

Brief epidemiological overview of PIDs and Allergies

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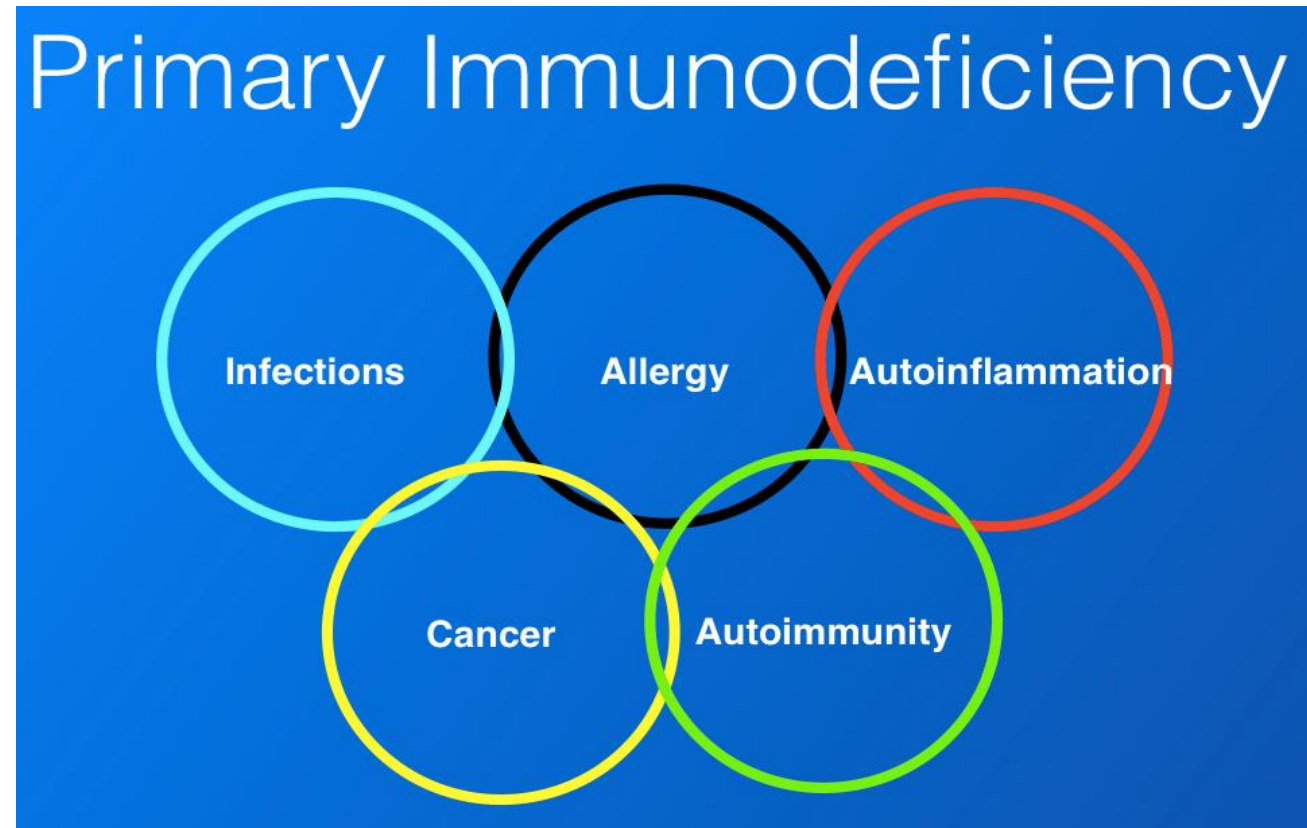
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- **PIDs are rare but multiple and complex**
- chronic=lifelong disease *and* therapy
- Prognosis often severe when misdiagnosed, inadequately treated
- Burden of disease
- Burden of treatments



Initial presenting manifestations in 16,486 patients with inborn errors of immunity include infections and noninfectious manifestations

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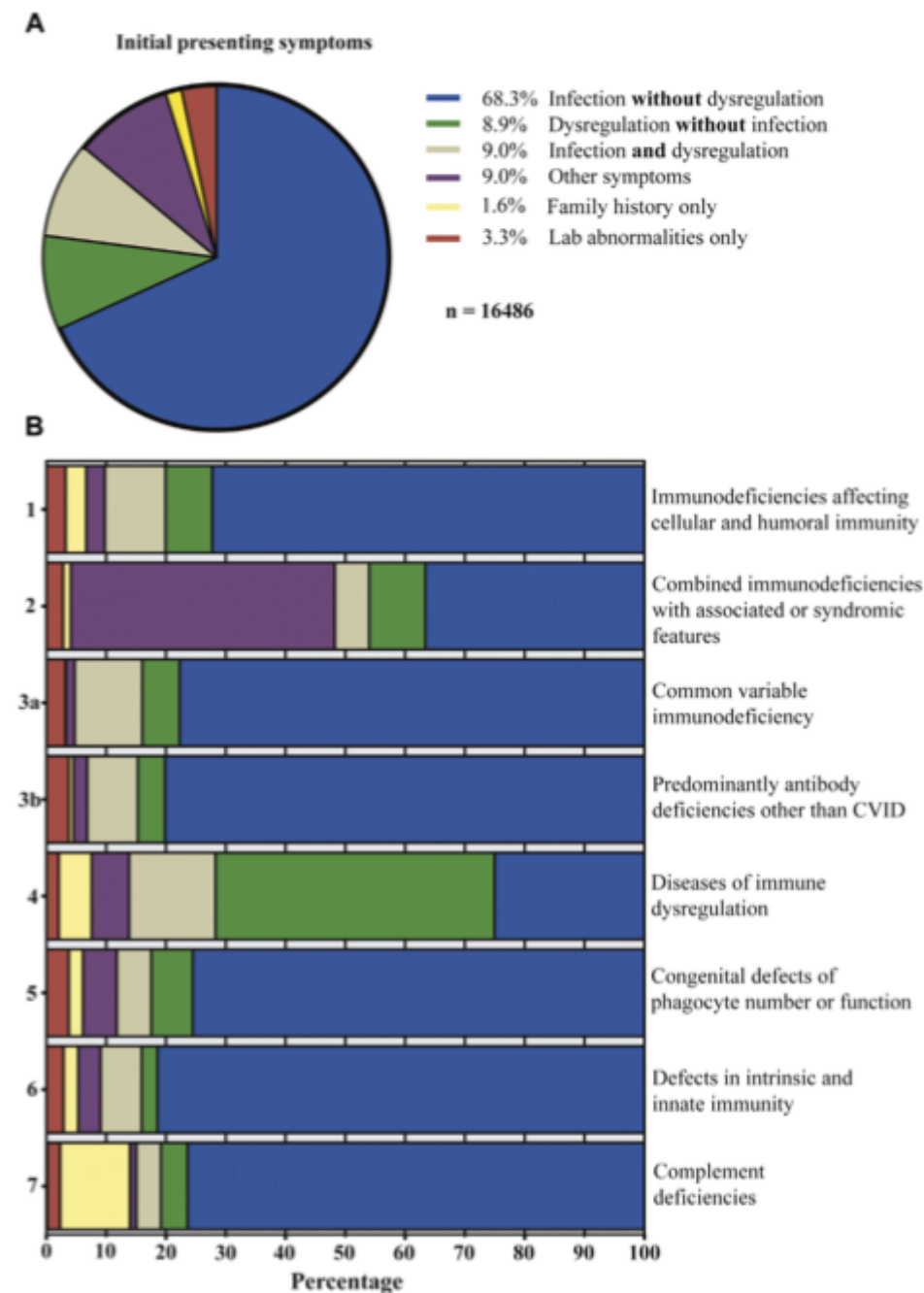
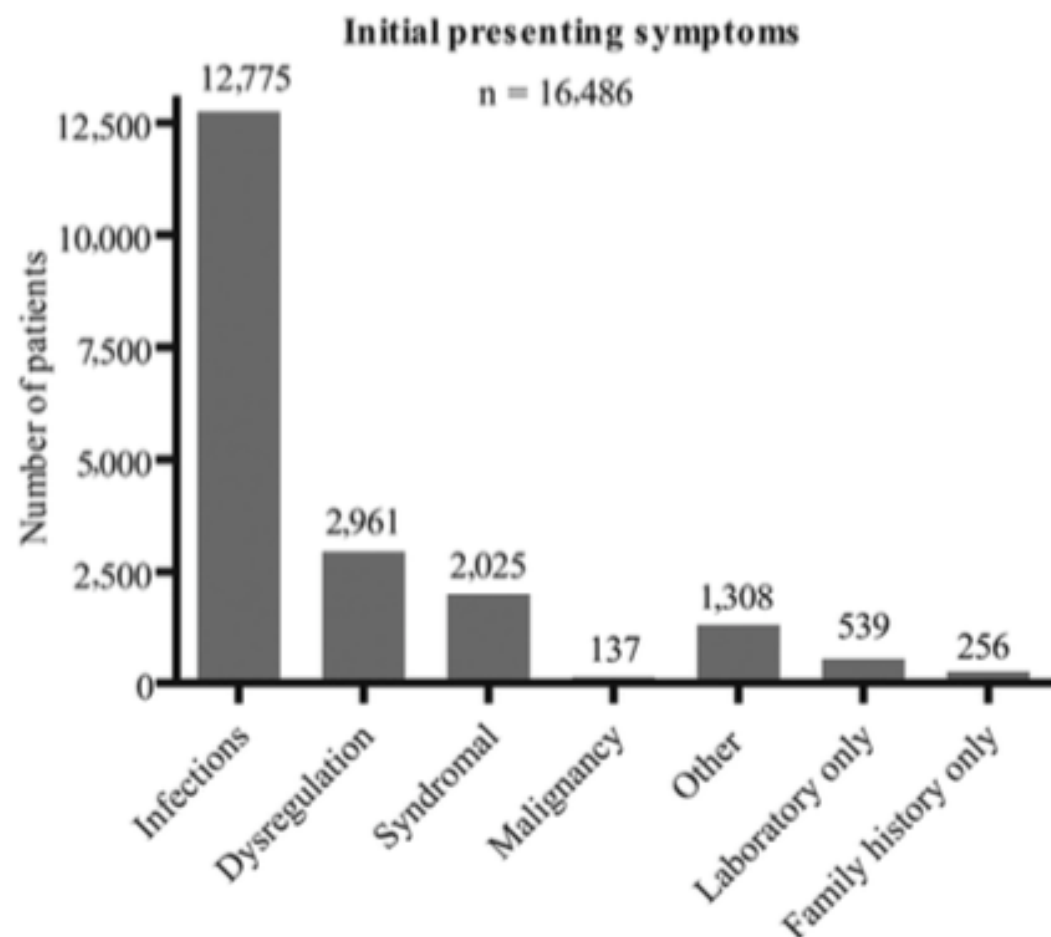
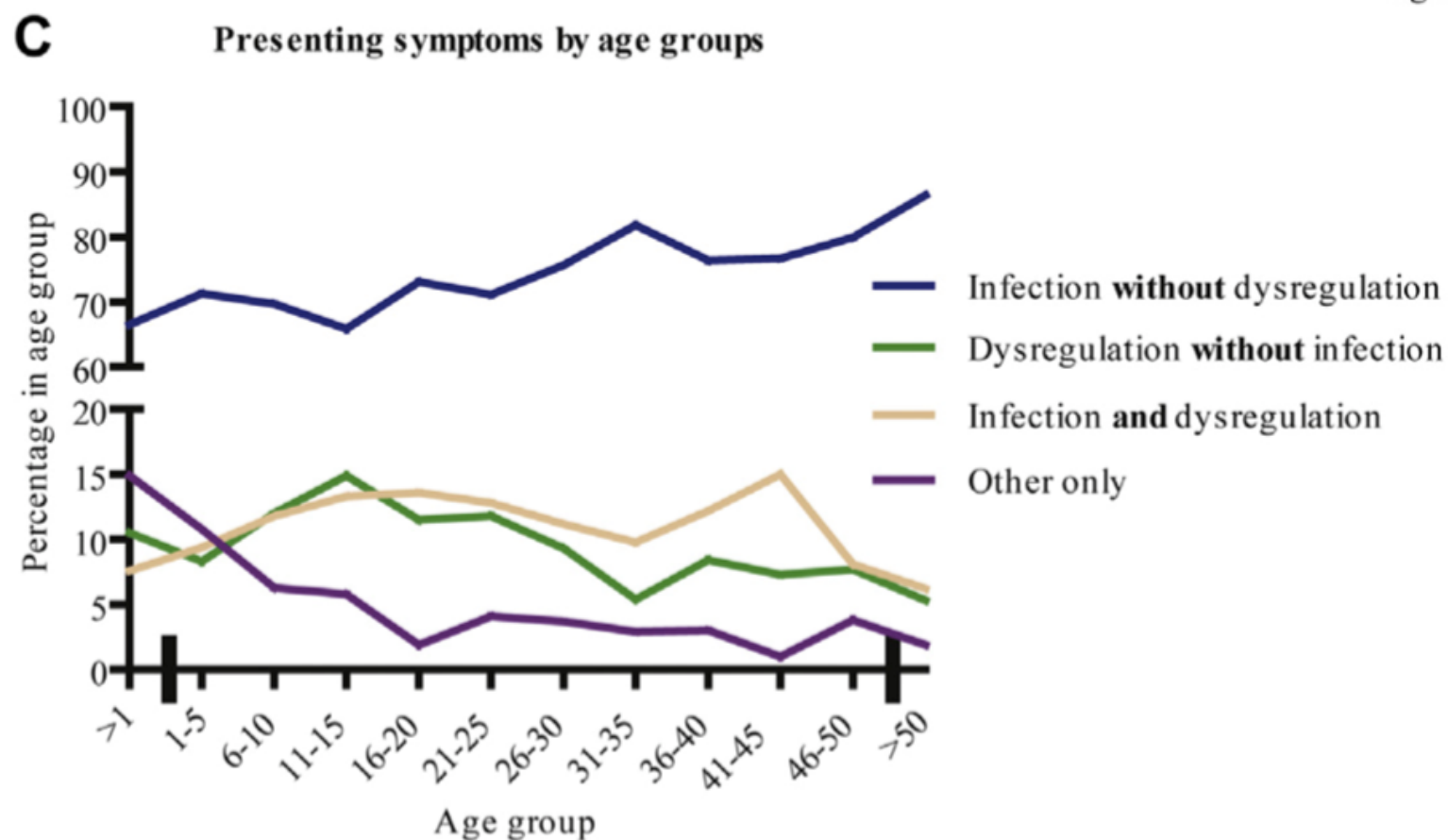
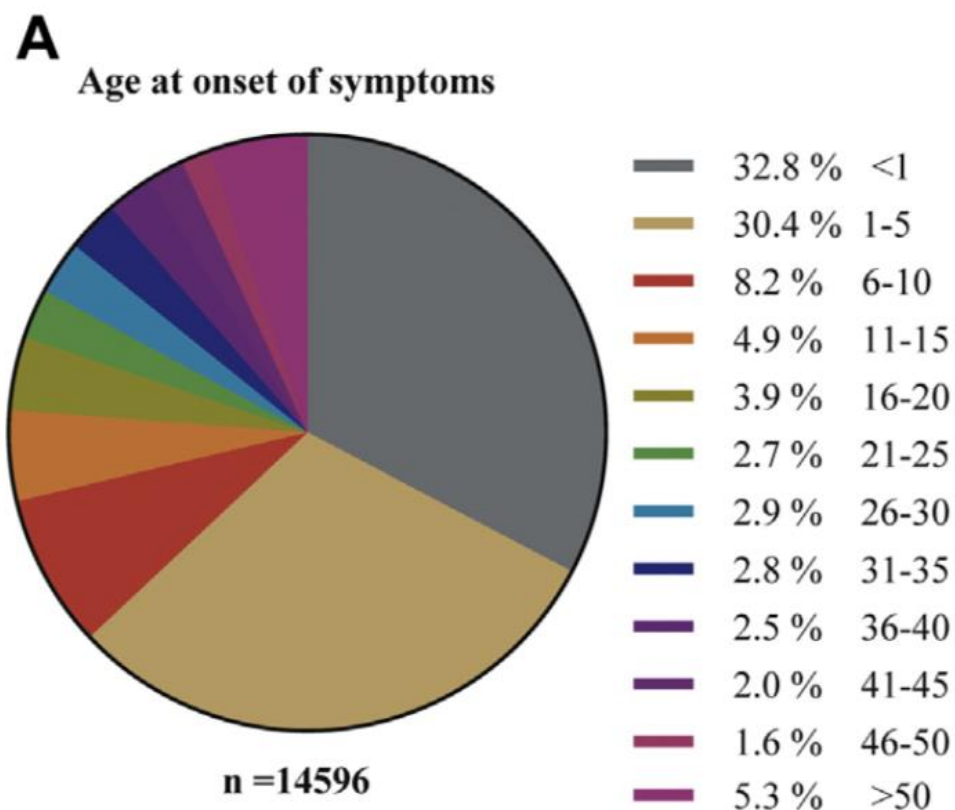


FIG 3. Pattern of initial presenting manifestations. **A**, Patterns of initial presenting manifestations in the complete cohort. "Other" summarizes initial presentation with syndromic features, malignancy, or other symptoms. **B**, Patterns of initial presenting manifestations by IEI disease groups.

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- True prevalence of atopic disorders in the setting of PID as a whole is difficult to pinpoint (Sokol & Milner, *Curr Opin Pediatr* 2018)
- USIDnet data (Tuano *et al.* *JACI*. 2014):
 - Food allergy: 1.8% vs 2.2% in gen. pop.
 - Atopic dermatitis: 6% vs 10.2% in gen. pop.
 - PIDs associated with both FA and AD were CVID, CID and HIES.

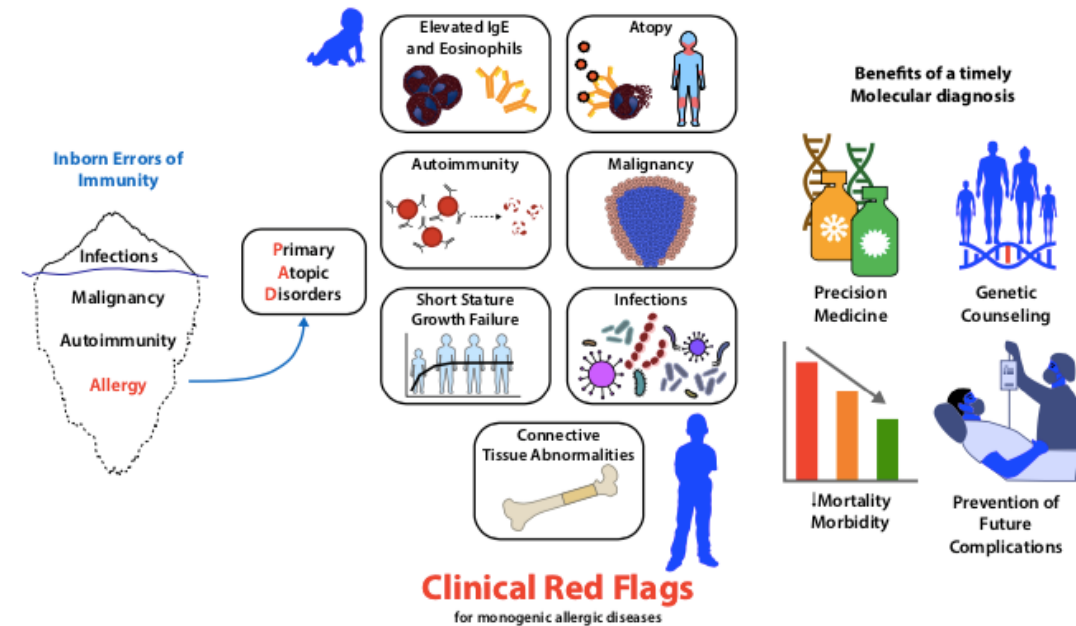


FIG 1. Clinical red flags and warning signs that warrant assessment for PADs, and the benefits of timely diagnosis and treatment of PADs. Traditional warning signs of IELs heavily emphasize the presence of infectious phenotypes, while omitting other important signs of IELs such as malignancy, autoimmunity, and allergy. Here, we provide 7 clinical red flags that should lower one's threshold for considering PADs, a subgroup of IELs that present with immune dysregulation and allergic inflammation. Early recognition and diagnosis of PADs can dramatically alter the treatment of affected individuals, leading to better patient outcomes.

CEREDIH registry — 200,000 patient-years

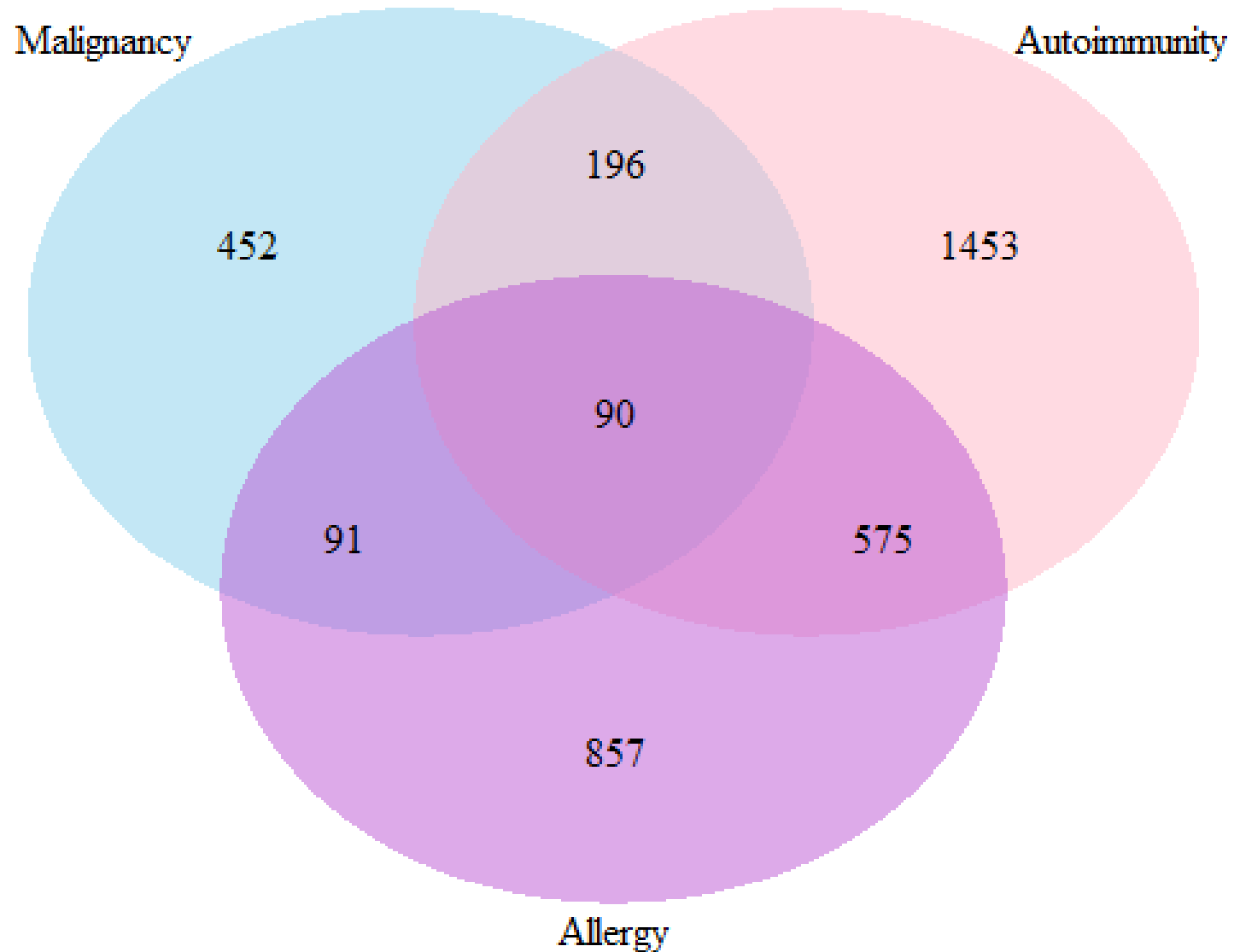


	Median or N (%)
Males (n=7983)	4427 (55)
Adults (n=7963)	4595 (58)
Age at last news (alive at last fup), years (n=6466)	23.33
Alive (n=7983)	5987 (75)
Lost (n=7983)	487 (6)
Deceased (n=7983)	1509 (19)
Age at death, years (n=1498)	14.37
Consanguinity (n=7316)	1124 (15)
Familial case (n=7573)	2157 (28)

Onset—Presenting symptoms

	Median or N (%)
Age at first symptom, years (n=6746)	2.3
<i>Immune dysregulation (n=7711)</i>	1245 (16)
Infection (n=7711)	4636 (60)
Malignancy (n=7711)	82 (1)
Syndromal manifestations (n=7711)	734 (10)
Lab. abnormalities (n=7711)	353 (5)
Only genetically diagnosed (n=7711)	244 (3)

Info on allergy in 6662 patients (83.4%)



Clinical manifestations — documented in a standardized way (ICD10 codes)



Covariates	Median (years) or N (%)
<u>Age at any first clinical manifestation</u> <u>(AI/INFLA or MALIG or INFECT or ALLERGY) (n=3831)</u>	7.2 years
<u>Autoimmunity/Inflammation</u> (n=6740)	2314 (34)
Age at first autoimmunity/flammation (n=1950)	10.9 years
<u>Malignancy</u> (n=7847)	829 (11)
Age at first malignancy (n=787)	36.4 years
<u>Infection</u> (n=3744)	3181 (85)
Age at first infection (n=1913)	4.0 years

List of respiratory allergies

Asthma

Respiratory disorder, unspecified

Allergic rhinitis, unspecified

Other allergic rhinitis

Allergic rhinitis due to pollen

Predominantly allergic asthma

Vasomotor rhinitis

Other specified respiratory disorders

List of systemic allergies

Angioneurotic oedema

Anaphylactic shock, unspecified

Contact with hornets, wasps and bees

List of cutaneous allergies

Other atopic dermatitis

Toxic epidermal necrolysis [Lyell]

Dermatitis, unspecified

Allergic urticaria

Urticaria, unspecified

Atopic dermatitis

Allergic contact dermatitis due to plants, except food

Urticaria

Allergic contact dermatitis due to other chemical products

Other urticaria

Allergic contact dermatitis due to other agents

Generalized skin eruption due to drugs and medicaments

Urticaria due to cold and heat

Rash and other nonspecific skin eruption

Seborrhoeic keratosis

List of digestive allergies

Malabsorption due to intolerance, not elsewhere classified

Allergic and dietetic gastroenteritis and colitis

Other adverse food reactions, not elsewhere classified

Anaphylactic shock due to adverse food reaction

Lactose intolerance

List of medication allergies

Unspecified adverse effect of drug or medicament

Personal history of allergy to sulfonamides

Personal history of allergy to other antibiotic agents

Personal history of allergy to serum and vaccine

Penicillins

Immunoglobulin

Anaphylactic shock due to adverse effect of correct drug or medicament properly administered

Personal history of allergy, other than to drugs and biological substances

Drug-induced acute pancreatitis

Analgesic nephropathy

Severe allergy (n=6662)

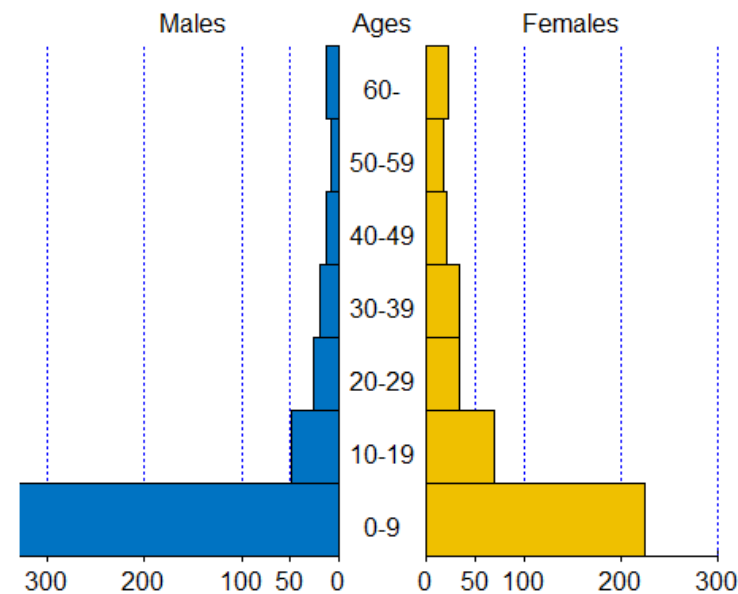
1628 (25%)

Age at first severe allergy (n=1005)

3.8 years

	N (%)
Allergy (n=6662)	1613 (24)
1 manifestation (n=6662)	1198 (18)
2 manifestations (n=6662)	294 (4)
3 manifestations (n=6662)	73 (1)
4 manifestations (n=6662)	13 (0)
5 manifestations (n=6662)	6 (0)

Distribution of age at first allergy



Category of PID	Whole cohort N=6610	No allergy N=4982	Allergy N=1628	p-value
1.Adaptive Immunity B-cell deficiencies CVID	1463 (22.13%)	1089 (21.86%)	374 (22.97%)	
2.Adaptive Immunity B-cell deficiencies non-CVID	1530 (23.15%)	1024 (20.55%)	506 (31.08%)	
3.Adaptive Immunity T-cell deficiencies SCID	323 (4.89%)	315 (6.32%)	8 (0.49%)	
4.Adaptive Immunity T-cell deficiencies CID	1398 (21.15%)	1017 (20.41%)	381 (23.4%)	<0.001
5.Adaptive Immunity Other T-cell deficiencies	788 (11.92%)	603 (12.1%)	185 (11.36%)	
6.Innate Immunity Deficiencies	1049 (15.87%)	891 (17.88%)	158 (9.71%)	
7.Unclassified PID	59 (0.89%)	43 (0.86%)	16 (0.98%)	

Covariate	Values	Whole cohort N=6610	CVID N=1463	non-CVID N=1530	SCID N=323	CID N=1398	Other T-cell N=788	Innate N=1049	Unclassified N=59	p-value
Allergy	0	4982 (75.37%)	1089 (74.44%)	1024 (66.93%)	315 (97.52%)	1017 (72.75%)	603 (76.52%)	891 (84.94%)	43 (72.88%)	<0.001
	1	1628 (24.63%)	374 (25.56%)	506 (33.07%)	8 (2.48%)	381 (27.25%)	185 (23.48%)	158 (15.06%)	16 (27.12%)	

Covariate	Values	Whole cohort N=1628	CVID N=374	non-CVID N=506	SCID N=8	CID N=381	Other T-cell N=185	Innate N=158	Unclassified N=16	p-value
Age at first allergy		3.67 [1.11;16.47]	22.3 [8;43]	3.89 [2.58;18.06]	0.24 [0.13;0.33]	2.27 [0.5;5.88]	3 [0.5;10.05]	3.32 [1.59;12.37]	3 [0.86;3.58]	<0.001
	NA	598	193	214	2	83	53	49	4	

Median age [Q1 ; Q3], years

Covariate	Values	Whole cohort	No allergy	Allergy	p-value
		N=6610	N=4982	N=1628	
Sex	F	2961 (44.8%)	2201 (44.18%)	760 (46.68%)	0.078
	M	3649 (55.2%)	2781 (55.82%)	868 (53.32%)	
Class of age at last news	Adults	3796 (57.45%)	2827 (56.77%)	969 (59.52%)	0.051
	Children	2812 (42.55%)	2153 (43.23%)	659 (40.48%)	
Consanguinity	N	5302 (84.78%)	3895 (82.89%)	1407 (90.48%)	<0.001
	Y	952 (15.22%)	804 (17.11%)	148 (9.52%)	
Age at clin. diag.		7 [1.3;31.86]	6.27 [1.02;29.76]	9.24 [2.34;37.34]	<0.001
Genetic documentation	0	3403 (51.48%)	2419 (48.55%)	984 (60.44%)	<0.001
	1	3207 (48.52%)	2563 (51.45%)	644 (39.56%)	
Age at gen. diag.		5.65 [0.97;15.53]	5.42 [0.82;14.91]	6.57 [1.37;18.16]	0.003
IgRT (alive patients)	N	3011 (56.7%)	2311 (59.07%)	700 (50.07%)	<0.001
	Y	2299 (43.3%)	1601 (40.93%)	698 (49.93%)	

Distribution of all allergy events (by type) per PID Category (per allergy)

Type of allergy	Whole cohort N=2125	CVID N=488	non-CVID N=668	SCID N=9	CID N=473	Other T-cell N=262	Innate N=200	Unclassified N=25
Respiratory	765 (36%)	174 (35.66%)	338 (50.6%)	2 (22.22%)	127 (26.85%)	58 (22.14%)	59 (29.5%)	7 (28%)
Cutaneous	581 (27.34%)	93 (19.06%)	111 (16.62%)	3 (33.33%)	206 (43.55%)	98 (37.4%)	63 (31.5%)	7 (28%)
Medication	385 (18.12%)	129 (26.43%)	97 (14.52%)	2 (22.22%)	73 (15.43%)	41 (15.65%)	39 (19.5%)	4 (16%)
Digestive	178 (8.38%)	20 (4.1%)	62 (9.28%)	1 (11.11%)	41 (8.67%)	38 (14.5%)	13 (6.5%)	3 (12%)
Ocular	37 (1.74%)	10 (2.05%)	16 (2.4%)	0 (0%)	3 (0.63%)	6 (2.29%)	0 (0%)	2 (8%)
Systemic	37 (1.74%)	16 (3.28%)	6 (0.9%)	1 (11.11%)	7 (1.48%)	4 (1.53%)	3 (1.5%)	0 (0%)
Other	142 (6.68%)	46 (9.43%)	38 (5.69%)	0 (0%)	16 (3.38%)	17 (6.49%)	23 (11.5%)	2 (8%)

Covariate	Values	Whole cohort	No allergy	Allergy	p-value
		N=6610	N=4982	N=1628	
Malignancy	N	5925 (89.72%)	4471 (89.83%)	1454 (89.37%)	0.591
	Y	679 (10.28%)	506 (10.17%)	173 (10.63%)	
Age at first malignancy		36.96 [15.4;57.25]	32.15 [13.37;53.68]	49.07 [27.91;61.51]	<0.001
Autoimmunity/Inflammation	N	4298 (65.16%)	3351 (67.38%)	947 (58.35%)	<0.001
	Y	2298 (34.84%)	1622 (32.62%)	676 (41.65%)	
Age at first AI		10.54 [2.19;28.18]	10.46 [2.17;27.93]	11.25 [2.21;28.39]	0.585
Infection	N	569 (14.09%)	478 (16.29%)	91 (8.26%)	<0.001
	Y	3468 (85.91%)	2457 (83.71%)	1011 (91.74%)	
Age at first infection		3.89 [0.92;18]	4.01 [0.96;18.08]	3.02 [0.87;18]	0.849

Covariate	Values	Whole cohort N=6610	ALLERGY 0 N=4982	ALLERGY 1 N=1628	p-value
Leuko_DXA		7.3 [5.3;10.2]	7.3 [5.2;10.3]	7.4 [5.6;9.9]	0.19
	NA	2437	1902	535	
Neutro_DXA		3.48 [2.18;5.41]	3.45 [2.08;5.5]	3.52 [2.37;5.17]	0.219
	NA	2814	2188	626	
Eosino_DXA		0.17 [0.07;0.34]	0.15 [0.06;0.32]	0.2 [0.1;0.39]	<0.001
	NA	3518	2733	785	
Mono_DXA		0.56 [0.4;0.88]	0.57 [0.39;0.9]	0.55 [0.4;0.82]	0.419
	NA	3447	2663	784	
Thrombo_DXA		264 [184;356]	264 [180;362]	265 [190;338]	0.429
IgG_DXA		5.4 [2.9;8.81]	5.26 [2.66;8.79]	5.62 [3.52;8.86]	0.001
	NA	2360	1874	486	
IgA_DXA		0.41 [0.1;1.08]	0.38 [0.08;1]	0.51 [0.19;1.25]	<0.001
	NA	2510	1983	527	
IgM_DXA		0.53 [0.24;1]	0.5 [0.22;1]	0.6 [0.29;1.01]	<0.001
	NA	2537	2009	528	
<u>IgE_DXA</u>		96.2 [5.9;1100]	90 [5;929]	100 [9.98;1259]	<u>0.184</u>
	NA	6006	4591	1415	

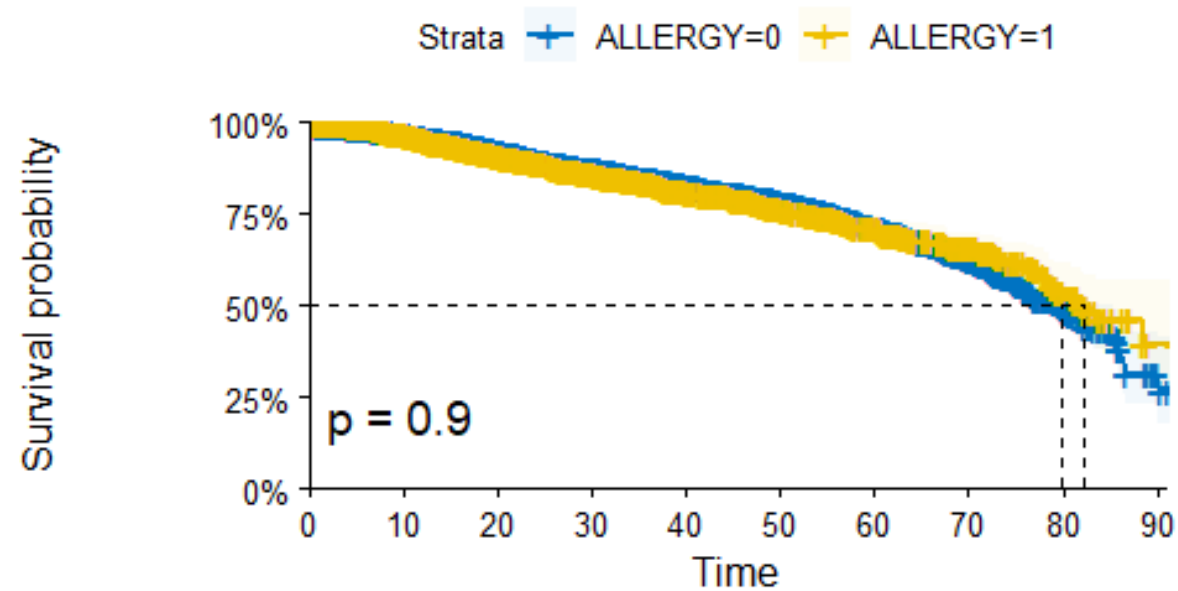
Covariate	Values	Whole cohort N=6610	ALLERGY 0 N=4982	ALLERGY 1 N=1628	p-value
Lympho_DXA		2.17 [1.3;3.56]	2.11 [1.29;3.55]	2.3 [1.4;3.58]	0.033
	NA	2590	2006	584	
CD3_DXA		1.41 [0.8;2.33]	1.35 [0.75;2.31]	1.55 [0.93;2.34]	<0.001
	NA	3843	2987	856	
CD4_DXA		0.79 [0.43;1.34]	0.76 [0.4;1.32]	0.88 [0.52;1.38]	<0.001
	NA	3845	2985	860	
CD8_DXA		0.5 [0.26;0.86]	0.49 [0.25;0.85]	0.52 [0.29;0.9]	0.042
	NA	3887	3023	864	
LymphoB_DXA		0.28 [0.1;0.65]	0.27 [0.09;0.64]	0.31 [0.13;0.67]	0.012
	NA	4074	3154	920	
CD19_DXA		0.28 [0.1;0.65]	0.27 [0.09;0.65]	0.31 [0.13;0.67]	0.012
	NA	4116	3186	930	
CD20_DXA		0.28 [0.1;0.63]	0.27 [0.1;0.62]	0.34 [0.13;0.7]	0.087
	NA	5666	4247	1419	
CD16.56_DXA		0.18 [0.1;0.34]	0.18 [0.09;0.34]	0.18 [0.1;0.33]	0.643
	NA	4206	3248	958	

Covariate	Values	Whole cohort	ALLERGY 0	ALLERGY 1	p-value
		N=6610	N=4982	N=1628	
Leuko_CTA		6.25 [4.8;8.3]	6.3 [4.8;8.4]	6.1 [4.8;7.9]	0.015
	NA	2470	1927	543	
Hb_CTA		13.1 [11.9;14.2]	13.1 [11.9;14.3]	13.1 [12;14.1]	0.559
	NA	2457	1917	540	
Neutro_CTA		3.3 [2.21;4.75]	3.38 [2.27;4.8]	3.1 [2.13;4.56]	0.01
	NA	2686	2098	588	
Eosino_CTA		0.14 [0.08;0.3]	0.13 [0.07;0.29]	0.17 [0.09;0.33]	<0.001
	NA	3203	2506	697	
Mono_CTA		0.51 [0.4;0.73]	0.53 [0.4;0.75]	0.5 [0.4;0.7]	0.171
	NA	3197	2498	699	
Thrombo_CT A		239 [174;309]	239 [174;312]	239 [173.5;302]	0.174
	NA	2472	1923	549	
IgG_CTA		8.96 [6.72;11.46]	8.92 [6.68;11.4]	9 [7.02;11.6]	0.083
	NA	2917	2305	612	
IgA_CTA		0.6 [0.15;1.37]	0.57 [0.11;1.33]	0.69 [0.24;1.41]	0.001
	NA	3247	2541	706	
IgM_CTA		0.55 [0.23;1.04]	0.55 [0.22;1.06]	0.54 [0.26;1]	0.947
	NA	3260	2554	706	
IgE_CTA		214 [18.05;2005.5]	200 [6.25;1107.5]	433 [38;3700]	0.018
	NA	6327	4828	1499	

Covariate	Values	Whole cohort	ALLERGY 0	ALLERGY 1	P-value
		N=6610	N=4982	N=1628	
Lympho_CTA		1.8 [1.2;2.6]	1.8 [1.2;2.6]	1.84 [1.22;2.6]	0.765
	NA	2971	2280	691	
CD3_CTA		1.29 [0.8;1.89]	1.26 [0.8;1.89]	1.32 [0.84;1.86]	0.356
	NA	4513	3447	1066	
CD4_CTA		0.68 [0.4;1.04]	0.66 [0.4;1.04]	0.73 [0.42;1.08]	0.034
	NA	4501	3436	1065	
CD8_CTA		0.48 [0.27;0.75]	0.49 [0.28;0.75]	0.47 [0.27;0.72]	0.52
	NA	4518	3454	1064	
LymphoB_CT A		0.21 [0.08;0.41]	0.2 [0.08;0.4]	0.22 [0.08;0.41]	0.648
	NA	4717	3599	1118	
CD19_CTA		0.21 [0.08;0.4]	0.2 [0.08;0.4]	0.22 [0.08;0.41]	0.455
	NA	4734	3610	1124	
CD20_CTA		0.2 [0.08;0.42]	0.2 [0.08;0.44]	0.2 [0.09;0.38]	0.956
	NA	6027	4543	1484	
CD16.56_CT A		0.15 [0.08;0.26]	0.16 [0.08;0.27]	0.15 [0.09;0.26]	0.575
	NA	4819	3670	1149	

Kaplan-Meier

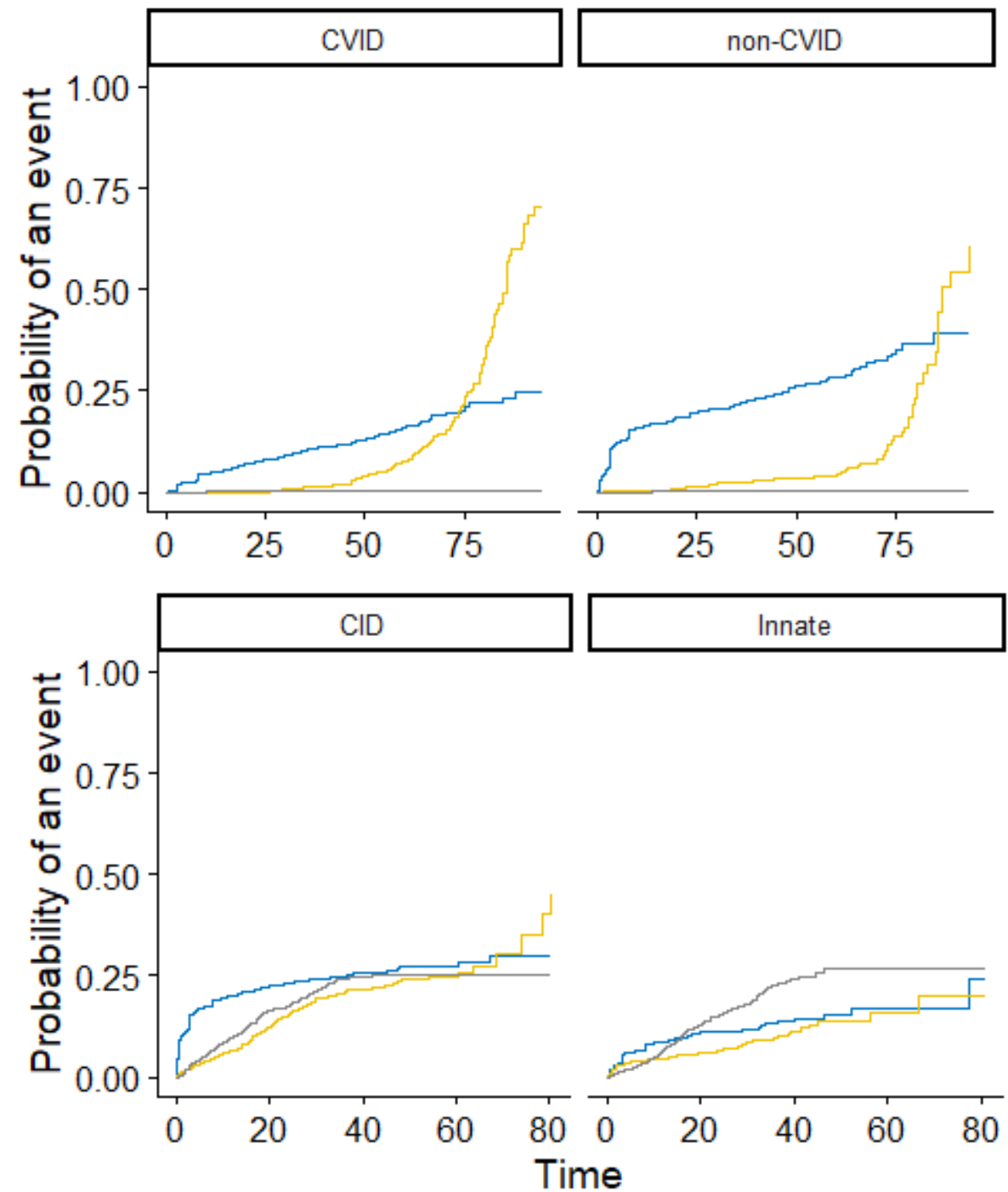
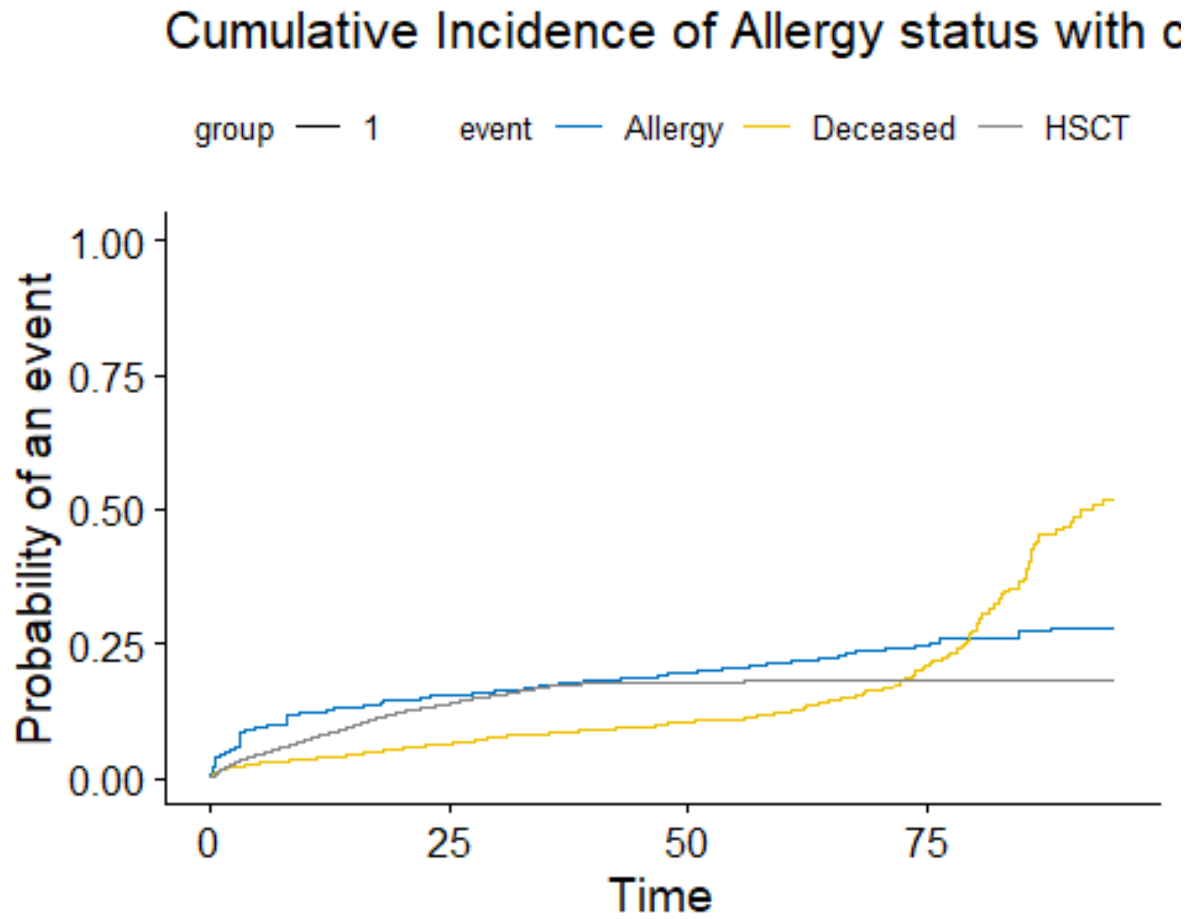
Survival curve according to their allerg



Number at risk

ALLERGY=0	1980	1762	2618	1821	1281	889	560	272	71	8
ALLERGY=1	1628	1277	906	673	482	354	241	131	36	2

Cumulative Incidence of Allergy status with competing risk



Summary

- Overlap with and relations between allergy & immunodeficiency are beginning to be recognized (partly through identification of novel genetic conditions).
- Allergic inflammation, among other types of immune dysregulation, occurs frequently in patients with inborn errors of immunity.
- PID specific allergic features have been more carefully described.
- Prevalence of allergic manifestations in PID is — at least — 24%.
- Variation across PID categories
- Lifelong occurrence of allergy