The estimation of immunoglobulin demand against a background of uncertainty

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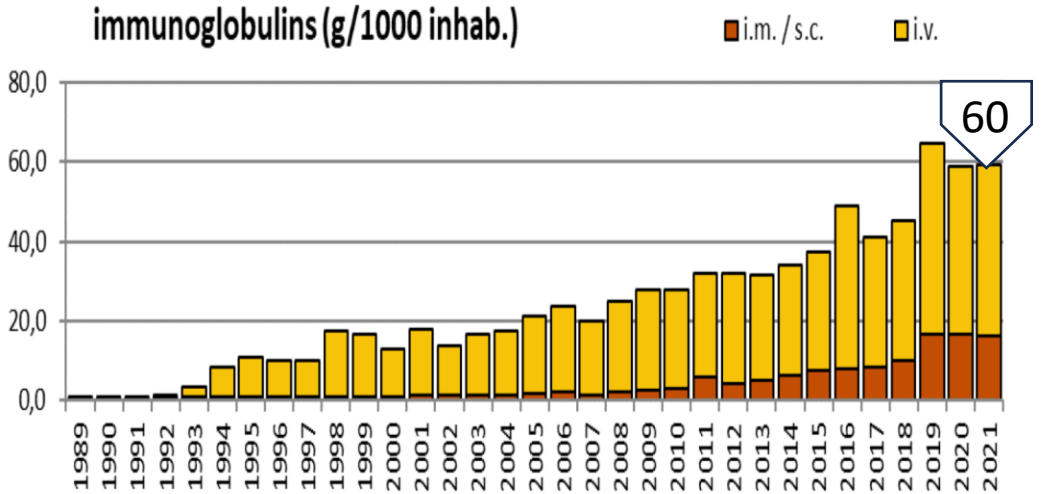
Conflicts of interest

- I provide paid consultancy services to organisations supplying therapies mentioned in this presentation.
- I provide pro-bono advisory services to patient organisations using therapies mentioned in this presentation.

The immunoglobulin supply-demand landscape

- The *demand* for immunoglobulin continues to rise in all geographies, mirroring an increased *usage* which is due to :
  - Increased diagnostic capacity
  - Enhanced survival in the key patient demographics
  - Widening of the evidence base for usage
  - Increased patient access to care
- Differentiating *usage* from *sufficiency* is important

The (never-ending) example of the Czech Republic



Plasma collection 2021 (Rehacek, Rome 2022)

Plasma recovered from WB 8.1L/10^3

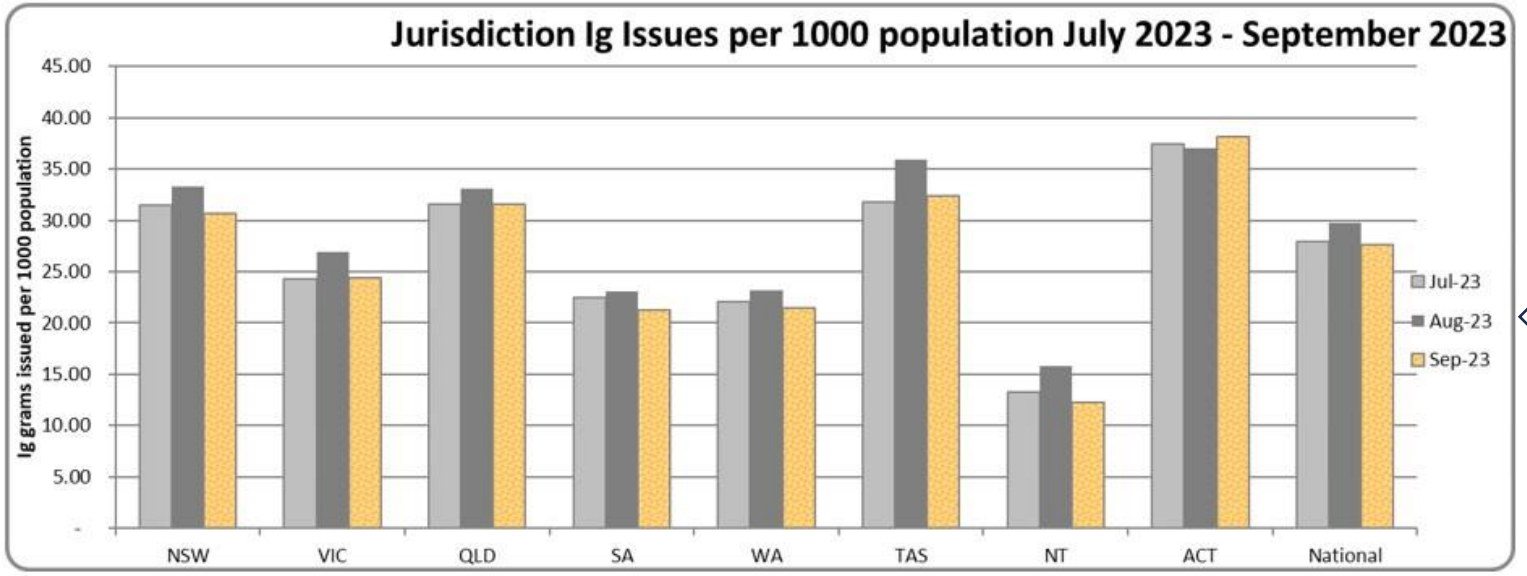
Source plasma from public sector 14.0L/ 10^3

Source plasma from for-profit 58.8L/ 10^3

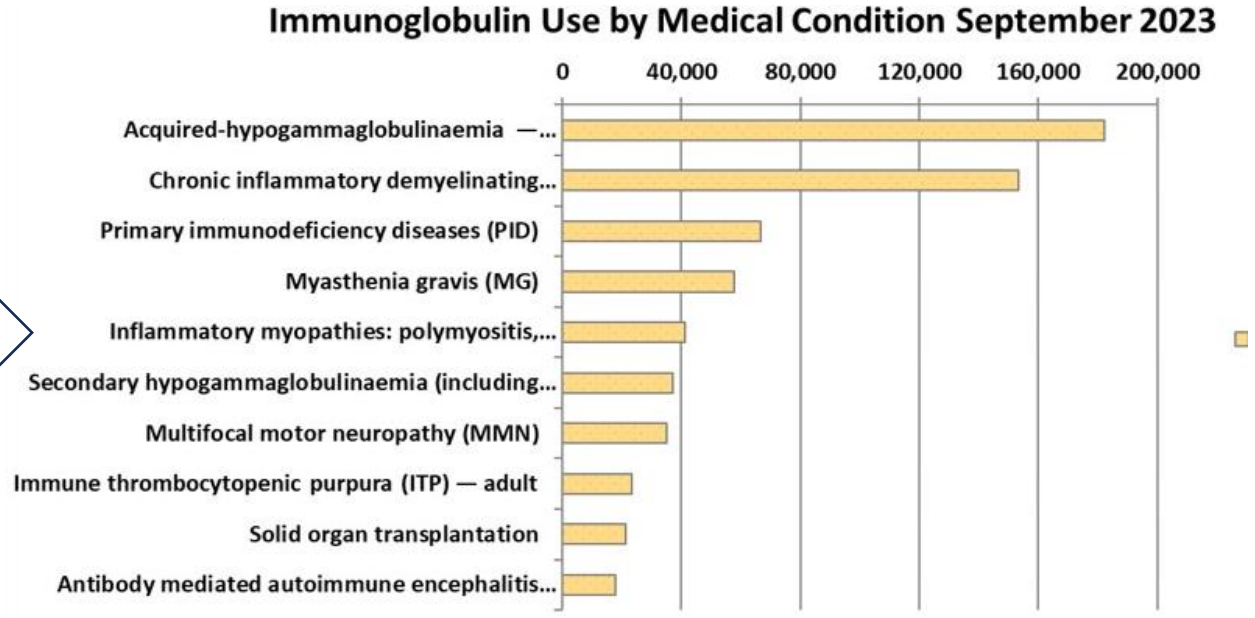
Total CR plasma collection 80.9l/ 10^3

- Able to yield 308 g Ig/103 population
- Actual usage (2021) 60 g Ig/ 103 population

“I come from a land down under….”



Ca 340 g/1000 population



- **Strongly controlled**
- **Level 1 evidence**

The concept of Latent Therapeutic Demand

- *Usage* approaches *sufficiency* as supply approaches the *latent therapeutic demand*
- We define Latent Therapeutic Demand (LTD) as *the underlying demand that represents how physicians would prescribe treatment and how patients would comply with the prescribed treatment if ample supplies were available and affordable, and access to therapy was unencumbered by issues other than evidence-based clinical need, such as financial constraints.*

Estimating latent therapeutic demand for IG

J Clin Immunol (2014) 34:233–244
DOI 10.1007/s10875-013-9975-1

ORIGINAL RESEARCH

Modeling Primary Immunodeficiency Disease Epidemiology and Its Treatment to Estimate Latent Therapeutic Demand for Immunoglobulin

Jeffrey S. Stonebraker · Albert Farrugia · Benjamin Gathmann · ESID Registry Working Party · Jordan S. Orange

Received: 6 January 2021 | Revised: 3 May 2021 | Accepted: 4 May 2021
DOI: 10.1111/vox.13134

ORIGINAL ARTICLE

Vox Sanguinis ISBT International Society of Blood Transfusion

Estimation of the latent therapeutic demand for immunoglobulin therapies in autoimmune neuropathies in the United States

Albert Farrugia[1] | Megha Bansal[2] | Ivan Marjanovic[3]

Vox Sanguinis (2018) **113**, 430–440

ORIGINAL PAPER

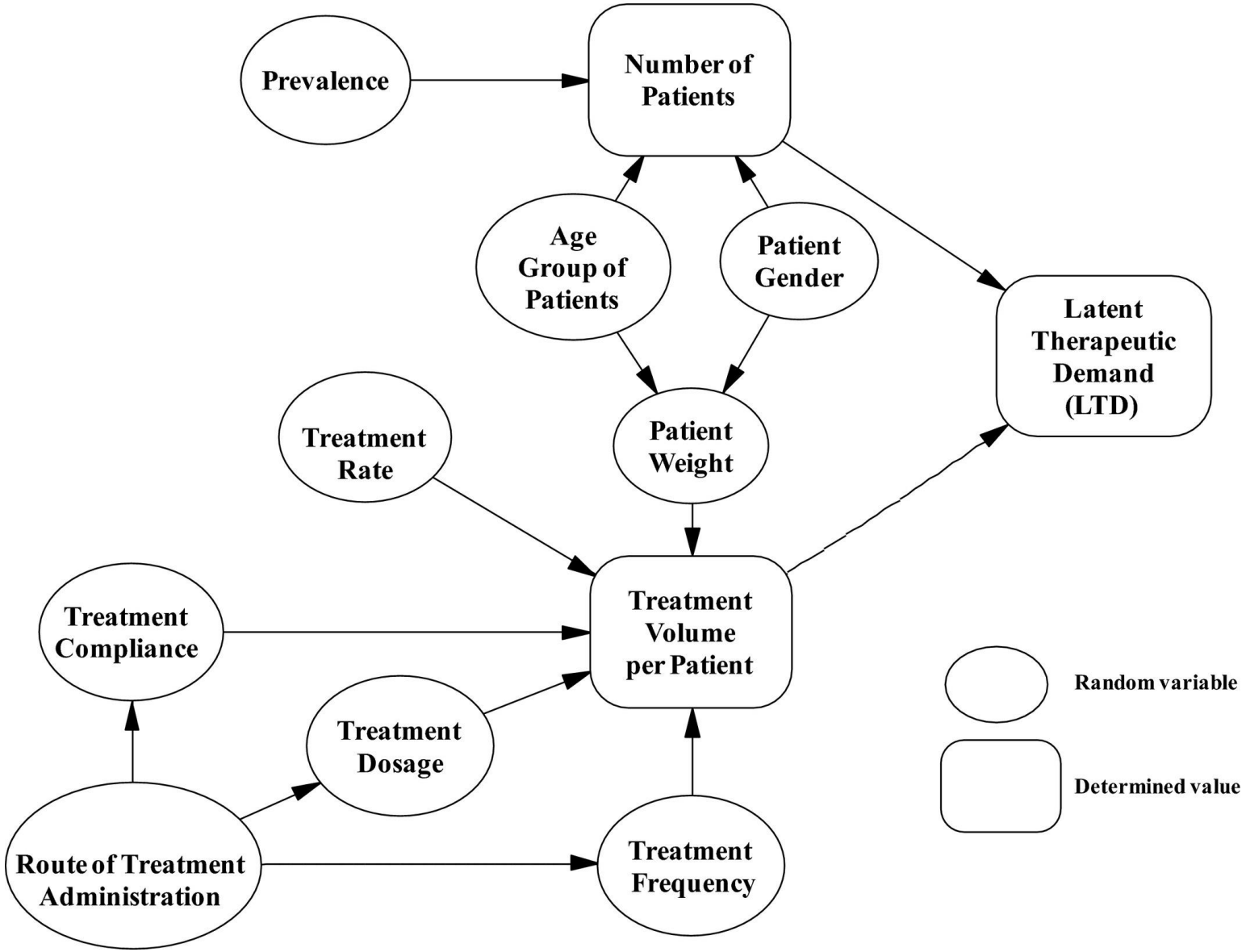
© 2018 International Society of Blood Transfusion
DOI: 10.1111/vox.12651

Latent therapeutic demand model for the immunoglobulin replacement therapy of primary immune deficiency disorders in the USA

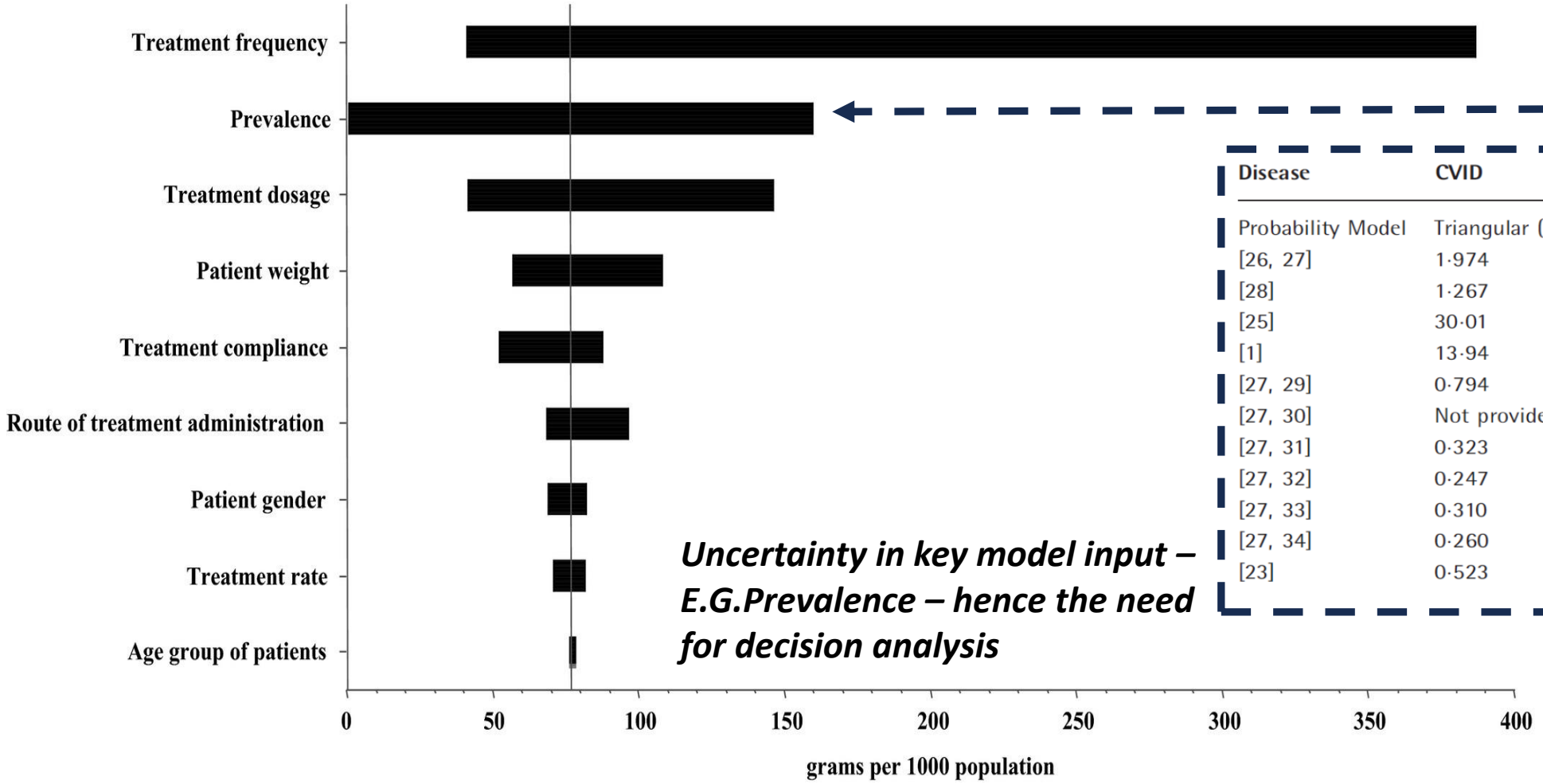
J. S. Stonebraker,[1] J. Hajjar[2] & J. S. Orange[2]
[1]*Department of Business Management, Poole College of Management, North Carolina State University, Raleigh, NC, USA*
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Estimating latent therapeutic demand for IG

Addressing uncertainty



LTD model for the immunoglobulin replacement therapy of PIDDs in the USA



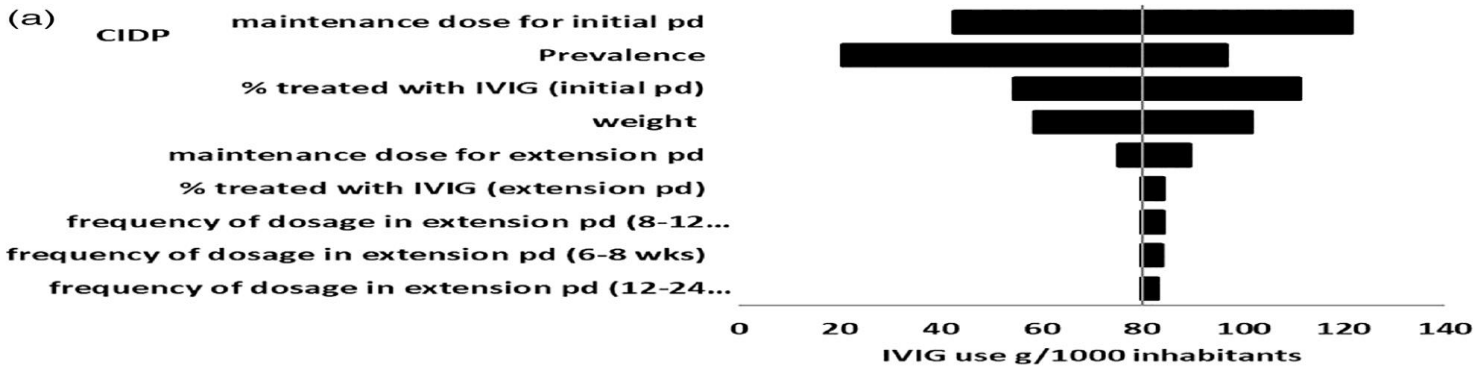
Disease	CVID
Probability Model	Triangular (0·247, 13·94, 30·01)
[26, 27]	1·974
[28]	1·267
[25]	30·01
[1]	13·94
[27, 29]	0·794
[27, 30]	Not provided
[27, 31]	0·323
[27, 32]	0·247
[27, 33]	0·310
[27, 34]	0·260
[23]	0·523

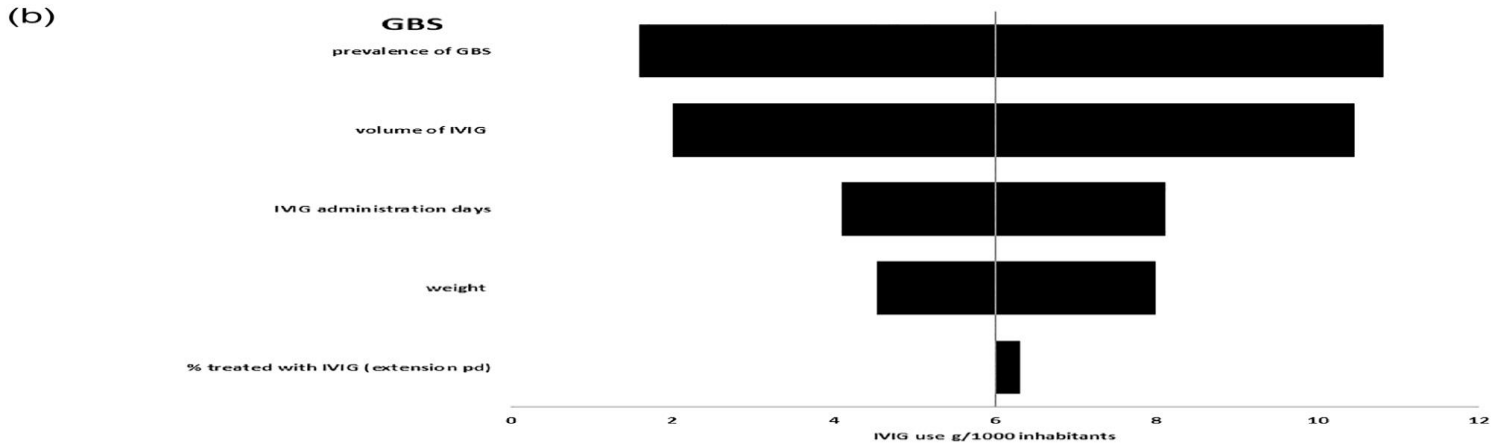
Uncertainty in key model input – E.G.Prevalence – hence the need for decision analysis

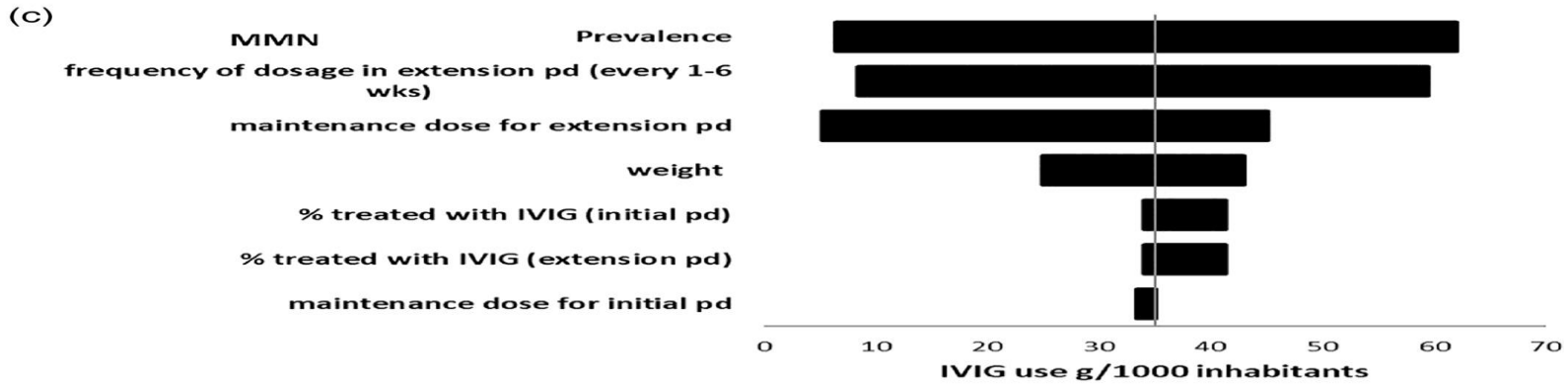
Vox Sanguinis, Volume: 113, Issue: 5, Pages: 430-440, First published: 20 April 2018, DOI: (10.1111/vox.12651)

Estimation of the latent therapeutic demand for immunoglobulin therapies in autoimmune neuropathies in the USA

Vox Sanguinis, Volume: 117, Issue: 2, Pages: 208-219, First published: 10 June 2021, DOI: (10.1111/vox.13134)







Which *research questions* ensue from interrogating these LTD models?

- Focus on the key contributors to the LTD estimate i.e.:
  - **Disease prevalence**
  - **Treatment dose**

Importance of diagnostic criteria

Diagnosis of Common Variable Immune Deficiency

Criteria	New Zealand (89 patients studied) Ameratunga, R.et al. Comparison of Diagnostic Criteria for Common Variable Immunodeficiency Disorders (CVID) in the New Zealand CVID Cohort Study. Clinic Rev Allerg Immunol 61, 236–244 (2021). https://doi.org/10.1007/s12016-021-08860-7	Finland (141 patients studied – prob+poss+def) Selenius JS et al. Unexpectedly High Prevalence of Common Variable Immunodeficiency in Finland. Front Immunol. 2017 Sep 28;8:1190. doi: 10.3389/fimmu.2017.01190. PMID: 29033928; PMCID: PMC5625003.
Ameratunga(1)	79	132
ESID(2)	43	132
ICON(3)	42	113

(1) Ameratunga R, Woon ST, Gillis D, Koopmans W, Steele R (2013) New diagnostic criteria for common variable immune deficiency (CVID), which may assist with decisions to treat with intravenous or subcutaneous immunoglobulin. Clin Exp Immunol 174:203–211

(2) Seidel MG, Kindle G, Gathmann B et al (2019) The European Society for Immunodeficiencies (ESID) Registry Working Definitions for the Clinical Diagnosis of Inborn Errors of Immunity. J Allergy Clin Immunol Pract

(3) Bonilla FA, Barlan I, Chapel H et al (2016) International Consensus Document (ICON): common variable immunodeficiency disorders. J Allergy Clin Immunol Pract 4:38–59

Prevalence of CVID

Country	CVID/10^5 inhabitants
Denmark	**3.8**
Northern	5.00
Central	4.8
Capital	4.0
Southern	3.03
Zealand	1.33
Finland (prob+poss)	**6.9**
HUS	7.7
Carea	2.9
Eksote	1.5
Iceland	**3.1**
Norway	**2.6**

The prevalence of CVID in Finland appears the highest recorded, likely reflecting the genetic isolation and potential founder effects in the Finnish population.

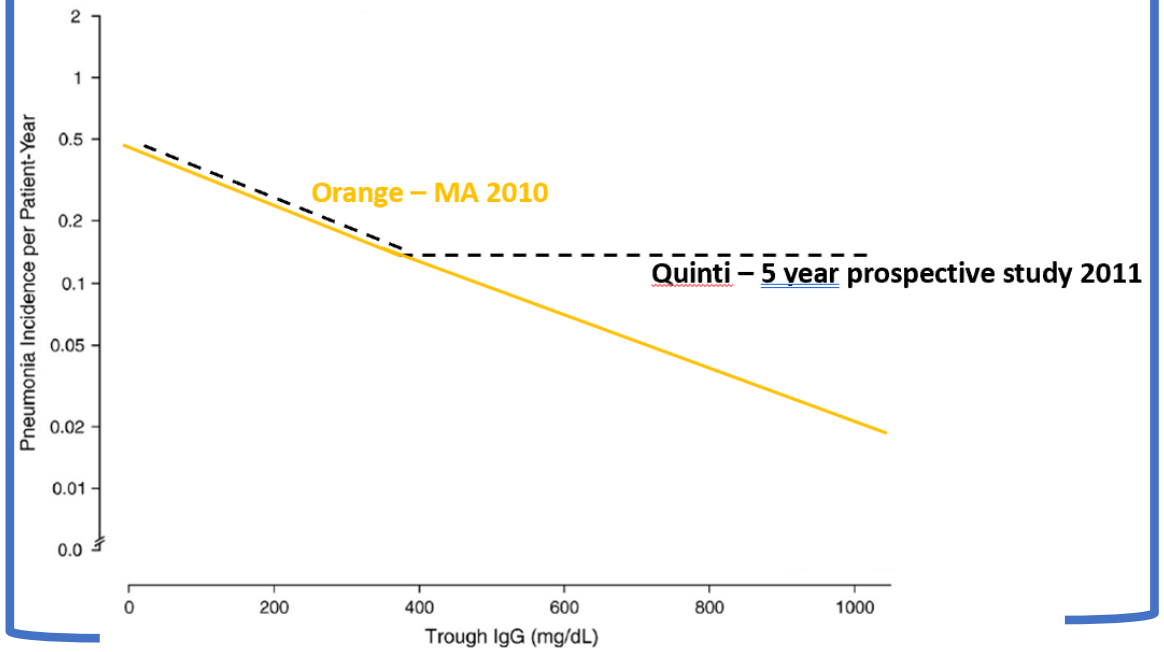
Country	CVID/10^5 inhabitants
Turkey	**1.4**
UK	**1.3**
Switzerland	**1.2**
France	**0.7**
Spain	0.6

- Selenius JS et al. Unexpectedly High Prevalence of Common Variable Immunodeficiency in Finland. Front Immunol. 2017 Sep 28;8:1190. doi: 10.3389/fimmu.2017.01190. PMID: 29033928; PMCID: PMC5625003.
- Westh L et al. Identification and Characterization of a Nationwide Danish Adult Common Variable Immunodeficiency Cohort. Scand J Immunol. 2017 Jun;85(6):450-461. doi: 10.1111/sji.12551. PMID: 28370285.

Comparison of treatment dose for PID (mg/kg) between USIDNET and ESID

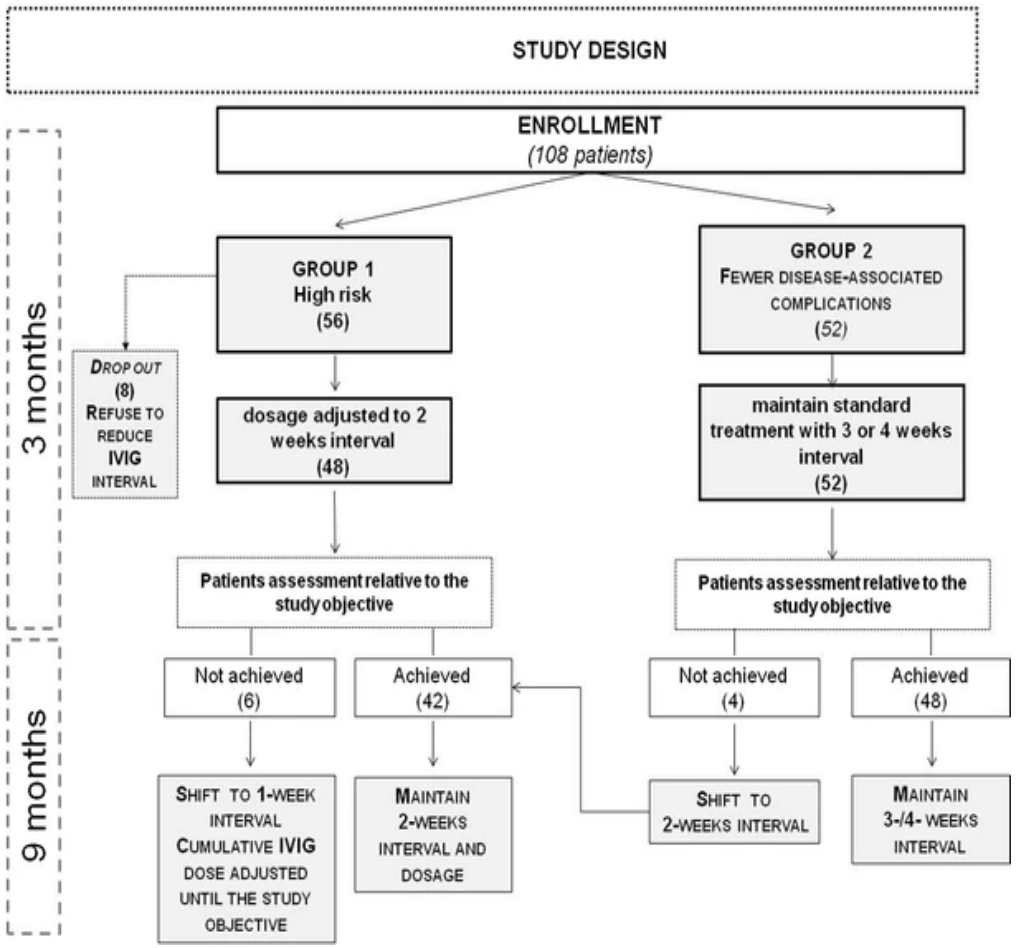
	Source	Mean	SD	N	
CVID					
IVIG	USIDNET 22	482	192	223	< 0.01
	ESID 21	373	152	748	
SCIG	USIDNET 22	188	168	110	< 0.01
	ESID 21	112	55	200	
XLA					
IVIG	USIDNET 22	478	226	43	0.14
	ESID 21	440	151	305	
SCIG	USIDNET 22	175	98	13	0.17
	ESID 21	147	96	114	

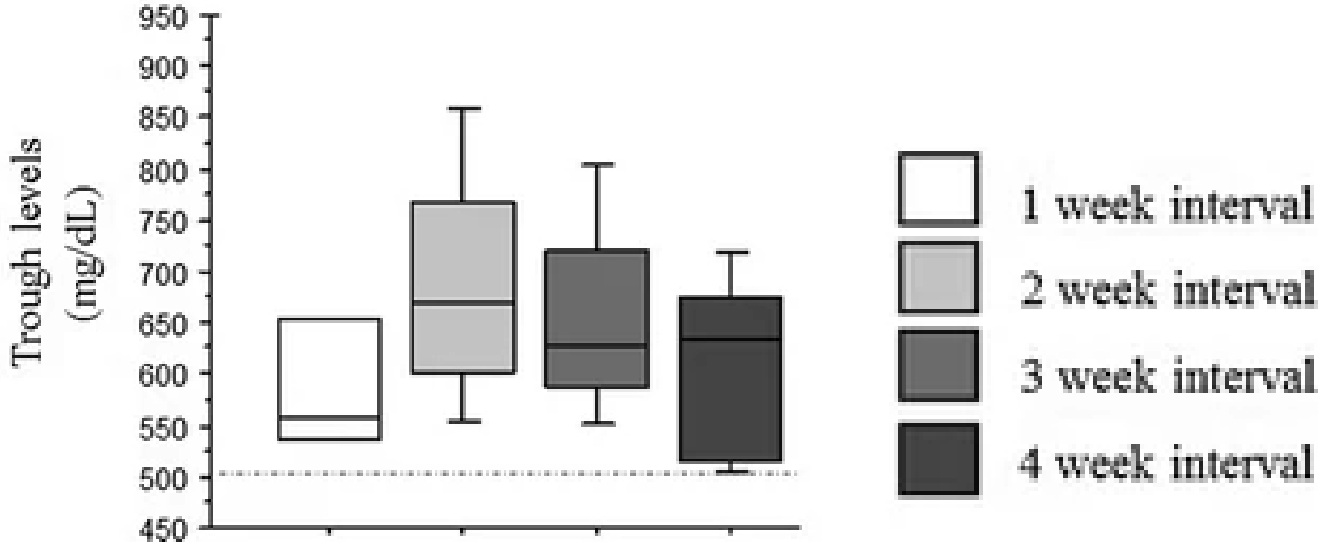
IgG levels and risk of pneumonia



Vox Sanguinis, Volume: 113, Issue: 5, Pages: 430-440, First published: 20 April 2018, DOI: (10.1111/vox.12651)

Personalised dosage - PID





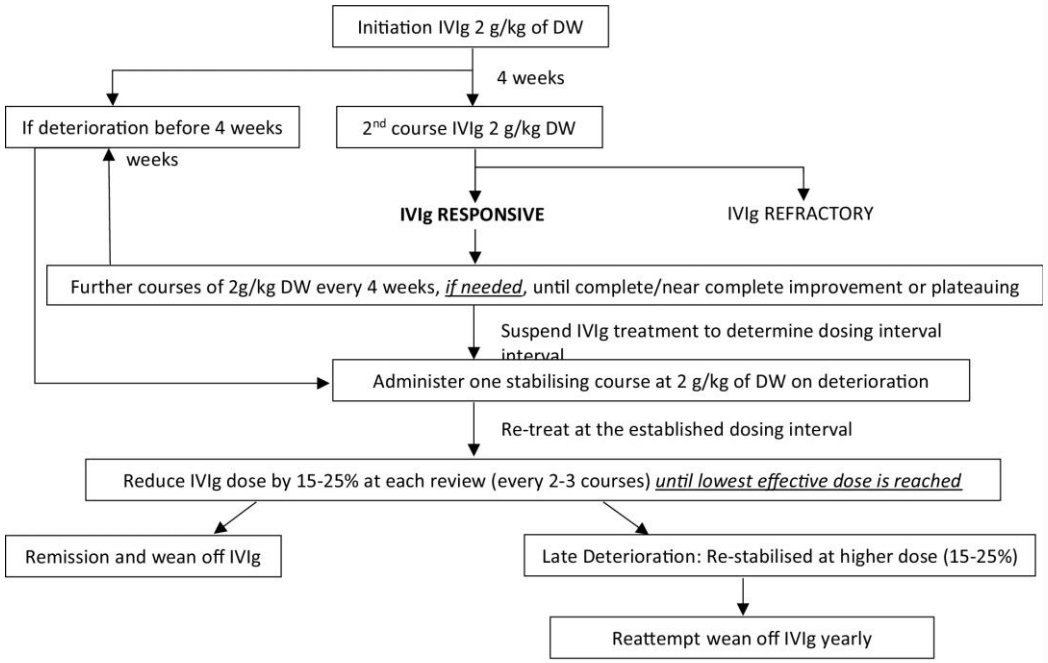
Quinti et l J Clin Immunol (2014) 34:813–819

CIDP Prevalence ? Australia

- Number of patients prescribed Ig 2017-2018 = 2795
- Prevalence estimate using EFNS/PNS criteria = 518 - 1593

(2019) *Immunoglobulin for Chronic Inflammatory Demyelinating Polyneuropathy (CIDP)*. MSAC Application 1564, Assessment Report. Commonwealth of Australia, Canberra, ACT
http://www.msac.gov.au/internet/msac/publishing.nsf/Content/2B740EDAE80B75DFCA25837E00096D86/$File/1564_MSAC_Assessment%20Report_Redacted.pdf

Individualised protocol vs. standard dosing for CIDP



Abbreviations: CIDP: chronic inflammatory demyelinating polyneuropathy; DW: Dosing weight; IVIg: intravenous immunoglobulins;

	Mean Weekly IVIg Dose Used (g/week)	Mean Yearly IVIg Dose Used (g/year)
Real IVIg consumption and costs incurred with Protocol and outcome measures used	22.06	1149
Consumption and costs with hypothetical standard dosing at 1 g/kg/ 3 weeks using dosing weight	25.50	1326
Consumption and costs with hypothetical standard dosing at 1 g/kg/ 3 weeks using recorded weight	29.60	1539

Journal of Neurology volume 266, pages 461–467 (2019)

Latent therapeutic demand for IG in the USA PIDs and neuropathies

Condition	Mean LTD immunoglobulin g/10^3 population
Common variable immune deficiency (CVID)	65.4 ± 73.6
X-linked agammaglobulinemia (XLA)	25.5 ± 27.6
Severe combined immune deficiency (SCID)	13.4 ± 13.5
Wiskott–Aldrich syndrome (WAS)	0.5 ± 0.4
hyper IGM syndrome (HIGM)	0.3 ± 0.3
Chronic inflammatory demyelinating polyneuropathy (CIDP)	83.05 ± 24.5
Guillain–Barré syndrome (GBS)	6.1 ± 3.2
Multifocal motor neuropathy (MMN)	36.1 ± 25.5
Total mean immunoglobulin consumption	230.35

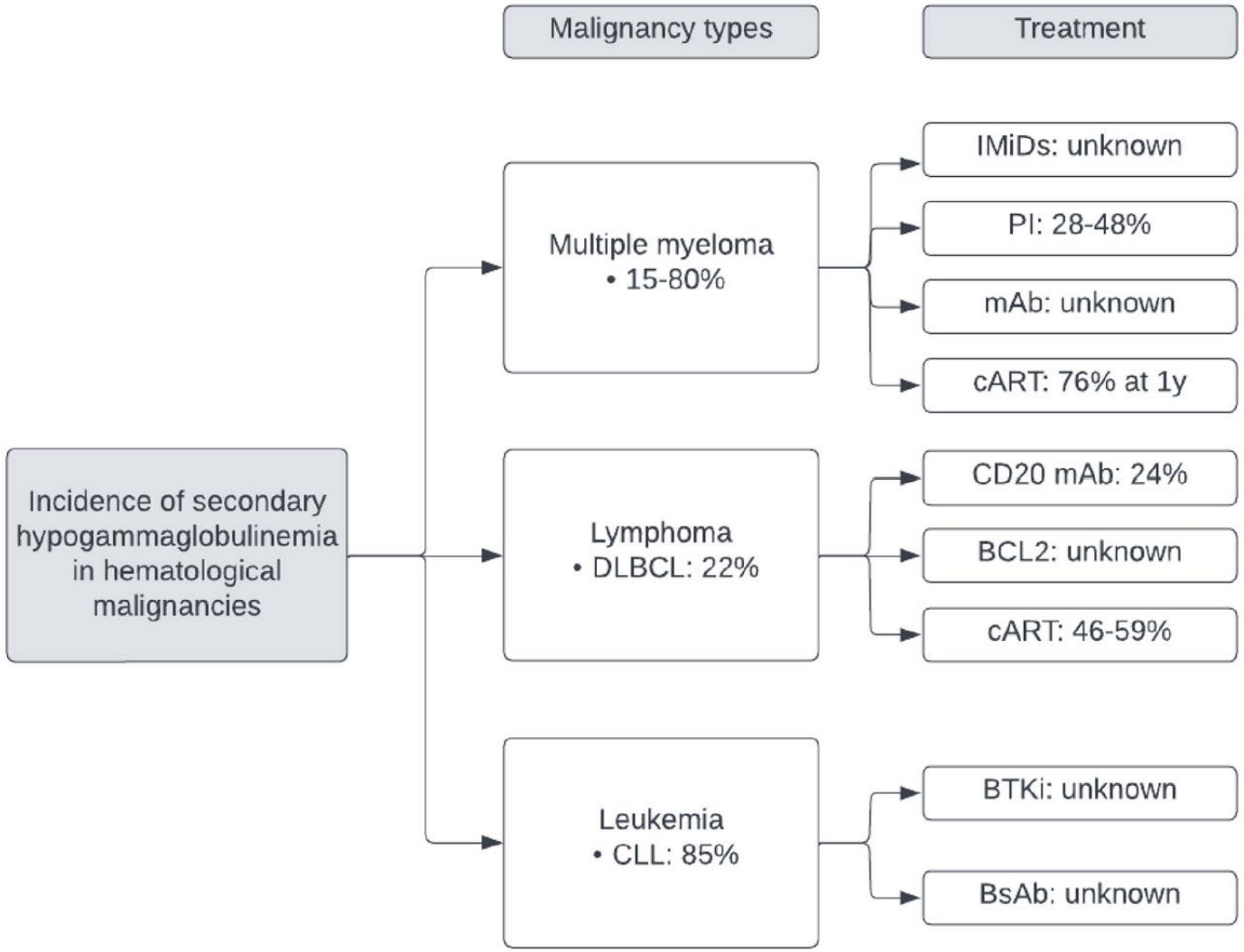
Vox Sang. 2022;117:208–219

Current core SmPC guideline for IVIg (effective 1 January, 2019)

	Dose	Frequency
Replacement therapy in Secondary immunodeficiencies in patients who suffer from severe or recurrent infections, ineffective antimicrobial treatment and either proven specific antibody failure (PSAF) [a] or serum IgG level of <4 g/L.	0.2-0.4 g/kg	Every 3-4 weeks

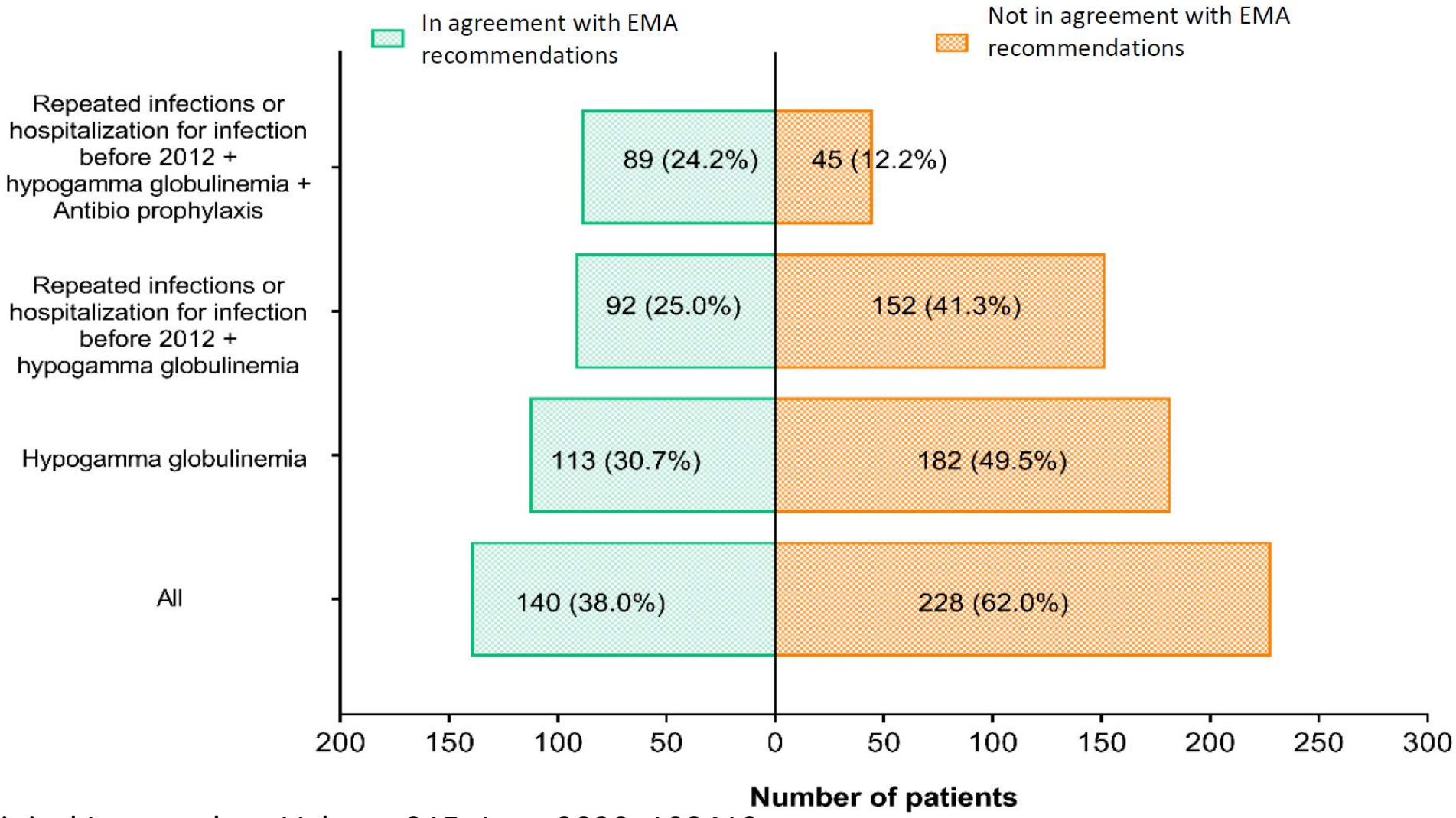
[a] PSAF = failure to mount at least a 2-fold rise in IgG antibody titre to pneumococcal polysaccharide and polypeptide antigen vaccines.

Incidence of secondary hypogammaglobulinemia in hematological malignancies



Leukemia & Lymphoma (2023) 64:1, 18-29, DOI: 10.1080/10428194.2022.2131424

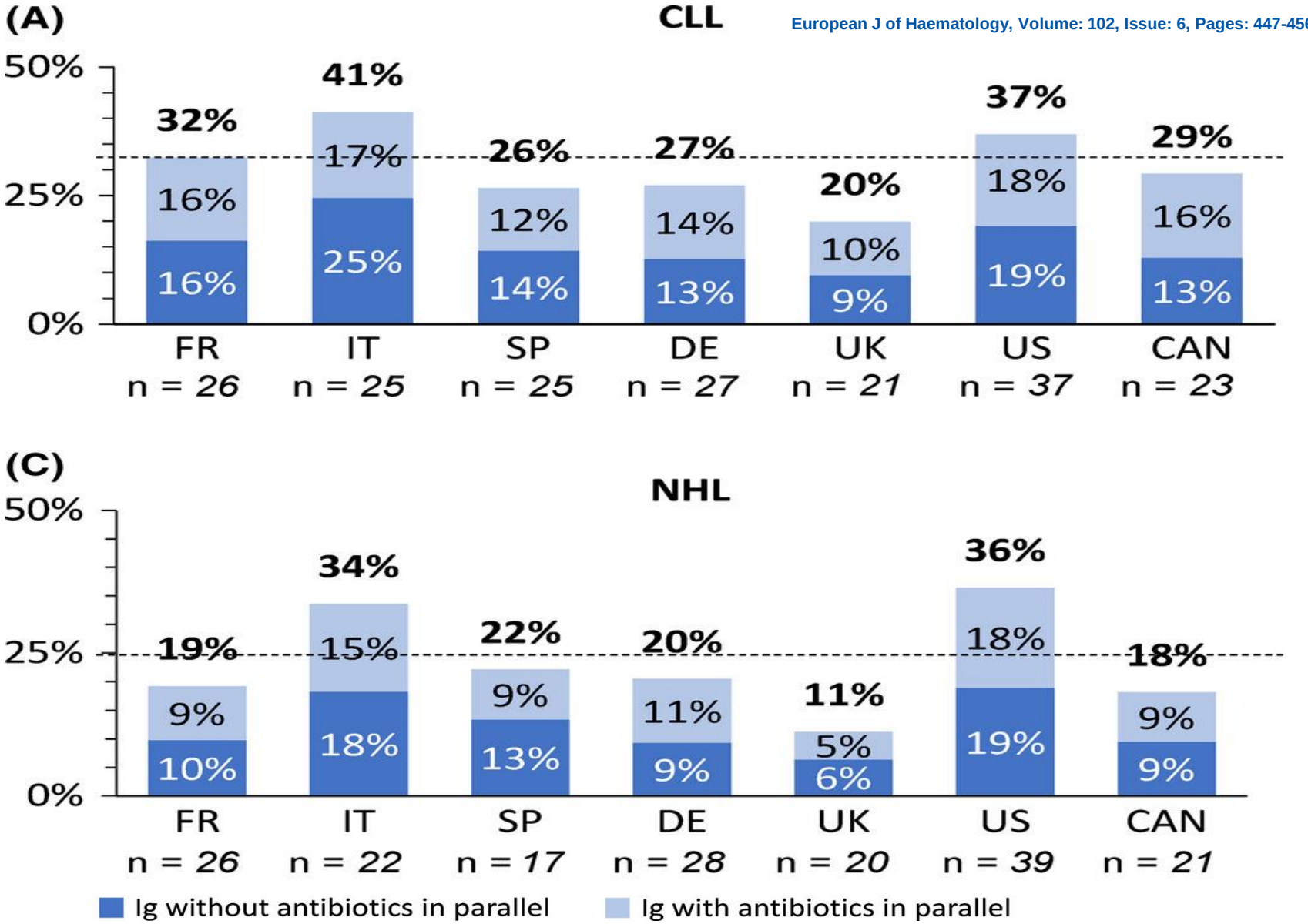
Compliance with European Medicines Agency recommendations for receiving immunoglobulin replacement therapy for SID



Clinical Immunology Volume 215, June 2020, 108419

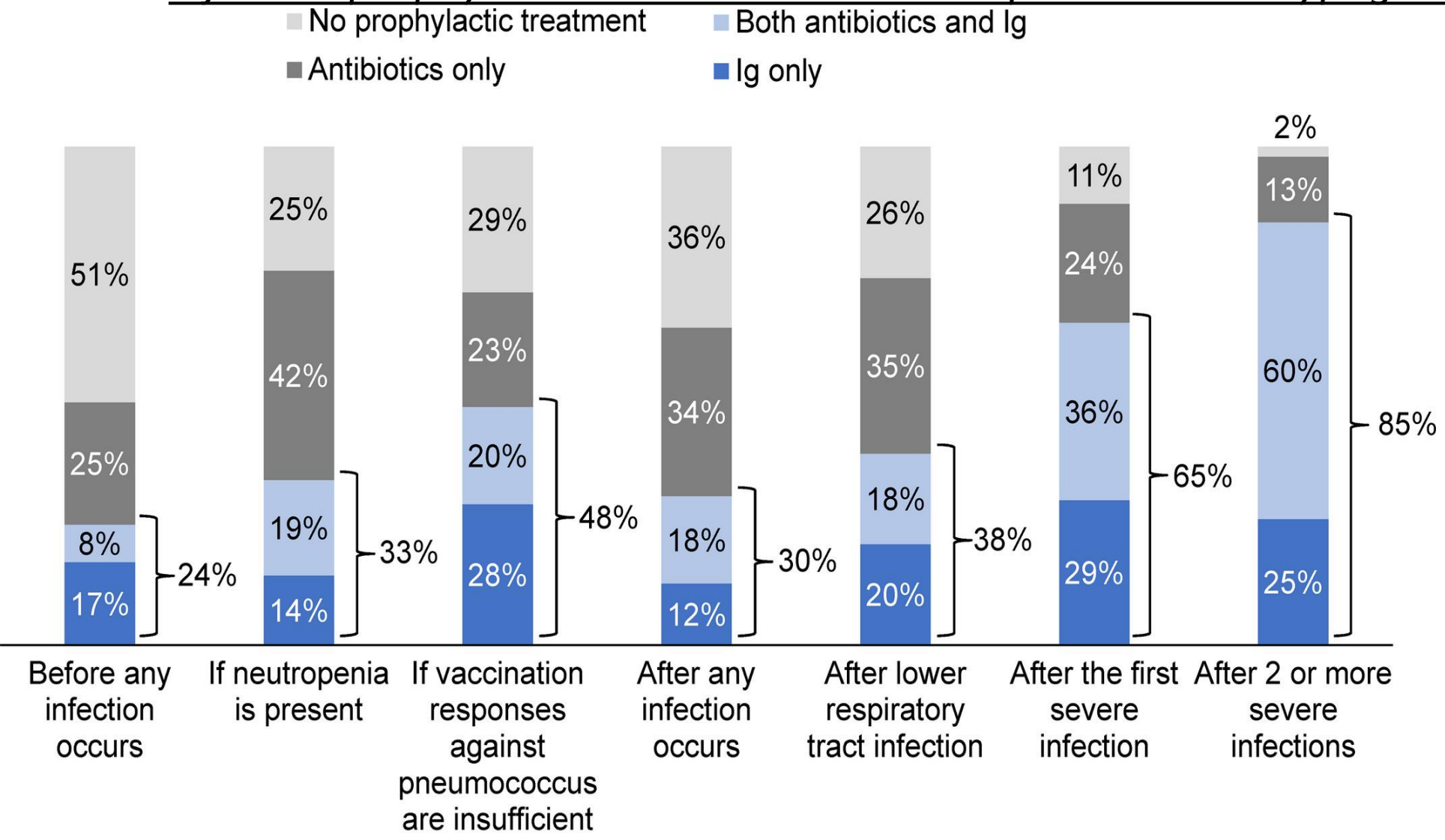
Current clinical practice and challenges in the management of secondary immunodeficiency in hematological malignancies

European J of Haematology, Volume: 102, Issue: 6, Pages: 447-456, First published: 22 February 2019, DOI: (10.1111/ejh.13223)



Current clinical practice and challenges in the management of secondary immunodeficiency in hematological malignancies

Infection prophylaxis across all countries in patients with hypogammaglobulinemia



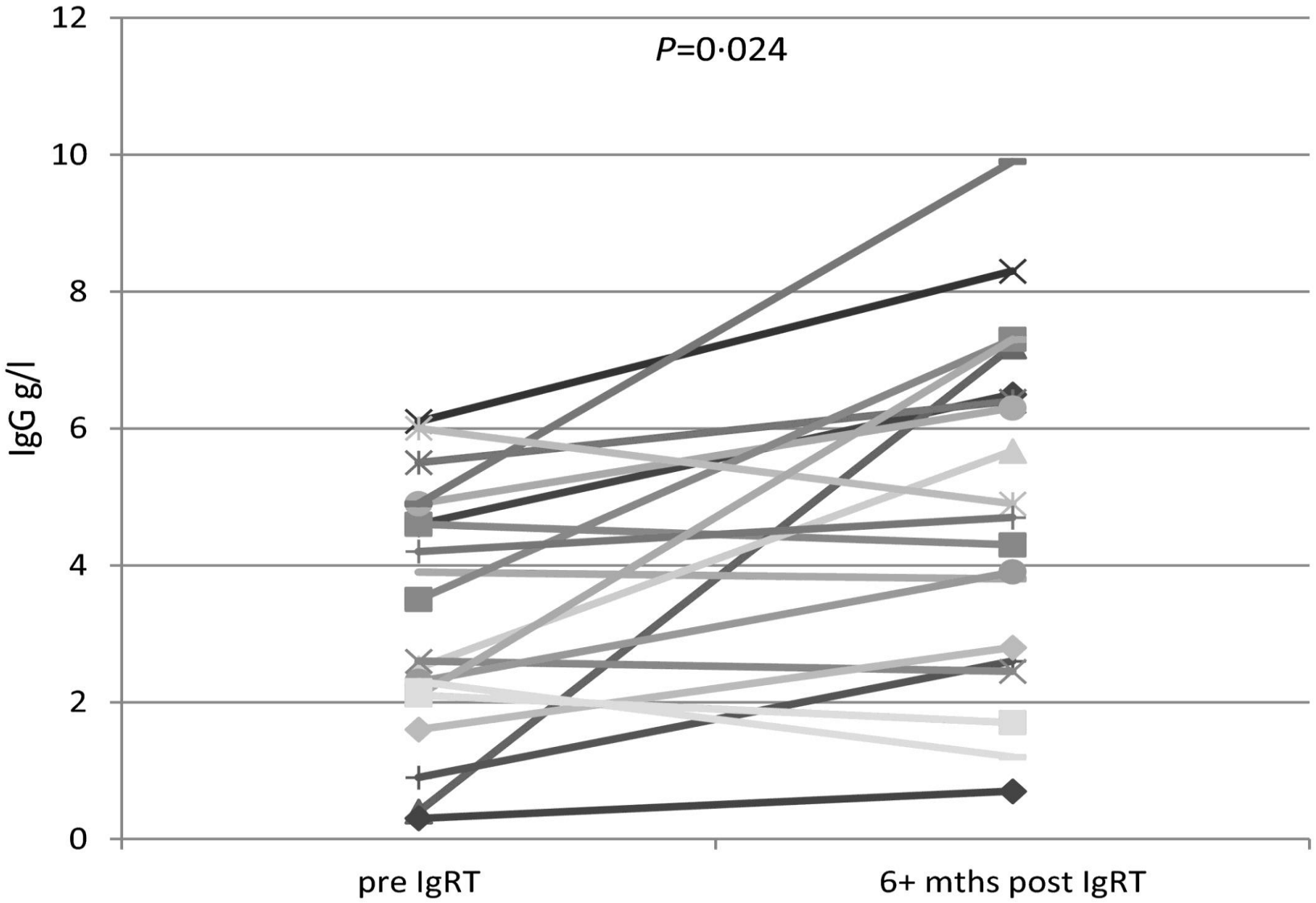
European J of Haematology, Volume: 102, Issue: 6, Pages: 447-456, First published: 22 February 2019, DOI: (10.1111/ejh.13223)

Optimization of dosing, duration, and cessation for immunoglobulin replacement

Area	Grade of evidence
IBW-based dosing	Moderate, from retrospective multicenter analyses
Duration of IgRT	Low
Cessation rules	Low

Leukemia & Lymphoma (2023) 64:1, 18-29, DOI: 10.1080/10428194.2022.2131424

Impact of stopping long-term immunoglobulin therapy in patients with secondary antibody deficiency due to haematological disease



Br J Haematol, Volume: 193, Issue: 2, Pages: e12-e15, First published: 13 March 2021, DOI: (10.1111/bjh.17328)

Which *research questions* ensue from assessing the SID-IG landscape?

- Outcome measures from different prophylactic regimens – focus on use of IG
- Cessation of therapy – WHEN?
- RCTs needed – EHA to champion?

We need to:

- Analyse and compare practice
- Define and measure outcomes
- Design and conduct studies

But……data for lg usage and demand…is hard to get…



We choose to …. do [these] things, not because they are easy, but <u>because they are hard</u>; because that goal will serve to organize and measure the best of our energies and skills, because that challenge is one that we are willing to accept, one we are unwilling to postpone, and one we intend to win……"