Secondary Immunodeficiency or is it?

Stephen Jolles
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Content

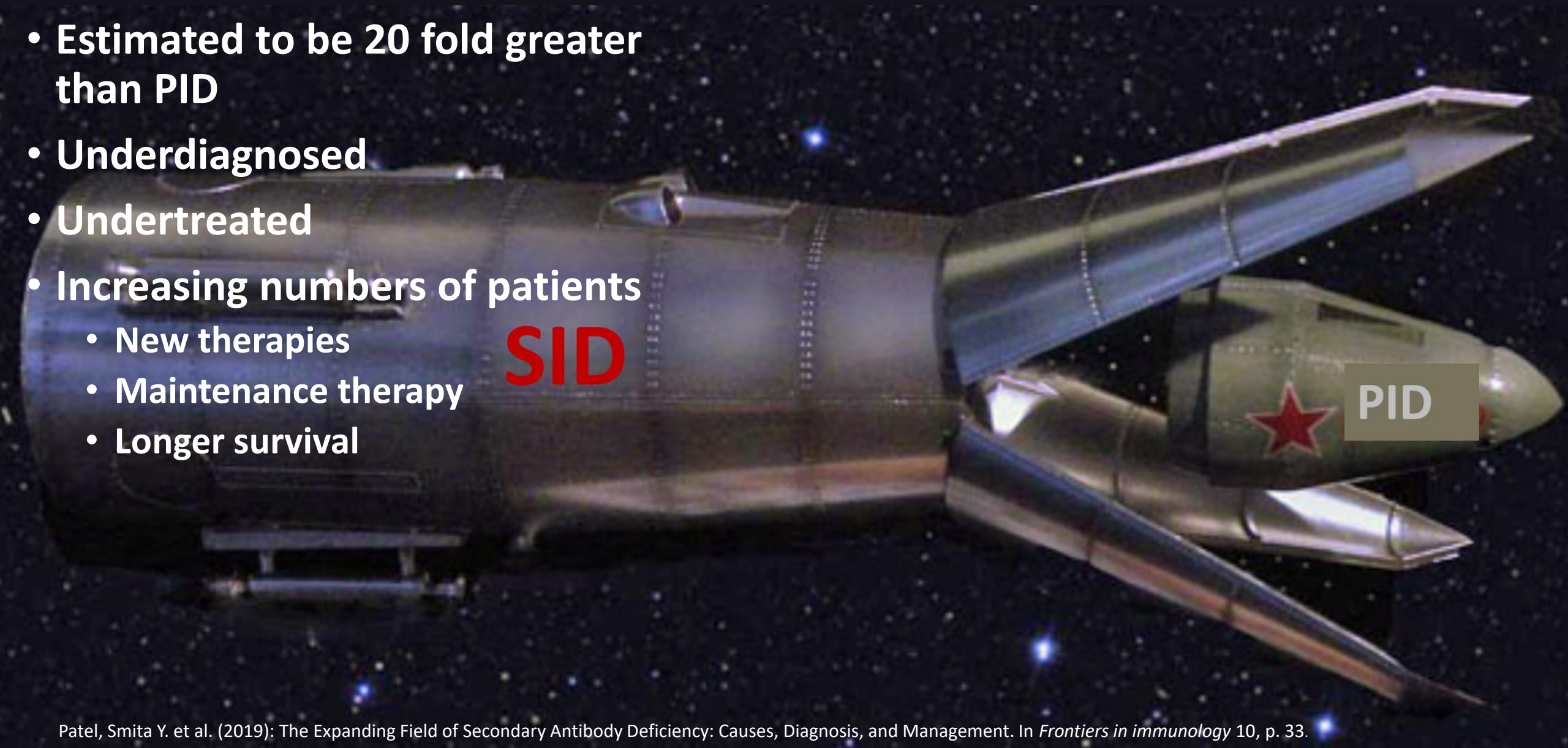
- A world of SAD
- Hawaii to Jupiter 16, Are you receiving?
- CG Highs and Lows
- PID manifestations
- Therapy – ‘Too close for missiles - switching to guns’
- A couple of cases
- Conclusions

A world of SAD

- Haematological Disease
- Drugs
- Transplantation
- Protein Loss
- Other

Hawaii to Jupiter 16, Are you receiving?

- **Estimated to be 20 fold greater than PID**
- **Underdiagnosed**
- **Undertreated**
- **Increasing numbers of patients**
  - **New therapies**
  - **Maintenance therapy**
  - **Longer survival**



Patel, Smita Y. et al. (2019): The Expanding Field of Secondary Antibody Deficiency: Causes, Diagnosis, and Management. In *Frontiers in immunology* 10, p. 33.

Drug Classes in Haematological Malignancy

Classes of drugs	Agents
Alkylating agents	Bendamustine, chlorambucil, cisplatin, cyclophosphamide, ifosfamide, and melphalan
Antimetabolites	Cladribine, cytarabine, fludarabine, methotrexate, nelarabine, pentostatin, and pralatrexate
Anti-tumor antibiotics	Doxorubicin and pixantrone
BH3 mimetic	Venetoclax
CAR T therapies	Axicabtagene ciloleucel, brexucabtagene autoleucel, idecabtagene vicleucel, and tisagenlecleucel
Corticosteroids	Prednisone and dexamethasone
HDAC inhibitors	Panobinostat and vorinostat
IMiDs	Lenalidomide, pomalidomide, and thalidomide
Kinase inhibitors	Acalabrutinib, duvelisib, ibrutinib, and idelalisib
Monoclonal antibodies	Alemtuzumab, belantamab mafodotin, brentuximab vedotin, daratumumab, elotuzumab, isatuximab, obinutuzumab, ofatumumab, and rituximab
Proteasome inhibitors	Bortezomib, carfilzomib, and ixazomib
SINE	Selinexor Selective inhibitors of nuclear export
Vinca alkaloids	Vincristine

BH3, Bcl-2 antagonism through Bcl-2 homology 3; CAR T, chimeric antigen receptor T-cell; HDAC, histone deacetylase; IMiDs, immunomodulatory imide drugs; SINE, selective inhibitors of nuclear export.

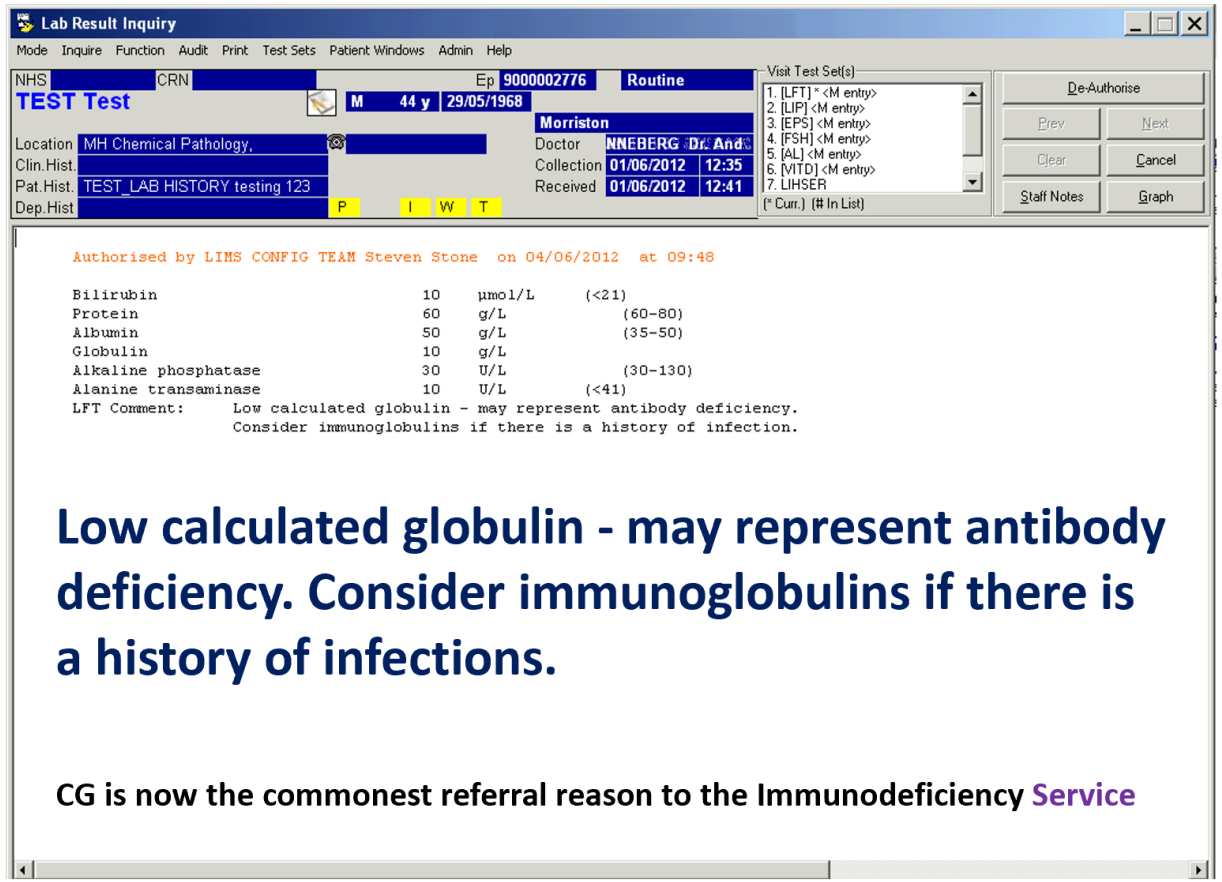
Jolles S Frontiers Oncology 2023

How to improve early detection

- Education
- JMF Warning signs
- New born screening
- AI – Nick Rider
- Screening – CG and other

Screening for antibody deficiency – Low CG

CG = Total Protein - Albumin



CG High Study

- Samples were collected between January and December 2021
- Roughly 4000 samples with a globulin >30g/L were flagged each week.
- Samples obtainable in University Hospital of Wales with sufficient serum volume from patients not already included in the study were collected where possible.
- Stratified sample selection resulted in a maximum of 250 samples for each 10g/L CG block.
- A total of 848 patients were included in the final analysis.

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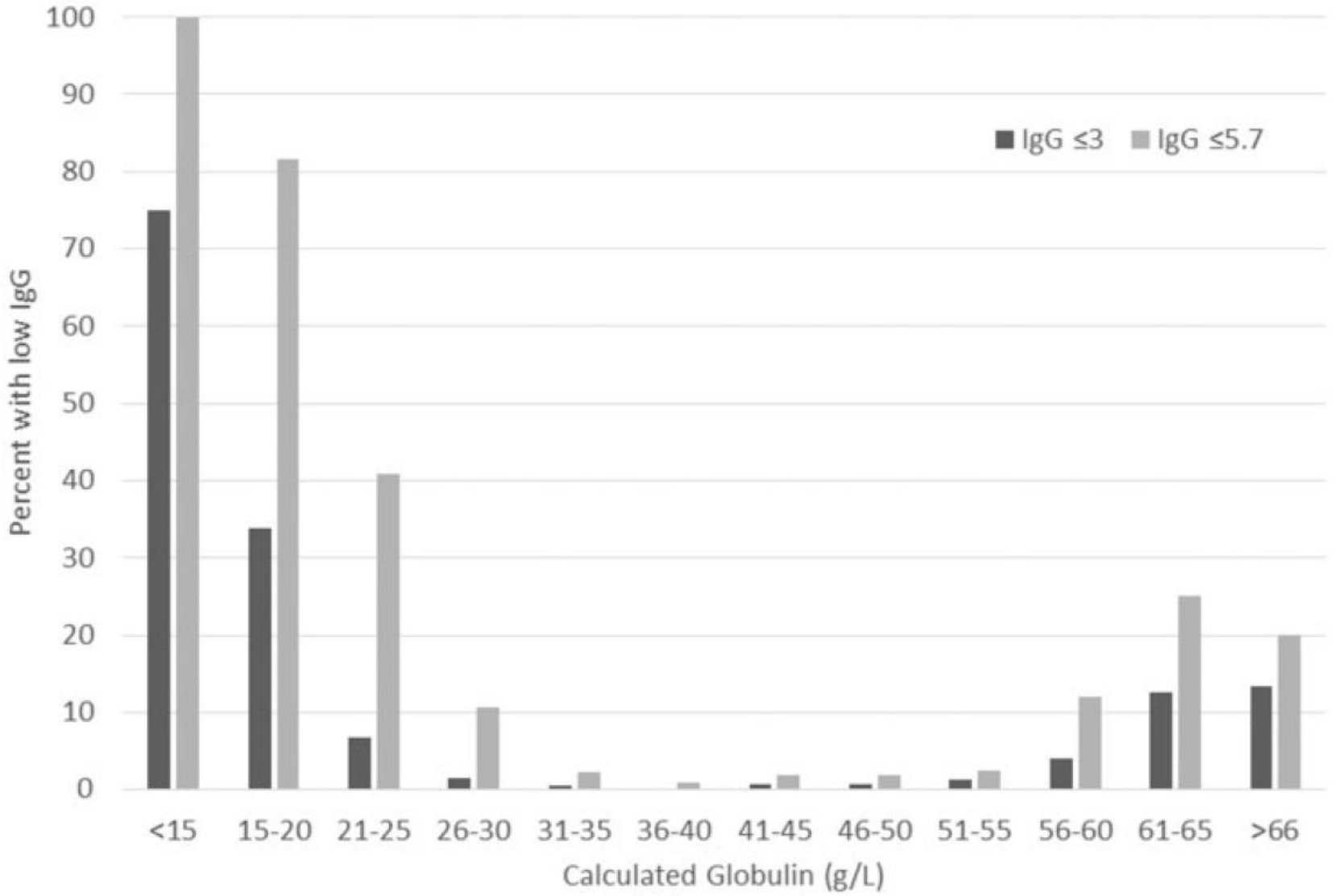
CG High - What kind of things to expect?

Hoo T Annals of Clinical Biochemistry 2021

Liver Disease	Haematological	Autoimmune	Infection	High Dose IVIg & Other
Cirrhosis	Multiple myeloma	Sjogrens synd	HIV	HdIVIg
Viral Hepatitis	Waldenstroms macroglobulinaemia	SLE	COPD exacerbation	Malignancy
Autoimmune Hepatitis	MGUS	RA	Bronchiectasis exacerbation	GATA2
Alcoholic liver disease	Lymphoma	IgA nephropathy	Bacterial endocarditis	End stage renal failure
Non alcoholic steatohepatitis	AML	Adult onset Stills	Mycetoma	Sarcoid
Primary Biliary cholangitis	CLL	Scleroderma	Acute rheumatic fever	
PBS	CML	Ulcerative colitis	Cholecystitis	
		Crohns disease		
		IPF		

Finding Antibody Deficiency in High CG

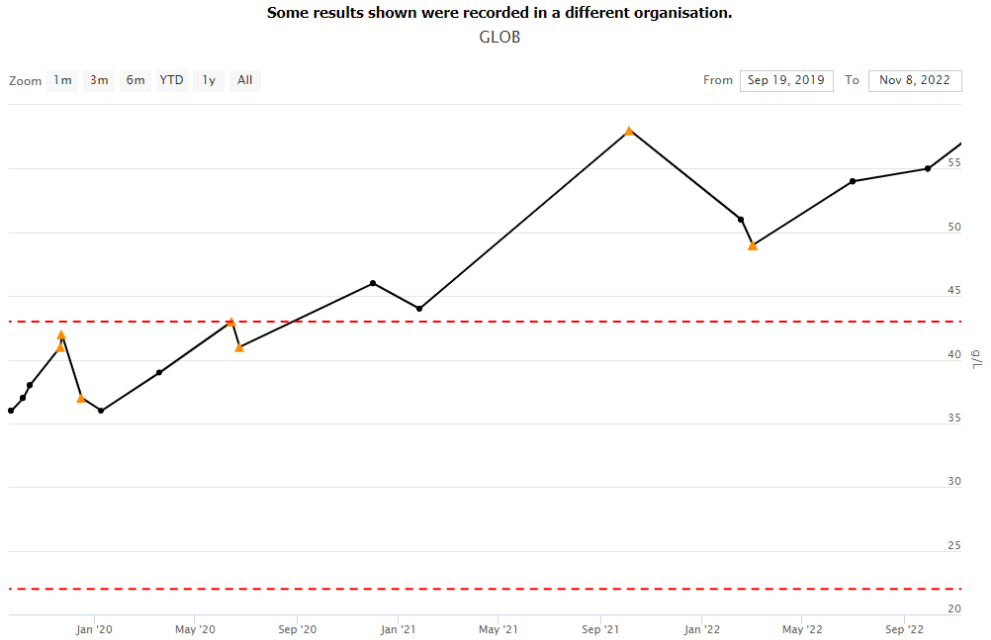


Hoo T 2021 Annals of Clinical Biochemistry

Case - CG

- Community blood tests in 2020 for warfarin/ACEi monitoring. Globulin in 30s
- In later half of 2020 CG gradually increased into the 40s with a further community blood form in **December 2020** for "general deterioration" with **<u>CG 46g/L</u>**
- CG peaked at **58g/L** in October 2021 when patient was admitted with abdominal pain
- Warfarin monitoring was performed in February 2022. CG was **51g/L**. Immunoglobulins appended by reporting biochemist due to raised globulin. This revealed a compact band in the gamma region and an IgM paraprotein of 21.8g/L
- Waldenstrom's Macroglobulinaemia
- Patient remains well on maintenance chemotherapy

29-Sep-22 11:40	*55	22	43	Llandough Hospital
29-Sep-22 11:40	*55	22	43	Llandough Hospital
30-Jun-22 11:00	*54	22	43	Llandough Hospital
30-Jun-22 11:00	*54	22	43	Llandough Hospital
30-Jun-22 11:00	*54	22	43	Llandough Hospital
02-Mar-22 12:05	*49	22	43	University Hospital of Wales
02-Mar-22 12:05	*49	22	43	University Hospital of Wales
02-Mar-22 12:05	*49	22	43	University Hospital of Wales
16-Feb-22 14:58	*51	22	43	Llandough Hospital
16-Feb-22 14:58	*51	22	43	Llandough Hospital
05-Oct-21 15:20	*58	22	43	University Hospital of Wales
25-Jan-21 11:50	*44	22	43	Llandough Hospital
01-Dec-20 00:00	*46	22	43	Llandough Hospital
01-Dec-20 00:00	*46	22	43	Llandough Hospital
23-Jun-20 12:55	41	22	43	University Hospital of Wales
14-Jun-20 05:10	43	22	43	University Hospital of Wales
19-Mar-20 09:40	39	22	43	Llandough Hospital



Points to note

- **Current CG normal range of 22-43g/L used**
- **Lack of evidence based guidelines results in inconsistent responses to raised CG result**
- **Diagnosis could have been made over 12 months earlier**

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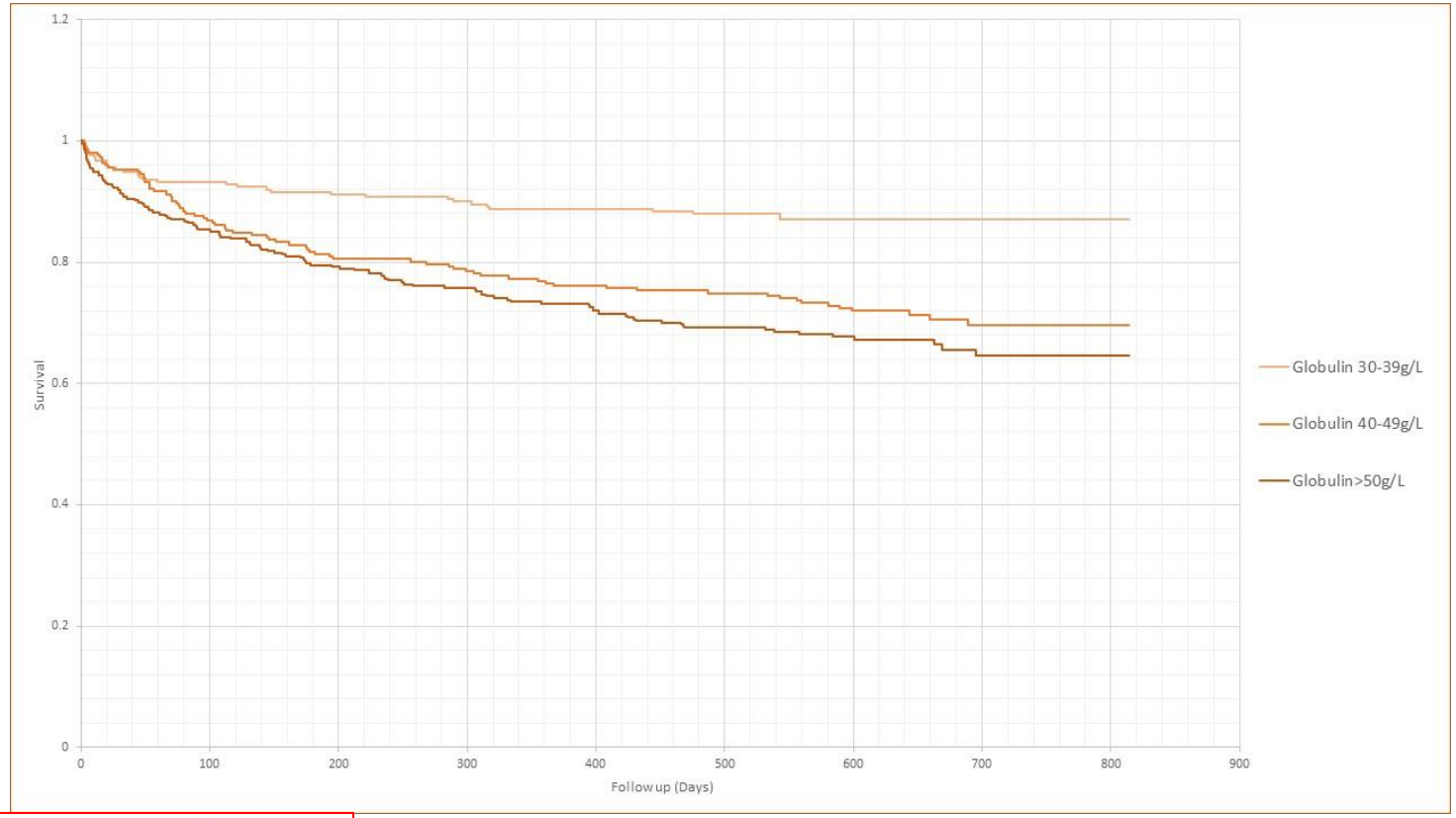
- **Follow up undertaken in March 2023**
- **15-26months after initial test**
- **220/848 deceased, average CG 50g/L**
- **54 deceased within 1 month**



RESEARCH ARTICLE

The Gamma Gap and All-Cause Mortality

Stephen P. Juraschek[1,2,3]*, Alison R. Moliterno[4], William Checkley[5,6], Edgar R. Miller, III[1,2,3]

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Annals of Oncology 25: 2260–2266, 2014
doi:10.1093/annonc/mdu274
Published online 23 July 2014

Low albumin-to-globulin ratio associated with cancer incidence and mortality in generally healthy adults

B. Suh[1,2,†], S. Park[3,†], D. W. Shin[2,4*], J. M. Yun[2], B. Keam[3], H.-K. Yang[5], E. Ahn[2], H. Lee[2,4], J. H. Park[2] & B. Cho[2,4]

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Received 29 April 2014; revised 27 June 2014; accepted 13 July 2014

OPEN

The gamma gap predicts 4-year all-cause mortality among nonagenarians and centenarians

Received: 6 July 2017
Accepted: 4 January 2018
Published online: 18 January 2018

Ming Yang[1], Linlin Xie[1], Xiu Liu[1], Qiukui Hao[1], Jiaojiao Jiang[2] & Birong Dong[1]

Recent studies have revealed the prognostic role of the gamma gap, the total serum proteins concentration minus the albumin concentration, for predicting all-cause mortality among adults. This study aims to investigate the relationship between the gamma gap and all-cause mortality among

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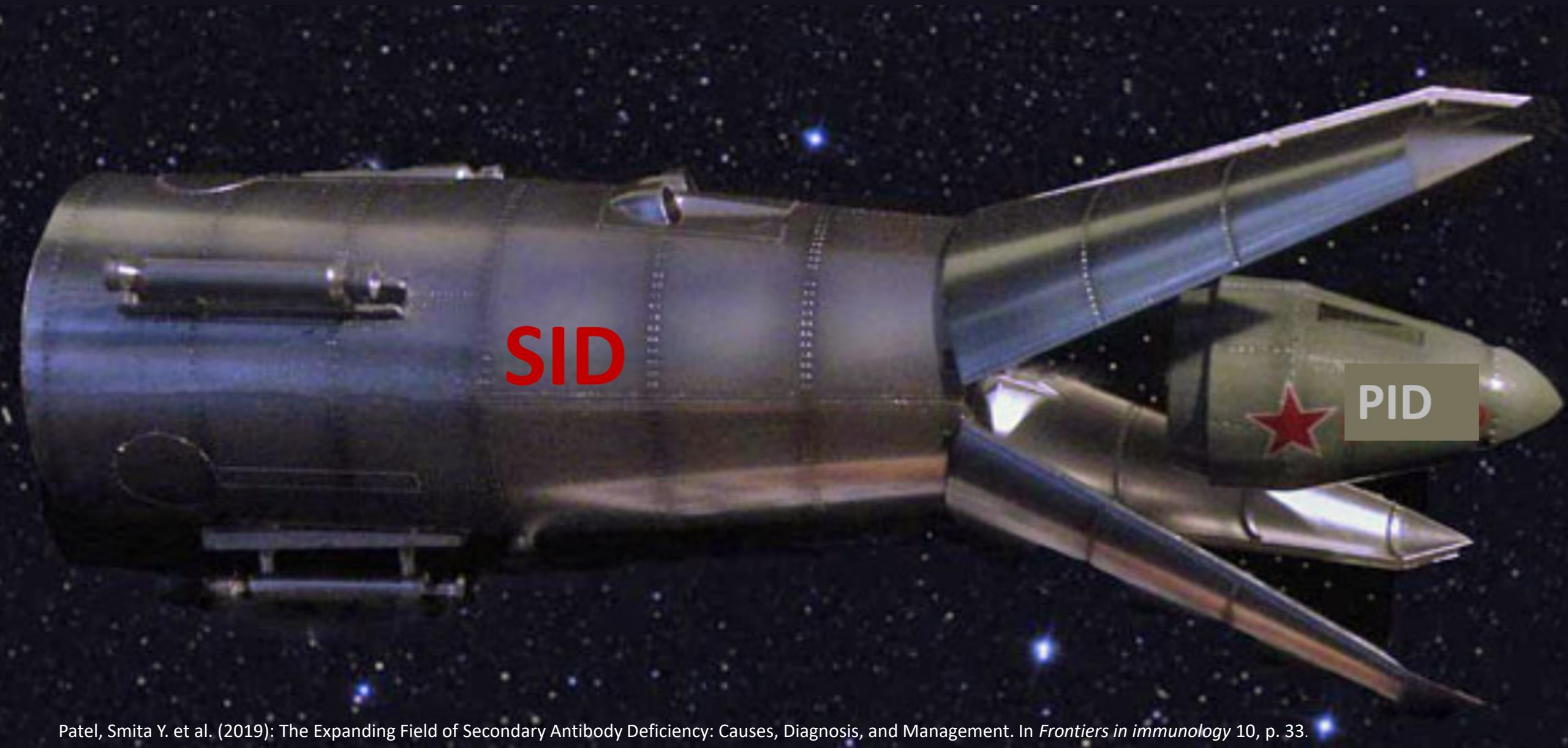
Hawaii to Jupiter 16, Are you receiving?



Patel, Smita Y. et al. (2019): The Expanding Field of Secondary Antibody Deficiency: Causes, Diagnosis, and Management. In *Frontiers in immunology* 10, p. 33.

SID Detection vs Newborn Screening

- Need to find SID first
- Should we screen for SID?

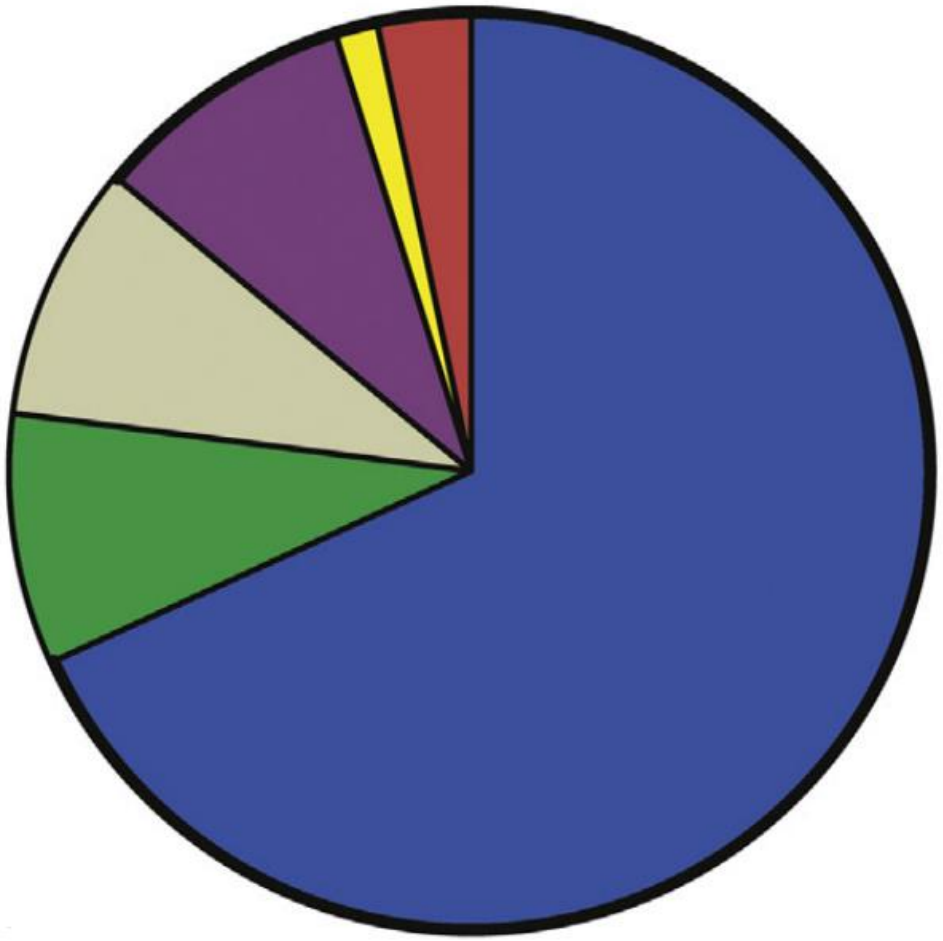
- Sickle cell disease (SCD)
- Cystic fibrosis (CF)
- Congenital hypothyroidism (CHT)
- Phenylketonuria (PKU)
- Medium-chain acyl-CoA dehydrogenase deficiency (MCADD)
- Maple syrup urine disease (MSUD)
- Isovaleric acidaemia (IVA)
- Glutaric aciduria type 1 (GA1)
- Homocystinuria (HCU)
- Tyrosinaemia
- Hopefully soon SCID in UK

SAD Screening in Haematological Malignancy?

- CLL – Hypogamma up to 85%
- MM – SID 25-90%
- Lymphoma – Hypogamma 15-54%

CLL, MM and Lymphoma should be assumed to have Immunodeficiency until proven otherwise

Initial presentations of PID

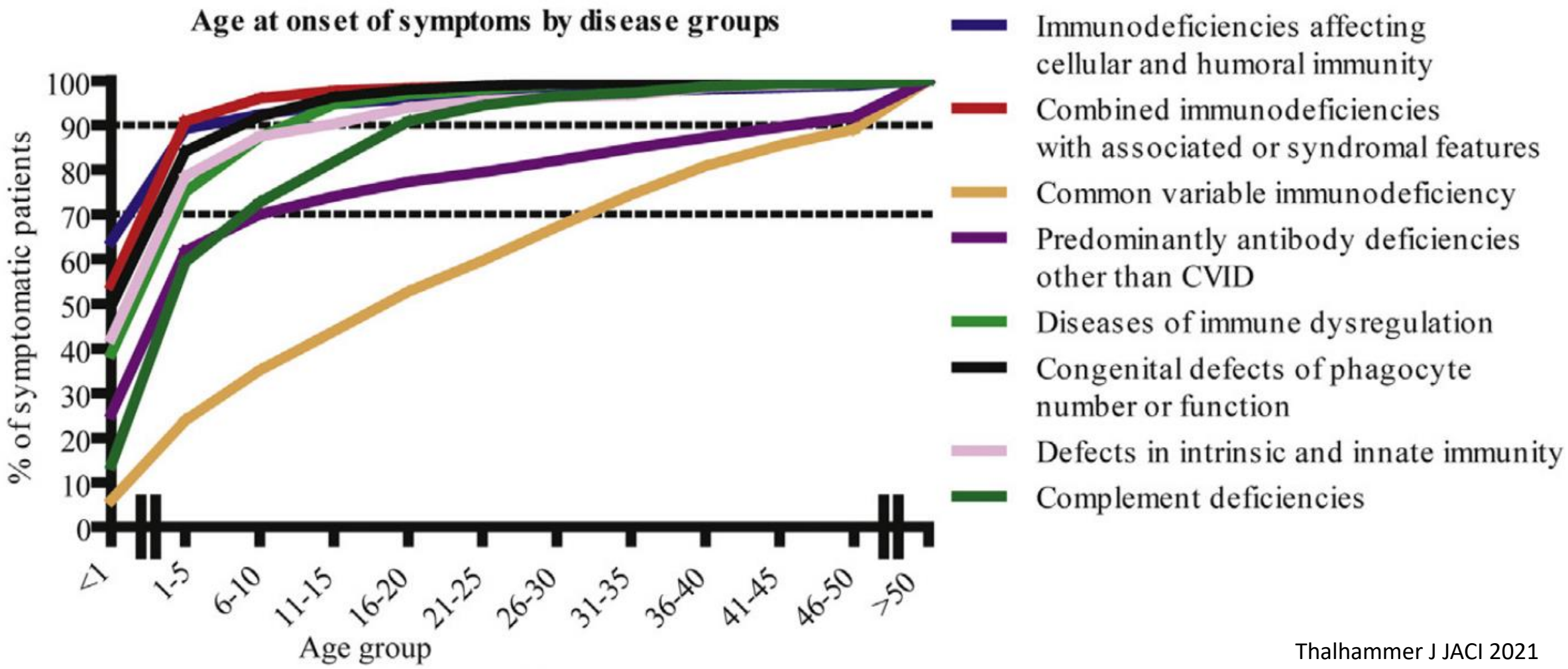


68.3% Infection **without** dysregulation
8.9% Dysregulation **without** infection
9.0% Infection **and** dysregulation
9.0% Other symptoms
1.6% Family history only
3.3% Lab abnormalities only

n = 16486

Thalhammer J JACI 2021

Symptom onset vs recognition of underlying cause



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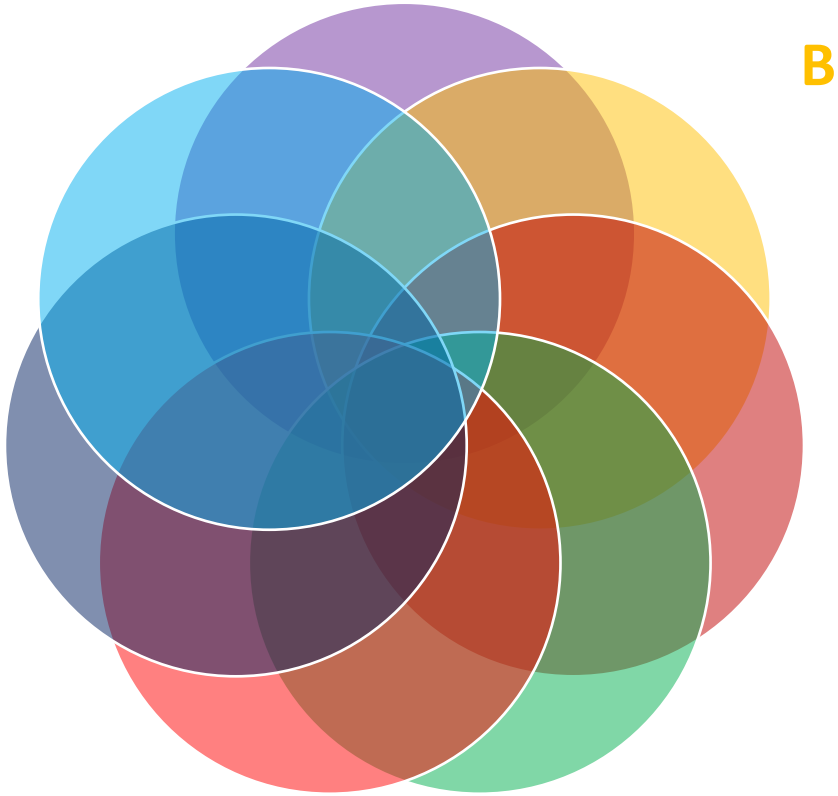
Manifestations of PID

Immunodeficiency

Malignancy

Bone marrow Failure



Allergy

Inflammation

Infection

Autoimmunity

Manifestations of PID

Immunodeficiency

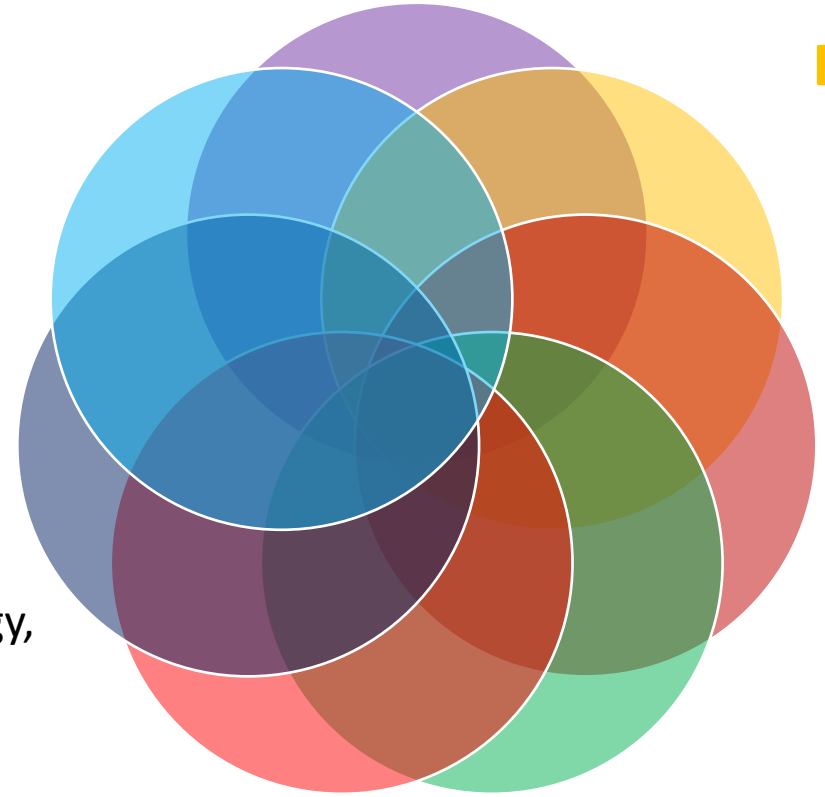
Immunology Haematology
Rheumatology Neurology, Renal
Transplant, Dermatology

Malignancy

Oncology, Haematology,
Gastroenterology,
Immunology
Rheumatology,
Transplant, Primary Care

Bone marrow Failure

Haematology, Transplant,
Immunology, Infectious
Disease



Allergy

Allergy, Respiratory, ENT,
Dermatology, Immunology,
Primary Care

Inflammation

Respiratory, Gastroenterology,
Hepatology, Dermatology, Renal,
Rheumatology, Neurology,
Immunology, Primary care

Infection

Infectious disease, Respiratory,
Gastroenterology, Dermatology, ENT,
Neurology, Opthalmology, Primary Care

Autoimmunity

Haematology, Rheumatology, Renal,
Neurology, Endocrine, Gastroenterology,
Primary care, Immunology

Malignancies in PID

- USIDNET – 1.42 fold excess relative risk of malignancy Mayor PC 2018
- Majority Haematological
- Mainly Lymphoid
- Linked to cell type affected by PID
- Lymphoma increase males 10 fold females 8.34 fold
- B cell lymphomas most common 8 fold increase in NHL for all PIDs
- DNA repair disorders – T cell lymphoma AT & B cell lymphoma Nijmegen BD
- Malignancy strongest factor affecting survival
- Congenital defects of stem cells or phagocytes – myeloid malignancies or myelodysplastic syndrome

Malignancies in PID mechanistic considerations

- **Intrinsic**
- Stem cell, myeloid and lymphoid development, differentiation and apoptosis defects
- Lymphocyte (co-)signalling, cytoskeleton, cytotoxicity and metabolism defects
- Defects of chromosome stability, telomere maintenance, and DNA repair

- **Extrinsic**
- Transforming (viral) infection
- Chronic tissue inflammation
- Impaired specific tumor immunosurveillance

Hauk F JACI 2018

Predictors of HM in CVID patients

- Pre existing lymphoproliferative disease
- Longstanding lymphadenopathy or splenomegaly
- Autoimmunity – cytopenias
- Non infectious GI involvement/enteropathy
- High IgM (or low)
- Older age at CVID diagnosis
- LOCID phenotype
- EBV susceptibility
- Mutations – CTLA4, BACH2, TNFSR13B, PIK3CD, PIK3R1, CD27, CD70, NFkB, CD19, TWEAK, CD21, ICOS, IRF2BP2

Ballow M Frontiers 2022

Clues within HM for PID in SID

- Early onset malignancy esp T cell origin
- Relapsed disease atypical eg extent and site skin/scalp
- Increased toxicity from conventional chemotherapy
- Low CSMB
- EBV PCR
- CMV PCR

PID in SID Clinical Clues

- Cancer therapy – toxicity, infections, second primary cancer, cancer recurrence
- Splenomegaly
- Lymphadenopathy – polyclonal reactive histology
- Short stature
- Early onset eg IBD other dysregulation
- Progression with age
- Combination of infectious and non infectious complications
- Other features – telangiectasia, microcephaly (NBS) growth retardation, dysmorphic features

PID in SID – Family History

- Consanguinity - eg first cousins, previous affected children
- FH of dysregulation - esp AD GoF
- FH of PID manifestations

PID in SID - Infections

- Sinopulmonary infections, bronchiectasis
- Opportunistic infections PCP, EBV, CMV – T cell
- Warts or severe molluscum
- EBV+ lymphoma – XLP, MAGT1, CD27, CD70, ITK, RASGRP1, CTPS1, CORO1A, DOCK8
- EBV+ lymphoma – widespread at diagnosis, extranodal eg GI, CNS
- Combination – sinopul, hypogamma, severe viral vzv, hsv, cmv (rule out HIV)

PID in SID - Dysregulation
Autoimmune, inflammation, Allergy

- Autoimmunity – cytopenias, IBD, DM and more
- Evans syndrome – 40% PID (Hadjadj J Blood 2019)
- Children with cytopenias (154) – 11% PID with 58% monogenic cause
- Rheumatological diseases with hypogamma – Note R15
- PIRDS
- Eczema – WAS, STAT3, DOCK8, +

CLINICAL SCIENCE

High frequency of variants in genes associated with primary immunodeficiencies in patients with rheumatic diseases with secondary hypogammaglobulinaemia

Georgios Sogkas, Natalia Dubrowinskaja, Ignatius Ryan Adriawan, Manfred Anim, Torsten Witte, Reinhold E Schmidt, Faranaz Atschekzei

PID in SID with Cytopenias

- Evans syndrome – 40% PID (Hadjadj J Blood 2019)
- Children with cytopenias (154) – 11% PID with 58% monogenic cause
- Short stature
- Splenomegaly
- Infections
- Low T cells
- Low Immunoglobulins
- More likely to fail first line therapy

(Westermann-Clark E Frontiers Immunology 2021)

PID in SID Laboratory clues

- Low levels of natural antibodies
- Low IgA and IgM
- Very low Freelite
- Low antibody responses at cancer diagnosis (primary and secondary)
- Germline vs somatic mutations associated with PID/Lymphoma

Germline & Somatic mutations in HM

REVIEW

Germline mutations predisposing to diffuse large B-cell lymphoma

OC Leeksma[1,2], NF de Miranda[3] and H Veelken[2]

Integration of molecular testing for the personalized management of patients with diffuse large B-cell lymphoma and follicular lymphoma

Ruth Stuckey, Hugo Luzardo Henríquez, Haridian de la Nuez Melian, José Carlos Rivero Vera, Cristina Bilbao-Sieyro, María Teresa Gómez-Casares

ND JOURNAL *of* MEDICINE

ORIGINAL ARTICLE

PD-1 Blockade in Tumors with Mismatch-Repair Deficiency

D.T. Le, J.N. Uram, H. Wang, B.R. Bartlett, H. Kemberling, A.D. Eyring, A.D. Skora, B.S. Luber, N.S. Azad, D. Laheru, B. Biedrzycki, R.C. Donehower, A. Zaheer, G.A. Fisher, T.S. Crocenzi, J.J. Lee, S.M. Duffy, R.M. Goldberg, A. de la Chapelle, M. Koshiji, F. Bhaijee, T. Huebner, R.H. Hruban, L.D. Wood, N. Cuka, D.M. Pardoll, N. Papadopoulos, K.W. Kinzler, S. Zhou, T.C. Cornish, J.M. Taube, R.A. Anders, J.R. Eshleman, B. Vogelstein, and L.A. Diaz, Jr.

PID in SID – Unusual responses to Therapy clues

- Failure to respond to first line therapies – ie requiring rituximab
- Recrudescence of dysregulatory symptoms within a time frame of ritux recovery from Ritux eg pulmonary nodules
- Lack of humoral immune reconstitution after therapy for HM
- Progression with age
- Combination of infectious and non infectious complications

Why is it important to know about PID in SID?

Alice came to a fork in the road. 'Which road do I take?' she asked. 'Where do you want to go?' responded the Cheshire Cat. 'I don't know,' Alice answered. 'Then,' said the Cat, 'it doesn't matter.

Lewis Carroll

Conventional Treatment Pathways

- Steroids
- Azathioprine
- Cyclophosphamide
- Chlorambucil
- Cladribine
- Methotrexate
- Mycophenolate
- Fludarabine
- And on and on…

Targeted Therapy

- CTLA4 – abatacept, belatacept
- APDS – PI3K inhibitors – leniolisib, nemiralisib, selatalisib
- DADA2 – TNF alpha inhibition
- STAT1 and STAT3 GoF – Jakinib
- Interferonopathies – Jakinibs, anifrolumab
- IPEX & ALPS - sirolimus
- PIRD category more than 129 disorders many with overlaps into CVID

Indications for HSCT in PID

- **Bone marrow failure** requiring long term blood, platelet or cytokine support. Risk transfusion associated iron overload or alloimmunisation
- **Lymphoma** or other cancer where delays in HSCT risk relapse, progression or treatment resistance
- **HLH** – high risk recurrence, refractory or relapsed with treatment
- **Vital organ dysfunction** (kidney, lung, gut, **?liver**) due to PID failed to respond to alternative therapies and where delay may preclude HSCT

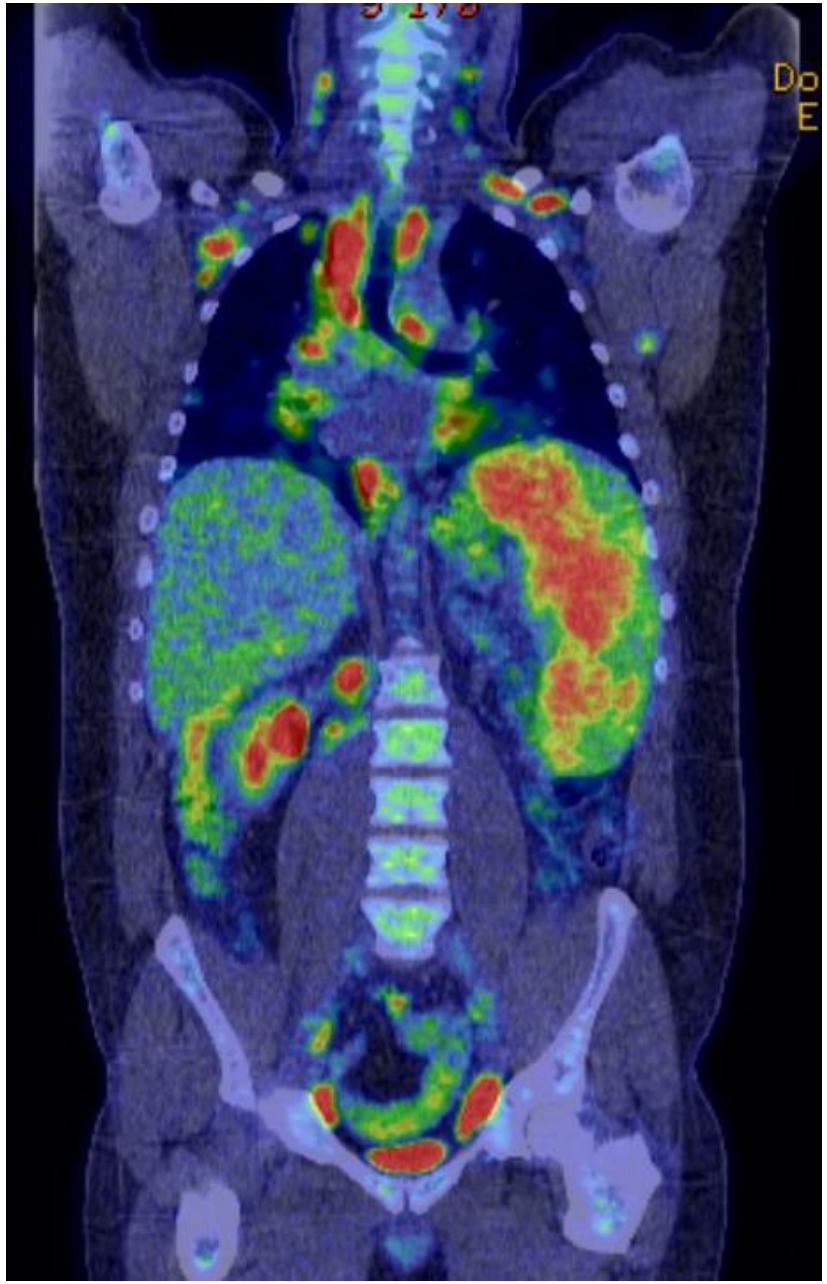
Adapted from the National UK PIDD HSCT MDT, Mustafa SS Immunosuppression in patients with primary immunodeficiency – walking the line. JACI-IP 2022

SAD or is it?

- 38 yr old man
- Aged 28 yrs ITP - hdIVIg
- Aged 30 yrs developed Hodgkin's Lymphoma
- Recurrent sinopulmonary infections began following RABVD for lymphoma
- IgG 1.67g/L, IgA <0.05g/L, IgM 0.11g/L, CSMB 0.03%
- IgRT commenced
- Aged 36 yrs – splenomegaly, multiple FDG avid pathological nodes, lung nodules

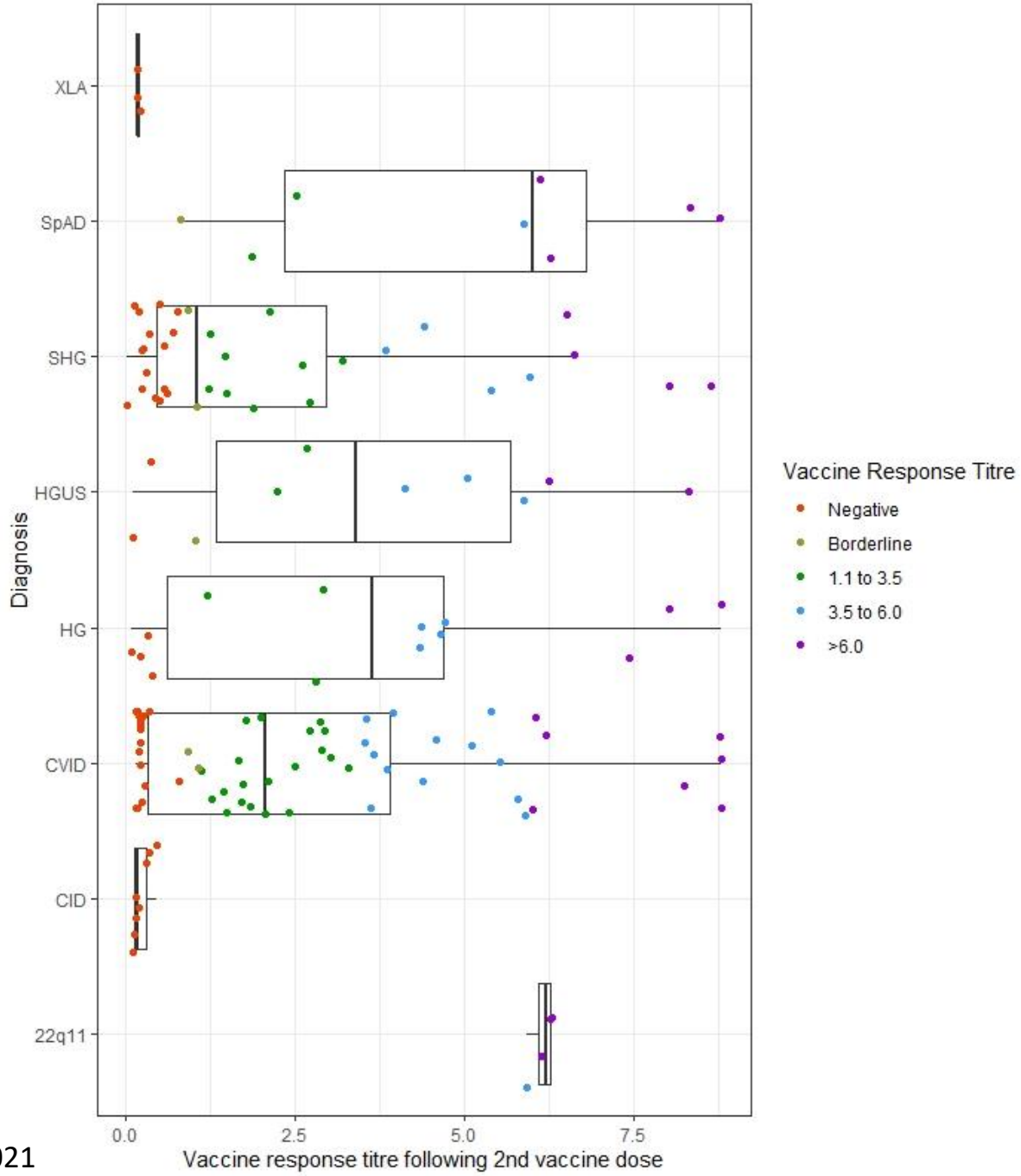
SAD or is it?

- FDGPET – suggestive of an active lymphoproliferative disease
- Biopsy – reactive lymphoproliferation no evidence of malignancy
- EBV and CMV negative
- Commenced rituximab for distension and pain due to splenomegaly
- Genetic PID panel – TNFRSF13B c.310T>C, p.(Cys104Arg)
- National PID HSCT MDT?



NHS Immunology Lab

- Development of functional assays to dissect the most relevant pathways as more targeted therapies become available
- Functional support for VUS analysis
- Assessment of degree of effect of therapies eg APDS
- Reliable and resilient core testing not dependent on ongoing grant funding
- Response to COVID with assays of humoral and cellular responses to vaccinations in immunodeficient patients



Ponsford MJ JoCI 2022, Tallantyre EC Ann Neurol 2021 , Moat SJ Ann Clin Biochem 2021

Conclusions

- Importance of early detection of SID and hence PID within SID
- Combination of education, screening approaches and a keen look out for clues
- Closer collaboration with a multiplicity of specialties where SID is born and also where PID may present
- Development of accessible functional assays (networked)
- Genetic diagnosis where possible
- Individualised PID informed approach to therapy – which may not be the standard
- How to advance HSCT in adult PID
- Revisit vaccination in ID – extend COVID learnings eg mRNA norovirus vaccination, post exposure and therapeutic settings