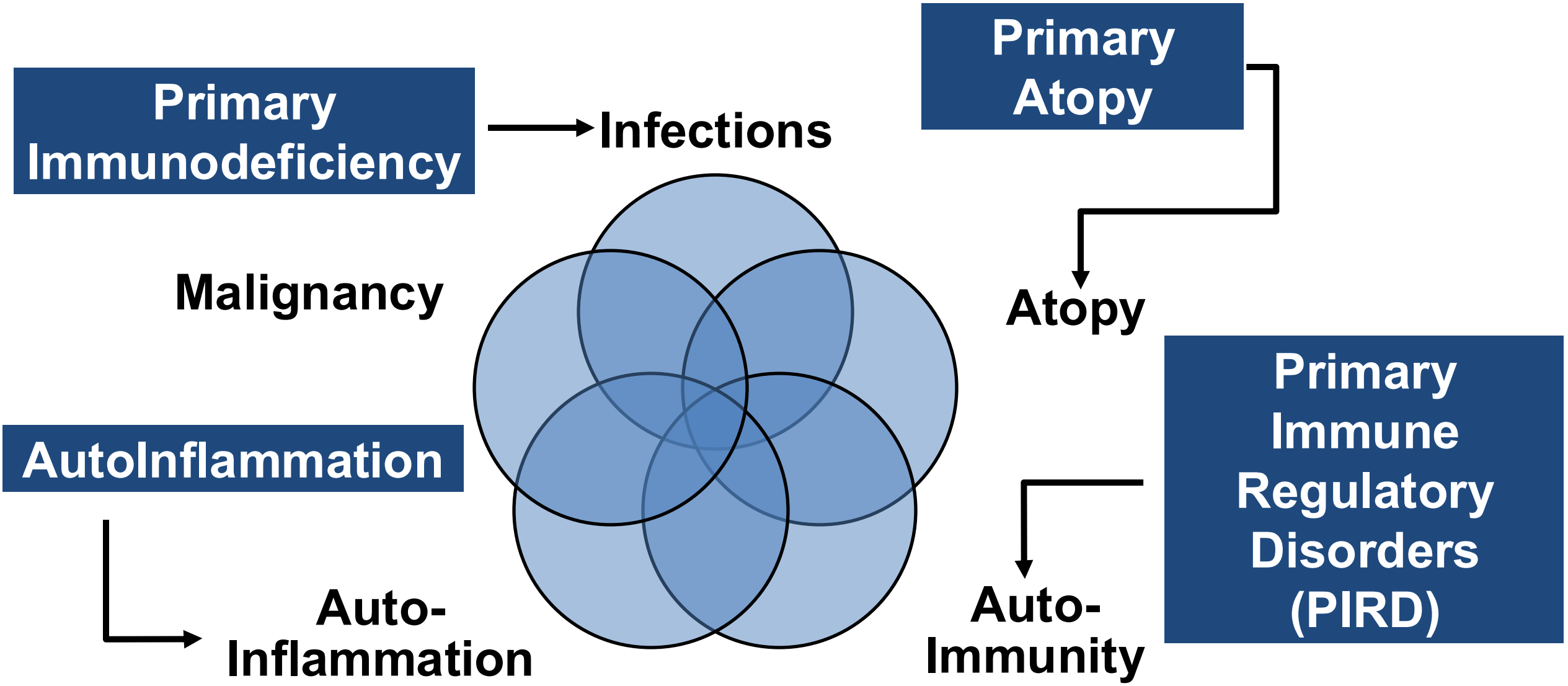


Clinical Immune Diagnostic Evaluation

Genetic Analysis Identification of Variants

Adapted from Abraham & Butte, 2021

IEI Categories Based on Clinical Phenotypes



IEI Categories Based on Clinical Phenotypes

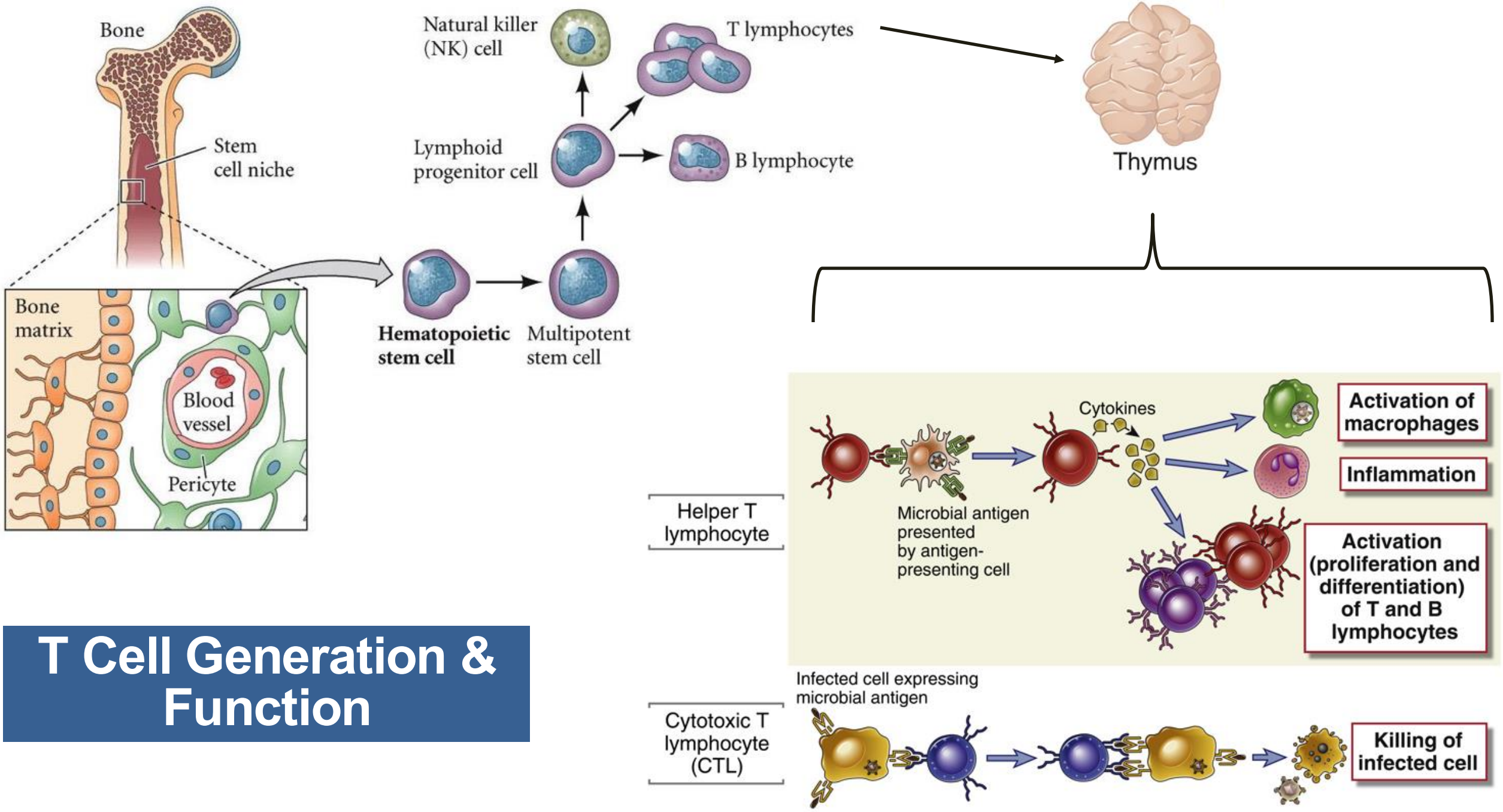
- (Severe) Combined Immunodeficiency
- Syndromic Combined Immunodeficiency
- Predominantly Antibody Deficiencies
- Immune Dysregulation Disorders
- Phagocyte Defects
- Innate Immunity Defects
- Autoinflammatory Diseases
- Complement Deficiency
- Bone Marrow Failure
- Phenocopies

‘Boy in the Bubble’ Moved a World He Couldn’t Touch

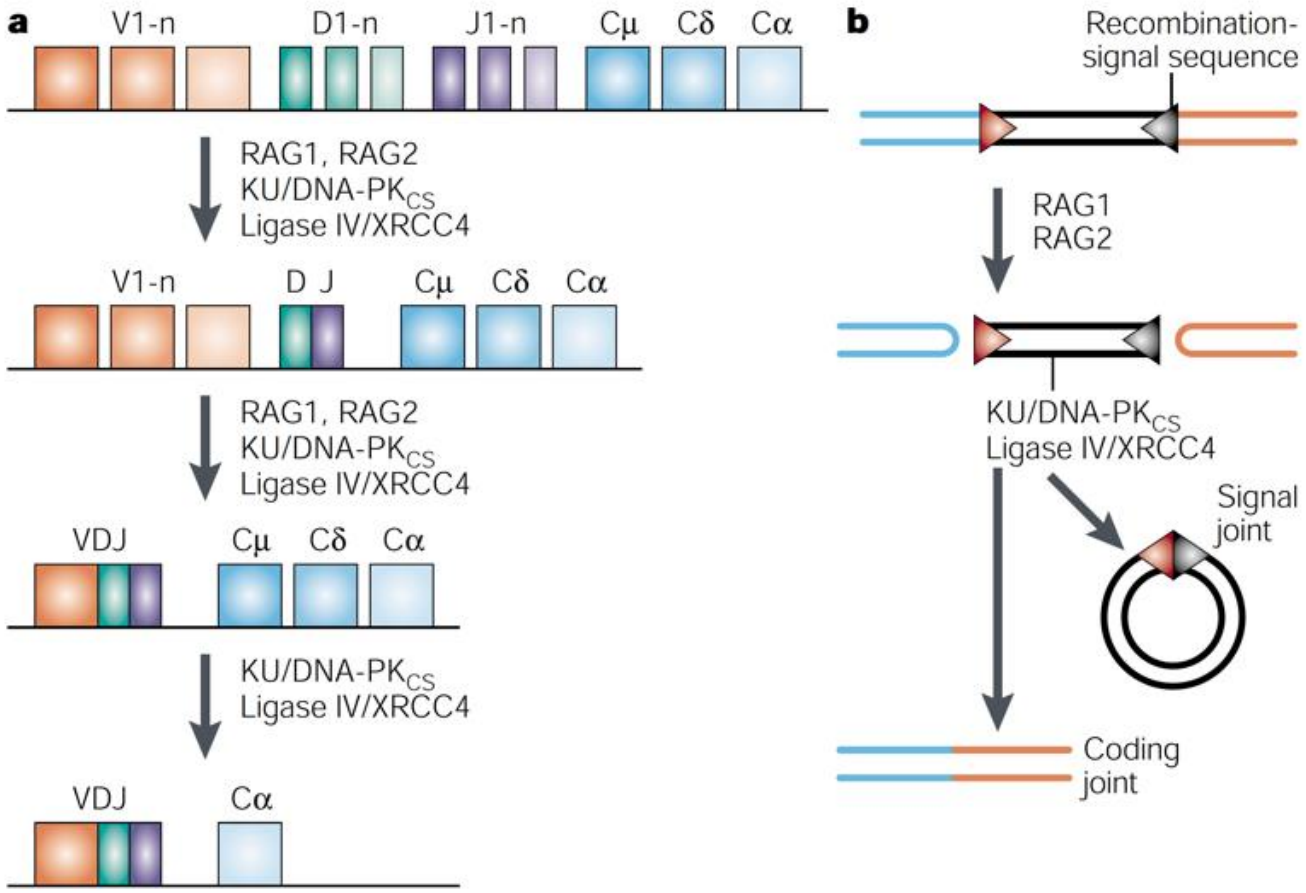
Severe Combined Immunodeficiency (SCID)

- Incidence of approximately **1 in 50,000** births
- Defects of cellular and humoral immunity, with the hallmark of a **severe deficiency of T cells**
- Collection of individual primary immunodeficiency diseases
- Although typically appearing normal at birth, infants are at risk for **life-threatening infections**
- Correctable by **hematopoietic stem cell transplantation (HSCT)**, **enzyme replacement therapy**, and/or **gene therapy**

T Cell Generation & Function



T Cell Development
VDJ Recombination (T & B Cells)



T Cells

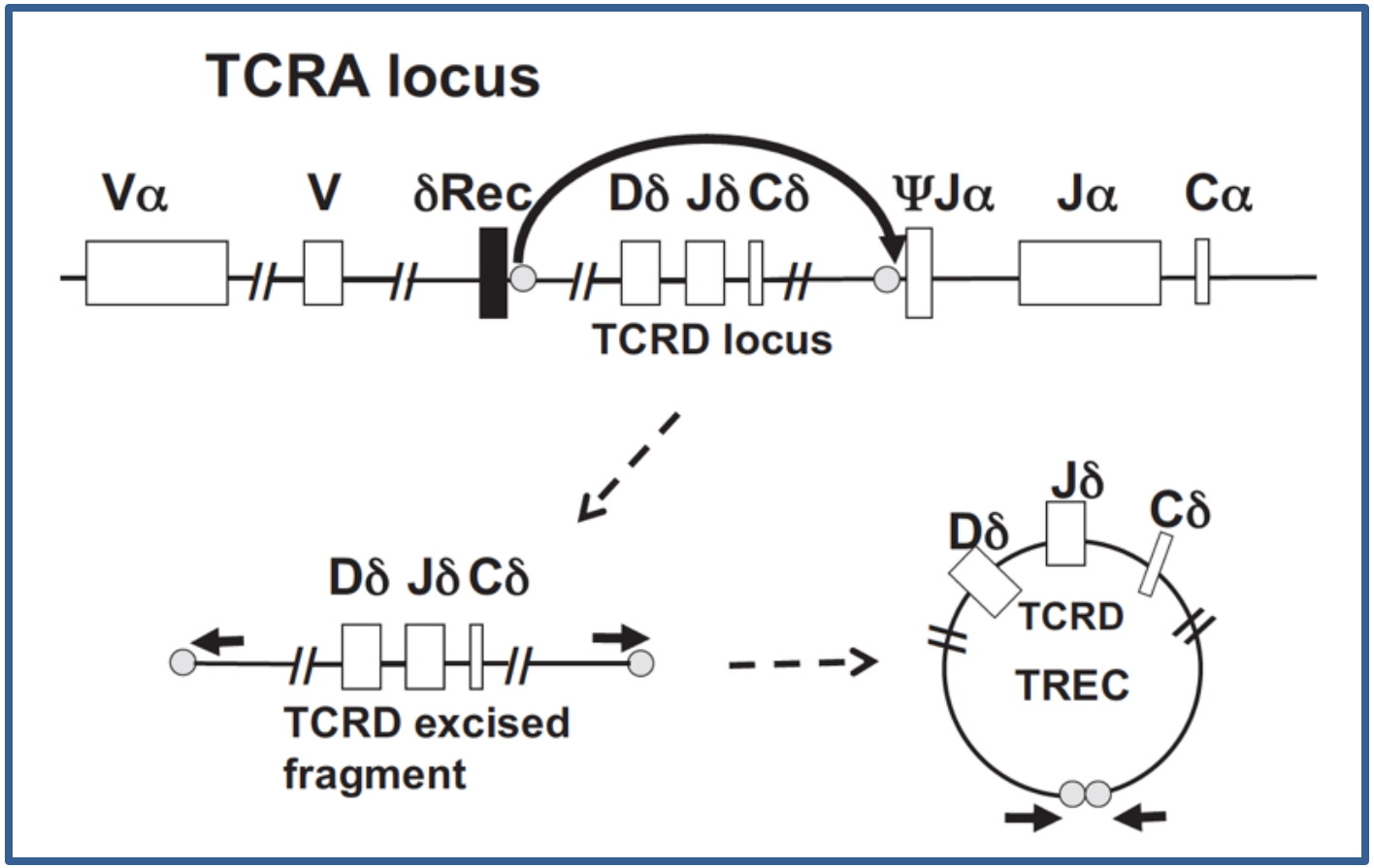
T Cell Receptor (TCR)
Gene Rearrangement

B Cells

B Cell Receptor (BCR)
Gene Rearrangement

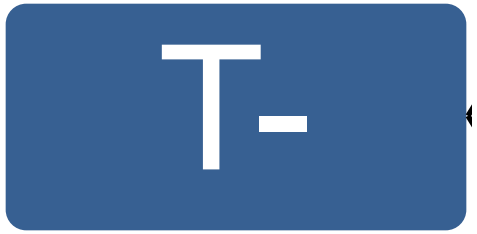
COLORADO
Department of Public Health & Environment

Severe Combined Immunodeficiency T-cell Receptor Excision Circle (TREC)



Puck JM, J Allergy Clin Immunol, 2012

SCID Genetic Etiologies: What is the Lymphocyte Phenotype?



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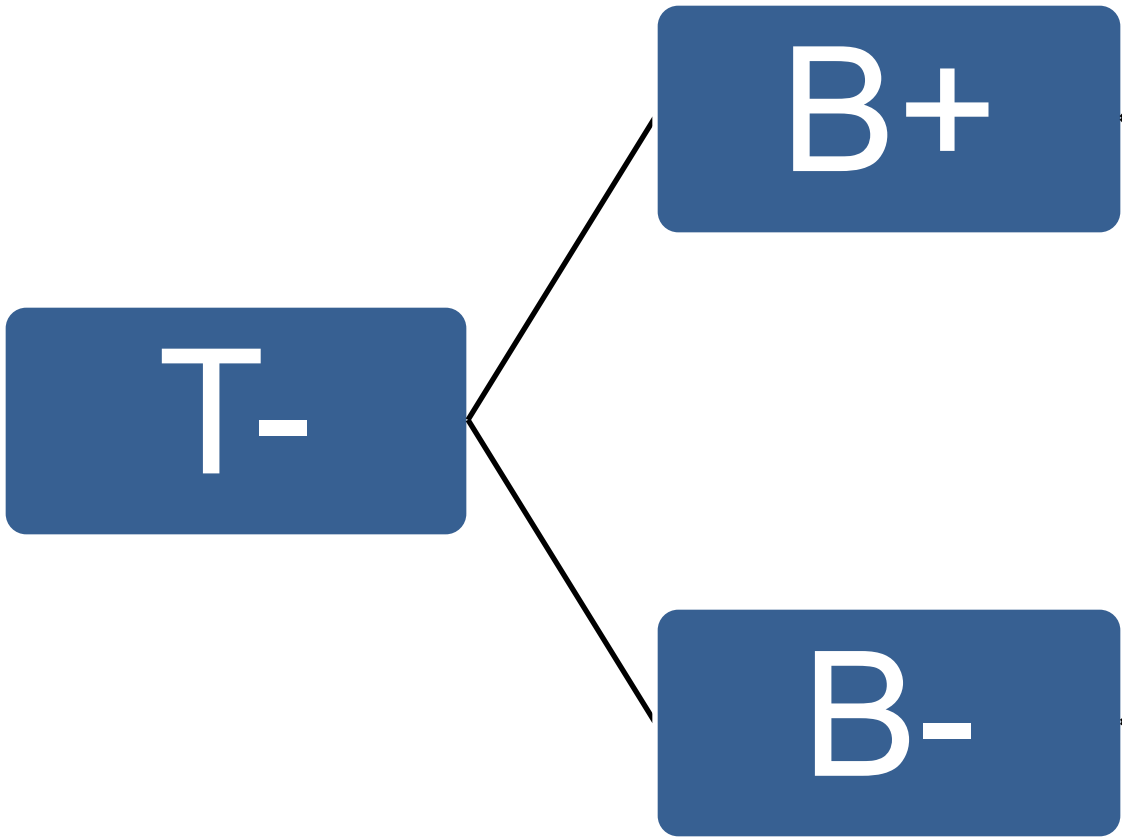

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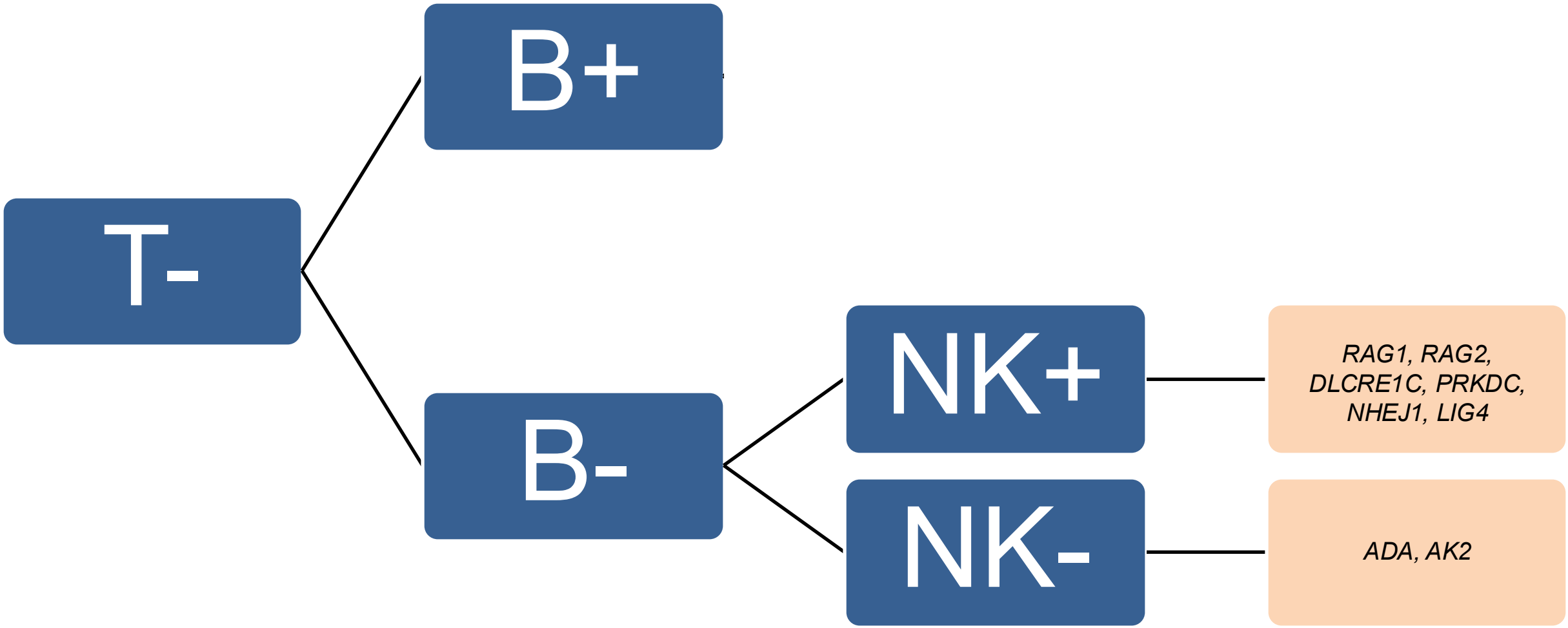

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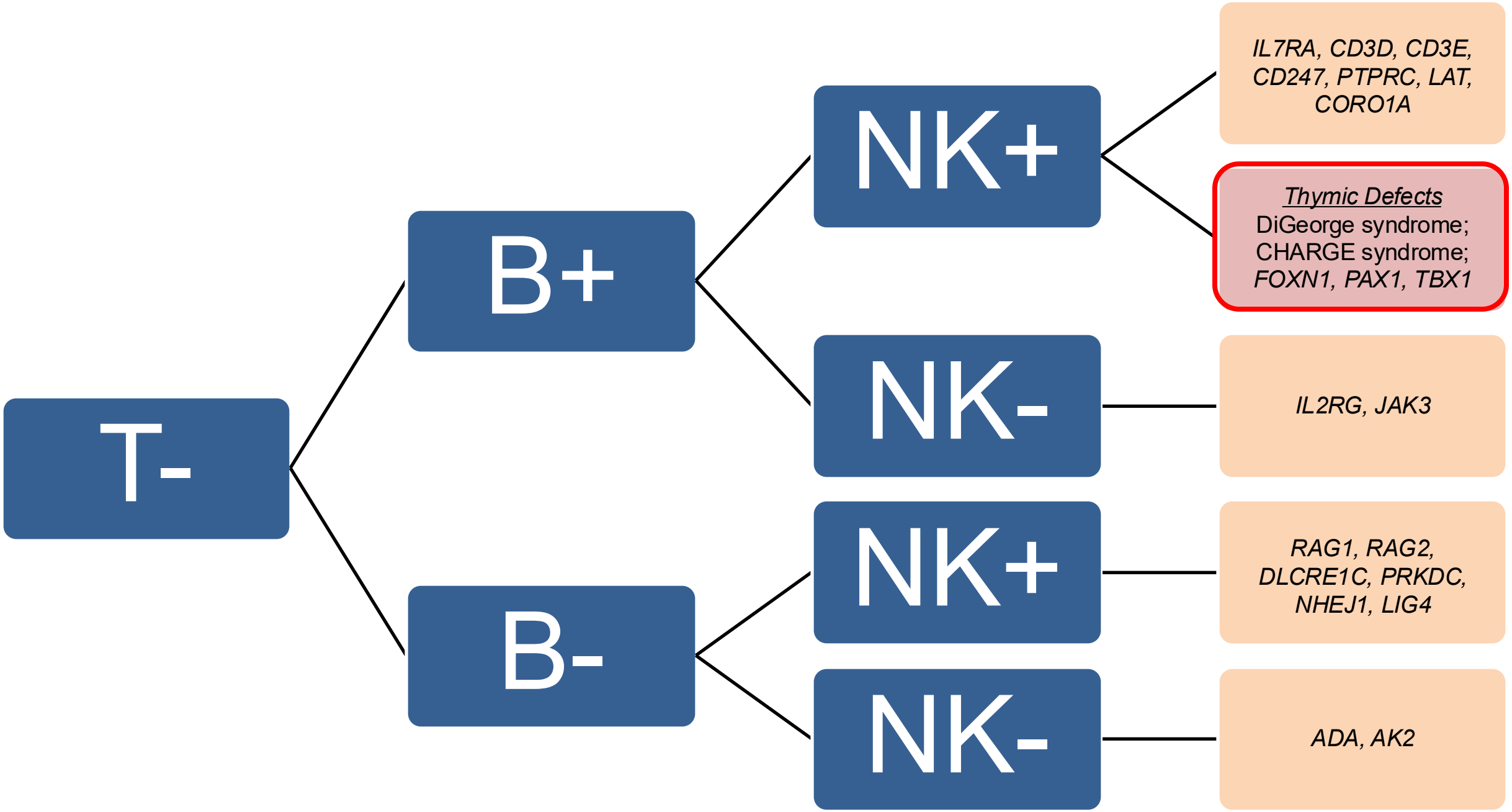
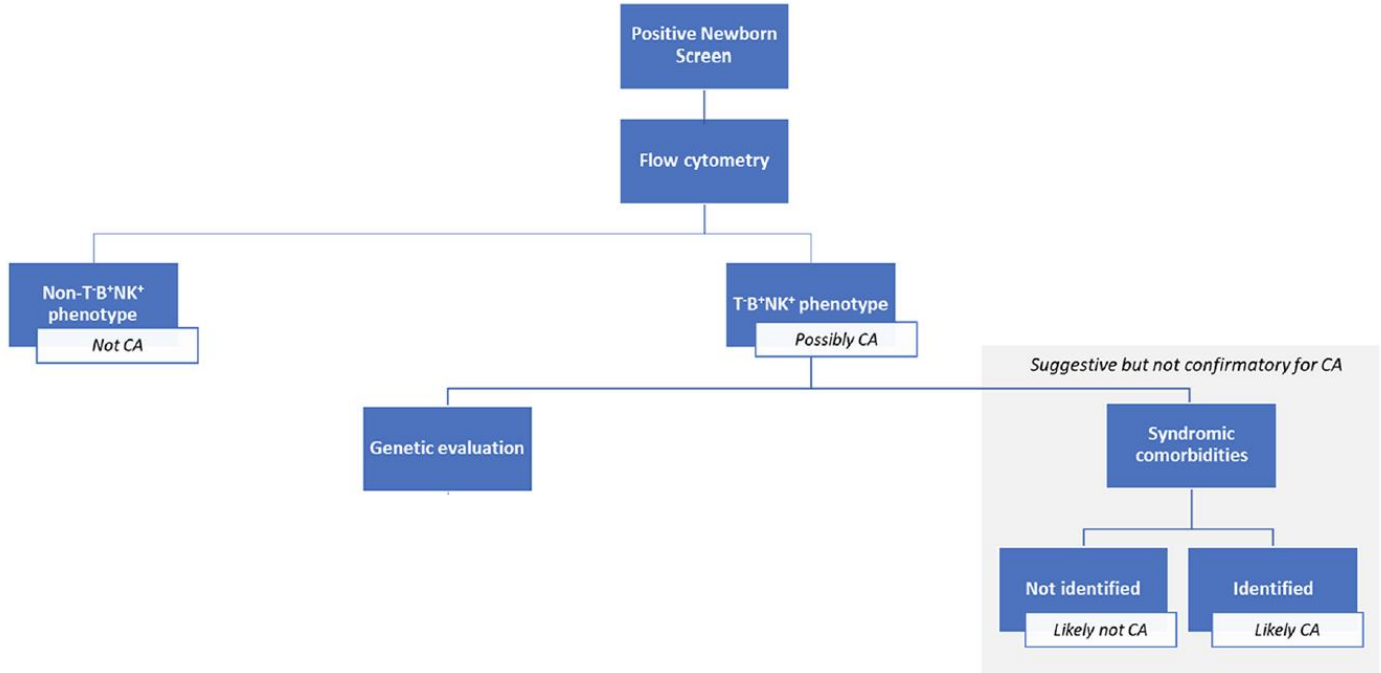
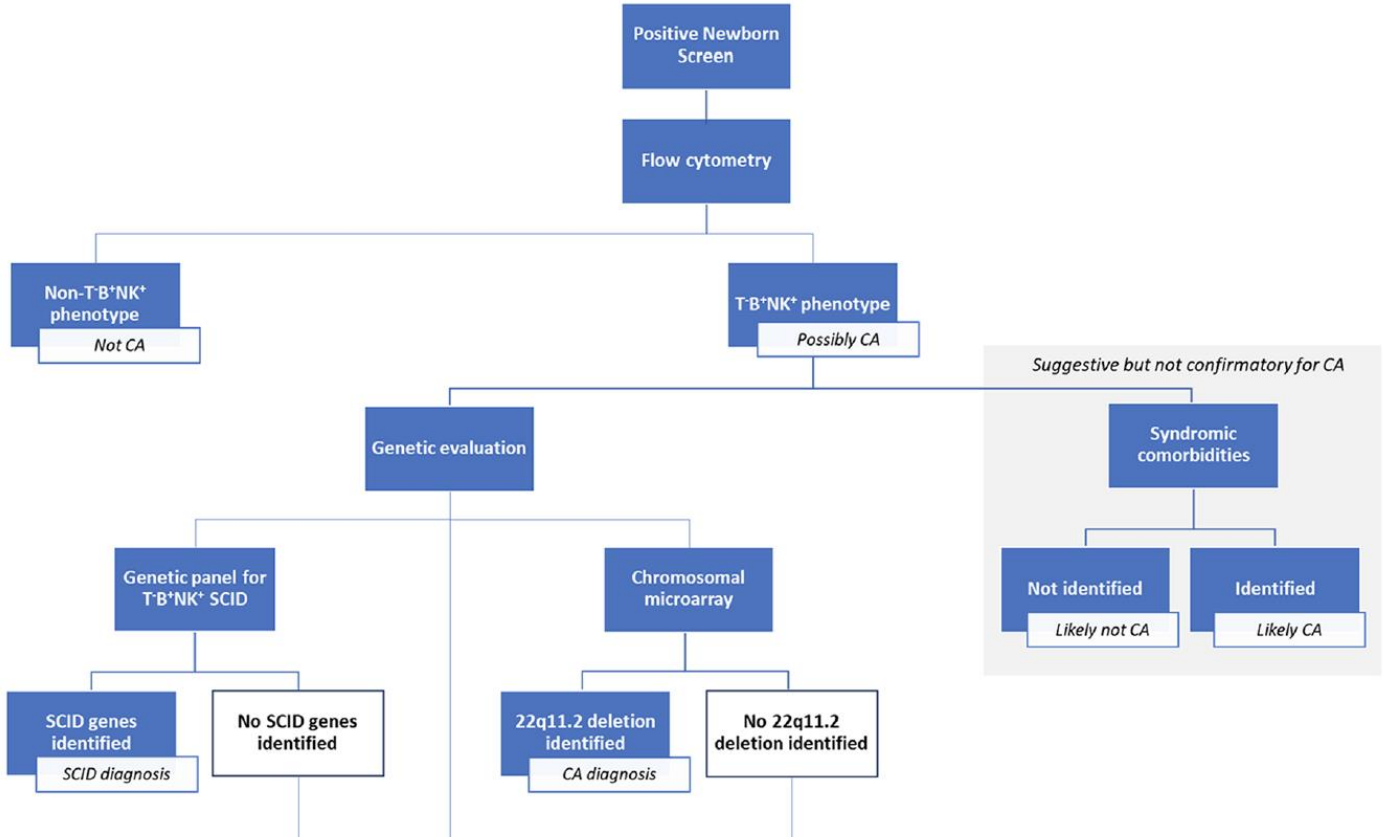




Collins et al., J Clin Immunol (JOCI), 2021



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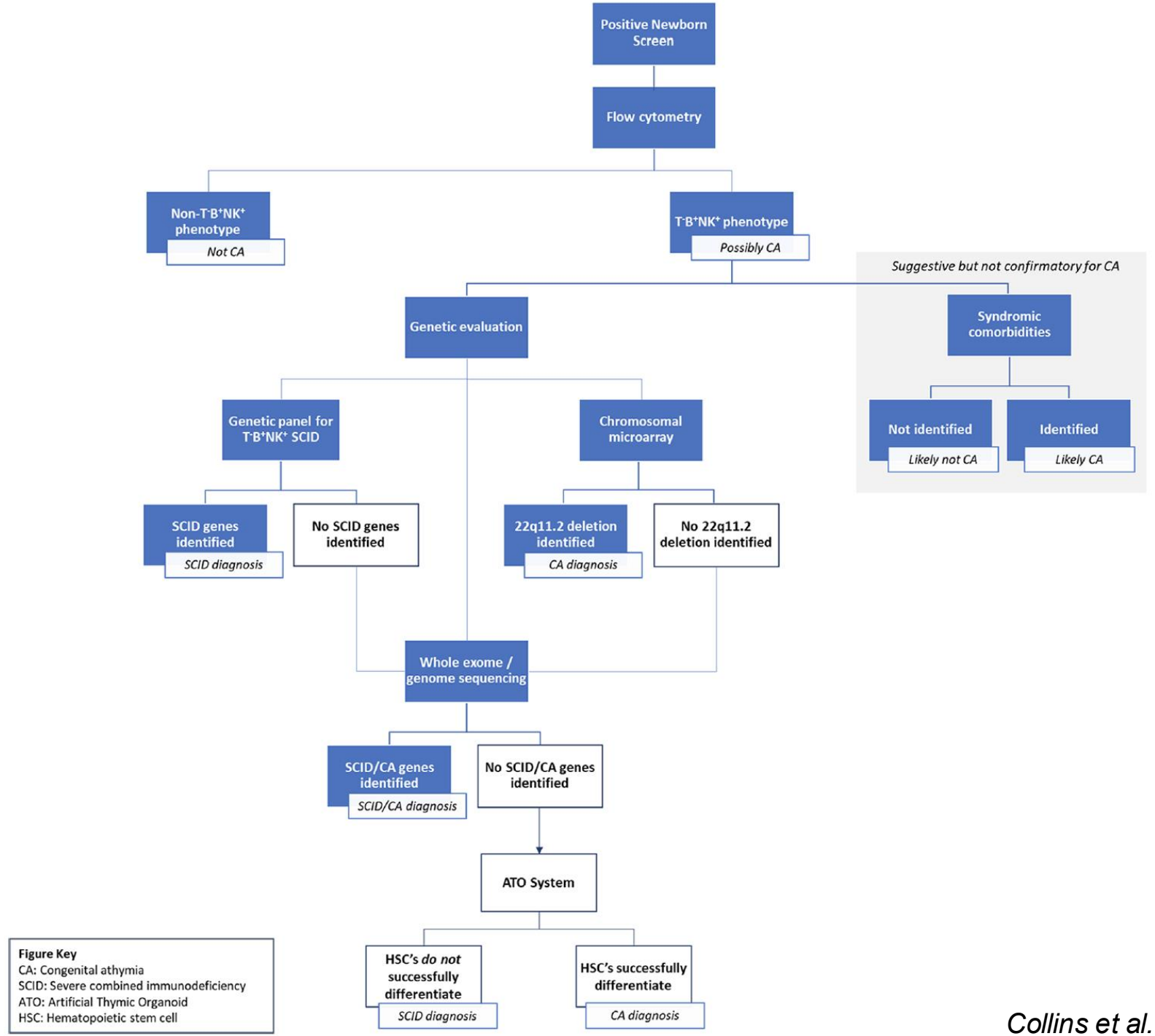
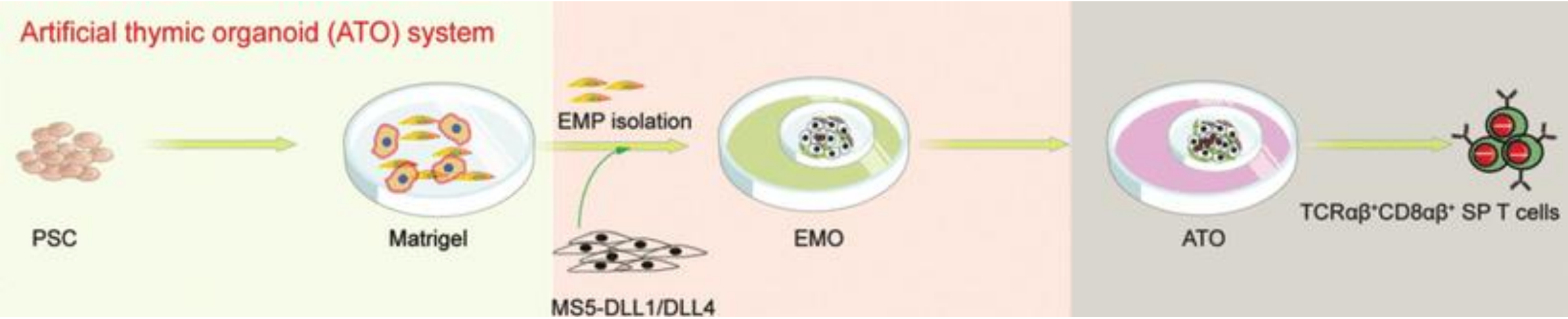


Collins et al., J Clin Immunol (JOCI), 2021

Artificial Thymic Organoids (ATO) as a Reliable Diagnostic Tool for Patients with Undifferentiated (Severe) Combined Immune Deficiency (SCID and CID)



Bosticardo et al., Blood Advances, 2020

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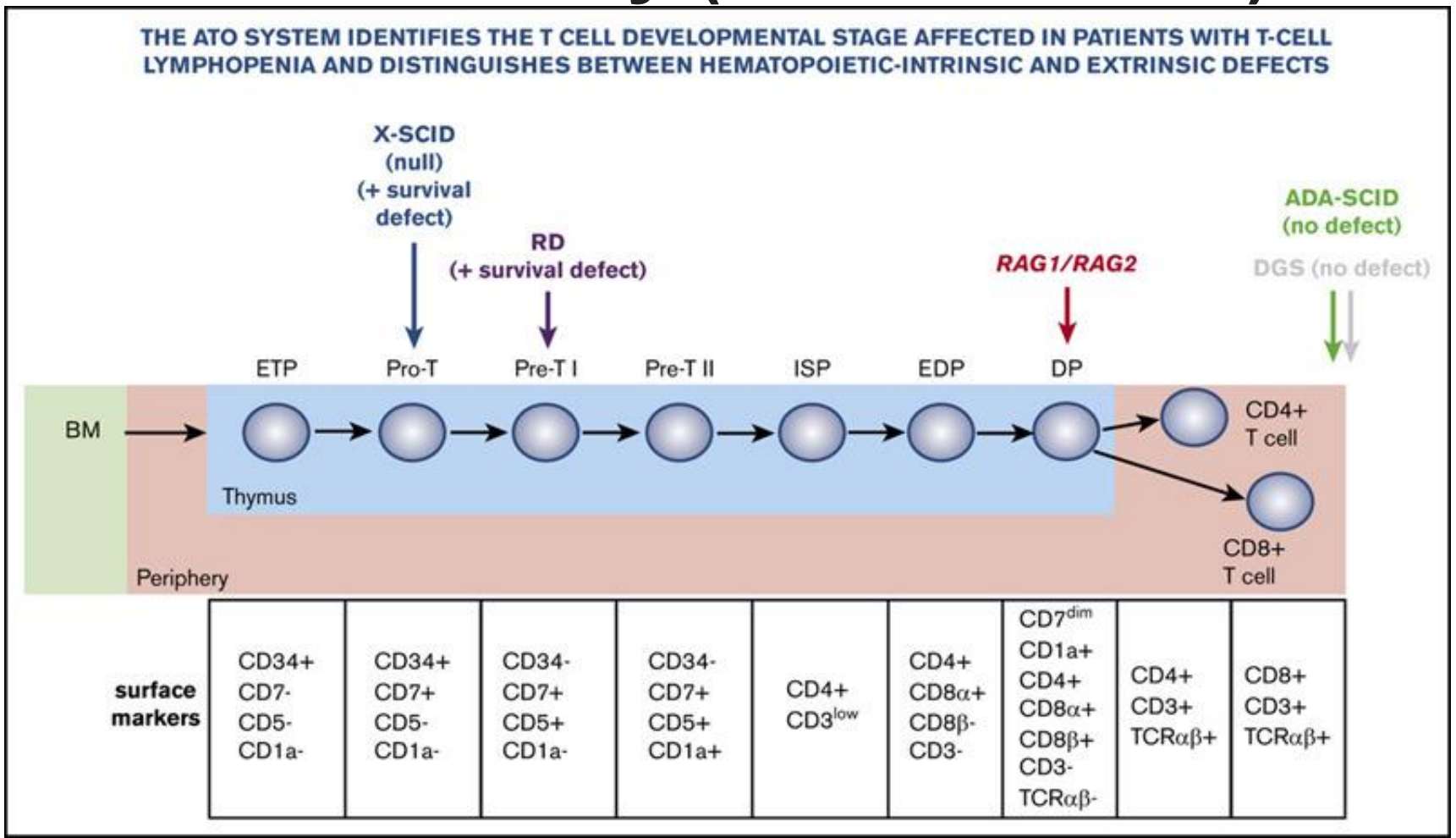

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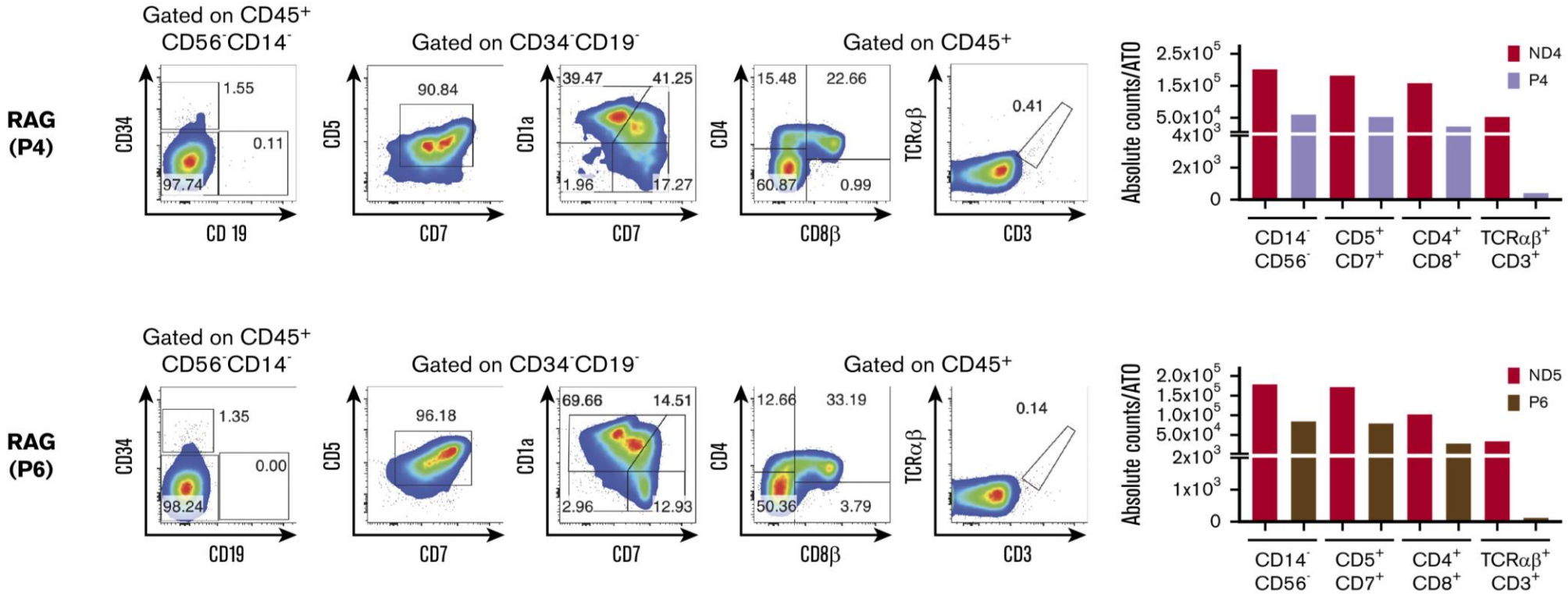
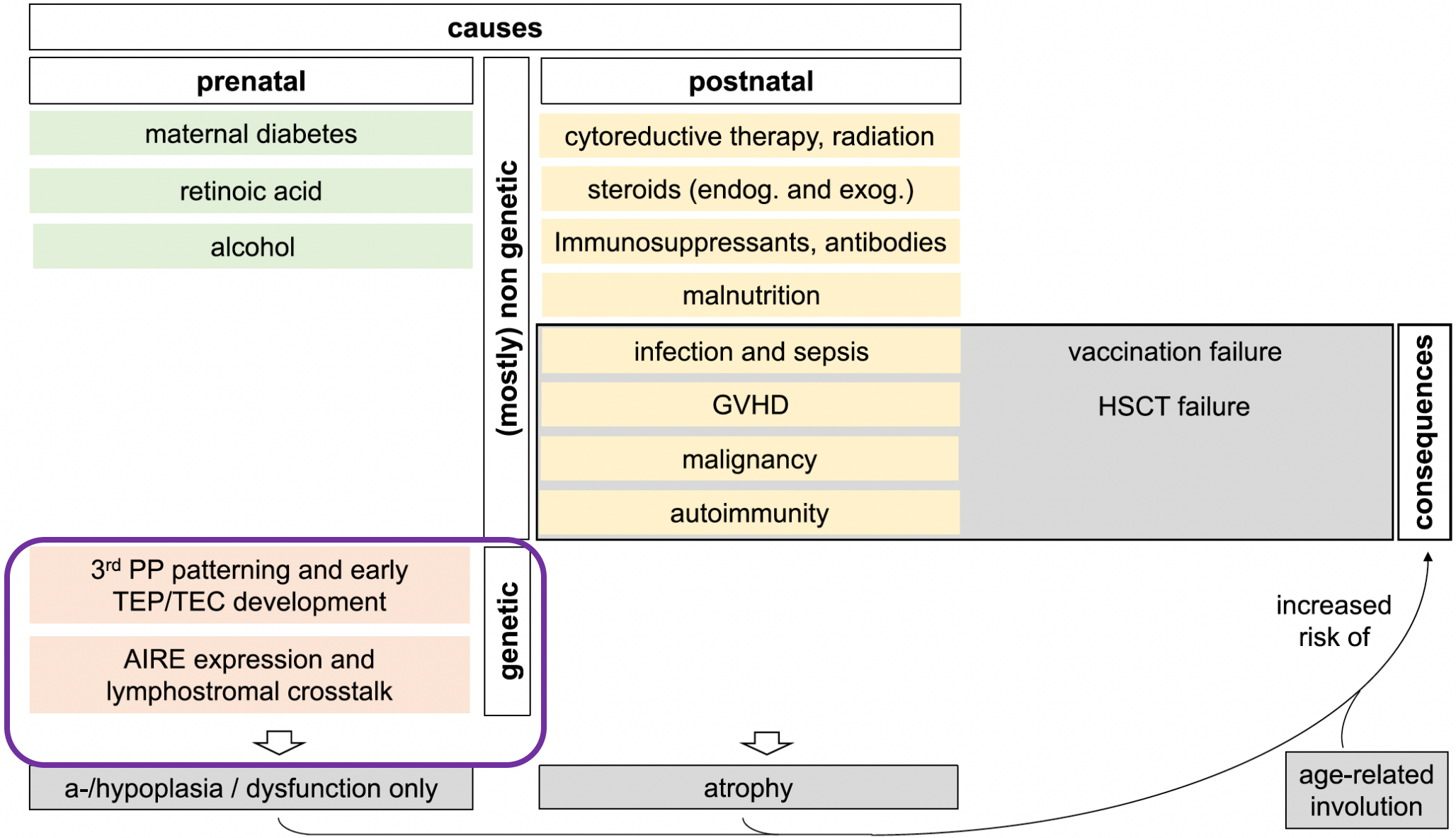


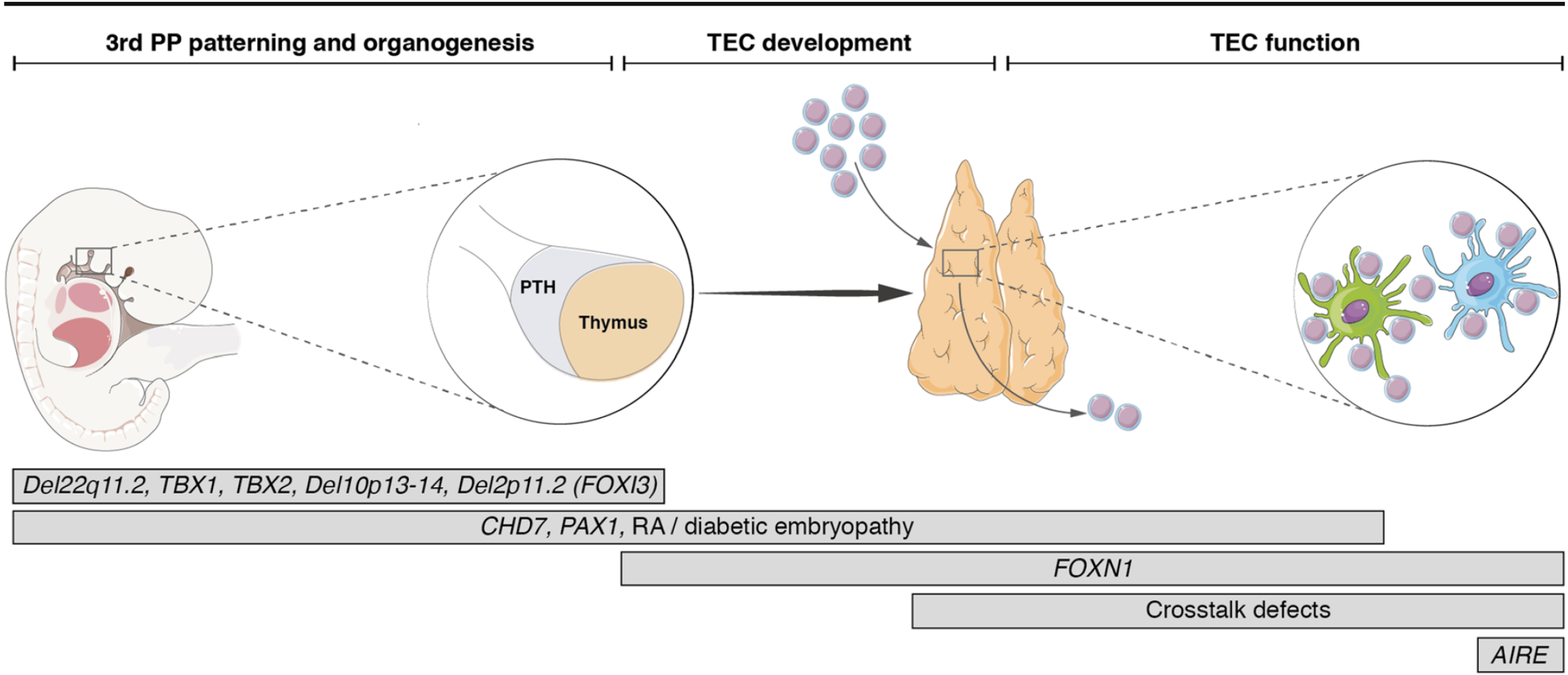
Bosticardo et al., Blood Advances, 2020

Primary & Secondary Defects of the Thymus



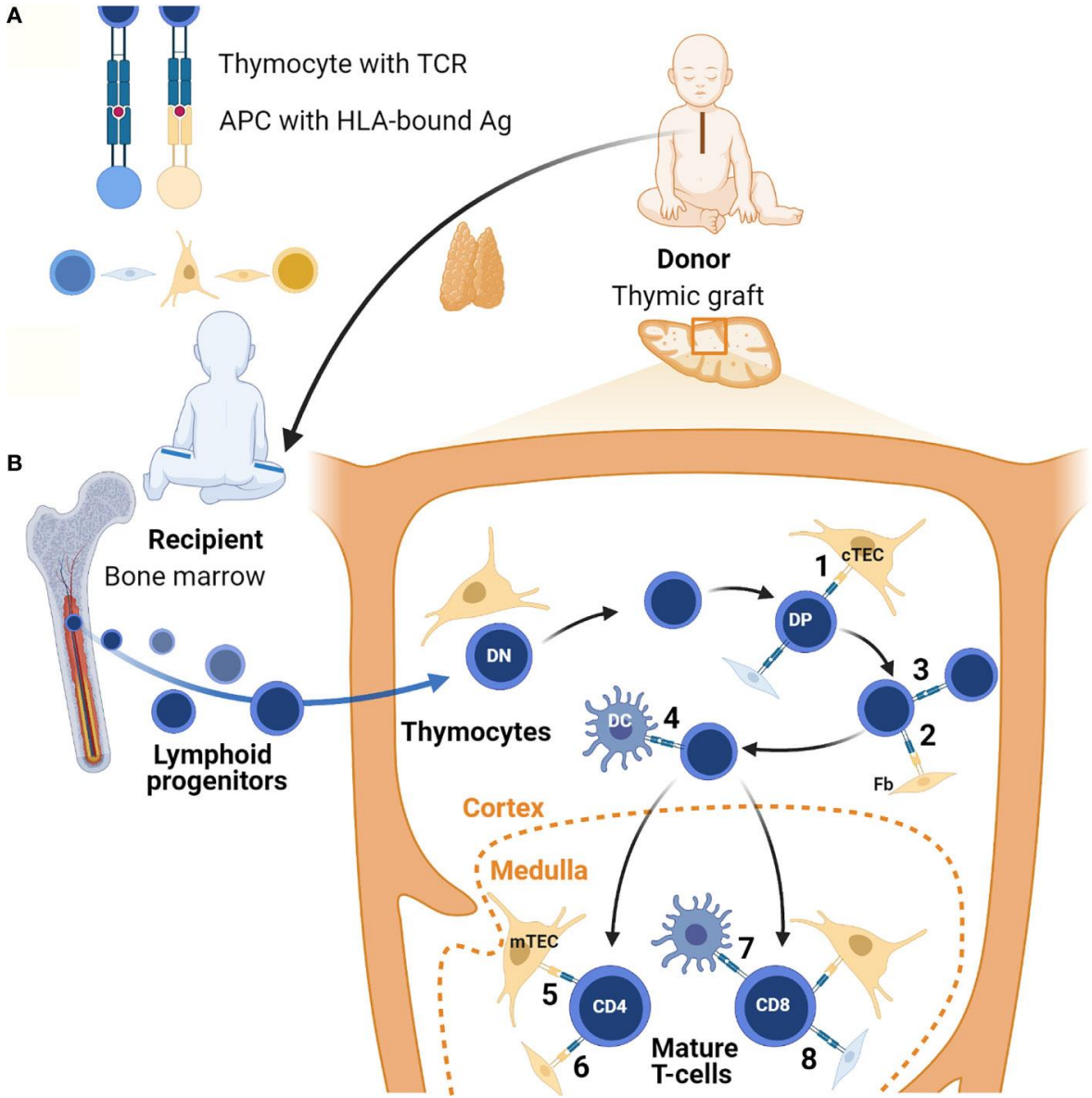
Dinges et al., Immunol Rev, 2024

Genetic Etiologies of Congenital Athymia and Impact of Embryogenesis



Kreins et al., Semin Immunopathol, 2021

Thymus Implant: Lymphostromal Crosstalk in Thymic Grafts



Kreins et al., Front Immunol, 2021

Congenital Athymia:
Rethymic® FDA Approved October 2021

RETHYMIC®
allogeneic processed thymus tissue-agdc

The engineering process

Unlike a transplant, RETHYMIC is engineered for one patient at a time through a complex process using donor thymus tissue[1,6]

Donation of thymus tissue

When an infant ≤9 months of age undergoes cardiac surgery, some thymus tissue may need to be removed to access the heart. **With consent of the infant donor's parents or guardian, the thymus tissue is donated and undergoes extensive testing** to determine the viability and safety of the tissue for making RETHYMIC.[6]

Unlike many other medications or specialty biologics, RETHYMIC is not an off-the-shelf product. **The thymus tissue from a single infant donor allows for the manufacturing of RETHYMIC for one patient.[1]**

The availability of RETHYMIC is largely dependent on the size and viability of the thymus tissue that is donated.[6,7]

Development of RETHYMIC

The time the engineering process takes depends on multiple factors and can be completed between **12 and 21 days.[7]**

RETHYMIC is engineered in a dedicated environment that follows strict FDA requirements. The manufacturing personnel have been extensively trained on proper safety protocols to maintain a sterile environment and avoid cross contamination.

The engineering process requires manufacturing personnel to manually change the media, preserving thymic epithelial cells and tissue structure while depleting most of the donor thymocytes. During this time, **the donor thymus tissue goes through multiple rigorous tests**—some of which are repeated—to ensure the product meets FDA safety standards.[1,7]

Implantation of RETHYMIC

The dosage is determined based on the total surface area of the RETHYMIC tissue slices, and **the amount implanted is calculated based on the recipient's BSA.[1]**

Once released from the manufacturing facility, RETHYMIC must be implanted within a limited time frame at the treatment center.[7]

Careful coordination of the engineering of RETHYMIC must coincide with the preparation of a potential patient to receive the product.[7]

Figure 1: Preparing for the Implantation Procedure

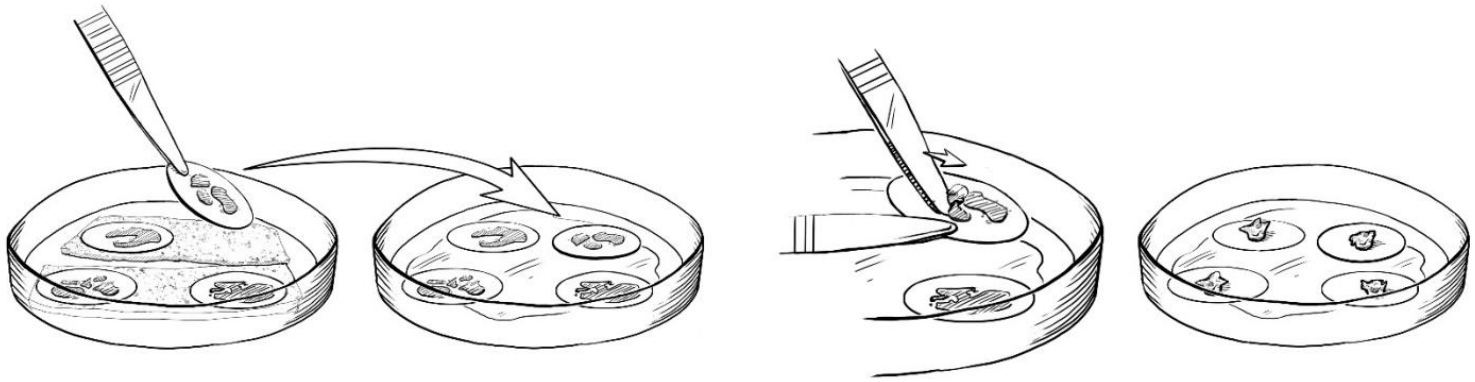


Figure 2: Surgical Incision and Opening of Fascia

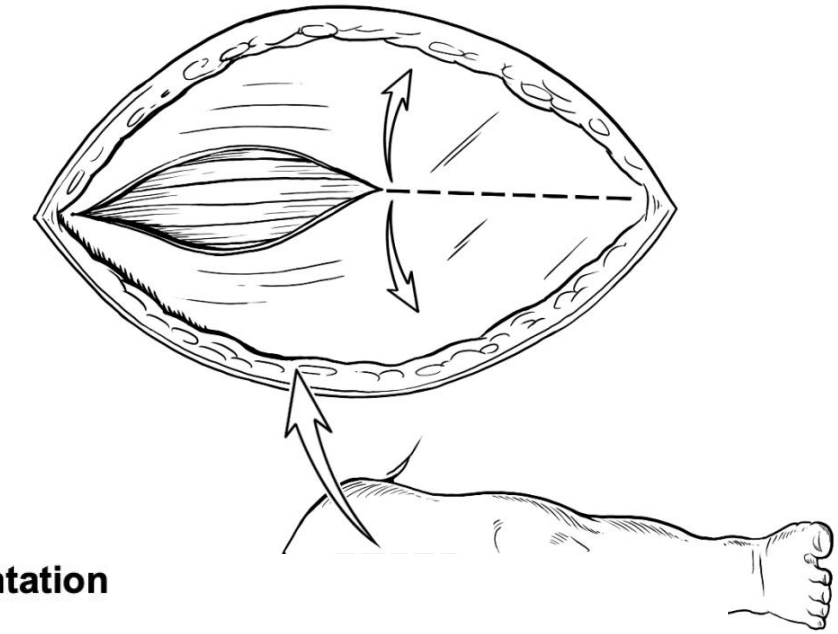


Figure 3: Implant Individual RETHYMIC Slices

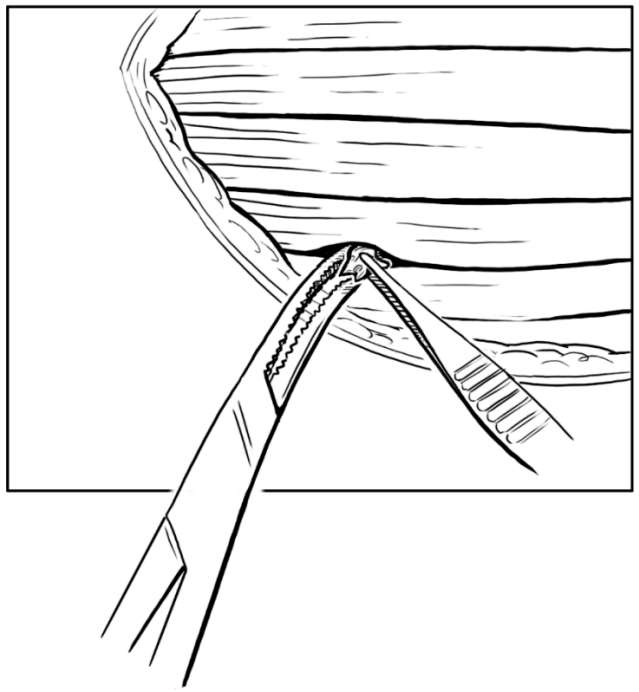
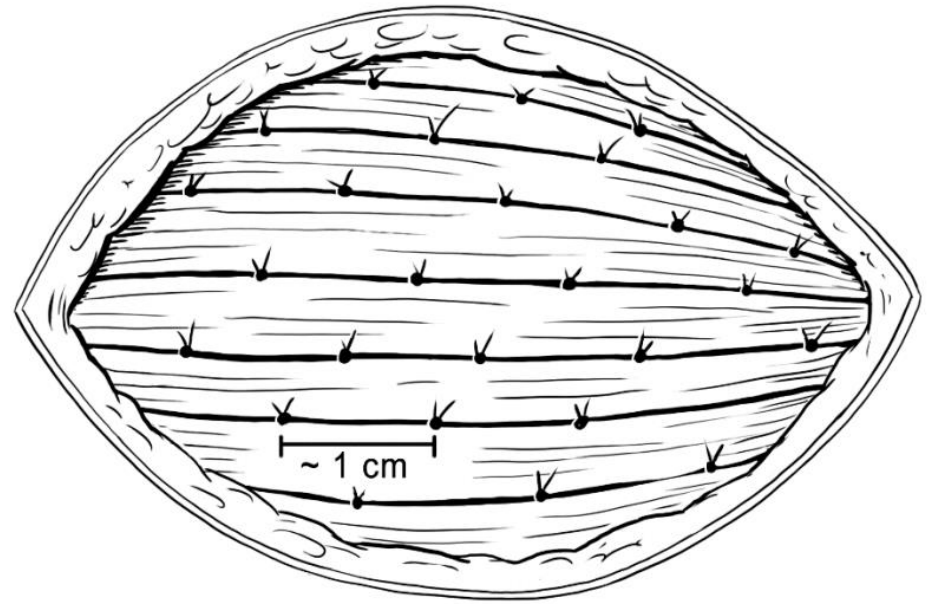
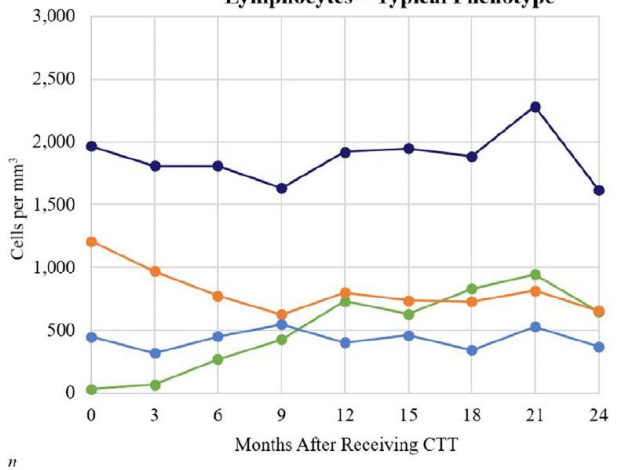


Figure 4: Close the Site of Implantation



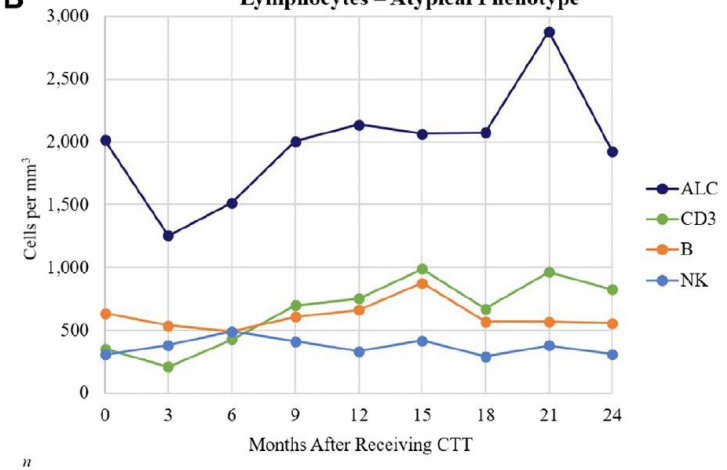
Congenital Athymia: Immune Reconstitution post Implantation

A



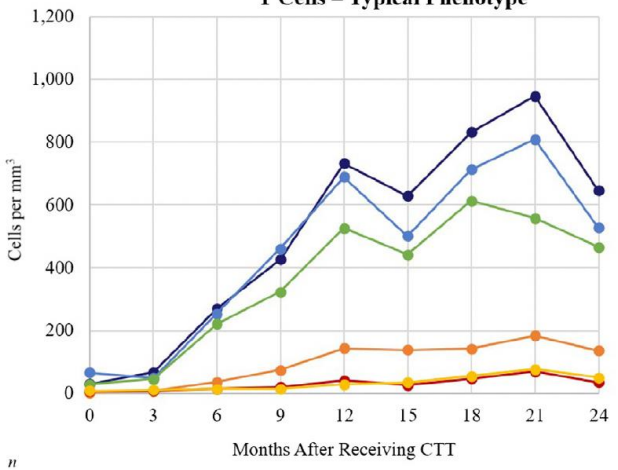
n									
ALC	50	45	38	31	28	16	18	12	18
CD3	50	45	39	33	30	20	18	12	18
B	49	45	39	32	30	19	18	12	18
NK	50	44	38	32	28	19	32	28	19

B



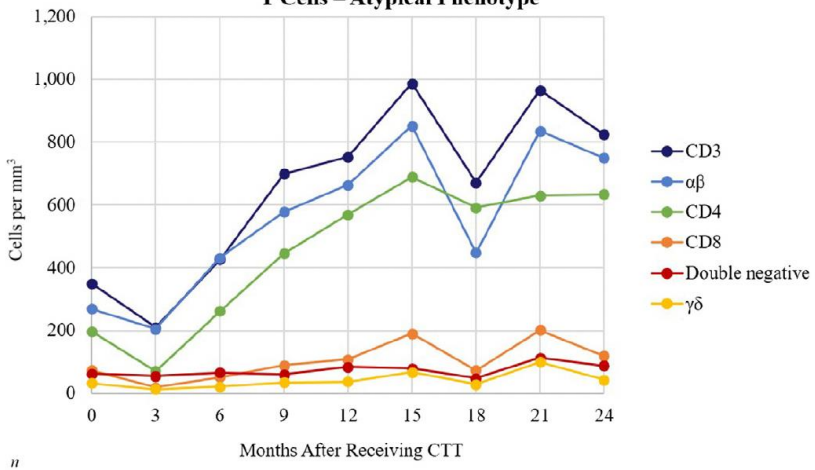
n									
ALC	42	36	32	27	24	17	11	8	12
CD3	42	36	34	28	24	17	12	9	12
B	42	36	33	28	25	17	12	9	10
NK	42	36	33	28	25	17	12	9	13

C



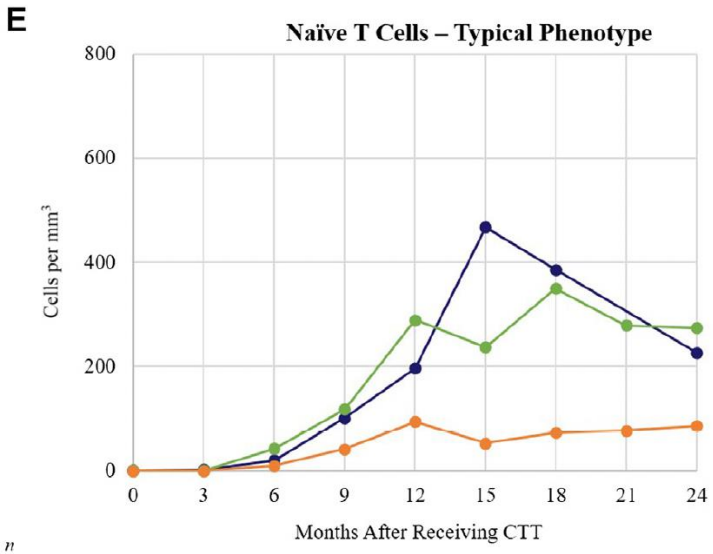
n									
CD3	50	45	39	33	30	20	18	12	18
αβ	31	38	33	25	23	9	14	9	15
CD4	40	41	38	32	29	20	18	12	18
CD8	38	38	38	32	29	19	18	12	18
db neg	18	23	23	19	19	9	14	8	11
γδ	31	38	33	25	23	9	14	9	14

D



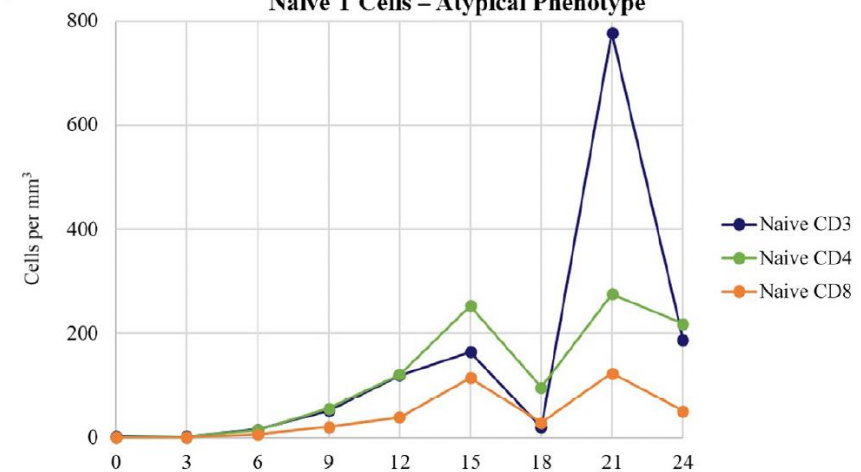
n									
CD3	42	36	34	28	24	17	12	9	12
αβ	40	32	32	26	20	13	11	7	9
CD4	42	36	34	28	25	18	13	10	13
CD8	42	35	34	27	24	17	13	10	13
db neg	31	24	24	19	16	11	8	6	8
γδ	40	32	32	26	21	13	11	7	9

E



n									
Naive CD3	18	11	11	5	5	4	3	0	3
Naive CD4	24	29	34	25	22	14	13	9	16
Naive CD8	21	20	28	21	18	11	11	8	16

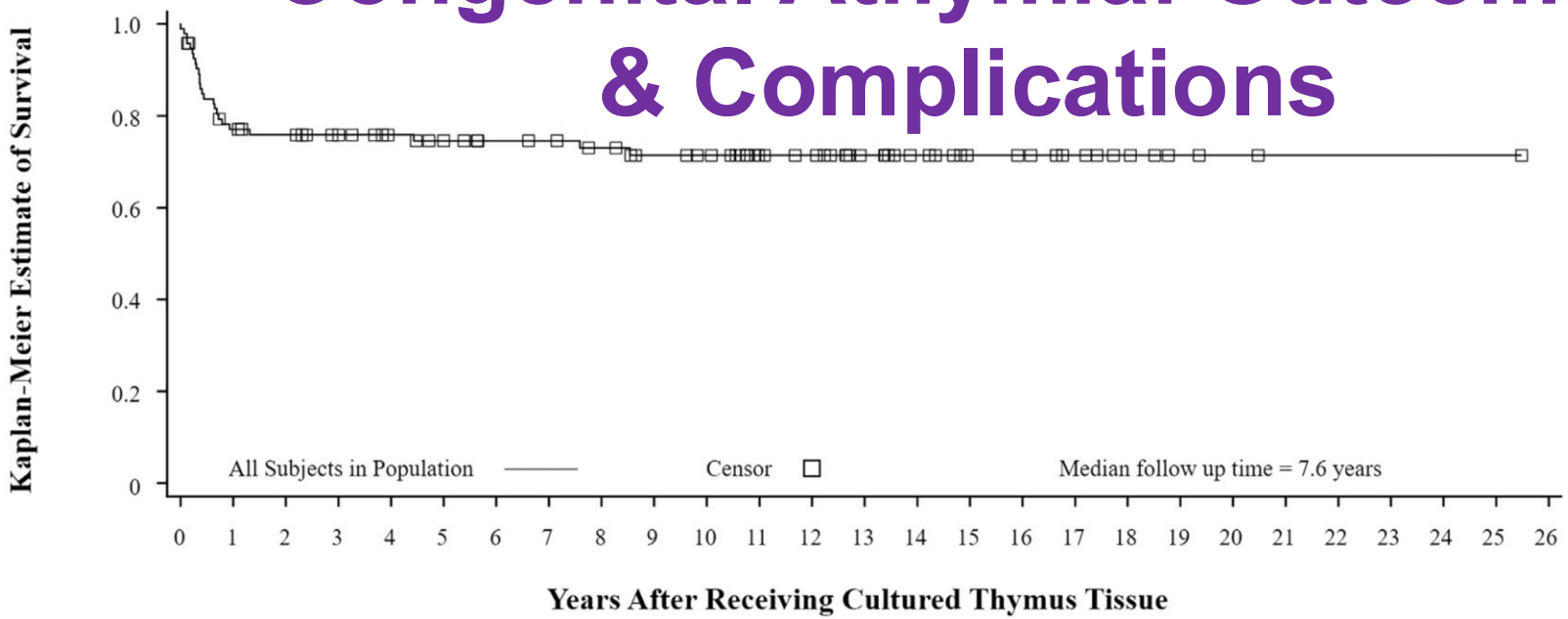
F



n									
Naive CD3	23	13	13	9	7	3	3	2	4
Naive CD4	39	28	28	25	20	13	8	7	10
Naive CD8	39	22	25	21	19	12	8	6	10

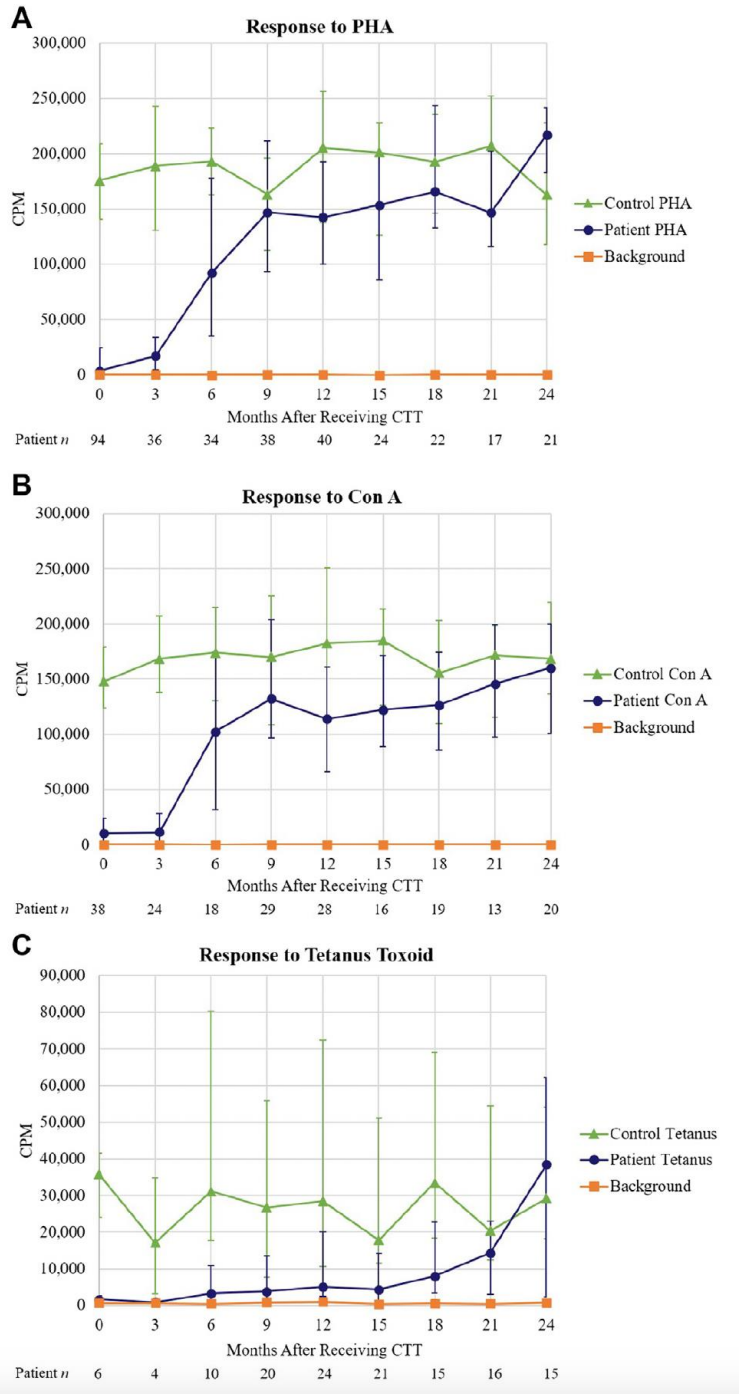
Markert et al., J Allergy & Clin Immunol (JACI), 2021

Congenital Athymia: Outcomes & Complications



At Risk	95	95	69	66	62	57	54	50	49	46	42	40	33	31	24	18	13	12	9	6	3	2	1	1	1	1
Events	0	21	1	0	0	1	0	0	1	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0

Blood and lymphatic system disorders	**21 (20.0)**	**32**
Thrombocytopenia	11 (10.5)	13
Neutropenia	8 (7.6)	8
Coombs-positive hemolytic anemia	3 (2.9)	3
Autoimmune hemolytic anemia	2 (1.9)	3
Hemolysis	2 (1.9)	2
Hemolytic anemia	2 (1.9)	2
Immune thrombocytopenic purpura	1 (1.0)	1



Markert et al., J Allergy & Clin Immunol (JACI), 2021

Thymus Implant: Future Directions

Approach	Standard thymus transplantation with cryopreserved thymus tissue	Engineered thymus using a natural scaffold seeded with expanded TEC progenitors	Engineered thymus using a natural scaffold seeded with gene-corrected iTEPCs
ADVANTAGES	-Improved treatment logistics -Potential for partial tissue type matching with possibly reduced autoimmunity	-Generation of large amounts of human thymus tissue -Potential for partial tissue type matching with possibly reduced autoimmunity	-Autologous procedure -Expected reduced autoimmunity
CURRENT STATUS	**Pre-clinical** **Mouse model** (147) Frozen & thawed human thymus tissue supporting murine T-cell development upon transplantation into nude mice	**Pre-clinical** **Mouse model** (35) Seeding of natural decellularized ECM with human thymic stromal cell progenitors by whole-organ perfusion; supporting human T-cell development upon transplantation into humanized NSG mice	**Pre-clinical** **Mouse model** (149) Small RTOCs containing (control) human iTEPCs mixed with mouse embryonic fibroblasts; supporting limited murine T-cell development upon transplantation into nude mice

Kreins et al., Front Immunol, 2021

Thymus Implant: Promoting Transplantation Tolerance

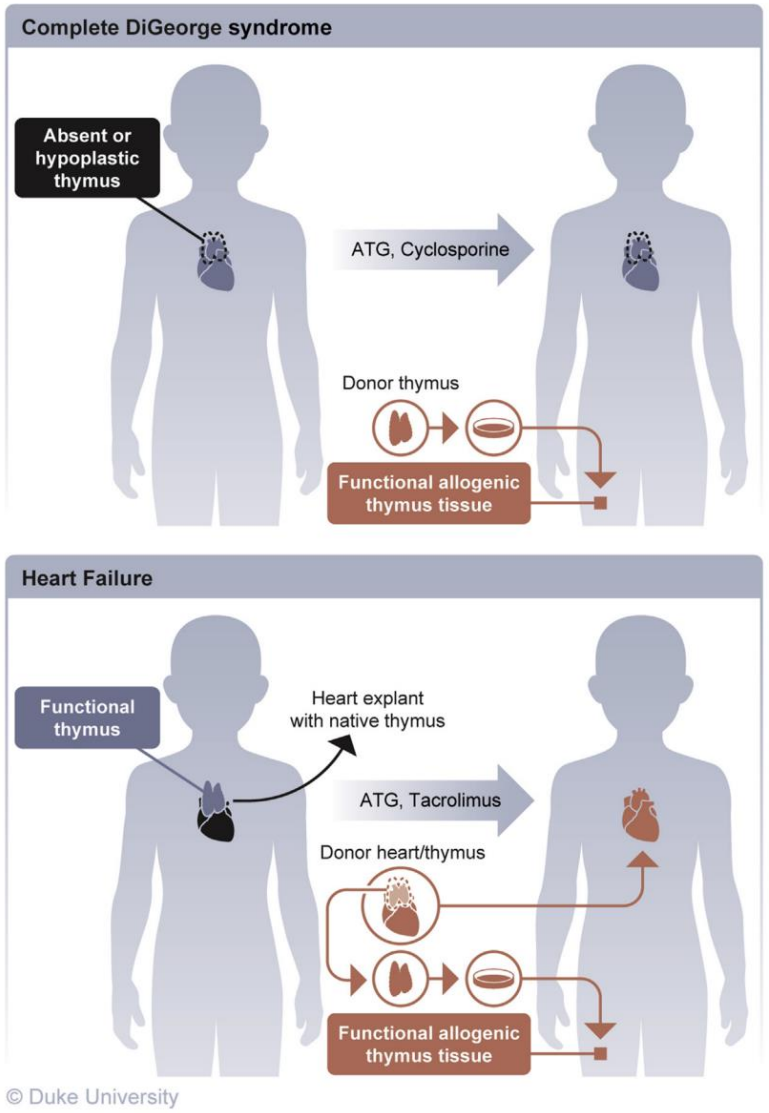
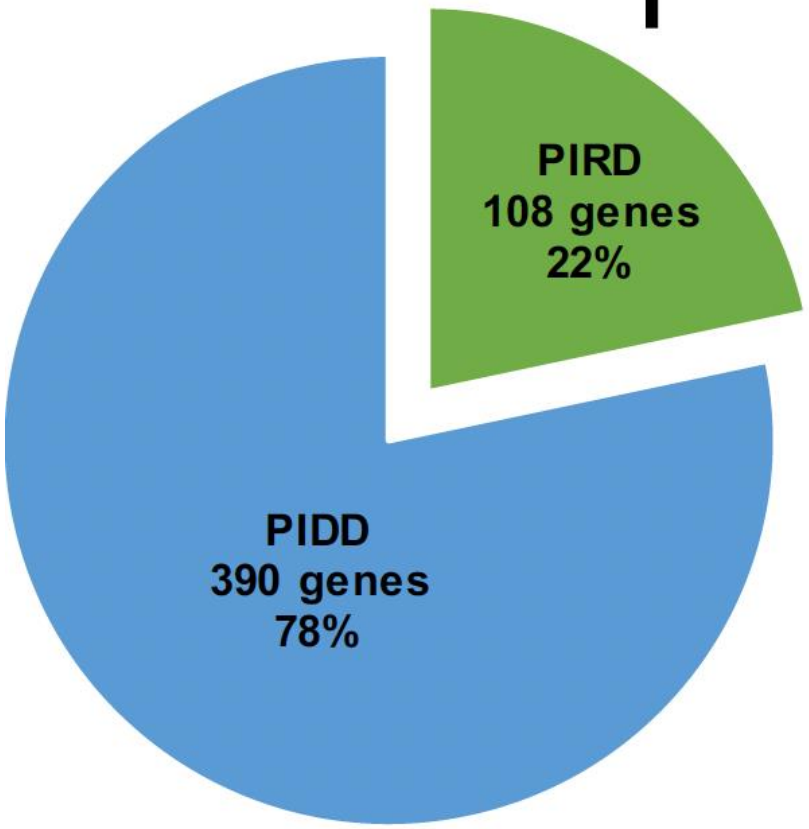


FIG 2. Schematic figures summarizing the steps in the process of implantation of CTT for DiGeorge syndrome and potential heart transplantation. *ATG*, Antithymocyte globulin.

Fitch et al., J Allergy Clin Immunol, 2022

IEI Categories Based on Clinical Phenotypes

- (Severe) Combined Immunodeficiency
- Syndromic Combined Immunodeficiency
- Predominantly Antibody Deficiencies
- Immune Dysregulation Disorders
- Phagocyte Defects
- Innate Immunity Defects
- Autoinflammatory Diseases
- Complement Deficiency
- Bone Marrow Failure
- Phenocopies



① **Disorders with multiple autoimmunity**

Defect in Treg number/function
Defect in central tolerance mechanisms
Peripheral lymphocyte expansion

② **Immune Dysregulation with colitis**

Defective IL -10 signaling causing unchecked T cell activation in the gut

③ **Disorders with HLH and/or EBV Susceptibility**

Deficiency of lymphocyte cytotoxic activity leading to lymphocyte proliferation and macrophage activation

④ **Autoinflammatory syndromes**

Hyperactivation of antigen -independent inflammatory pathways (i.e. inflammasome)

⑤ **Type 1 Interferonopathies**

Upregulation of type 1 interferons

⑥ **Disorders of sterile inflammation**

Varied mechanisms

Nelson & Baloh, 2024

- 5yo girl with previous diagnosis of **C**ommon **V**ariable **I**mmuno**D**eficiency (CVD). For the past 3-4 months she has had large cervical and inguinal lymphadenopathy and splenomegaly, bloody stools, on/off fevers

- History of recurrent pneumonias, hypogammaglobunemia, mild T cell lymphopenia, currently on IVIG

- Mother says she sleeps poorly and stops breathing sometimes, and has many URIs

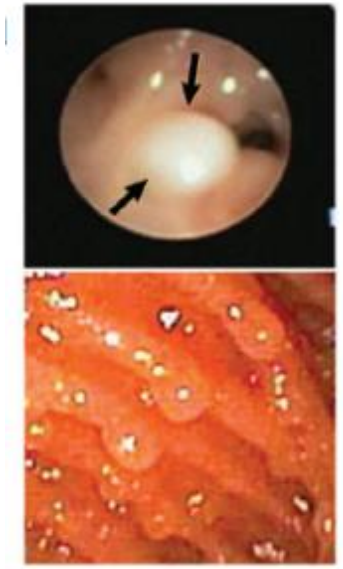
- History of positive EBV and CMV PCR in blood

- Previous lymph node biopsy was negative for malignancy

- No increased number of double negative T cells

The Issue is in the Tissue

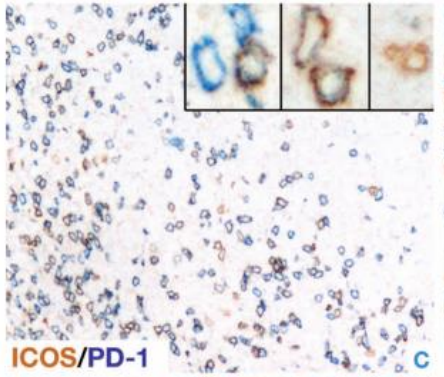
Lymphoid Hyperplasia

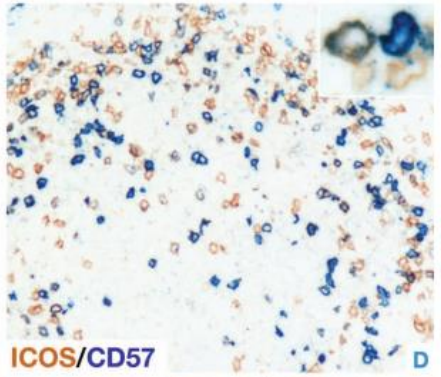


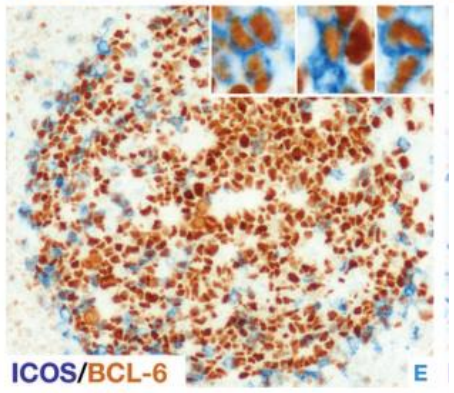
Respiratory Tract

Gastrointestinal Tract

Predominance of T follicular helper (Tfh) cells in GI Tissue







Lucas et al, 2014; Hatzi et al, 2015

PI3 Kinase Catalytic Subunit p110δ GOF result in T cell Senescence and Human Immunodeficiency Activated PI3K Delta Syndrome (APDS)

Whole Exome Sequencing of 3 kindreds

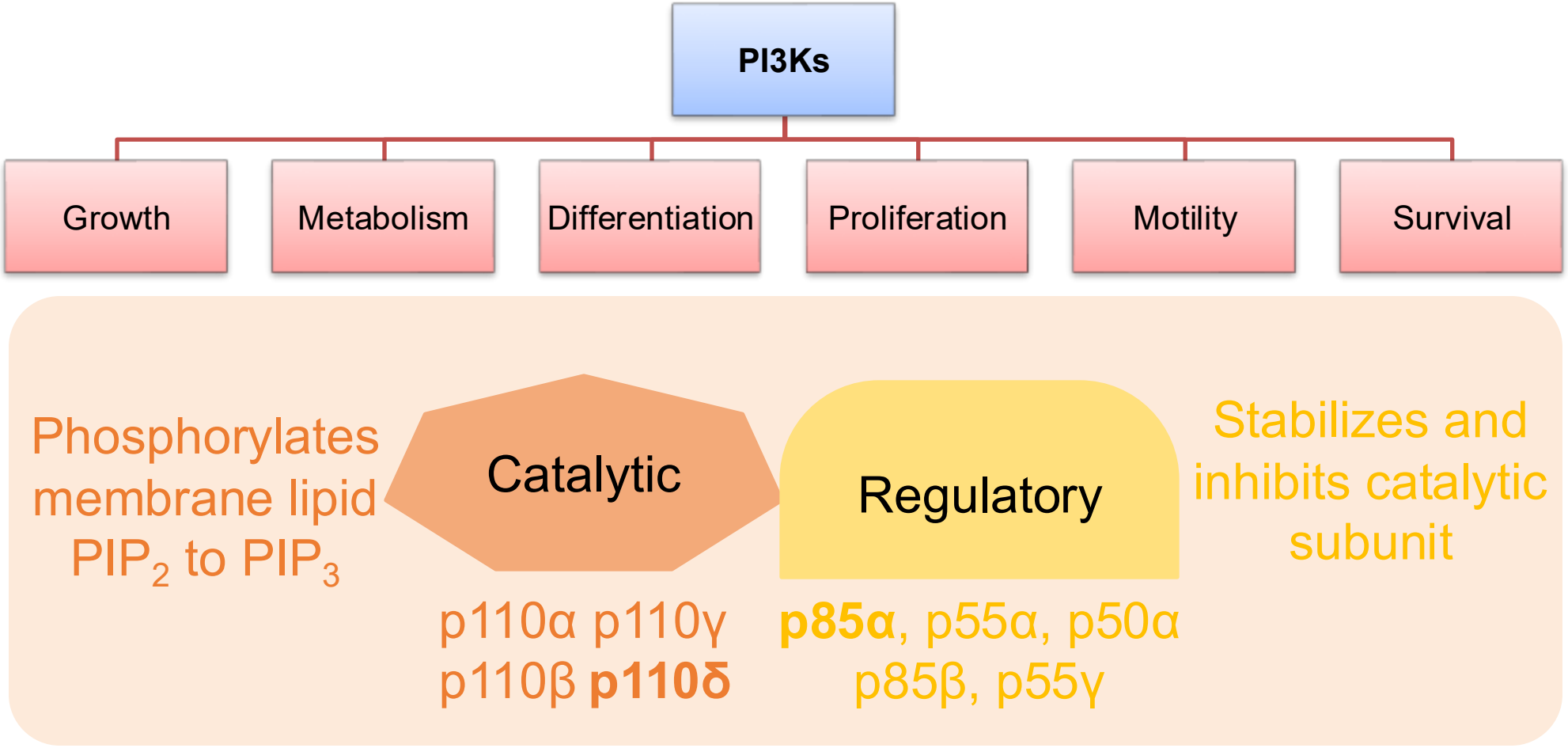
- Sinopulmonary infections
- Lymphadenopathy
- Nodular lymphoid hyperplasia
- Viremia with EBV and/or CMV
- Deficiency of naïve T cells but over representation of senescence effector T cells
- *In vitro:* T cells from patients exhibited ***increased phosphorylation of kinase Akt and hyperactivation of mTOR → Gain-Of-Function (GOF) mutation***

Lucas et al, 2014

Back to our Patient

- Whole Exome Sequencing demonstrated a ***new PI3K p110δ mutation*** – new phenotype with Tfh predominance (2015)

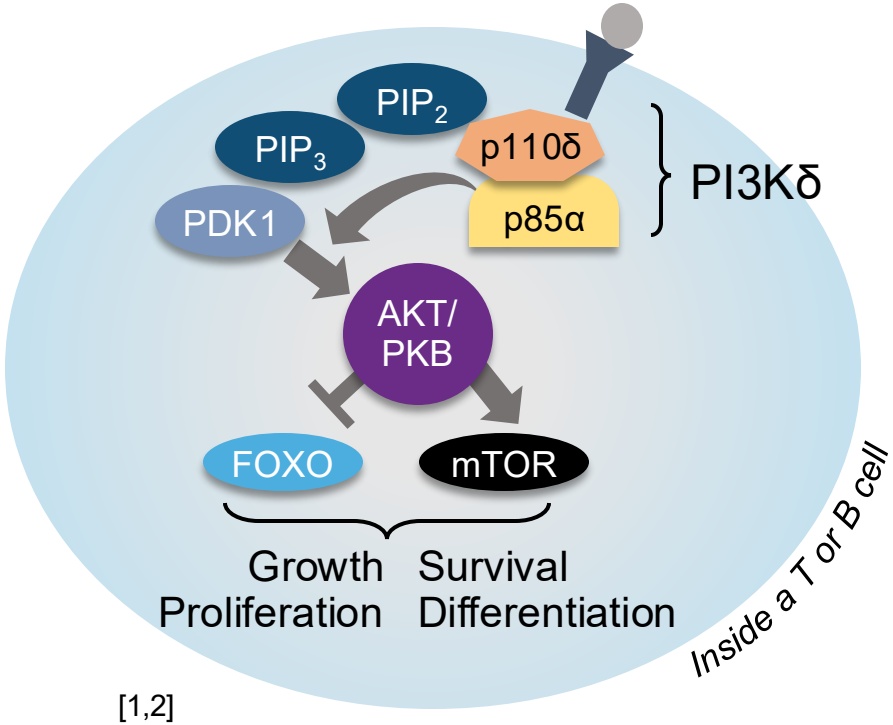
Immune Cells Are Regulated By Phosphoinositide 3-Kinases (PI3Ks)



PIP_2, phosphatidylinositol 4,5-bisphosphate; PIP_3, phosphatidylinositol 3,4,5-trisphosphate.

Fruman DA, et al. *Cell*. 2017;170(4):605-635.

Balanced Signaling In The PI3Kδ Pathway Is Essential For Growth, Cognition, And Healthy Immune Function

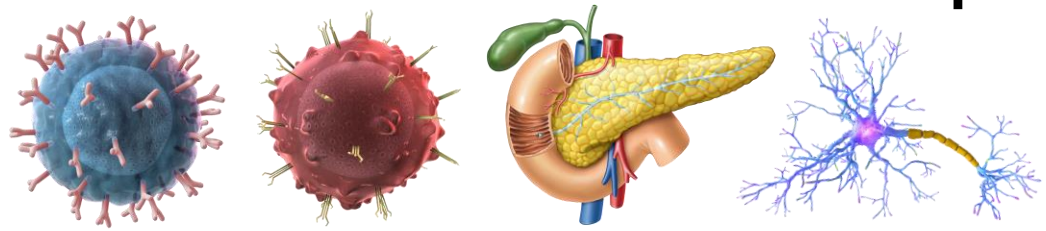


[1,2]

PI3Kδ

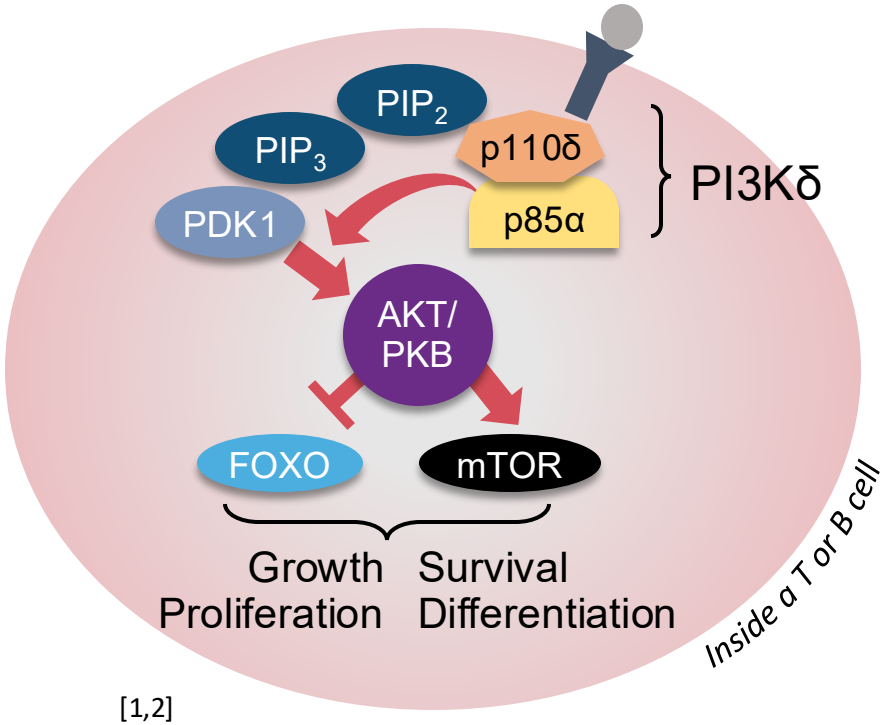
Catalytic p110δ subunit	Regulatory p85α subunit
Primarily expressed in immune system	***Ubiquitous expression***

[3] **Fine-tuning of PI3Kδ activity results in normal development of B and T cells, normal growth and cognitive development[1,2,4-6]**



FOXO, forkhead box O; mTOR, mammalian target of rapamycin; PDK1, phosphoinositide-dependent protein kinase 1; PI3Kδ, phosphoinositide 3-kinase δ; PIP_2, phosphatidylinositol 4,5-bisphosphate; PIP_3, phosphatidylinositol 3,4,5-trisphosphate; PKB, protein kinase B.

APDS1 And APDS2 Result In PI3Kδ Pathway Hyperactivity And Altered Immune Function



[1,2]

Catalytic p110δ subunit

GOF mutation in the *PIK3CD* gene

Hyperactive PI3Kδ pathway

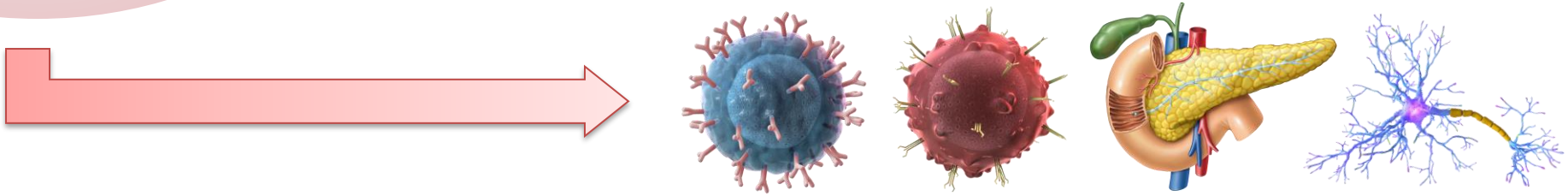
APDS1

Regulatory p85α subunit

LOF mutation in the *PIK3R1* gene

APDS2

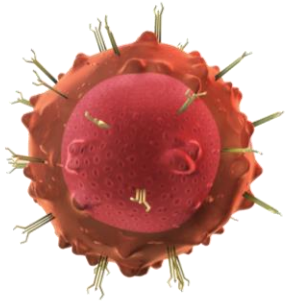
[1,3-6]



1. Fruman DA, et al. Cell. 2017;170(4):605-635. 2. Okkenhaug K, Vanhaesebroeck B. Nat Rev Immunol. 2003;3(4):317-330. 3. Lucas CL, et al. Nat Immunol. 2014;15(1):88-97. 5. Angulo I, et al. Science. 2013;342(6160):866-871. 5. Lucas CL, et al. J Exp Med. 2014;211(13):2537-2547. 6. Deau MC, et al. J Clin Invest. 2014;124(9):3923-3928. 7. Coulter TI, et al. J Allergy Clin Immunol. 2017;139(2):597-606. 8. Elkaim E, et al. J Allergy Clin Immunol. 2016;138(1):210-218. 9. Petrovski S, et al. J Clin Immunol. 2016;36(5):462-471. 10. Tangye SG, et al. J Clin Immunol. 2019;39(2):148-158.

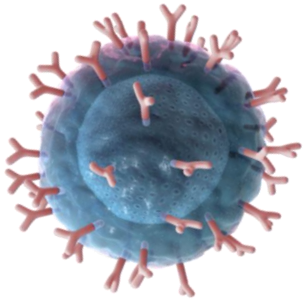
Hyperactive PI3Kδ Alters Immune Cell Phenotypes

T cells[1-4]



- ↓ CD4+
- ↑ CD8+
- ↑ Effector memory CD8+
- Inverted CD4+/CD8+ ratio
- ↑ Follicular T helper
- Total CD8+ skewed to T_{EM}/T_{EMRA} (senescent)
- ↓ NK cells

B cells[1-4]



- ↓ B cells (CD19+)
- ↓ Transitional B cells
- ↓ Memory B cells
- Defects in class-switch recombination

Common Symptoms of APDS[2,3]

Severe, Recurrent, Persistent Infections:
- Sinopulmonary
- Herpesvirus (especially EBV and CMV)

Lymphoproliferation:
- Lymphadenopathy
- Splenomegaly/hepatomegaly
- Nodular lymphoid hyperplasia

Enteropathy

Autoimmunity:
- Cytopenias
- Autoimmune disorders
- Autoinflammatory disorders

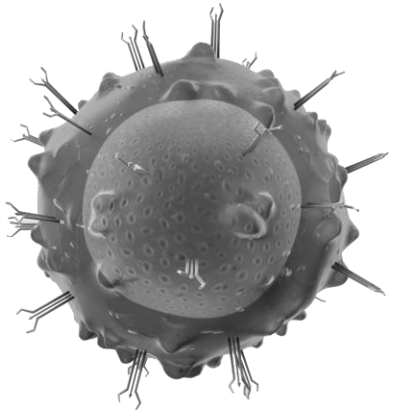
Bronchiectasis

Lymphoma

1. Lucas CL, et al. Nat Immunol. 2014;15(1):88-97.
2. Coulter TI, et al. J Allergy Clin Immunol. 2017;139(2):597-606.
3. Elkaim E, et al. J Allergy Clin Immunol. 2016;138(1):210-218.
4. Jamee M, et al. Clin Rev Allergy Immunol. 2020;59(3):323-333.

Hyperactive PI3Kδ Alters Immune Cell Development

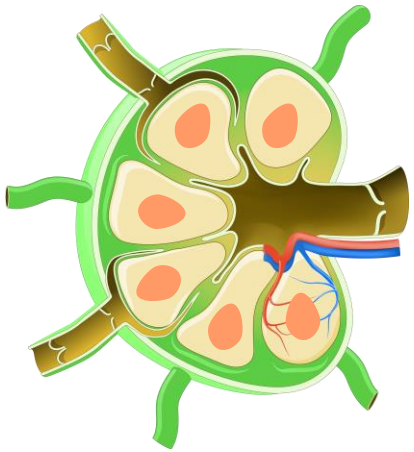
Senescent T effector cells[1-4]



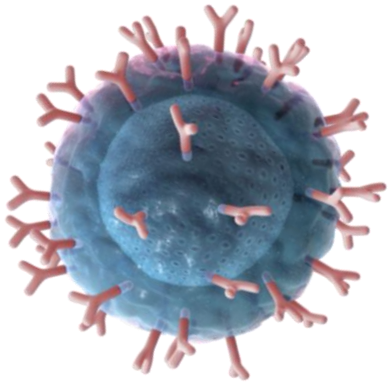
APDS was known as **PASLI** because GOF of **p**110δ-**a**ctivation leads to

- **S**enescence of T effector cells
- **L**ymphadenopathy, and
- **I**mmunodeficiency

Increased infections
Autoimmunity
Lead to lymphadenopathy[2,3,5]



Elevated circulating transitional B cells[1-4]



Impaired generation of memory B cells

Outcomes of Hyperactive PI3Kδ[2,3]

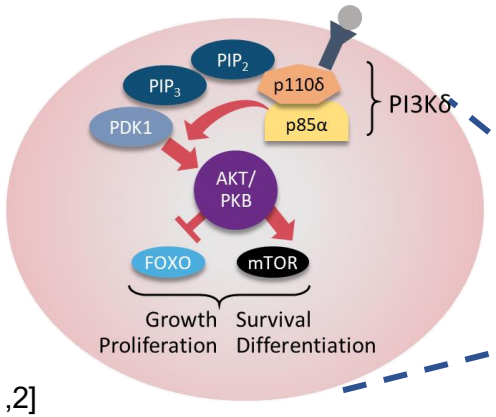
Immune deficiency and dysregulation, lymphoproliferation, autoimmunity, cytopenias

APDS, activated phosphoinositide 3-kinase δ syndrome; GOF, gain-of-function; PASLI, p110δ-activating mutation causing senescent T cells, lymphadenopathy, and immunodeficiency; PI3Kδ, phosphoinositide 3-kinase δ.

1. Lucas CL, et al. *Nat Immunol.* 2014;15(1):88-97. 2. Coulter TI, et al. *J Allergy Clin Immunol*. 2017;139(2):597-606. 3. Elkaim E, et al. *J Allergy Clin Immunol*. 2016;138(1):210-218. 4. Jamee M, et al. *Clin Rev Allergy Immunol*. 2020;59(3):323-333. 5. Maini R, Nagalli S. In: *StatPearls Internet*. Treasure Island, FL: StatPearls Publishing; 2021-.

PI3Kδ Hyperactivity Alters Immune Phenotypes, Leading To APDS Symptoms

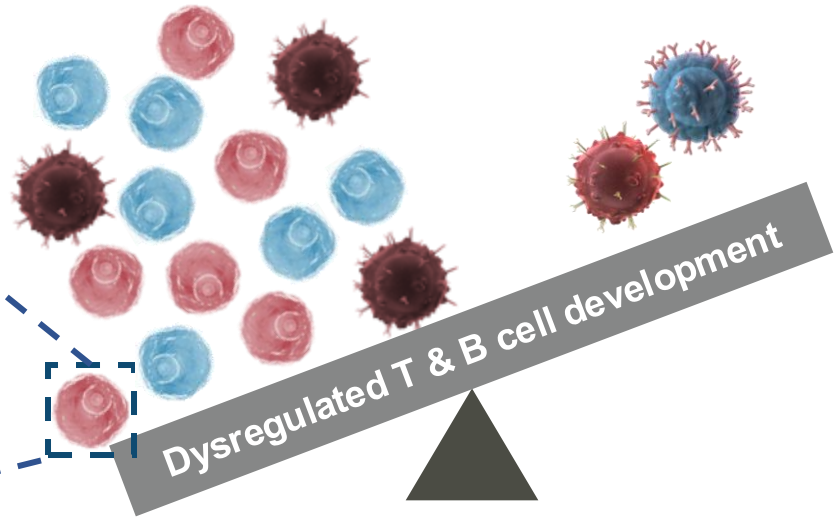
Hyperactive PI3Kδ activity



[1,2]

Excess of immature or senescent cells

Deficit of functional cells[3-6]



↑ CD8+ effector/memory T cells
↑ CD8+ T cell senescence
↻ Inverted CD4+/CD8+ T cell ratio
↑ Transitional B cells
↔ or ↑ IgM

↓ Naïve and CD4+ T cells
↓ Memory T cell function
↓ B cells (lymphopenia)
↓ Memory B cells
↔ or ↓ IgG/IgA

Common Symptoms of APDS[4,5]

Severe, Recurrent, Persistent Infections:
- Sinopulmonary
- Herpesvirus (especially EBV and CMV)

Lymphoproliferation:
- Lymphadenopathy
- Splenomegaly/hepatomegaly
- Nodular lymphoid hyperplasia

Enteropathy

Autoimmunity:
- Cytopenias
- Autoimmune disorders
- Autoinflammatory disorders

Bronchiectasis

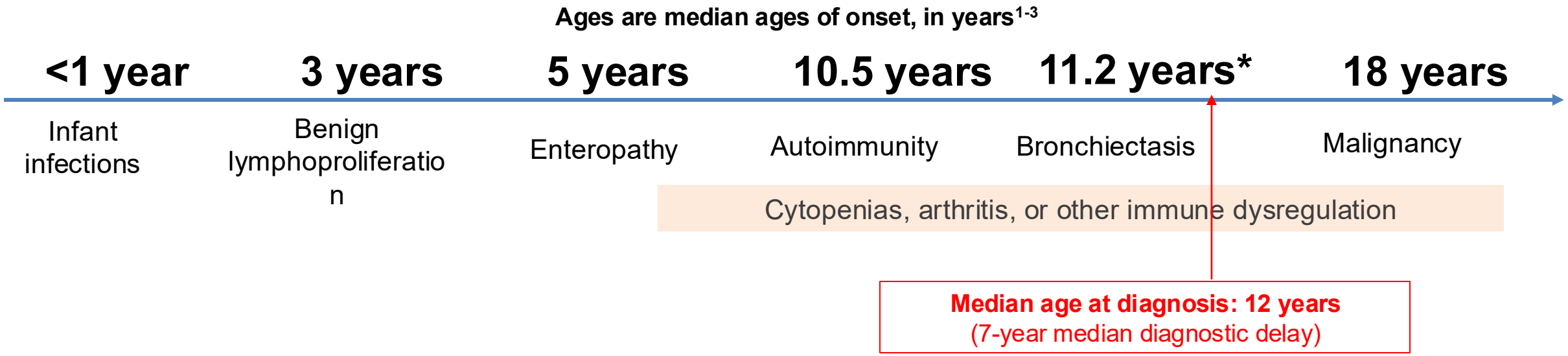
Lymphoma

APDS, activated phosphoinositide 3-kinase δ syndrome; CMV, cytomegalovirus; EBV, Epstein-Barr virus; FOXO, forkhead box O; Ig, immunoglobulin; PDK1, phosphoinositide-dependent protein kinase 1; PIP_2, phosphatidylinositol 4,5-bisphosphate; PIP_3, phosphatidylinositol 3,4,5-trisphosphate; PI3Kδ, phosphoinositide 3-kinase δ; PKB, protein kinase B.

1. Fruman DA, et al. *Cell*. 2017;170(4):605-635. 2. Okkenhaug K, Vanhaesebroeck B. *Nat Rev Immunol*. 2003;3(4):317-330. 3. Lucas CL, et al. *Nat Immunol.* 2014;15(1):88-97. 4. Coulter TI, et al. *J Allergy Clin Immunol*. 2017;139(2):597-606. 5. Elkaim E, et al. *J Allergy Clin Immunol*. 2016;138(1):210-218. 6. Jamee M, et al. *Clin Rev Allergy Immunol*. 2020;59(3):323-333.

APDS Evolves Over Time And May Be Underdiagnosed

Timeline of the Most Common Pathologies Seen in APDS



A careful family history may be especially useful in diagnosis. A goal of early diagnosis and treatment is to interrupt the disease evolution[1-4]

*In Elkaim APDS2 cohort, median age of bronchiectasis is 13, in Maccari ESID cohort median age is 11.2.
APDS, activated phosphoinositide 3-kinase δ syndrome; ESID, European Society for Immunodeficiencies.

1. Jamee M, et al. *Clin Rev Allergy Immunol*. 2020;59(3):323-333. 2. Maccari ME, et al. *Front Immunol*. 2018;9:543. 3. Elkaim E, et al. *J Allergy Clin Immunol*. 2016;138(1):210-218.e9. 4. Condliffe AM, Chandra A. *Front Immunol*. 2018;9:338.

Back to our Patient

- Whole Exome Sequencing demonstrated a ***new PI3K p110δ mutation*** – new phenotype with Tfh predominance (2015)
- **Rapamycin** (mTOR inhibitor) treatment resulted in improvement of symptoms (2015)
- Several PI3K inhibitors in trials: Idelalisib FDA approved in 2014 for CLL (combination therapy with rituximab), **Leniolisib** (2015)

Precision Medicine in Real Time!

Regular Article

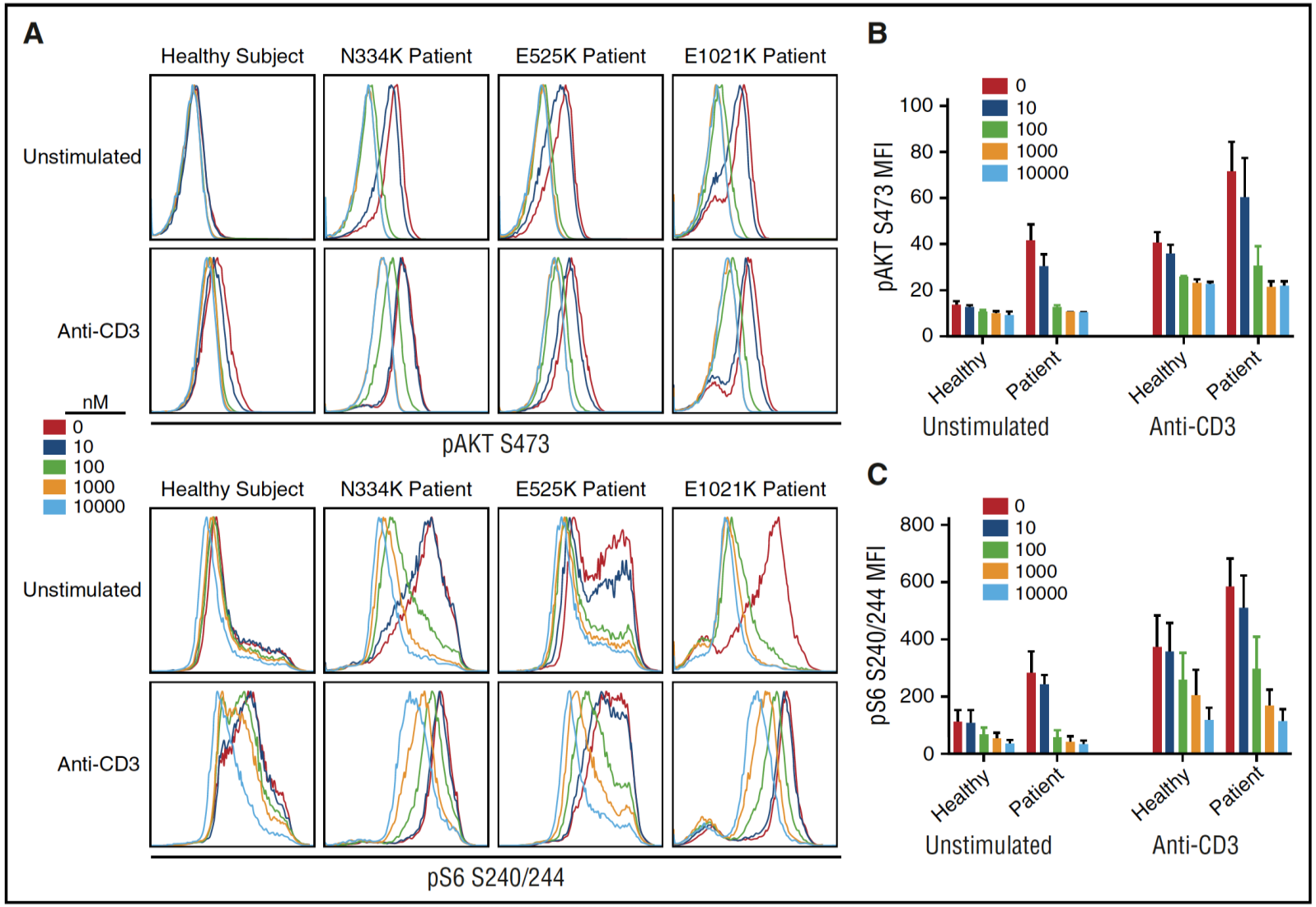
blood 2017

IMMUNOBIOLOGY AND IMMUNOTHERAPY

Effective "activated PI3Kδ syndrome"–targeted therapy with the PI3Kδ inhibitor leniolisib

V. Koneti Rao,[1] Sharon Webster,[1] Virgil A. S. H. Dalm,[2,3] Anna Šedivá,[4] P. Martin van Hagen,[2,3] Steven Holland,[1] Sergio D. Rosenzweig,[5] Andreas D. Christ,[6] Birgitte Sloth,[6] Maciej Cabanski,[6] Aniket D. Joshi,[6,7] Stefan de Buck,[6] Julie Doucet,[6] Danilo Guerini,[6] Christoph Kalis,[6] Ilona Pylvaenaeinen,[6] Nicolas Soldermann,[6] Anuj Kashyap,[1] Gulbu Uzel,[1] Michael J. Lenardo,[1] Dhavalkumar D. Patel,[6] Carrie L. Lucas,[1] and Christoph Burkhart[6]

[1]National Institute of Allergy and Infectious Diseases, National Institutes of Health (NIH), Bethesda, MD; [2]Department of Internal Medicine and [3]Department of Immunology, Erasmus MC, Rotterdam, The Netherlands; [4]Department of Immunology, Motol University Hospital, Prague, Czech Republic; [5]NIH Clinical Center, Bethesda, MD; [6]Novartis Institutes for BioMedical Research, Novartis Pharma AG, Basel, Switzerland; and [7]Novartis Institutes for BioMedical Research, Novartis Pharma AG, Cambridge, MA


A
Healthy Subject
N334K Patient
E525K Patient
E1021K Patient
Unstimulated
Anti-CD3
nM
0
10
100
1000
10000
pAKT S473
Healthy Subject
N334K Patient
E525K Patient
E1021K Patient
Unstimulated
Anti-CD3
pS6 S240/244
B
pAKT S473 MFI
0
10
100
1000
10000
Healthy
Patient
Healthy
Patient
Unstimulated
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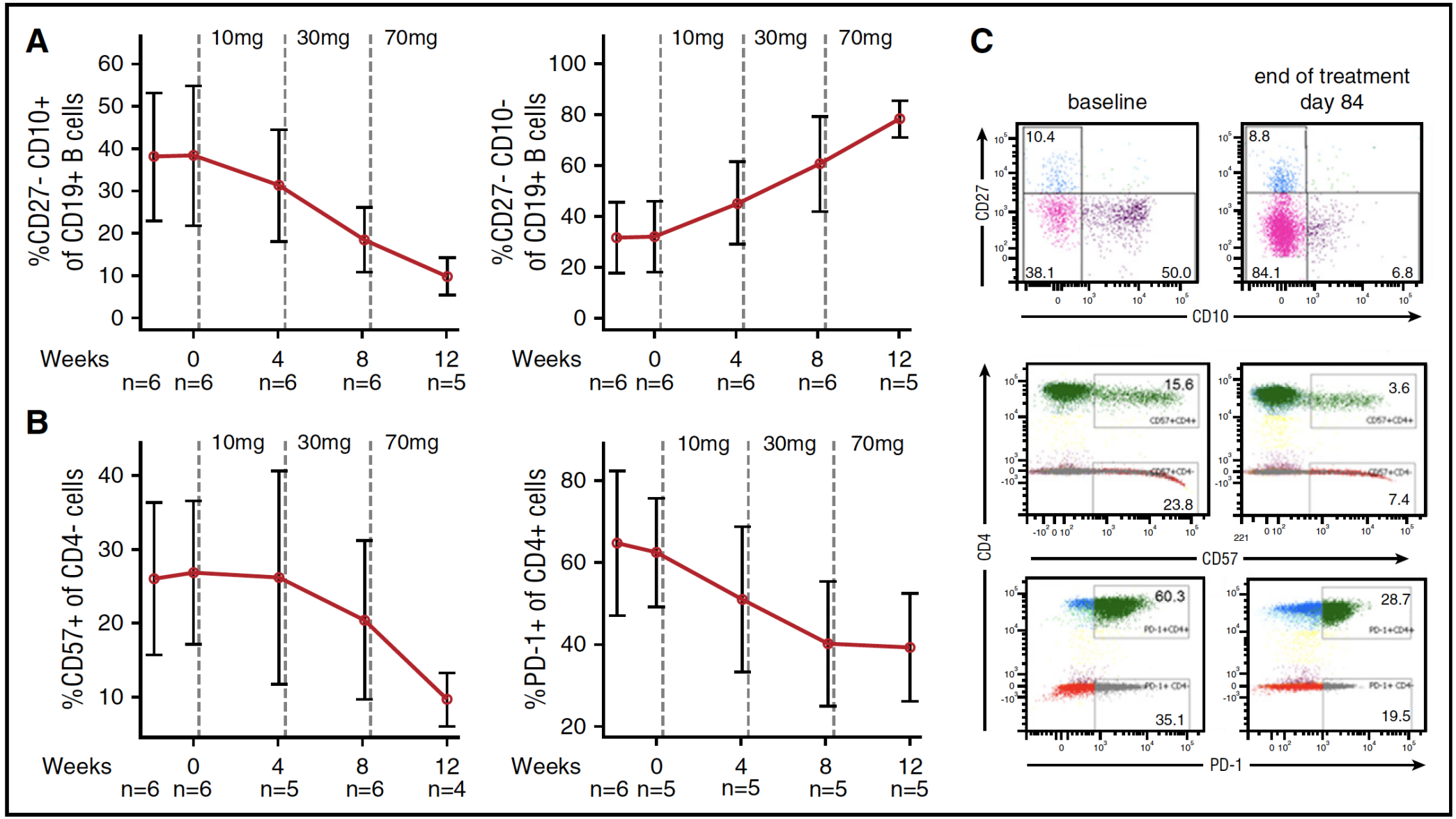
1000
10000
Healthy
Patient
Healthy
Patient
Unstimulated
Anti-CD3

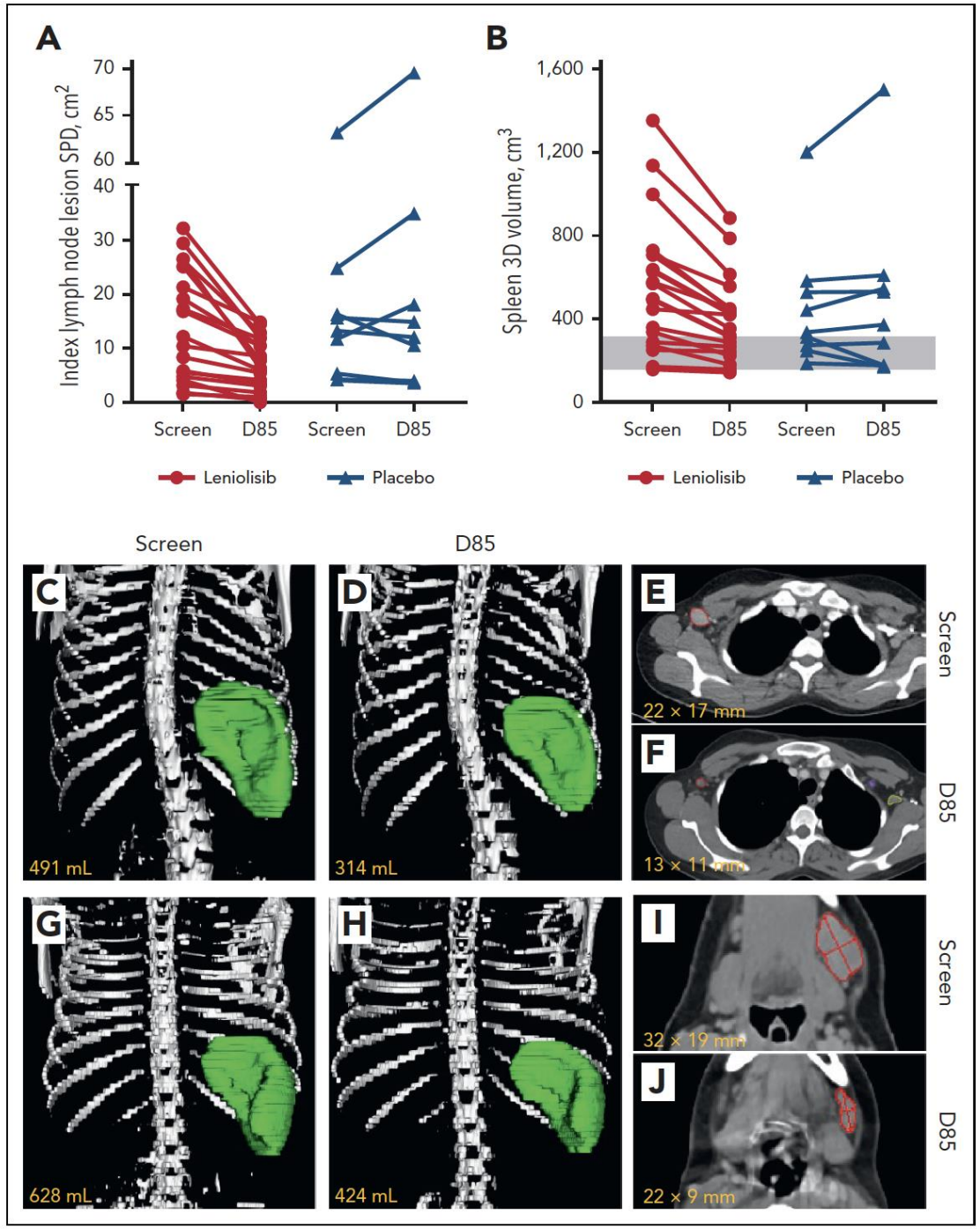

A
%CD27- CD10+ of CD19+ B cells
10mg
30mg
70mg
Weeks
0
4
8
12
n=6 n=6 n=6 n=6 n=5
%CD27- CD10- of CD19+ B cells
n=6 n=6 n=6 n=6 n=5
B
%CD57+ of CD4- cells
n=6 n=6 n=5 n=6 n=4
%PD-1+ of CD4+ cells
n=6 n=5 n=5 n=5 n=5
C
baseline
end of treatment
day 84
CD27
CD10
10.4
38.1
50.0
8.8
84.1
6.8
CD4
CD57
15.6
23.8
3.6
7.4
PD-1
60.3
35.1
28.7
19.5

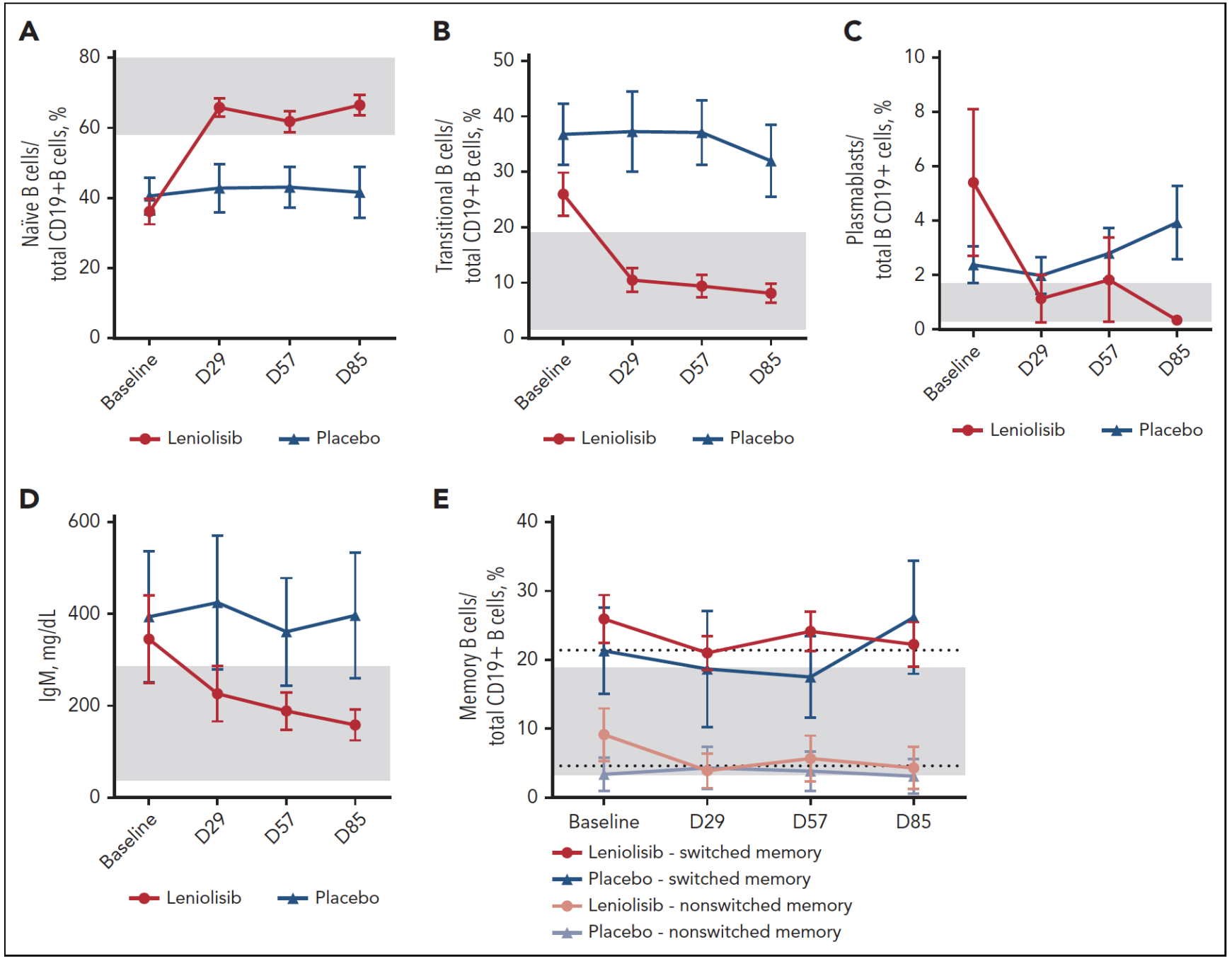
CLINICAL TRIALS AND OBSERVATIONS

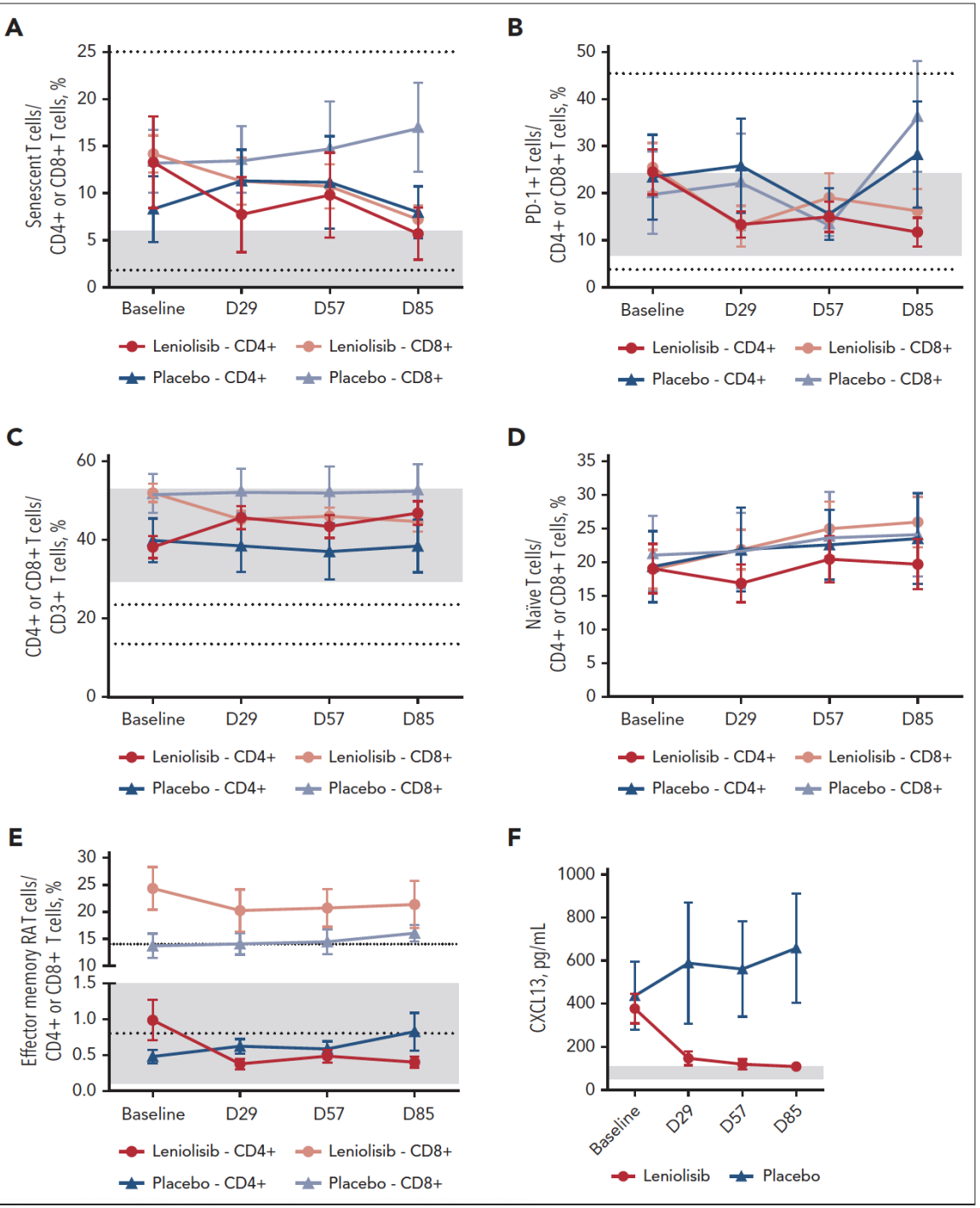
A randomized, placebo-controlled phase 3 trial of the PI3Kδ inhibitor leniolisib for activated PI3Kδ syndrome

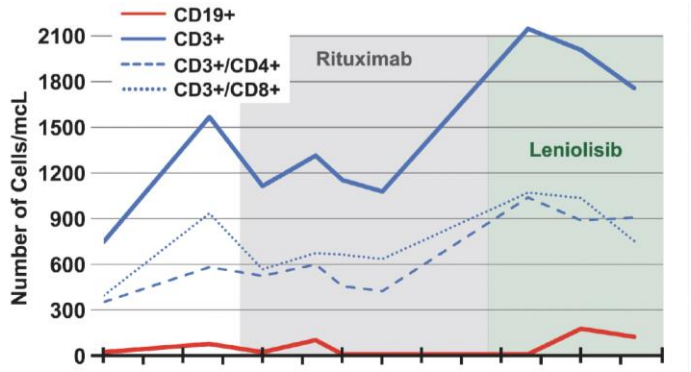
V. Koneti Rao,[1] Sharon Webster,[1] Anna Šedivá,[2] Alessandro Plebani,[3] Catharina Schuetz,[4] Anna Shcherbina,[5] Niall Conlon,[6] Tanya Coulter,[7] Virgil A. Dalm,[8] Antonino Trizzino,[9] Yulia Zharankova,[10] Elaine Kulm,[11] Julia Körholz,[4] Vassilios Lougaris,[3] Yulia Rodina,[5] Kath Radford,[12] Jason Bradt,[13] Klaus Kucher,[14] Anurag Relan,[13] Steven M. Holland,[1] Michael J. Lenardo,[1] and Gulbu Uzel[1]

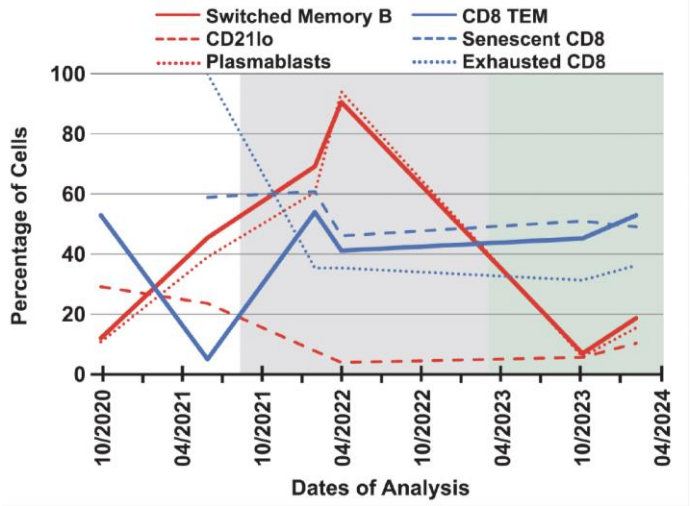
2023

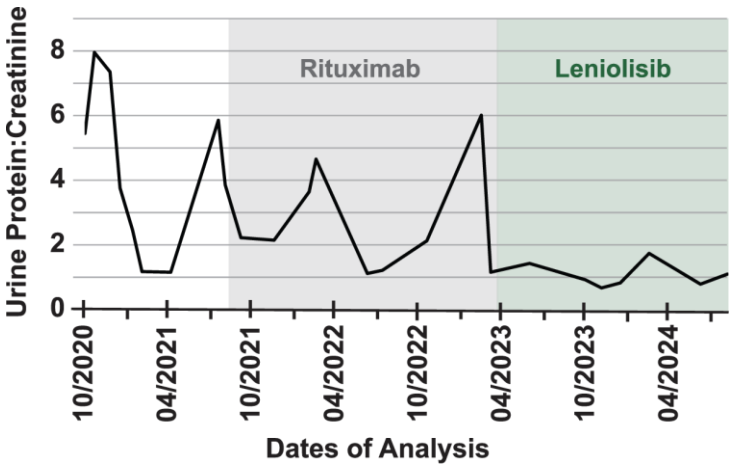

A
Index lymph node lesion SPD, cm2
70
65
60
40
30
20
10
0
Screen
D85
Screen
D85
Leniolisib
Placebo
B
Spleen 3D volume, cm3
1,600
1,200
800
400
0
Screen
D85
Screen
D85
Leniolisib
Placebo
Screen
D85
C
491 mL
D
314 mL
E
22 × 17 mm
F
13 × 11 mm
Screen
D85
G
628 mL
H
424 mL
I
32 × 19 mm
J
22 × 9 mm
Screen
D85


A
Naïve B cells/ total CD19+B cells, %
80
60
40
20
0
Baseline
D29
D57
D85
Leniolisib
Placebo
B
Transitional B cells/ total CD19+B cells, %
50
40
30
20
10
0
Baseline
D29
D57
D85
Leniolisib
Placebo
C
Plasmablasts/ total B CD19+ cells, %
10
8
6
4
2
0
Baseline
D29
D57
D85
Leniolisib
Placebo
D
IgM, mg/dL
600
400
200
0
Baseline
D29
D57
D85
Leniolisib
Placebo
E
Memory B cells/ total CD19+ B cells, %
40
30
20
10
0
Baseline
D29
D57
D85
Leniolisib - switched memory
Placebo - switched memory
Leniolisib - nonswitched memory
Placebo - nonswitched memory



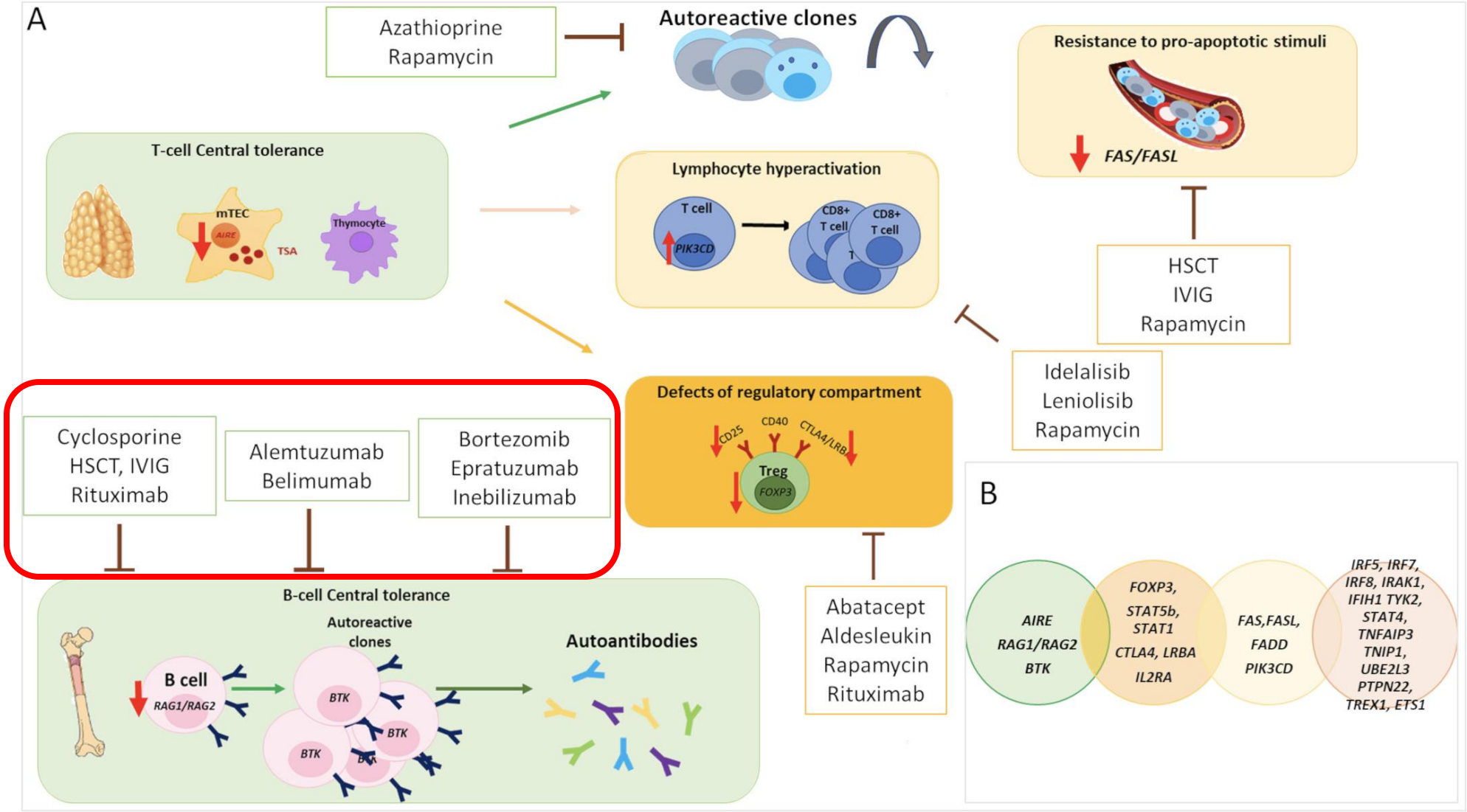






Lim et al., 2025

Mechanisms Impaired in IEI with Autoimmunity and relative Therapeutic Approaches

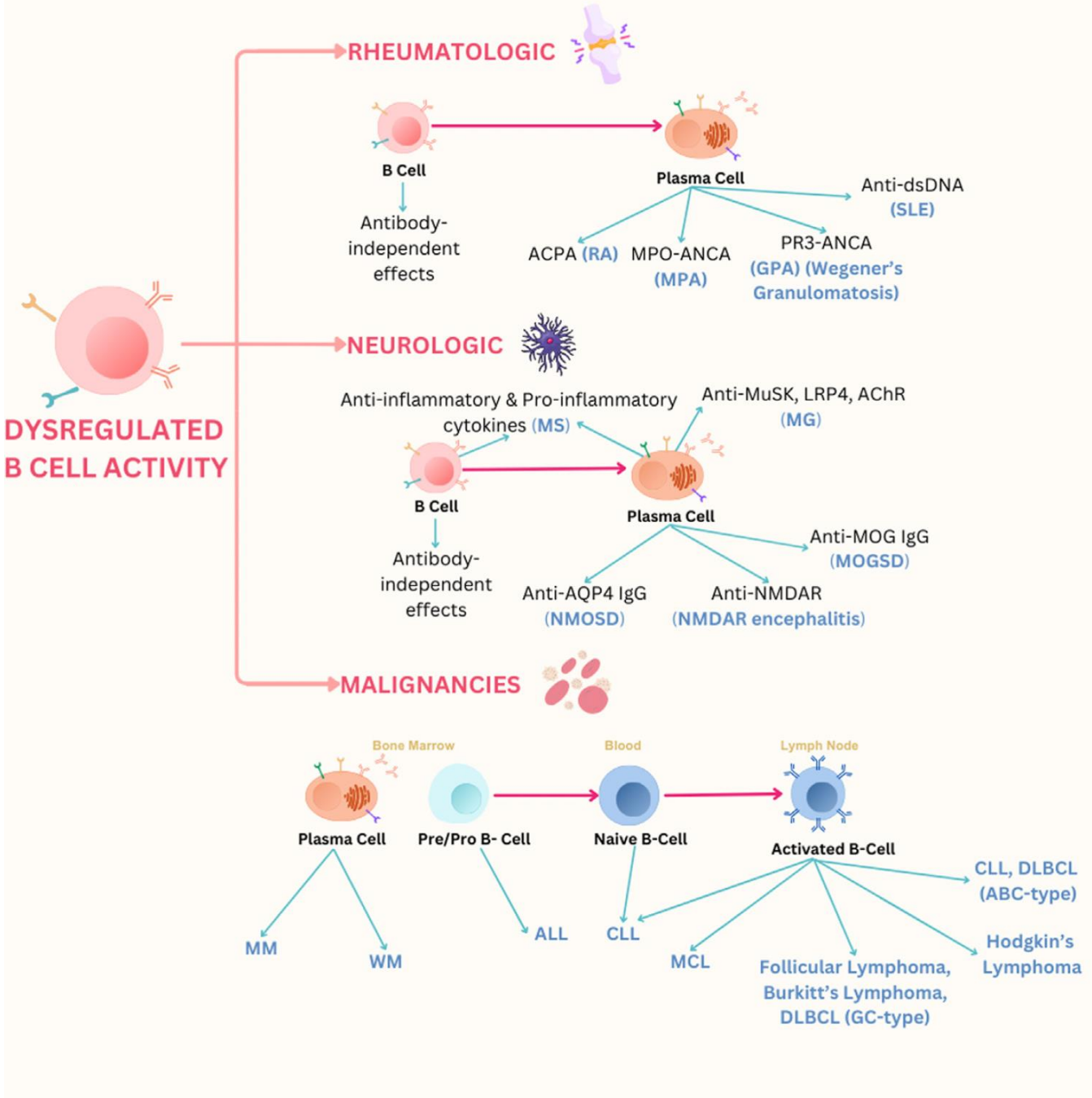


Giardino et al., 2023

Secondary Immunodeficiency in Hematological Malignancies in the Era of Modern Oncology

Class	MOA	Drug	Target
Monoclonal antibodies targeting cell surface epitopes on B cells	Depletes B-cells	• Rituximab	• CD20
		• Obinutuzumab	• CD20
		• Ofatumumab	• CD20
		• Veltuzumab	• CD20
		• Daratumumab	• CD38
		• Isatuximab	• CD38
		• Alemtuzumab	• CD52
		• Milatuzumab	• CD74
	Inhibits B-cell activation	• Epratuzumab	• CD22
BCR pathway inhibitors	Inhibits B-cell receptor signaling	• Ibrutinib	• BCR
		• Idelalisib	• PI3K
BCL-2 inhibitors (BH3 mimetics)	Promotes apoptosis of malignant B cells	• Venetoclax	• BCL-2
Purine analogs	Suppress T cells and B cells	• Fludarabine	• N/A
CAR-T	Suppress B cells	• Axicabtagene ciloleucel	• CD19
		• Tisagenlecelucel	• CD19
Alkylating agents	B-cell and T-cell death	• Cyclophosphamide	• N/A
		• Chlorambucil	• N/A
		• Bendamustin	• N/A
Steroids	Suppress immunomodulatory transcription factors	• Prednisone	• N/A
Stem cell transplant	Conditioning treatment depletes B cells	• N/A	• N/A

Shah et al., 2023



FDA-Approved B Cell-Targeted Therapies

Rituximab (RA, GPA, MPA)

Ocrelizumab (MS)
Ofatumumab (MS)
Inebilizumab (NMOSD)

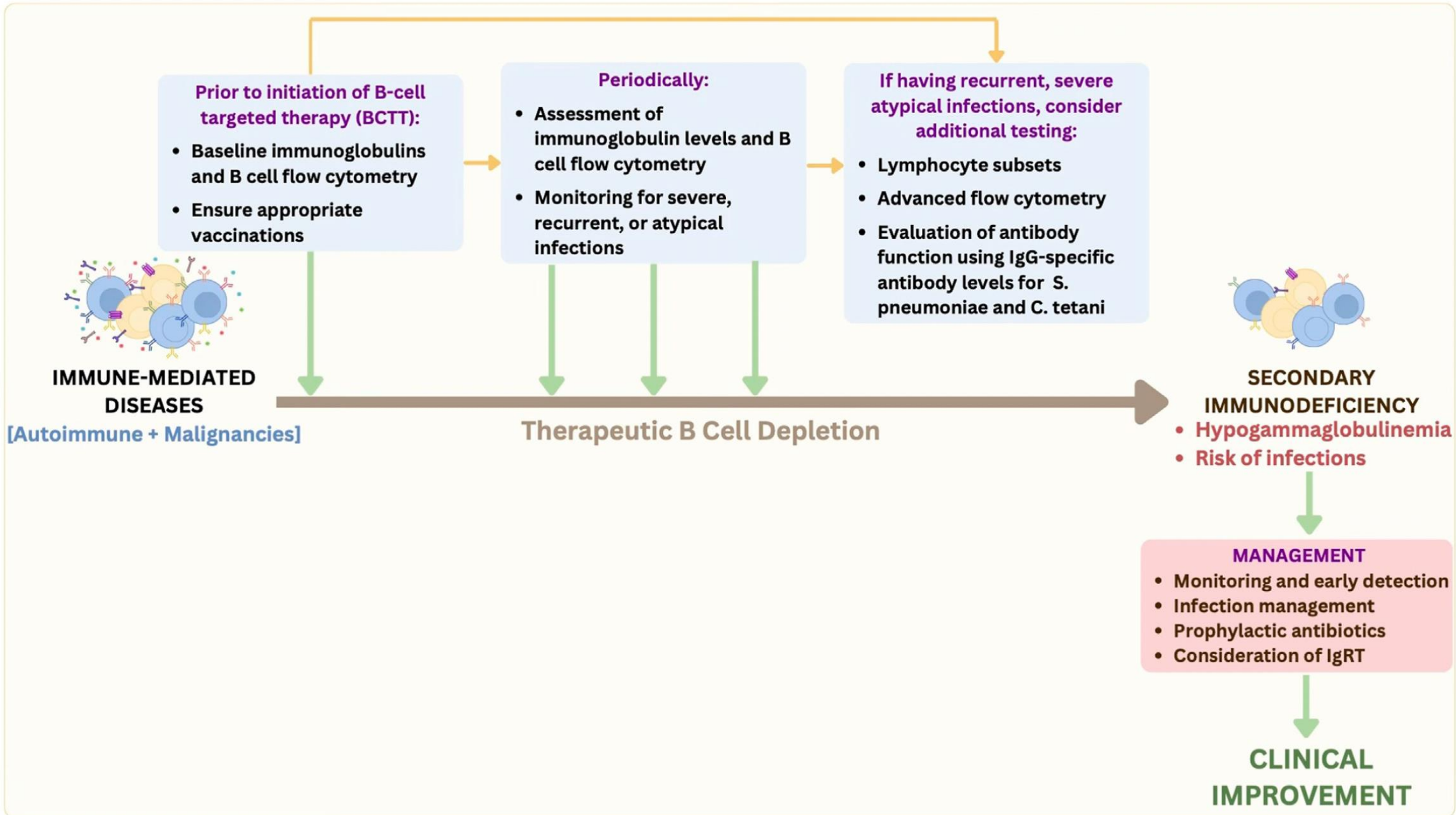
CD20 Targeted Therapies
Rituximab (WM, CLL, DLBCL, MCL)
Obinutuzumab (CLL)
Ofatumumab (CLL)

CD19 CAR-T Cell Therapies
Tisagenlecleucel (ALL, DLBCL)
Axicabtagene ciloleucel (DLBCL, FL)
Lisocabtagene maraleucel (DLBCL, FL)
Brexucabtagene autoleucel (MCL)

BCMA CAR-T Cell Therapies
Idecabtagene vicleucel (MM)
Ciltacabtagene autoleucel (MM)

Other B Cell-Targeted Therapies
Daratumumab (MM)
Tafasitamab (Relapsed/Refractory DLBCL)
Loncastuximab tesirine (Relapsed/Refractory DLBCL)

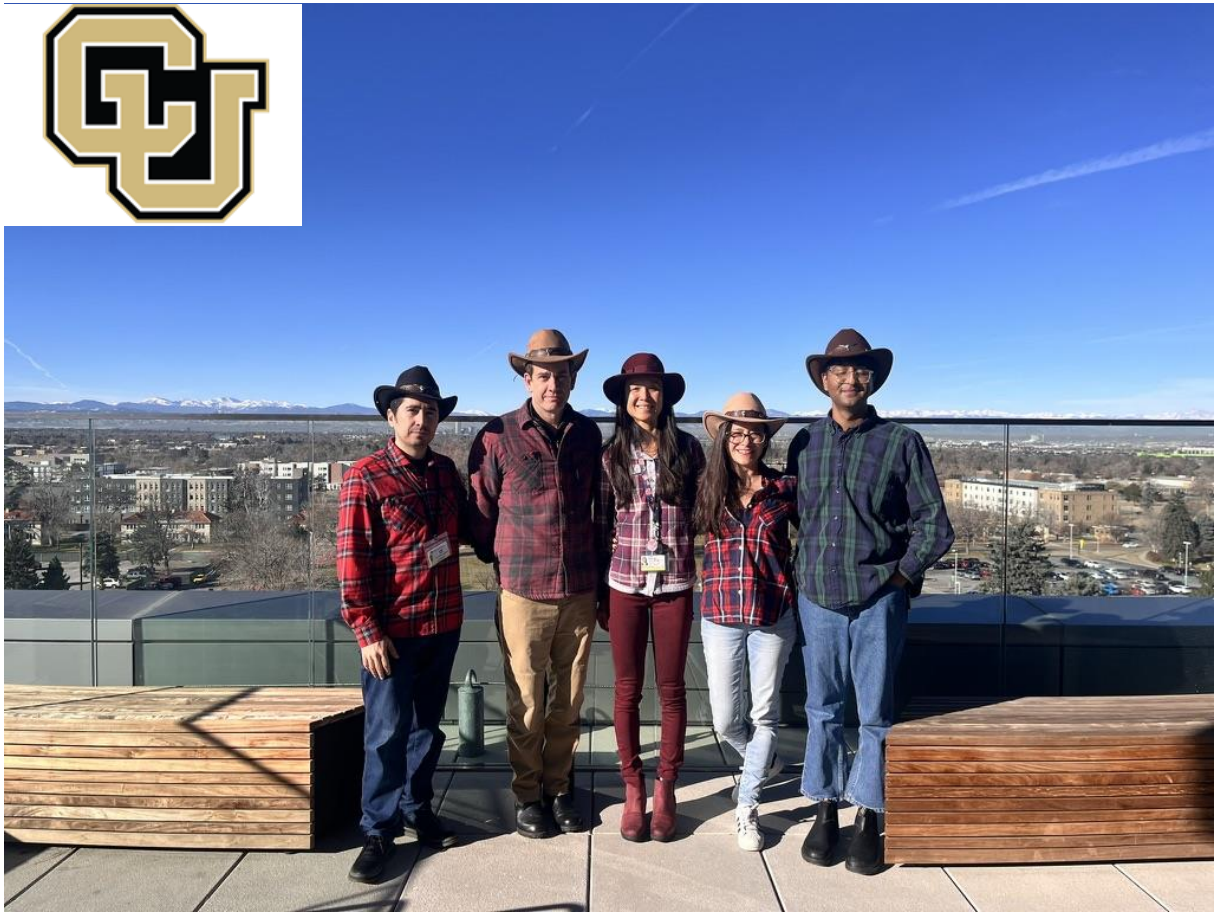
Elmoursi & Barmettler, JACI, 2025



Elmoursi & Barmettler, JACI, 2025

¡Muchas Gracias!

unlocking HSIEH LAB



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Hsieh Lab and Division of Allergy & Immunology is HIRING!!!