

Does the severity of T cell lymphopenia predict immune dysregulation in DiGeorge syndrome?

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Immune Deficiency in DiGeorge Syndrome

- Substantial heterogeneity with variable degree of immune deficiency
- Cellular immunity: T cell lymphopenia, T cell repertoire defects
- Humoral immunity: Low IgG, low IgM and low IgA levels
- Immune dysregulation
 - Infections
 - Autoimmunity
 - Atopy

Gap in knowledge:

The role of T cell lymphopenia severity in predicting immune dysregulation in DiGeorge syndrome remains unknown

Hypothesis:

We hypothesize that the severity of T cell lymphopenia will be associated with infections, autoimmunity and atopy in patients with DiGeorge syndrome

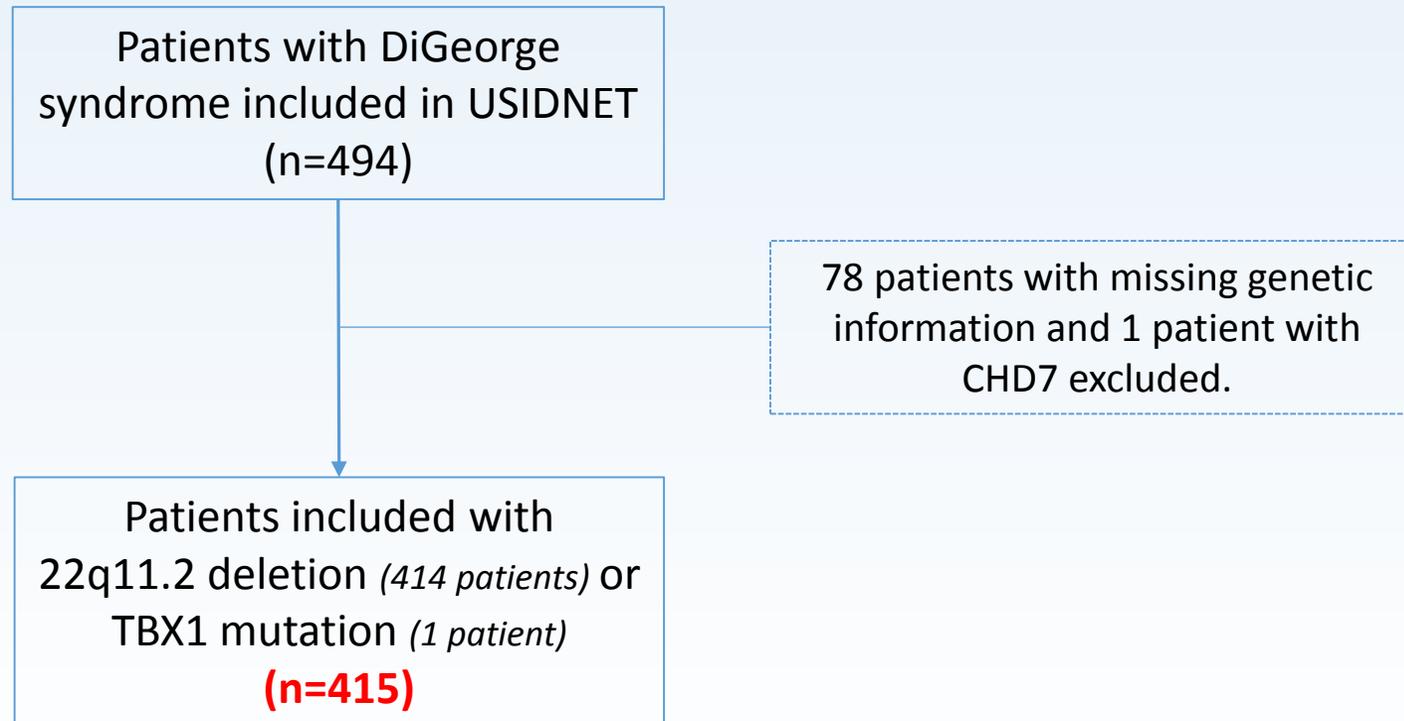
Specific Aims:

In patients with DiGeorge syndrome:

1. Determine the frequency of infections, autoimmunity and atopy
2. Assess the relationship between severity of T cell lymphopenia and the odds of infections, autoimmunity and atopy

Methods

Retrospective analysis of patients with DiGeorge syndrome in the United States Immunodeficiency Network (USIDNET) registry



Methods

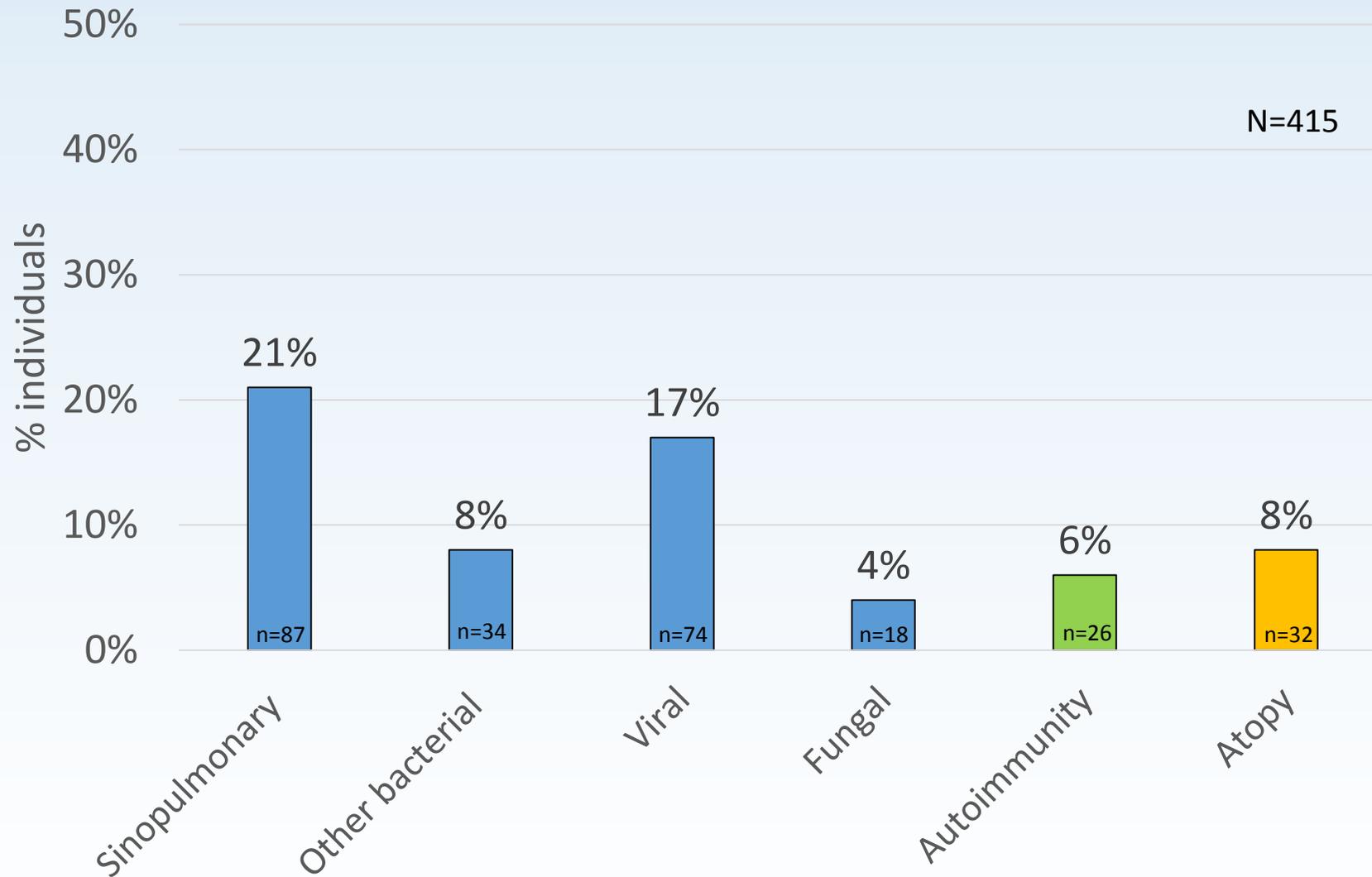
- Predictor: CD3 count

- Absolute CD3 level expressed as a proportion of the lower limit of age adjusted normal and categorized into
 1. Normal
 2. 50-99% of the lower limit of normal
 3. <50% of the lower limit of normal

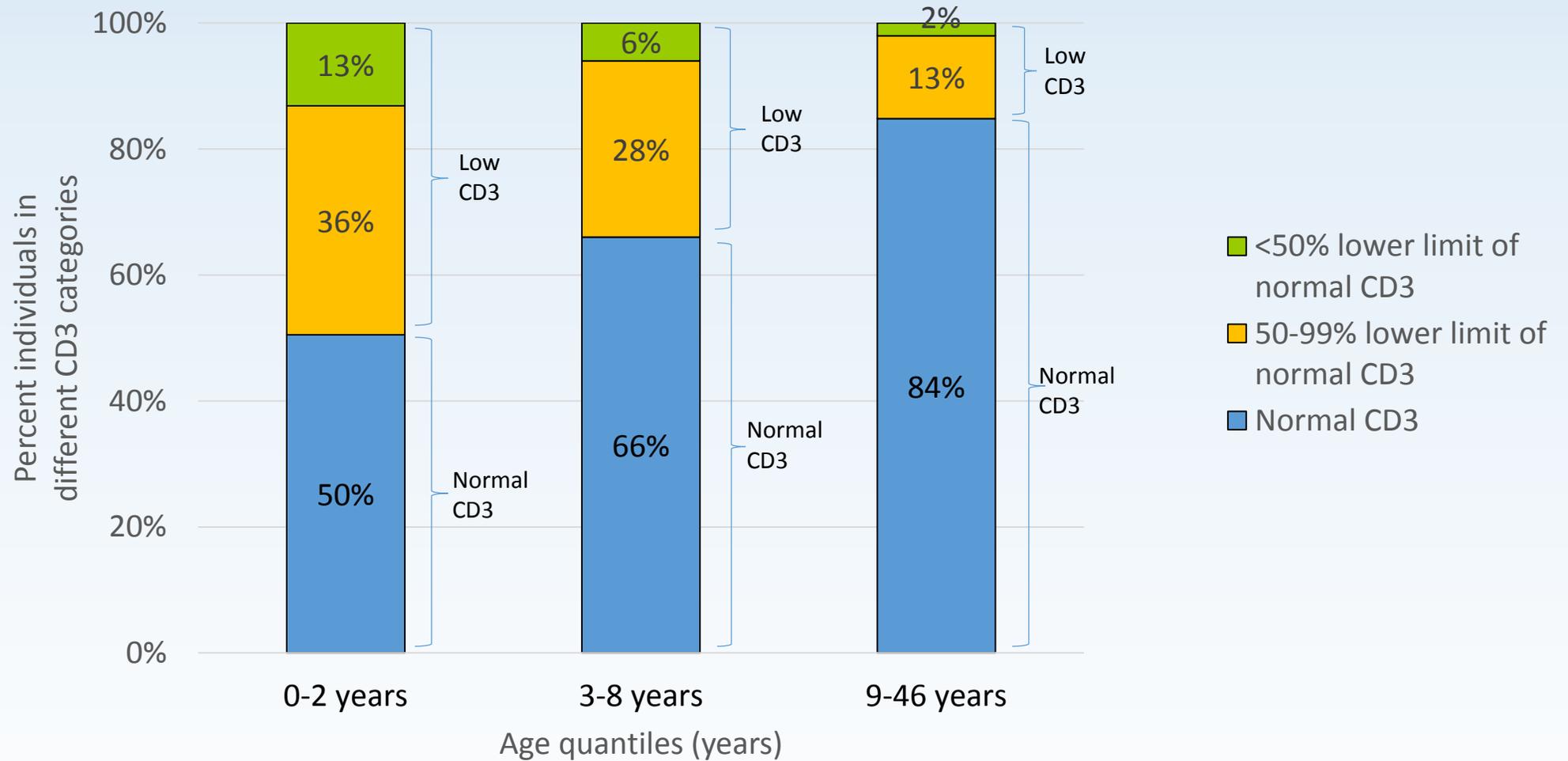
- Outcomes

- Infections: Presence of reported sino-pulmonary, other bacterial, viral and fungal infections
- Autoimmunity: Presence of any autoimmune condition (cytopenias, thyroid disease and others)
- Atopy: Presence of any atopic condition (asthma, allergic rhinitis or atopic dermatitis)

Reported frequency of Infections, Autoimmunity & Atopy

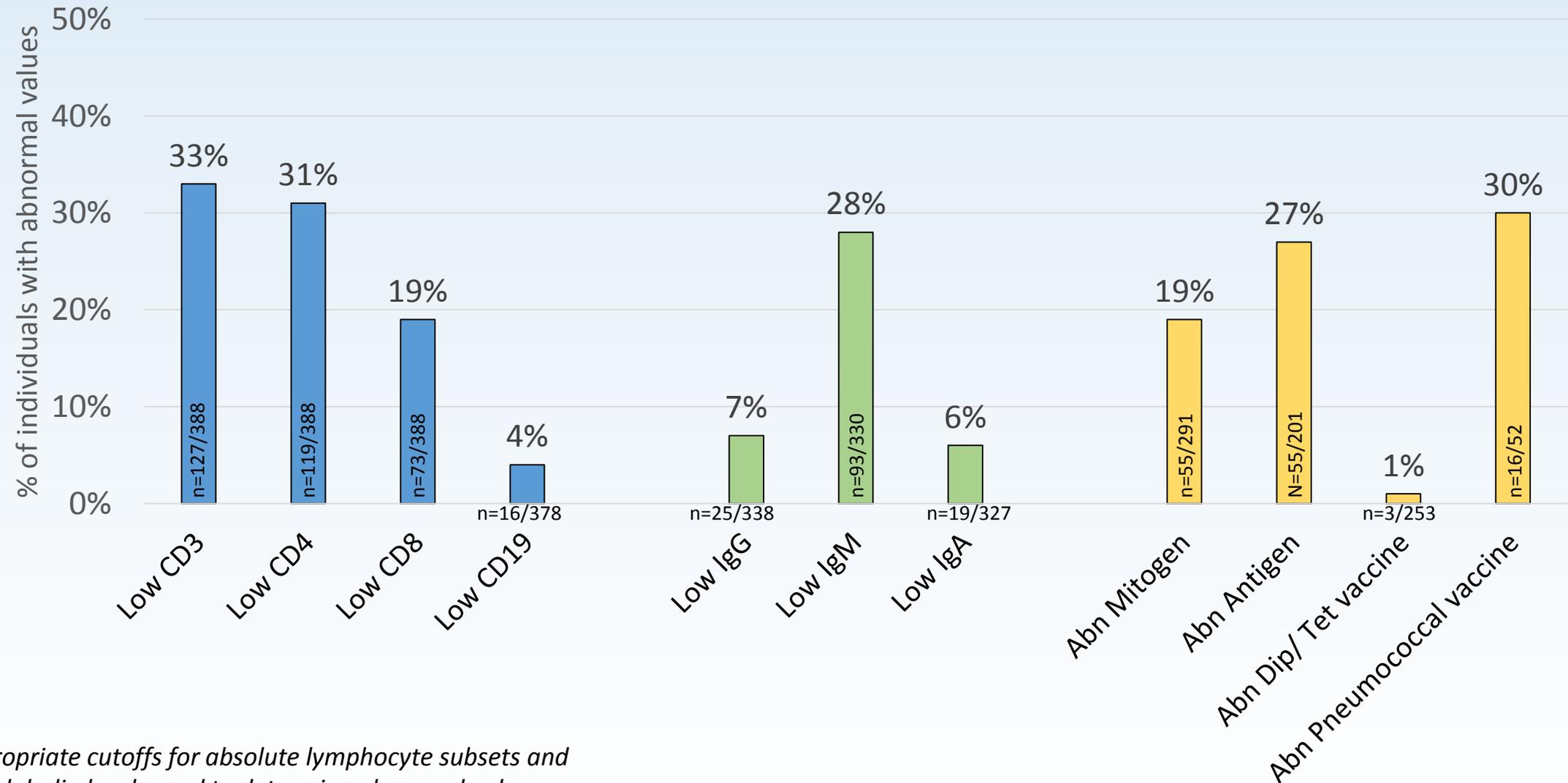


Absolute CD3 categories by age



Absolute CD3 numbers converted to a proportion of the lower limit of age-adjusted normal and expressed as a percentage

Abnormal immune characteristics



Age-appropriate cutoffs for absolute lymphocyte subsets and immunoglobulin levels used to determine abnormal values.

Lowest CD3 counts (<50% lower limit of normal) associated with higher odds of reported autoimmunity and atopy

AUTOIMMUNITY		n=319
	Odds Ratio	95% C.I.
CD3		
50-99% CD3	2.37	(0.83-6.74)
<50% CD3	4.8	(1.11-20.6)

ATOPY		n=319
	Odds Ratio	95% C.I.
CD3		
50-99% CD3	0.82	(0.22-3.02)
<50% CD3	6.15	(1.62-23.37)

Multivariate logistic regression, adjusted for hypogammaglobulinemia and age quantiles

Absolute CD3 numbers converted to a proportion of the lower limit of age-adjusted normal and expressed as a percentage

Conclusions

- DiGeorge patients with absolute CD3 values of less than 50% of the lower limit of age adjusted normal may have higher odds of reported autoimmunity and atopy as compared to those with normal CD3 values.
- CD3 values less than 50% of the lower limit of age adjusted normal may be a useful clinical threshold to potentially identify a high risk subset.
- LIMITATIONS: Missing data, risk of misclassification bias, reporting bias, cross-sectional

Immunopathology of immune dysregulation?

↓↓ CD3 (<50% lower limit of normal)

↑↑ Homeostatic proliferation

Pathways associated with Th2 polarization?

Pathways associated with impaired tolerance?

Th2 polarization

Impaired tolerance

Atopy

Autoimmunity

Future studies are needed to :

- Validate absolute CD3 < 50% lower limit of normal as a high risk cutoff in other cohorts
- Assess the role of duration and timing of T cell lymphopenia
- Investigate the underlying molecular pathways to look for unique transcriptomic signatures and differential gene expression in this high risk subset.

Genome

Multiomics

Clinical Phenotype

Thank you

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