

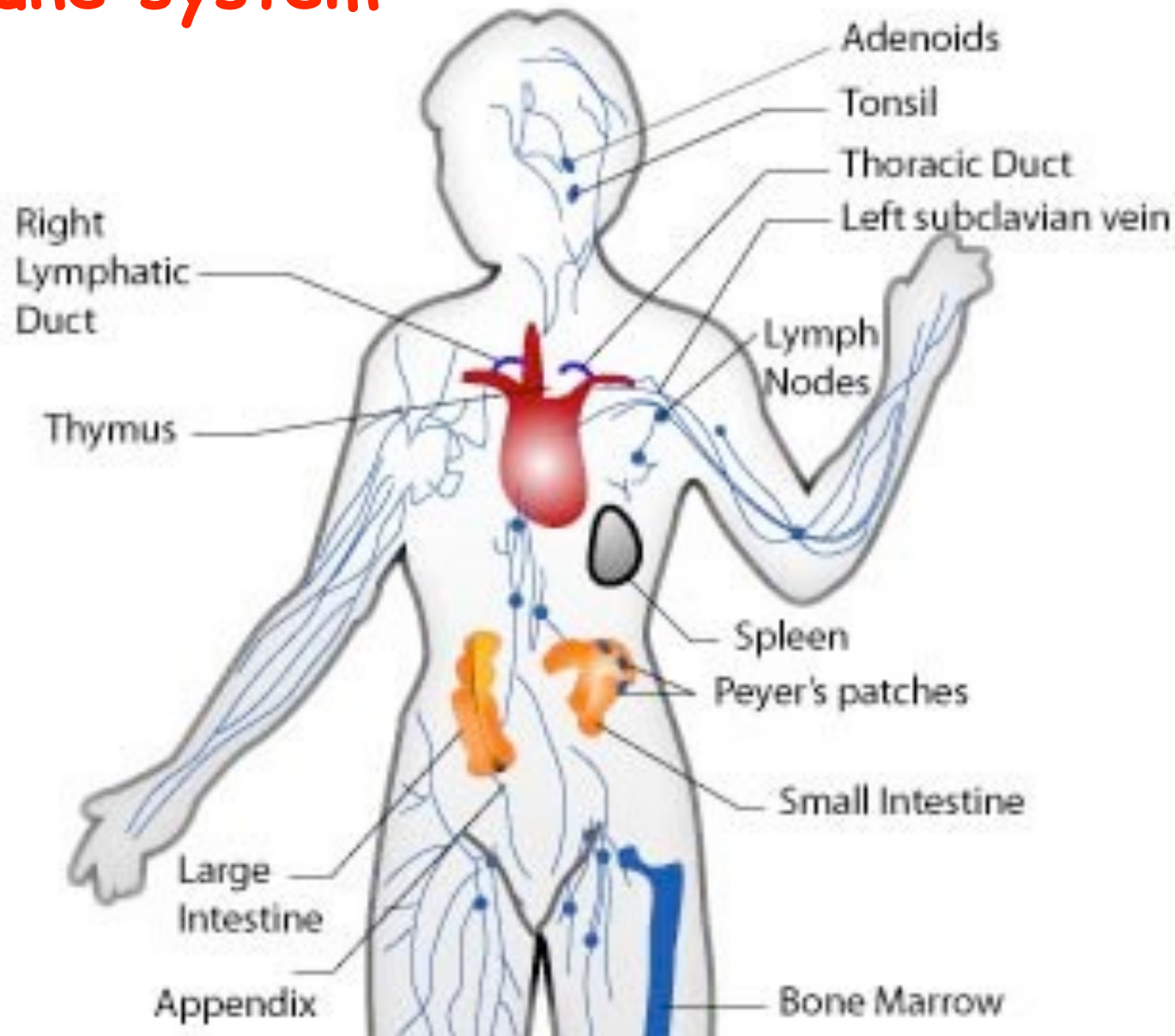
New information on CVID



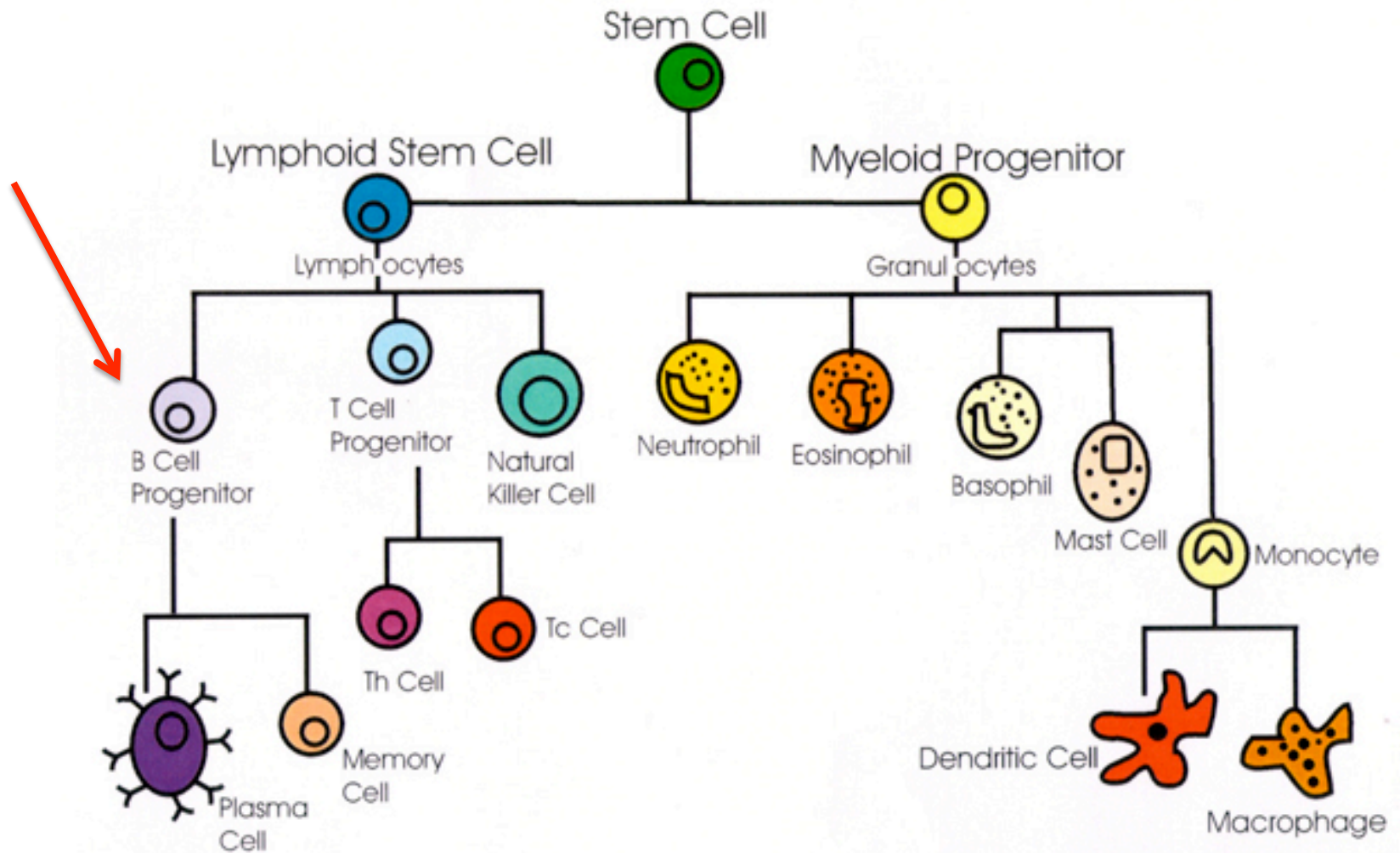
Mount Sinai Medical Center New York City

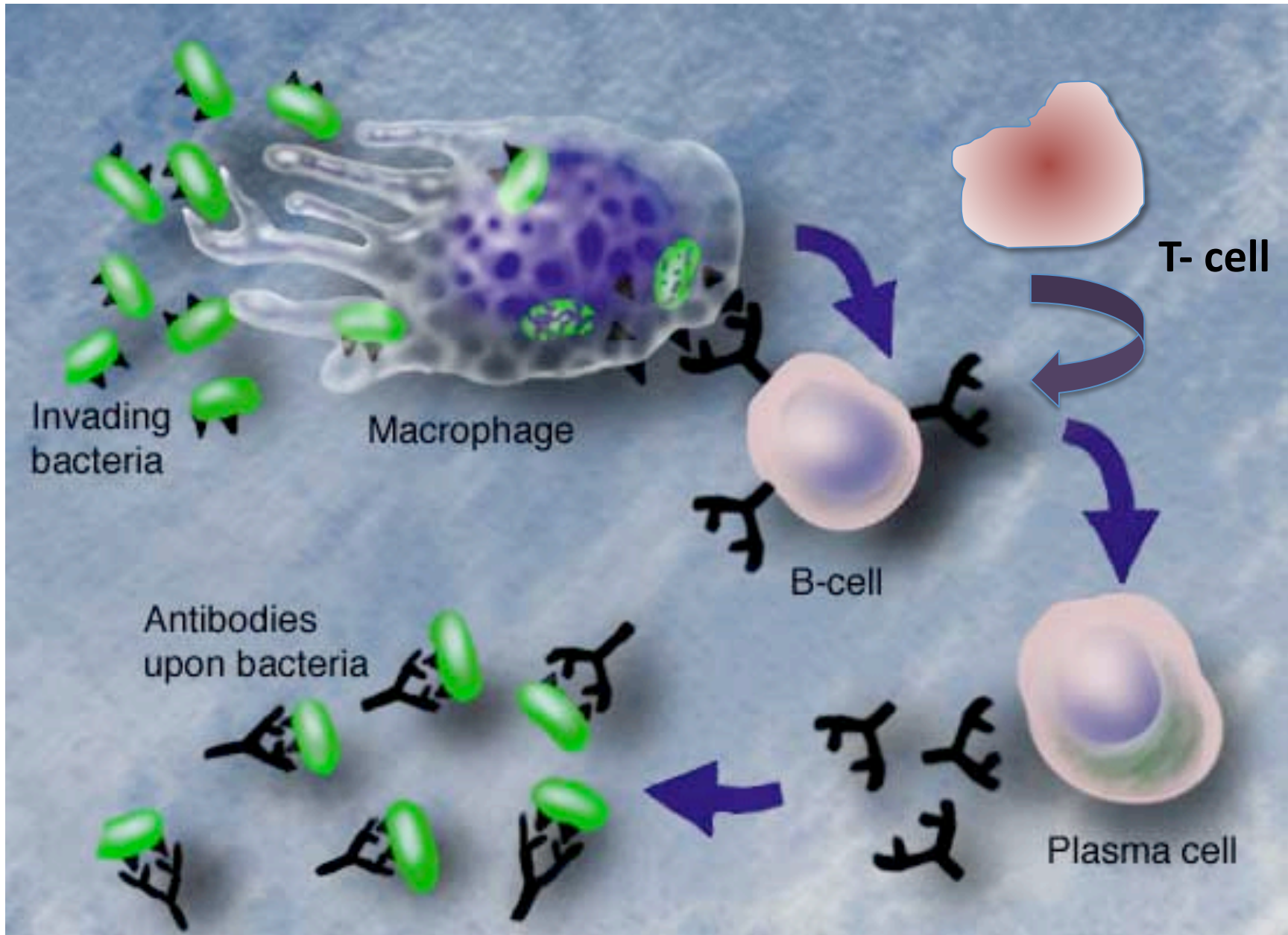


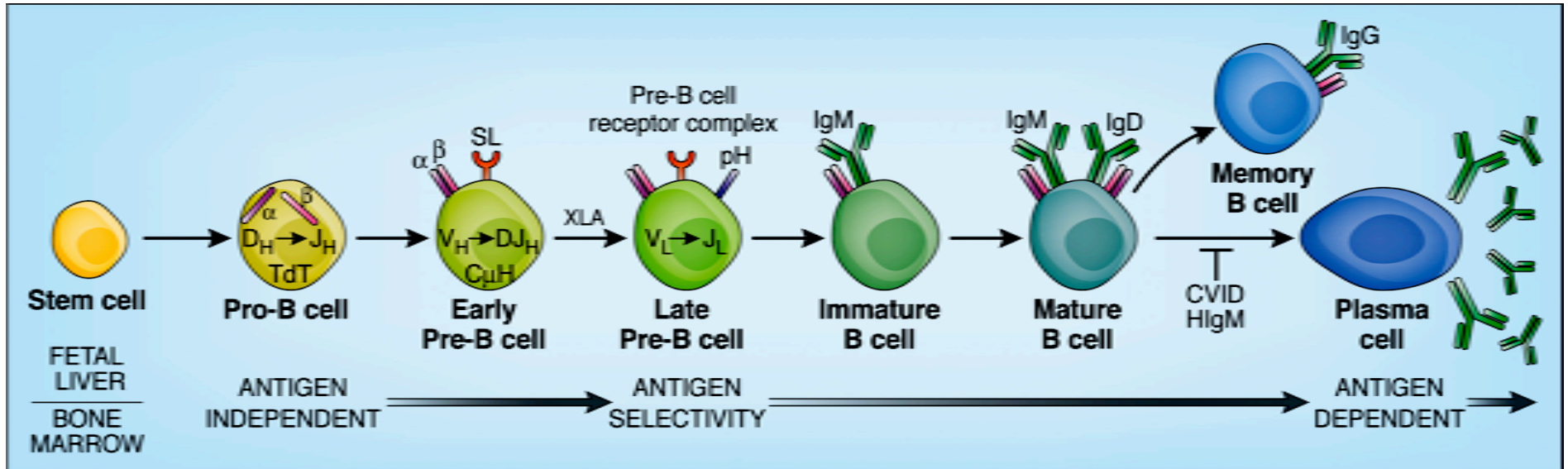
Immune system



Cells of the Immune System







XLA

Hyper IgM

CVID

Others!

CVID: what is new?

Definitions

Treatment

Complications

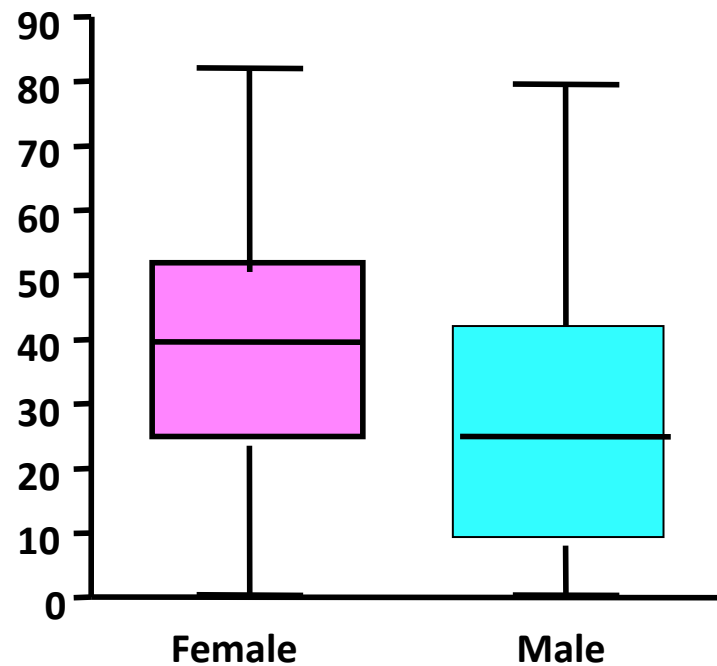
Laboratory evaluations

Genetics

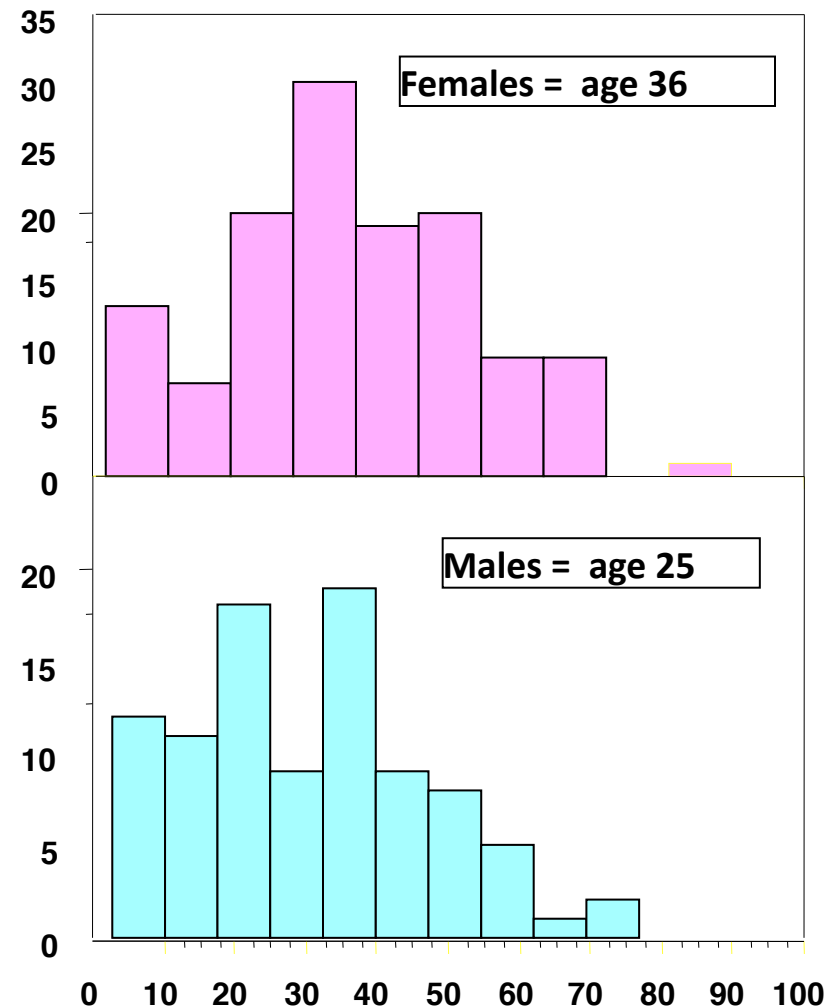
CVID: A Basic Definition

1. Four years of age or older.
2. Low Serum IgG and IgA or IgM levels for age.
3. Lack of antibody to bacteria and viruses
4. Exclusion of all other known causes of low serum immune globulins.

Age at diagnosis: mostly are adults



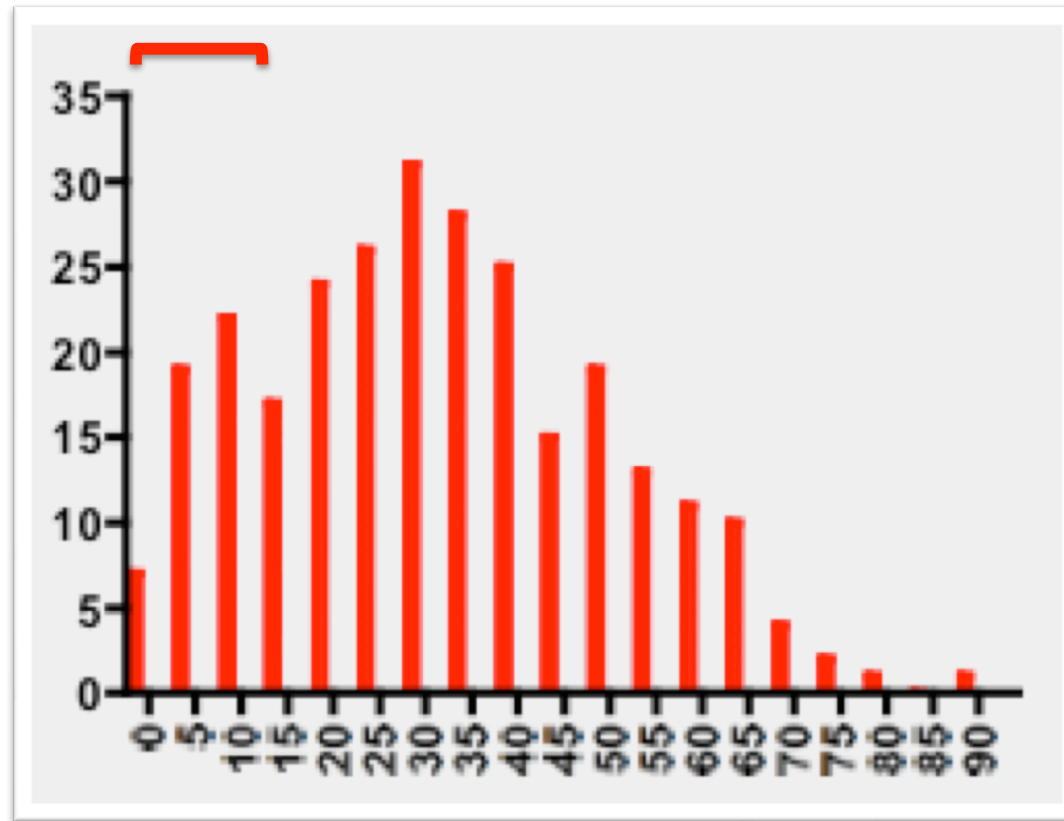
Males are diagnosed earlier
 $P < .001$



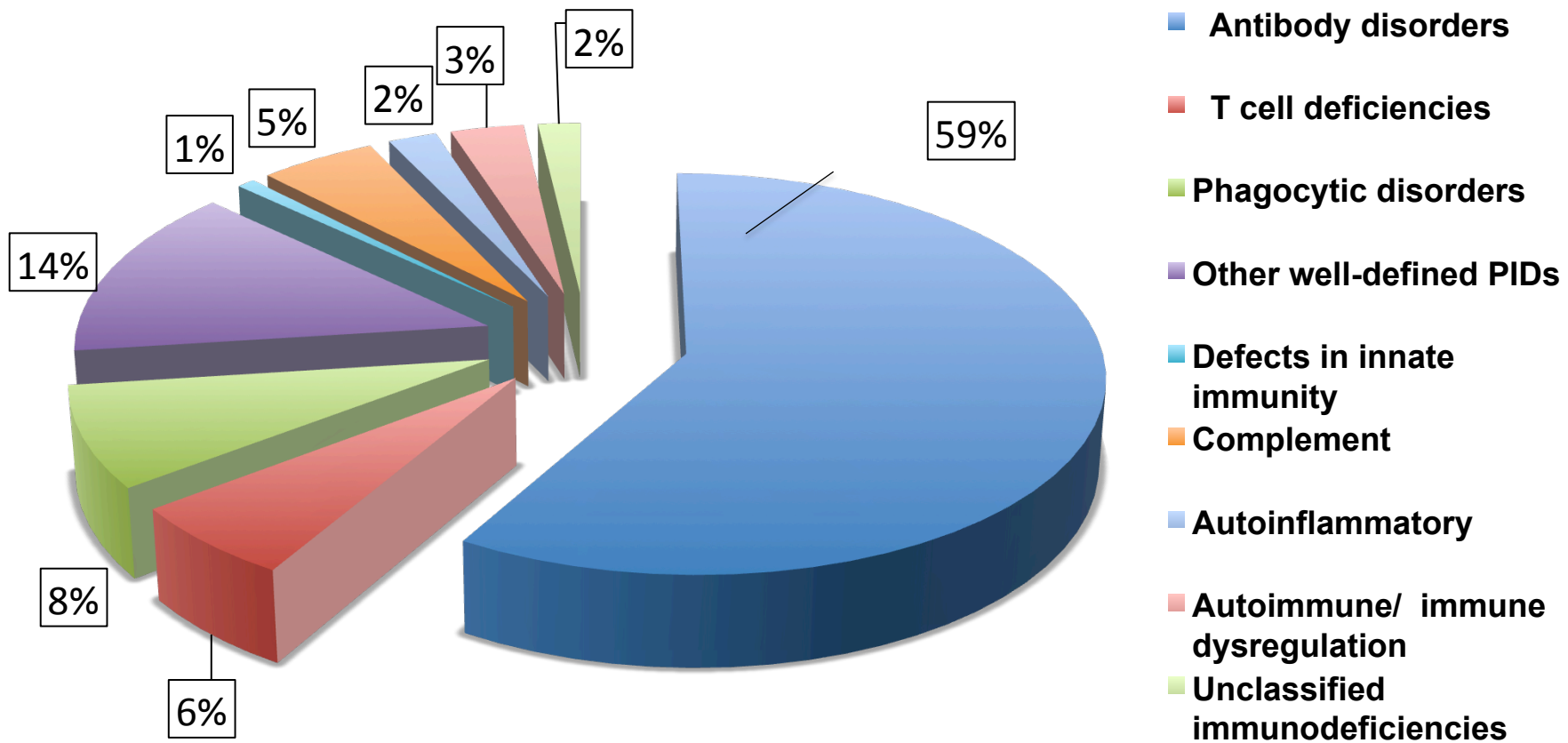
But 10% are under 10 years of age

Of 276: 18 patients were age 2 and 5

20 patients were between ages 5 and 10



European Society for Immune deficiency (ESID) Patient Registry



Antibody defects are prominent in the ESID Registry

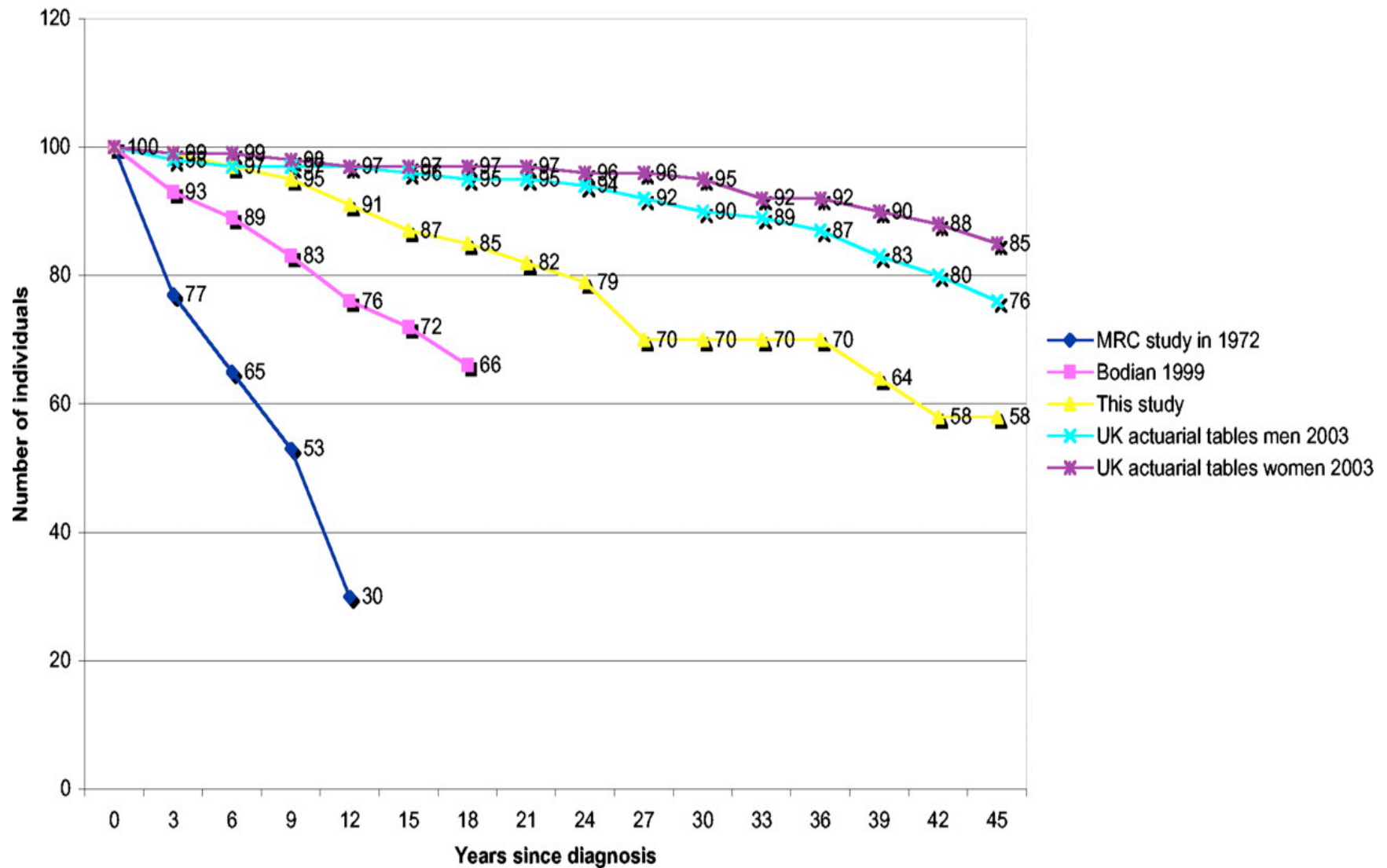
type	number	0-10	10-17	17-34	34-98
Predominantly antibody disorders	7227	23·3%	26·3%	25·0%	25·4%
Phagocytic disorders	1026	56·3%	21·7%	18·6%	3·4%
Other well-defined PIDs	1721	30·4%	27·6%	36·0%	6·1%
Predominantly T cell deficiencies	760	31·6%	29·6%	17·4	21·4%
Complement deficiencies	631	47·9%	24·6%	22·9%	4·6%
Autoimmune dysregulation	395	32·7%	32·5%	28·8%	6·0%
Autoinflammatory syndromes	263	25·5%	27·1%	37·6%	9·8%
Unclassified immunodeficiencies	228	20·4%	20·6%	24·0%	35·1%
Defects in innate immunity	98	7·9%	13·3%	28·5%	50·2%
Total	12,349	24·8%	23·1%	26·2%	25·9%

Gathmann et al Clin exp Immunol 167, 2012

What is new?

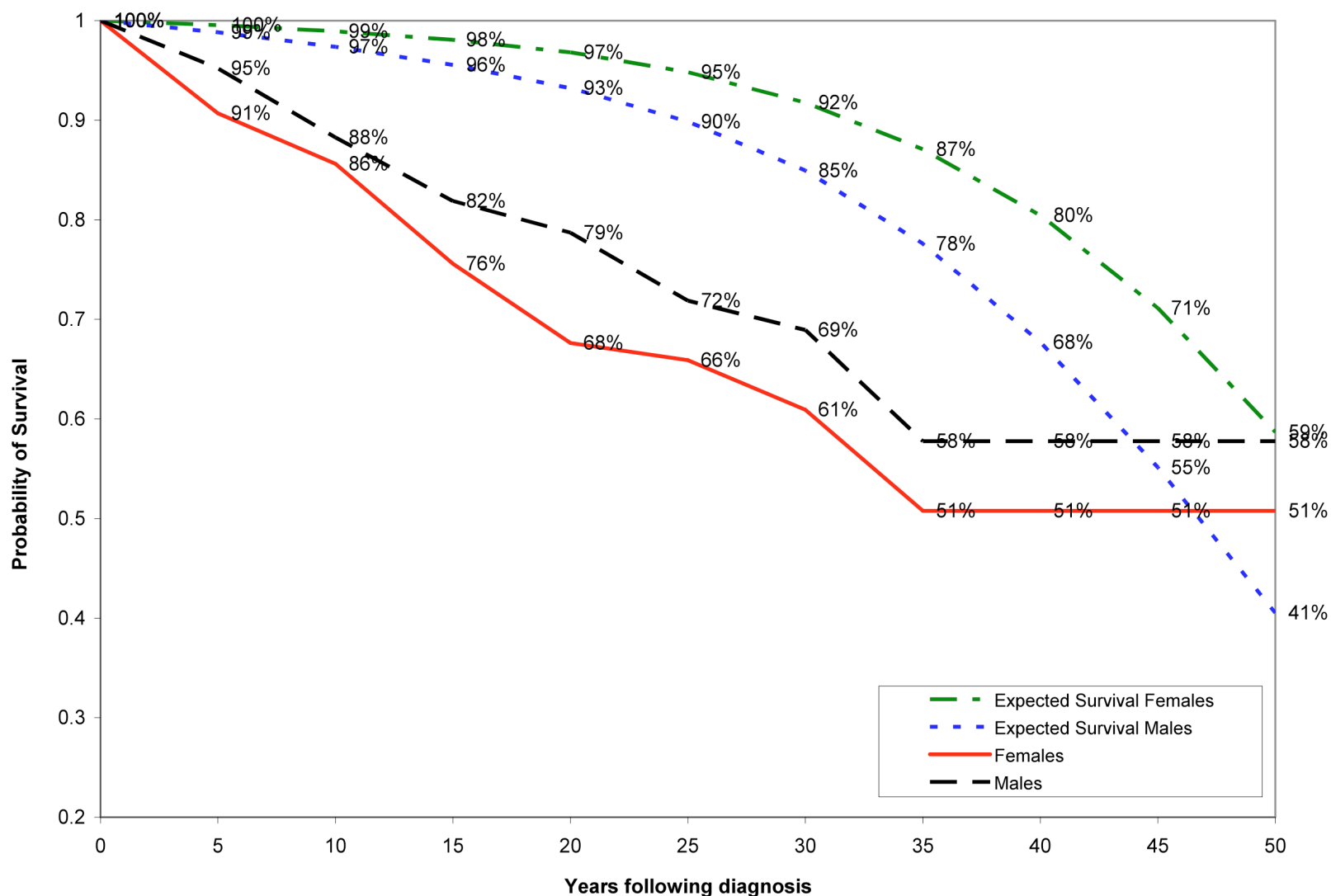
1. Clinical and treatment information
 - a) Studies of large groups of patients
 - b) Best treatments

CVID and improved long term survival over time



Chapel H, et al Blood. 112: 277, 2008, CVID: division into distinct clinical phenotypes.

473 CVID subjects (compared to US male and female standards)

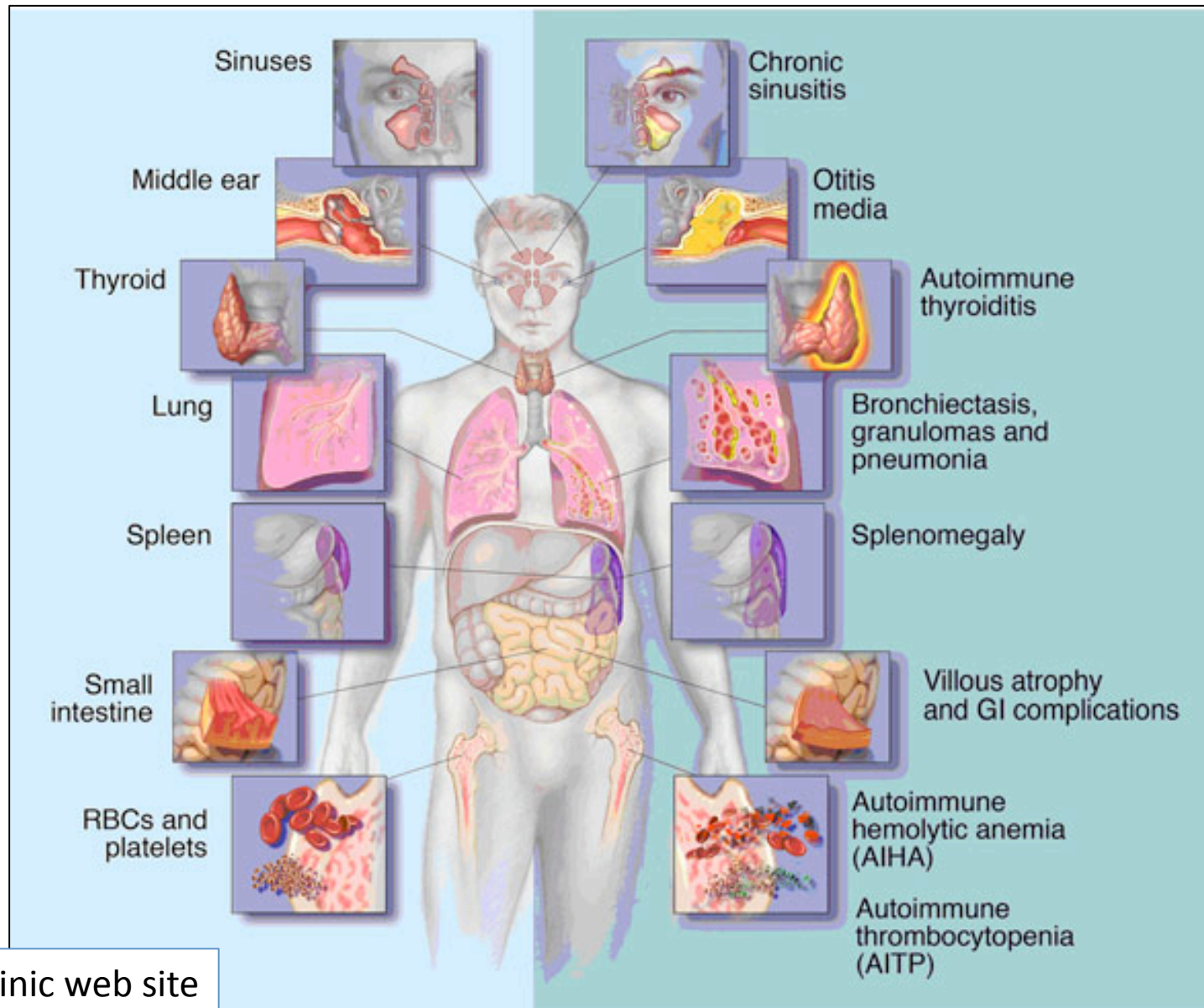


Resnick et al, Blood: 2012

Average age start for normal males = 30; for females = age 35

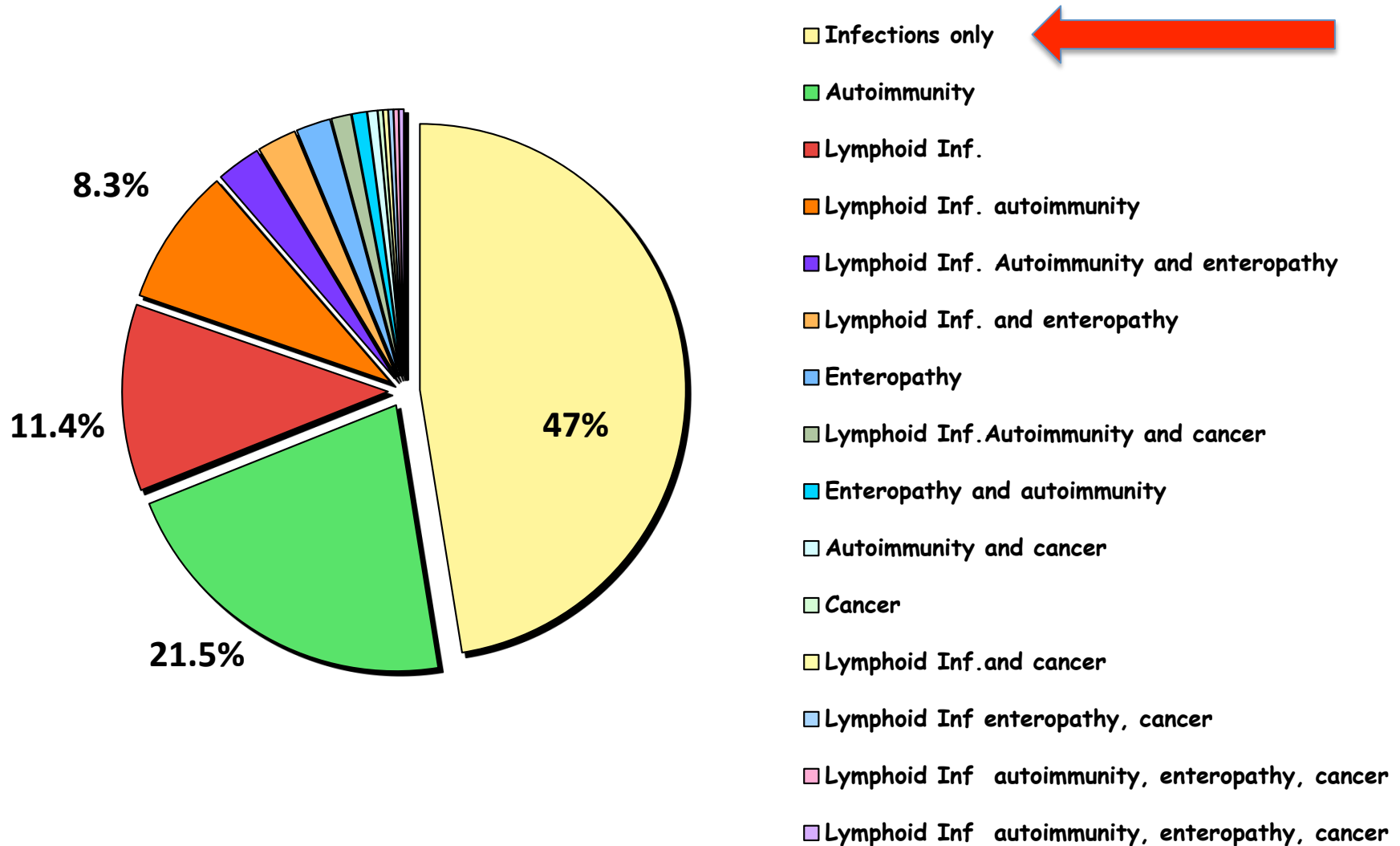
Normal

Affected Organ



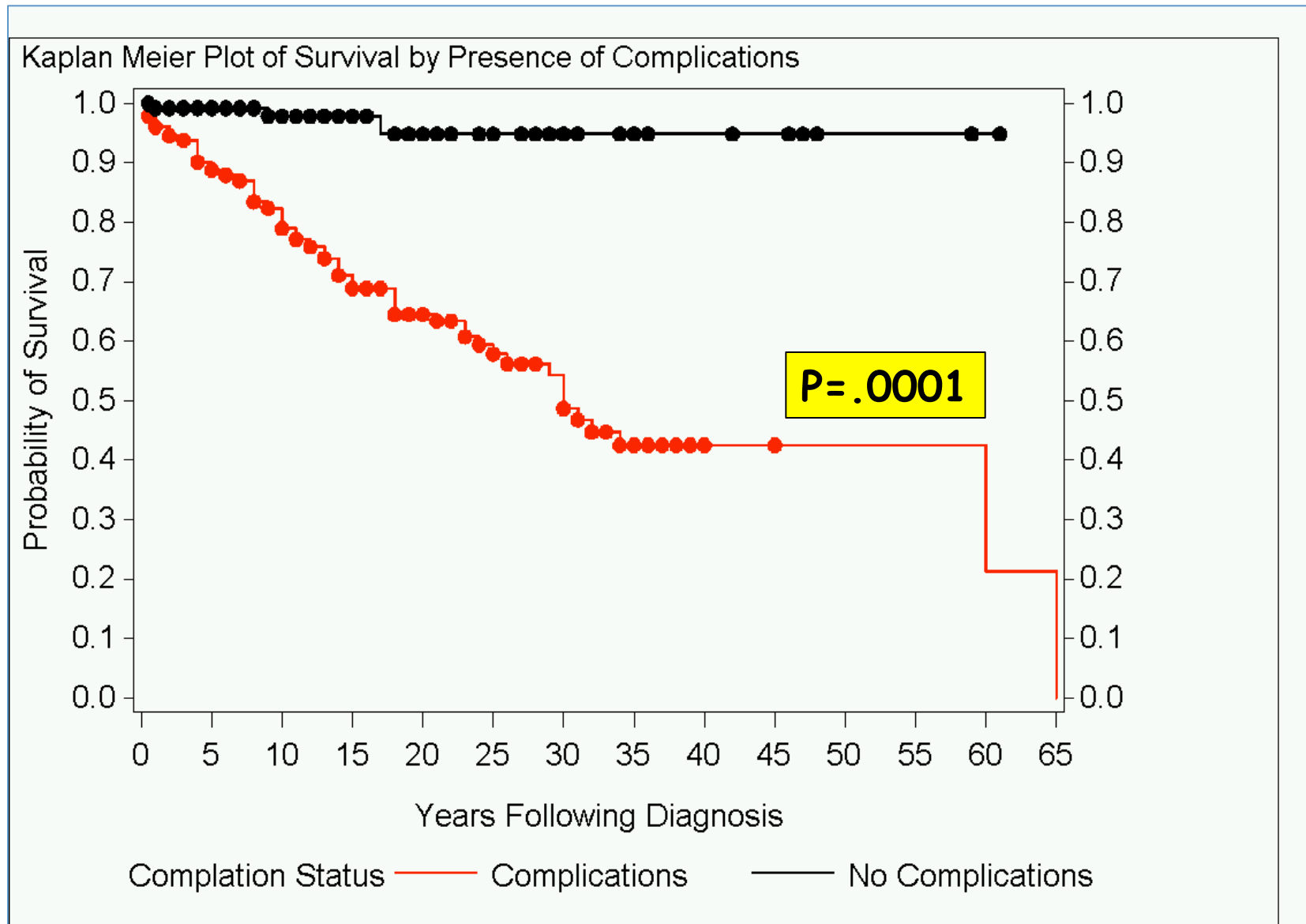
Mayo Clinic web site

ESID registry: Clinical Phenotypes 334 pts

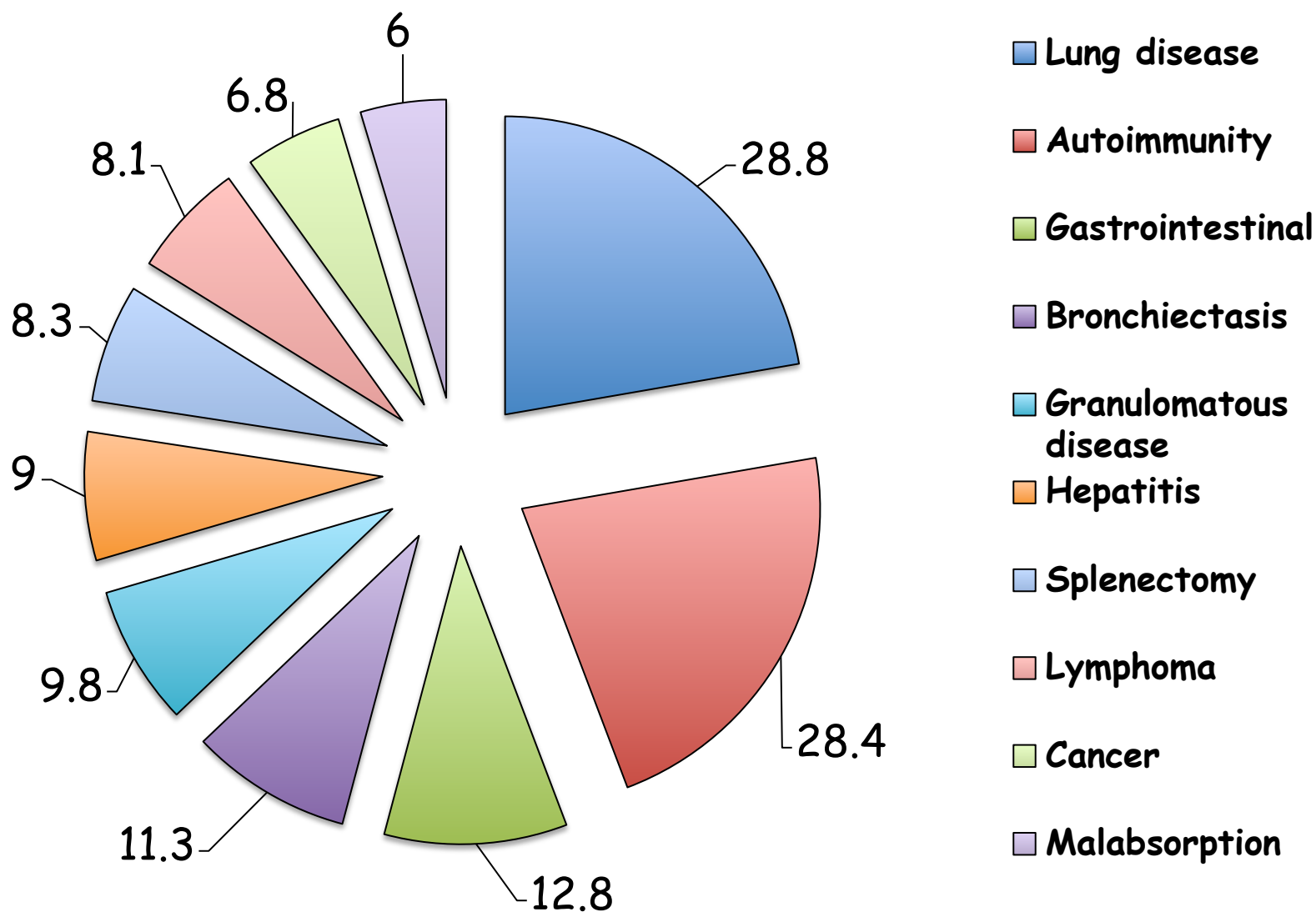


Adapted from Chapel et al, Blood;112:277-86. 2008

Presence of complications



473 CVID subjects from Mount Sinai Medical Center

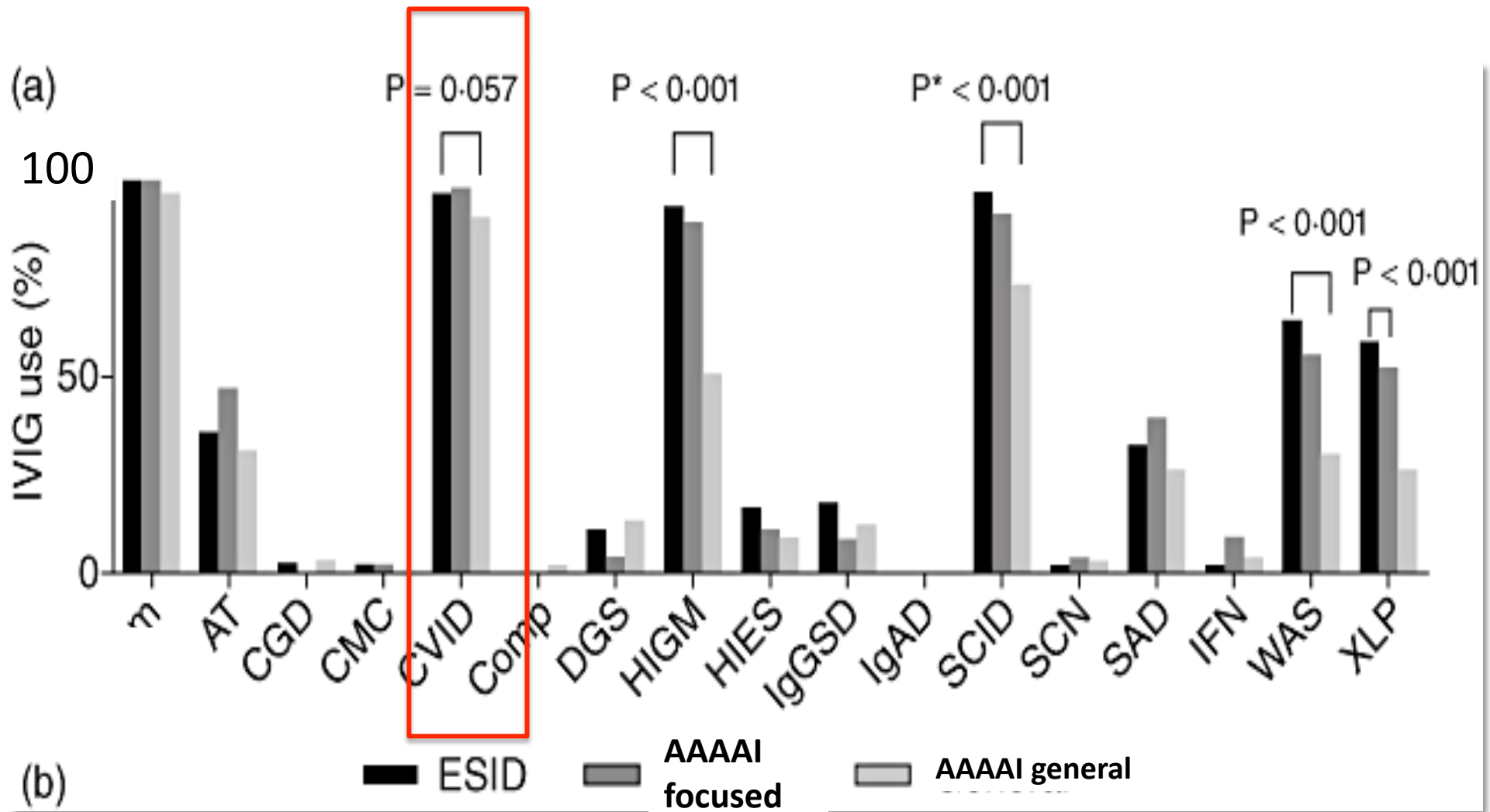


Elena Resnick et al Blood 2012

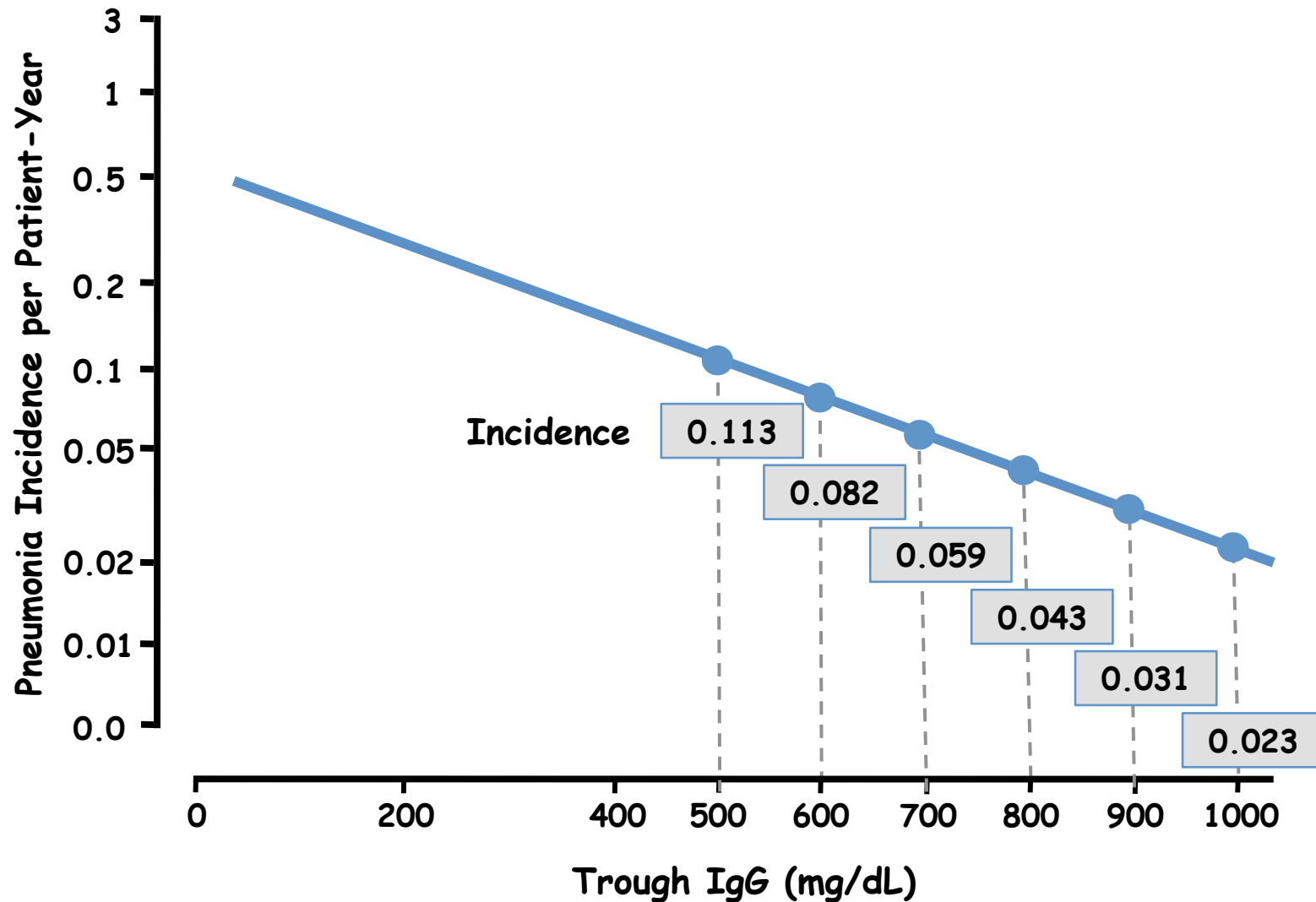
What is new?

1. Clinical and treatment information
 - a) Studies of large groups of patients
 - b) Best treatments**

Immunoglobulin usage parameters.

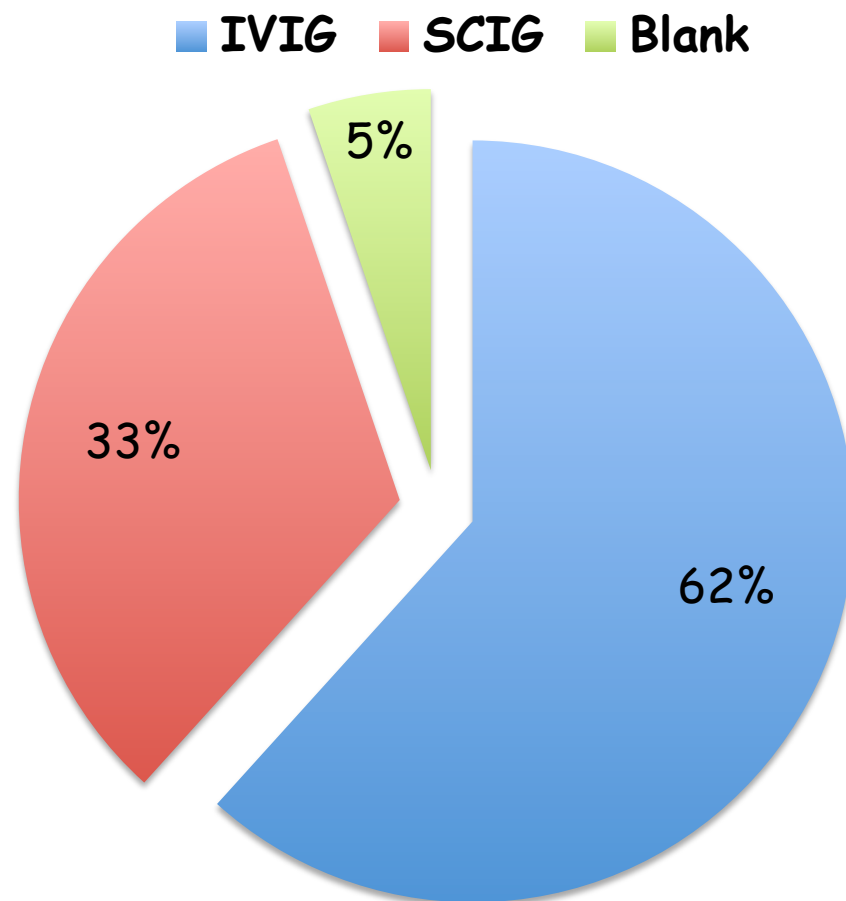


Trough IgG levels and Incidence of Pneumonia



J.S. Orange et al., Impact of trough IgG on pneumonia incidence in primary immunodeficiency: A meta-analysis of clinical studies. Clin. Immunol (2010), doi :10. 1016/j.clim.2010.06012

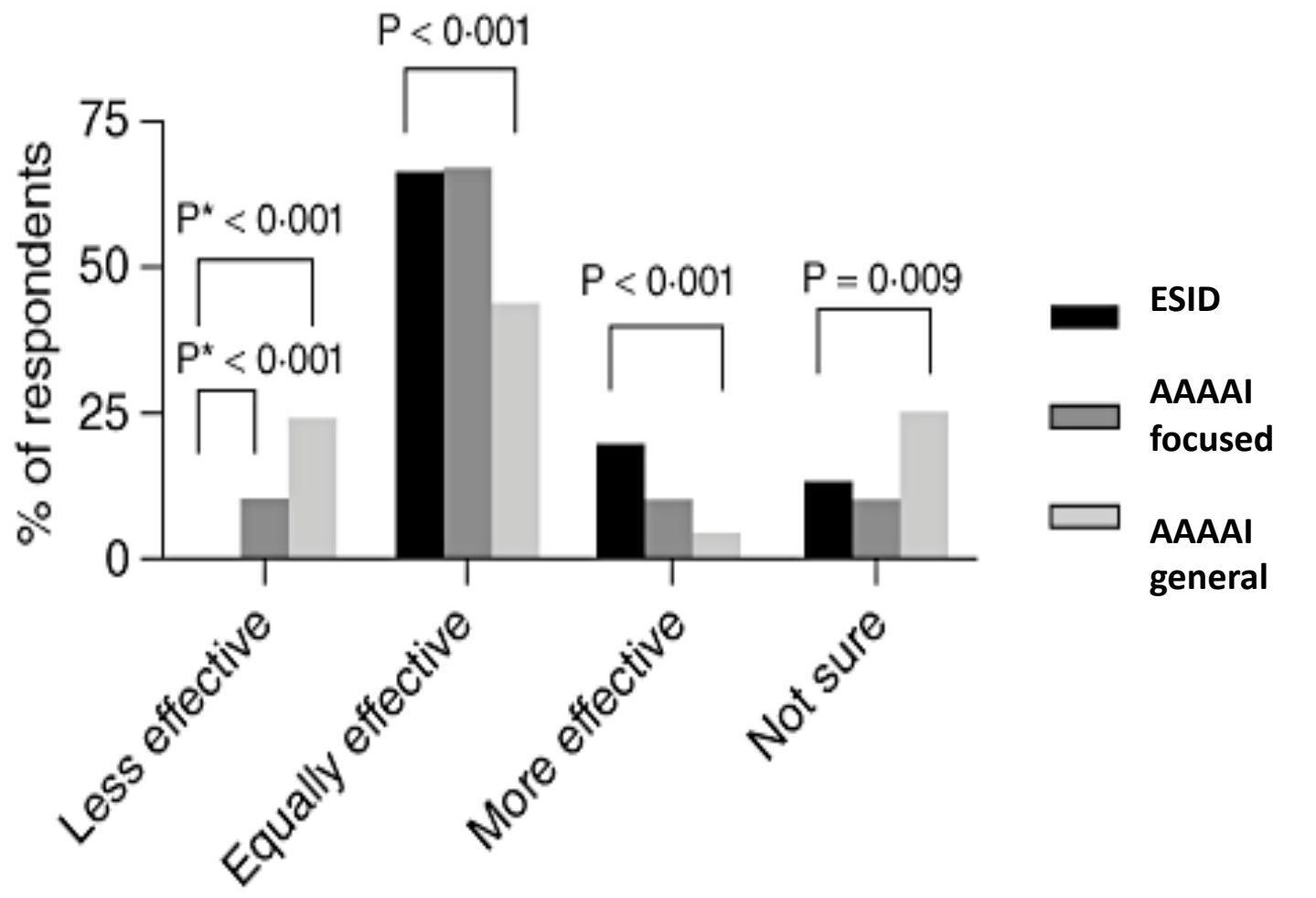
Type of IgG Therapy in the US (n=882)



Source: 2009 Immune Deficiency Foundation Survey

Comparing ESID and the US

Perceived efficacy of subcutaneous immunoglobulin therapy (SCIg)



But I can't achieve everything

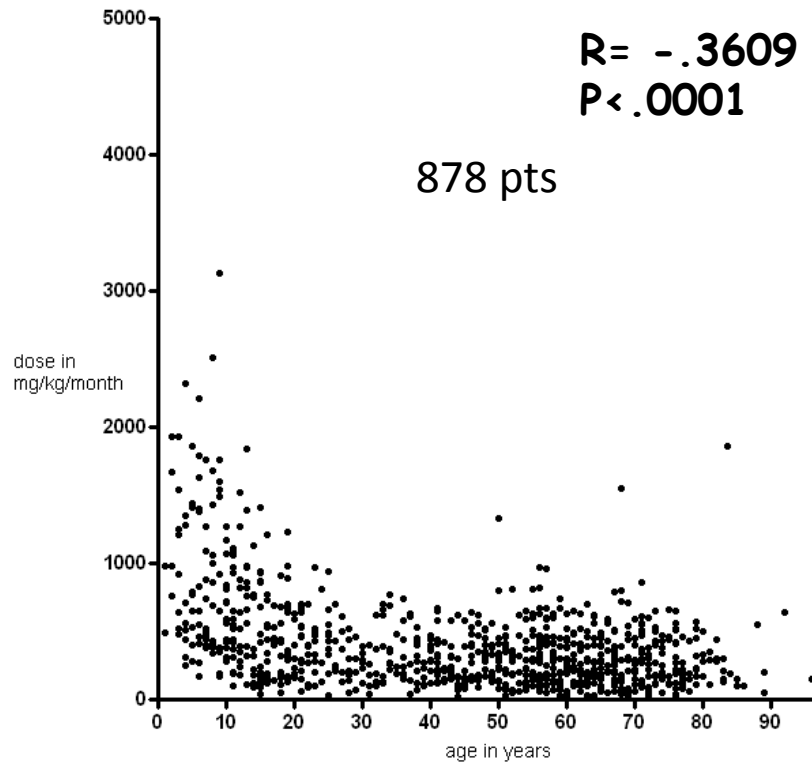
Residual Infections in three recent trials of SQ Ig

	SQ study 1	SQ 2	SQ3
Patients	80	51	49
Sinusitis	31.3%	57%	39%
Nasopharyngitis	22.5%	-	11%
URI	18.8%	51%	5%
Bronchitis	13.8%	13%	6%
Rhinitis	13.8%	10%	-
Influenza	12.5%	12%	-
Gastroenteritis	8.8%	-	14.3%
Conjunctivitis	7.5%	10%	-
Ear infection	7.5%	12%	-
Urinary tract	7.5%	10%	-

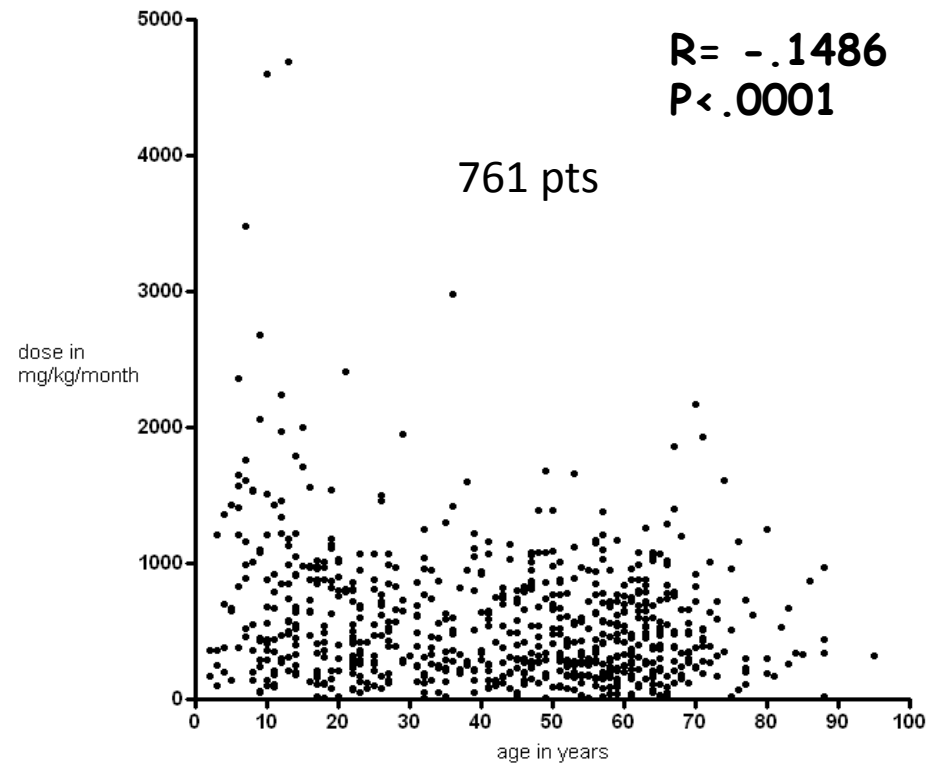
And another surprise

In the US: IVIg and SCIG dosing correlated with age

Subcutaneous



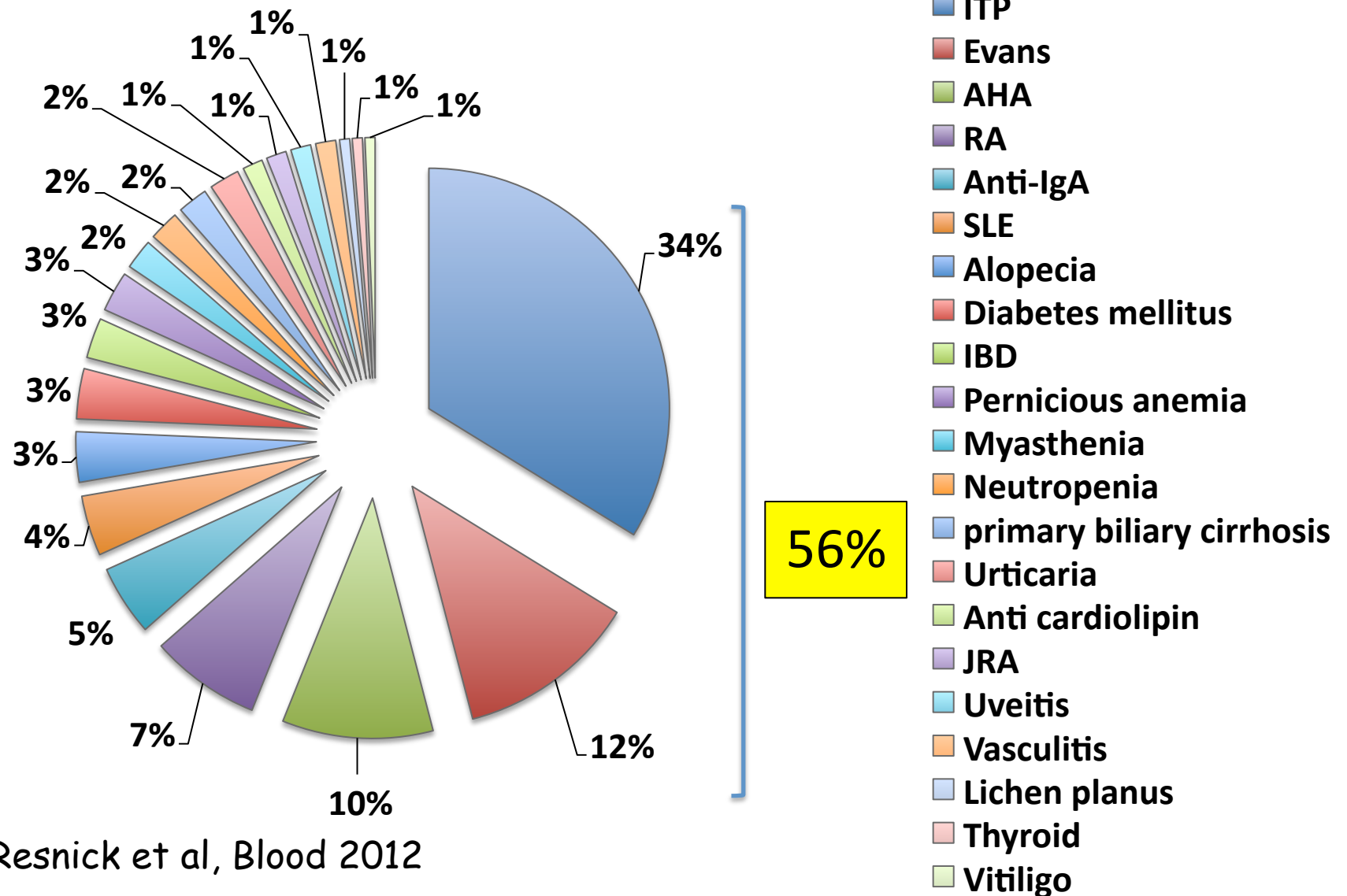
Intravenous



Huang et al J. Clin Immunol 2012

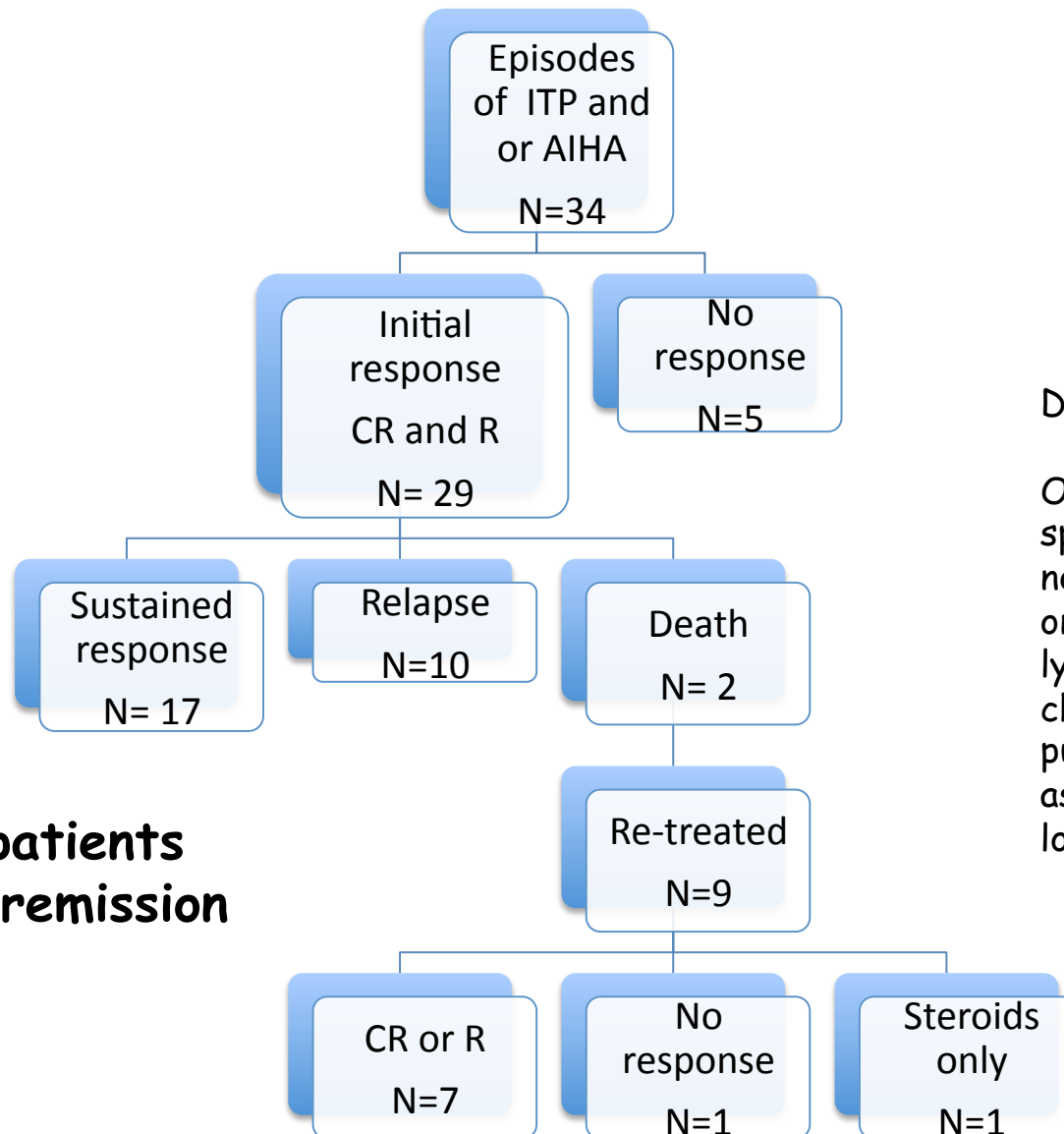
Complications and Treatment

Autoimmune diseases



E Resnick et al, Blood 2012

Rituximab for Cytopenias in 33 CVID subjects



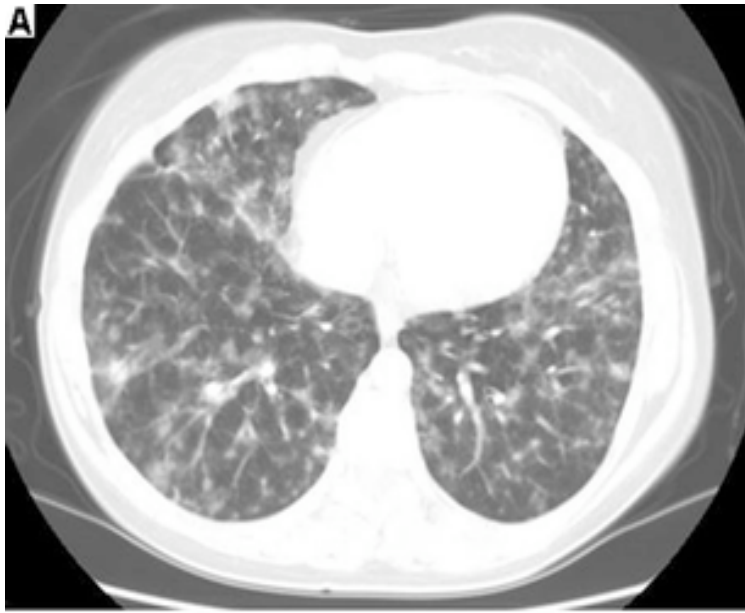
Deaths:

One with prior splenectomy and not on IG therapy;
one with hx of lymphoma and chemotherapy;
pulmonary aspergilloma/
lobectomy

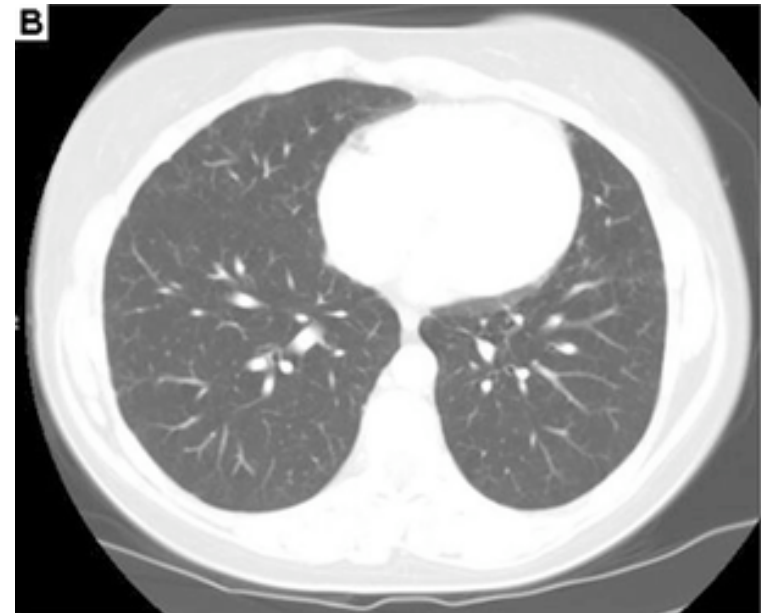
**Out of 34 patients
61.5% had remission**

Granulomatous inflammation of the lungs

Treatment with Rituximab and immuran



Pre



Post

What else is new?

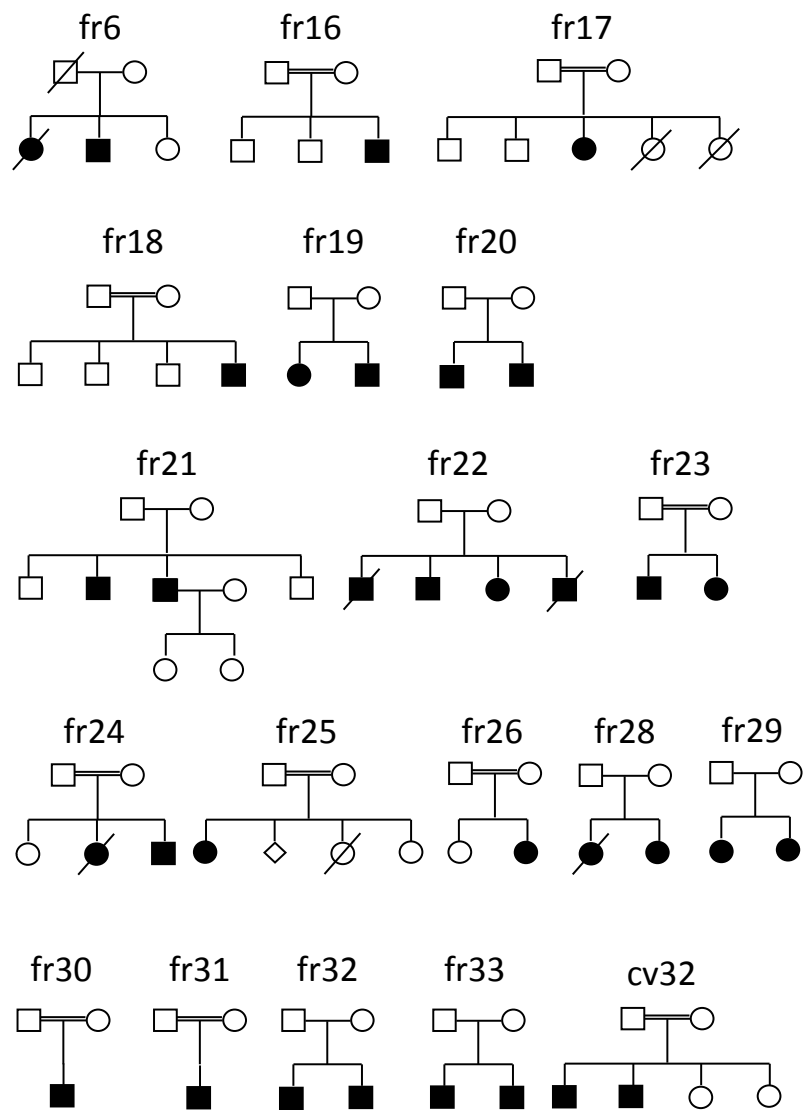
1. Clinical and treatment information
 - a) Studies of large groups of patients
 - b) Best treatments
2. **Laboratory news**

What is new?

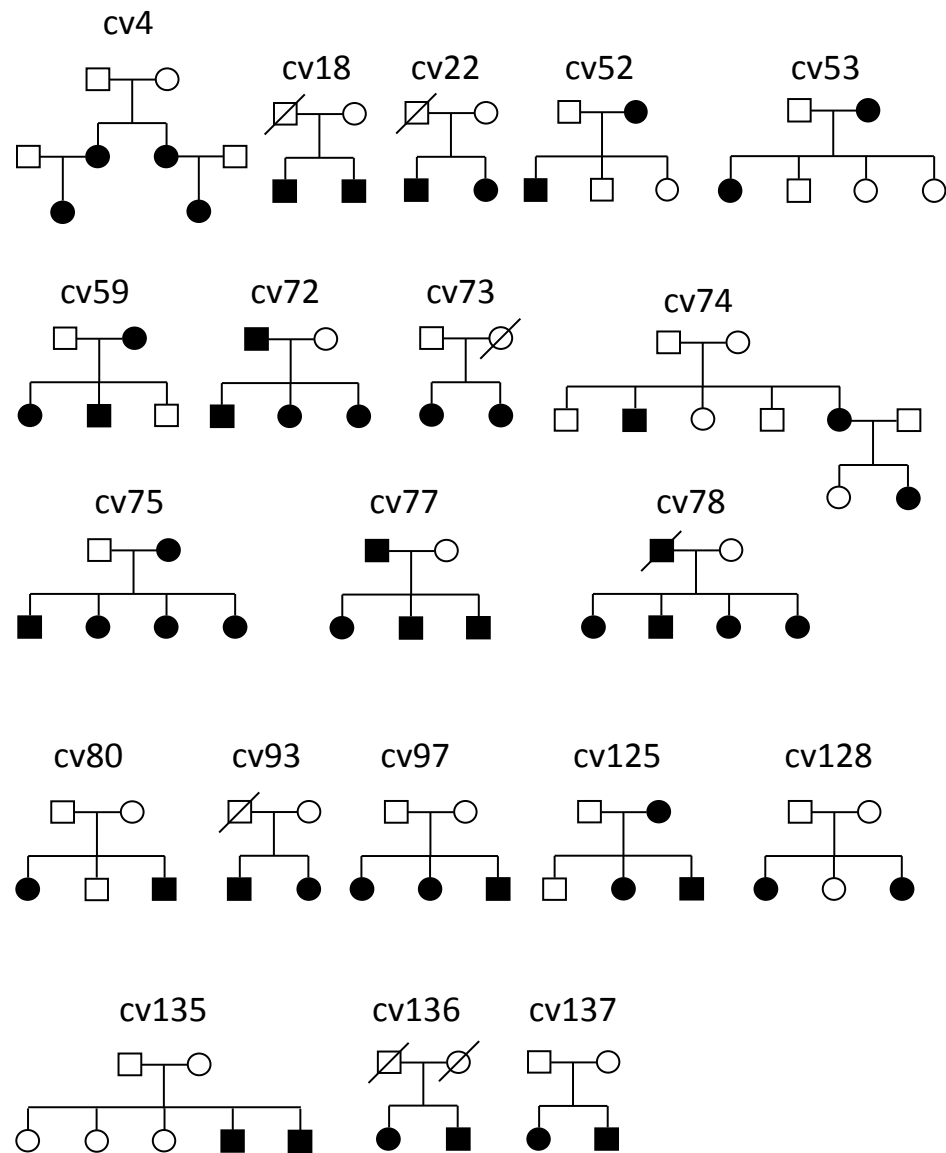
1. Clinical and treatment information
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2. Laboratory news
 - a) Genetics

10% have other affected family members

Autosomal recessive CVID families



„linked“ CVID families



Monogenic and complex genetics

Gene	numbers	Inheritance	Phenotype
MHC linked	unclear	complex	Early and late
ICOS	under 15	AR	Early and late
CD19	5?	AR	Early and late
CD81	2	AR	Unclear
CD20	1-2?	AR	Unclear
CD21	2	AR	Unclear
CD27	2	AR	EBV viremia
BAFFr	2?	AR	Unclear
TACI	8-10%	AR AD sporadic	Early and late
PLC γ ?	Rare?	AR, unclear	Unclear

Genome-wide association study

Helen Chapel Charlotte Cunningham-Rundles Elena Resnick
Jordan Orange Kate Sullivan Hakon Hakonarson Joe Glessner Elena Perez



Mary Lucas, Berne Ferry
Cecilia Kim, Cuiping Hou,
Fengxiang Wang, Amber Bender,
Rosetta Chiavacci, Subra
Kugathasan, Robert Baldassano
John Sleasman



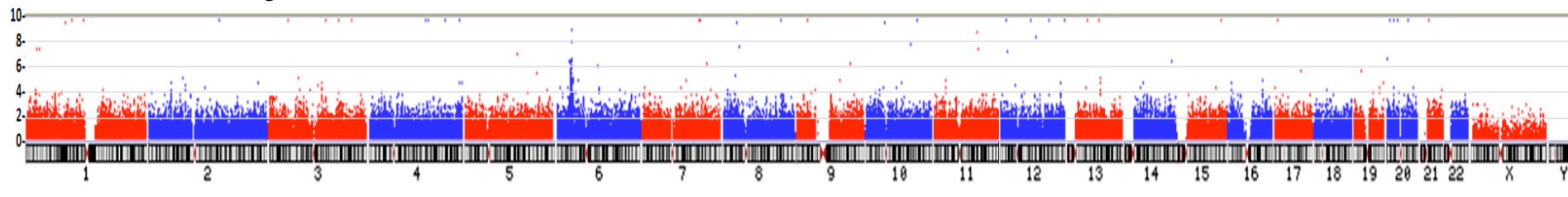
The Children's Hospital of Philadelphia



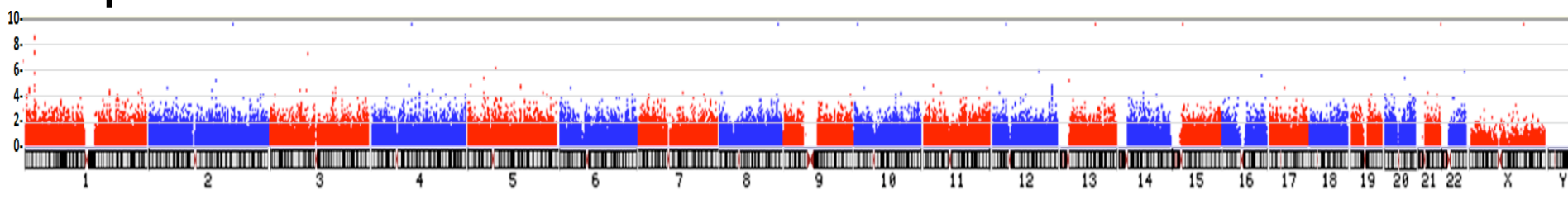
Mount Sinai School of Medicine

Genome wide study in CVID

Discovery



Replication



Discovery
Genotypes
Calls

10,713 SNPs Genotyping below 90%
23,206 SNPs MAF < 1%
Genomic Inflation Factor = 1.02783

87 Regions
Containing Multiple
Significant SNPs

6 Regions
Replicated

11,000 SNPs Genotyping below 90%
19,237 SNPs MAF < 1%
Genomic Inflation Factor = 1.04789

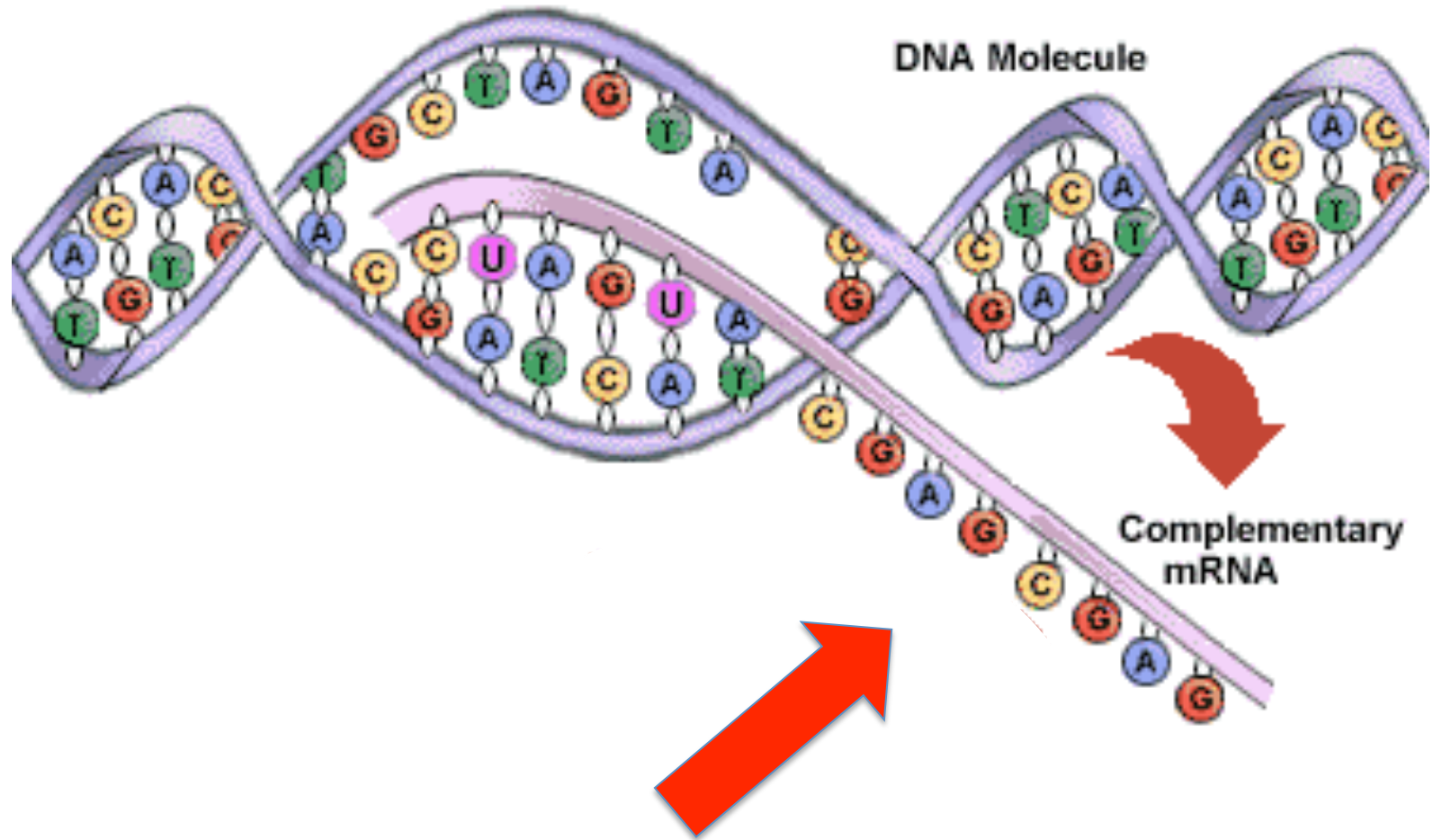
Associated SNP Genotypes

Chr	gene	P value	Allele	Freq aff	Freq unaff	Replica- tion P value
Chr 6	<u>MHC</u>	8.62×10^{-10}	T	0.328	0.1907	.0004
Chr 8	ADAM28, <u>ADAM7</u> ,ADAM DEC1,STC1	6.24×10^{-6}	A	0.0391	0.0107	.0314
Chr 7	<u>SDK1</u>	4.70×10^{-5}	T	0.2905	0.4003	.0235
Chr 1	FLJ32784, <u>UBXN10</u>	9.09×10^{-5}	C	0.2654	0.1808	2.25E-8

Orange et al, J. Allergy Clin Immunol April 2011

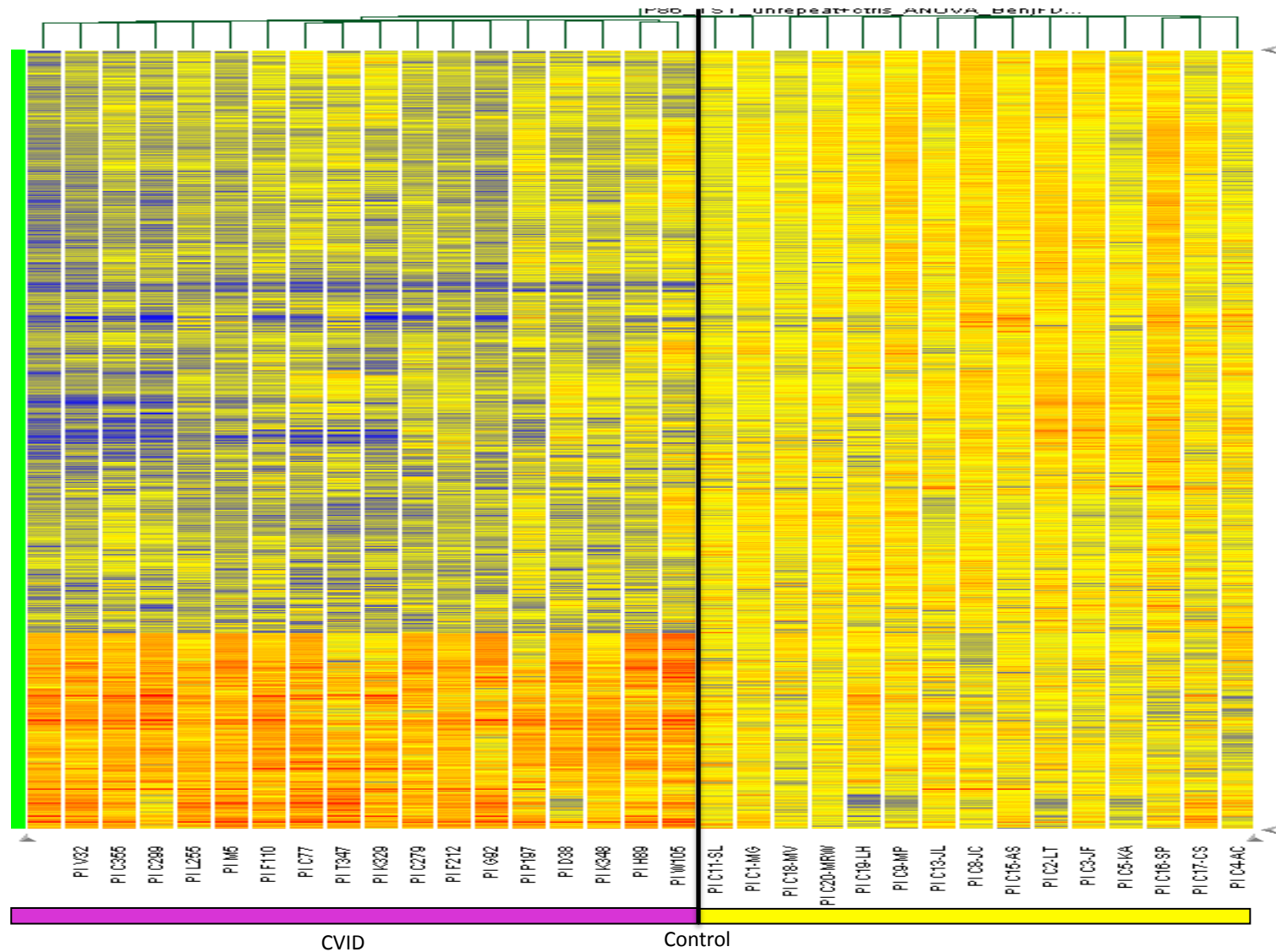
And another approach

DNA reflects all the genetic “equipment” a person has,
but RNA shows what is actually being used.

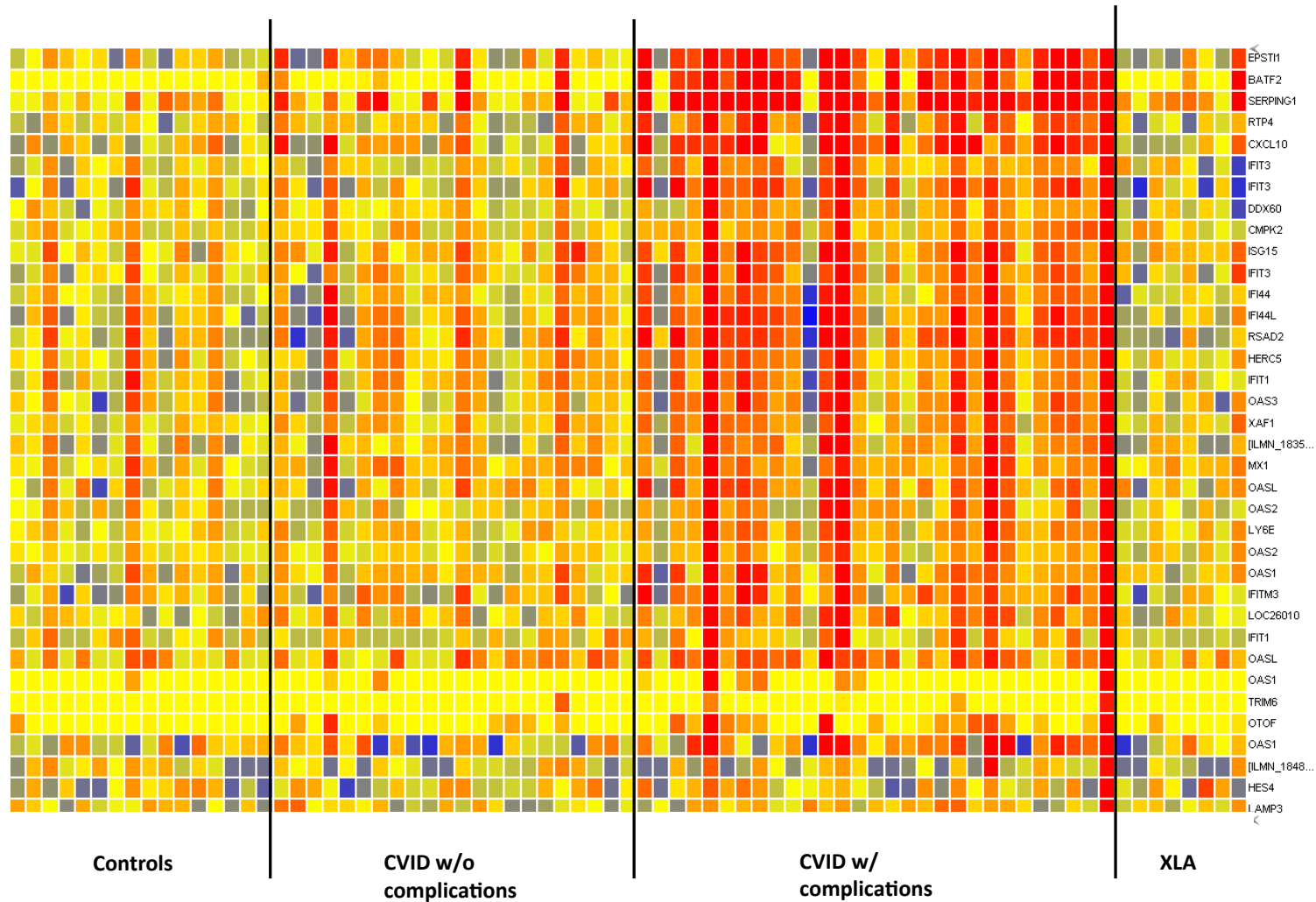


Many genes are underused and a large number are over active!

Heatmap of Transcriptional Expression:
2786 genes



Looking at the RNA networks that are over active
(may give a clue about best new treatments)



Heatmap of genes from IFN module, M1.2

Conclusions

- CVID: a heterogeneous clinical phenotype
- B cells do not work and
- Other cellular defects are common
- Single gene defects in a minority
- Complex inheritance
- Studying large populations is important
- Using new techniques may offer clues to best treatments