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24-25 MARCH 2024

TOKYO, JAPAN

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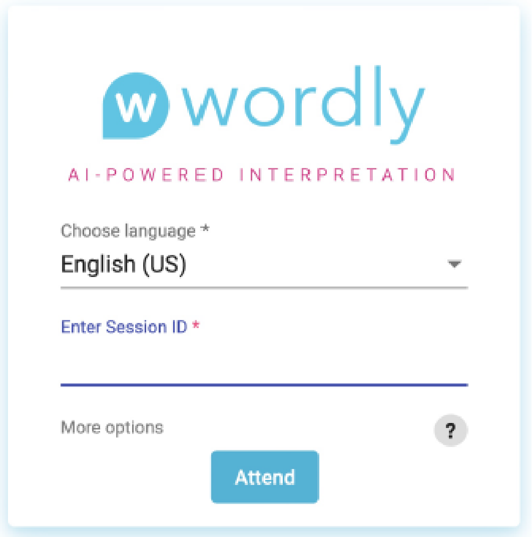

Step 3

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Asian perspectives on PID diagnostics and screening

Moderators:

Mr Bruce Lim (IPOPI Vice-President)
Dr Narissara Suratannon (Thailand)

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Specific infectious agents relevant to PID in the Asian region

Prof Surjit Singh | India

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Specific infectious agents relevant to PID in the Asian region

50 Glorious years of PGIMER

Dr. Surjit Singh

MD; DCH (Lon.); FRCP (Lon.); FRCPCH (Lon.); FAMS

Head, Department of Pediatrics, and Chief, Allergy Immunology Unit,

Advanced Pediatrics Centre, PGIMER, Chandigarh, India

WHO Collaborating Centre for Pediatric Immunology (2022-2026)

Centre of Excellence, Asia Pacific Society for Immunodeficiencies (2023-2026)

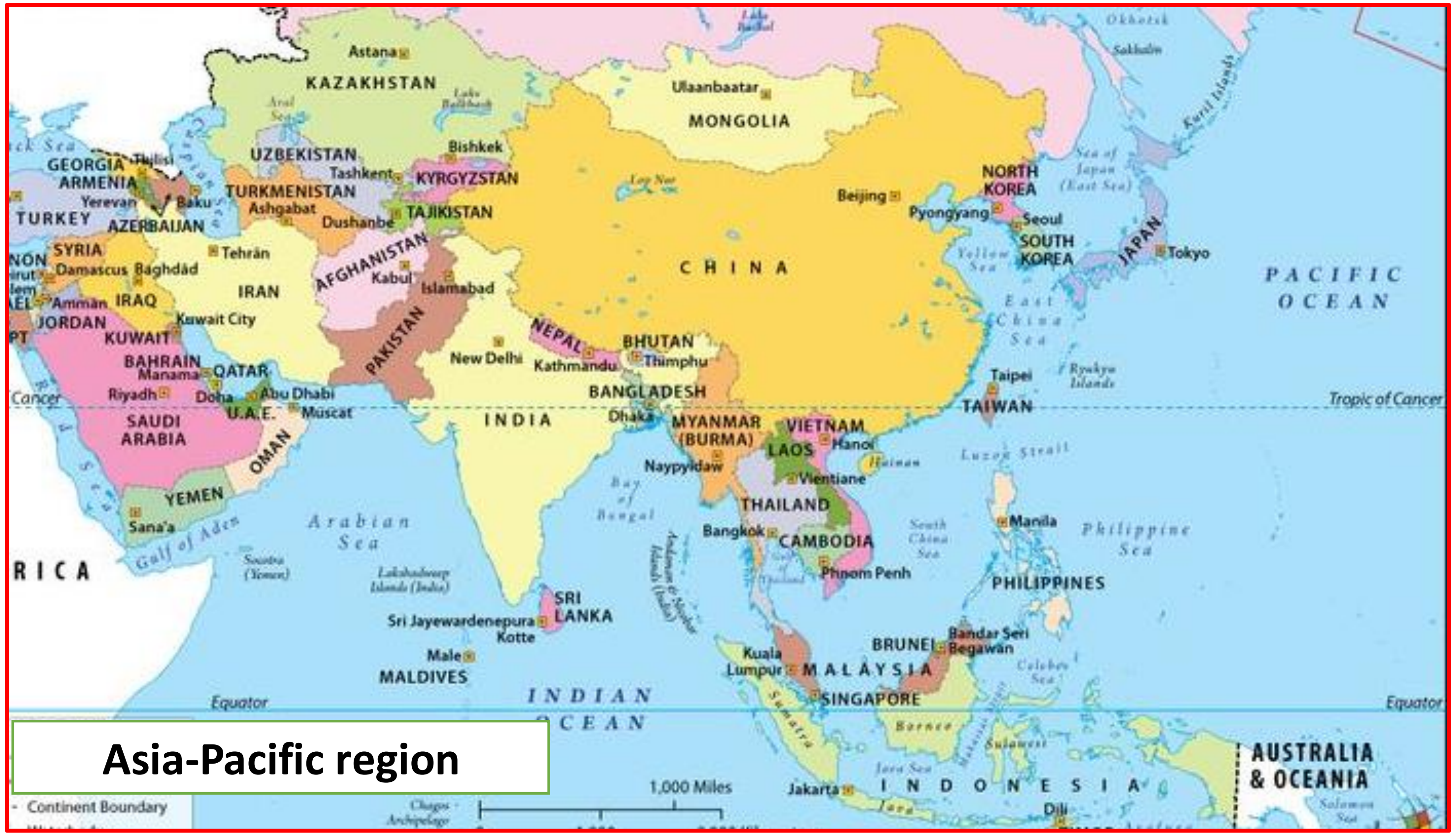
President, Asia Pacific Society for Immunodeficiencies (2020-2024)

Indian Council of Medical Research Collaborating Centre of Excellence in Pediatric Immunology (2023-2028)

Why is the Asia-Pacific region so important?

It is home to **2/3rd. of the world's population**

India and China together comprise **1/3rd. of the world's population**



Why is the Asia-Pacific region so different?

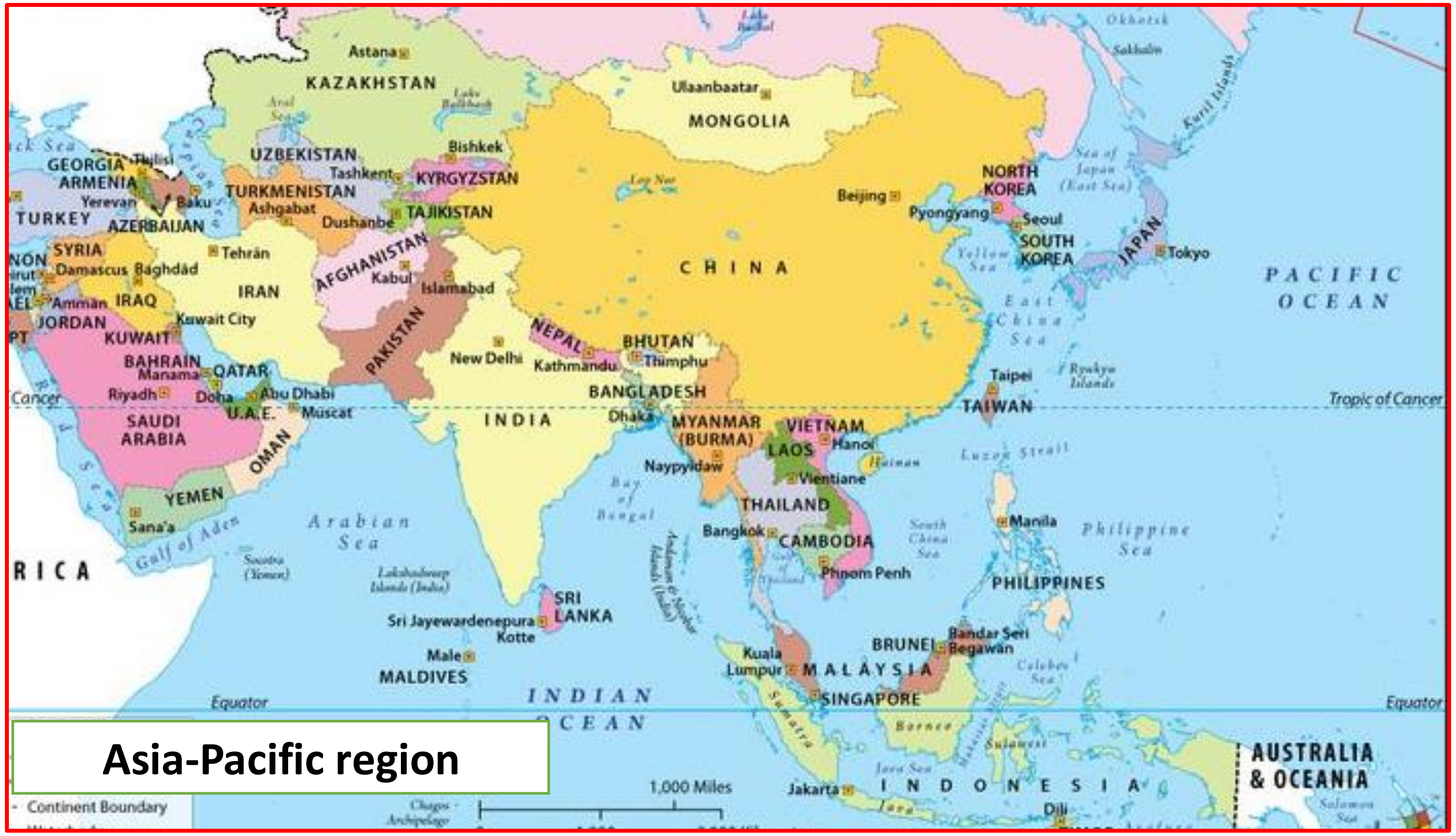
Breakthrough infections are more common

Profile of infections is different

Problems associated with:

i) widespread use of oral polio vaccine

ii) widespread use of BCG vaccine



Asia-Pacific region

Yu Lung Lau
University of Hong Kong

Chronic granulomatous disease

> Pediatr Infect Dis J. 2008 Mar;27(3):224-30. doi: 10.1097/INF.0b013e31815b494c.

Susceptibility to mycobacterial infections in children with X-linked chronic granulomatous disease: a review of 17 patients living in a region endemic for tuberculosis

Pamela P W Lee [1], Koon-Wing Chan, Liping Jiang, Tongxin Chen, Chengrong Li, Tsz-Leung Lee, Priscilla H S Mak, Susanna F S Fok, Xiqiang Yang, Yu-Lung Lau

Multicenter Study > Front Immunol. 2021 Feb 25:12:625320. doi: 10.3389/fimmu.2021.625320. eCollection 2021.

Clinical, Immunological, and Molecular Profile of Chronic Granulomatous Disease: A Multi-Centric Study of 236 Patients From India

Amit Rawat [1], Pandiarajan Vignesh [1], Murugan Sudhakar [1], Madhubala Sharma [1], Deepti Suri [1], Ankur Jindal [1], Anju Gupta [1], Jitendra Kumar Shandilya [1], Sathish Kumar Loganathan [1], Gurjit Kaur [1], Sanchi Chawla [1], Pratap Kumar Patra [1], Alka Khadwal [2], Biman Saikia [3], Ranjana Walker Minz [3], Vaishali Aggarwal [1], Prasad Taur [4], Ambreen Pandrowala [4], Vijaya Gowri [4], Mukesh Desai [4], Manasi Kulkarni [5], Gauri Hule [5], Umair Bargir [5], Priyanka Kambli [5], Manisha Madkaikar [5], Sagar Bhattad [6], Chetan Ginigeri [6], Harish Kumar [6], Ananthvikas Jayaram [7], Deenadayalan Munirathnam [8], Meena Sivasankaran [8], Revathi Raj [9], Ramya Uppuluri [9], Fouzia Na [10], Biju George [10], Harsha Prasada Lashkari [11], Manas Kalra [12], Anupam Sachdeva [12], Shishir Seth [13], Tapas Sabui [14], Aman Gupta [15], Karin van Leeuwen [16], Martin de Boer [16], Koon Wing Chan [17], Kohsuke Imai [18] [19], Osamu Ohara [20], Shigeaki Nonoyama [18], Yu Lung Lau [17], Surjit Singh [1]

Case Reports > IDCases. 2020 Dec 29:23:e01038. doi: 10.1016/j.idcr.2020.e01038. eCollection 2021.

BCGitis as the primary manifestation of chronic granulomatous disease

Nastaran Khalili [1] [2], Iraj Mohammadzadeh [3], Neda Khalili [1] [2], Raúl Jimenez Heredia [4], Samaneh Zoghi [4] [5] [6], Kaan Boztug [4] [5] [7], Nima Rezaei [8] [9] [10]

Mycobacterial disease	No of patients (Organism positive) (n = 44)	%
***Mycobacterium* sp.**	27 (2, non-tuberculous)	61.3
• Pneumonia	24	54.5
• Lymphadenitis	6	13.6
• Abdominal	2	4.5
• Osteomyelitis	2	4.5
• CNS	1	2.2
• Skin (Lupus vulgaris)	1	2.2
• Disseminated tuberculosis	9	20.4
BCG infection	17	38.6
• Localized BCG adenitis	13	29.5
• Disseminated BCG	4	9

Multicenter Study > J Clin Immunol. 2018 Apr;38(3):260-272. doi: 10.1007/s10875-018-0486-y. Epub 2018 Mar 20.

A Cohort of 169 Chronic Granulomatous Disease Patients Exposed to BCG Vaccination: a Retrospective Study from a Single Center in Shanghai, China (2004–2017)

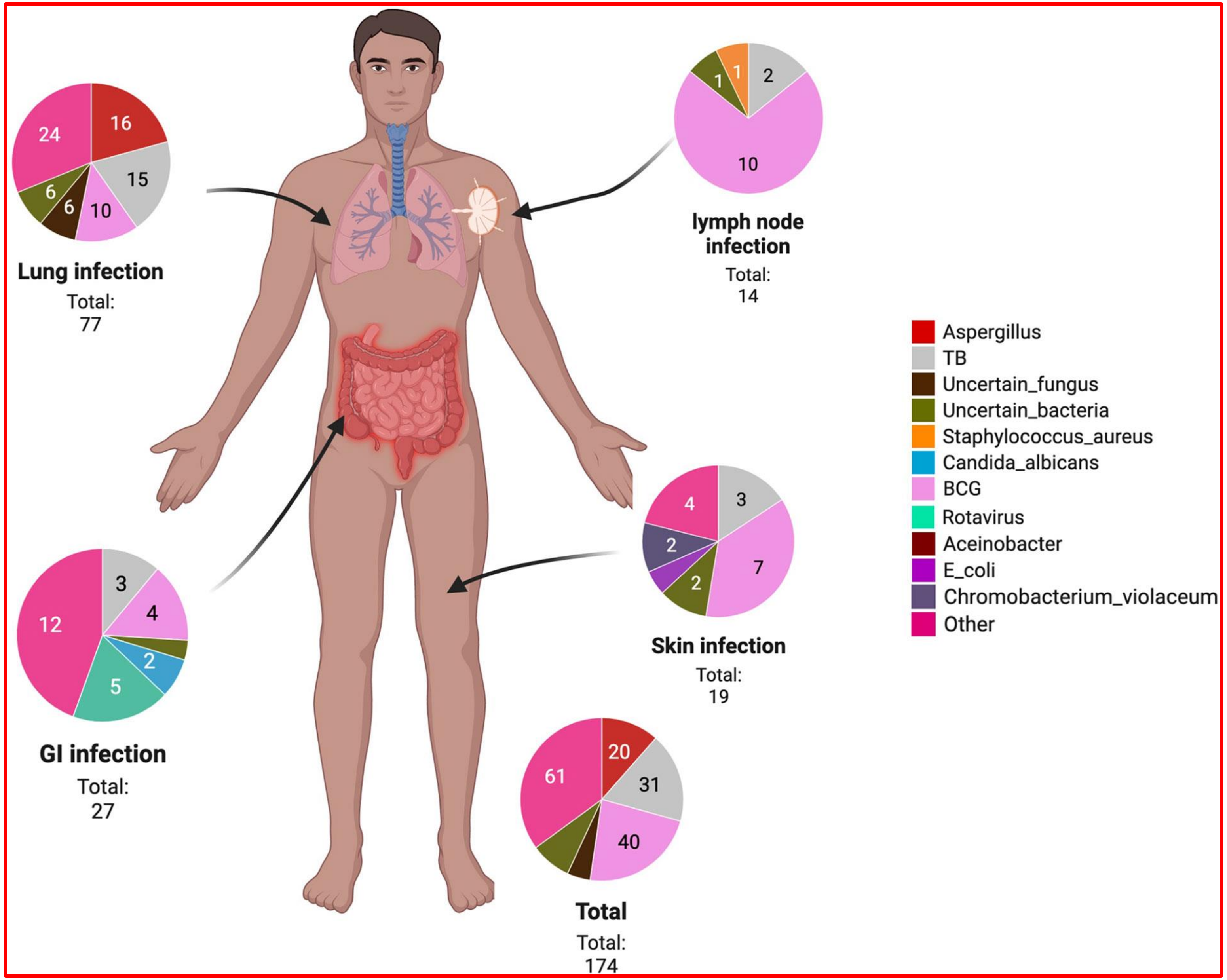
Qinhua Zhou [1], Xiaoying Hui [1], Wenjing Ying [1], Jia Hou [1], Wenjie Wang [1], Danru Liu [1], Ying Wang [1], Yeheng Yu [1], Jingyi Wang [1], Jinqiao Sun [1], Qian Zhang [2], Xiaochuan Wang [3]

- **Infections with mycobacteria have been reported in children with CGD, especially from countries where tuberculosis is endemic and BCG vaccine is given as a routine**

Mycobacterial infections in CGD patients in Hong Kong and China

Study, Year	No. of patients	BCG related complications	Tuberculosis
Lau YL et al, 1998 (Hong Kong)	**11**	-	**6/11 patients (54%)** • All had pulmonary tuberculosis • 2 had lymph node tuberculosis in addition
Lee et al, 2008 (China)	**17**	**BCG complications:** • Chronic ulceration, discharge, abnormal scarring at BCG injection: 7 • BCG adenitis: 4 • Dissemination: 2	**Tuberculosis: 7** • Culture proven: 6 • Dissemination: 3 • Recurrence: 3
Zhou et al, 2018 (China)	**169**	**130 received vaccination:** • Definitive BCG infection: 17/130 (13.1%) • Probable BCG infection: 60/130 (46.2%) • No BCG-related disease: 12/130 (9.2%) • Unknown status: 41/130 (31.5%)	

Common sites of infection in patients with CGD

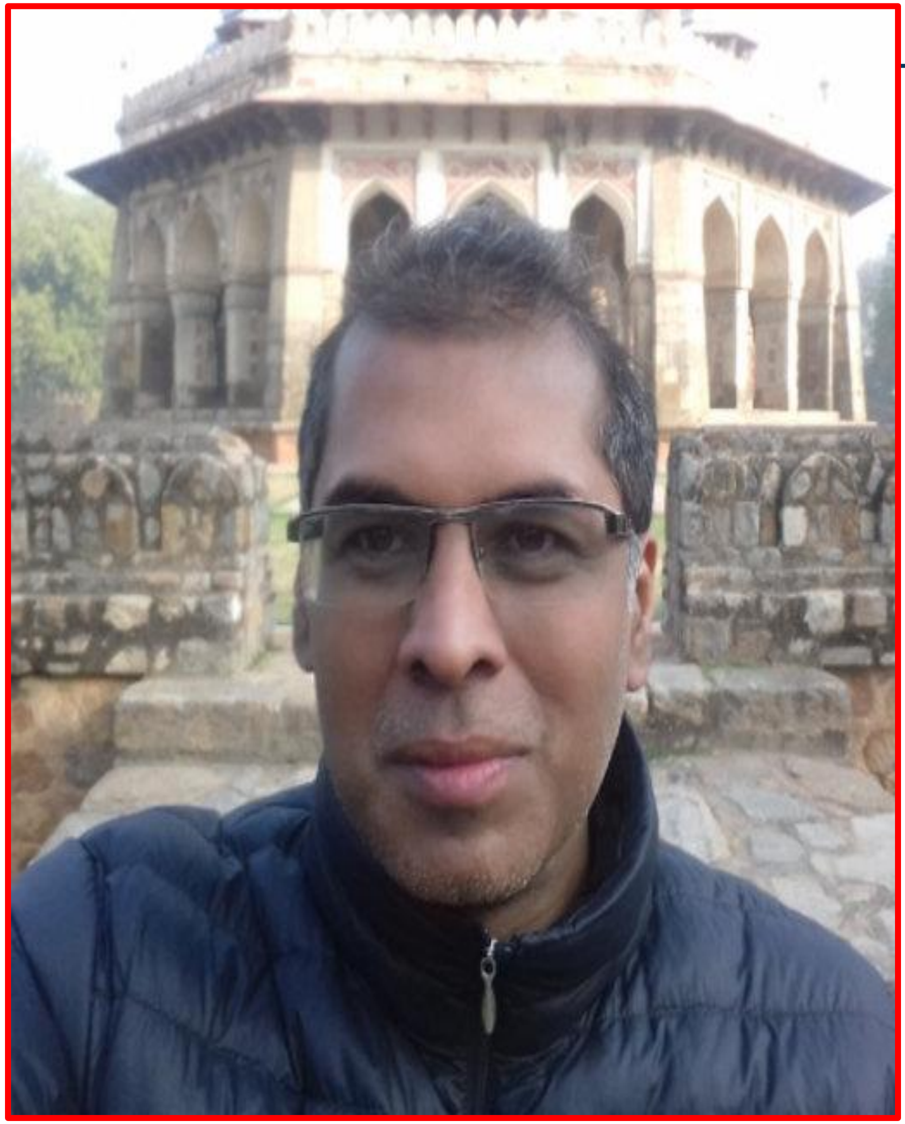


> Front Immunol. 2022 Jan 24:12:803763. doi: 10.3389/fimmu.2021.803763. eCollection 2021.

Phenomic Analysis of Chronic Granulomatous Disease Reveals More Severe Integumentary Infections in X-Linked Compared With Autosomal Recessive Chronic Granulomatous Disease

Timothy Lok-Hin Chiu [1], Daniel Leung [1], Koon-Wing Chan [1], Hok Man Yeung [1], Chung-Yin Wong [1], Huawei Mao [2], Jianxin He [3], Pandiarajan Vignesh [4], Weiling Liang [5], Woei Kang Liew [6], Li-Ping Jiang [7], Tong-Xin Chen [8], Xiang-Yuan Chen [9], Yin-Bo Tao [9], Yong-Bin Xu [10], Hsin-Hui Yu [11], Alta Terblanche [12], David Christopher Lung [13], Cheng-Rong Li [14], Jing Chen [15], Man Tian [16], Brian Eley [17], Xingtian Yang [1], Jing Yang [1], Wen Chin Chiang [6], Bee Wah Lee [18] [19], Deepti Suri [4], Amit Rawat [4], Anju Gupta [4], Surjit Singh [4], Wilfred Hing Sang Wong [1], Gilbert T Chua [1], Jaime Sou Da Rosa Duque [1], Kai-Ning Cheong [20], Patrick Chun-Yin Chong [21], Marco Hok-Kung Ho [21], Tsz-Leung Lee [20], Wanling Yang [1], Pamela P Lee [1], Yu Lung Lau [1]

Chandigarh, North India



Amit Rawat

Vignesh Pandiarajan

Chronic granulomatous disease

Multicenter Study > Front Immunol. 2021 Feb 25:12:625320. doi: 10.3389/fimmu.2021.625320. eCollection 2021.

Clinical, Immunological, and Molecular Profile of Chronic Granulomatous Disease: A Multi-Centric Study of 236 Patients From India

Amit Rawat [1], Pandiarajan Vignesh [1], Murugan Sudhakar [1], Madhubala Sharma [1], Deepti Suri [1], Ankur Jindal [1], Anju Gupta [1], Jitendra Kumar Shandilya [1], Sathish Kumar Loganathan [1], Gurjit Kaur [1], Sanchi Chawla [1], Pratap Kumar Patra [1], Alka Khadwal [2], Biman Saikia [3], Ranjana Walker Minz [3], Vaishali Aggarwal [1], Prasad Taur [4], Ambreen Pandrowala [4], Vijaya Gowri [4], Mukesh Desai [4], Manasi Kulkarni [5], Gauri Hule [5], Umair Bargir [5], Priyanka Kambli [5], Manisha Madkaikar [5], Sagar Bhattad [6], Chetan Ginigeri [6], Harish Kumar [6], Ananthvikas Jayaram [7], Deenadayalan Munirathnam [8], Meena Sivasankaran [8], Revathi Raj [9], Ramya Uppuluri [9], Fouzia Na [10], Biju George [10], Harsha Prasada Lashkari [11], Manas Kalra [12], Anupam Sachdeva [12], Shishir Seth [13], Tapas Sabui [14], Aman Gupta [15], Karin van Leeuwen [16], Martin de Boer [16], Koon Wing Chan [17], Kohsuke Imai [18] [19], Osamu Ohara [20], Shigeaki Nonoyama [18], Yu Lung Lau [17], Surjit Singh [1]

> J Clin Immunol. 2017 Apr;37(3):319-328. doi: 10.1007/s10875-017-0382-x. Epub 2017 Mar 22.

Infection Profile in Chronic Granulomatous Disease: a 23-Year Experience from a Tertiary Care Center in North India

Amit Rawat [1], Pandiarajan Vignesh [2], Avinash Sharma [2], Jitendra K Shandilya [2], Madhubala Sharma [2], Deepti Suri [2], Anju Gupta [2], Vikas Gautam [3], Pallab Ray [3], Shivaprakash M Rudramurthy [3], Arunaloke Chakrabarti [3], Kohsuke Imai [4], Shigeaki Nonoyama [4], Osamu Ohara [5], Yu L Lau [6], Surjit Singh [2]

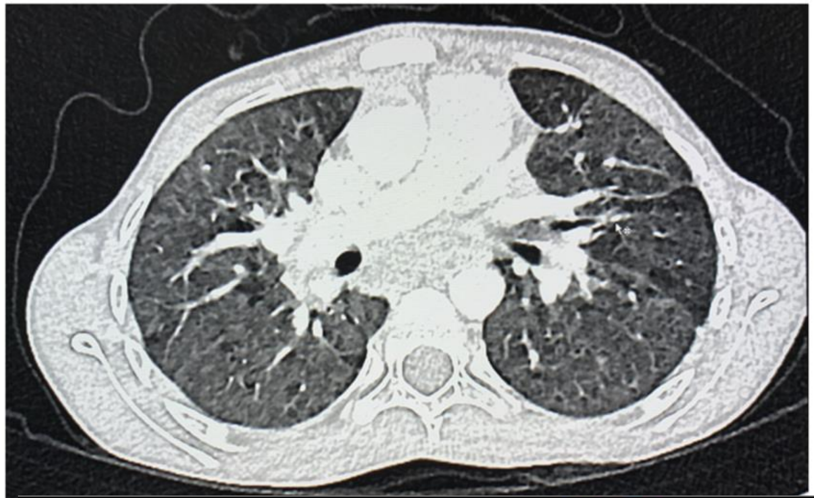
- Apart from signature organisms such as Aspergillus sp. and Staphylococcus sp., a ***high incidence of mycobacterial infections (18.5%)*** was documented in India
- Pulmonary infection due to ***Mucor*** **sp.** was documented in 2 patients
- Unusual bacteria documented with pneumonia include

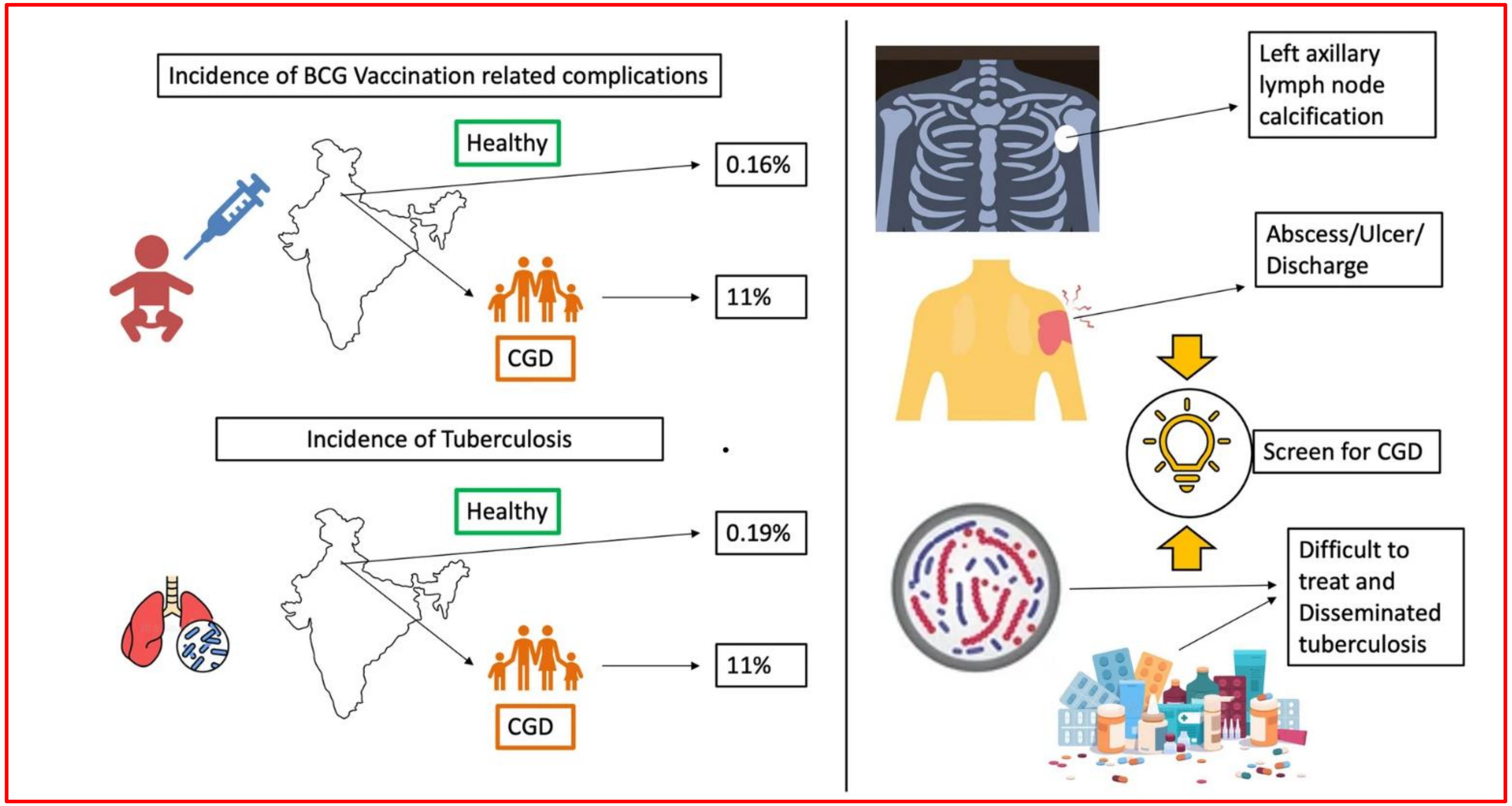
  Chryseobacterium gleum**,** ***Citrobacter*** **sp., and** ***Francisella noatuensis***

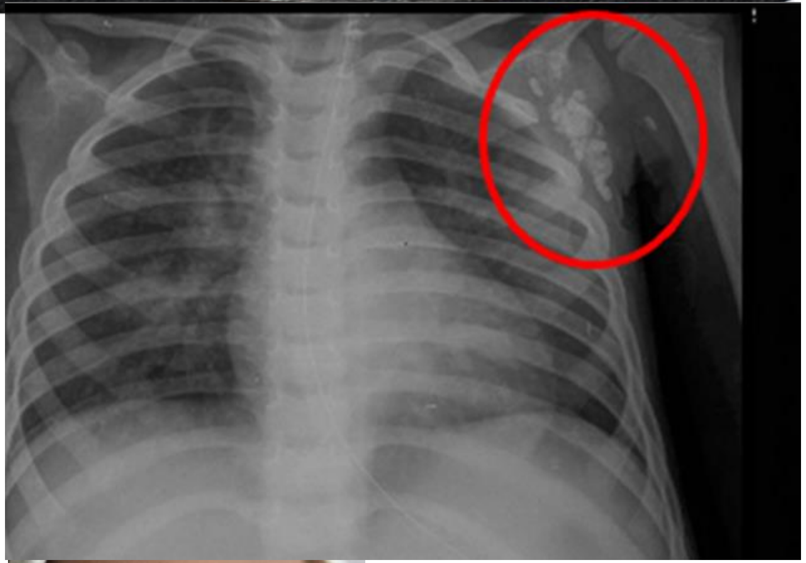
Review > J Clin Immunol. 2023 Nov;43(8):2049-2061. doi: 10.1007/s10875-023-01581-w.
Epub 2023 Sep 18.

Tuberculosis and Bacillus Calmette-Guérin Disease in Patients with Chronic Granulomatous Disease: an Experience from a Tertiary Care Center in North India

Pandiarajan Vignesh [1], Archan Sil [2], Ridhima Aggarwal [2], Wrik Laha [2], Sanjib Mondal [2], Manpreet Dhaliwal [2], Saniya Sharma [2], Rakesh Kumar Pilania [3], Ankur Kumar Jindal [2], Deepti Suri [2], Sunil Sethi [4], Amit Rawat [5], Surjit Singh [3]







Clin Immunol. 2023 Oct:255:109769. doi: 10.1016/j.clim.2023.109769. Epub 2023 Sep 11.

Infections due to Salmonella sp. in children with chronic granulomatous disease: Our experience from North India

Suprit Basu [1], Pandiarajan Vignesh [2], K Prithiviraj [1], Pallavi L Nadig [1], Aravind Sekar [3], Amit Rawat [1]

Pediatr Infect Dis J. 2023 Jul 1;42(7):e243-e245. doi: 10.1097/INF.0000000000003927. Epub 2023 Mar 31.

Stenotrophomonas maltophilia : An Emerging Pathogen in Chronic Granulomatous Disease

Ridhima Aggarwal [1], Sanjib Mondal [1], Archana Angrup [2], Pandiarajan Vignesh [3], Amit Rawat [3]

- 3/99 patients had blood stream infections with Salmonella sp.:
  - 1 patient had severe typhoidal sepsis despite cotrimoxazole prophylaxis
- **Vaccination with killed typhoidal vaccines should be given to children with CGD to avoid typhoidal bacteremia**

Case Reports J Clin Immunol. 2021 May;41(4):814-816. doi: 10.1007/s10875-020-00939-8. Epub 2021 Jan 16.

Aspergillus fumigatus Skull Bone Osteomyelitis and Native Valve Endocarditis in a Young Boy: an Unusual Presentation of Chronic Granulomatous Disease

Gummadi Anjani [1], Ankur Kumar Jindal [2], Ashwini Prithvi [1], Harsimran Kaur [3], Madhubala Sharma [1], Sanjeev Naganur [4], Pandiarajan Vignesh [1], Amit Rawat [1], Surjit Singh [1]

Case Reports J Clin Immunol. 2021 Feb;41(2):486-490. doi: 10.1007/s10875-020-00919-y. Epub 2020 Nov 20.

Infection Due to Serratia sp. in Chronic Granulomatous Disease-Is the Incidence Low in Tropical Countries?

Dharmagat Bhattarai [1], Aman Gupta [1], Pandiarajan Vignesh [2], Hitender Rao [1], Archana Angrup [3], Amit Rawat [1]

Review > Asian Pac J Allergy Immunol. 2013 Sep;31(3):217-26.

Endemic infections in Southeast Asia provide new insights to the phenotypic spectrum of primary immunodeficiency disorders

Pamela Pui-Wah Lee [1], Yu-Lung Lau

Review > Genes Dis. 2019 Sep 12;7(1):3-11. doi: 10.1016/j.gendis.2019.09.004. eCollection 2020 Mar.

Current status and prospects of primary immunodeficiency diseases in Asia

Rakesh Kumar Pilania [1], Himanshi Chaudhary [1], Ankur Kumar Jindal [1], Amit Rawat [1], Surjit Singh [1]

Melioidosis in CGD

Year	Locality	Gender	CGD type	Age at the time of melioidosis	Presentation
1971 (Tarlow)[33]	Caucasian residing in Singapore	Male	Unknown	2 years	Fever, irritability, meningism Membrane formation in pharynx, culture positive for *B. pseudomallei* Toe and finger abscesses, bone curettings positive for *B. pseudomallei*
Present report	Hong Kong	Male	X-CGD	40 years	Fulminant pulmonary melioidosis and systemic diseases
Present report	Singapore	Male	X-CGD	12 years	Fever, acute encephalopathy, right middle lobe pneumonia, *B. pseudomallei* bacteremia, multi-organ failure Younger brother died of *B. pseudomallei* septicemia at 2 years

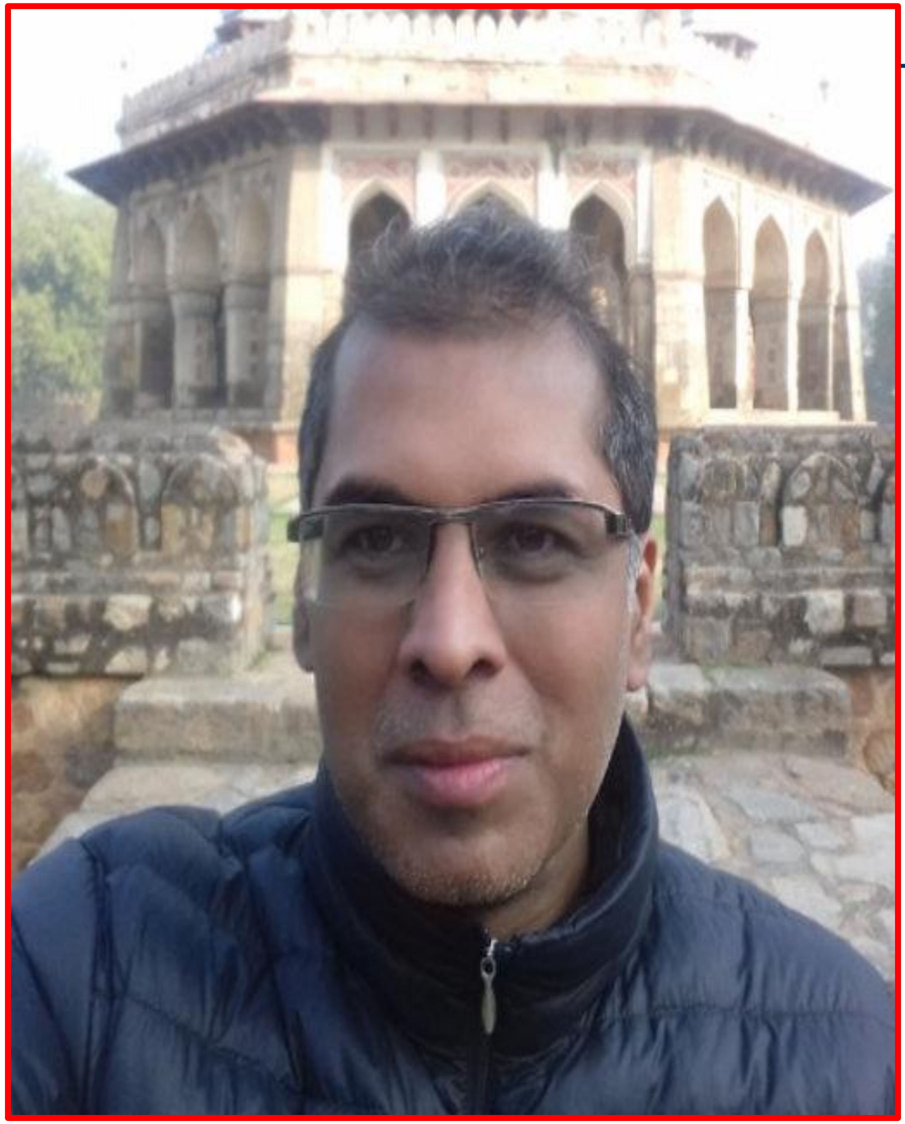
- **Chromobacterium violaceum** has been reported as signature organism for CGD in many Asian countries
- Initially reported in patients from Malaysia and later from Vietnam, Thailand, Sri Lanka, India, Hong Kong SAR and Taiwan
- **Mortality rates as high as 50% have been reported**

Common infections in CGD cohorts worldwide

Organisms isolated	Winkelstein et al, 2000, USA (n=368)	Van den Berg et al, 2009, European cohort (n=429)	Fattahi et al, 2011, Iran; (n=93)	Oliveira-Junior et al, 2015, LASID Registry; (n=71)	Marcino et al, 2015, USA; (n=268)	Blancas-Galicia et al, 2020, Mexico; (n=93)	Rawat et al, 2021, India; (n=236)
Staphylococcus aureus	12%	**30%**	7.5%	20.3%	**33%**	**53.7%**	**20.3%**
Pseudomonas sp	3%	2%	1.1%			19.3%	9.4%
Burkholderia sp	8%	1%			17%	10.7%	8.9%
Gram negative septicemia	**18%**	16% (Salmonella sp)	10.7%	**25.1%**	**33%**	**54.8%**	13.5%
Aspergillus fumigatus	**41%**	**26%**	**18.3%**	13%	**46%**	32.3%	**16.9%**
Mycobacteria	4%	8%	**55.9%**	**30.4%**		**53.4%**	**18.5%**

X-linked agammaglobulinemia

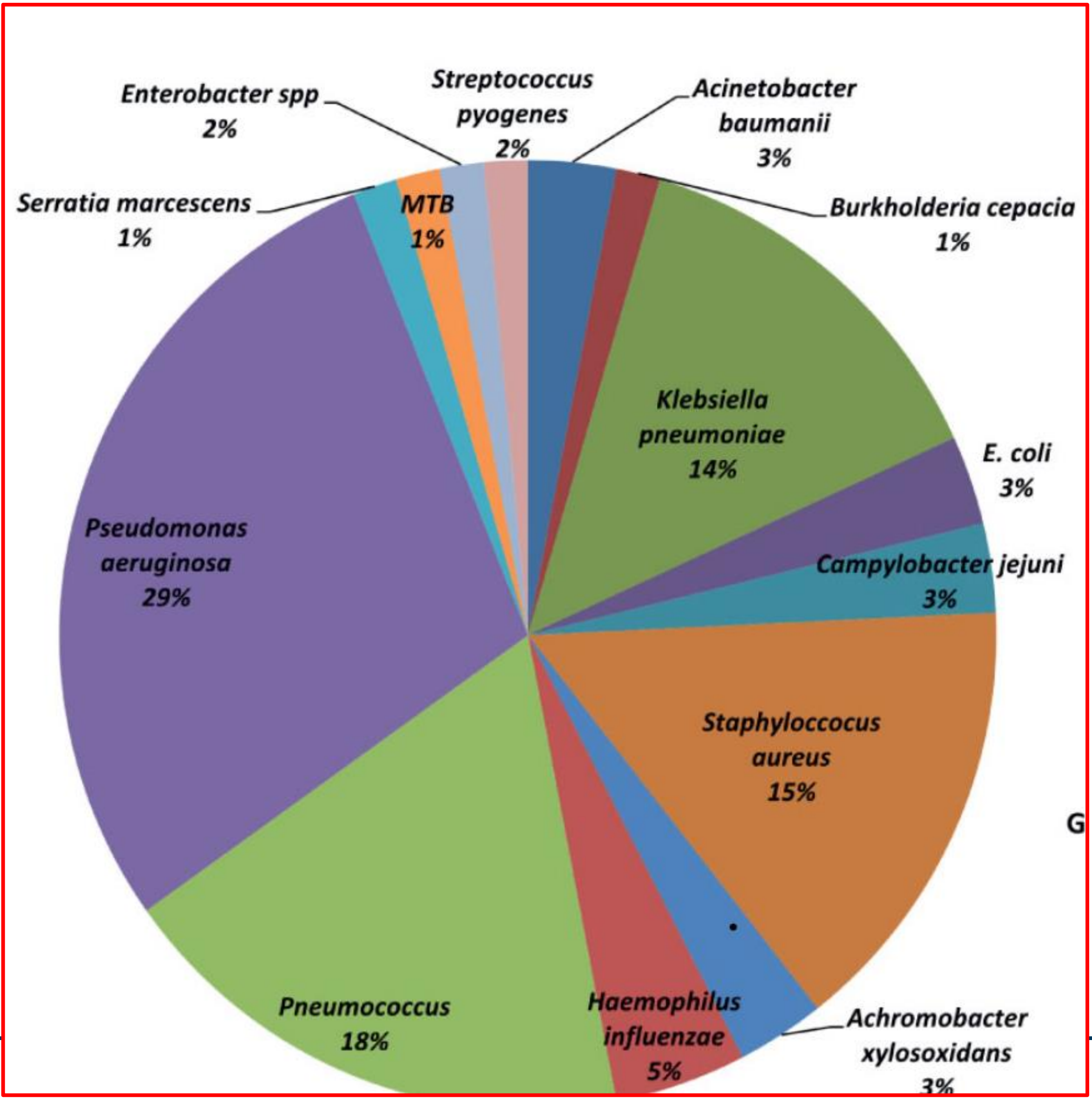
Chandigarh, North India



Amit Rawat

Ankur Jindal

X linked agammaglobulinemia



Multicenter Study > Front Immunol. 2021 Jan 15:11:612323. doi: 10.3389/fimmu.2020.612323. eCollection 2020.

Clinical and Genetic Profile of X-Linked Agammaglobulinemia: A Multicenter Experience From India

Amit Rawat [1], Ankur Kumar Jindal [1], Deepti Suri [1], Pandiarajan Vignesh [1], Anju Gupta [1], Biman Saikia [2], Ranjana W Minz [2], Aaqib Zaffar Banday [1], Rahul Tyagi [1], Kanika Arora [1], Vibhu Joshi [1], Sanjib Mondal [1], Jitendra Kumar Shandilya [1], Madhubala Sharma [1], Mukesh Desai [3], Prasad Taur [3], Ambreen Pandrowala [4], Vijaya Gowri [3], Sneha Sawant-Desai [5], Maya Gupta [5], Aparna Dhondi Dalvi [5], Manisha Madkaikar [5], Amita Aggarwal [6], Revathi Raj [7], Ramya Uppuluri [7], Sagar Bhattad [8], Ananthvikas Jayaram [9], Harsha Prasad Lashkari [10], Liza Rajasekhar [11], Deenadayalan Munirathnam [12], Manas Kalra [13], Anuj Shukla [14], Ruchi Saka [1], Rajni Sharma [1], Ravinder Garg [1], Kohsuke Imai [15], Shigeaki Nonoyama [16], Osamu Ohara [17], Pamela P Lee [18], Koon Wing Chan [18], Yu-Lung Lau [18], Surjit Singh [1]

- ***Pseudomonas aeruginosa***, followed by ***Streptococcus pneumoniae, Staphylococcus aureus*** and ***Klebsiella pneumoniae*** were the most common organisms
- *While Pseudomonas aeruginosa is not a signature organism for XLA patients, it was noted that patients with XLA who have had episodes of neutropenia are at increased risk of Pseudomonas sepsis*

Common infections in XLA cohorts worldwide

Author	Common infections
Rawat et al. (India), 2021, (n=145)	*Pseudomonas aeruginosa* (overall) Giardia (diarrhea)
Yeh et al. (Taiwan), 2020, (n=29)	*Pseudomonas aeruginosa* (overall)
Lougaris et al. (Italy), 2020, (n=168)	*Hemophilus influenzae* followed by *Streptococcus pneumoniae*
Aadam et al. (North Africa), 2016, (n=50)	*Pseudomonas aeruginosa* (overall)
García et al. , (Mexico), 2016, (n=26)	*Pseudomonas sp.* (overall)
Winkelstein et al. (USA), 2006, (n=201)	Pneumococcus (pneumonia) Giardia (diarrhea) Pseudomonas (sepsis)

J Neuroimmunol. 2022 Oct 15:371:577952. doi: 10.1016/j.jneuroim.2022.577952. Epub 2022 Aug 18.

Meningoencephalitis in primary antibody deficiency: Our experience from northwest India

Ankur Kumar Jindal [1], Himanshi Chaudhary [2], Rahul Tyagi [2], Amit Rawat [2], Deepti Suri [2], Pratap Kumar Patra [2], Kanika Arora [2], Sanchi Chawla [2], Sameer Vyas [3], Munish Arora [2], Ridhima Aggarwal [2], Suprit Basu [2], Reema Bansal [4], Man Updesh Singh Sachdeva [5], Anju Gupta [2], Vignesh Pandiarajan [2], Naveen Sankhyan [6], Renu Suthar [6], Jitendra Kumar Sahu [6], Mini Singh [7], Reeta Mani [8], Rajni Sharma [2], Ruchi Saka [2], Kohsuke Imai [9], Osamu Ohara [10], Shigeaki Nonoyama [11], Lennart Hammarström [12], Koon Wing Chan [13], Yu Lung Lau [13], Surjit Singh [2]

- **Meningoencephalitis is usually caused by enteroviruses (e.g., echovirus, coxsackievirus, and poliovirus)**
- 13/135 patients had meningoencephalitis (5 with XLA, 7 with CVID and 1 NEMO defect)
- Herpes simplex virus, Cytomegalovirus, and Streptococcus pneumoniae were isolated in 1 patient each
- Eight patients in the present series have died, 3 have recovered with varying degrees of neurological sequelae and 2 patients are showing gradual recovery

Front Cell Infect Microbiol. 2021; 11: 807136. PMCID: PMC8855360
Published online 2022 Feb 4. doi: 10.3389/fcimb.2021.807136 PMID: 35186782

Infections With Enterohepatic Non-*H. pylori Helicobacter* Species in X-Linked Agammaglobulinemia: Clinical Cases and Review of the Literature

Carolina Romo-Gonzalez,[1] Juan Carlos Bustamante-Ogando,[2] Marco Antonio Yamazaki-Nakashimada,[3] Francisco Aviles-Jimenez,[4] Francisco Otero-Mendoza,[5] Francisco Javier Espinosa-Rosales,[6] Sara Elva Espinosa-Padilla,[2] Selma Cecilia Scheffler Mendoza,[3] Carola Durán-McKinster,[7] Maria Teresa García-Romero,[7] Marimar Saez-de-Ocariz,[7] and Gabriela Lopez-Herrera[2,*]

- Of 21 cases, Helicobacter cinaedi was present in 8 cases and Helicobacter bilis in 8
- Other species included H. fennelliae, H. equorum, H. canis and H. canadiensis
- Infections in these patients were frequently associated with cellulitis that progressed to sepsis and, in some cases, to pyoderma gangrenosum-like ulcers or osteomyelitis
- Cholangitis, abdominal abscess, and pleurisy was reported in 1 case each

Kuala Lumpur, Malaysia

Intan Hakimah Ismail

IP

Ulcerative skin lesion of a patient with X-linked agammaglobulinemia (XLA) due to *Helicobacter sp.* infection

> Front Immunol. 2023 Sep 22:14:1252765. doi: 10.3389/fimmu.2023.1252765. eCollection 2023.

Clinical features and mutational analysis of X-linked agammaglobulinemia patients in Malaysia

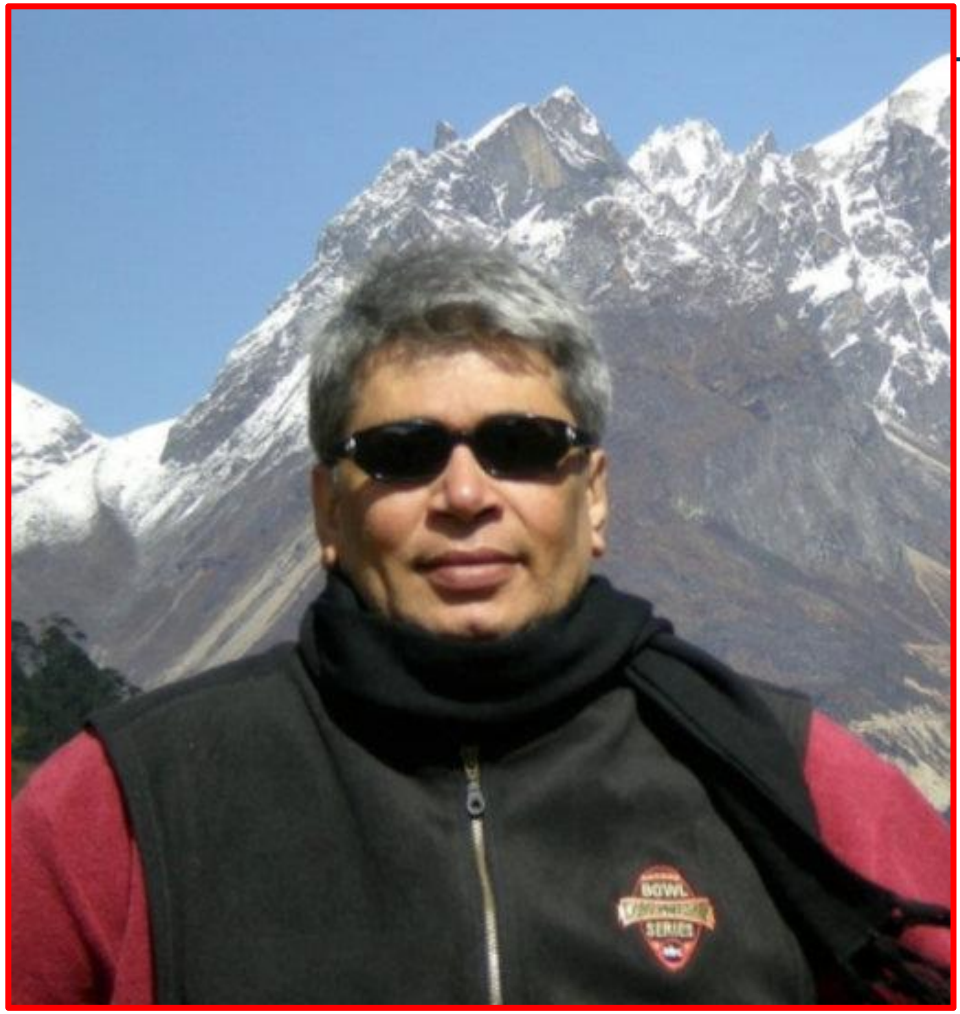
Chai Teng Chear [1], Intan Hakimah Ismail [2], Kwai Cheng Chan [3], Lokman Mohd Noh [4], Asiah Kassim [4], Amir Hamzah Abdul Latiff [5], Sandeep Singh Gill [6], Nazatul Haslina Ramly [4], Kah Kee Tan [7], Charlotte Sundaraj [8], Chong Ming Choo [9], Sharifah Adlena Syed Mohamed [10], Mohd Farid Baharin [1], Amelia Suhana Zamri [1], Sharifah Nurul Husna Syed Yahya [1], Saharuddin Bin Mohamad [11] [12], Adiratna Mat Ripen [1]

Mendelian susceptibility to mycobacterial disease (MSMD)

MSDM

- Increased susceptibility to intracellular pathogens like mycobacteria (including Mycobacterium bovis, nontuberculous mycobacteria), Salmonella sp., fungi and parasites (e.g. Leishmania)

Mumbai, Western India



Mukesh Desai

Manisha Madkaikar

> Front Immunol. 2021 Feb 25:12:631298. doi: 10.3389/fimmu.2021.631298. eCollection 2021.

Clinical and Molecular Findings in Mendelian Susceptibility to Mycobacterial Diseases: Experience From India

Prasad D Taur [1], Vijaya Gowri [1], Ambreen Abdulwahab Pandrowala [1], Vaishnavi V Iyengar [1], Akshaya Chougule [1], Zainab Golwala [1], Shraddha Chandak [1], Reepa Agarwal [1], Purva Keni [1], Neha Dighe [1], Minnie Bodhanwala [1], Shakuntala Prabhu [1], Biju George [2], N A Fouzia [2], Eunice Sindhuvi Edison [2], Arun Kumar Arunachalam [2], Manisha Rajan Madkaikar [3], Aparna Dhondi Dalvi [3], Reetika Malik Yadav [3], Umair Ahmed Bargir [3], Priyanka Madhav Kambli [3], Amit Rawat [4], Jhumki Das [4], Vibhu Joshi [4], Rakesh Kumar Pilania [4], Ankur Kumar Jindal [4], Sunil Bhat [5], Sagar Bhattad [6], Jeeson Unni [6], Nita Radhakrishnan [7], Revathi Raj [8], Ramya Uppuluri [8], Shivani Patel [8], Harsha Prasada Lashkari [9], Amita Aggarwal [10], Manas Kalra [11], Zarir Udwadia [12], Vibha Sanjay Bafna [13], Tarun Kanade [14], Anne Puel [15 16 17], Jacinta Bustamante [15 16 17 18], Jean Laurent Casanova [15 16 17 19], Mukesh M Desai [1]

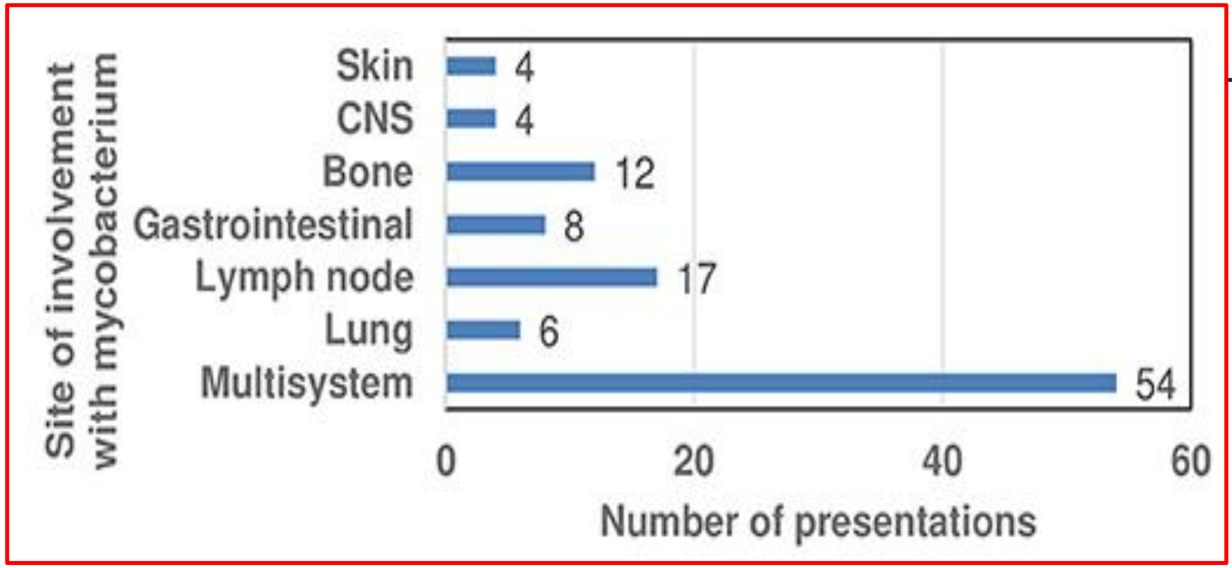
Review > Expert Rev Clin Immunol. 2021 Oct;17(10):1103-1120.

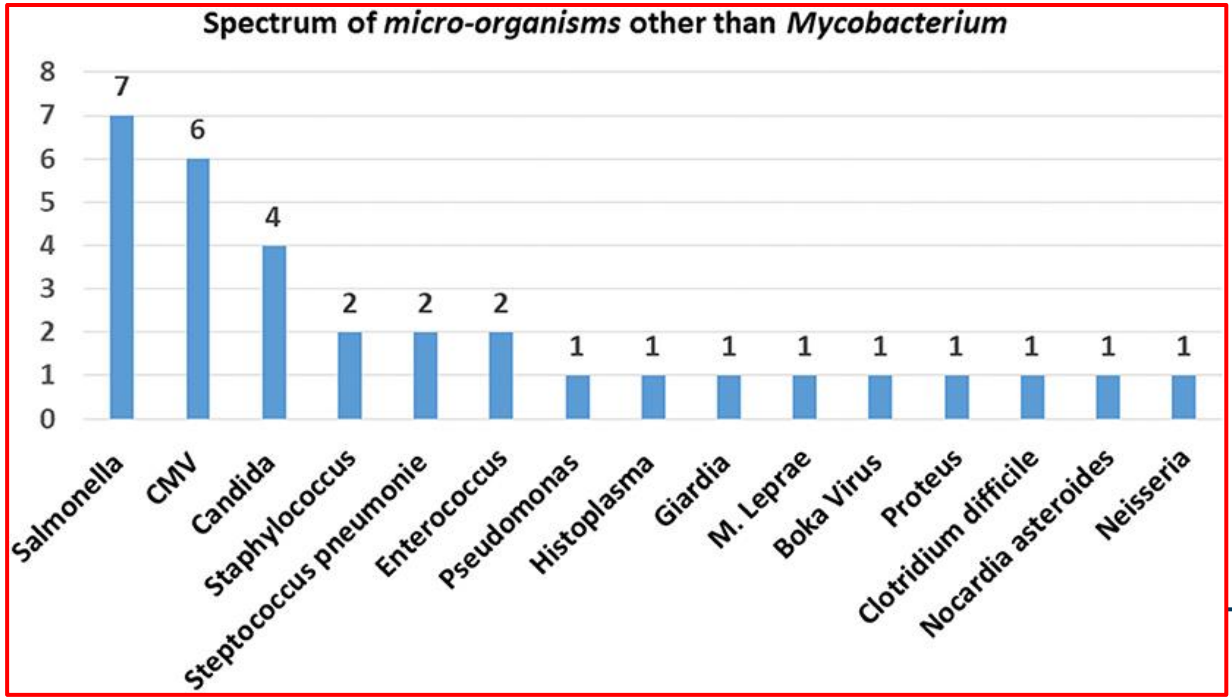
doi: 10.1080/1744666X.2021.1956314.

An updated review on Mendelian susceptibility to mycobacterial diseases- a silver jubilee celebration of its first genetic diagnosis

Jhumki Das [1], Aaqib Zaffar Banday [1], Jitendra Shandilya [1], Madhubala Sharma [1], Pandiarajan Vignesh [1], Amit Rawat [1]

- All patients (n=55) had mycobacterial disease
- **MTB complex (96%) and NTM (4%)**
- Multisystem involvement with mycobacteria was the commonest followed by lymph node involvement, tubercular osteomyelitis, pulmonary, skin, and CNS involvement in decreasing order of frequency
- **36% of patients in the cohort were infected with more than one organism**


Site of involvement with mycobacterium
Skin 4
CNS 4
Bone 12
Gastrointestinal 8
Lymph node 17
Lung 6
Multisystem 54
0
20
40
60
Number of presentations


Spectrum of micro-organisms other than Mycobacterium
0
1
2
3
4
5
6
7
8
Salmonella 7
CMV 6
Candida 4
Staphylococcus 2
Steptococcus pneumonie 2
Enterococcus 2
Pseudomonas 1
Histoplasma 1
Giardia 1
M. Leprae 1
Boka Virus 1
Proteus 1
Clotridium difficile 1
Nocardia asteroides 1
Neisseria 1

Case Reports > Indian J Tuberc. 2021 Apr;68(2):292-297. doi: 10.1016/j.ijtb.2020.07.027. Epub 2020 Jul 30.

Clinical and immunological profile of children with Mendelian Susceptibility to Mycobacterial Diseases (MSMD) from an Indian tertiary care hospital

C K Indumathi [1], Jacinta Bustamante [2]

4 children with mycobacterial disease

- 3 had M. bovis infection
- 1 had M. chelonae infection
- 1 also had S. typhimurium infecion

Case Reports > J Clin Immunol. 2015 Jul;35(5):459-62. doi: 10.1007/s10875-015-0173-1. Epub 2015 Jun 9.

Disseminated Mycobacterium avium complex infection in a child with partial dominant interferon gamma receptor 1 deficiency in India

Varun K Sharma [1], Gautham Pai, Caroline Deswarte, Rakesh Lodha, Sarman Singh, Liew Woei Kang, Chong Chia Yin, Jean-Laurent Casanova, Jacinta Bustamante, Sushil K Kabra

> Pediatr Allergy Immunol. 2023 Sep;34(9):e14027. doi: 10.1111/pai.14027.

Disseminated Mycobacterium fortuitum infection in a young girl with IFN-γR1 defect masquerading as histiocytosis

Archan Sil [1], Suprit Basu [1], Jhumki Das [1], Sunil Sethi [2], Debajyoti Chatterjee [3], Pandiarajan Vignesh [1], Deepti Suri [1], Ankur Kumar Jindal [1]

Heliyon. 2023 Dec; 9(12): e22632. PMCID: PMC1069618

Published online 2023 Nov 25. doi: 10.1016/j.heliyon.2023.e22632 PMID: 3805843

Adult-onset Mendelian Susceptibility to Mycobacterial Diseases: A case report and systematic literature review

Yang Yang,[a,1] Lu Xia,[a,1] and Shuihua Lu[b,*]

Severe combined immunodeficiency (SCID)

Hong Kong

Yu Lung Lau

Pamela Lee

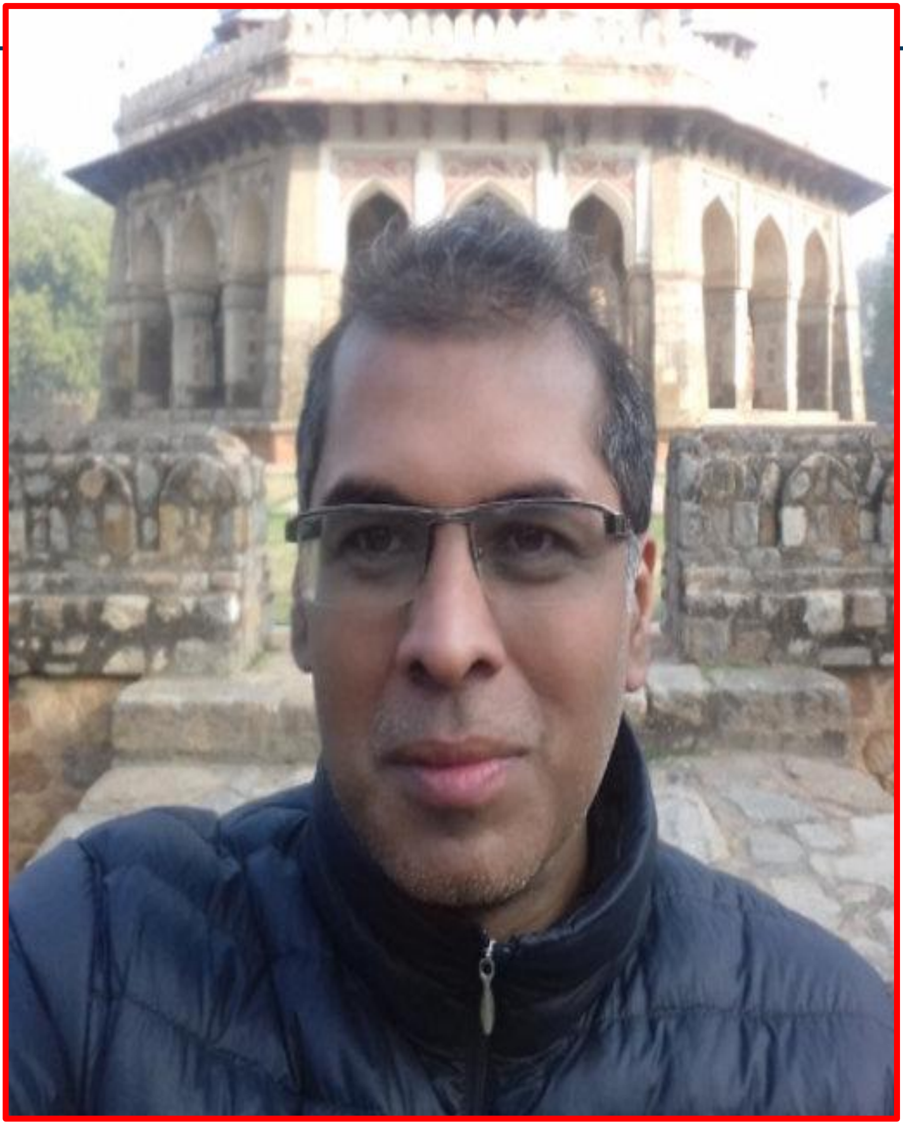
J Clin Immunol. 2011 Apr;31(2):281-96. doi: 10.1007/s10875-010-9489-z. Epub 2010 Dec 24.

Molecular diagnosis of severe combined immunodeficiency--identification of IL2RG, JAK3, IL7R, DCLRE1C, RAG1, and RAG2 mutations in a cohort of Chinese and Southeast Asian children

Pamela P W Lee [1], Koon-Wing Chan, Tong-Xin Chen, Li-Ping Jiang, Xiao-Chuan Wang, Hua-Song Zeng, Xiang-Yuan Chen, Woei-Kang Liew, Jing Chen, Kit-Man Chu, Lee-Lee Chan, Lynette Shek, Anselm C W Lee, Hsin-Hui Yu, Qiang Li, Chen-Guang Xu, Geraldine Sultan-Ugdoracion, Zarina Abdul Latiff, Amir Hamzah Abdul Latiff, Orathai Jirapongsananuruk, Marco H K Ho, Tsz-Leung Lee, Xi-Qiang Yang, Yu-Lung Lau

- **Pneumonia and chronic diarrhea were the most common infections**
- **BCG complications seen in 10/42 patients (23.8 %):** abscess (n = 6), axillary adenopathy (n = 3), disseminated BCG (n = 3)

- 2 had disseminated Cytomegalovirus disease
- 2 had Pneumocytis jiroveci pneumonia
- 1 had Pulmonary aspergillosis
- 12 (28.6%) had persistent oral candidiasis
- 2 had candidemia



Chandigarh, North India

Vignesh Pandiarajan

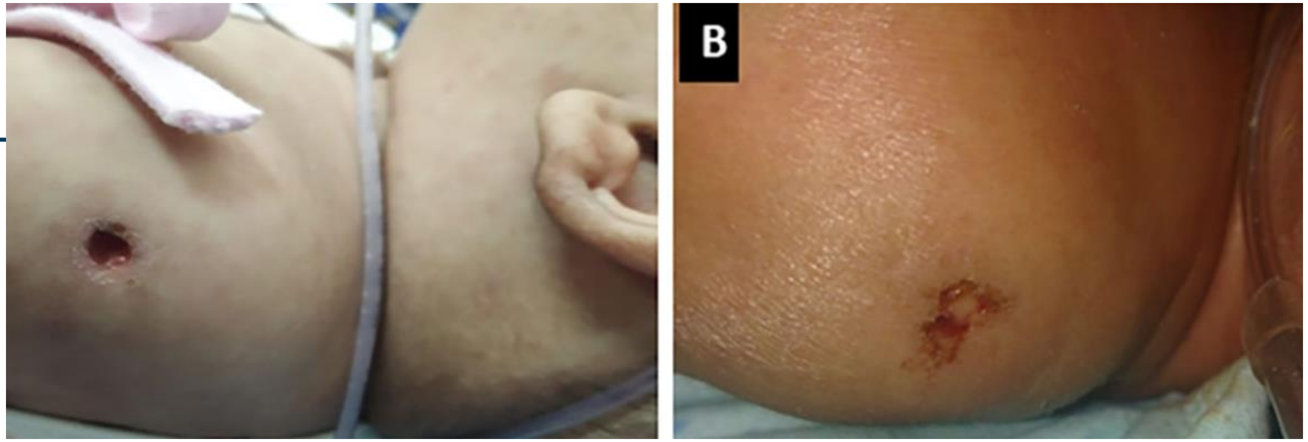
Amit Rawat

Multicenter Study > Front Immunol. 2021 Feb 8:11:619146. doi: 10.3389/fimmu.2020.619146. eCollection 2020.

Clinical, Immunological, and Molecular Features of Severe Combined Immune Deficiency: A Multi-Institutional Experience From India

Pandiarajan Vignesh [1], Amit Rawat [1], Rajni Kumrah [1], Ankita Singh [1], Anjani Gummadi [1], Madhubala Sharma [1], Anit Kaur [1], Johnson Nameirakpam [1], Ankur Jindal [1], Deepti Suri [1], Anju Gupta [1], Alka Khadwal [2], Biman Saikia [3], Ranjana Walker Minz [3], Kaushal Sharma [1], Mukesh Desai [4], Prasad Taur [4], Vijaya Gowri [4], Ambreen Pandrowala [5], Aparna Dalvi [6], Neha Jodhawat [6], Priyanka Kambli [6], Manisha Rajan Madkaikar [6], Sagar Bhattad [7], Stalin Ramprakash [8], Raghuram Cp [8], Ananthvikas Jayaram [9], Meena Sivasankaran [1], Deenadayalan Munirathnam [10], Sarath Balaji [11], Aruna Rajendran [11], Amita Aggarwal [12], Komal Singh [12], Fouzia Na [13], Biju George [13], Ankit Mehta [14], Harsha Prasada Lashkari [15], Ramya Uppuluri [16], Revathi Raj [16], Sandip Bartakke [17], Kirti Gupta [18], Sreejesh Sreedharanunni [19], Yumi Ogura [20], Tamaki Kato [20], Kohsuke Imai [20] [21], Koon Wing Chan [22], Daniel Leung [22], Osamu Ohara [23], Shigeaki Nonoyama [20], Michael Hershfield [24], Yu-Lung Lau [22], Surjit Singh [1]

N=277



BCG site ulceration and pus discharge

- Opportunistic infections were the presenting manifestation in most patients
- These included pneumonia (82%), diarrhea (43.7%), oral thrush (18.4%), BCG site ulceration (17%), otitis media (12.6%), and meningitis (4%)

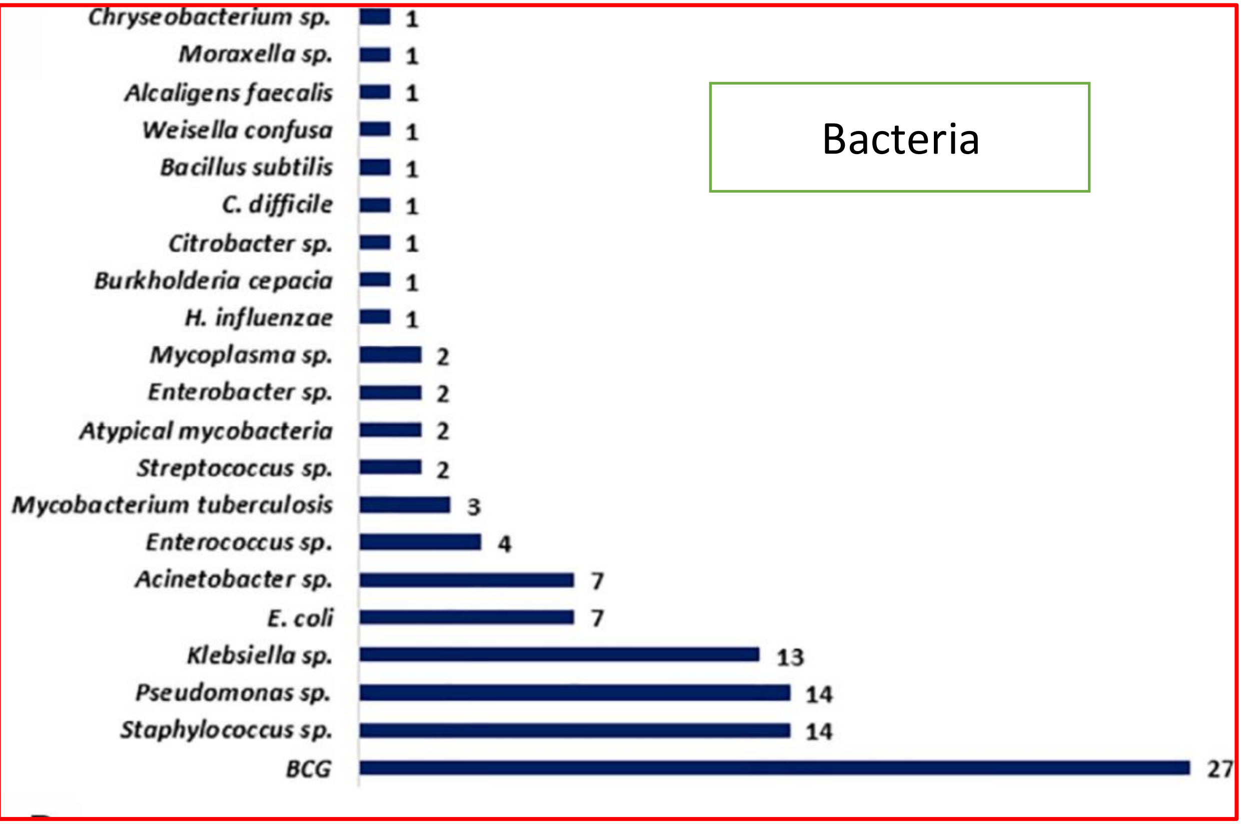
- Blood culture proven septicemia: 63 (23%)
- Disseminated CMV infection: 23 (8.3%)
- CMV retinitis: 6 (0.02%)

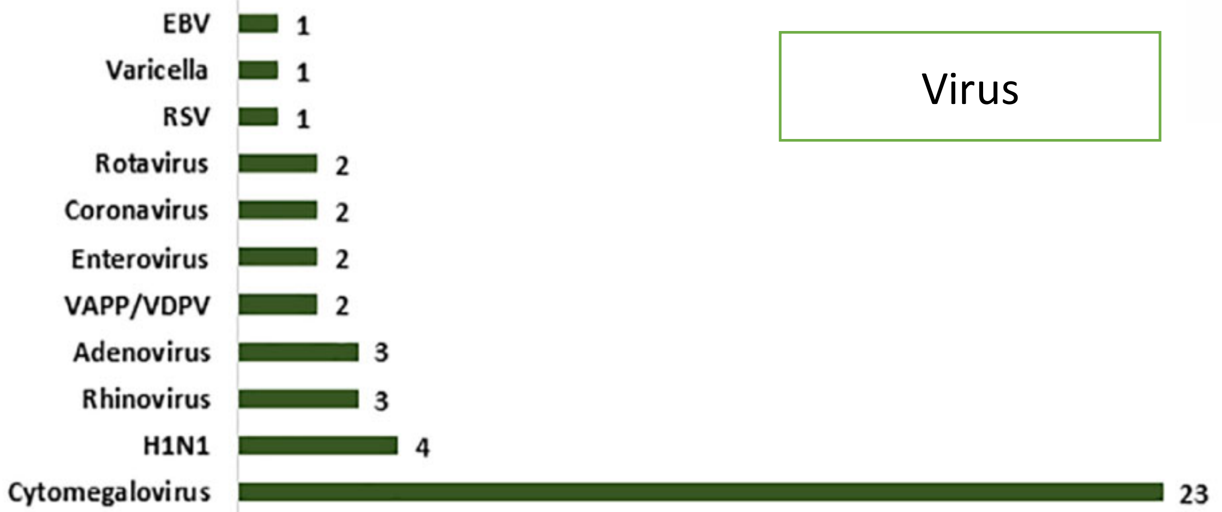
- Intestinal lymphangiectasia due to CMV was noted on autopsy of a child with X-linked SCID
- Prolonged excretion of vaccine-derived poliovirus in a child with leaky SCID

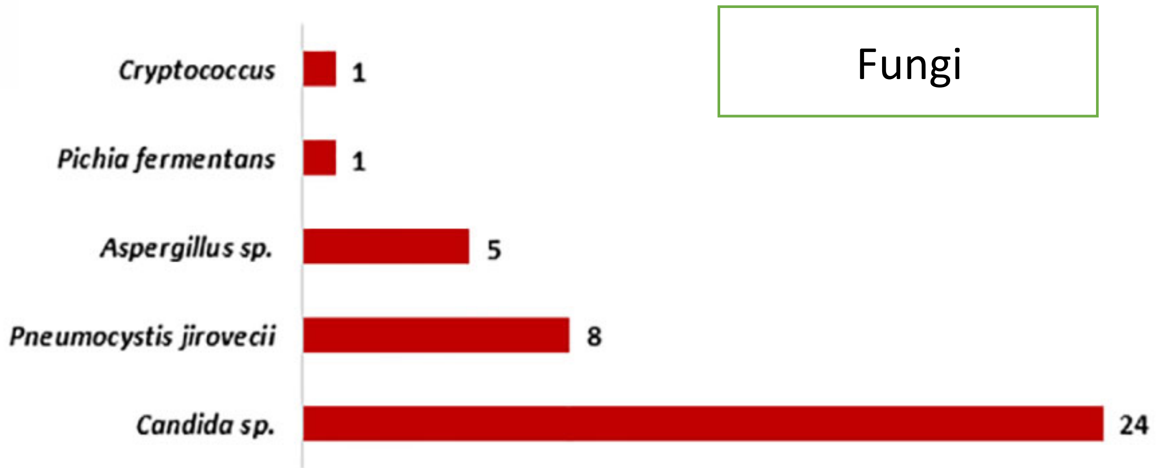
Multicenter Study > Front Immunol. 2021 Feb 8:11:619146. doi: 10.3389/fimmu.2020.619146. eCollection 2020.

Clinical, Immunological, and Molecular Features of Severe Combined Immune Deficiency: A Multi-Institutional Experience From India

Pandiarajan Vignesh [1], Amit Rawat [1], Rajni Kumrah [1], Ankita Singh [1], Anjani Gummadi [1], Madhubala Sharma [1], Anit Kaur [1], Johnson Nameirakpam [1], Ankur Jindal [1], Deepti Suri [1], Anju Gupta [1], Alka Khadwal [2], Biman Saikia [3], Ranjana Walker Minz [3], Kaushal Sharma [1], Mukesh Desai [4], Prasad Taur [4], Vijaya Gowri [4], Ambreen Pandrowala [5], Aparna Dalvi [6], Neha Jodhawat [6], Priyanka Kambli [6], Manisha Rajan Madkaikar [6], Sagar Bhattad [7], Stalin Ramprakash [8], Raghuram Cp [8], Ananthvikas Jayaram [9], Meena Sivasankaran [10], Deenadayalan Munirathnam [10], Sarath Balaji [11], Aruna Rajendran [11], Amita Aggarwal [12], Komal Singh [12], Fouzia Na [13], Biju George [13], Ankit Mehta [14], Harsha Prasada Lashkari [15], Ramya Uppuluri [16], Revathi Raj [16], Sandip Bartakke [17], Kirti Gupta [18], Sreejesh Sreedharanunni [19], Yumi Ogura [20], Tamaki Kato [20], Kohsuke Imai [20] [21], Koon Wing Chan [22], Daniel Leung [22], Osamu Ohara [23], Shigeaki Nonoyama [20], Michael Hershfield [24], Yu-Lung Lau [22], Surjit Singh [1]







Mumbai, Western India

Mukesh Desai

Manisha Madkaikar

> Front Immunol. 2019 Feb 4:10:23. doi: 10.3389/fimmu.2019.00023. eCollection 2019.

Clinical, Immunological, and Molecular Findings in 57 Patients With Severe Combined Immunodeficiency (SCID) From India

Jahnavi Aluri [1], Mukesh Desai [2], Maya Gupta [1], Aparna Dalvi [1], Antony Terance [3], Sergio D Rosenzweig [4], Jennifer L Stoddard [4], Julie E Niemela [4], Vasundhara Tamankar [5], Snehal Mhatre [1], Umair Bargir [1], Manasi Kulkarni [1], Nitin Shah [6], Amita Aggarwal [7], Harsha Prasada Lashkari [8], Vidya Krishna [9], Geeta Govindaraj [10], Manas Kalra [11], Manisha Madkaikar [1]

- Most common clinical manifestations were **pneumonia (66%), failure to thrive (60%), chronic diarrhea (35%), gastrointestinal infection (21%), oral candidiasis (21%) and BCG-osis (12%)**

Bacteria:
- *Staphylococcus aureus* (*n* = 2)
- *Klebsiella pneumoniae* (*n* = 8)
- *Pseudomonas aeruginosa* (*n* =4)
- *Burkholderia sp.* (*n* =1)
- *Chryseobacterium sp.* (*n* = 1)

Viruses:
- Rotavirus (*n* = 1)
- Cytomegalovirus (*n* = 2)
- Rubella (*n* = 1)
- RSV (*n* = 1)
- Varicella (*n* = 1)

Fungi:
- Pneumocystis jiroveci (*n* = 1)

Leukocyte adhesion deficiency (LAD)

Multicenter Study > Front Immunol. 2020 Dec 16:11:612703. doi: 10.3389/fimmu.2020.612703. eCollection 2020.

Clinical and Genetic Spectrum of a Large Cohort of Patients With Leukocyte Adhesion Deficiency Type 1 and 3: A Multicentric Study From India

Priyanka Madhav Kambli[1], Umair Ahmed Bargir[1], Reetika Malik Yadav[1], Maya Ravishankar Gupta[1], Aparna Dhondi Dalvi[1], Gouri Hule[1], Madhura Kelkar[1], Sneha Sawant-Desai[1], Priyanka Setia[1], Neha Jodhawat[1], Nayana Nambiar[1], Amruta Dhawale[1], Pallavi Gaikwad[1], Shweta Shinde[1], Prasad Taur[2], Vijaya Gowri[2], Ambreen Pandrowala[3], Anju Gupta[4], Vibhu Joshi[4], Madhubala Sharma[4], Kanika Arora[4], Rakesh Kumar Pilania[4], Himanshi Chaudhary[4], Amita Agarwal[5], Shobita Katiyar[5], Sagar Bhattad[6], Stalin Ramprakash[7], Raghuram Cp[7], Ananthvikas Jayaram[8], Vinod Gornale[9], Revathi Raj[10], Ramya Uppuluri[10], Meena Sivasankaran[11], Deenadayalan Munirathnam[11], Harsha Prasad Lashkari[12], Manas Kalra[13], Anupam Sachdeva[13], Avinash Sharma[14], Sarath Balaji[15], Geeta Madathil Govindraj[16], Sunil Karande[17], Ruchi Nanavati[18], Mamta Manglani[19], Girish Subramanyam[20], Abhilasha Sampagar[21], Indumathi Ck[22], Parinitha Gutha[23], Swati Kanakia[24], Shiv Prasad Mundada[25], Vidya Krishna[26], Sheela Nampoothiri[27], Sandeep Nemani[28], Amit Rawat[4], Mukesh Desai[2], Manisha Madkaikar[1]

- Umbilical cord related complications like omphalitis (64%) and delayed cord separation (62%) were the most common manifestations
- Pneumonia 41%; sepsis 37%
- Perianal region was the commonest site for skin ulcers (27%)

Infectious organisms were isolated from 69/106 cases:

Bacteria:

- Pseudomonas aeruginosa (n=28)
- Staphylococcus aureus (n=17)
- Klebsiella pneumoniae (n=11)

- Fungal infections (n=7)
- Unusual organisms included: ***Proteus sp., Citrobacter sp., Stingomonas paucimobilis, and Acinetobacter baumanii***

Case Reports > Pediatr Dermatol. 2023 Dec 27. doi: 10.1111/pde.15492. Online ahead of print.

Extensive perineal ecthyma gangrenosum in leukocyte adhesion deficiency type 1 associated with Staphylococcus hominis bacteremia

Balamurugan Kalyanaprabhakaran [1], Venkataraman Ranjith Kumar [1], Jaikumar Govindaswamy Ramamoorthy [1], Pediredla Karunakar [1], Dhandapany Gunasekaran [1], Bibekanand Jindal [2]

Case Reports > J Pediatr Hematol Oncol. 2013 Aug;35(6):468-9.

doi: 10.1097/MPH.0b013e31827e57b2.

Congenital CMV with LAD type 1 and NK cell deficiency

Narendra Rai [1], Neha Thakur

Case Reports > J Clin Immunol. 2016 Oct;36(7):624-6. doi: 10.1007/s10875-016-0315-0. Epub 2016 Jul 15.

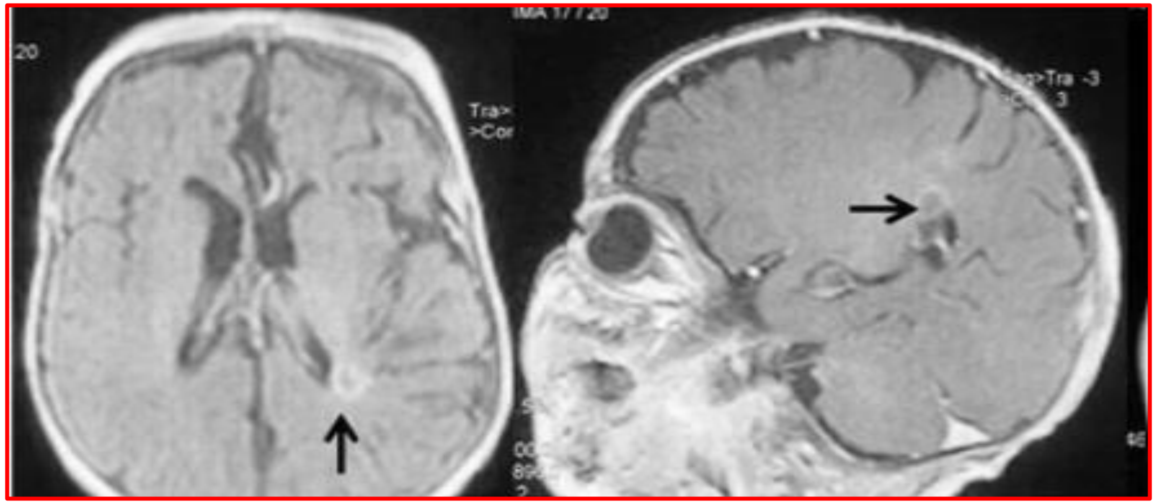
Brain Abscess in a Child with Leukocyte Adhesion Defect: An Unusual Association

Ankur Kumar [1], Aman Gupta [1], Amit Rawat [2], Chirag Ahuja [3], Deepti Suri [1], Surjit Singh [1]

Affiliations + expand

PMID: 27422622 DOI: 10.1007/s10875-016-0315-0

Pseudomonas aeruginosa



Case Reports > J Allergy Clin Immunol Pract. 2022 Sep;10(9):2448-2449.

doi: 10.1016/j.jaip.2022.06.019. Epub 2022 Jul 15.

Healing With Complication: An Unusual Case of Nasal Tip Ulceration in Leukocyte Adhesion Deficiency Type 1

Pseudomonas aeruginosa

Archan Sil [1], Ridhima Aggarwal [1], Sivanesan S [1], Saniya Sharma [1], Pandiarajan Vignesh [2], Amit Rawat [1]

Hyper-IgM syndrome

Clin Immunol. 2018 Oct:195:59-66. doi: 10.1016/j.clim.2018.07.013. Epub 2018 Jul 25.

Clinical and molecular features of X-linked hyper IgM syndrome - An experience from North India

Amit Rawat [1], Babu Mathew [1], Vignesh Pandiarajan [1], Ankur Jindal [1], Madhubala Sharma [1], Deepti Suri [1], Anju Gupta [1], Shubham Goel [2], Adil Karim [2], Biman Saikia [2], Ranjana W Minz [2], Kohsuke Imai [3], Shigeaki Nonoyama [4], Osamu Ohara [5], Silvia Clara Giliani [6], Luigi D Notarangelo [7], Koon-Wing Chan [8], Yu-Lung Lau [9], Surjit Singh [10]

- **Recurrent sinopulmonary infections noted in 8/10 children**
- **Infectious organisms isolated included:**

  Pneumocystis jiroveci (n=2), Klebsiella pneumoniae (n=2),

  Mycobacterium tuberculosis (n=1), Clostridium difficile (n=1)

Anti-interferon-γ autoantibody immunodeficiency

Steven Holland

N Engl J Med. 2012 Aug 23;367(8):725-34. doi: 10.1056/NEJMoa1111160.

Adult-onset immunodeficiency in Thailand and Taiwan

N=97

Sarah K Browne [1], Peter D Burbelo, Ploenchan Chetchotisakd, Yupin Suputtamongkol, Sasisopin Kiertiburanakul, Pamela A Shaw, Jennifer L Kirk, Kamonwan Jutivorakool, Rifat Zaman, Li Ding, Amy P Hsu, Smita Y Patel, Kenneth N Olivier, Viraphong Lulitanond, Piroon Mootsikapun, Siriluck Anunnatsiri, Nasikarn Angkasekwinai, Boonmee Sathapatayavongs, Po-Ren Hsueh, Chi-Chang Shieh, Margaret R Brown, Wanna Thongnoppakhun, Reginald Claypool, Elizabeth P Sampaio, Charin Thepthai, Duangdao Waywa, Camilla Dacombe, Yona Reizes, Adrian M Zelazny, Paul Saleeb, Lindsey B Rosen, Allen Mo, Michael Iadarola, Steven M Holland

- **Mycobacteria**

Rapidly growing	75
Slowly growing	23
Nontuberculous mycobacteria	7
Mycobacterium tuberculosis	14

- **Varicella–zoster virus**

Disseminated	3
Localized	15

- **Bacteria**

Salmonella sp.	25
Burkholderia pseudomallei	4

- **Fungi**

Cryptococcus neoformans	10
Histoplasma capsulatum	7
Penicillium marneffei	7

PLoS One. 2013; 8(9): e76371.
Published online 2013 Sep 27. doi: 10.1371/journal.pone.0076371
PMCID: PMC3785451
PMID: 24086734

Autoantibody to Interferon-gamma Associated with Adult-Onset Immunodeficiency in Non-HIV Individuals in Northern Thailand

Panuwat Wongkulab,[1] Jiraprapa Wipasa,[2] Romanee Chaiwarith,[1] and Khuanchai Supparatpinyo[1,2,*]

- **Opportunistic infections among 20 cases included:** disseminated NTM infection (19 patients/24 episodes), disseminated Penicilliosis marneffei (12 patients/12 episodes), and non-typhoidal Salmonella bacteremia (7 patients/8 episodes)

- Level of antibody to IFN-γ in patients who had active opportunistic infection was relatively higher than in those without active infection

Opportunistic infections[*]	Cases (N=20)
Infections caused by non-tuberculous mycobacteria	24
Rapid-grower mycobacteria	11
M. chelonae	3
M. abscessus	4
M. chelonae-abscessus complex	3
M. fortuitum	1
Slow grower mycobacteria	7
M. avium	3
M. avium/paratuberculosis/solitarium	1
M. kansassii	3
Species not specified	6
Penicilliosis marneffei	12
Cryptococcosis	1
Histoplasmosis	1

Infections in PID patients in the Asia Pacific region

Breakthrough infections are more common

Profile is different

Polymicrobial infections may be more common

Facilities for isolating the causative organism may not be adequate

Threshold for starting antimicrobials is much lower

Clinical decisions need to be based on local experience

Acknowledgements

POSTGRADUATE INSTITUTE OF MEDICAL EDUCATION AND RESEARCH CHANDIGARH

आर्त सेवा सर्व भद्र शोधश्च

Q&A

IPOPI
5TH REGIONAL
ASIAN PID MEETING
24-25 MARCH 2024
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Flow Cytometry for Diagnostics: Value, Context, and Sustainability

Dr Jaime Sou da Rosa Duque | Hong Kong

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5TH REGIONAL
ASIAN PID MEETING
24-25 MARCH 2024
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IPOPI.org

Jaime Rosa Duque, MD, PhD, FHKAM (Paed), FAAP, FAAAAI

Presenter

Clinical Assistant Professor
The University of Hong Kong

HKU Med School of Clinical Medicine
Department of Paediatrics & Adolescent Medicine
香港大學兒童及青少年科學系

Honorary Distinguished Professor
Immunology and Rheumatology
Guangzhou Women and Children's Medical Center

Guangzhou Women and Children's Medical Center
广州市妇女儿童医疗中心

IPOPI
5TH REGIONAL ASIAN PID MEETING
24-25 MARCH 2024
TOKYO, JAPAN
an IPOPI event

COLLABORATION

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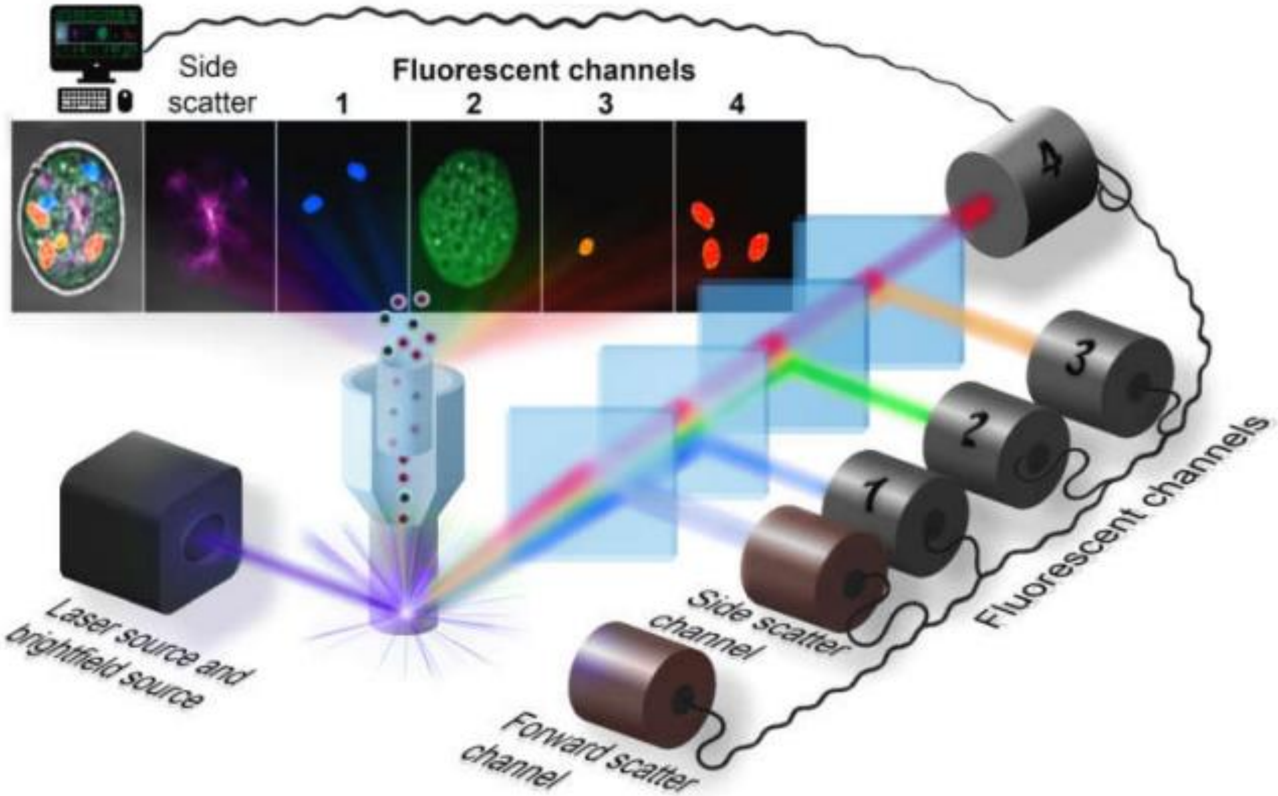
GRIFOLS

Flow Cytometry for Diagnostics: Value, Context, and Sustainability

Introduction to Flow Cytometry

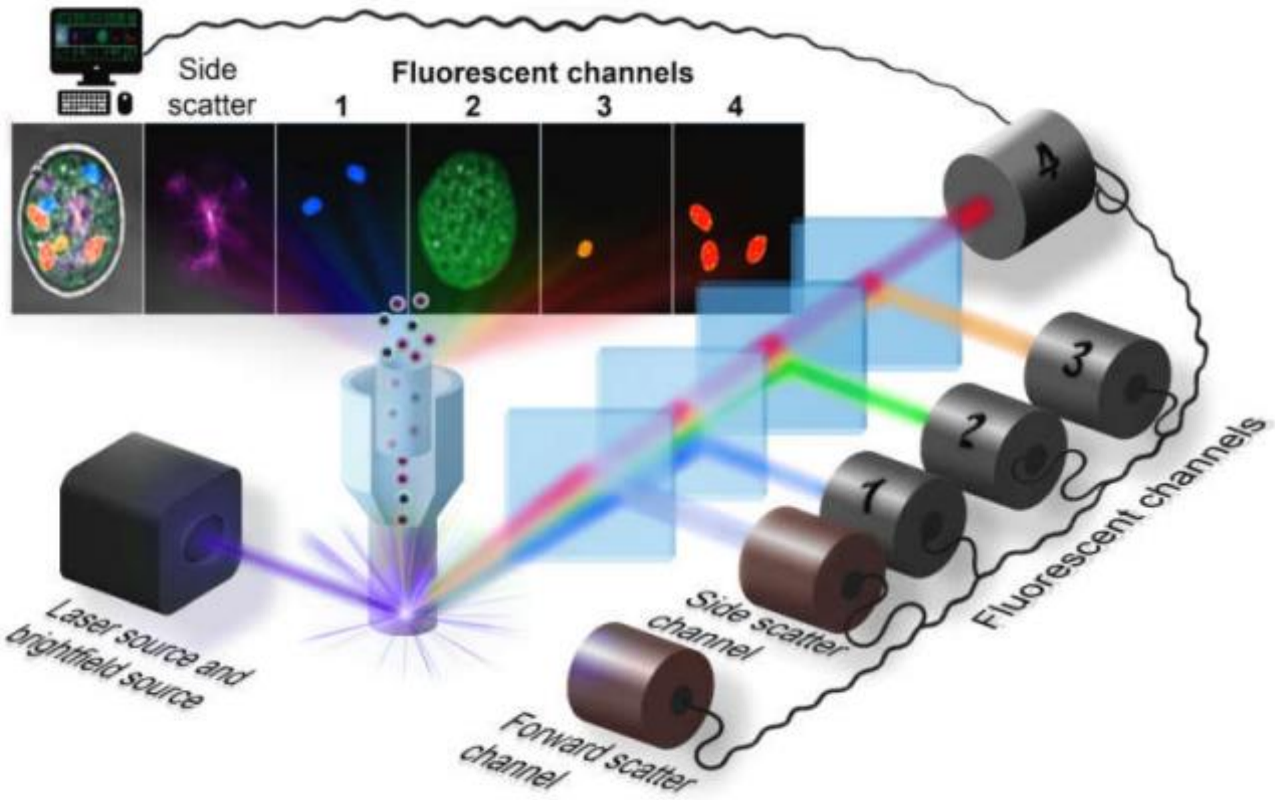
- a precise technique for measurement of multiple characteristics of individual cells within heterogeneous populations



Voronin DV, Kozlova AA, Verkhovskii RA, Ermakov AV, Makarkin MA, Inozemtseva OA, Bratashov DN. Detection of Rare Objects by Flow Cytometry: Imaging, Cell Sorting, and Deep Learning Approaches. Int J Mol Sci. 2020 Mar 27;21(7):2323. doi: 10.3390/ijms21072323. PMID: 32230871; PMCID: PMC7177904.

Introduction to Flow Cytometry

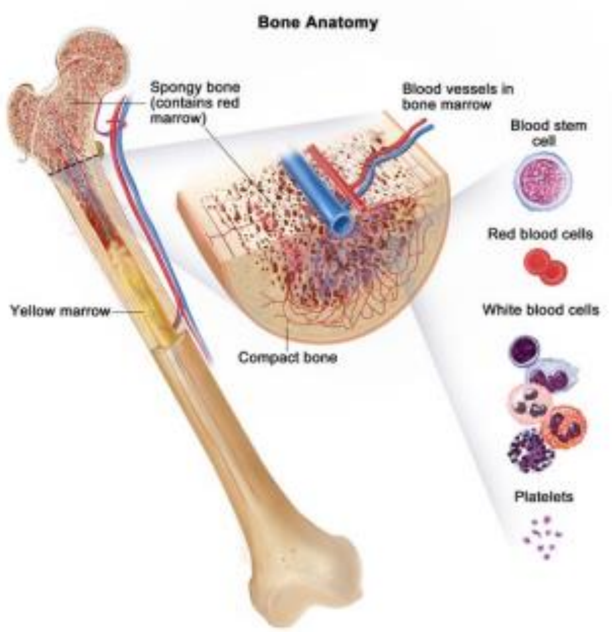
- a precise technique for measurement of multiple characteristics of individual cells within heterogeneous populations
- consists of five main components:
  - a flow cell (through which cells flow)
  - a laser
  - optical components
  - detectors to amplify signals
  - electronics/computer system

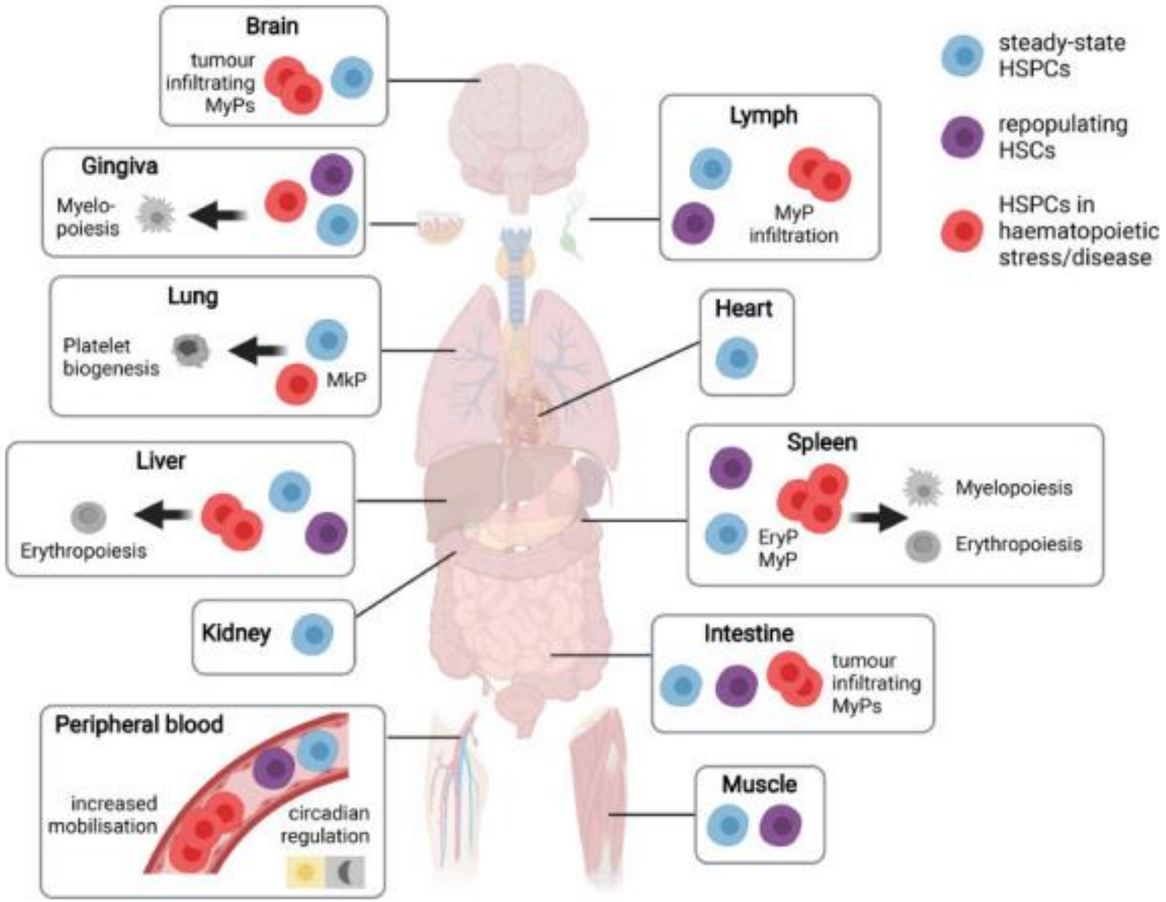


Voronin DV, Kozlova AA, Verkhovskii RA, Ermakov AV, Makarkin MA, Inozemtseva OA, Bratashov DN. Detection of Rare Objects by Flow Cytometry: Imaging, Cell Sorting, and Deep Learning Approaches. Int J Mol Sci. 2020 Mar 27;21(7):2323. doi: 10.3390/ijms21072323. PMID: 32230871; PMCID: PMC7177904.

Introduction to Flow Cytometry

- although peripheral blood is the most common and normal ranges have been better delineated, any biologic sample (peripheral blood, bone marrow, CSF, BAL) can be analyzed

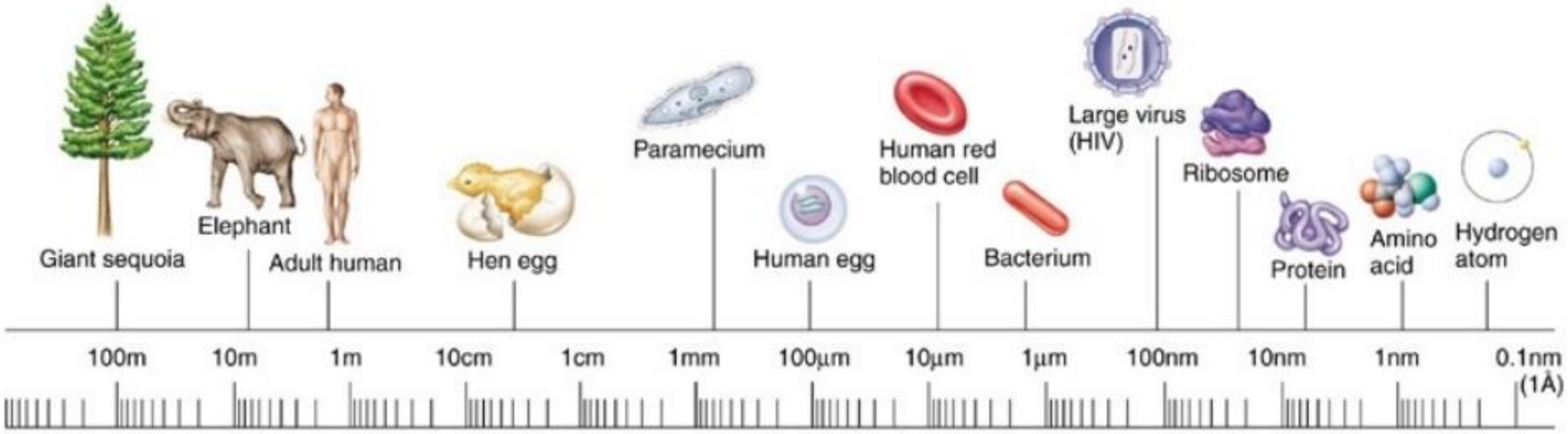




Mende N, Laurenti E. Hematopoietic stem and progenitor cells outside the bone marrow: where, when, and why. Exp Hematol. 2021 Dec;104:9-16. doi: 10.1016/j.exphem.2021.10.002. Epub 2021 Oct 20. PMID: 34687807.

Introduction to Flow Cytometry

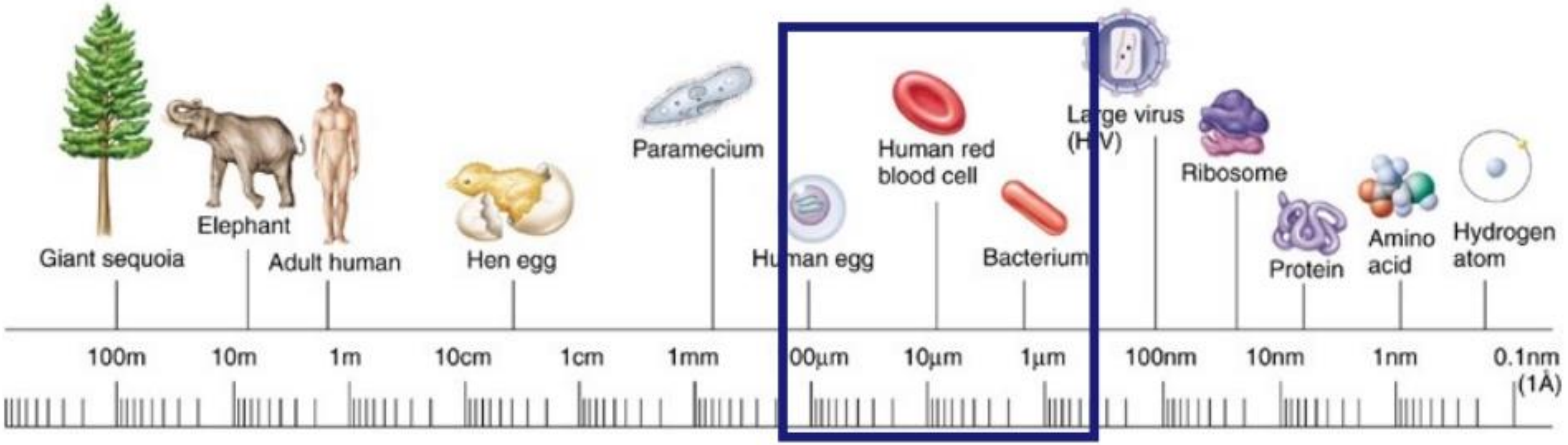
- any suspended cell or particle ranging from 0.2 to 150 micrometers in size is suitable for analysis



http://www.zo.utexas.edu/faculty/sjasper/bio301l/cells.html

Introduction to Flow Cytometry

- any suspended cell or particle ranging from 0.2 to 150 micrometers in size is suitable for analysis



http://www.zo.utexas.edu/faculty/sjasper/bio301l/cells.html

Introduction to Flow Cytometry

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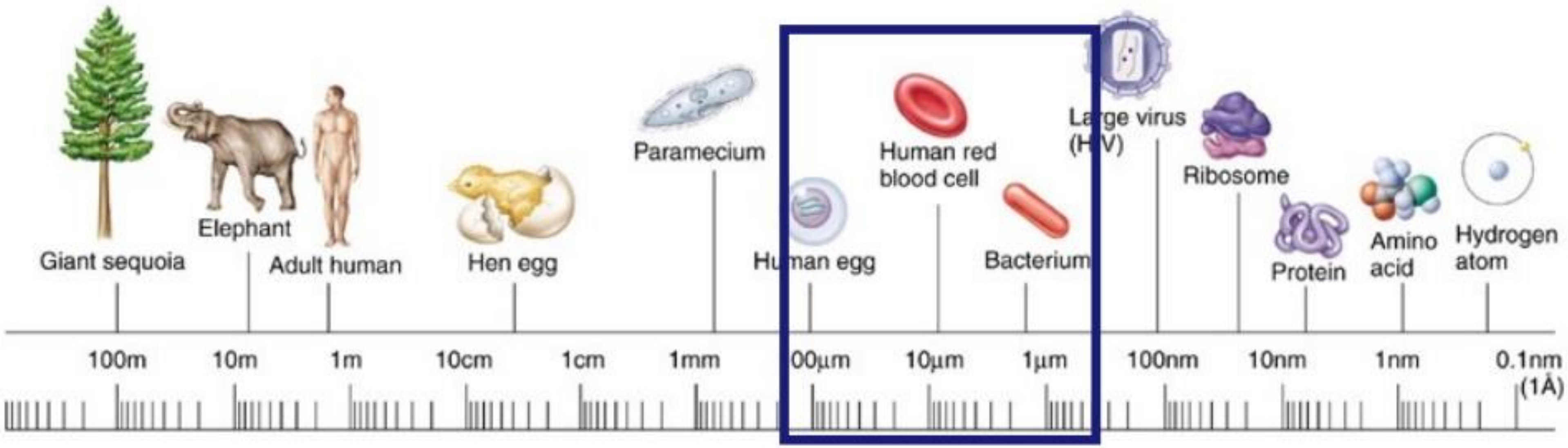
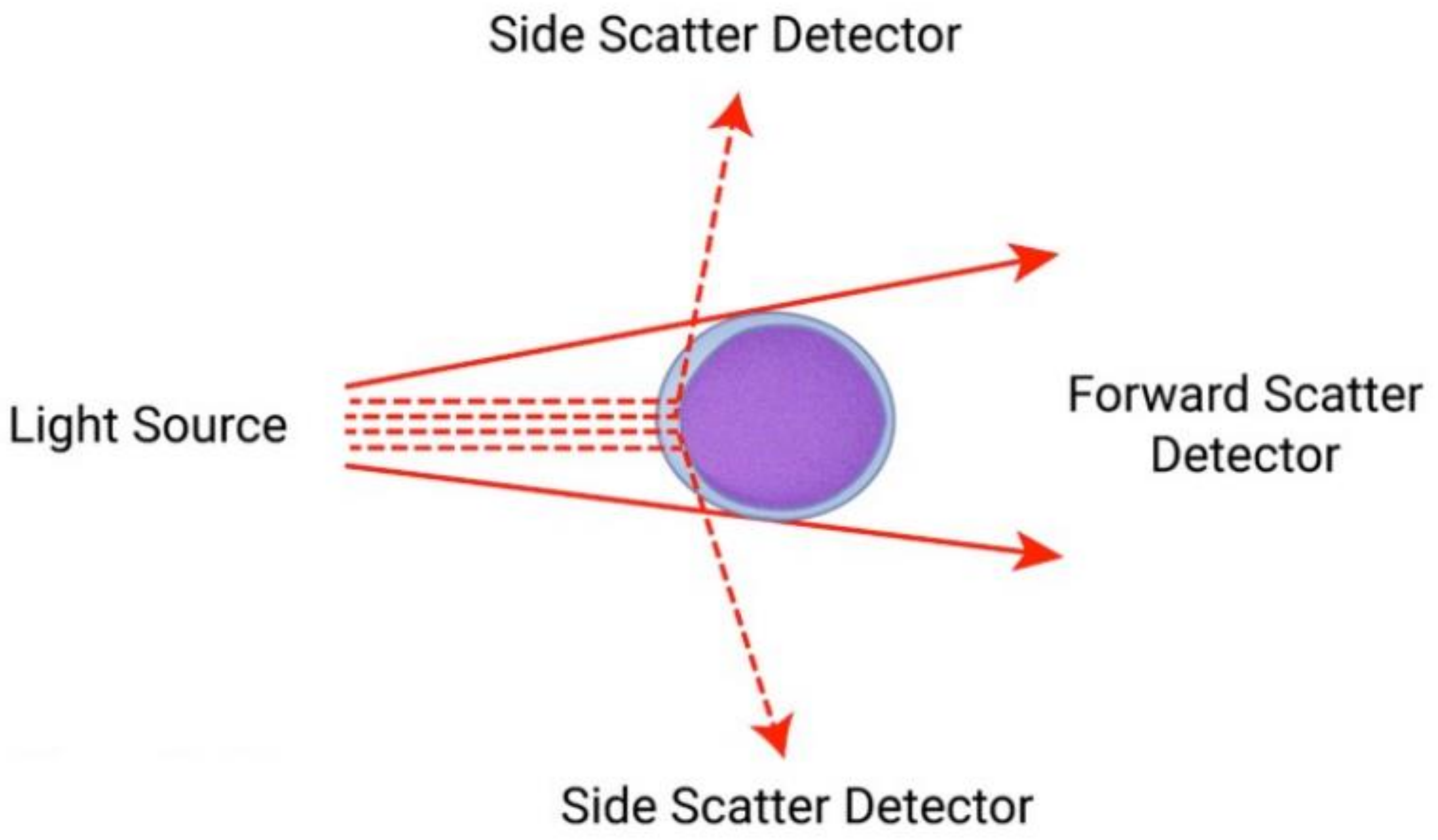


- analyses to determine cellular characteristics: size, granularity, viability, and immunophenotyping, which are the most common types of studies

Parameters



https://www.learnhaem.com/courses/flow-cytometry/

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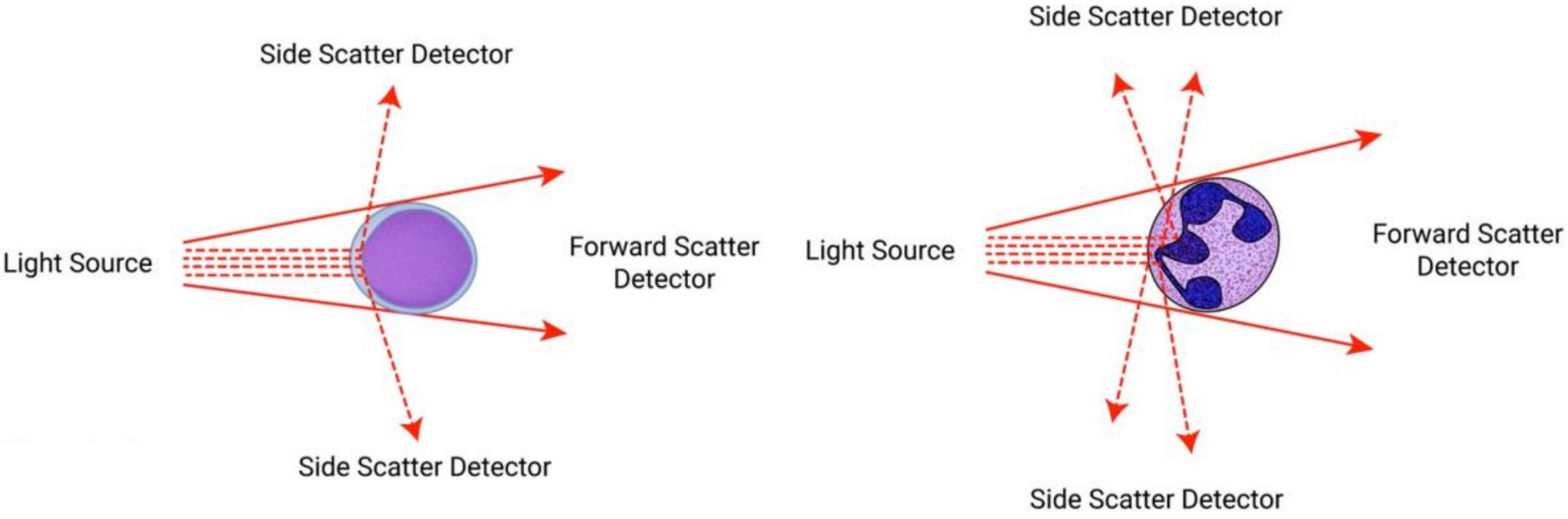

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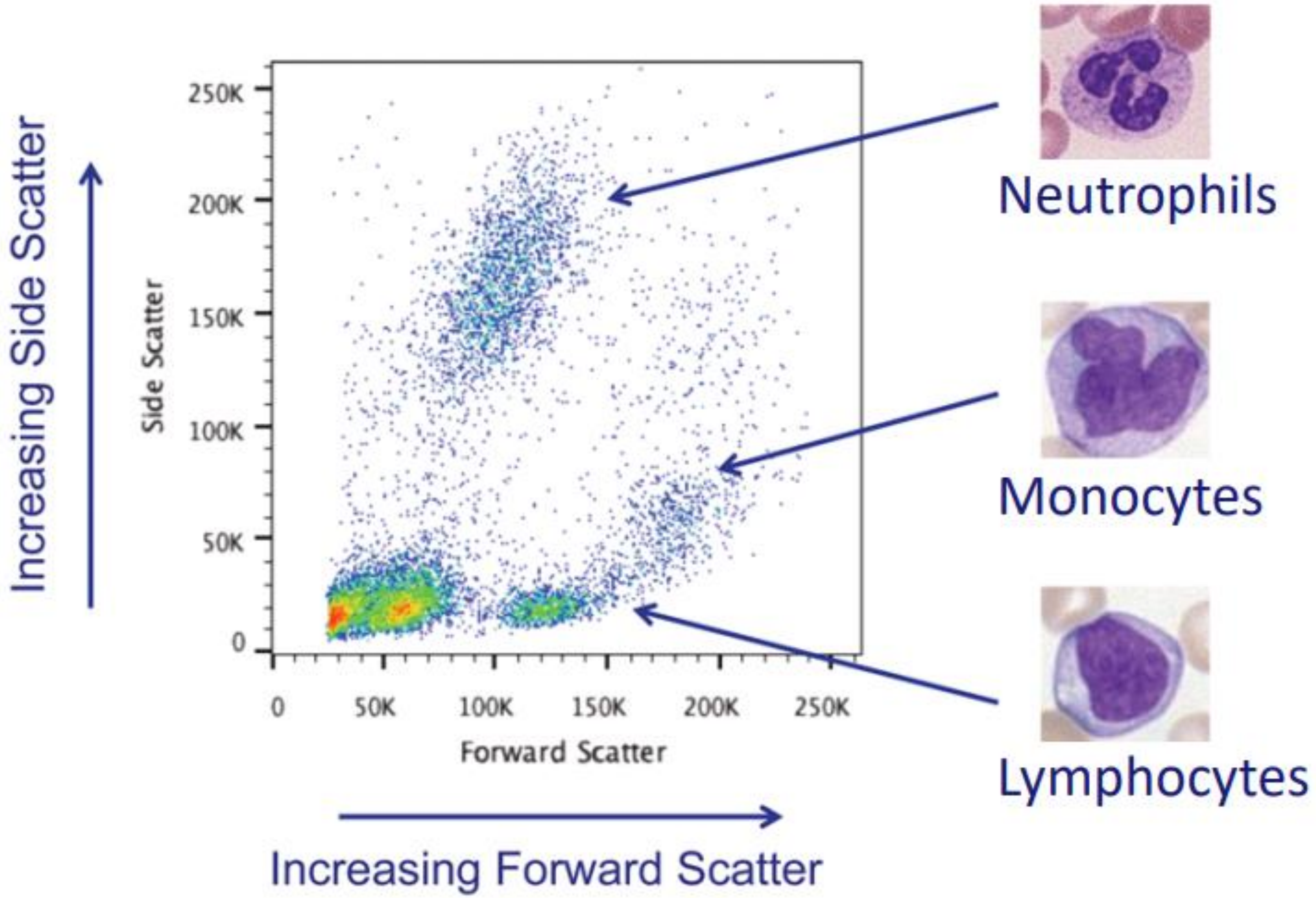
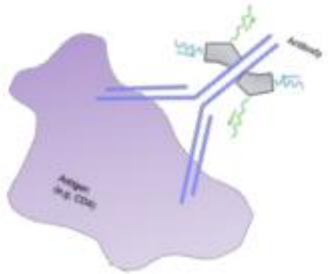
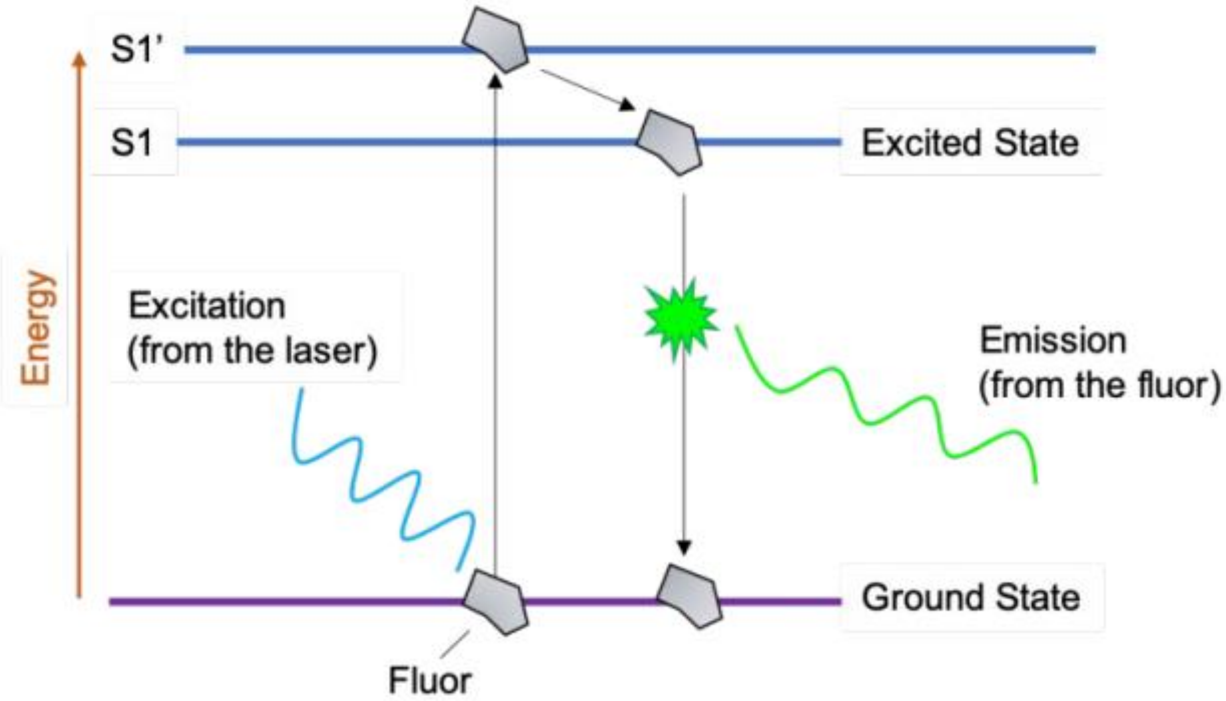

Increasing Side Scatter
Side Scatter
250K
200K
150K
100K
50K
0
0
50K
100K
150K
200K
250K
Forward Scatter
Increasing Forward Scatter
Neutrophils
Monocytes
Lymphocytes

Immunophenotyping

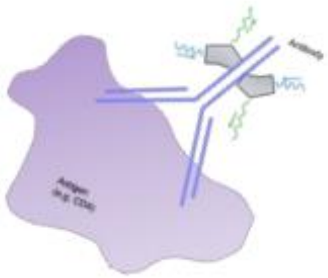
- a technique used to characterize the makeup of cell populations by detecting cellular protein expression





https://marissafahlberg.com/fluorescence-and-fluorochromes-in-flow-cytometry/

Immunophenotyping



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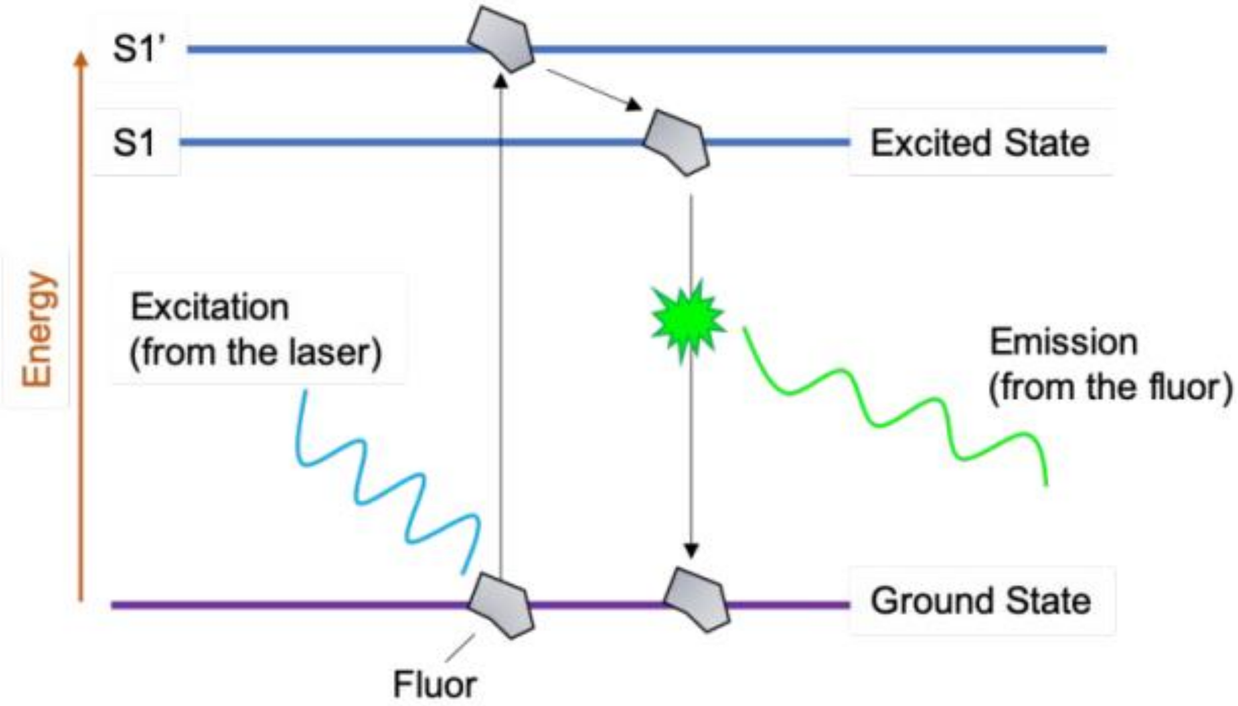
- uses an antibody specific for the antigen of interest that is conjugated to a fluorescent compound known as a fluorophore or fluorochrome



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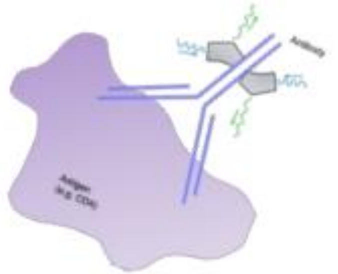

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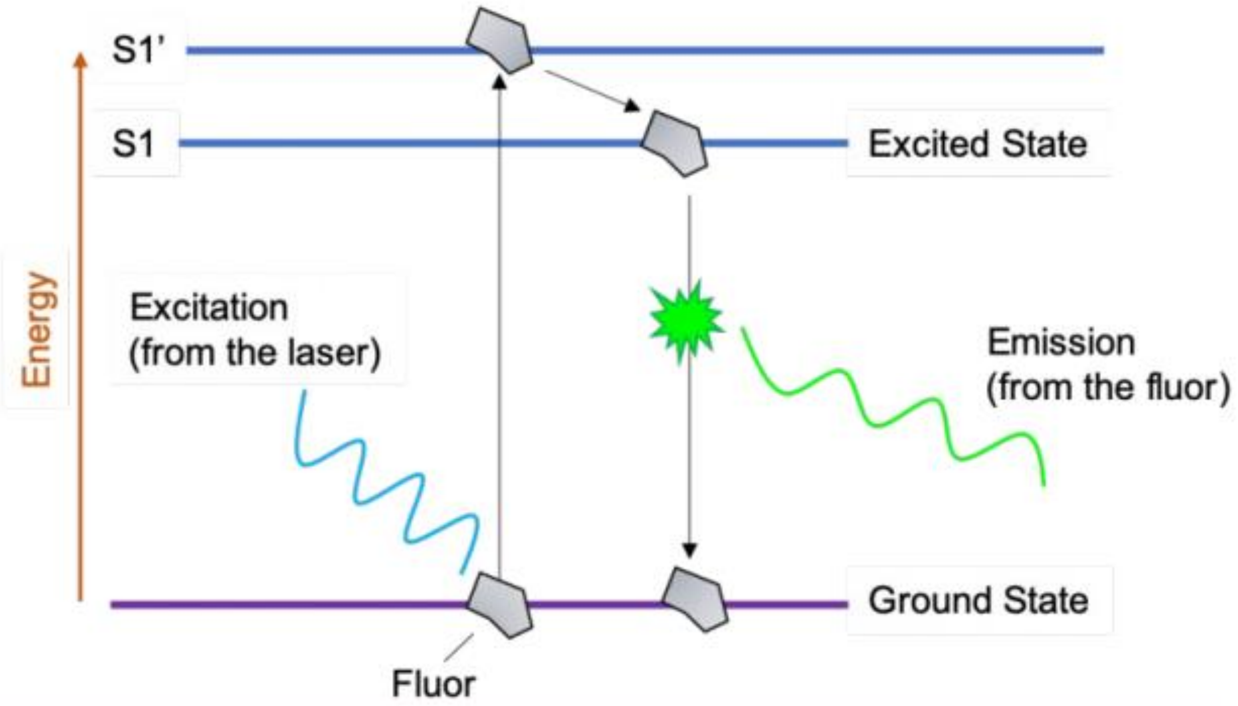

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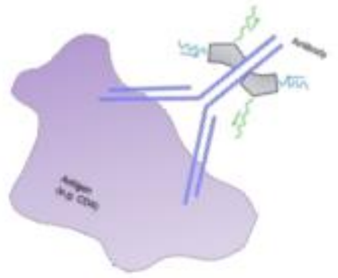

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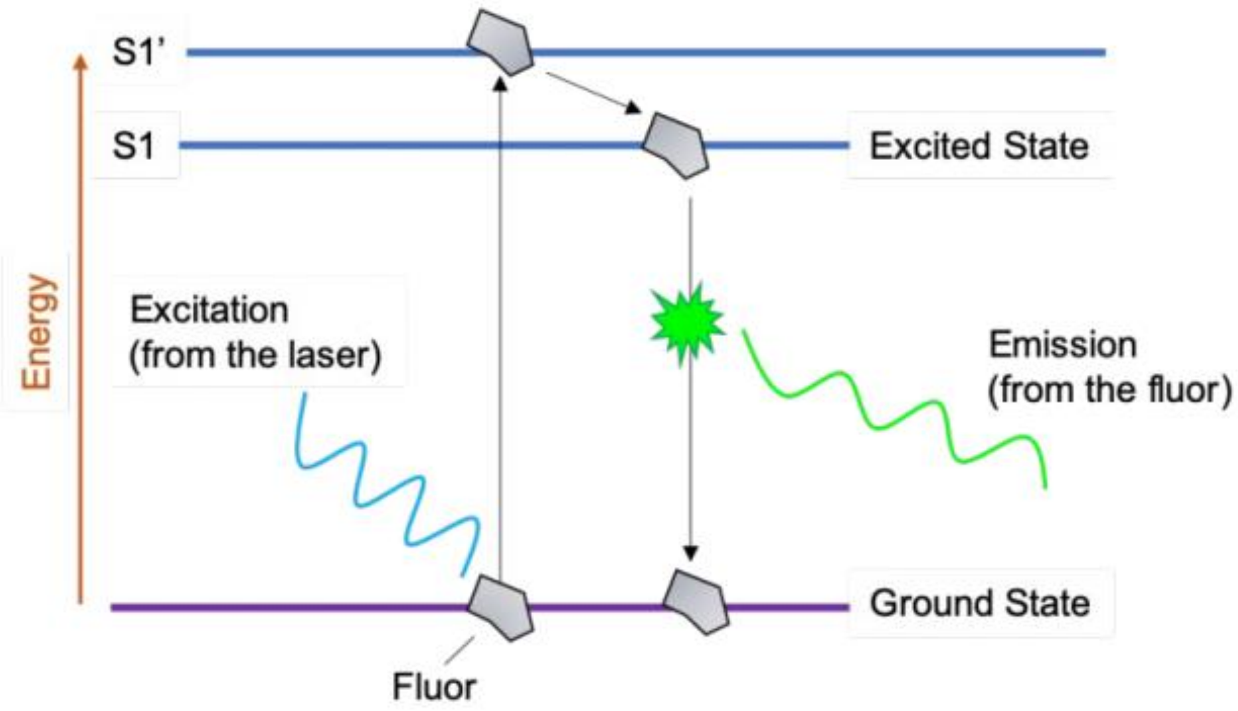
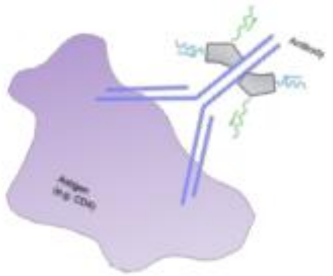


Immunophenotyping



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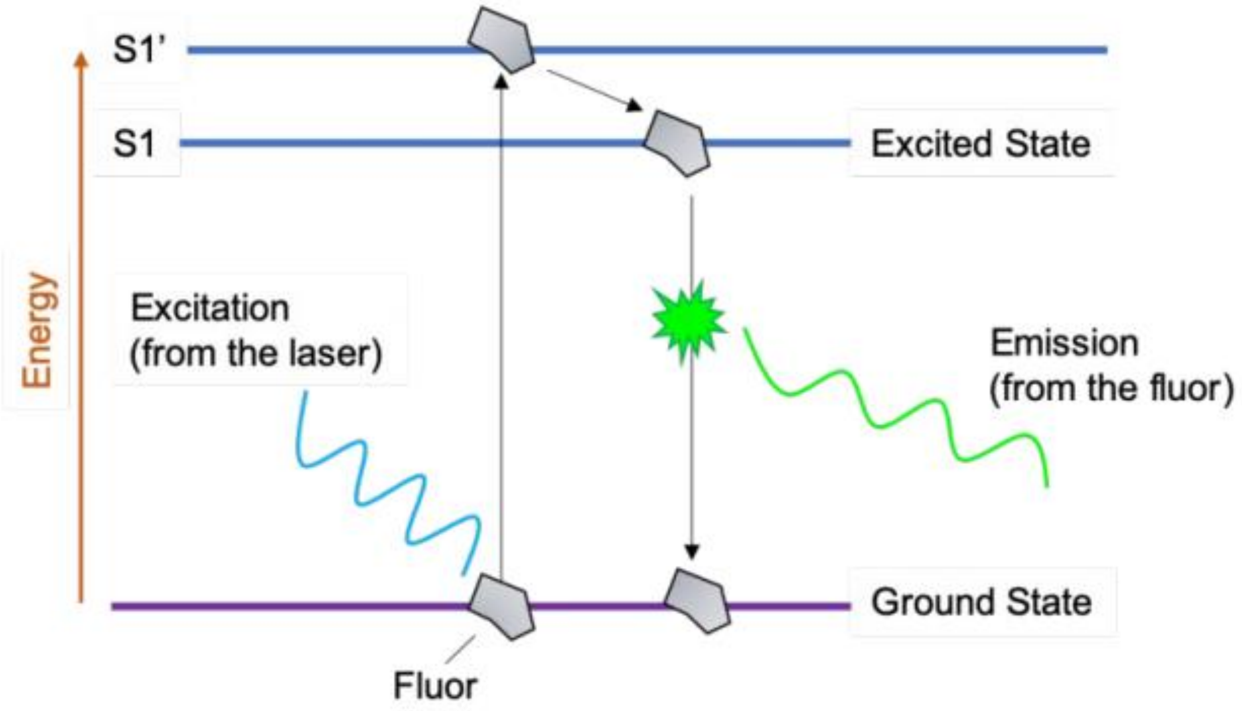
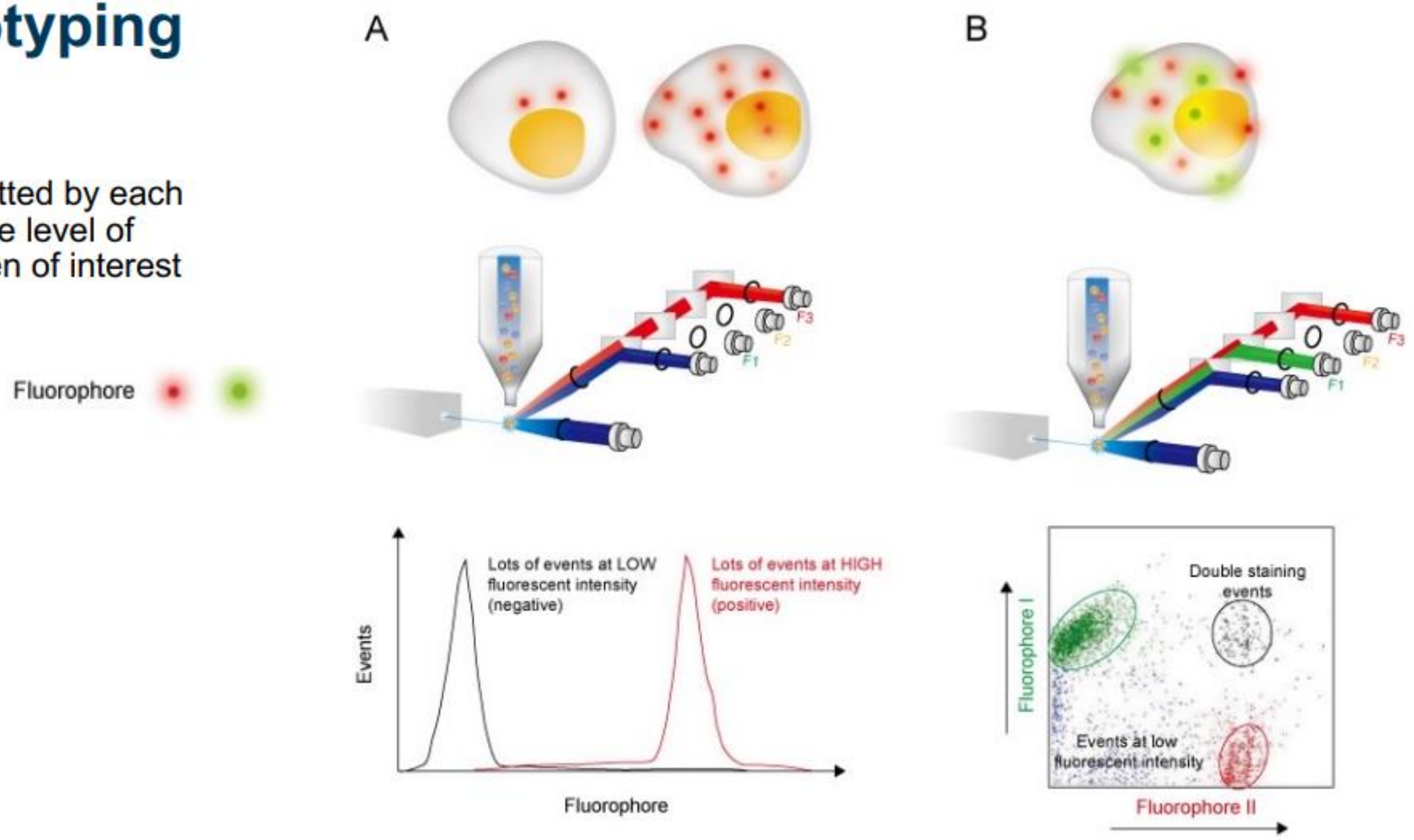
- the excited electron quickly returns to its ground state, emitting the excess energy as a photon of light of a characteristic wavelength that is detected by the flow cytometer
- different fluorochromes are excited by different wavelengths of light and emit light at different wavelengths

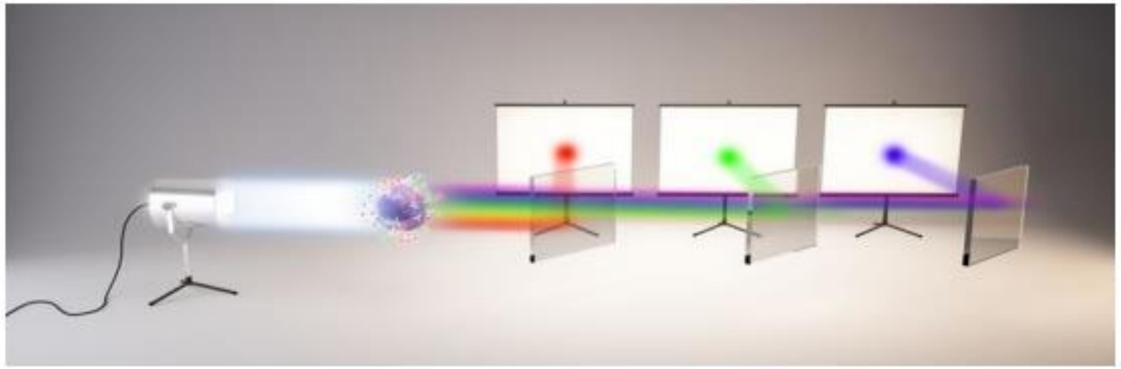


Immunophenotyping

- the intensity of light emitted by each fluorochrome reflects the level of expression of the antigen of interest



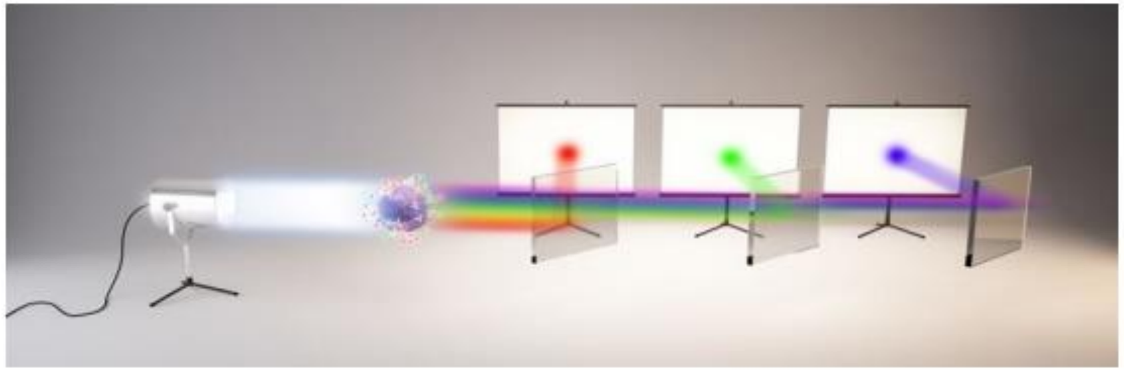
Conventional vs Spectral Flow Cytometry



Conventional Flow Cytometry

- most conventional flow cytometry in clinical use consist of 10 to 12 different markers with separate detectors

Conventional vs Spectral Flow Cytometry



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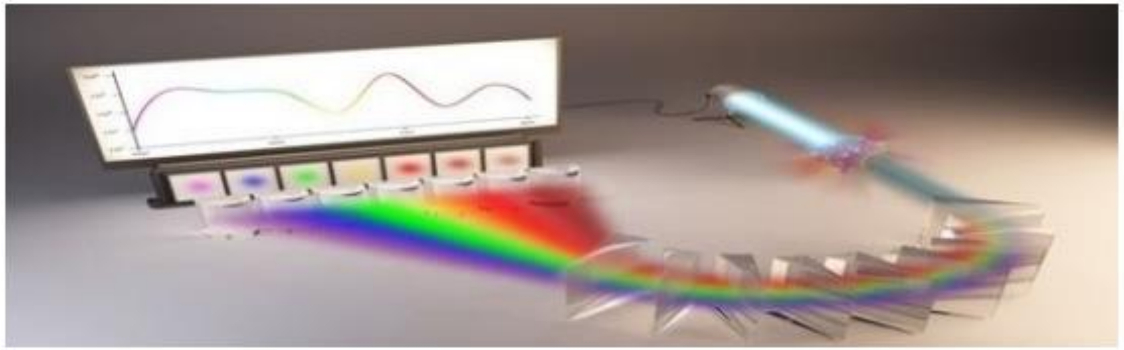


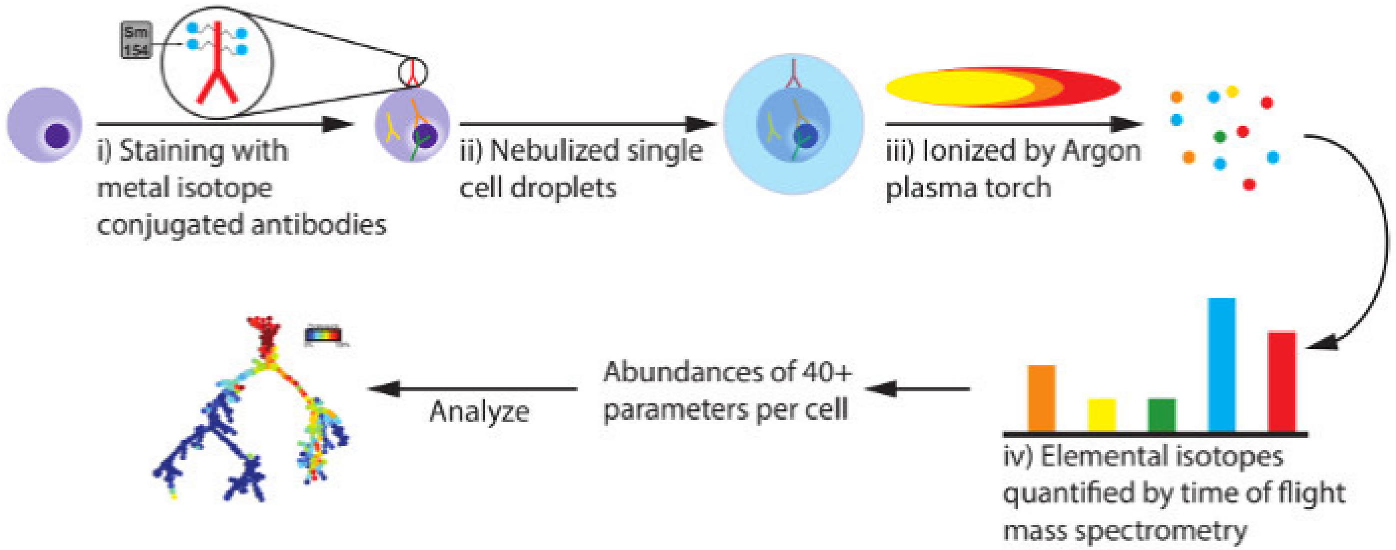
Spectral Flow Cytometry

- similar to conventional flow cytometry but with multiple detectors for each fluorochrome rather than one detector
- this allows for better differentiation of fluorochromes based upon the fluorescent spectral signature of each fluorochrome, enabling the use of more fluorochromes in a single sample
- some can resolve 40 different fluorochromes in one sample

https://www.scientistlive.com/content/spectral-analyser-technology

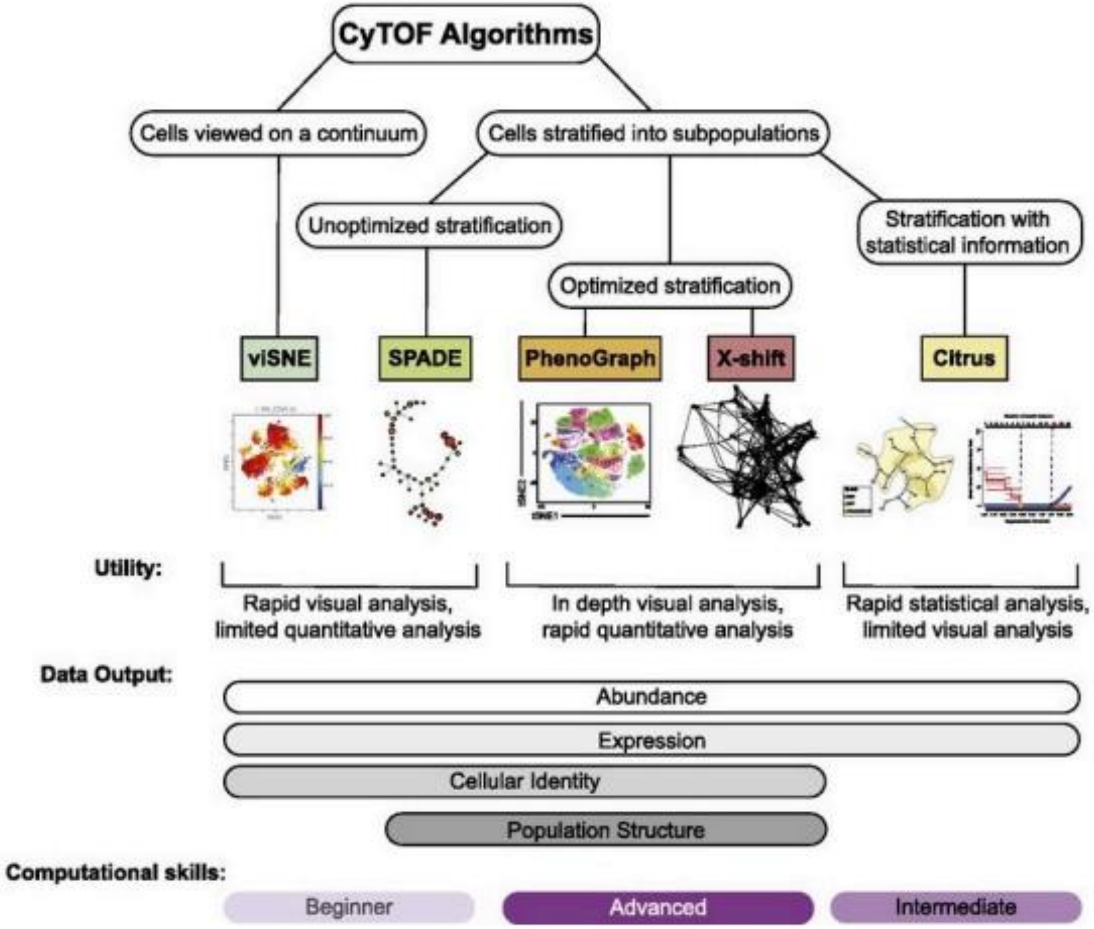
Mass Cytometry or Cytometry by Time-of-flight (CyTOF)

- technology that combines flow cytometry with mass spectrometry
- antibodies labeled with heavy-metal ions
- readout is based on the atomic number of the heavy metal, and there is little overlap between the isotopes
- a greater number of antibodies can be used simultaneously, allowing for analysis of over 40 targets per cell
- not widely available clinically but possibly become more prominent in the future



Kimball AK, Oko LM, Bullock BL, Nemenoff RA, van Dyk LF, Clambey ET. A Beginner's Guide to Analyzing and Visualizing Mass Cytometry Data. J Immunol. 2018 Jan 1;200(1):3-22. doi: 10.4049/jimmunol.1701494. PMID: 29255085; PMCID: PMC5765874.

Mass Cytometry or Cytometry by Time-of-flight (CyTOF)



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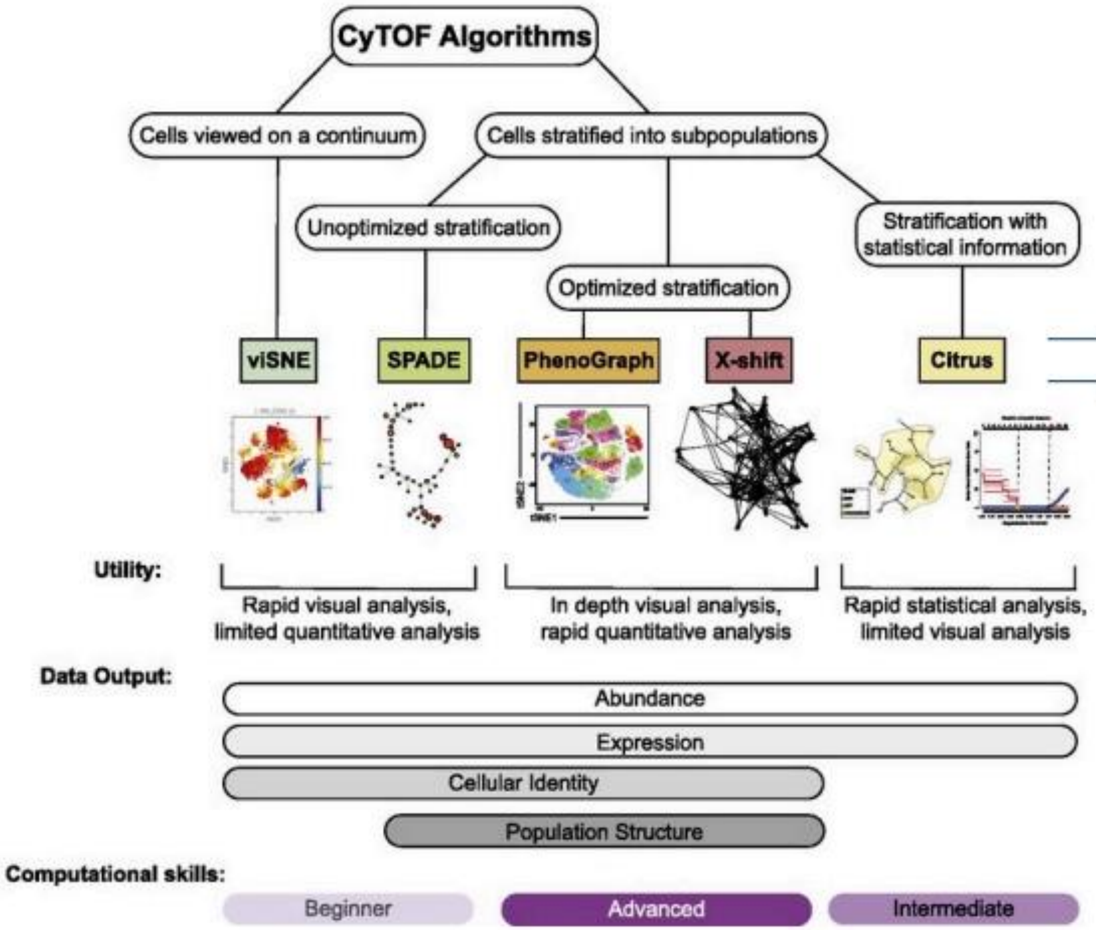

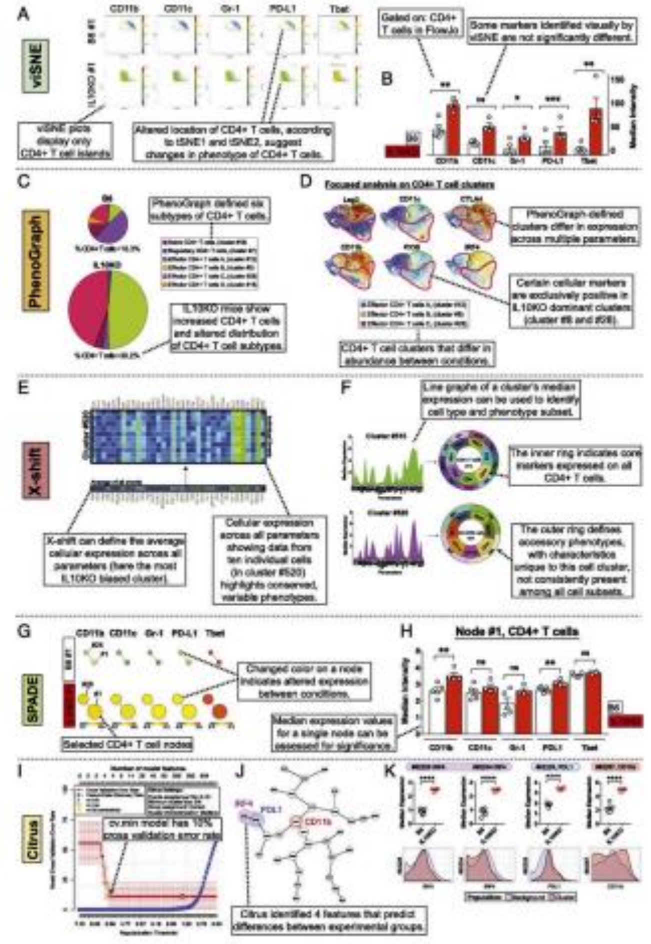

Flow Cytometry for Diagnosis of IEI (routine)

- useful in determination of absence of specific leukocytes and lymphocyte subpopulations
- routine screening includes:

Cell Marker	Lymphocyte Subpopulation	Absence Suggests
$CD3^+$	T cells	SCID
$CD4^+$	T helper cells	SCID or HIV/AIDS
$CD8^+$	Cytotoxic T cells	SCID or CID
$CD19^+$	B cells	Agammaglobulinemia
$CD16^+56^+$	Natural killer cells	Variable

Bonilla FA, et al; Joint Task Force on Practice Parameters, representing the AAAAI; ACAAI; and JCAAI. Practice parameter for the diagnosis and management of primary immunodeficiency. J Allergy Clin Immunol. 2015 Nov;136(5):1186-205.e1-78. doi: 10.1016/j.jaci.2015.04.049. Epub 2015 Sep 12. PMID: 26371839.

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$CD45RA^+$	Naïve T cells	SCID
$CD45RO^+$	Memory T cells	Expected in newborns

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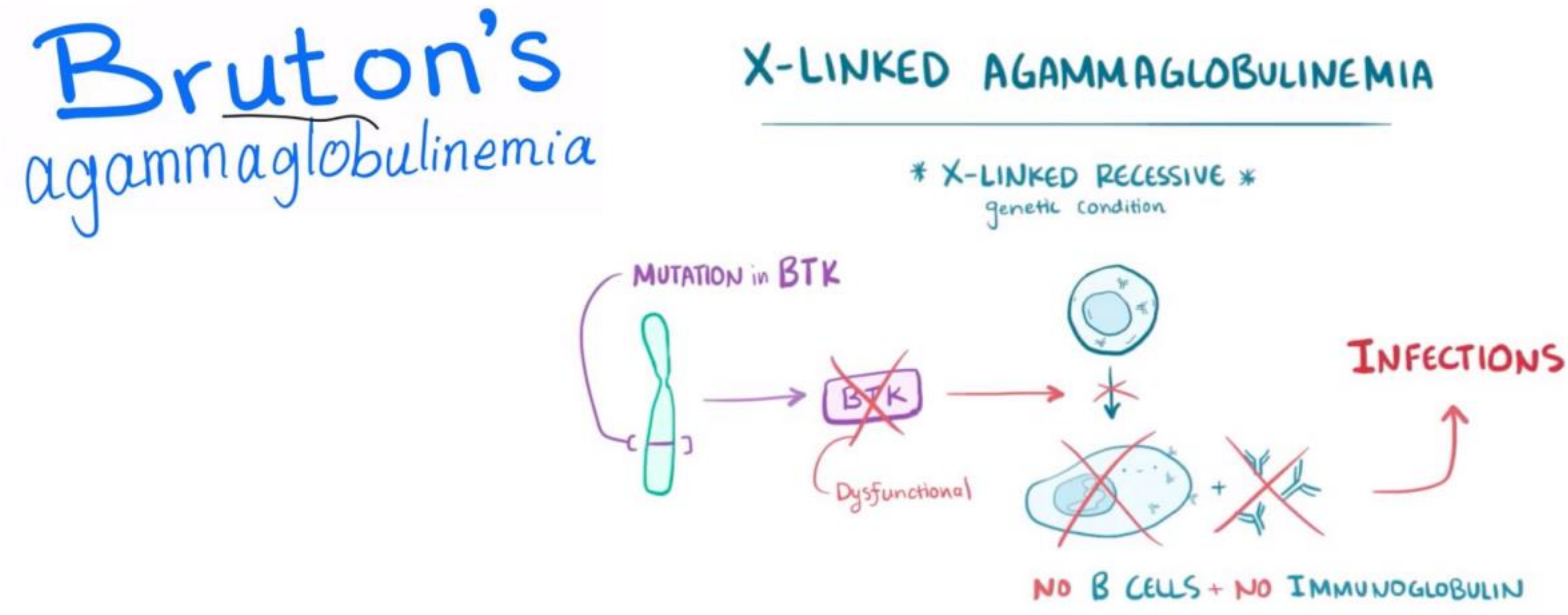
Flow Cytometry for Screening and Diagnosis of Severe Combined Immunodeficiencies (SCID)

TABLE E8. Lymphocyte phenotype classification of SCID

Disease	Genes	References
$T^-B^-NK^-$		
Adenosine deaminase	*ADA*	89, 90
Adenylate kinase (reticular dysgenesis)	*AK2*	91-93
$T^-B^-NK^+$		
Artemis	*DCLRE1C*	94, 95
Cernunnos	*NHEJ1*	96, 97
DNA-dependent protein kinase	*PRKDC*	98
DNA ligase IV	*LIG4*	99, 100
RAG1 and RAG2	*RAG1*, *RAG2*	101-104
$T^-B^+NK^-$		
X-linked SCID	*IL2RG*	67, 105-108
JAK3 deficiency	*JAK3*	106, 109
CD25 deficiency	*IL2RA*	110, 111
$T^-B^+NK^+$		
CD3 complex defects	*CD3D, CD3E, CD3Z*	112-115
Coronin 1A deficiency	*CORO1A*	88
CD45 deficiency	*PTPRC*	116, 117
IL-7 receptor deficiency	*IL7RA*	115, 118

Bonilla FA, et al; Joint Task Force on Practice Parameters, representing the AAAAI; ACAAI; and JCAAI. Practice parameter for the diagnosis and management of primary immunodeficiency. J Allergy Clin Immunol. 2015 Nov;136(5):1186-205.e1-78. doi: 10.1016/j.jaci.2015.04.049. Epub 2015 Sep 12. PMID: 26371839.

Flow Cytometry for Diagnosis of IEI (XLA)



Thomas JD, Sideras P, Smith CI, Vorechovský I, Chapman V, Paul WE. Colocalization of X-linked agammaglobulinemia and X-linked immunodeficiency genes. Science. 1993 Jul 16;261(5119):355-8. doi: 10.1126/science.8332900. PMID: 8332900.

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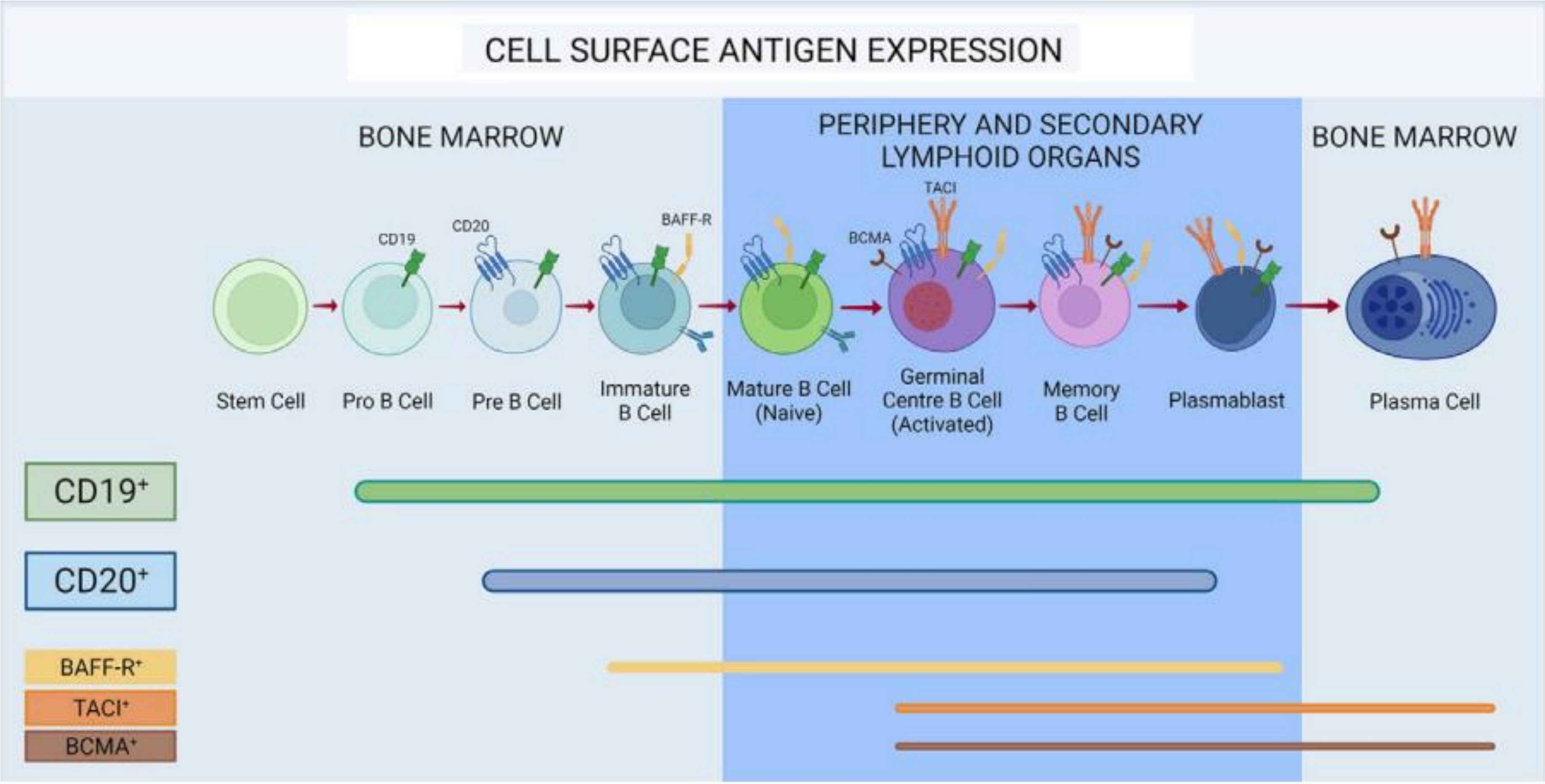
Flow Cytometry for Diagnosis of IEI (XLA)

Bruton's agammaglobulinemia



Kanatas P, Stouras I, Stefanis L, Stathopoulos P. B-Cell-Directed Therapies: A New Era in Multiple Sclerosis Treatment. Can J Neurol Sci. 2023 May;50(3):355-364. doi: 10.1017/cjn.2022.60. Epub 2022 May 16. PMID: 35570581.

Flow Cytometry for Diagnosis of IEI (XLA)

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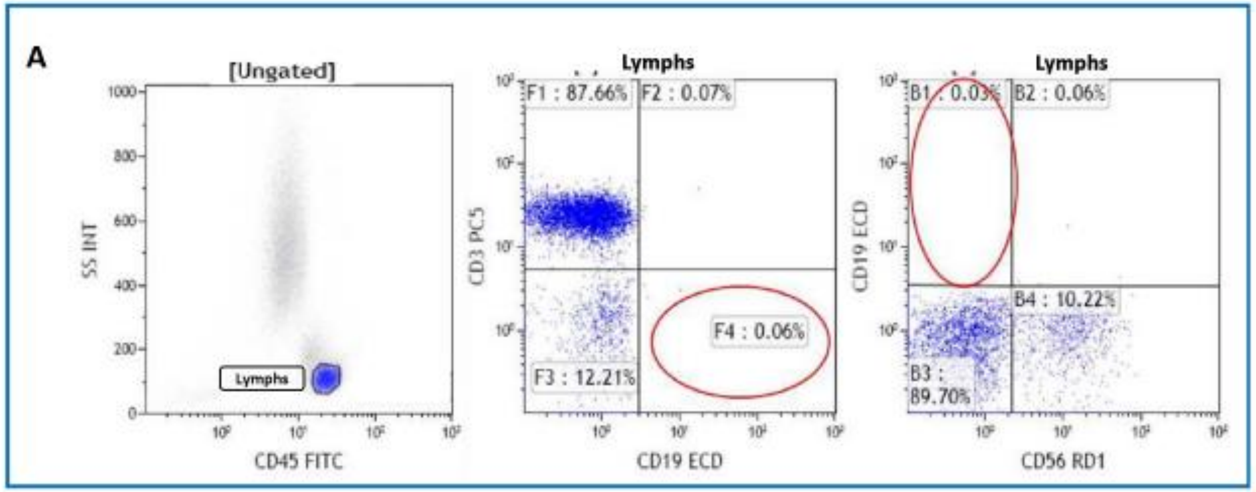
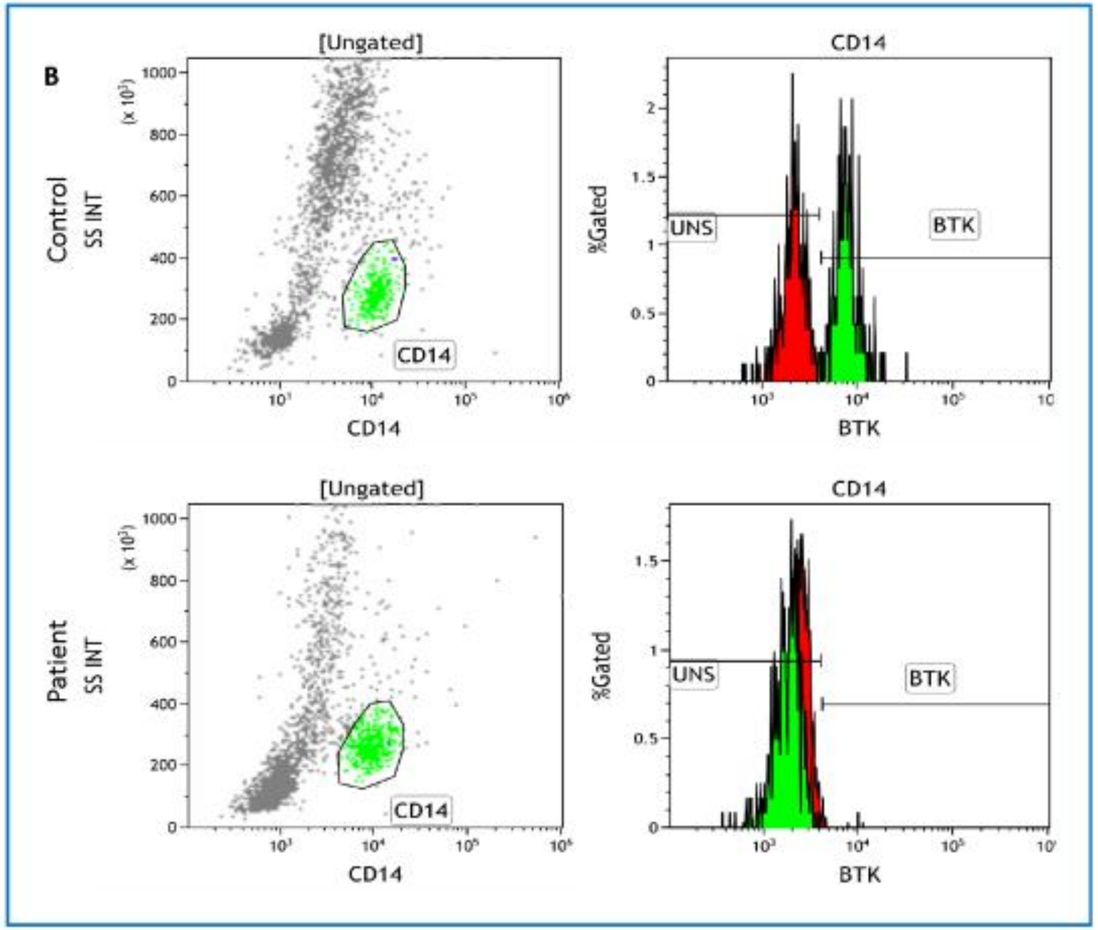


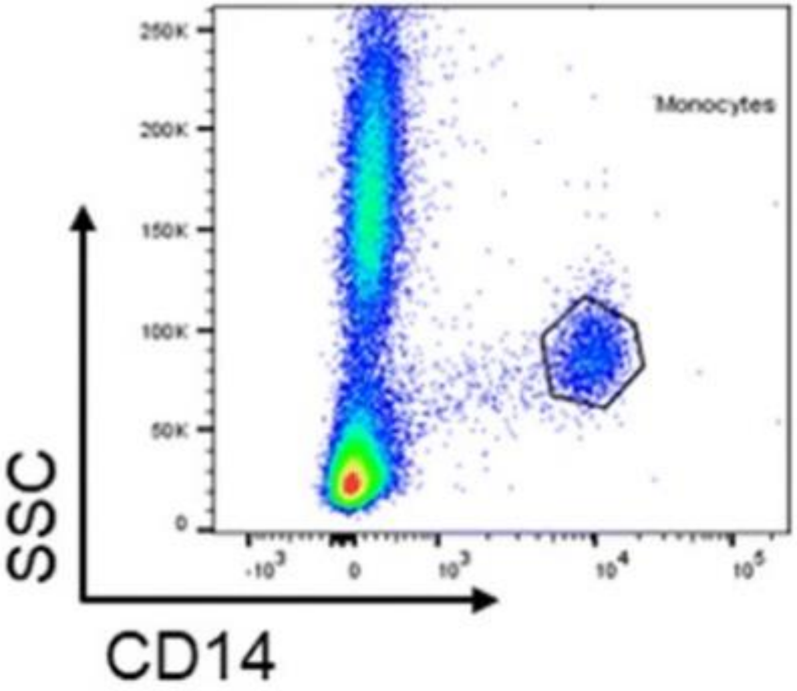


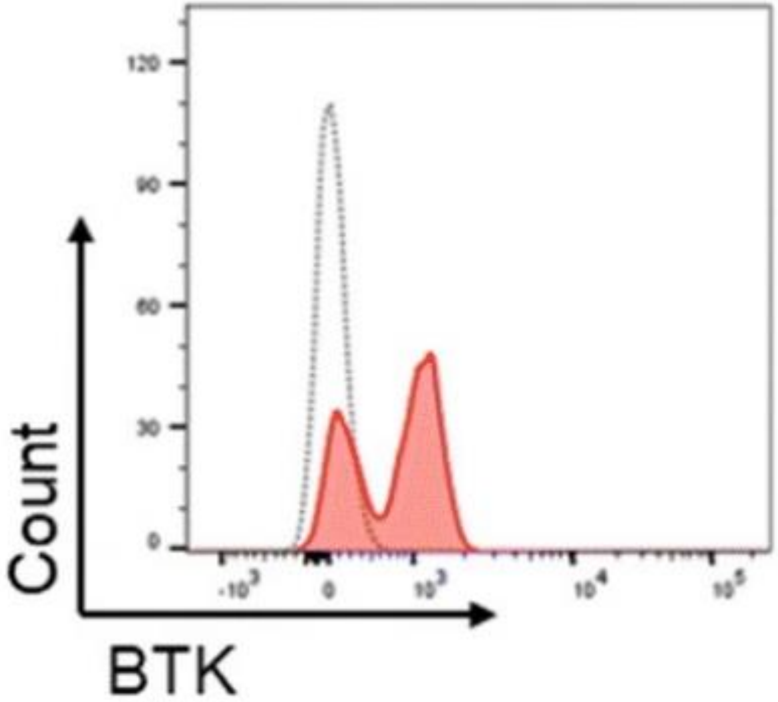
Rawat A, Arora K, Shandilya J, Vignesh P, Suri D, Kaur G, Rikhi R, Joshi V, Das J, Mathew B, Singh S. Flow Cytometry for Diagnosis of Primary Immune Deficiencies-A Tertiary Center Experience From North India. Front Immunol. 2019 Sep 11;10:2111. doi: 10.3389/fimmu.2019.02111. PMID: 31572360; PMCID: PMC6749021.

Flow Cytometry for Diagnosis of IEI (XLA)

Bruton's agammaglobulinemia

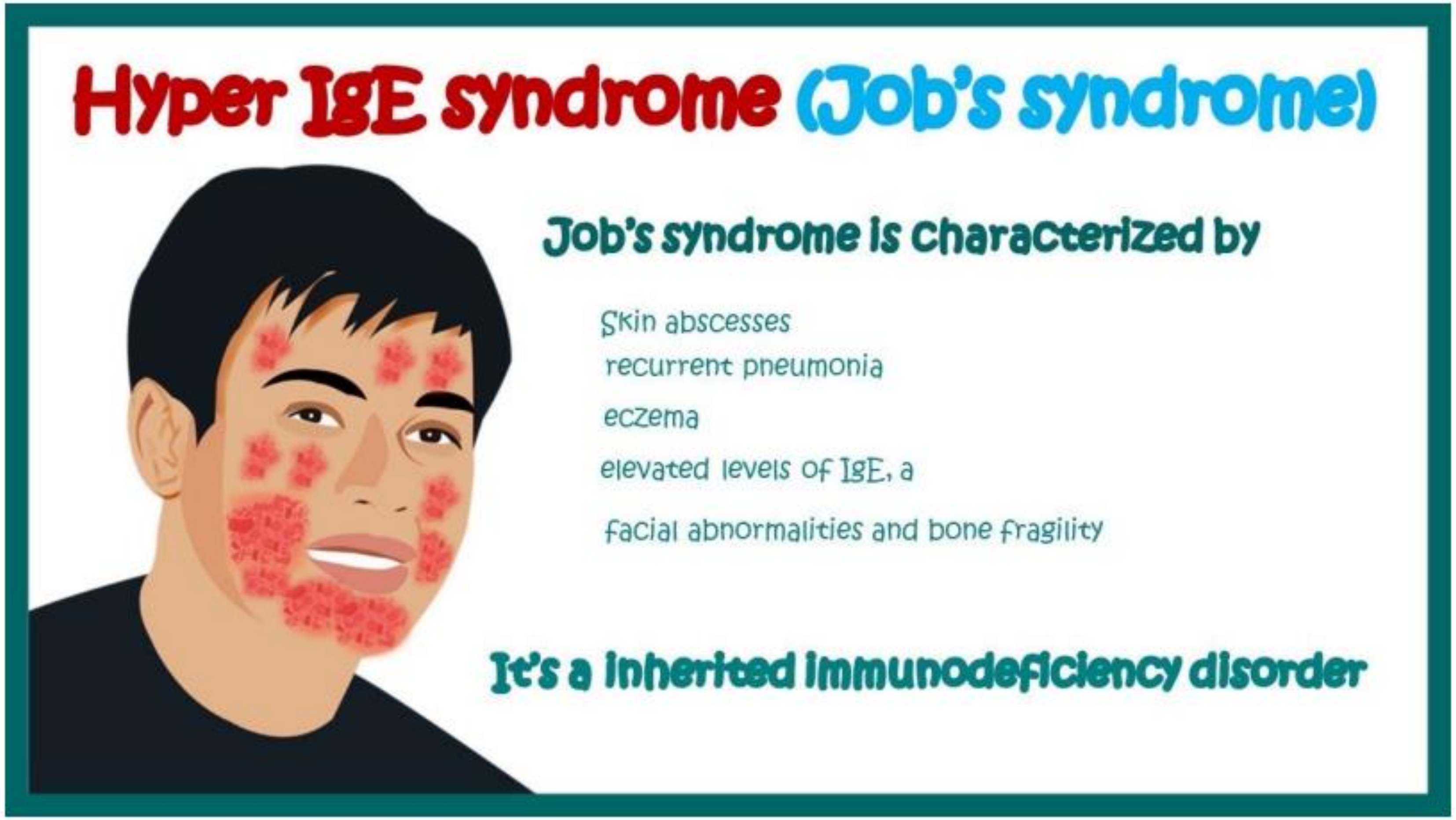
Mother





Chear CT, Nallusamy R, Chan KC, Mohd Tap R, Baharin MF, Syed Yahya SNH, Krishnan PB, Mohamad SB, Ripen AM. Atypical Presentation of Severe Fungal Necrotizing Fasciitis in a Patient with X-Linked Agammaglobulinemia. J Clin Immunol. 2021 Aug;41(6):1178-1186. doi: 10.1007/s10875-021-01017-3. Epub 2021 Mar 13. PMID: 33713249.

Flow Cytometry for Diagnosis of IEI (Job's syndrome)



https://youtu.be/BIx313yp-RA?si=Xg81k8jD3WElK_0S

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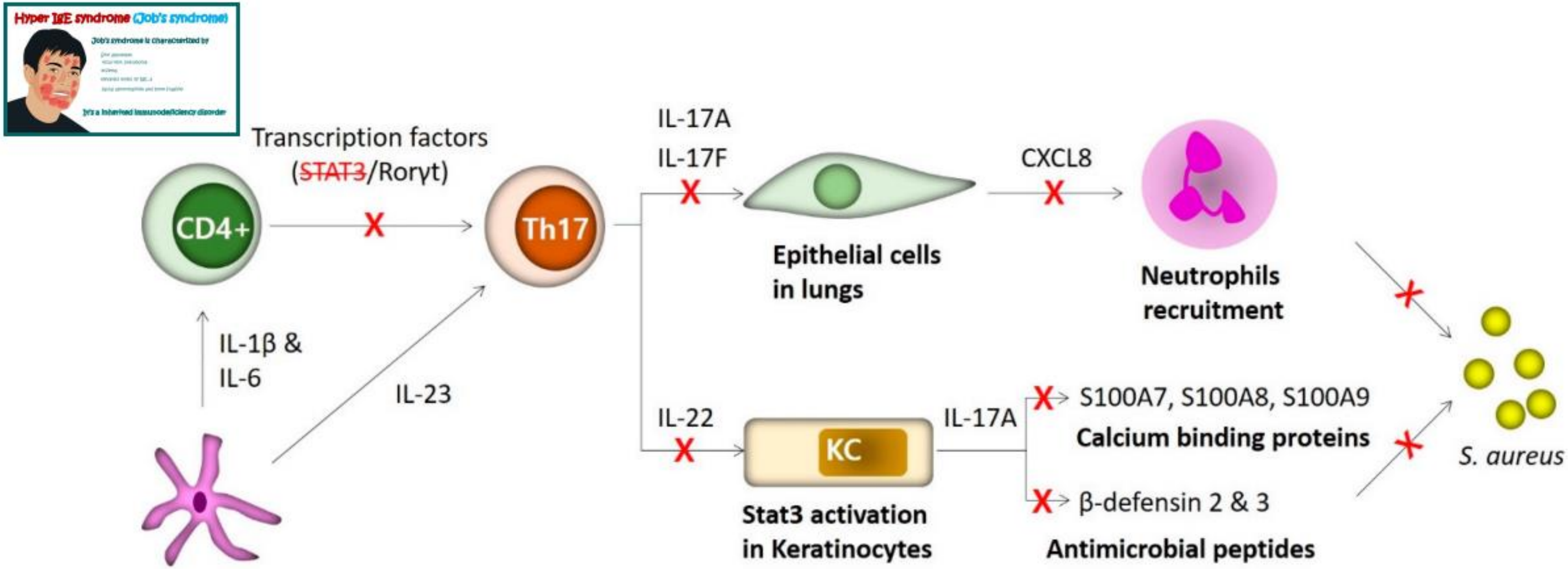

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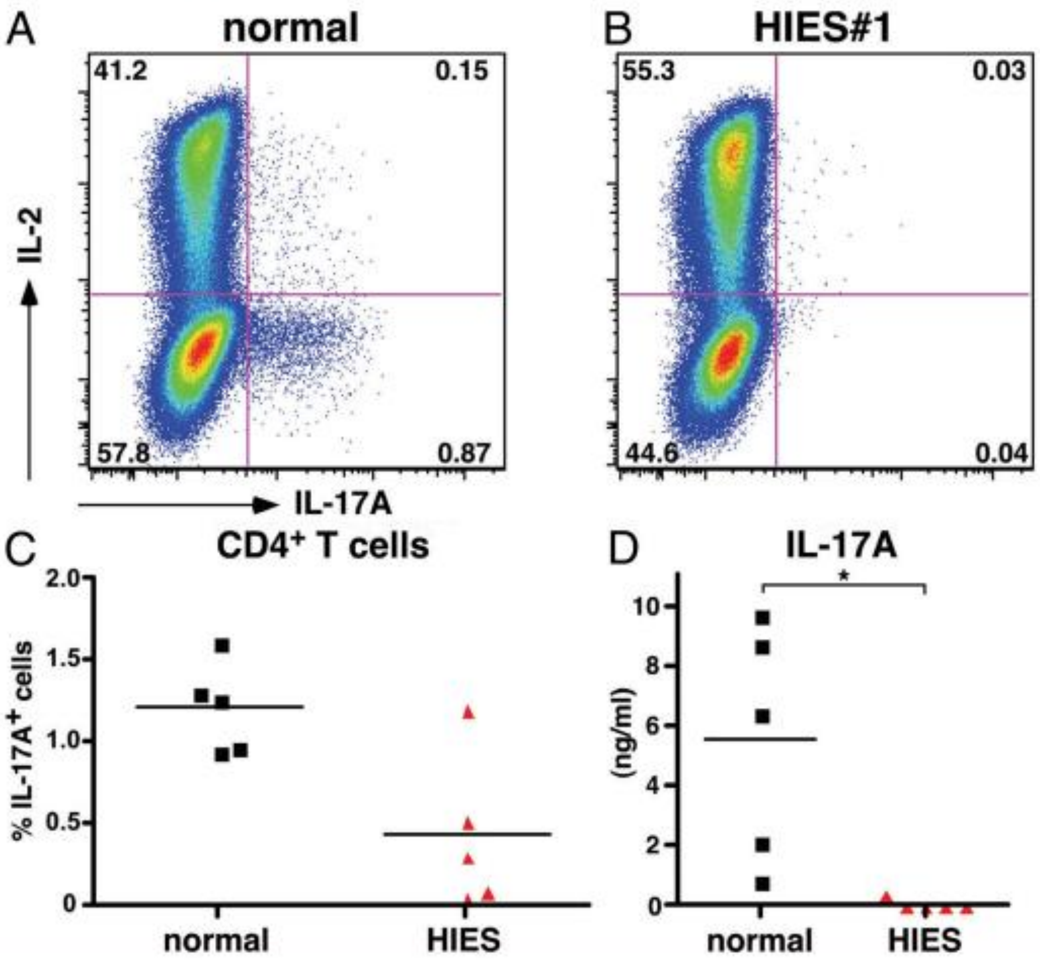

Ma CS, Chew GY, Simpson N, Priyadarshi A, Wong M, Grimbacher B, Fulcher DA, Tangye SG, Cook MC. Deficiency of Th17 cells in hyper IgE syndrome due to mutations in STAT3. J Exp Med. 2008 Jul 7;205(7):1551-7. doi: 10.1084/jem.20080218. PMID: 18591410; PMCID: PMC2442632.

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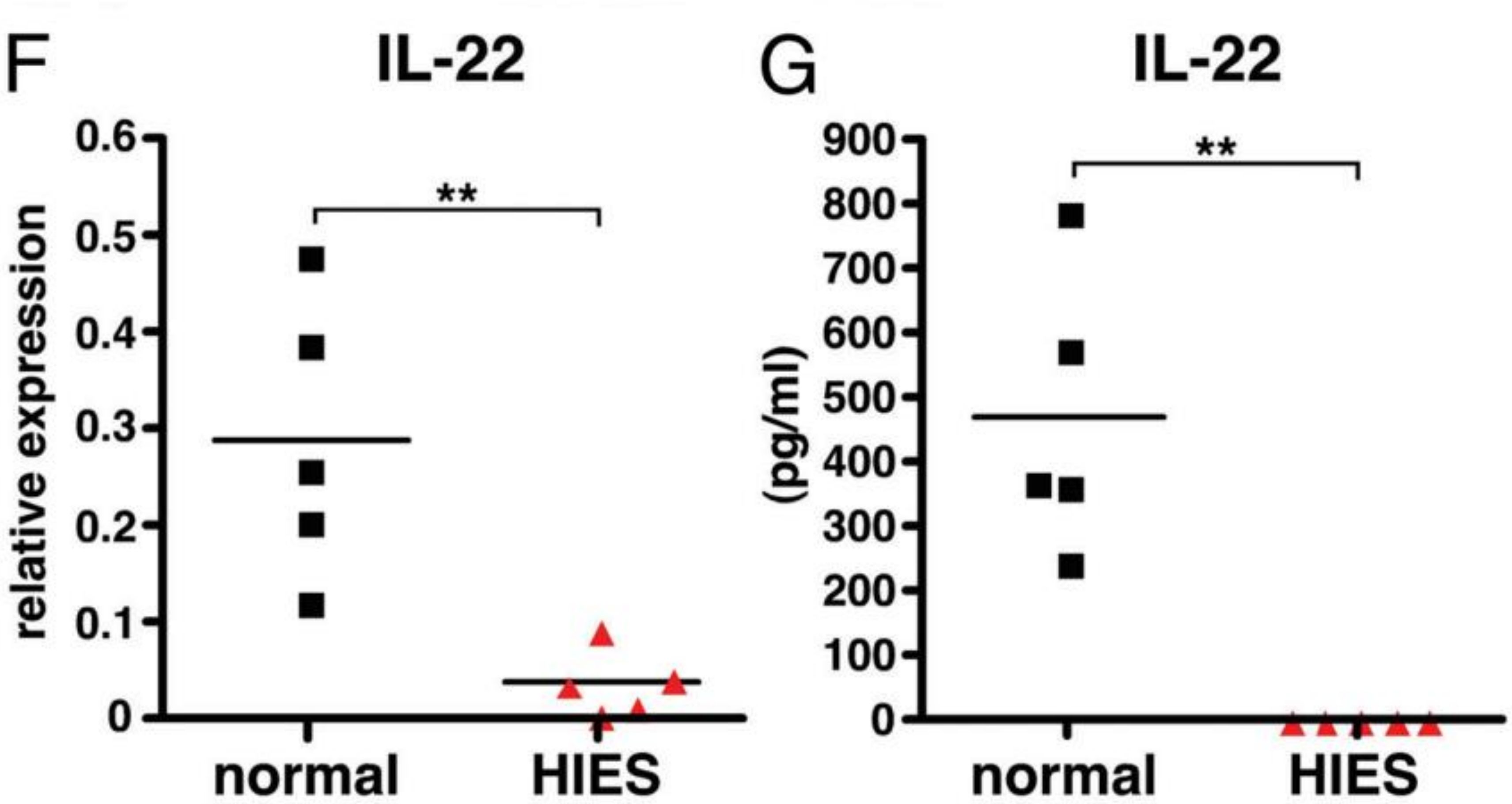

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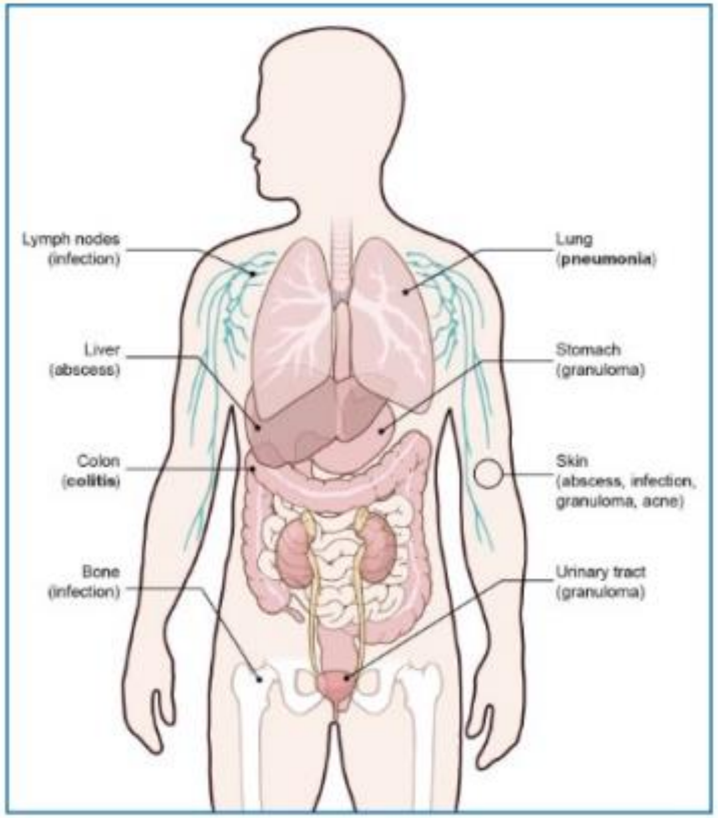
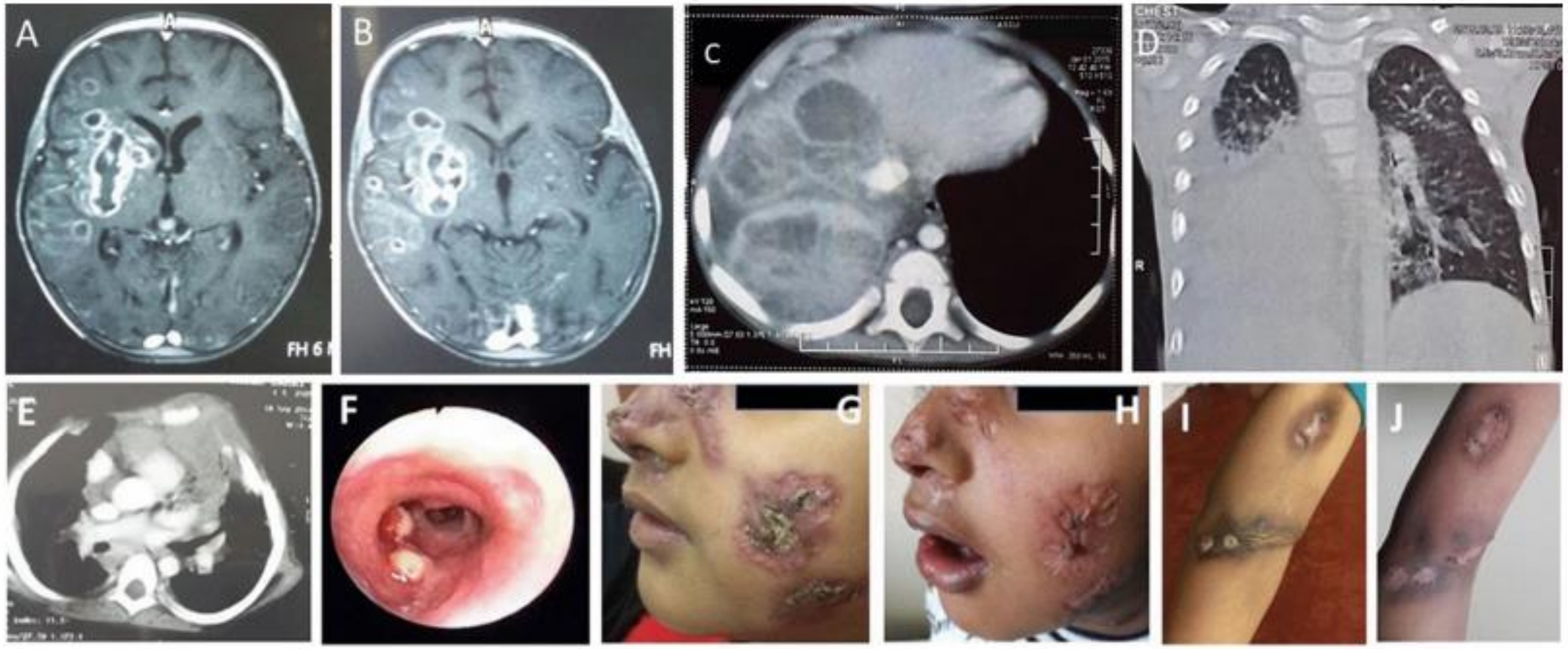
Flow Cytometry for Diagnosis of IEI (CGD)





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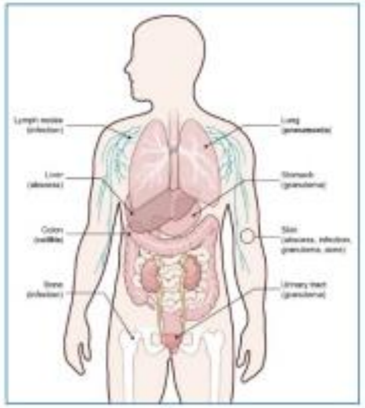
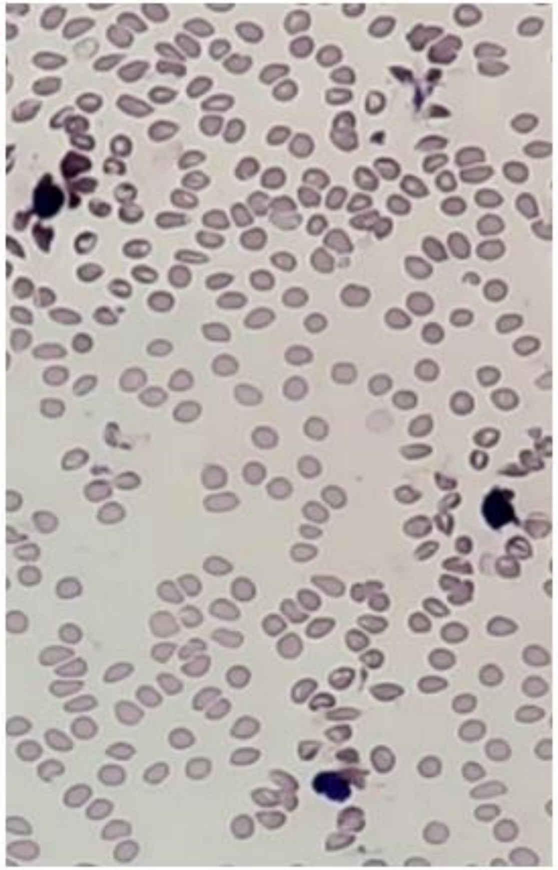
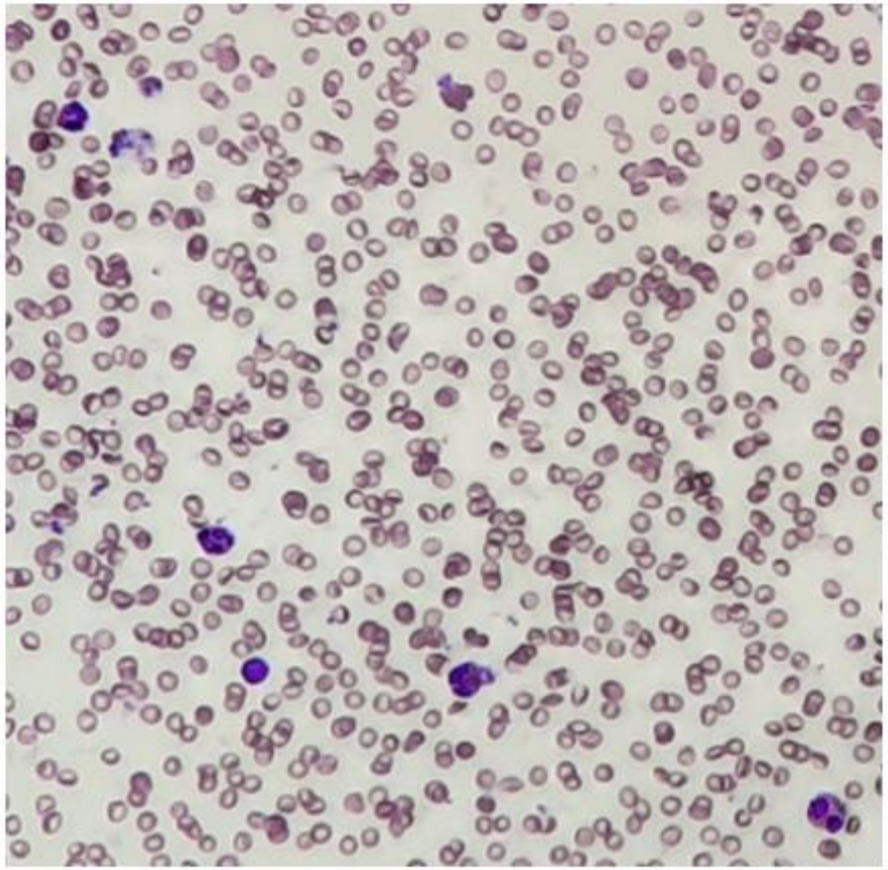
Flow Cytometry for Diagnosis of IEI (CGD)



Healthy

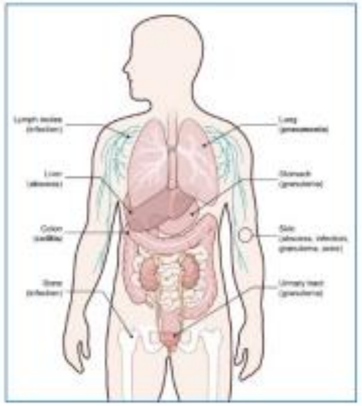


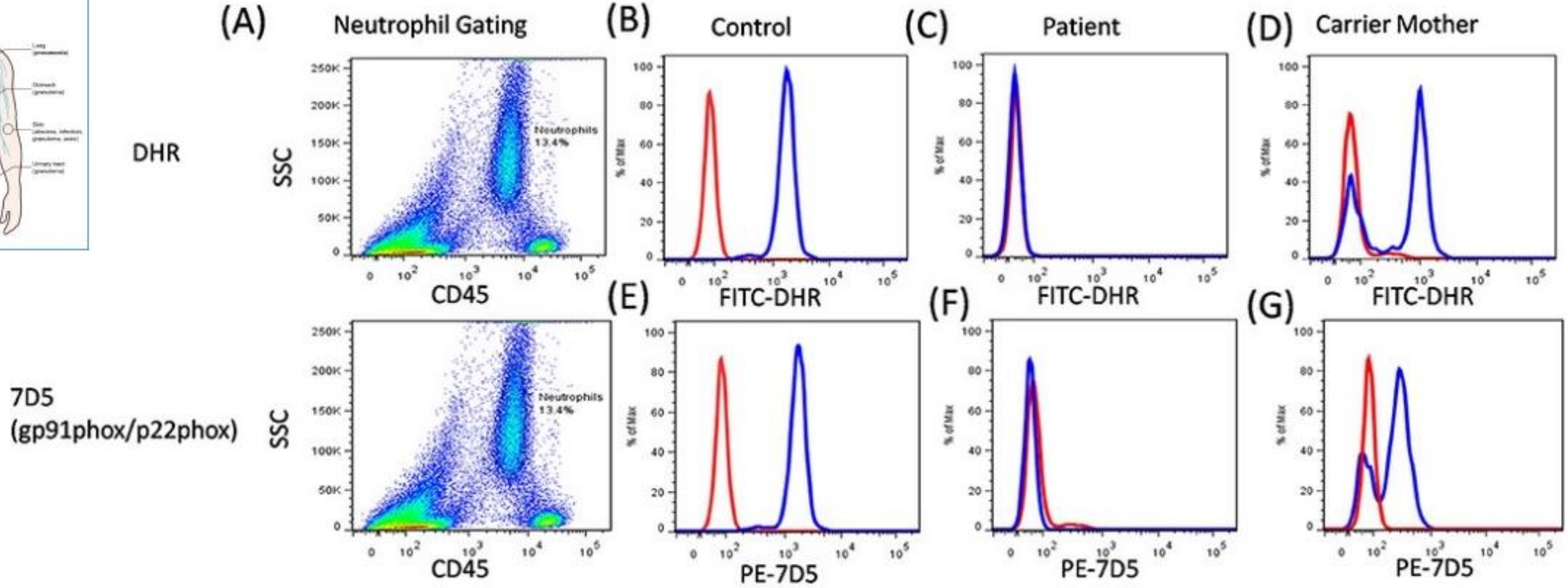
Patient



Madkaikar MR, Shabrish S, Kulkarni M, Aluri J, Dalvi A, Kelkar M, Gupta M. Application of Flow Cytometry in Primary Immunodeficiencies: Experience From India. Front Immunol. 2019 Jun 11;10:1248. doi: 10.3389/fimmu.2019.01248. PMID: 31244832; PMCID: PMC6581000.

Flow Cytometry for Diagnosis of IEI (CGD)





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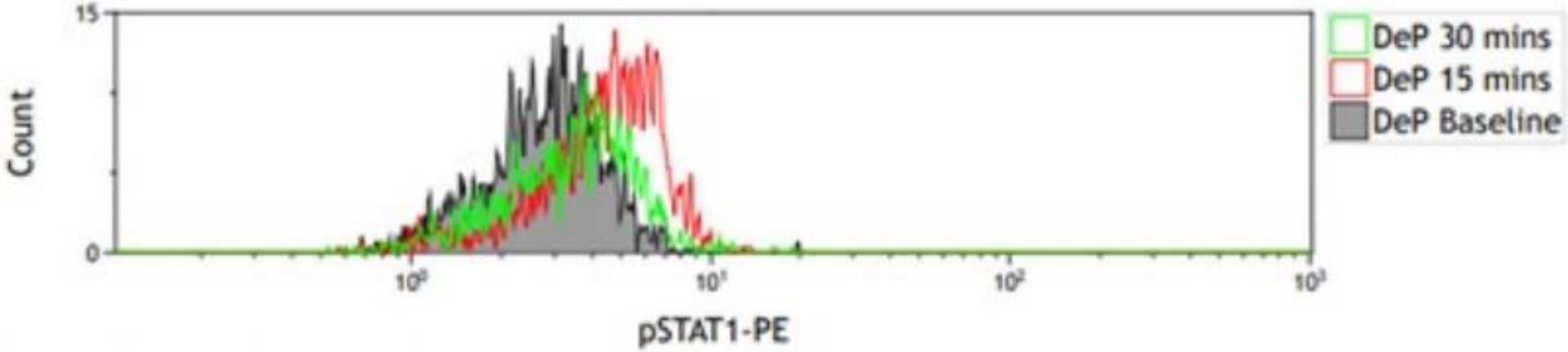
Flow Cytometry for Diagnosis of IEI (STAT1 GOF)

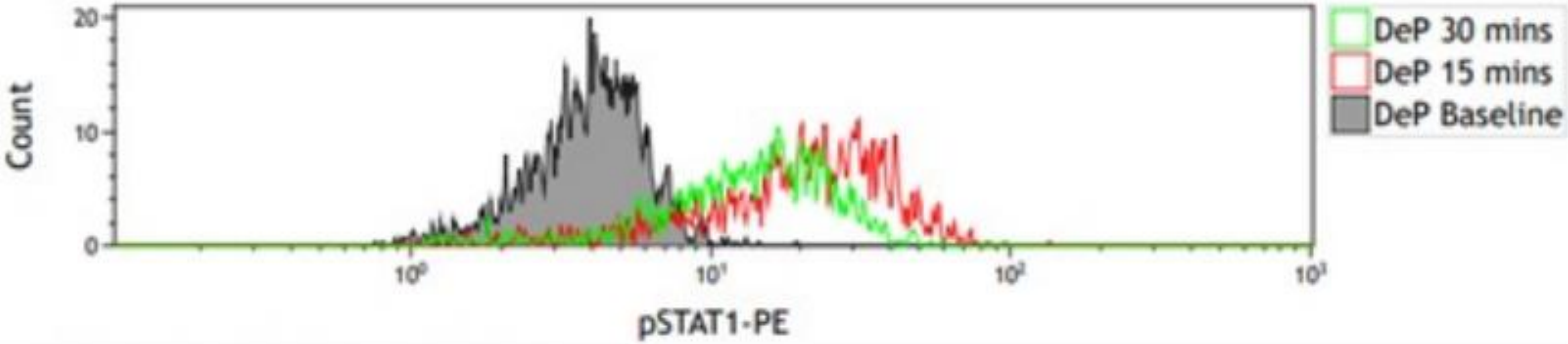
van de Veerdonk FL, Plantinga TS, Hoischen A, Smeekens SP, Joosten LA, Gilissen C, Arts P, Rosentul DC, Carmichael AJ, Smits-van der Graaf CA, Kullberg BJ, van der Meer JW, Lilic D, Veltman JA, Netea MG. STAT1 mutations in autosomal dominant chronic mucocutaneous candidiasis. N Engl J Med. 2011 Jul 7;365(1):54-61. doi: 10.1056/NEJMoa1100102. Epub 2011 Jun 29. PMID: 21714643.

Flow Cytometry for Diagnosis of IEI (STAT1 GOF)

Healthy



Patient



Flow Cytometry for Diagnosis of IEI (STAT6 GOF)

Sharma M, Leung D, Momenilandi M et al. Human germline heterozygous gain-of-function STAT6 variants cause severe allergic disease. J Exp Med. 2023 May 1;220(5):e20221755. doi: 10.1084/jem.20221755. Epub 2023 Mar 8. PMID: 36884218; PMCID: PMC10037107.

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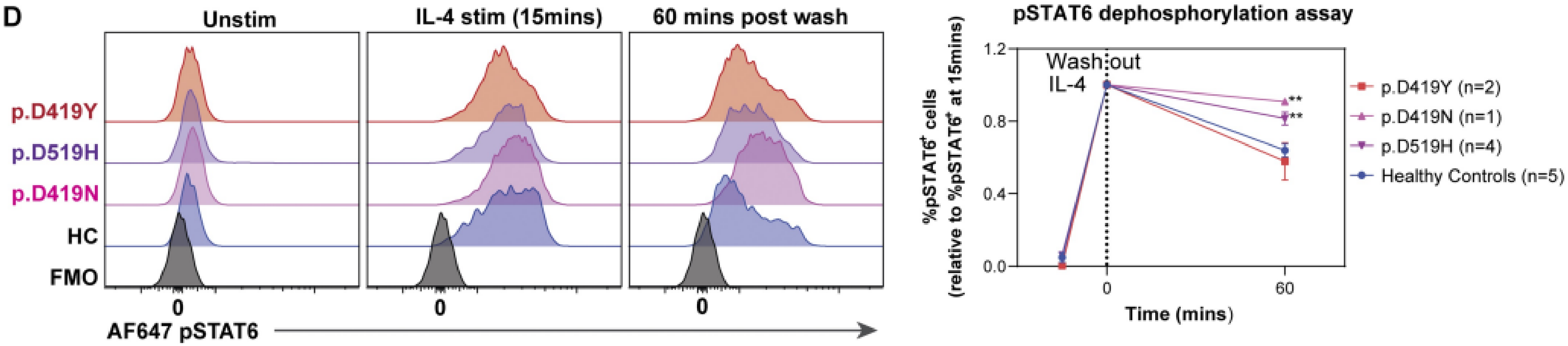

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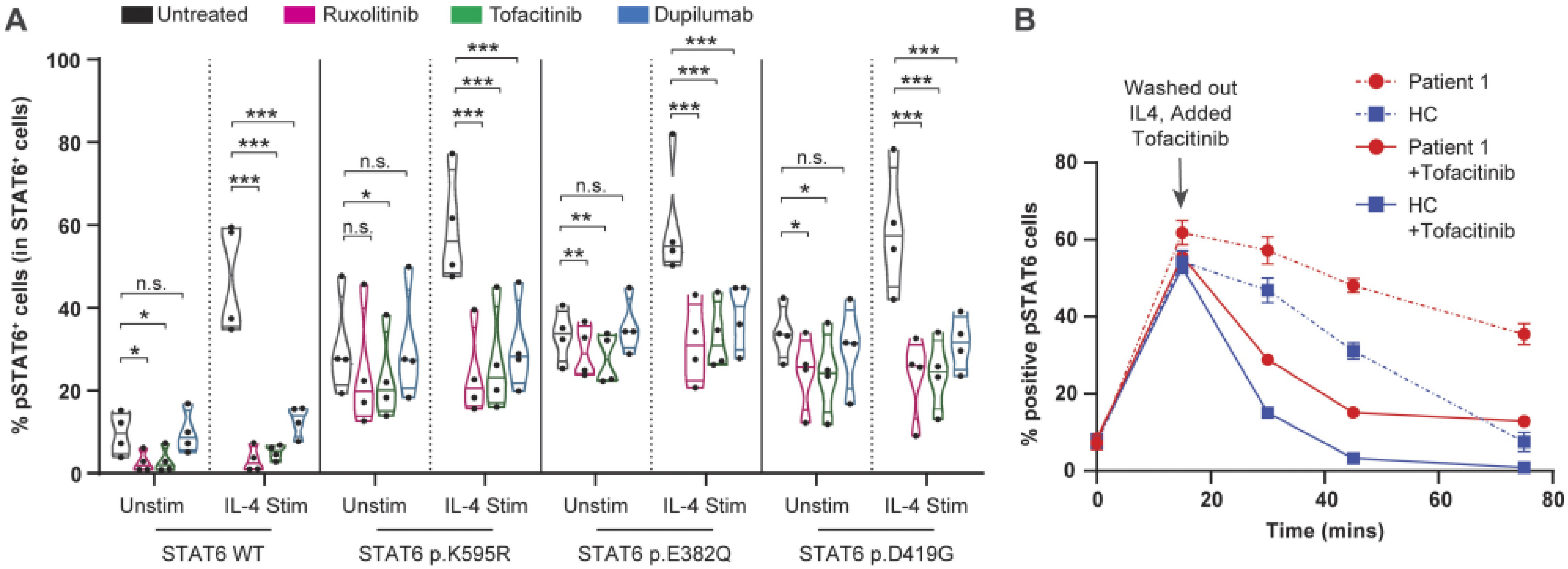

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Flow Cytometry for Diagnosis of IEI (STAT6 GOF)

Jesse, maroon shirt in the middle, says he is finally able to do "normal" activities such as going out with friends (Photo and caption provided by B.C. Children's Hospital)

Sharma M, Leung D, Momenilandi M et al. Human germline heterozygous gain-of-function STAT6 variants cause severe allergic disease. J Exp Med. 2023 May 1;220(5):e20221755. doi: 10.1084/jem.20221755. Epub 2023 Mar 8. PMID: 36884218; PMCID: PMC10037107.

COLLABORATION

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Q&A

IPOPI
5TH REGIONAL
ASIAN PID MEETING
24-25 MARCH 2024
TOKYO, JAPAN
an IPOPI event

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Tailoring Newborn Screening for Severe Combined Immunodeficiency in Asian Context

Insights from Japan | Dr Manabu Wakamatsu *(Japan)*

Insights from Malaysia | Dr Adli Ali *(Malaysia)*

IPOPI
5TH REGIONAL
ASIAN PID MEETING
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TOKYO, JAPAN
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Tailoring Newborn Screening for Severe Combined Immunodeficiency in Asian Context: Insights from Japan

Department of Pediatrics, Nagoya University Graduate School of Medicine, Nagoya, Japan

Manabu Wakamatsu

IPOPI 5th Regional Asian PID Patients and Doctors' Meeting

COI Disclosure Information

Presenter：Manabu Wakamatsu

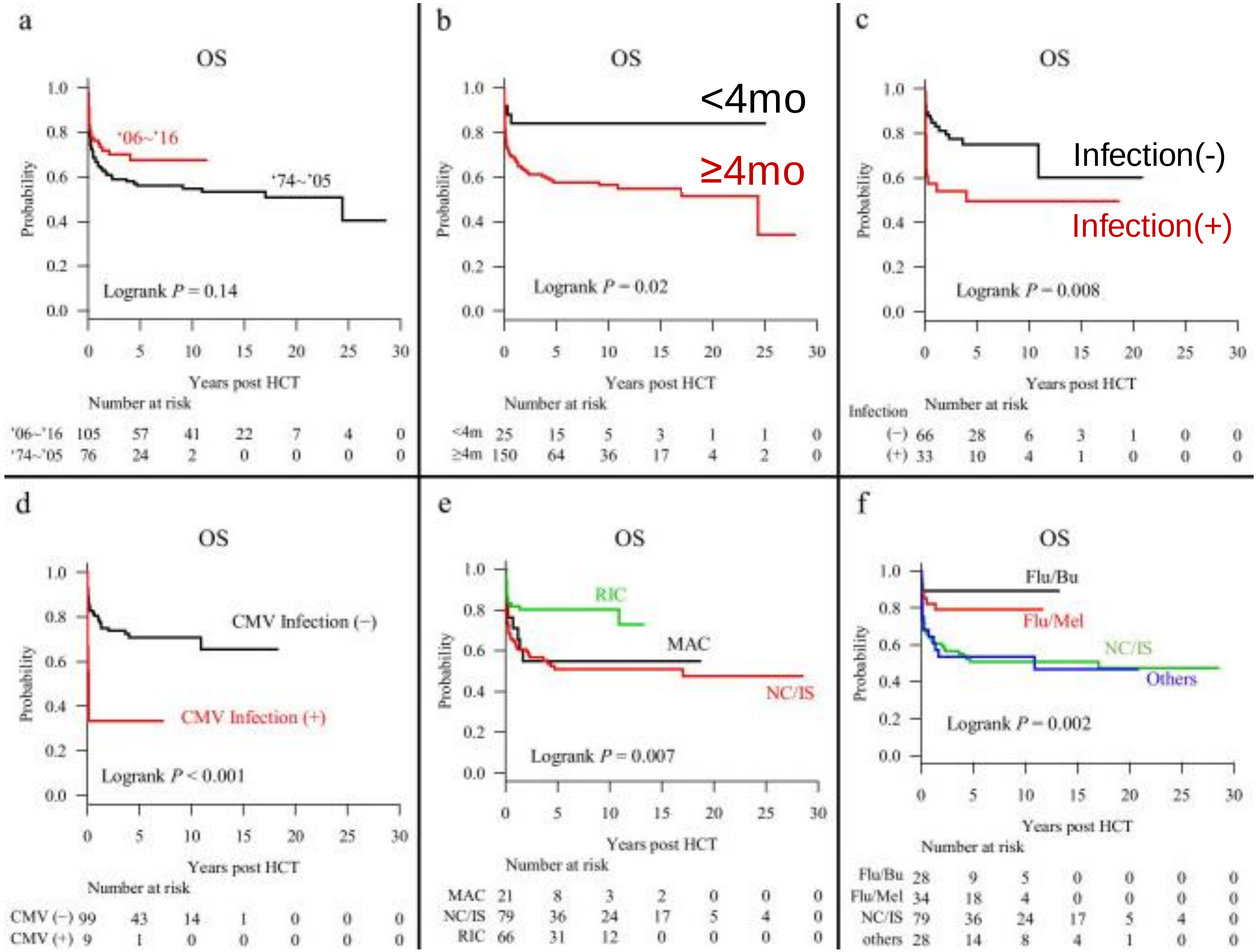
I have no financial relationships to disclose.

Severe Combined ImmunoDeficiency (SCID)

The severe dysfunction of cellular and humoral immunity owing to impaired T/B cell development or function.

Without any treatment, SCID develop opportunistic and/or severe infections during infancy, leading to death.

A cohort of 181 SCID patients undergoing their first allogeneic HSCT in 1974–2016.



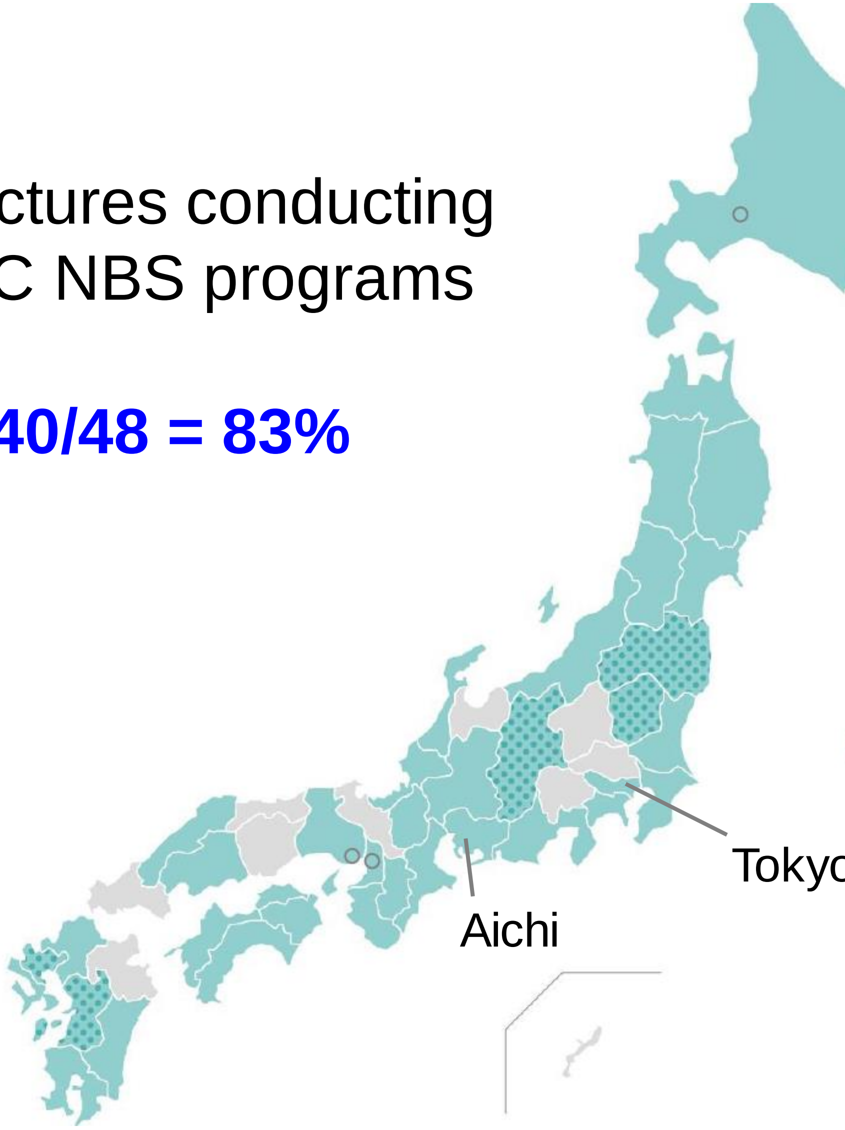
Miyamoto S,et,al. JOCl. 2021;41:1865-77.

PIDJ-NBS
PID 新生児スクリーニングコンソーシアム

National Landscape of the TREC Newborn Screening Programs

Prefectures conducting TREC NBS programs

40/48 = 83%



2017.4：愛知 Aichi
2019.2：熊本
2019.4：CReARID (埼玉・千葉・群馬の一部など13自治体)
2020.4：宮崎
2020.5：千葉
2020.8：大阪市・大阪府
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2020.11：新潟
2021.1：宮城
2021.4：岐阜・兵庫・（佐賀：一部）
2021.5：島根
2021.10：愛媛
2022：栃木、茨城、神奈川、山形、広島、鹿児島、長崎、石川、長野
2023：佐賀、東京、福岡、秋田、岩手、福島、三重、香川、徳島、高知、福井、青森、静岡、滋賀、和歌山
（準備中：11：埼玉、山梨、群馬、富山、京都、奈良、鳥取、岡山、山口、大分、沖縄）
公費化：5：熊本、栃木、佐賀、安曇野、高崎

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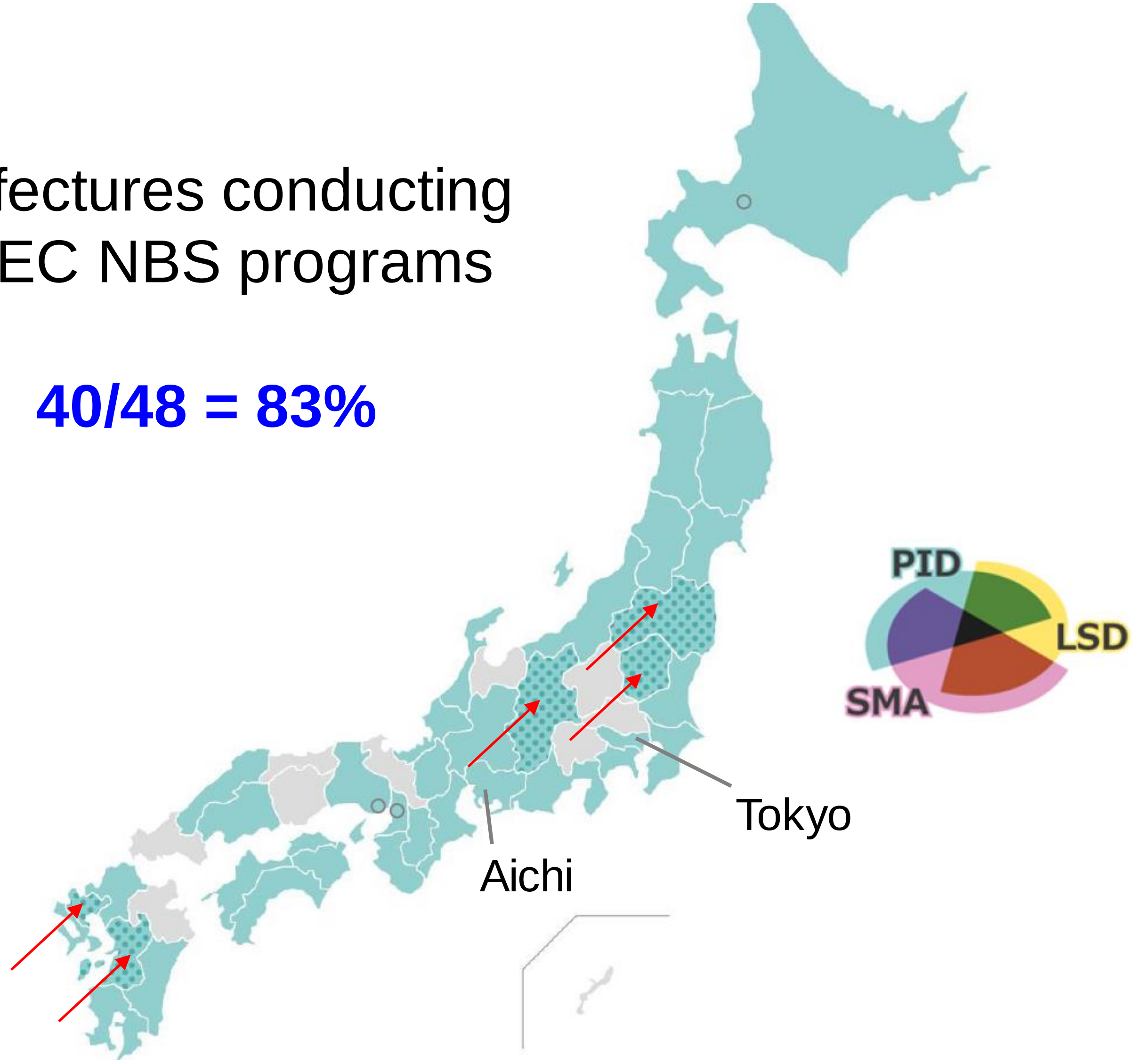

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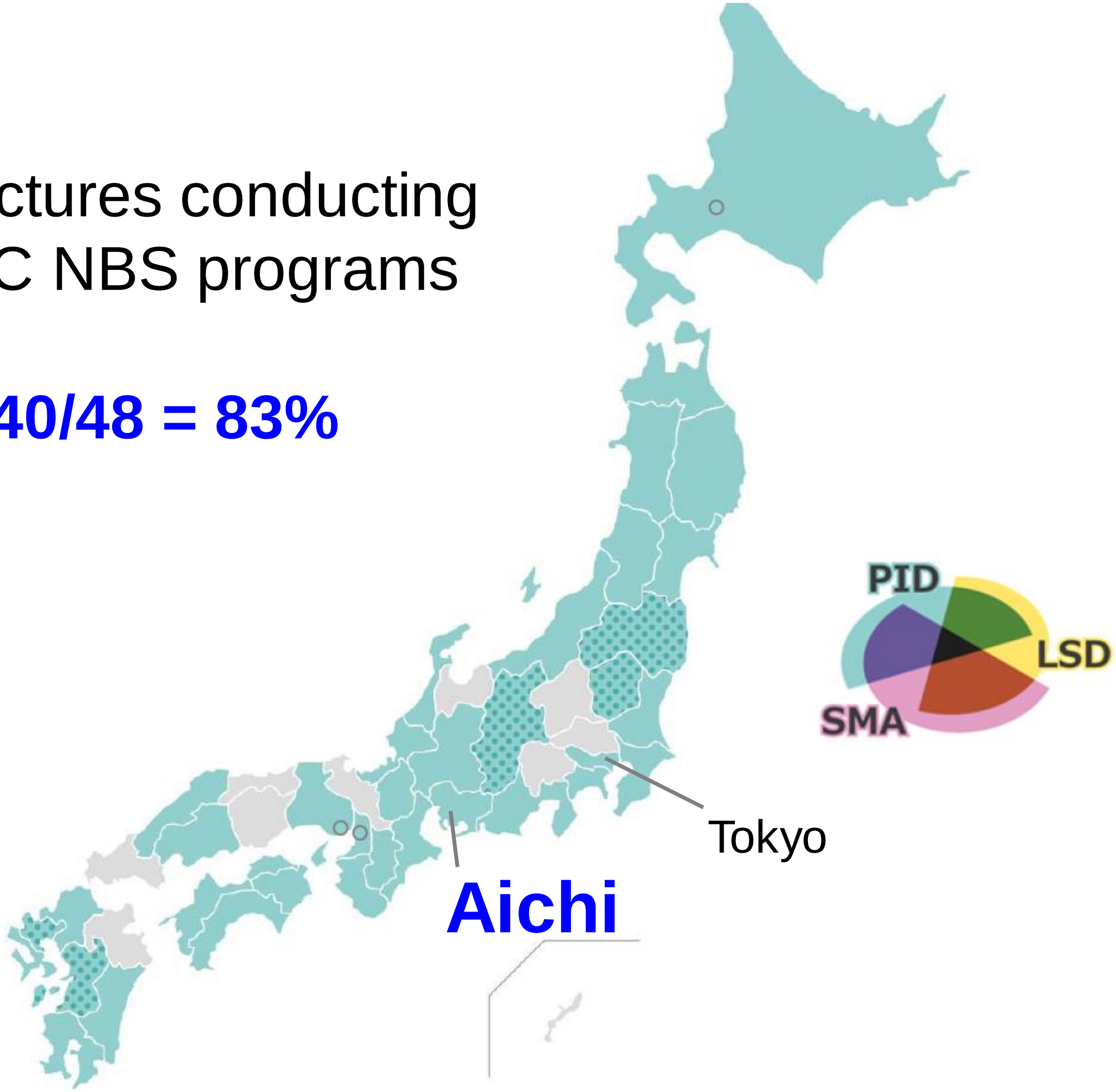
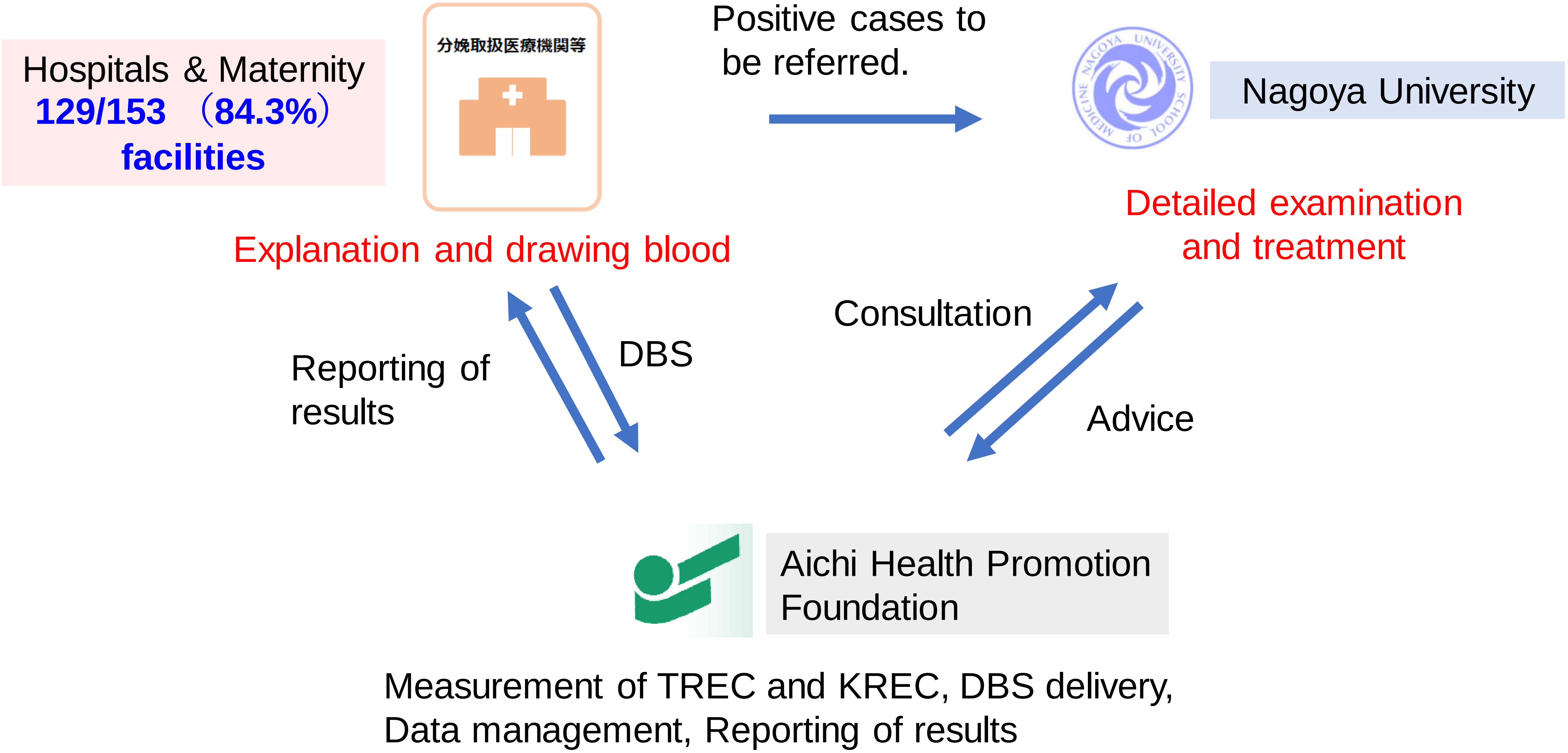


Aichi Prefecture

- Nagoya is the capital of Aichi Prefecture, and the fourth-largest city in Japan.
- A population of 7.5 million.
- 40,000-50,000 newborns per year.

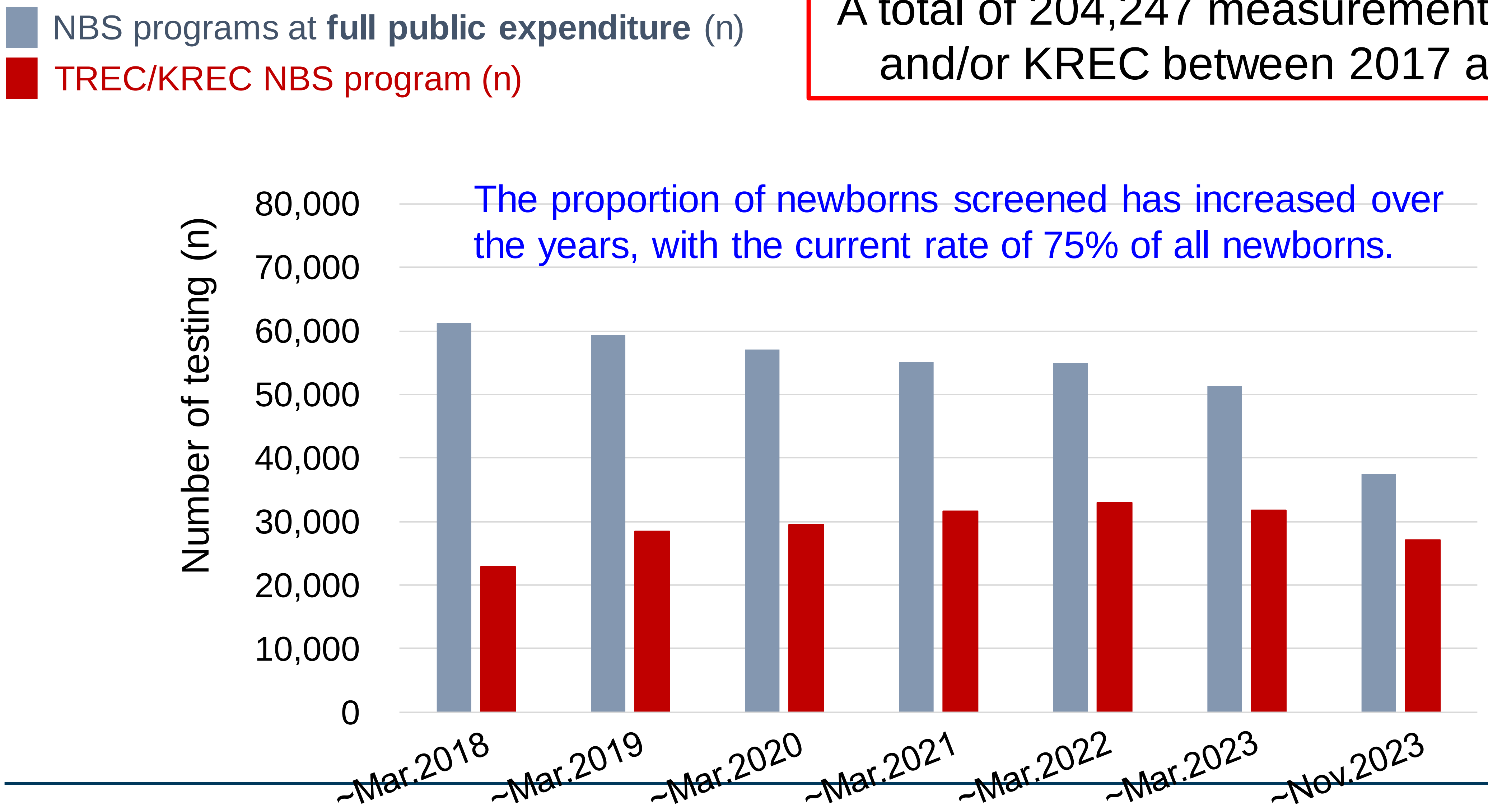
Nagoya Castle

Organization of TREC/KREC NBS program in Aichi Prefecture



Results of TREC/KREC NBS program in Aichi Prefecture

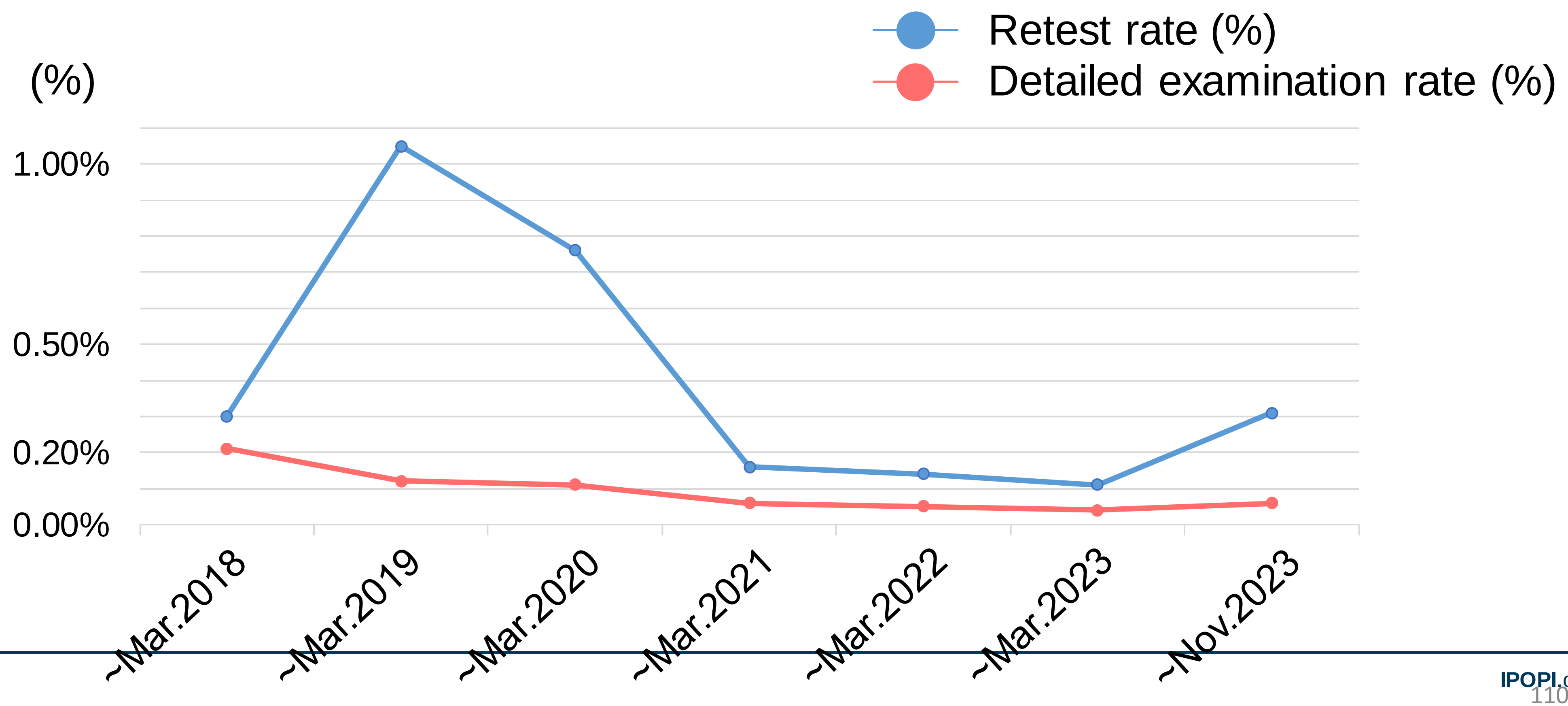
A total of 204,247 measurements of TREC and/or KREC between 2017 and 2023



Rates of retest and detailed examination

Retest；measurement of TREC/KREC using other DBSs.

Detailed examination；retests also had abnormal values, and NGS and FCM analysis were performed.

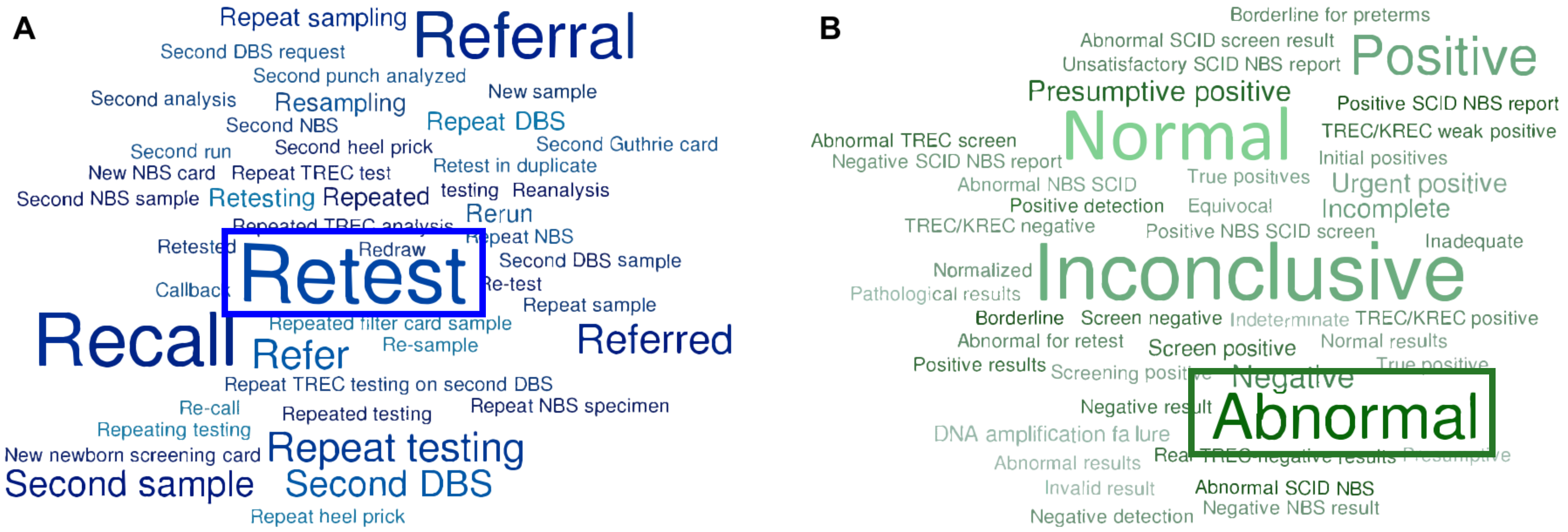


an IPOPI event

Recommendations for uniform definitions used in newborn screening for severe combined immunodeficiency

Check for updates

Maartje Blom, MD,[a] Rolf H. Zetterström, MD, PhD,[b,c] Asbjørg Stray-Pedersen, MD, PhD,[d,e] Kimberly Gilmour, PhD,[f,g,h] Andrew R. Gennery, MD, PhD,[i,j] Jennifer M. Puck, MD,[k,l] and Mirjam van der Burg, PhD[a] *Leiden, The Netherlands; Stockholm, Sweden; Oslo, Norway; London and Newcastle upon Tyne, United Kingdom; and San Francisco, Calif*

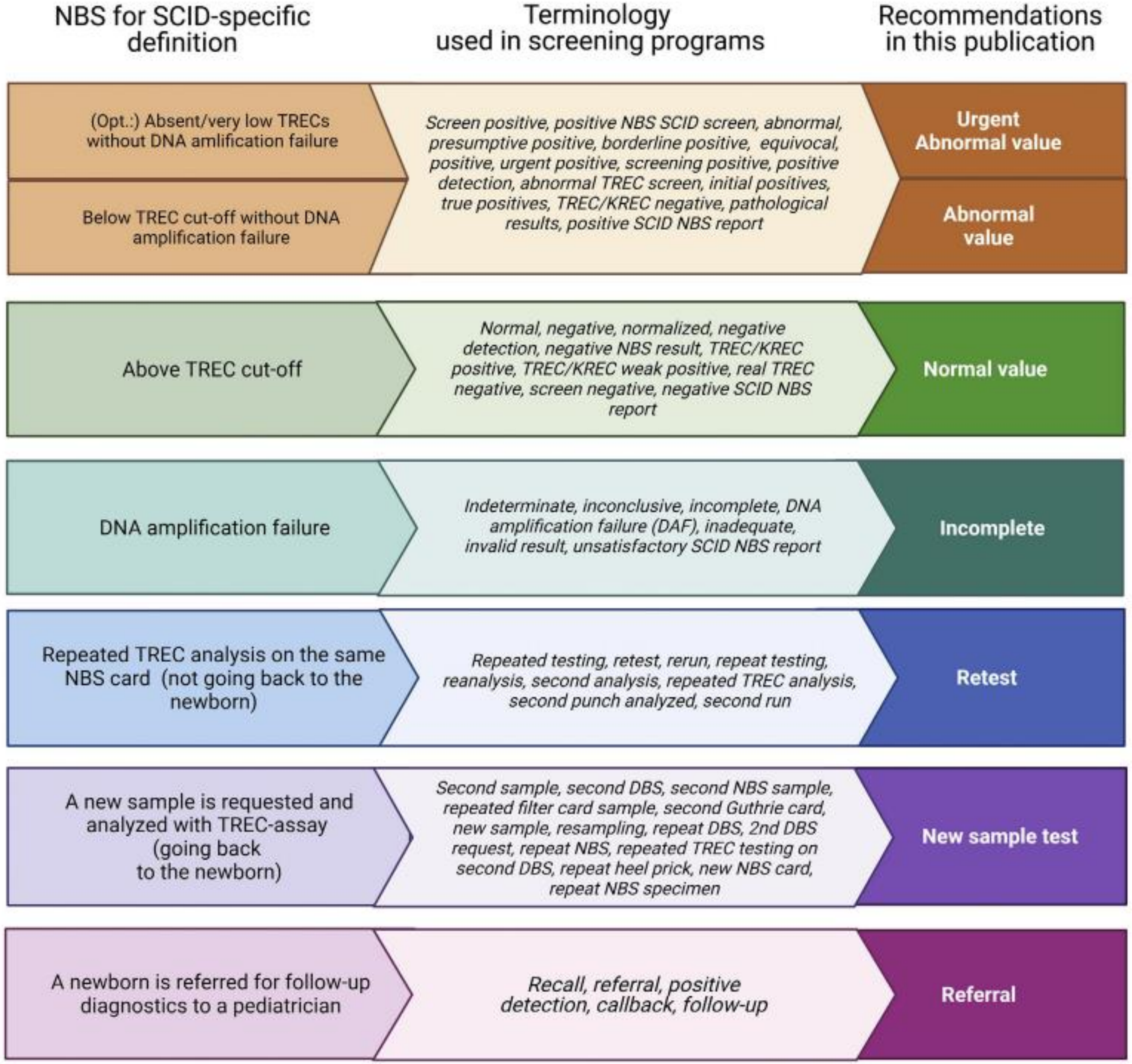


Comparison of screening outcomes has been hampered by use of disparate terminology and variable case definitions for non-SCID PIDs with T-cell lymphopenia.

Maartje Blom, et al. JACI. 2022;149:1428-36.

Definitions of terms related to the TREC/KREC NBS programs

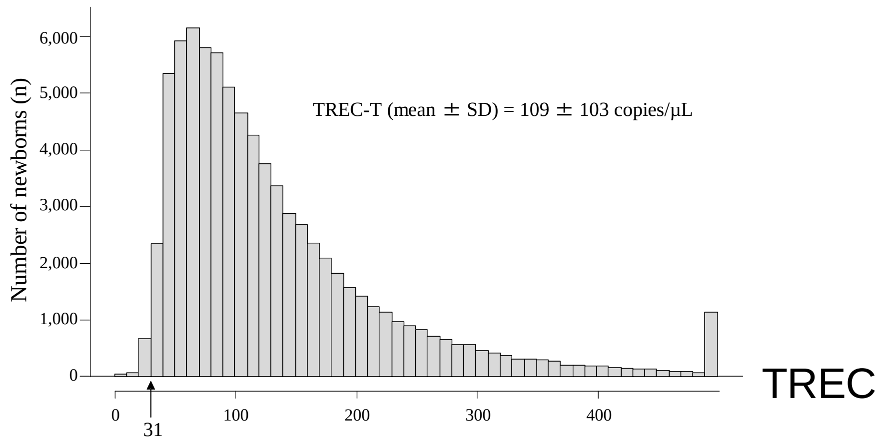
Uniformity of terminology in the TREC/KREC NBS programs is proposed.



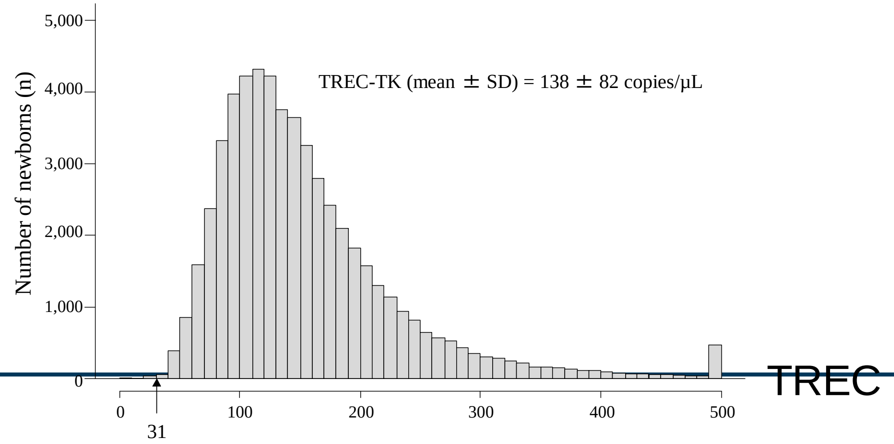
Maartje Blom, et al. JACI. 2022;149:1428-36.

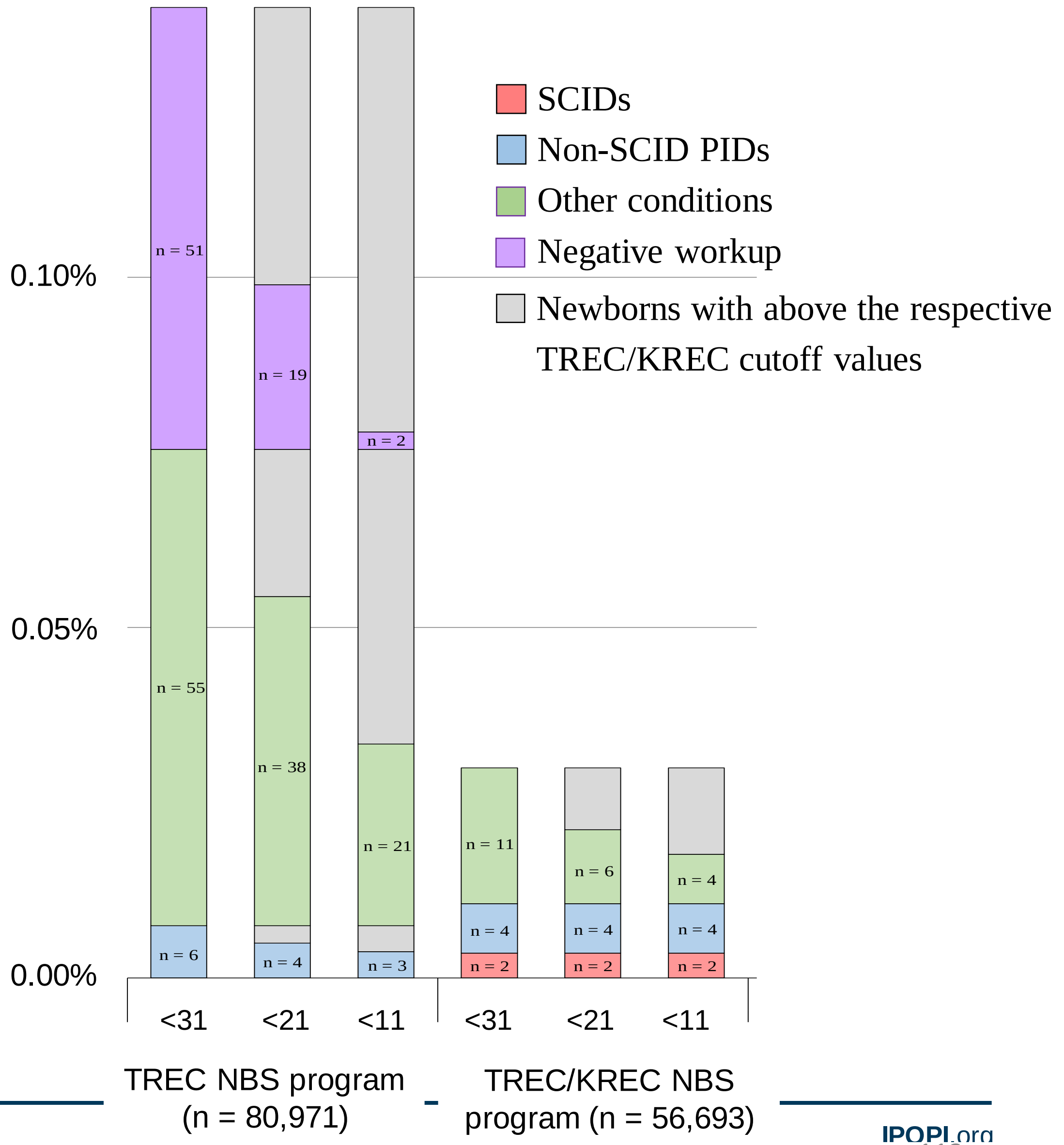
EnLite™ Neonatal TREC vs. TREC/KREC Kits

EnLite™ Neonatal TREC



EnLite™ Neonatal TREC/KREC

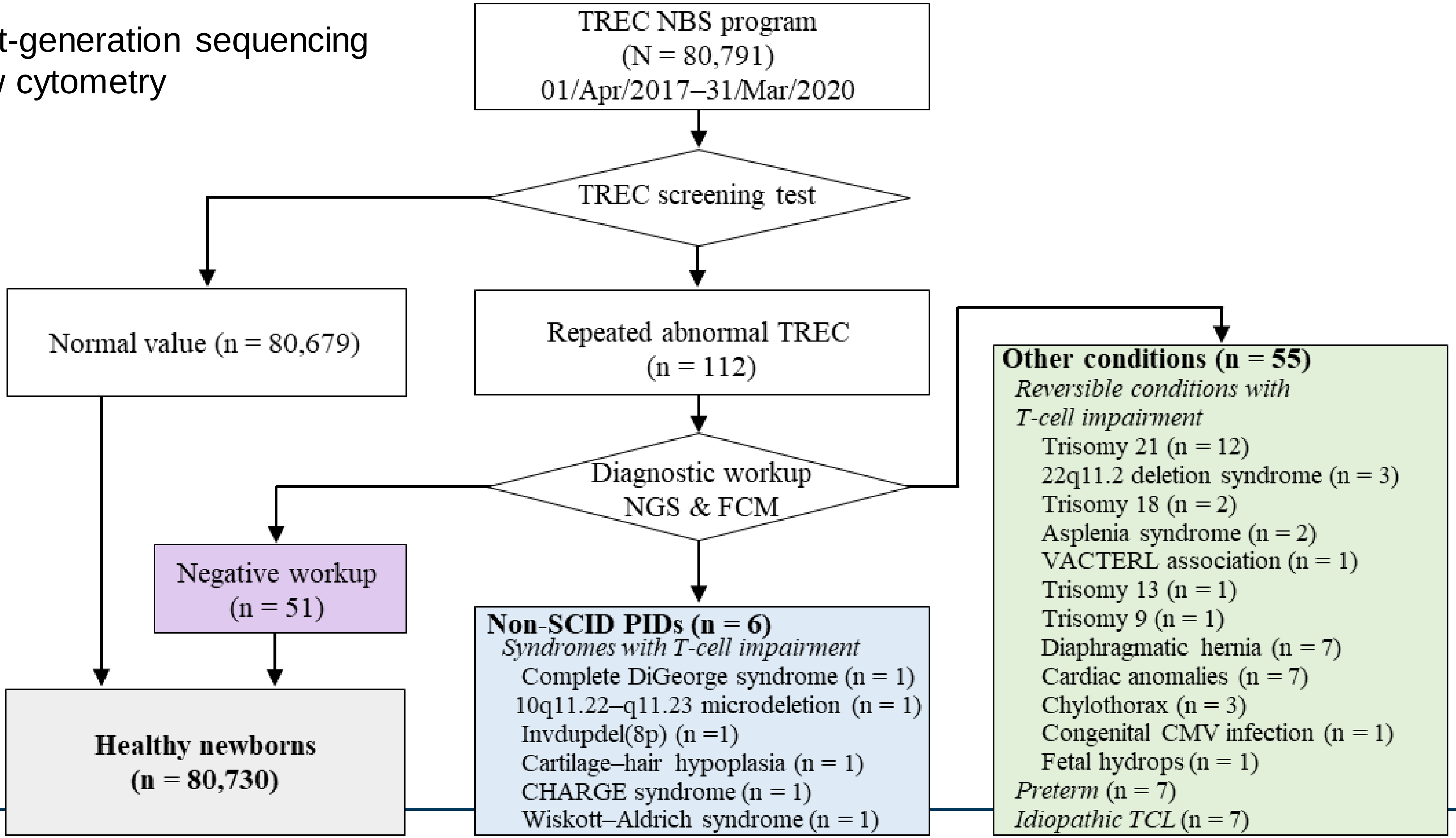




Wakamatsu M, et al. JCI. 2022;42:1696-1707.

TREC NBS program（2017/4/1～2020/3/31）

NGS; next-generation sequencing
FCM; flow cytometry



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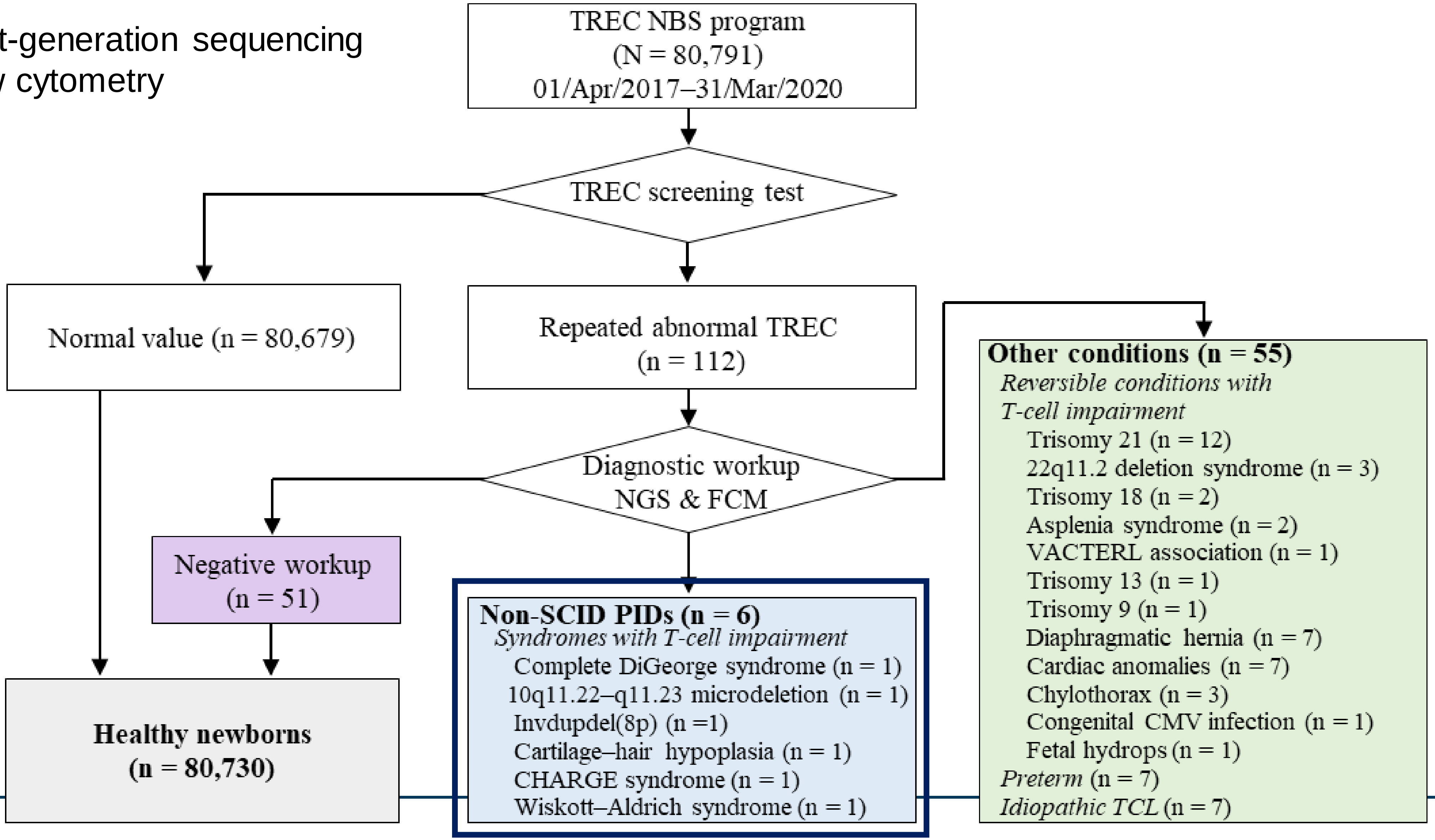
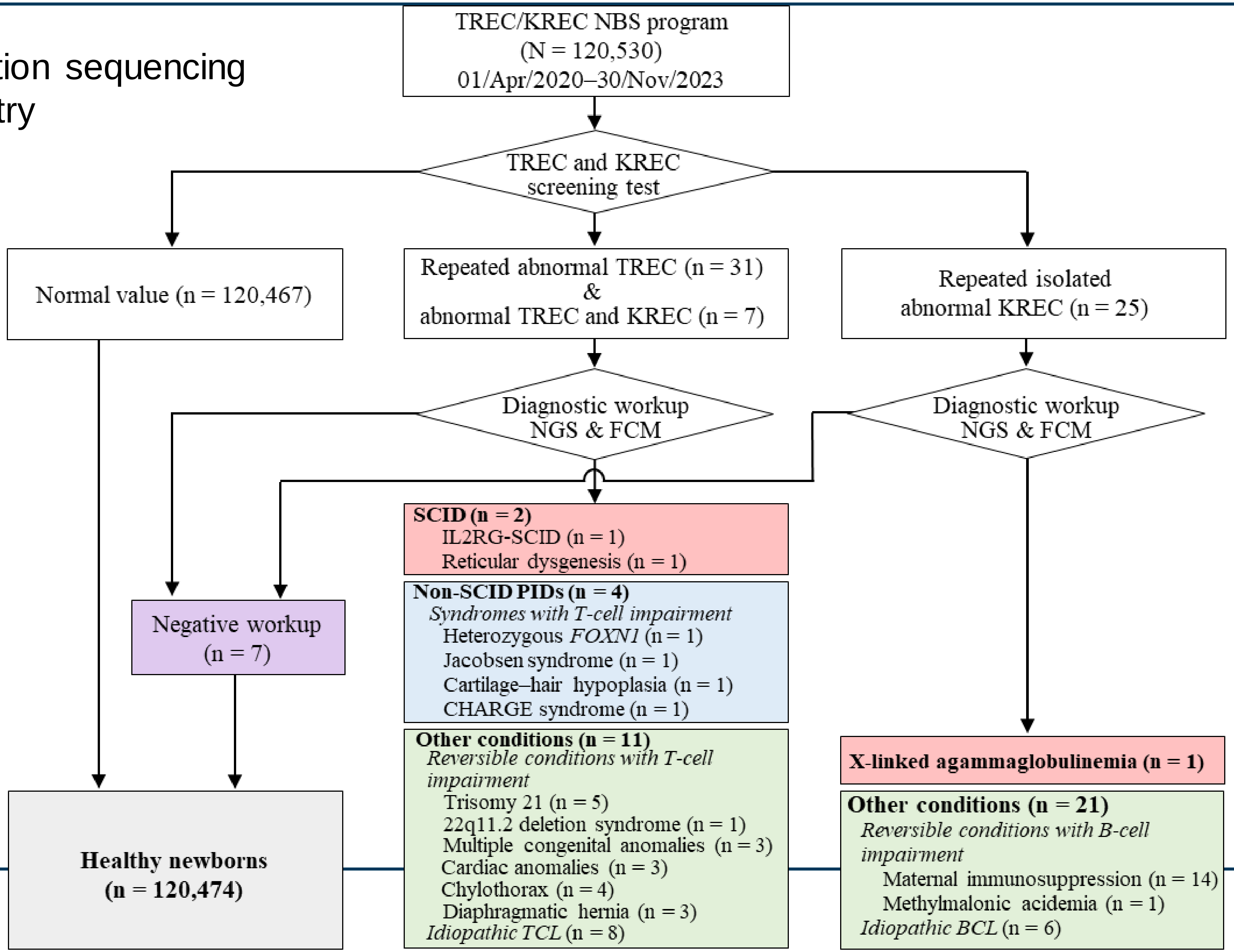


TREC・KREC NBS programs (2020/4/1～2023/11/30)

NGS; next-generation sequencing
FCM; flow cytometry



TREC・KREC NBS programs (2020/4/1～2023/11/30)

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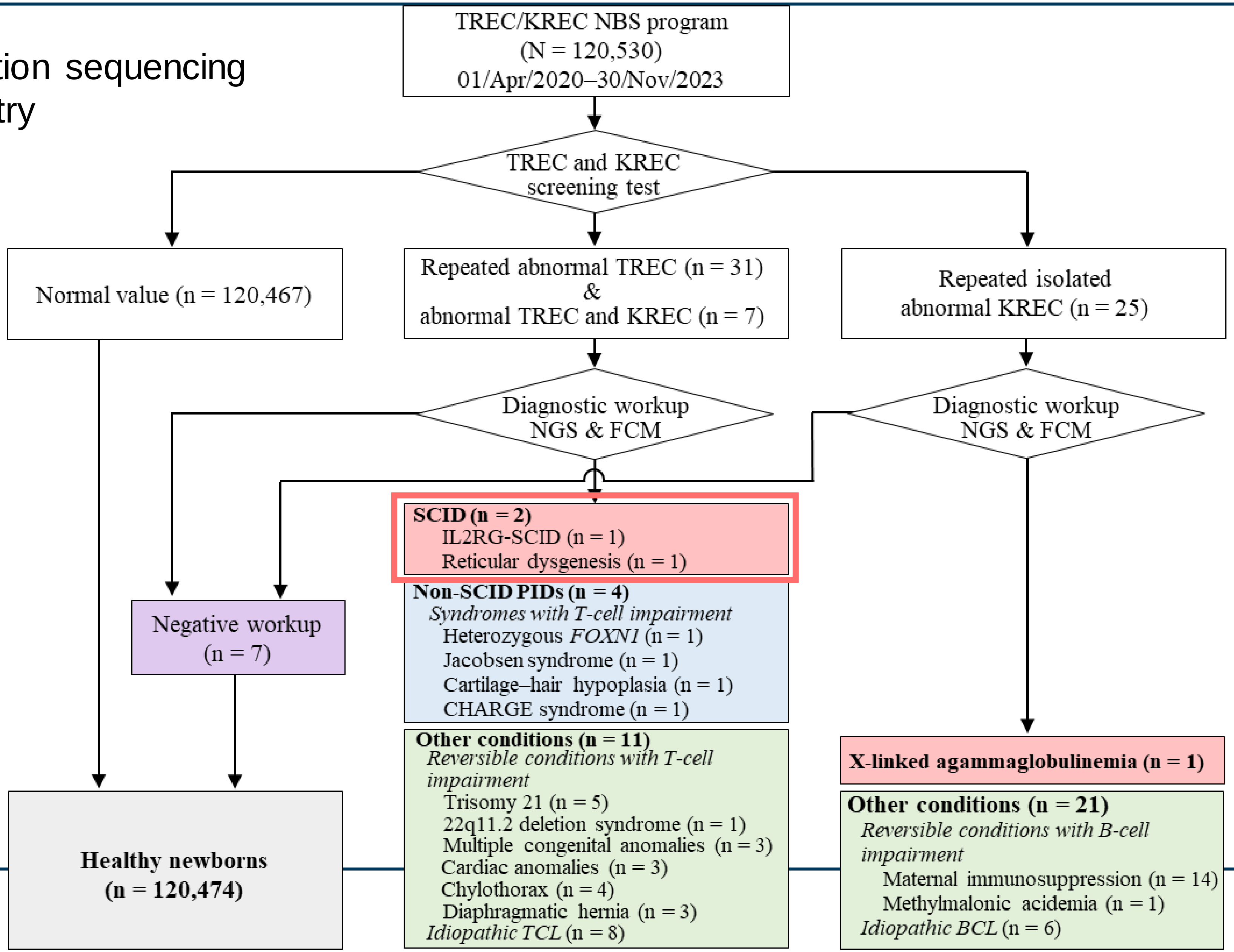

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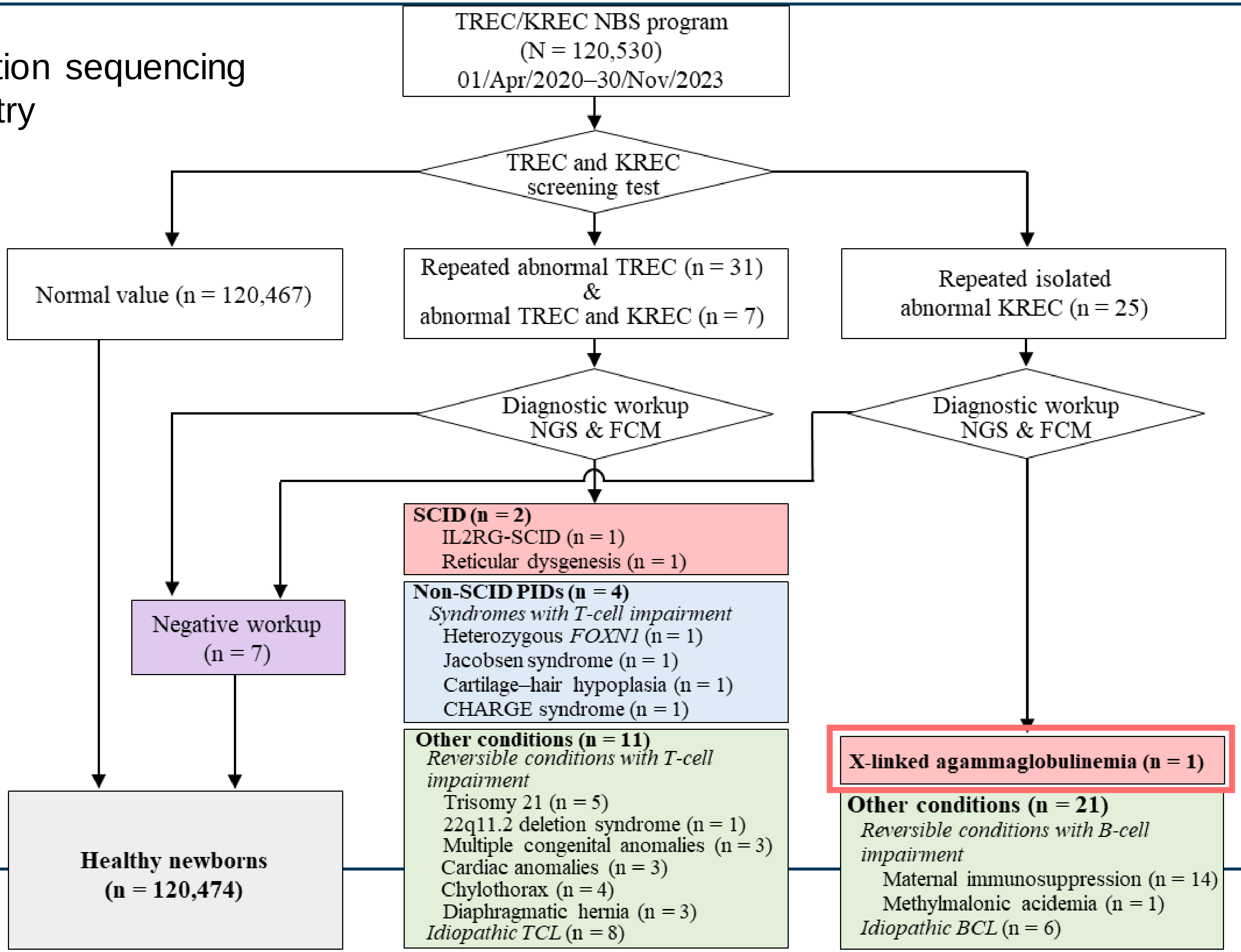

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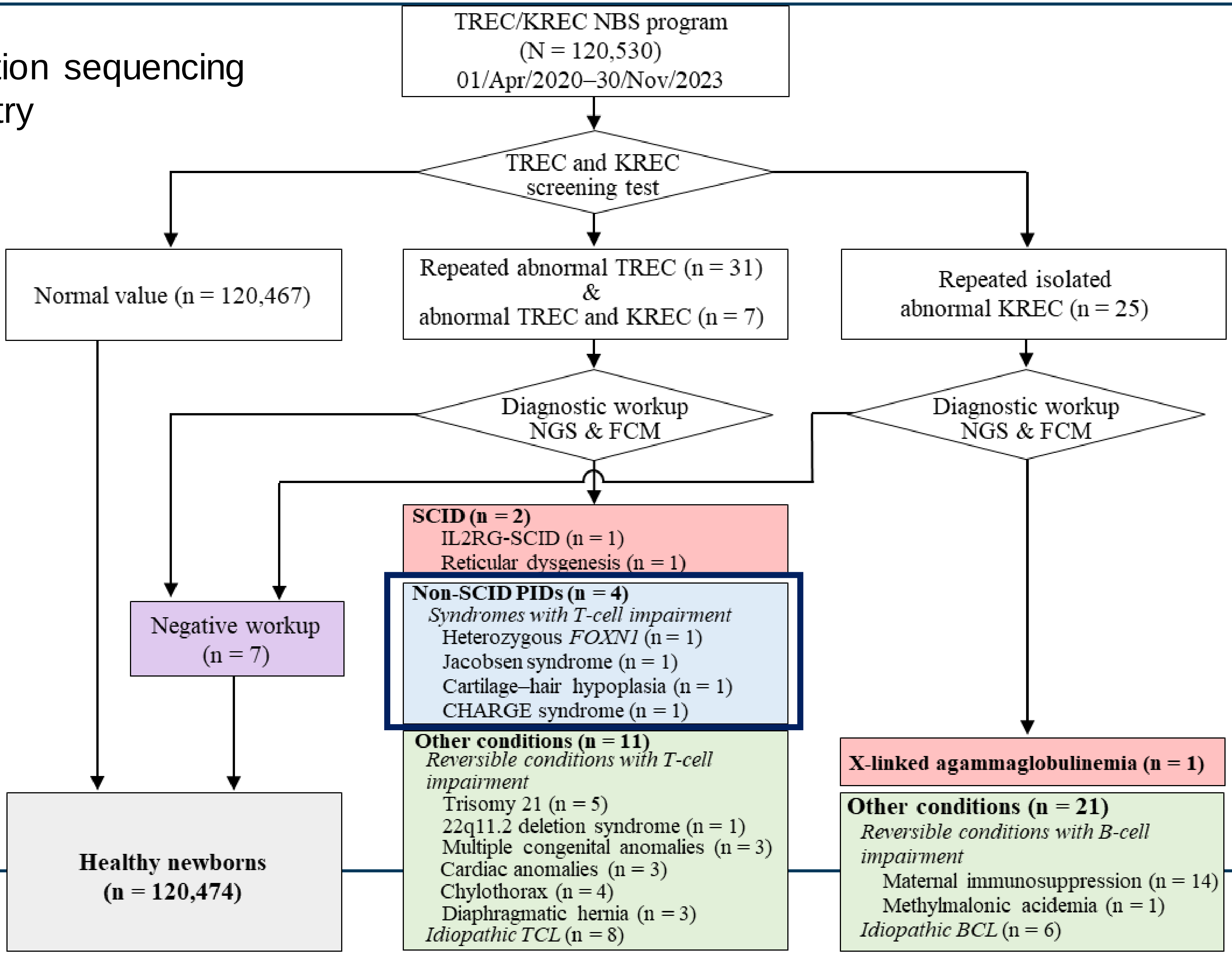
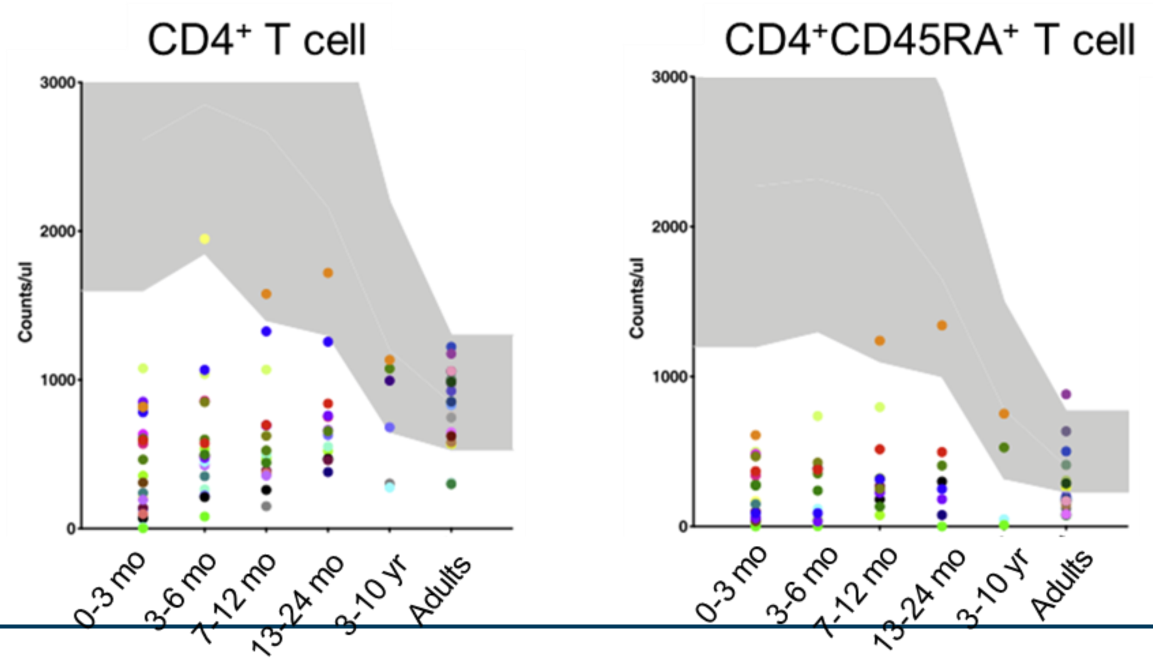


FOXN1-SCID

In 2019, 21 newborns with low TREC and T-cell lymphopenia and heterozygous *FOXN1* variants were initially reported.

FOXN1 is the causative gene in nude mice and is a transcription factor essential for thymic epithelial progenitor cells to initiate T cell differentiation and maturation.



Bosticardo M, et al. Am J Hum Genet.2019;105:549-61.

Non-SCID with low T-cell counts identified by TREC NBS programs

Combined immunodeficiency, including single-gene and syndromic disorders of T-cell development, such as the following:
● Ataxia-telangiectasia
● Disorders of folate absorption or metabolism
● MHC class I and II defects
● Nijmegen breakage syndrome
● Trisomy 21 and other chromosomal aneuploidies
Disorders of thymic stromal cell development, such as the following:
● CHARGE syndrome
● DiGeorge syndrome (complete or partial)
● Other disorders of thymic stromal cell development (eg, pathogenic variants in genes such as *FOXN1*, *FOXI3*, *TBX1*, *TBX2*, *CHD7*, or *PAX1*)
Idiopathic T-cell lymphopenia
Secondary T-cell lymphopenia due to:
● Advanced *in utero* HIV infection
● Chylous effusions, spontaneous or postsurgery
● Gastrointestinal or cardiac malformations
● Hydrops
● Maternal immunosuppressive medications
● Preterm birth, very low birth weight

Dvorak CC, et al. JACI. 2023.

Summary

In Aichi Prefecture, TREC/KREC NBS programs have been performed for more than 200,000 newborns to date.

TREC/KREC NBS programs are further expected to be expanded as a publicly funded screening test in Japan.

SCIDs should be promptly referred to a hospital for the detailed examination, and prepared for the prevention of infection and appropriate therapeutic intervention.

The development of management frameworks and specific guidelines regarding follow-up for Non-SCID PIDs is a challenge to be addressed in the future.

Acknowledgments

Patients and family members

Department of Pediatrics, Nagoya University
Graduate School of Medicine, Nagoya, Japan.

Nobuhiro Nishio, Atsushi Narita, Kotaro Narita,
Ayako Yamamori, Yusuke Tsumura, Ryo Maemura,
Sajiki Daichi, Yamashita Daiki

NAGOYA UNIVERSITY SCHOOL OF MEDICINE

Japanese Society for Immunodeficiency and Autoinflammatory Diseases
JSIAD

名古屋小児がん基金
NAGOYA PEDIATRIC CANCER FUND

公益財団法人 愛知県健康づくり振興事業団
Aichi Health Promotion Public Interest Foundation

IPOPI.org

TAILORING NBS FOR SCID IN ASIA: INSIGHT FROM MALAYSIA

Presenter

Associate Professor Dr Adli Ali

Consultant Pediatric Immunologist

Universiti Kebangsaan Malaysia

IPOPI 5TH REGIONAL ASIAN PID MEETING

24-25 MARCH 2024

TOKYO, JAPAN

an IPOPI event

COLLABORATION

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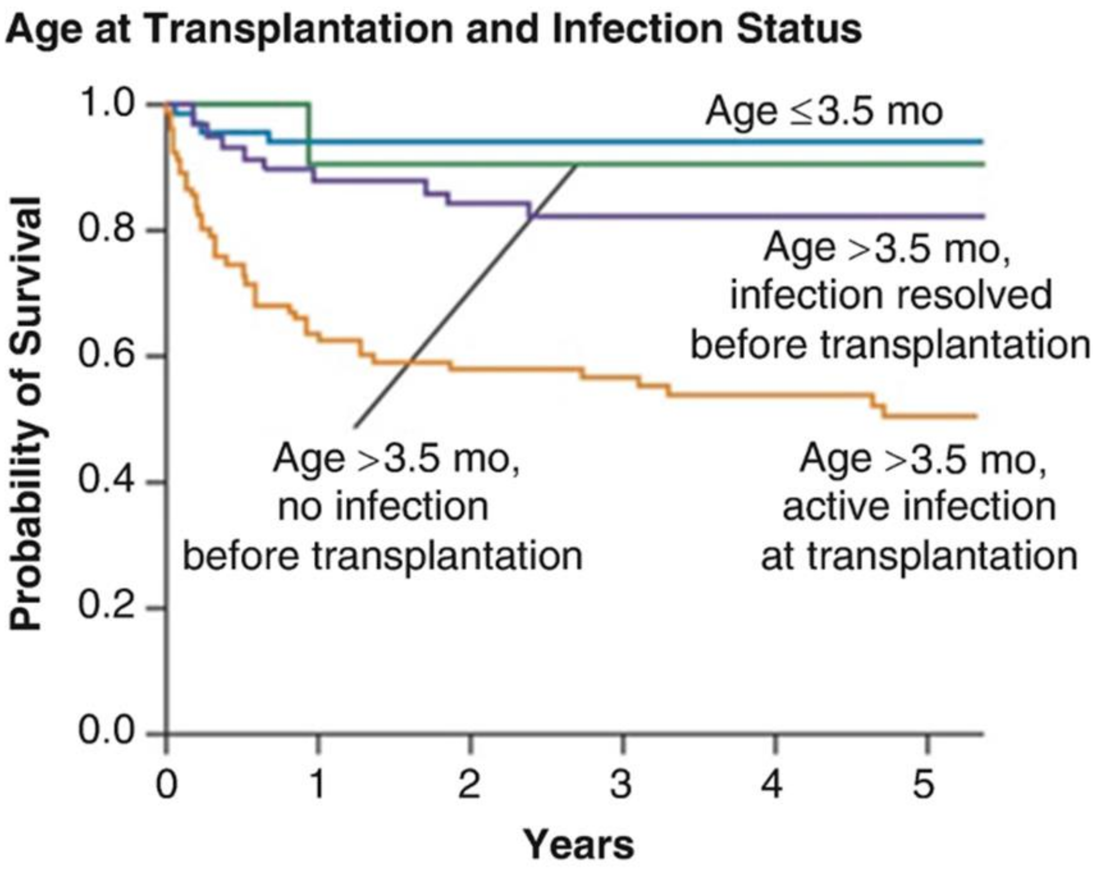
WHAT IS SCID AND WHY?

- Severe Combined Immunodeficiency (SCID)
  - absence of both cellular and humoral immunity
    - 30 different genes known to cause SCID
  - profound defects in T lymphocyte
- Affected infants develop infections (SPUR)
  - Recurrent infections, chronic diarrhea, sepsis, FTT
  - Death usually before 1 year of age
  - Treatment/ prevention of infections- not curative
- Curative-HSCT/ gene therapy
  - Preferably before the onset of infections
  - Preferably before 3.5 months



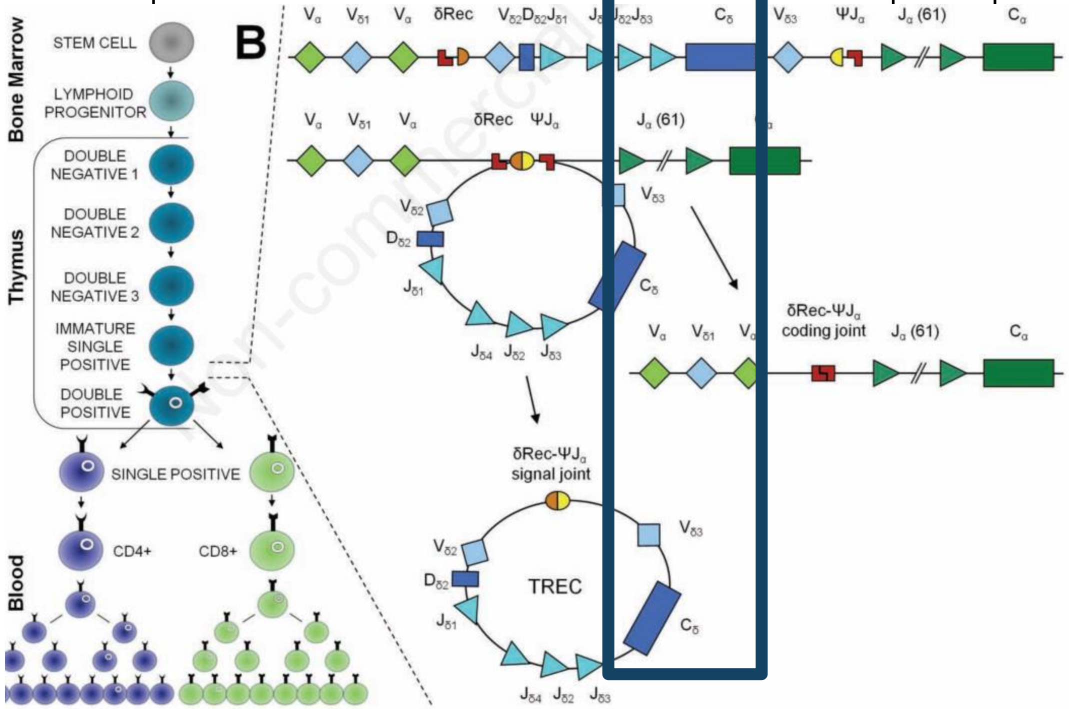
WHY SCID IS A PERFECT "NBS" MODEL DISEASE?

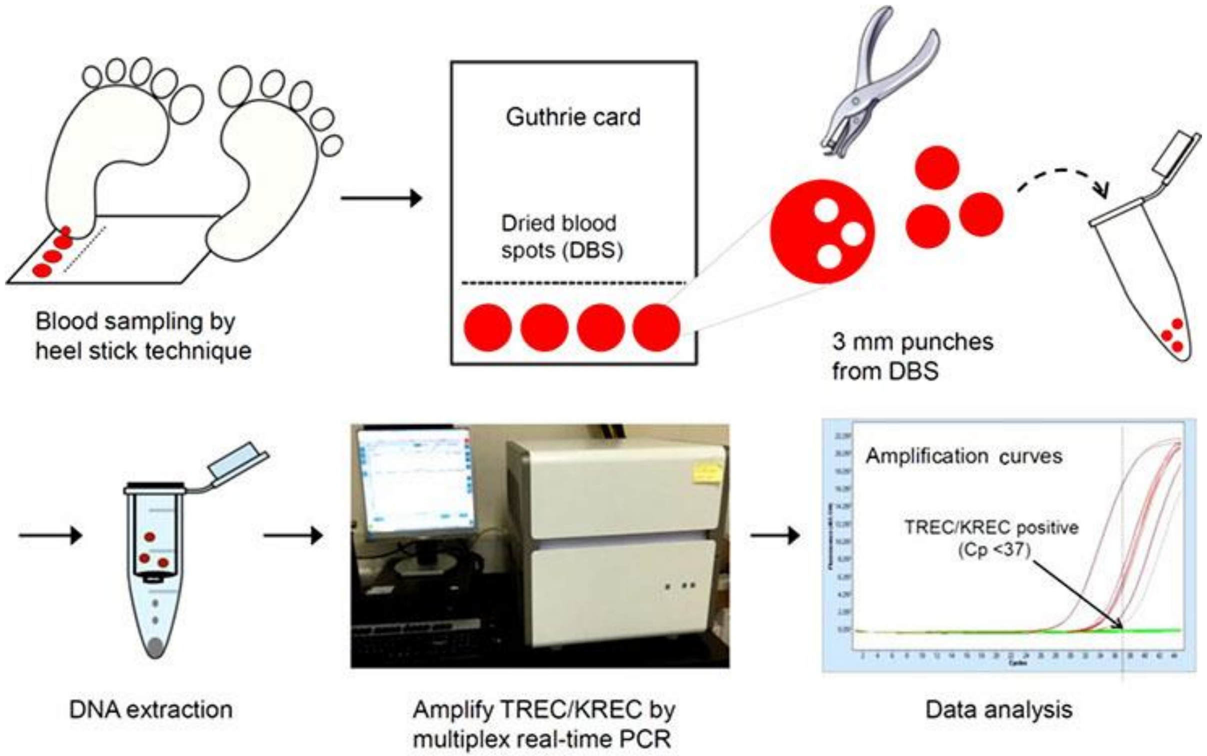
THE SCIENTIFIC ANGLE

- Different gene mutations causing SCID
  - with around 25% yet to be known mutation
  - Nearly all SCID- **absent/ non-functional T- cells**
    - The unique position of ***TREC***

- What is ***T-cell receptor excision circles (TREC)*** ?
  - **By-products of TCR genes** during thymocyte maturation
    - Episomal DNA→ **do not replicate during mitosis**
  - **detected in peripheral blood** by quantitative PCR
    - **correlate with numbers of naïve T-cells**
    - Low TREC levels → SCID, DiGeorge syndrome, congenital lymphopenia

IL2Ry	T-	B+	NK-
JAK3	T-	B+	NK-





TREC quantification

WHY SCID IS A PERFECT "NBS" MODEL DISEASE?

PUBLIC HEALTH ANGLE

Prevalence of the disease 1:100,000 or greater
SCID: 1:50,000-1:100,000

Can the disorder be detected by routine physical exam?
SCID: Baby appears normal at birth.

Does the disease cause serious medical complications?
SCID: 100% fatal within the first year of life

Is there a cheap, sensitive and specific screening test?
SCID: Real time PCR to enumerate T cell receptor excision circles

Is there a confirmatory test?
SCID: Lymphocyte subpopulation analysis

Does early detection improve outcome?
SCID: Early HSCT decreases mortality from SCID

SCID Newborn Screening in Malaysia: The Initial Phase

2014

Interest of starting Newborn Screening for SCID

2015

Exploration of technology

Engagement with the diagnostic provider

2016

Feasibility & Framework

Program withheld


Harian Metro

Setempat 27

DAMAILAH KAU MARISSA

Kanak-kanak pertama jalani pemindahan sum-sum tulang meninggal

'Bubble girl' Marissa Hani dies

Bernama
Published: Aug 14, 2015 4:21 PM · Updated: 5:16 PM

Marissa Hani Mohammed Zubir, aged two, who suffered from Severe Combined Immunodeficiency Disease (SCID) or better known as 'bubble boy disease' passed away 47 days after being admitted to the Serdang Hospital intensive care unit (ICU).

Marissa, the first child in Malaysia to have successfully undergone a bone marrow transplant last year in which the donor was her own mother, Nazellynakmar Kamarudin, died in the hospital at 2.26 pm yesterday from severe ventriculitis with hydrocephalus (compressing of the brain stem due to SCID).

SCID NEWBORN SCREENING IN MALAYSIA: THE INCUBATION PHASE

- Enhancing ecosystem: Strengthening expertise in curative management
- Establishing Database : real-national data of SCID
- Observation: Experiences from other countries
- Capacity Building: Learning and understanding the technology
- Pondering : The need, the feasibility in Malaysia

Solís et al. Orphanet Journal of Rare Diseases (2022) 17:11
https://doi.org/10.1186/s13023-021-02161-0

Orphanet Journal of Rare Diseases

RESEARCH **Open Access**

The PID Life Index: an interactive tool to measure the status of the PID healthcare environment in any given country

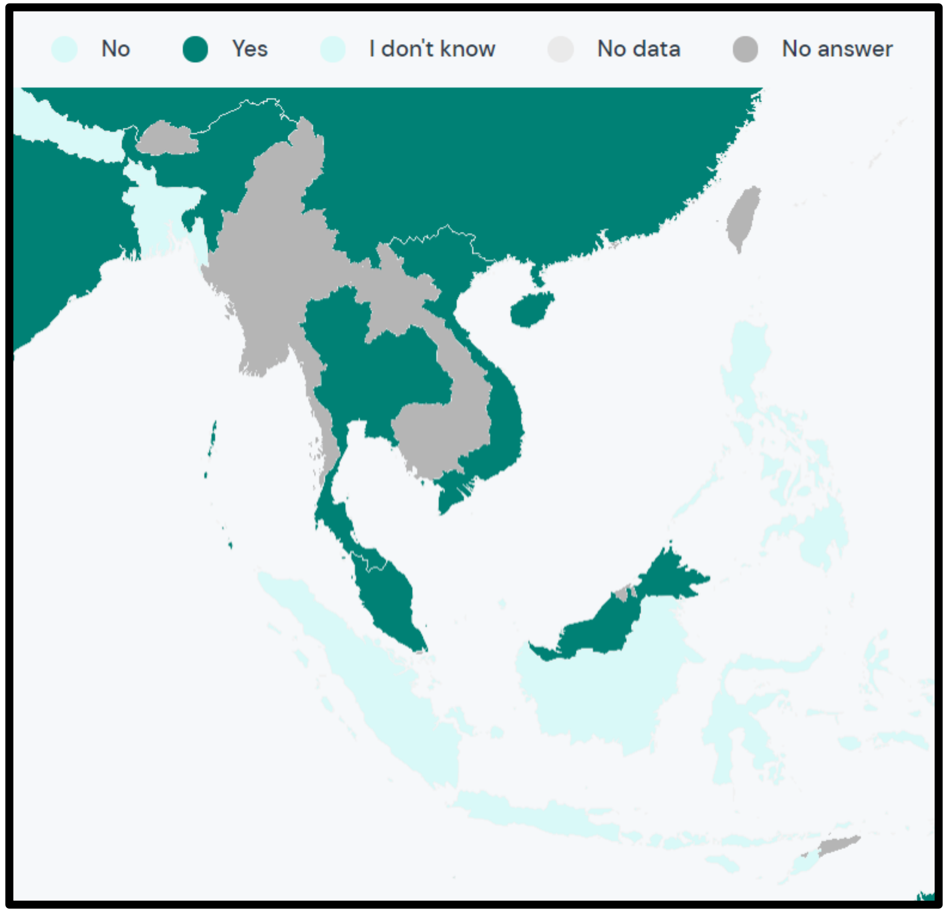
Leire Solís[1], Julia Nordin[1], Johan Prevot[1], Nizar Mahlaoui[2,3], Silvia Sánchez-Ramón[4,5], Adli Ali[6,7], Elodie Cassignol[8], John W. Seymour[1,9] and Martine Pergent[1*]

PID Treatment:
Curative treatment (BMT/ HSCT)

Bone marrow transplantation or haematopoietic progenitor cell transplantation

Specialised treatments in which HSC of an HLA compatible donor are provided to patients with usually severe PIDs (SCID, severe CGD) when the immune cells are missing or malfunctioning.

- **Gene Therapy**
- **Thymic Transplant**



SCID STATUS IN MALAYSIA: DATA

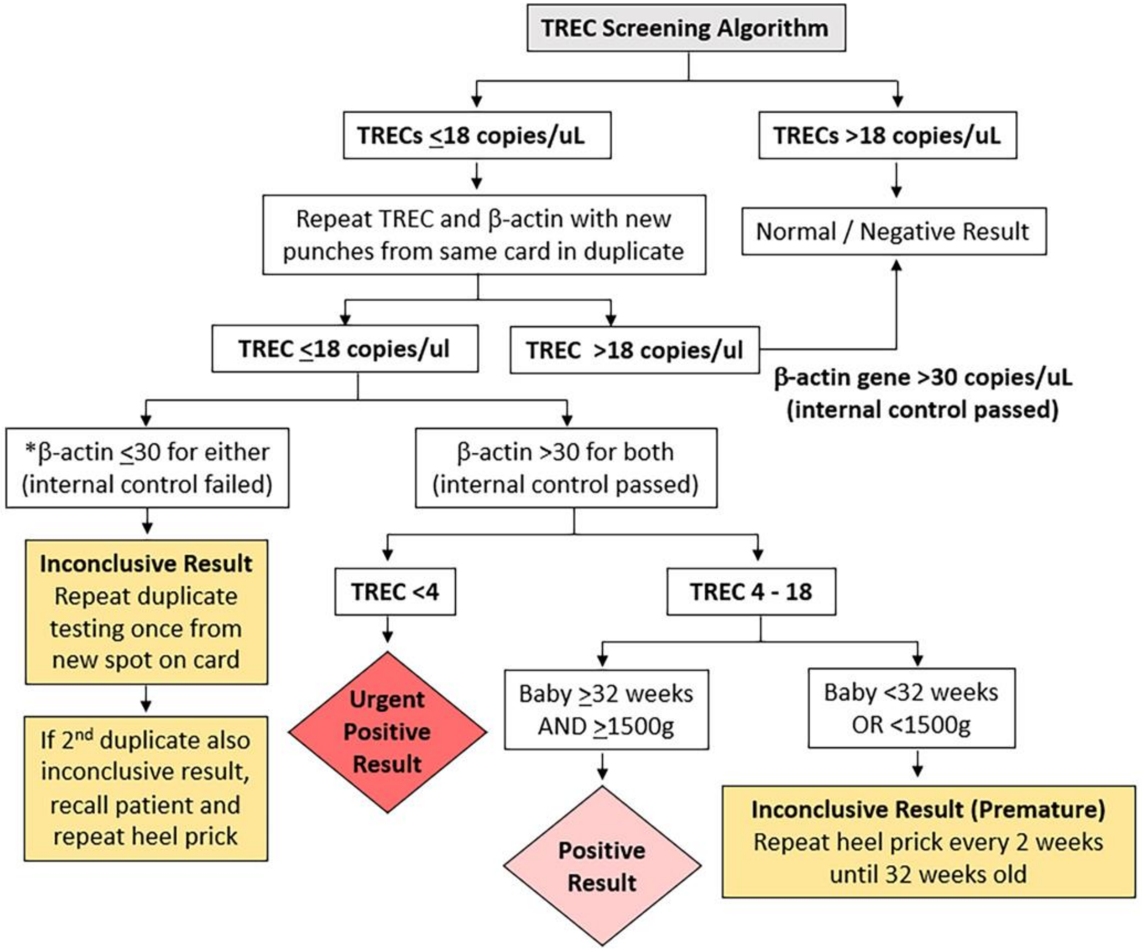
- Before 2014
  - all the 16 diagnosed cases- died (Mortality is 100%)
  - Many underdiagnosed/ misdiagnosed
  - Lack of awareness/ inability to provide appropriate test/ no treatment
- After 2014
  - Cases diagnosed increased 3-4 cases per year (better awareness, faster accurate diagnosis, treatment)
  - Survival is 85% (15% because of delayed diagnosis)
- In 2023 (Collective data from Assoc. Prof. Dr. Intan Hakimah and Dr Intan Juliana)
  - 5 cases in 2023 (with 2 suspected SCID-presented to late for diagnosis)
  - Estimated if universal data (1:58000 – should be 10 cases)
    - If following latest Singapore based estimation (1: 20000)- missed 22 cases (diagnosing 18%)

Real apac experience:
NBS FOR SCID IN SINGAPORE

- TREC assay : 10 October 2019 to 9 October 2020
- using the Enlite Neonatal TREC kit.
- 35888 newborns screened in 1 year
- no SCID cases were detected
- 13 cases of non-SCID T-cell lymphopenia (TCL
- Retest rate was 0.1%
- Referral rate to immunologist was 0.04%.
- **Latest update in 2023**
- **2 cases of SCID (38,000 live birth in 2022)**
- **Incidence of 1: 18000**
- **If Malaysia: 27-28 cases/ year (500,000 live birth)**

Severe Combined Immunodeficiency Newborn Screening in Southeast Asia : Outlook from SEAPID consortium,

Wai Leng Chang, Adli Ali et al, Under Review, 2024



Front. Immunol., 03 January 2022

Newborn Screening for SCID in Malaysia:

Determining the needs:

Survey, Pilot Project, Expert Discussion

Evaluating the technology :

Private-Clinician Partnership (Revvity-Arcadia Life Sciences- HPKK)

Partners Engagement :

IPOPI, Other NGO, MOH, MOHE, Pharma, Tech Provider

Advocacy:

WPIW campaign, Whitepaper, Screen4Rare

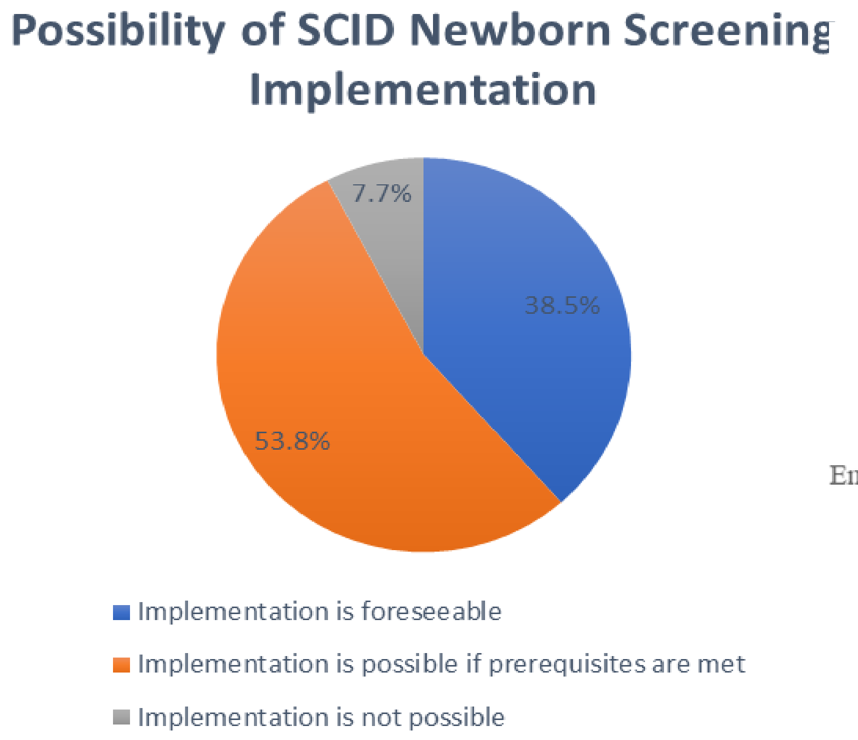
Feasibility and the cost-benefit analyses :

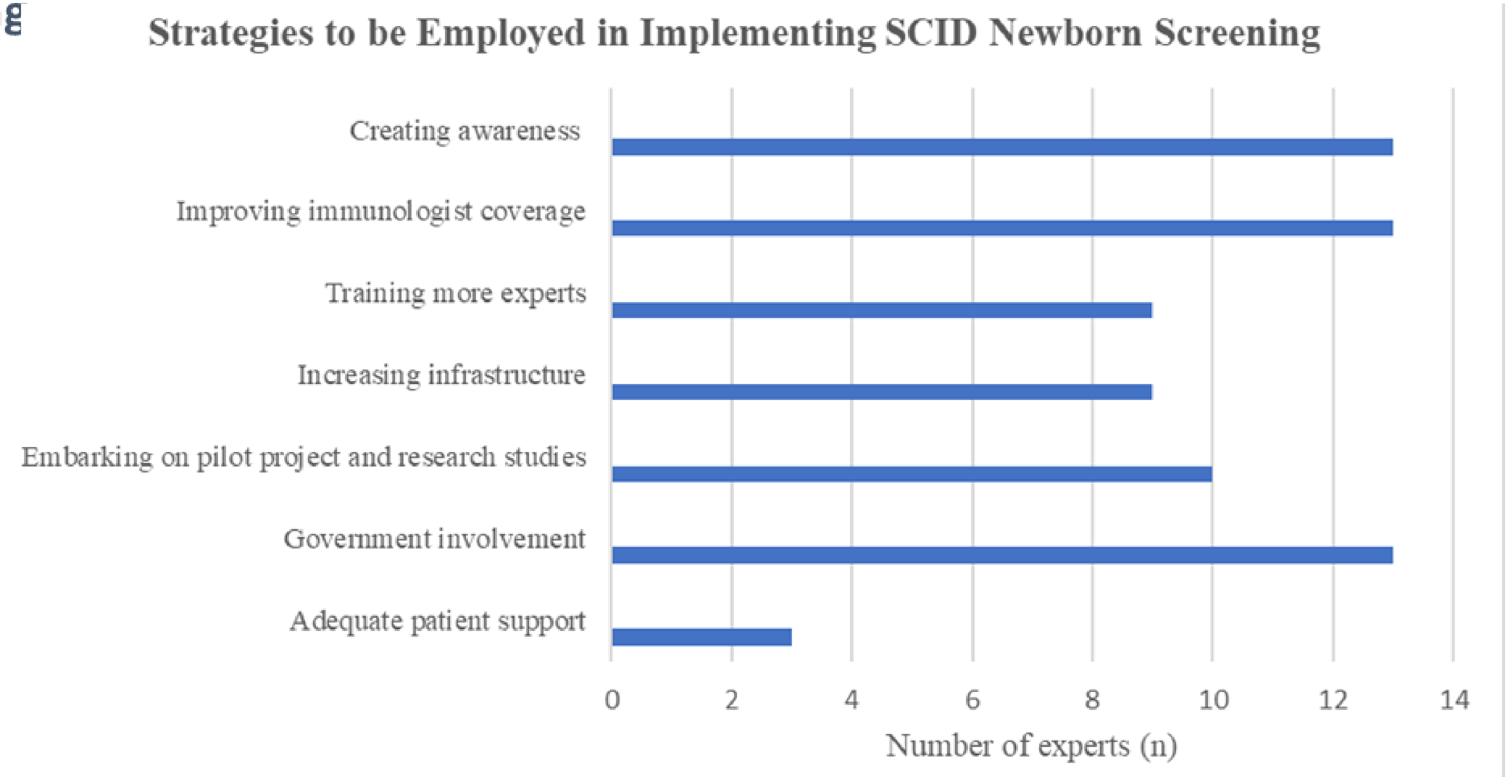
Framework and Pilot evaluation

OUTLOOK OF SCID NBS IN MALAYSIA:
ADVOCACY: WPIW, WHITEPAPER, INTERNATIONAL OUTREACH

Time	Presentation	Speaker
3rd Session: PID diagnostics in Asia Moderator: Martine Pergent		
09:00	Opening remarks	Martine Pergent IPOPI Chair
09:10	Keynote Opening Lecture: State of the art of PID diagnosis in Asia	Dr Narissara Suratannon, Chulalongkorn University Hospital
09:30	Cytokine auto-antibodies: from regulation to disease	Dr Wim Dik
09:45	IPOPI PIDetect programme: Bangladesh/India	TBC
09:55	Newborn screening for rare diseases – real life experiences and future opportunities	Dr Nizar Mahlaoui, country experience from France (10 min) Dr Adli Ali, Screen4Rare & Malaysia (10 min)
10.15	Questions & Answers	ALL
10:35	COFFEE BREAK	

OUTLOOK OF SCID NBS in MALAYSIA:
determining the needs: Experts' opinion





Newborn Screening for Severe Combined Immunodeficiency (SCID) in Malaysia: Current Status, Challenges and Progress, Wai Leng Chang, Adli Ali et al, Under Review, 2024


Arcadia
Life Sciences
OUTLOOK OF SCID NBS in MALAYSIA:
screen4rare, industry-clinician partnership

OUTLOOK OF SCID NBS IN MALAYSIA: PARTNERS ENGAGEMENT (MOHE-MOH-NGO-PHARMA)

FUTURE OUTLOOK

- **NBS for SCID in developing nation: Malaysia and SEA**
  - Understanding why, when, and how
  - The pre-requisite ecosystem

- **Importance of understanding local context**
  - Knowing the disease burden and management
  - Identifying the stakeholders and the game changer
  - Framing a practical roadmap

- **Potential interesting date to observe: 28th June 2024**

COFFEE BREAK
15 MIN

COLLABORATION

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