# Wanneer zijn “allergologische problemen” redenen te denken aan een immuundeficiëntie?


**Virgil Dalm**
**Internist-klinisch immunoloog**
**Erasmus MC**
**v.dalm@erasmusmc.nl**

# Disclosures

| Disclosure belangen spreker | |
|---|---|
| **Voor bijeenkomst mogelijk relevante relaties[1]** | **Bedrijfsnamen** |
| • Sponsoring of onderzoeksgeld[2] | CSL Behring, Shire, Lamepro, Novartis, Actelion bv |
| • Honorarium of andere (financiële) vergoeding[3]<br>• Aandeelhouder[4]<br>• Andere relatie, namelijk …[5] | Shire, Lamepro, Actelion bv, Lilly |

# Inhoud

- Zeldzame aandoeningen
- Onbekende oorzaak
- Beperkte behandelmogelijkheden

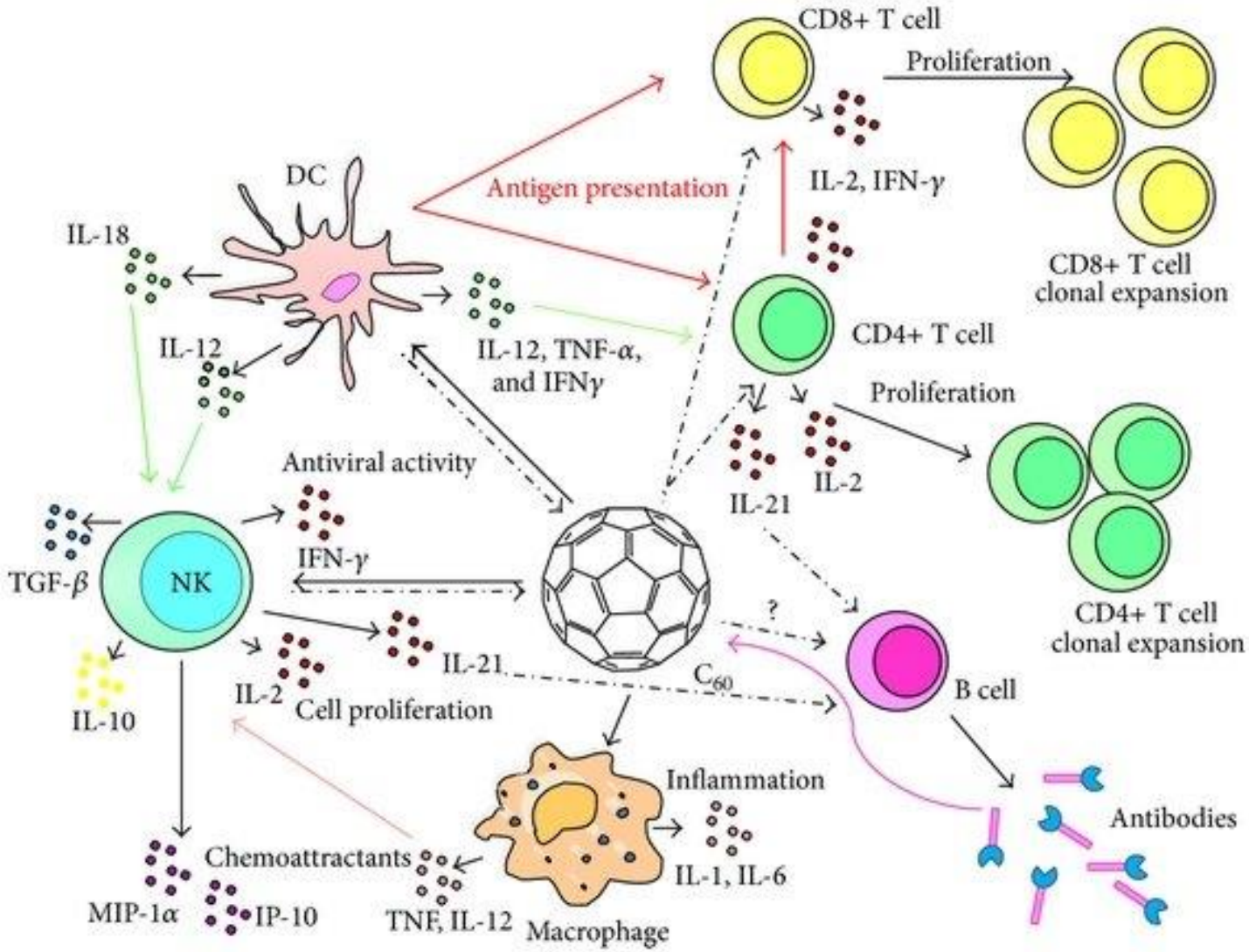
# Waarom (mogelijk) toch interessant?

- Zeldzame ziekten : maar minder zeldzaam dan we denken
- Onbekende oorzaken : meer genetische diagnostiek
- Beperkte behandelmogelijkheden : innovatie
- Overlap tussen klinische immunologie en allergologie

# Inhoud

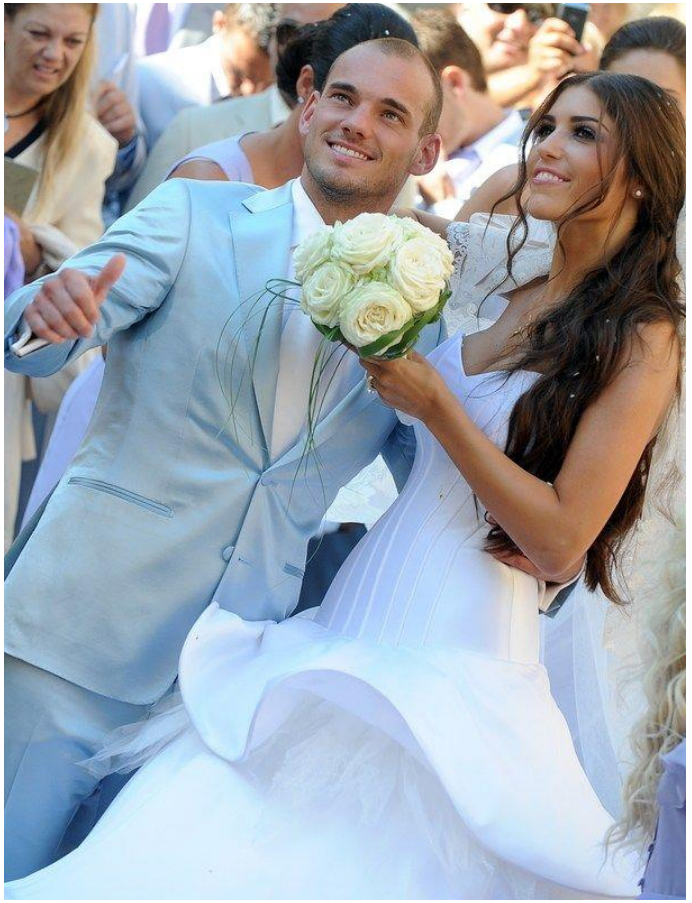
- Het immuunsysteem
- Primaire immuundeficiënties (PIDs)
- Allergologische problemen en PID
- Conclusies / aanbevelingen

# Het immuunsysteem



# Het immuunsysteem

”



k is

# Auto-immuniteit versus immuundeficiëntie

Immuundeficiëntie

Auto-immuniteit

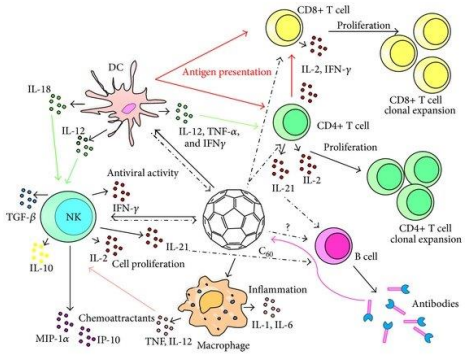
# Auto-immuniteit versus immuundeficiëntie

Immuundysregulatie

Immuundeficiëntie

Auto-immuniteit

# Primaire immuundeficiënties

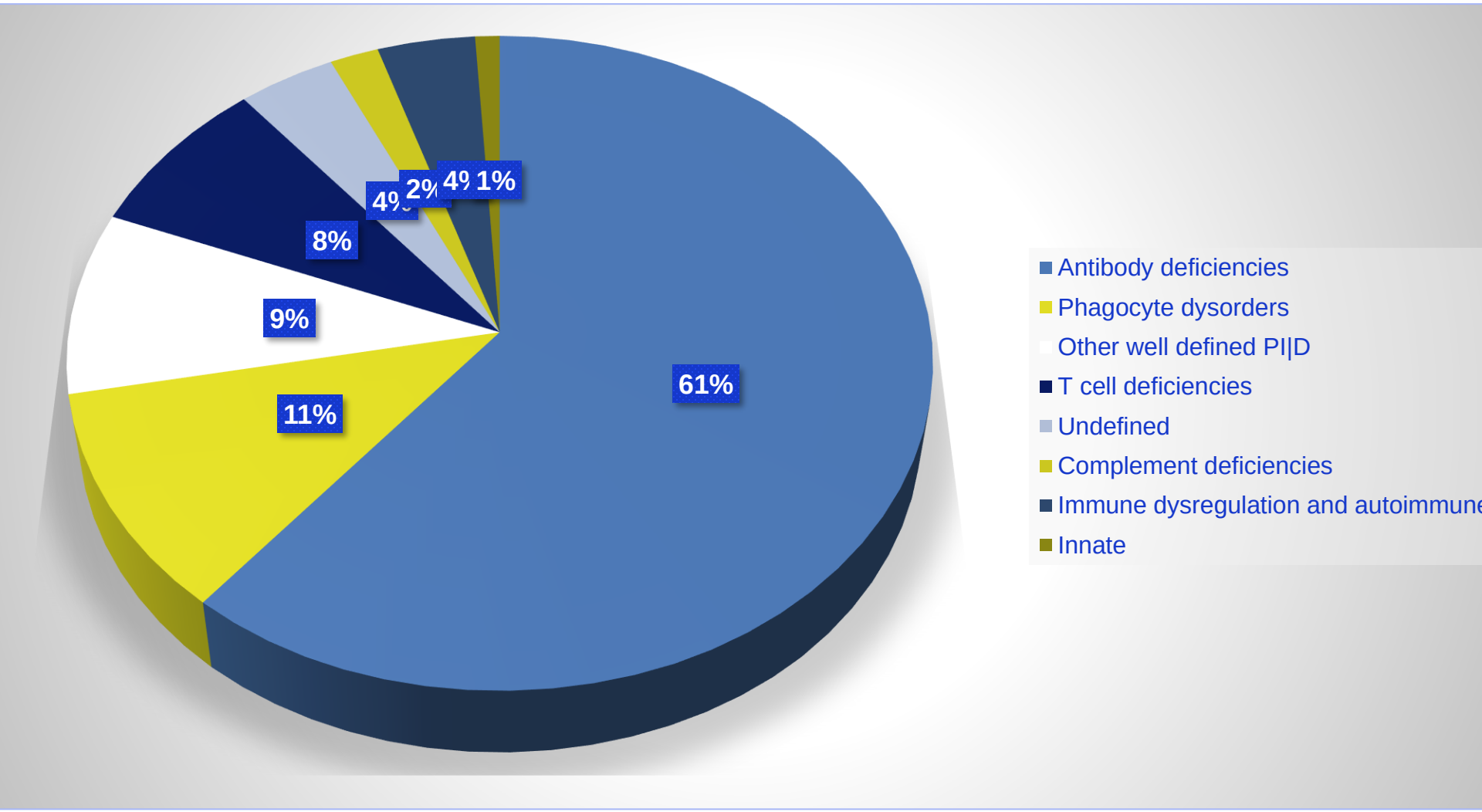



- **Aangeboren**
- **Verschillende celtypen aangedaan**

  **(B lymfocyt, T lymfocyt, neutrofiele granulocyt)**
- **Heterogene klinische presentatie**

  **Infecties**, auto-immuniteit, granulomen, maligniteiten

# Primaire immuundeficiënties

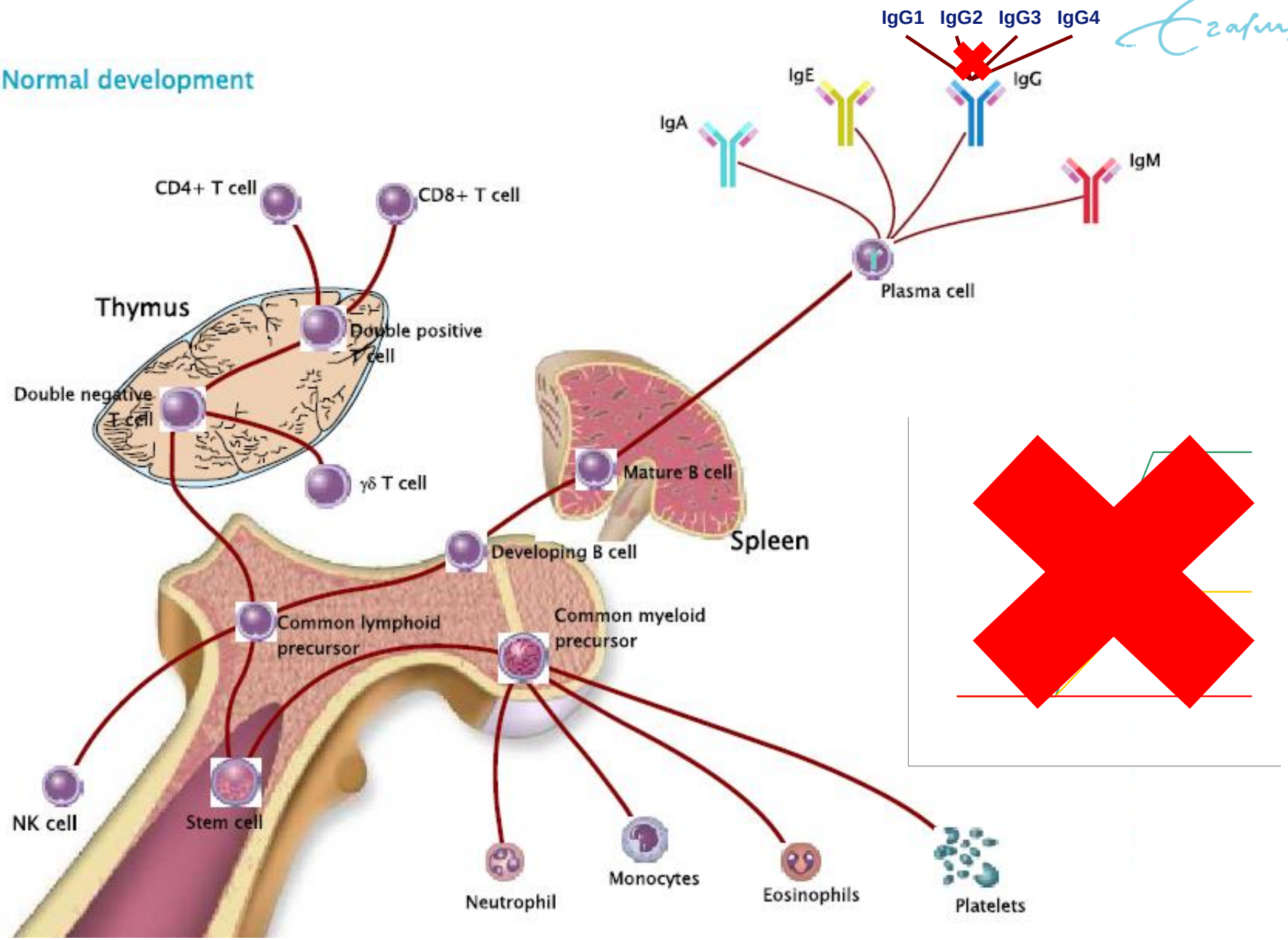



Jonkman-Berk et al. J Clin Immunol 2015

# Primaire antistof deficiënties

Erasmus MC

## Normal development



# Kliniek primaire antistof deficiënties

- **Recidiverende infecties bovenste en onderste luchtwegen**

  Gekapselde bacteriën

  *S. pneumoniae, H. influenzae, N meningitides*

- **Recidiverende gastro-intestinale infecties**

  *Giardia, Campylobacter, Shigella, Salmonella, enterovirus, rotavirus*

# Kliniek primaire antistof deficiënties

- **Maligniteiten**

  Hematologische maligniteiten [1]

- **Autoimmuun complicaties** [2-5]

  Autoimmuun hemolytische anemie

  Idiopathisch trombocytopenische purpura

  Systemische lupus erythematosus

  Artritis

  Hepatitis

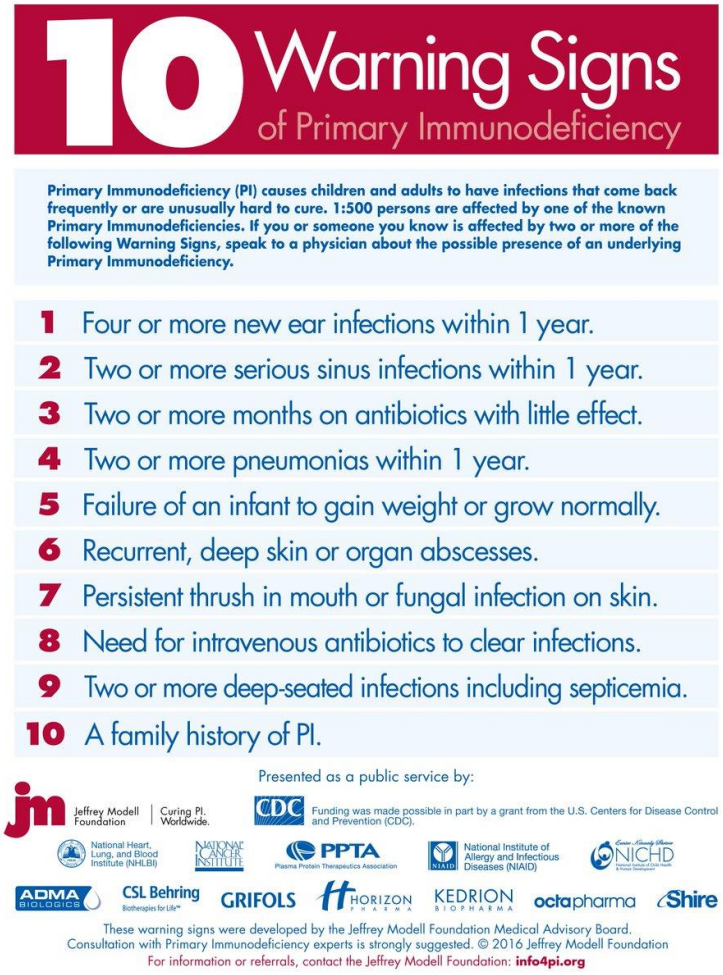
  Vasculitis

  ……

[1] Mellemkjaer L et al. 2002 Clin Exp Immunol
[2] Bonilla FA et al. 2016 J Allergy Clin Immunol Pract
[3] Baldovino S et al. 2013 Autoimmun Rev
[4] Cunningham-Rundles C. 2002 Blood Rev
[5] Chapel H et al. 2012 J Allergy Clin Immunol

# Primaire immuundeficiënties zijn zeldzaam

## Hoe te herkennen?



# Primaire immuundeficiënties zijn zeldzaam

## Hoe te herkennen?

1. Four or more infections requiring antibiotics within 1 year (otitis, bronchitis, sinusitis, pneumonia)
2. Recurring infections or infection requiring prolonged antibiotic therapy
3. Two or more severe bacterial infections (osteomyelitis, meningitis, septicemia, cellulitis)
4. Two or more radiologically proven pneumonia within 3 years
5. Infection with unusual localization or unusual pathogen
6. PID in the family

# Maar niet altijd zo “typisch”

# 1ste (ernstige) infectie al PID overwegen?

- **Evaluatie van jongvolwassenen (18-40) met 1ste invasieve infectie**

  *Streptococcus pneumoniae* (SP), *Neisseria meningitidis* (NM), *Neisseria gonorrhoeae* (NG), *Haemophilus influenzae* (HI), groep A *Streptococcus* (GAS))

- **In 3 jaar 36 patiënten geïncludeerd**

- **In 7 (19%) patiënten werd een PID gevonden**

Sanges S et al. Clin Microbiol Infect 2017

# 1ste (ernstige) infectie al PID overwegen?

Characteristics of patients with a diagnosis of PID

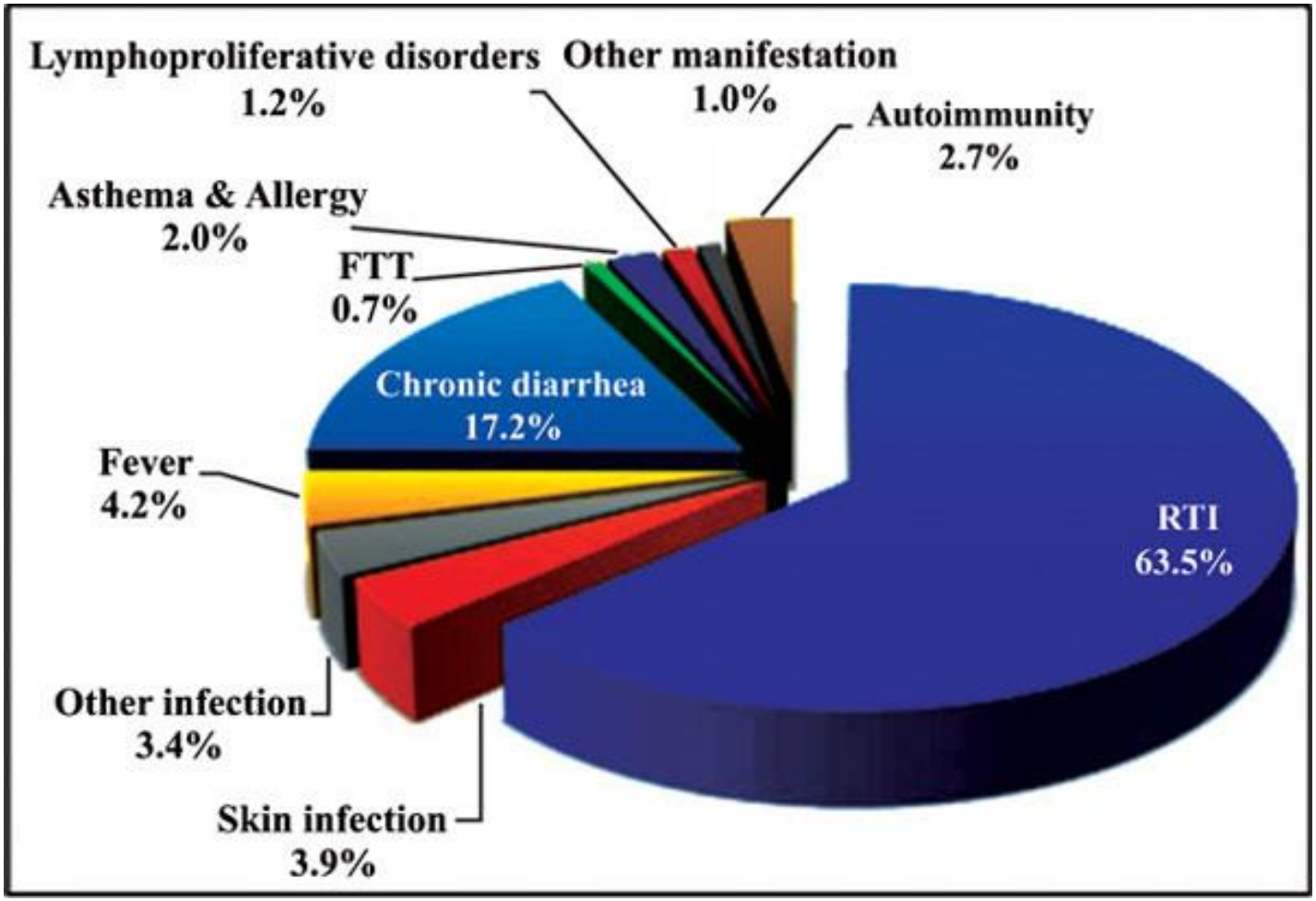
| # | Gender | Age | Infection site | Pathogen | Personal history of infection | Family history of infection | PID |
|---|---|---|---|---|---|---|---|
| 1 | F | 20 | Meningitis | *N. meningitidis* ungrouped | No | No | C6 |
| 2 | M | 19 | Meningitis, bacteraemia | *N. meningitidis* Y | Rare URT infections | No | IPH |
| 3 | F | 18 | Bacteraemia | Group A *Streptococcus* | No | No | IgG2/4 |
| 4 | M | 40 | Pneumonia, bacteraemia | *S. pneumoniae* | Recurrent BRO and URT infections | No | CVID |
| 5 | M | 18 | Meningitis | *N. meningitidis* Y | No | No | C7 |
| 6 | M | 30 | Pneumonia, bacteraemia | *S. pneumoniae* | Rare URT infections | Daughters: URT infections, PNE | CVID |
| 7 | F | 20 | Meningitis | *H. influenzae* | Rare URT infections[a] | Sister: PNE | SPAD |
| 8 | M | 37 | Arthritis, bacteraemia | *N. gonorrhoeae* | *N. gonorrhoeae* arthritis and bacteraemia | Brother and maternal aunt: MEN | C7 |
| 9 | M | 23 | Meningitis | *N. meningitidis* C | *N. meningitidis* Y meningitis | No | C8 |

BRO, bronchitis; C, complement fraction; C6, C6 deficiency; C7, C7 deficiency; C8, C8 deficiency; CH50, total haemolytic complement; CVID, common variable immunodeficiency; F, female; Ig, immunoglobulin; Ig2/4, IgG2 and IgG4 subclasses deficiency; IPH, idiopathic primary hypogammaglobulinaemia; M, male; MEN, meningitis; PID, primary immunodeficiency; PNE, pneumonia; SPAD, specific polysaccharide antibody deficiency; URT, upper respiratory tract.

[a] Patient #7 experienced bilateral pneumococcal pneumonia 2 years after *Haemophilus influenzae* meningitis (after the study period).

Sanges S et al. Clin Microbiol Infect 2017

# Andere “eerste presentaties” van PID




Azizi G et al. Endocr Metab Immune Disord Drug Targets 2018

# Patiënt met huidafwijkingen als 1ste uiting?

# Patiënt met chronisch spontane urticaria

**Man, 41 jaar**

**2018 RvK:** **angio-oedeem en urticaria sinds 3 maanden**

**aanvalsgewijze buikpijnen**

**2x verhoogd serum tryptase**

| | | | |
|---|---|---|---|
| Tryptase | 20.3 | µg/L | <11.4 |
| IgA | 0.49 | g/L | 0.76 - 3.9 |
| IgG | 4.3 | g/L | 7.0 - 16.0 |
| IgM | 1.03 | g/L | 0.45 - 2.30 |

# Patiënt met chronisch spontane urticaria

Verhoogd tryptase, klinisch geen verdenking mastocytose

DD chronisch spontane urticaria + angio-oedeem

secundaire hypogammaglobulinemie bij prednison

lymfoom met sec hypogamma en mastocytose?

Start omalizumab 300 mg

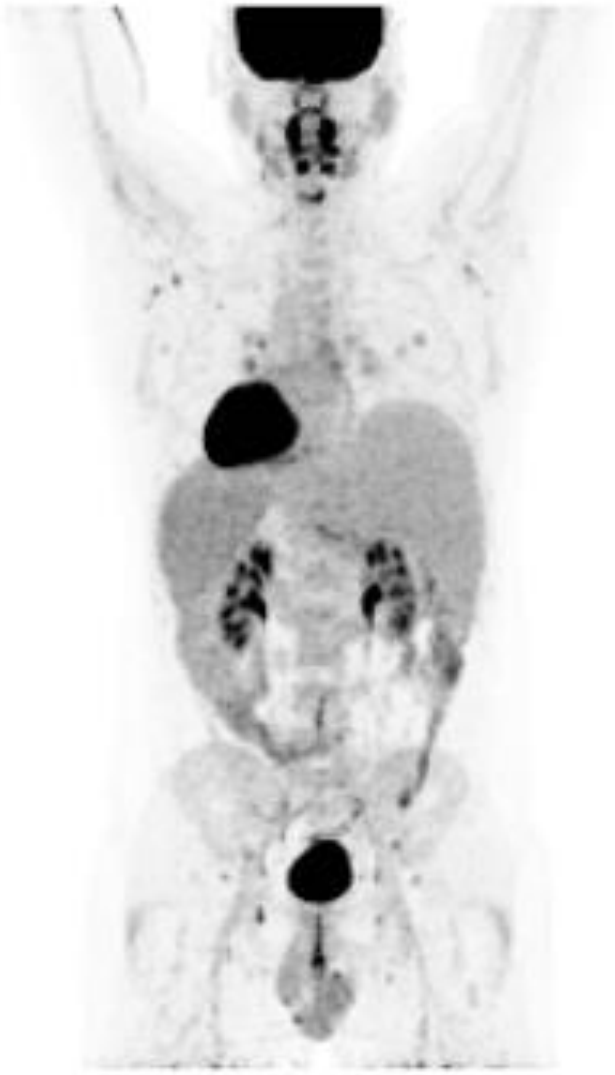
# Patiënt met chronisch spontane urticaria

**Beenmergonderzoek:**

**Geen mastocytose**

**Geen aanwijzingen voor monoklonale B- of T-cel populatie**

# PET-CT scan



# Patiënt met chronisch spontane urticaria

**Excisie klier lies:**

**Kleine reactieve lymfklier**

**Geen aanwijzingen voor lymforeticulaire maligniteit**

# Terug naar de hypogammaglobulinemie

| | | | |
|---|---|---|---|
| IgA | 0.49 | g/L | 0.76 - 3.9 |
| IgG | 4.3 | g/L | 7.0 - 16.0 |
| IgM | 1.03 | g/L | 0.45 - 2.30 |

| Vaccaniatierespons na vaccinatie Pneumovax | Voor | Na | Eenheid | Ref waarde |
|---|---|---|---|---|
| anti-pnecS.typ 1 | 0.03 | 1.71 | µg/mL | >0.35 |
| anti-pnecS.typ 3 | 0.17 | 0.43 | µg/mL | >0.35 |
| anti-pnecS.typ 4 | 0.00 | 0.34 | µg/mL | >0.35 |
| anti-pnecS.typ 5 | 0.01 | 0.11 | µg/mL | >0.35 |
| anti-pnecS.typ 6B | 0.00 | 0.14 | µg/mL | >0.35 |
| anti-pnecS.typ 7F | 0.04 | 0.42 | µg/mL | >0.35 |
| anti-pnecS.typ 8 | 0.08 | 0.76 | µg/mL | >0.35 |
| anti-pnecS.typ 9V | 0.04 | 0.56 | µg/mL | >0.35 |
| anti-pnecS.typ 14 | 0.01 | 0.00 | µg/mL | >0.35 |
| anti-pnecS.typ 15B | 0.02 | 2.22 | µg/mL | >0.35 |
| anti-pnecS.typ18C | 0.00 | 0.01 | µg/mL | >0.35 |
| anti-pnecS.typ19A | 0.00 | 4.90 | µg/mL | >0.35 |
| anti-pnecS.typ19F | 0.39 | 0.86 | µg/mL | >0.35 |
| anti-pnecS.typ 20 | 0.05 | 0.08 | µg/mL | >0.35 |
| anti-pnecS.typ23F | 0.01 | 0.18 | µg/mL | >0.35 |
| anti-pnecS.typ 33F | 0.01 | 0.38 | µg/mL | >0.35 |

# Terug naar de hypogammaglobulinemie

| | | | |
|---|---|---|---|
| T-Cellen | 1.17 | 10^9/L | 0.7-2.1 |
| CD4+T-Cellen | 0.89 | 10^9/L | 0.3-1.4 |
| CD8+T-Cellen | 0.23 | 10^9/L | 0.2-0.9 |
| B-Cellen | 0.19 | 10^9/L | 0.1-0.5 |
| NK-cellen | 0.17 | 10^9/L | 0.09-0.6 |
| Transitioneel B | 13 | cellen/µL | 3-50 |
| naief matuur B | 137 | cellen/µL | 57-447 |
| natural effector B | 26 | cellen/µL | 9-88 |
| memory B | 6 | cellen/µL | 13-122 |
| %IgM+ memory B | 44.0 | % van de B-cellen | |
| %IgG+ memory B | 32.0 | % van de B-cellen | |
| %IgA+ memory B | 24.0 | % van de B-cellen | |
| %IgE+ memory B | <0.1 | % van de B-cellen | |
| %plasmablasten | 1.2 | % van de B-cellen | |
| %CD21-CD38- B | 6.1 | % van de B-cellen | |

# Conclusie

**Toch een primaire immuundeficientie? CVID?**

**Maar geen infectieuze complicaties**

**Aanvullend onderzoek?**

**Behandeling?**

# CSU: een zeldzame uiting van CVID

**Complement activatie (infectie-geinduceerd)**

**Auto-antistof vorming tegen IgE receptor (mestceldegranulatie en urticaria)**

Smith AA et al. J Am Acad Dermatol 2008

# CSU: een zeldzame uiting van CVID

**TABLE I.** Results of diagnostic parameters

| Patient no. | Duration of urticaria symptoms | Immunoglobulin level (mg/dL) IgG (range, 800-1800*) | IgA (range, 90-450*) | IgM (range, 80-300*) | Infections | Protective Ab responses† | Circulating immune complexes‡ | Responded to IVIG therapy |
|---|---|---|---|---|---|---|---|---|
| 1 | Months | 85 | <7 | 10 | + | – Diphtheria, tetanus<br>– *H influenza* | NE | Yes |
| 2 | 10 wk | 246 | <15 | 142 | None | + Tetanus<br>+ Isohemagglutinins | Yes | Yes |
| 3 | 1 y | 481 | <6 | 37 | ++ | – 12/12 pneumococcal serotypes<br>– Rubella<br>+ VZV<br>+ Tetanus | Yes | Yes |
| 4 | 16 mo | 278 | 16.7 | 19.3 | None | + Diphtheria, tetanus<br>– 10/12 pneumococcal serotypes | No | Yes |
| 5 | 6 mo | 345 | 40 | 139 | None | + Tetanus, diphtheria<br>+ Pneumococcus | NE | NR |
| 6 (age 30 y) | Intermittent for 3 y | 538 | < 7 | 57 | None | + Tetanus<br>– 12/12 pneumococcal serotypes | NE | NR |
| 6 (age 38 y) | 8 y | 455 | 5.9 | 131 | +++ | – 12/12 pneumococcal serotypes<br>– *H influenza*<br>+ Measles, rubella, diphtheria | NE | NA |

*IVIG,* Intravenous immunoglobulin; +/++/+++, degree of infections; –/+, not protective/protective; *NE,* not evaluated; *NR,* not recommended; *NA,* information not available.

*Normal range taken as the range including 2 SDs above and below the mean for normals of age range for subjects 18 to 45 years of age.[4]

†The presence of circulating immune complexes was tested by raji immune complex assays.

Altschul A et al. J Allergy Clin Immunol 2002

# Huidafwijkingen relevant in PID?

1. Four or more infections requiring antibiotics within 1 year (otitis, bronchitis, sinusitis, pneumonia)
2. Recurring infections or infection requiring prolonged antibiotic therapy
3. Two or more severe bacterial infections (osteomyelitis, meningitis, septicemia, cellulitis)
4. Two or more radiologically proven pneumonia within 3 years
5. Infection with unusual localization or unusual pathogen
6. PID in the family

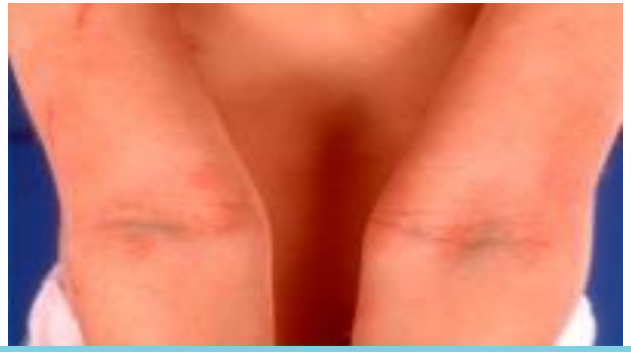
# Huidafwijkingen in PID

## Niet alleen infectieuze aandoeningen van de huid

**Table 2. Groups of primary immunodeficiencies: Associated infections and eczema.**

| Immunodeficiencies | Case No. (%) | Skin infections No. (%) | Bacterial No. (%) | Viral No. (%) | Mycotic No. (%) | Eczema-dermatitis No. (%) |
|---|---|---|---|---|---|---|
| Humoral | 68(32.4) | 32(30.9) | 9(13.2) | 5(7.3) | 12(17.6) | 19(27.9) |
| Cellular & Combined | 22(10.5) | 21(95.5) | 12(54.5) | 4(18.2) | 14(63.6) | 5(22.7) |
| Phagocytic | 57(27.1) | 48(84.2) | 48(84.2) | 1(1.7) | 9(15.7) | 2(3.5) |
| Other PIDs | 63(30) | 9(14.3) | 2(3.2) | 4(6.3) | 2(3.2) | 1(1.6) |
| Total | 210 | 99(47.1) | 71(33.8) | 14(6.6) | 37(17.6) | 27(12.8) |

## In 32% gaan huidafwijkingen vooraf aan diagnose PID

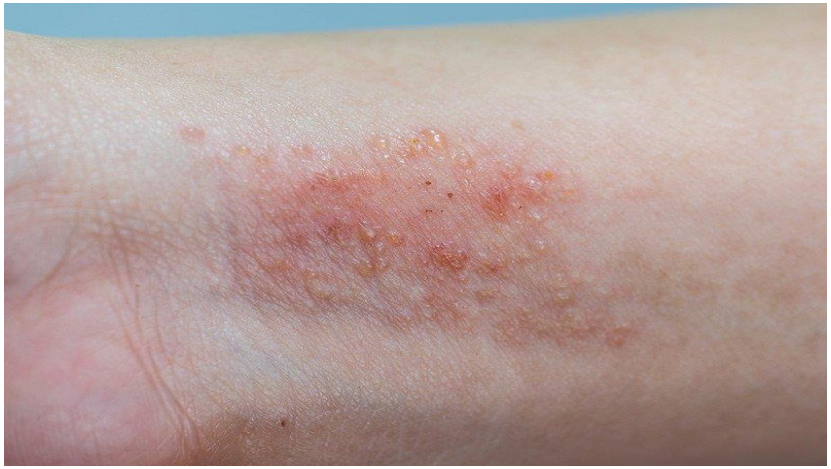


Moin A et al. Iran J Allergy Asthma Immunol 2006

# Huidafwijkingen in PID

Atopische dermatitis in kinderen

75 kinderen met diagnose (ernstige) atopische dermatitis

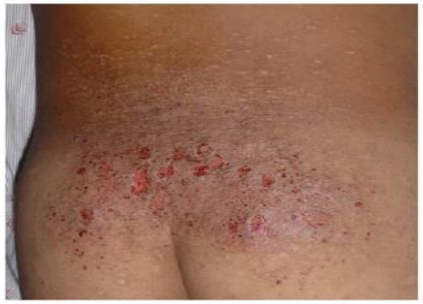


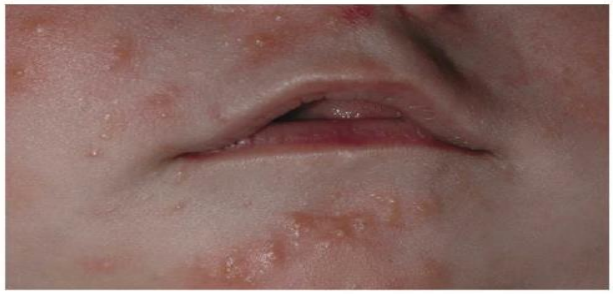
5 kinderen (6.6%) Hyper IgE

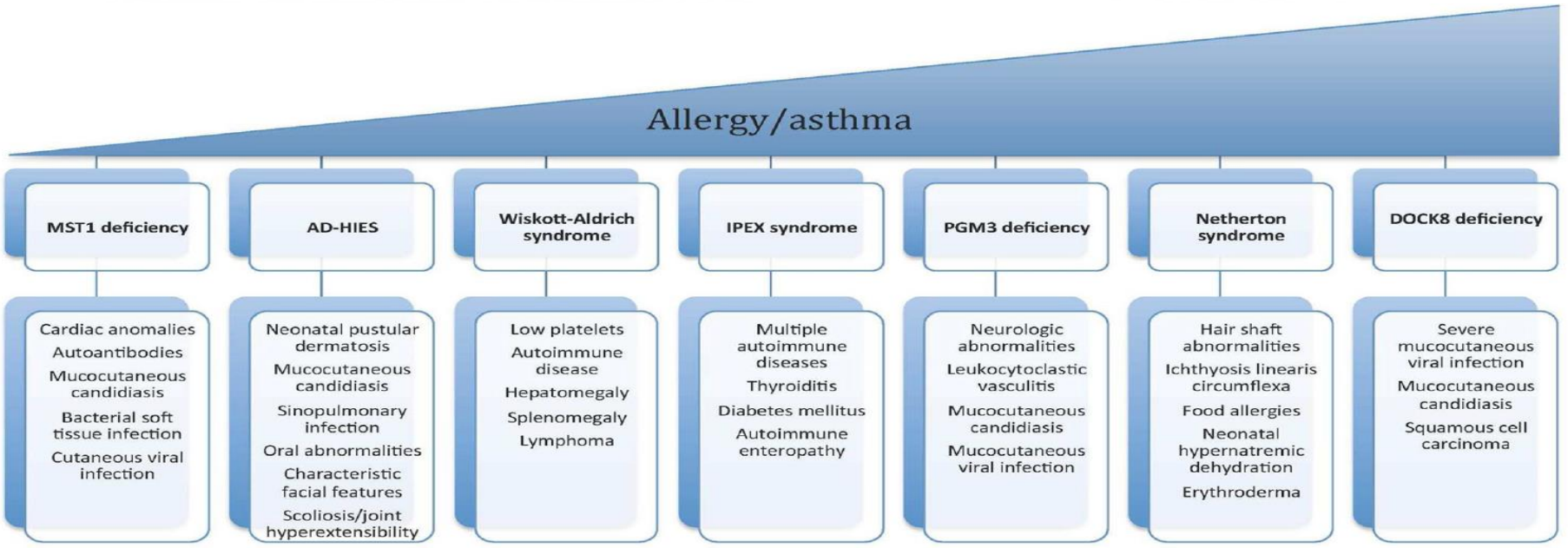
1 kind (1.3%) Wiskott-Aldrich

Aghamohammadi A et al. Allergol Immunopathol (Madr) 2014

# Niet elke huidaandoening is een PID








Pichard DC et al. J Am Acad Dermatol 2015

# When hyper IgE is not an allergy

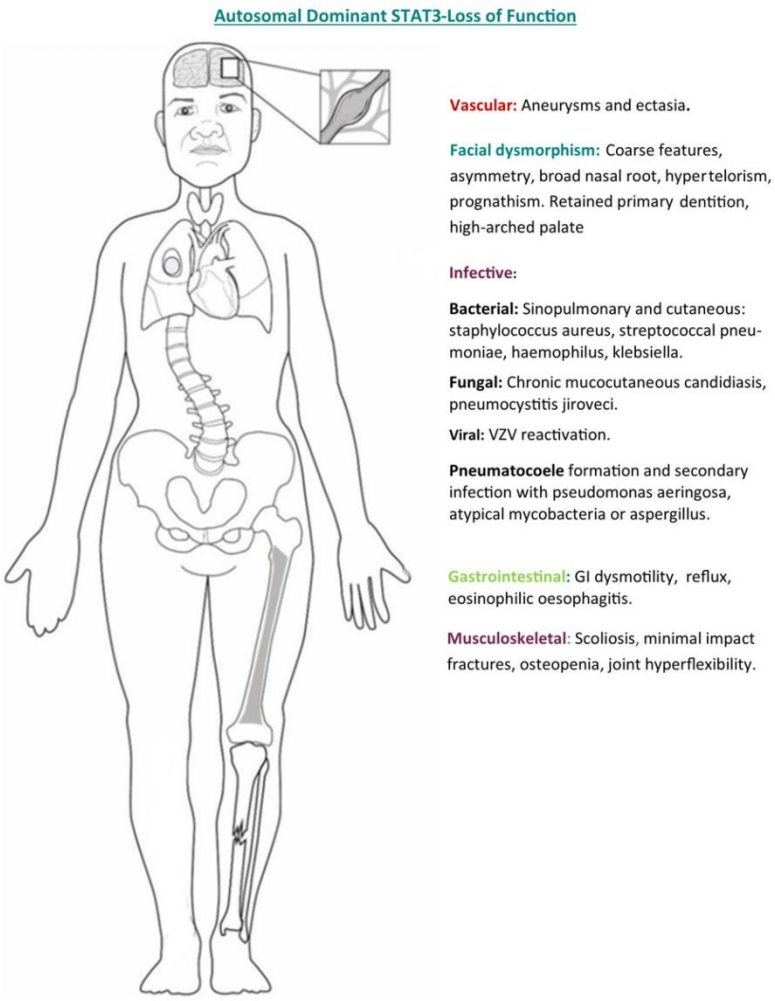
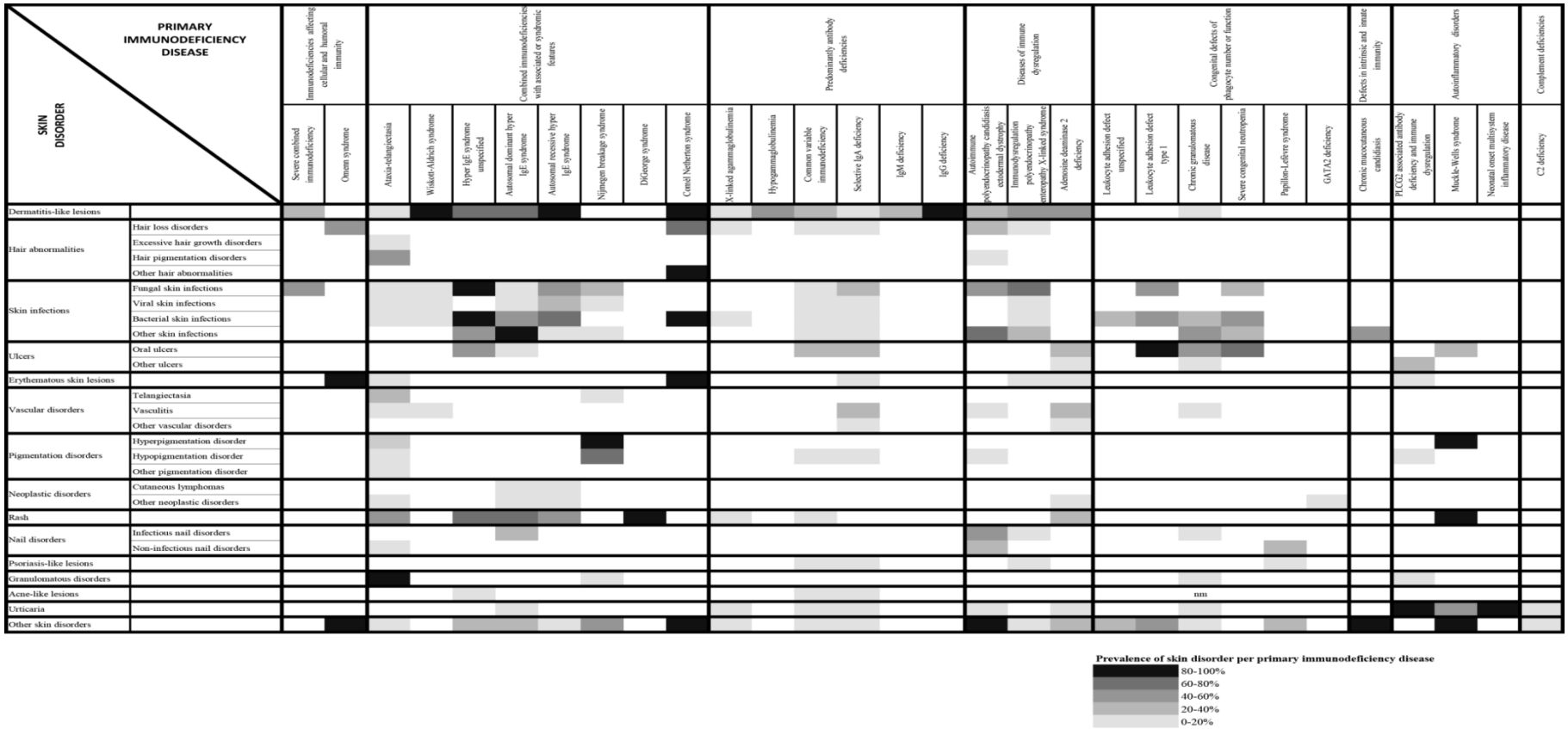



**FIGURE 5** Diagram showing syndromic features of AD-HIES.
Courtesy of Cardiff University Medical Illustration Department

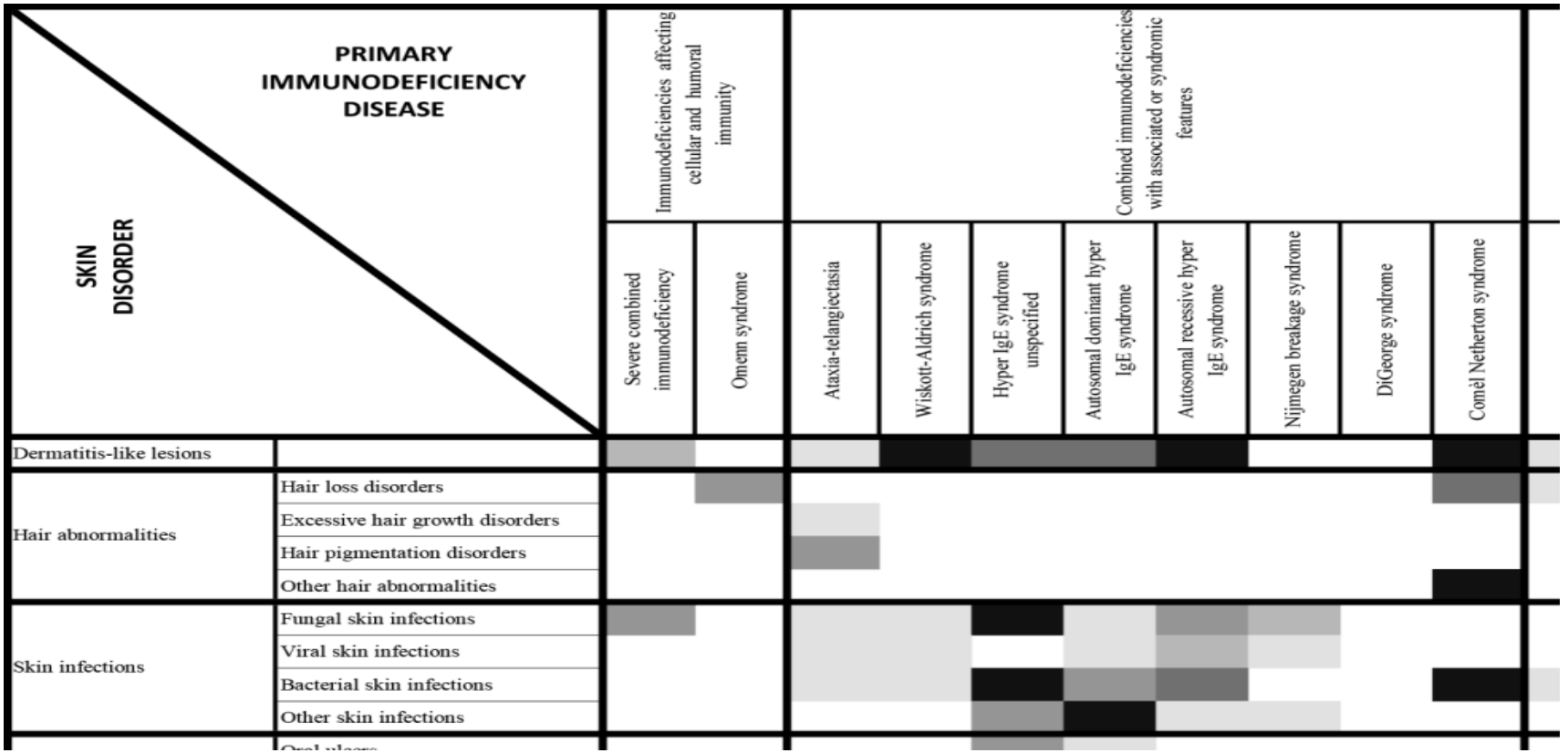
Ponsford M et al. Allergy 2018

# Huidafwijkingen in PID




De Wit J et al. Allergy 2019

# Huidafwijkingen in PID




De Wit J et al. Allergy 2019

# Huidafwijkingen in PID

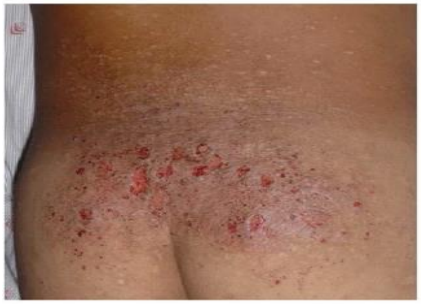
| | N=214 (100%) |
|---|---|
| Huidafwijkingen in voorgeschiedenis | 174 (81%) |

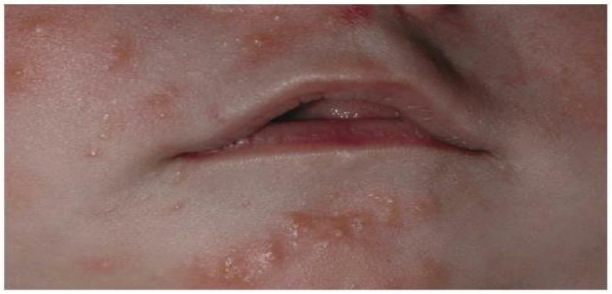
| | N=214 |
|---|---|
| Leeftijd van eerste huidklachten | 19.8 |
| Leeftijd van eerste niet-huid klachten | 24.7 |

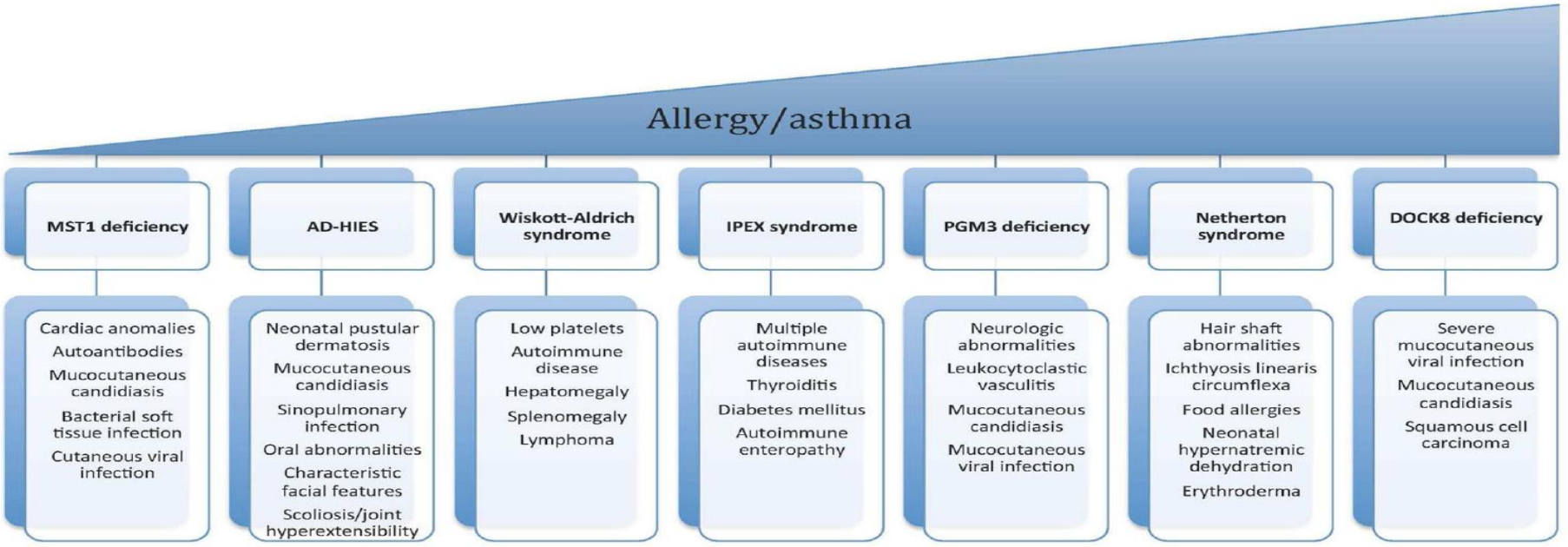
Huidafwijkingen een “early warning sign”?

De Wit J et al. *Unpublished data*

# Afwijkende patronen








Pichard DC et al. J Am Acad Dermatol 2015

# Te veel infecties in patiënten met COPD?

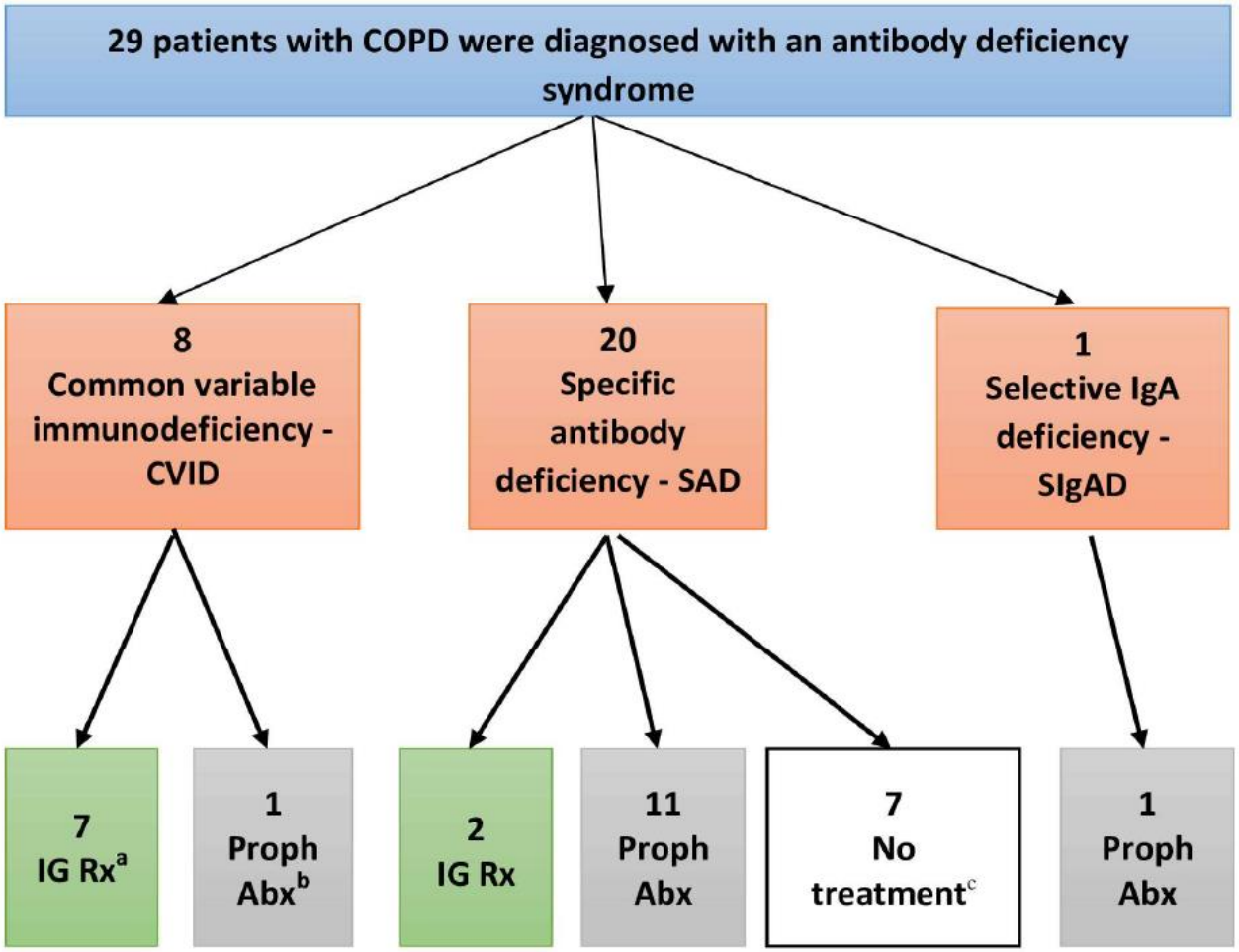
# Onbekende antistof deficiëntie in COPD?

- 913 patiënten met COPD met recidiverende exacerbaties[1]
  - 17 patiënten met bekende CVID
  - 18 patiënten met verdenking op CVID bevestigd
  - 5 nieuwe patiënten met CVID

- 1665 patiënten met COPD en recidiverende exacerbaties[2]
  - 20 patiënten met hypogammaglobulinemie
  - 2 patiënten met secundaire immuundeficiëntie
  - 18 patiënten met CVID

[1] Exley AR et al. Am J Respir Crit Care Med 2010
[2] Baleeiro C et al. Am J Respir Crit Care Med 2010

# Onbekende antistof deficientie in COPD?




McCullagh BN et al. PLOS One 2017

# Onbekende antistof deficiëntie in COPD?

**Table 5. Data on exacerbations, hospitalizations, prednisone use, and rescue antibiotic use, before and after treatment of antibody deficiency, in patients diagnosed with COPD and concomitant antibody deficiency syndrome.**

| Variable | n | Before | After | Change | p-value[a] |
|---|---|---|---|---|---|
| Exacerbations/year, median [IQR][b] | 18 | 4 [3–6] | 1 [0–2] | -3.5 [-5 to -2] | <0.0001 |
| Hospitalizations for AECOPD/year | 17 | 1 [0–2] | 0 [0–0] | -1 [-1 to 0] | 0.037 |
| ICU admissions | 18 | 2 (11%) | 0 (0%) | | 0.500 |
| Prednisone cumulative annual dose | 12 | 930 [0–3075] | 0 [0–40] | -310 [-1990 to 0] | 0.031 |
| Average courses of prednisone/year | 15 | 4 [0–12] | 0 [0–1] | -3 [-11 to 0] | 0.004 |
| Average courses of rescue antibiotics/year | 19 | 6 [4–12] | 0 [0–1] | -6 [-10 to -3] | <0.0001 |
| Oxygen use | 20 | 7 (35%) | 9 (45%) | | 0.157 |

[a] p-value from Wilcoxon signed-rank test, except ICU admissions and Oxygen use which was from McNemar's test

[b] IQR = Interquartile range (25th-75th percentile)

doi:10.1371/journal.pone.0172437.t005

McCullagh BN et al. PLOS One 2017

# COPD versus astma

# Astma in CVID

| CVID | N=33 |
|---|---|
| Bronchiaal asthma | 6 (18%) |
| COPD | 3 (9%) |
| **Algemene populatie (Tsjechie)** | |
| Bronchiaal asthma | 5% |

Milota T et al. Int Arch Allergy Immunol 2019

# Astma in CVID

| CVID | N=160 |
|---|---|
| Bronchiaal astma | 60 (37.5%) |
| Voedselallergie | 18 (11%) |

Primair of secundair?

Bjelac JA et al. Ann Allergy Asthma Immunol 2018

# Maar wanneer te denken aan PID in astma?

**TABLE 1 |** Clinical clues to alternative diagnosis in children with wheezing.

| Clinical clue | Possible diagnosis |
|---|---|
| **PERINATAL AND FAMILY HISTORY** | |
| Symptoms present from birth | Chronic lung disease of prematurity, PCD, CF |
| Family history of unusual chest disease | CF, Neuromuscular disorders, PCD |
| Severe upper respiratory tract disease | PCD |
| **SYMPTOMS AND SIGNS** | |
| Persistent moist cough | PBB, Bronchiectasis, Recurrent aspiration, PCD, CF |
| Excessive vomiting | GERD (w/without aspiration) |
| Dysphagia | Swallowing problems (w/without aspiration) |
| Breathlessness with light headedness and peripheral tingling | Dysfunctional breathing, Panic attacks |
| Inspiratory stridor | Tracheal or laryngeal disorder |
| Abnormal voice or cry | Laryngeal problems |
| Focal signs in chest | Developmental anomaly, FB, Post-infective syndrome |
| Persistent wheeze | Extrinsic intra thoracic airway compression, Airway-malacia, Luminal obstruction, CF, FB |
| Finger clubbing | CF, Bronchiectasis |
| Failure to thrive | CF, GERD |

*CF, cystic fibrosis; FB, foreign body; GERD, gastro-esophageal reflux disease; PBB, protracted bacterial bronchitis; PCD, primary ciliary dyskinesia.*

Ullmann N et al. Front Pediatr 2018

# Maar wanneer te denken aan PID in astma?

**TABLE 2 |** When to suspect specific alternative diagnosis and initial useful diagnostic examinations.

| Alternative diagnosis | When to suspect |
|---|---|
| Cystic fibrosis and bronchiectasis | Daily cough productive of sputum, clubbing, malabsorption and failure to thrive, recurrent chest infections, airways bacterial colonization |
| Immunodeficiency | Recurrent airway infections, Systemic infections (from a few months of age) |
| Primary ciliary dyskinesia | Neonatal upper airway symptoms, Chronic rhinosinusitis, Recurrent otitis media, Daily wet cough, Laterality defects |
| Protracted Bacterial Bronchitis | Cronich wet cough, Poor response to Beta-2 agonists, Good response to prolonged course of antibiotics |
| Airway malacia | Monophonic wheeze when the child is active, High risk setting (i.e., pt operated for tracheo-esophageal fistula or vascular ring), Presence of associated stridor |
| Airway foreign body | Abrupt onset of symptoms, History of choking, Unilateral monophonic wheeze, Focal hyperinflation of lung |
| Habit cough | Prolonged dry, honking cough; Absence of cough during sleep; Absence of any physical findings |
| Vocal cord dysfunction | Absence of structural abnormalities, Sudden worsening of "asthma" symptoms, No response to asthma medications |
| Bronchiolitis obliterans | History of severe viral respiratory infection in the first 3 years of life |

*CT, computed tomography; EM, eletcron microscopy; HSVM, high speed video microscopy; NO, nitric oxide.*

Ullmann N et al. Front Pediatr 2018

# Allergie in PID

Letters

## Allergic disease in patients with common variable immunodeficiency at a tertiary care referral center

**Table 1**
Characteristics of Patients With Positive Allergen Test Results[a]

| Patient No. | Age, y | Sex | Age at CVID diagnosis, y | Allergen(s) tested | Positive results | Diagnosis of asthma | Serum IgE, kU/L[b] | Serum IgG, mg/dL[b] | Serum IgA, mg/dL[b] | Serum IgM, mg/dL[b] | Serum IgG1, mg/dL[b] | Serum IgG2, mg/dL[b] | Serum IgG3, mg/dL[b] | Serum IgG4, mg/dL[b] |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | 64 | Female | 58 | Environmental | Mold<br>Weed | Yes | 27 | 391 | 7 | 302 | 217 | 104 | 49 | 14 |
| 2 | 75 | Male | 65 | Food (fish)<br>Environmental | *Dermatophagoides farinae*, *Dermatophagoides pteronyssinus* | Yes | 4 | 483 | 15 | 22 | 207 | 215 | 35 | 3 |
| 3 | 73 | Male | 60 | Drug (latex, penicillin) | Latex | No | 0 | 416 | 9 | 67 | U | U | U | U |
| 4 | 72 | Male | 68 | Environmental | *D farinae*, *D pteronyssinus* | No | 0 | 279 | 0 | 27 | U | U | U | U |
| 5 | 57 | Male | 38 | Food (peanut)<br>Environmental | Peanut | Yes | 13 | 509 | 40 | 23 | 329 | 123 | 34 | 24 |
| 6 | 60 | Male | 56 | Environmental | Dog, horse[c] | No | 47 | 470 | 108 | 108 | 343 | 98 | 17 | 12 |
| 7 | 60 | Male | 58 | Environmental | Grass | Yes | 28 | 346 | 187 | 220 | U | U | U | U |
| 8 | 58 | Female | 55 | Food (shellfish)<br>Drug (penicillin) | Shellfish | No | 239 | 427 | 4 | 21 | 301 | 75 | 40 | 19 |
| 9 | 72 | Male | 63 | Environmental | *D pteronyssinus* | No | 3 | 263 | 18.3 | 125 | 163 | 52 | 20 | 52 |
| 10 | 27 | Male | 22 | Environmental | Cat, *D farinae*, *D pteronyssinus*, trees grass | No | U | 550 | 4 | 8 | U | U | U | U |
| 11 | 13 | Female | 7 | Environmental | Dog,[c] mold,[c] weed[c] | No | 12 | 80 | 0 | 0 | 64 | 15 | 12 | 0 |
| 12 | 60 | Male | 51 | Environmental | *D pteronyssinus* | Yes | 3 | 400 | 52 | 38 | U | U | U | U |
| 13 | 33 | Female | 30 | Environmental | Cat | Yes | 0 | 69 | 0 | 0 | 0 | 0 | 0 | 0 |

Abbreviations: CVID, common variable immunodeficiency; U, unknown.
[a]Our panel assesses for sensitivity to cat, dog epithelia, cockroach, *Dermatophagoides farinae*, *Dermatophagoides pteronyssius*, *Alternaria tenuis*, *Aspergillus fumigatus*, *Cladosporium sphaerospermum*, *Epicoccum nigrum*, *Fusarium solari*, *Bipolaris sorokiniana*, penicillium mix, ash, beech, birch, maple, cottonwood, elm, hickory, mulberry, black oak, American sycamore, black walnut, willow, Bermuda grass, Kentucky bluegrass, Timothy grass, meadow fescue, Johnson grass, orchard grass, perennial ryegrass, cocklebur, sheep sorrel, English plantain, lamb's quarter, marsh elder, pigweed, and ragweed mix.
[b]At diagnosis or earliest value available in the electronic medical record.
[c]In vitro only.

Bjelac JA et al. Ann Allergy Asthma Immunol 2018

# Take home messages

Primaire immuundeficienties komen vaker voor dan we denken

Presenteren zich niet altijd met infecties

Veelvoud aan “normale” symptomen

Combinaties van “rare” bevindingen

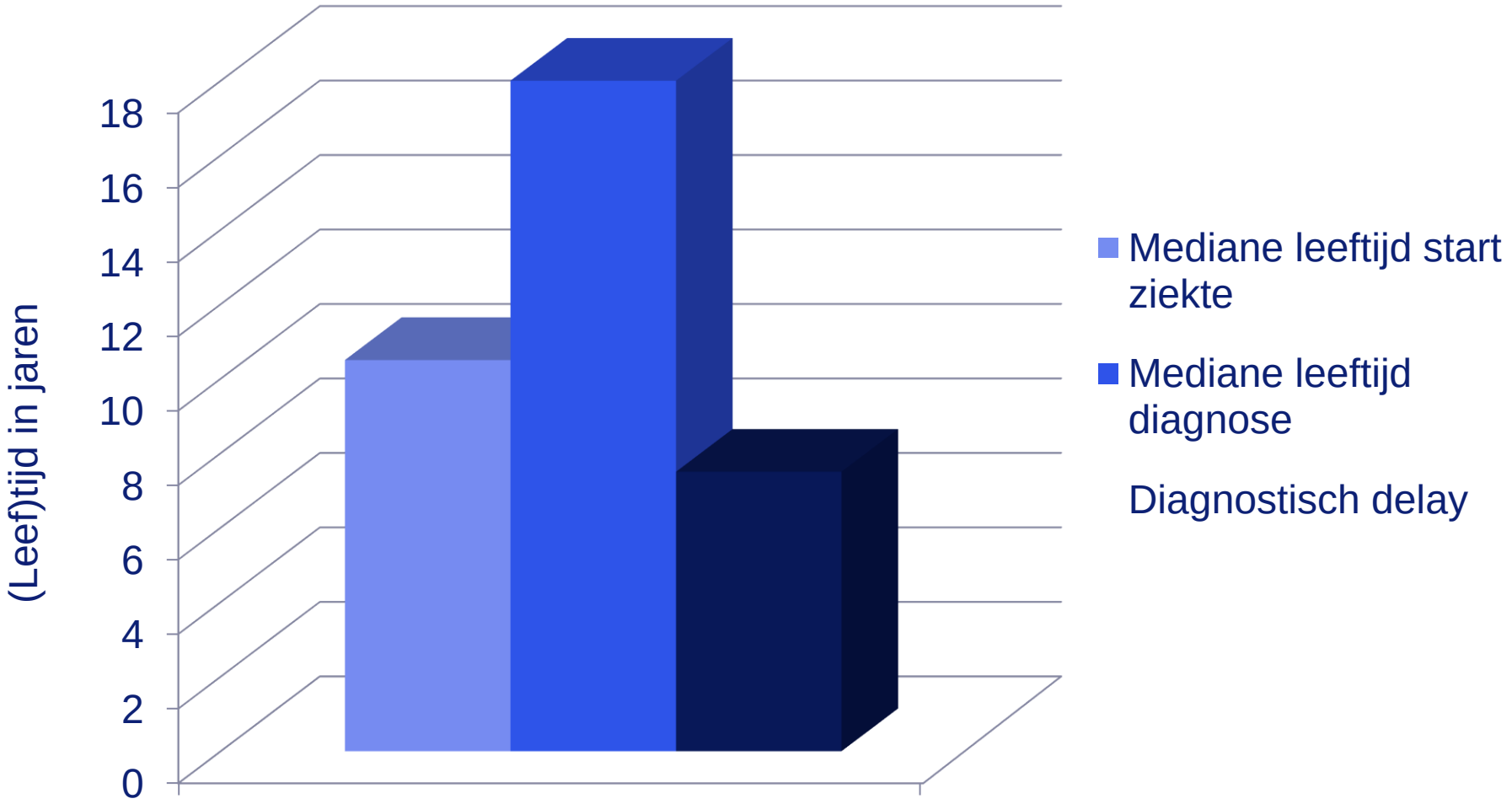
Moeilijk te behandelen aandoeningen

Laagdrempelig eenvoudige analyse immuundeficientie

Verkorten delay

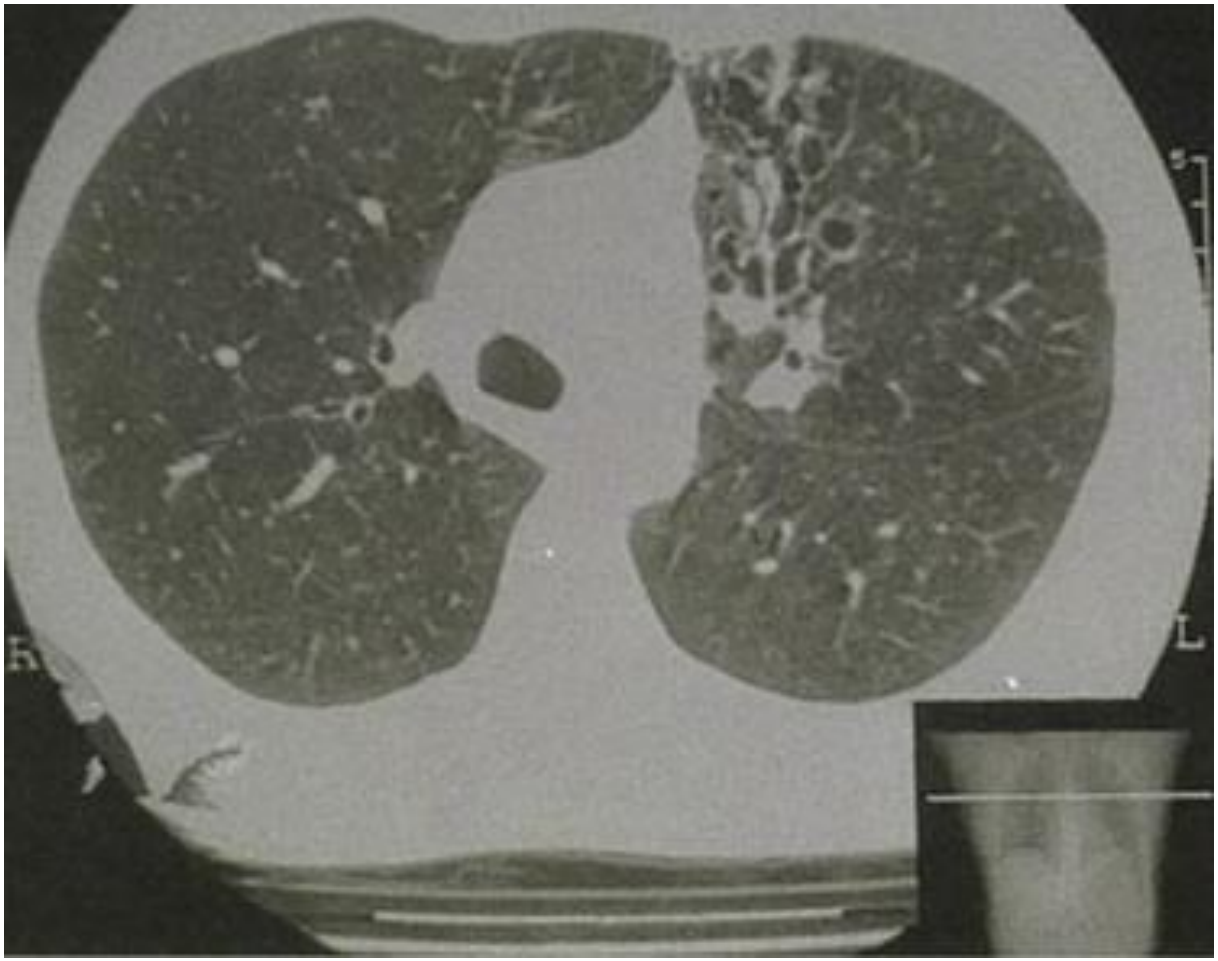
Voorkomen eindorgaanschade

# Verkorten delay




Jonkman-Berk et al. J Clin Immunol 2015

# Voorkomen eindorgaanschade



Cozijnsen M et al. 1994 NTvG

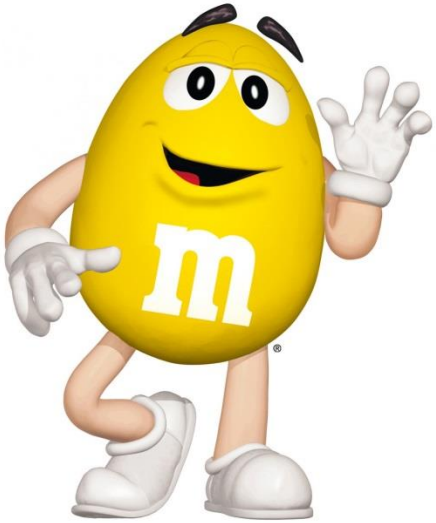
# Nieuwe (betere) behandelingen ?

- The heterogeneity of CVID as defined by clinical phenotypes has advanced to the identification of specific disease-causing gene mutations in a small proportion of patients with CVID-like phenotype that have inflammatory and autoimmune comorbid conditions.
- The ever-expanding list of new GOF monogenic disorders has led to a better understanding of the immunobiology and function of these defective genes, and new therapies to better optimize the treatment of the autoimmune and inflammatory conditions that plague these patients.

Leiding JW et al. Curr Opin Allergy Clin Immunol 2018

# Specifieke primaire antistof deficiënties

APDS



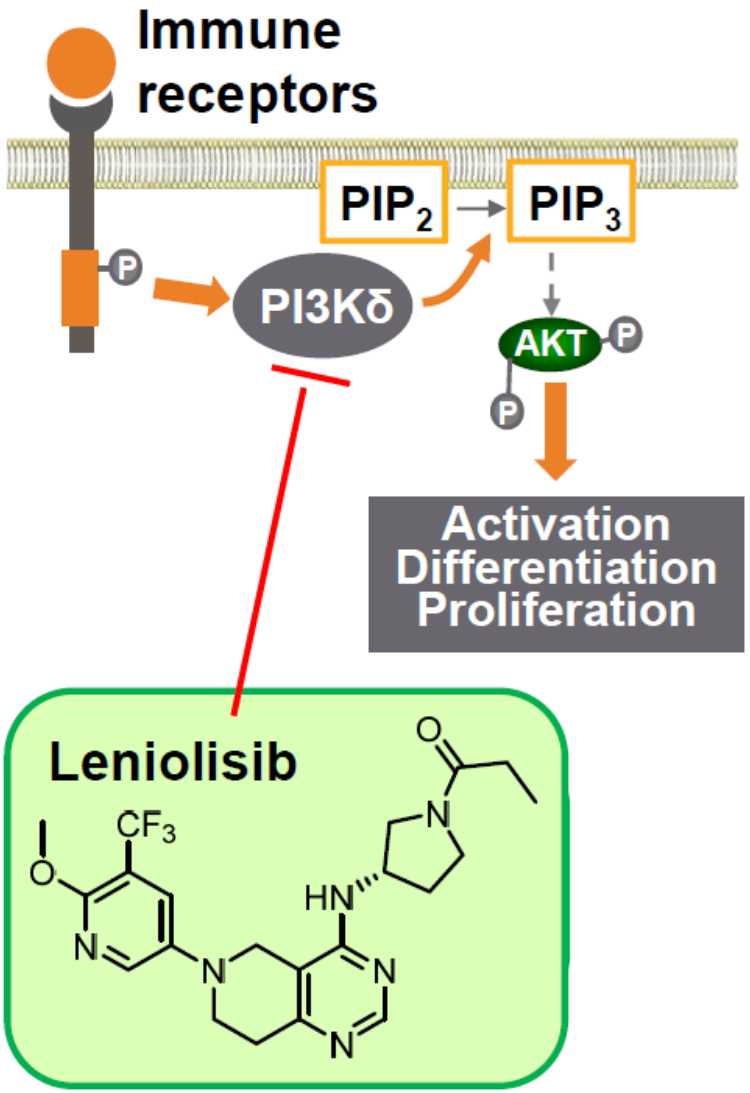
CTLA4

*X-MAID*

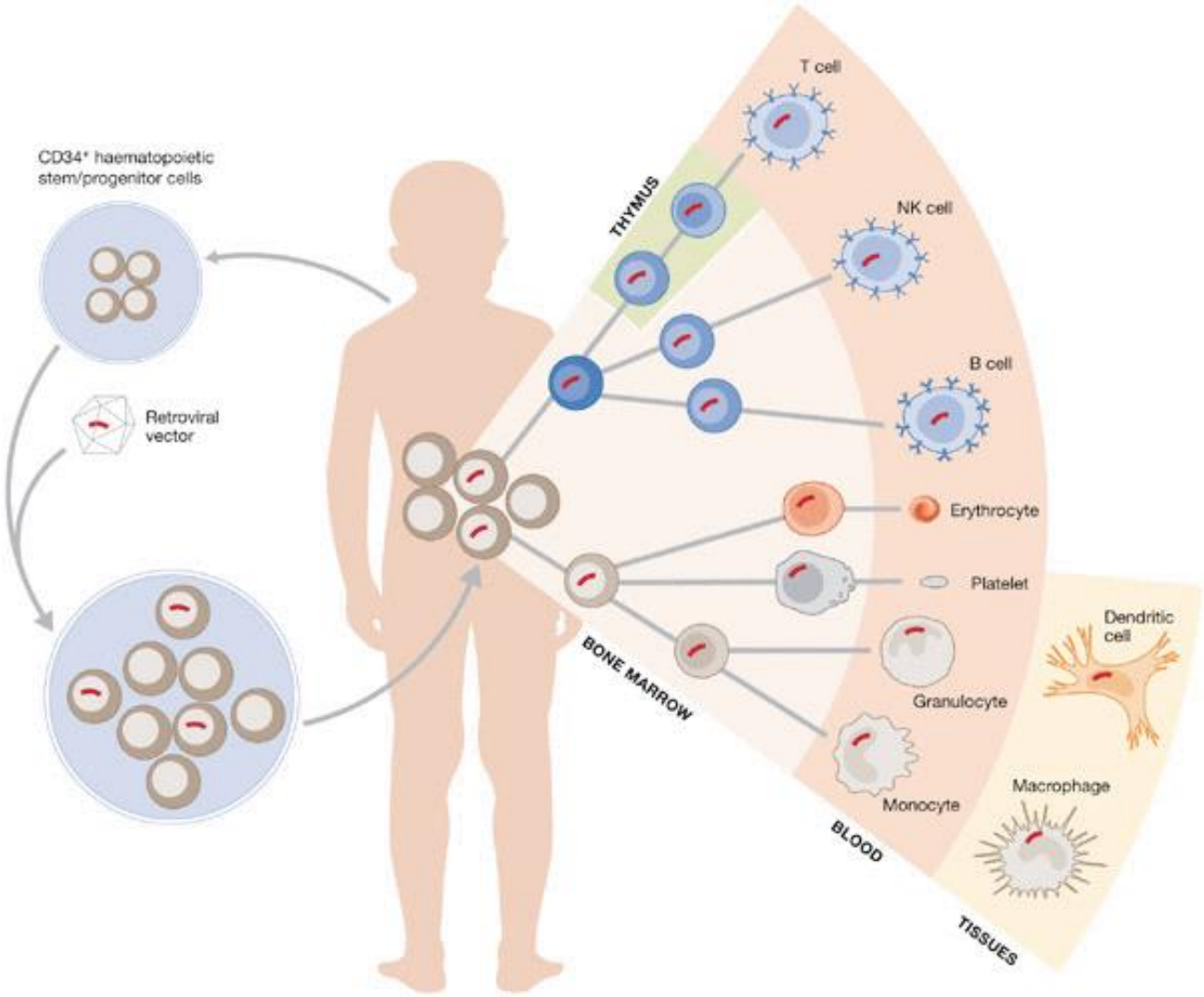
CD27

LRBA

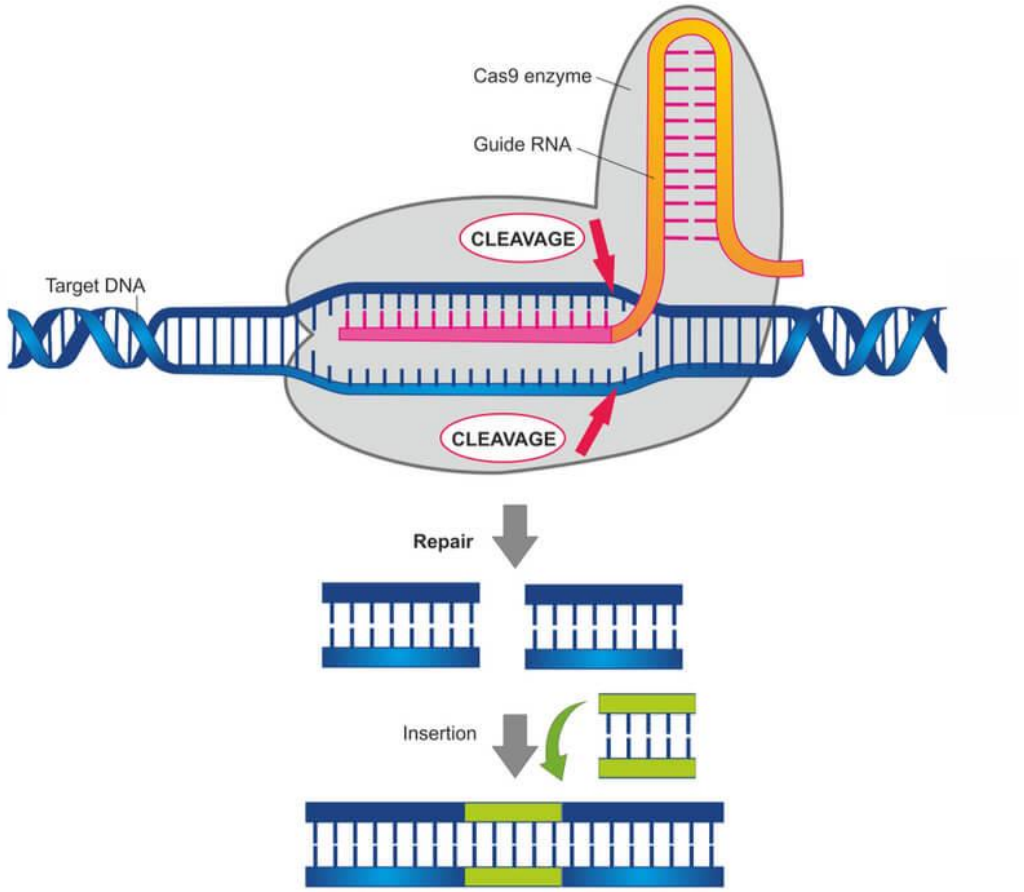
# APDS : GOF mutatie in PI3Kδ leidt tot CVID



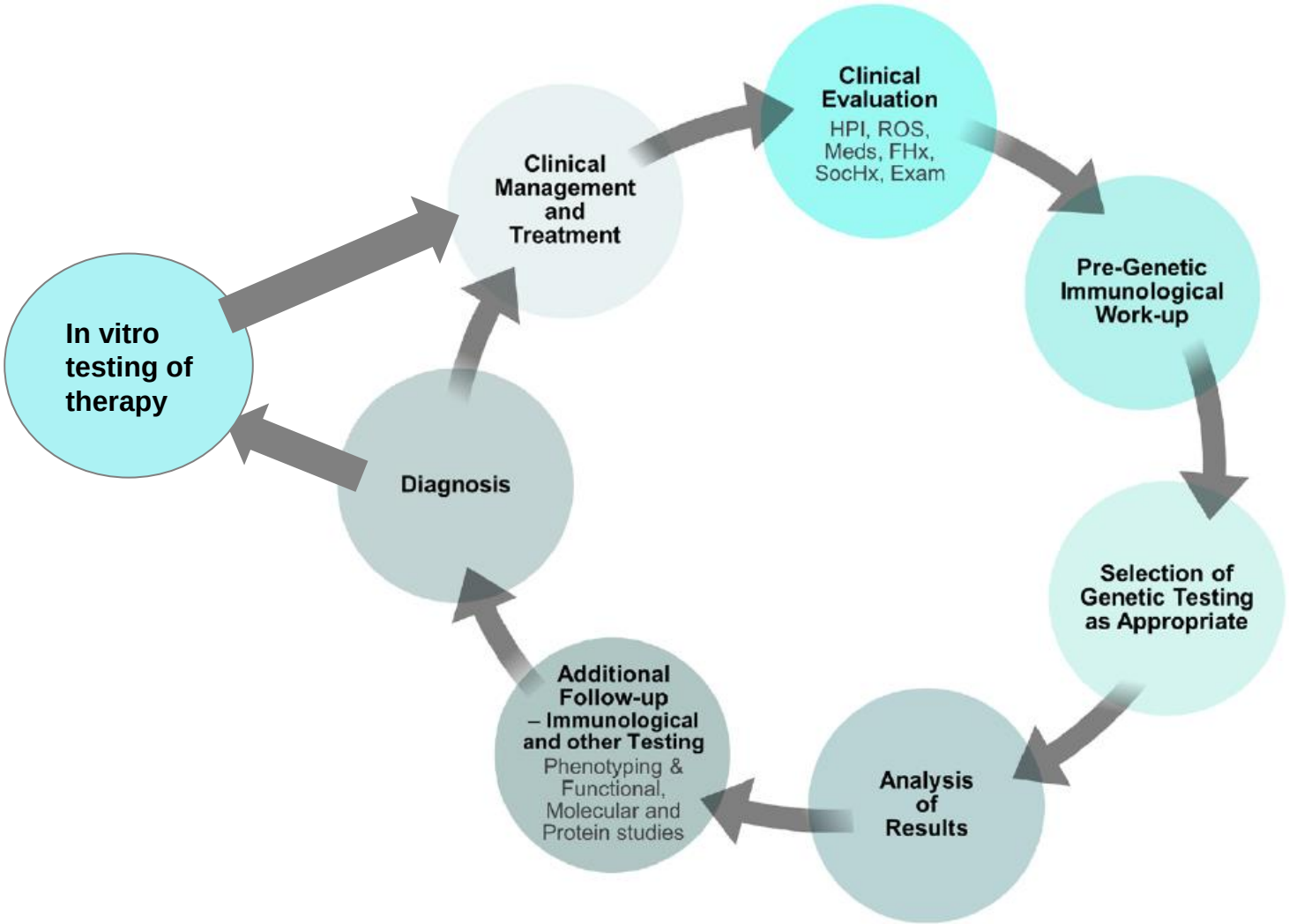
# Gen therapie in PID : Severe Combined Immunodeficiency



# De toekomst van monogenetische PIDs



# Gene-targeted en *in vitro* based therapy




Adapted from Richardson AM et al. Curr Allergy Asthma Rep 2018

# Dank voor uw aandacht