

Severe Combined Immunodeficiency, SCID-screening Onderzoek Nederland met TRECs SONNET

SONNET - SCID screening

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Achtergrond immuniteit

SCID

Nederlandse situatie

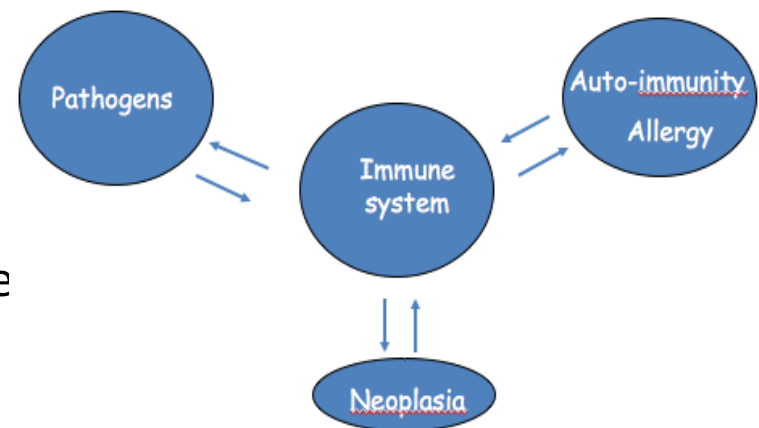
Behandeling van ernstige immuunstoornissen



Wat doet het afweersysteem?

- Infecties opruimen
- Kwaadaardige ziektes, maligniteiten weghouden
- Zorgen dat er geen (overmatige) ontsteking of autoimmunititeit of allergie ontstaat
- (Vreemd weefsel afstoten)

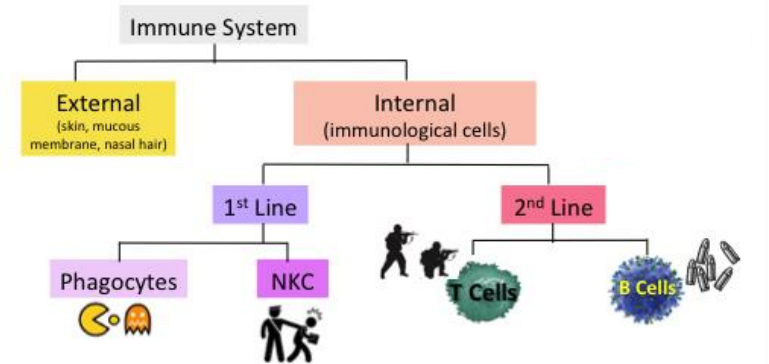
The immune system



Zonder afweersysteem gaat het mis

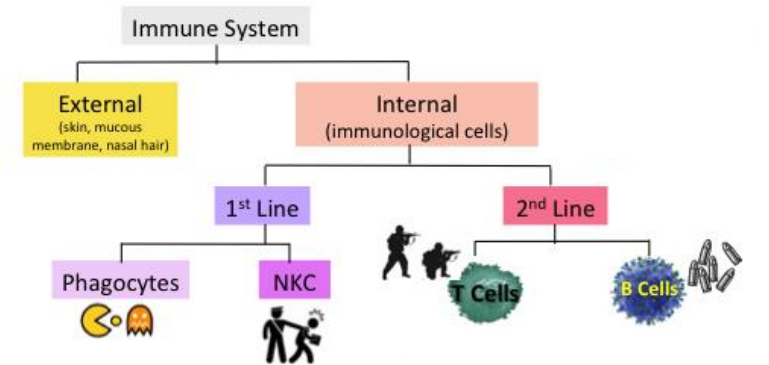
Het immuunsysteem - samenstelling

- barrière
 - huid en slijmvliezen
 - zuurgraad (e.g. maag)
 - commensale flora (e.g. darm)
 - trilharen (luchtwegen)



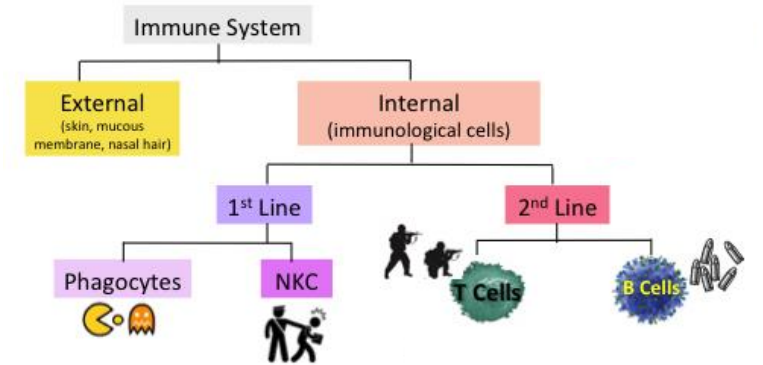
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- aangeboren afweer – aspecifiek ('innate')
 - granulocyten
 - macrofagen
 - natural killer (NK) cellen

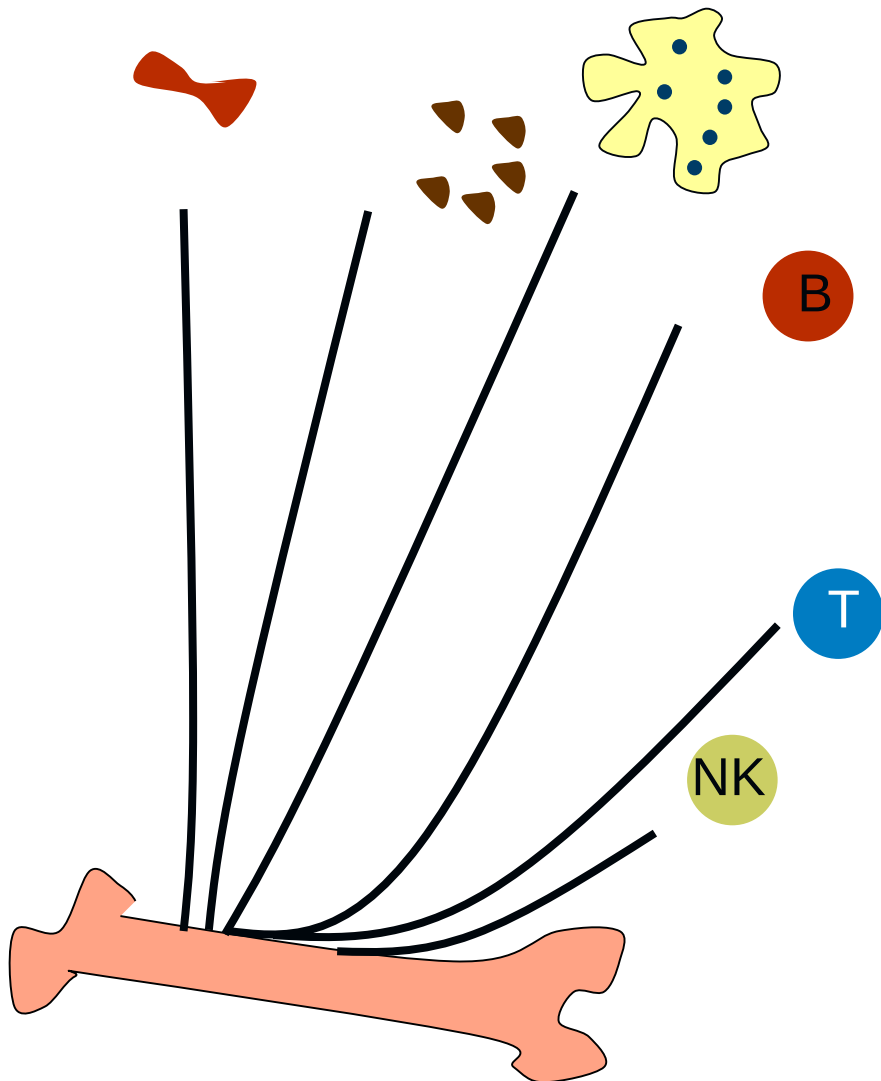


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 - macrofagen
 - natural killer (NK) cellen
- verworven afweer – specifiek ('adaptive')
 - B cellen
 - T cellen



Hoe is normale afweer opgebouwd?



Granulocyten / monocyten / macrofagen
- fagocyteren bacterien

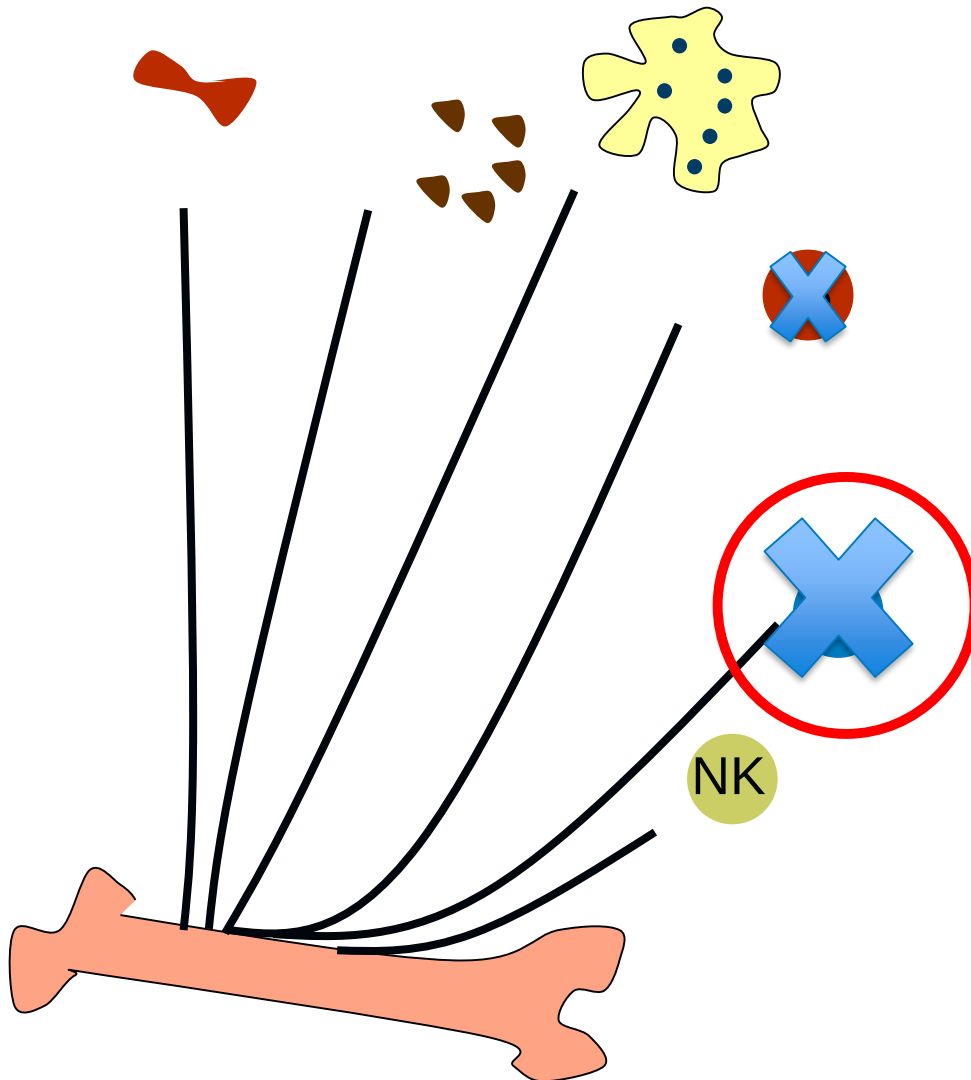
B cellen

- maken antistoffen > fagocytose

T lymfocyten, NK lymfocyten

- killing van geïnfecteerde cellen

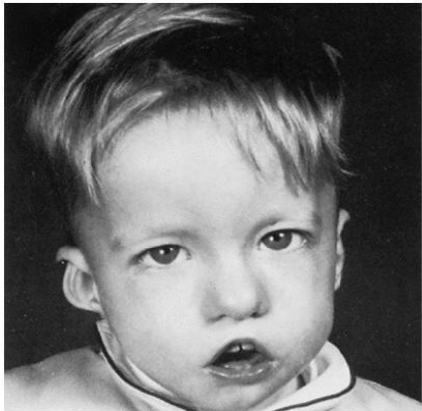
Wat is essentie van SCID (Severe Combined Immuno Deficiency)?



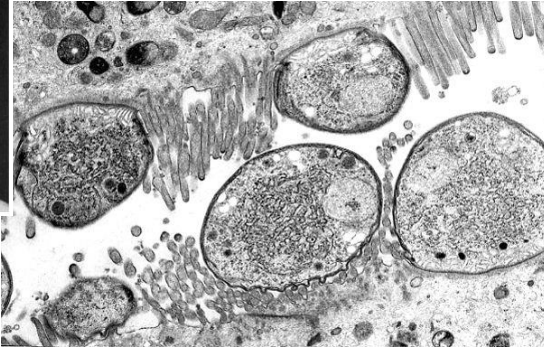
Geen functionele T lymfocyten:

- Geen normale B cel functie, en
- Infecties met:
 - Virus
 - Bacterie
 - Schimmel / gist

Balans immuniteit vs ziekteverwekker



Opportunistische parasiet



Hoe zwakker de 'pathogeen'



Hoe zwakker immuniteit



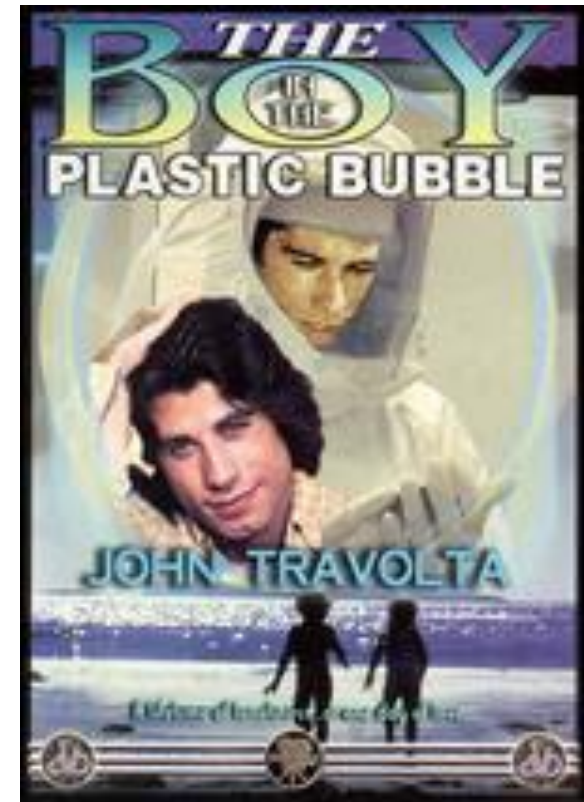
Ebolavirus

Case presentaties:

- Pt 1, 4 maanden oud
 - Koorts, infecties, rash, FTT
 - Diepe T cel lymfopenie
 - Diagnose SCID op lft 4 maanden
 - Overleden ttv HSCT (stamceltransplantatie) traject aan virale reactivaties
-
- Pt 2, 1^{ste} week post-partum
 - Rash, schilferig eczeem achtige huidontsteking
 - Grote lever en milt
 - Na 3 weken diagnose Omenn – rag SCID
 - HSCT met succes

The Boy in the Bubble – New York Times

<https://www.nytimes.com/video/us/100000004077071/the-boy-in-the-bubble.html>



Severe Combined Immunodeficiency (SCID)

incidentie - pathofysiologie

- meest ernstige primaire immuundeficiëntie (PID)

afwezigheid van functionele T cellen + afwezigheid/dysfunctie B cellen

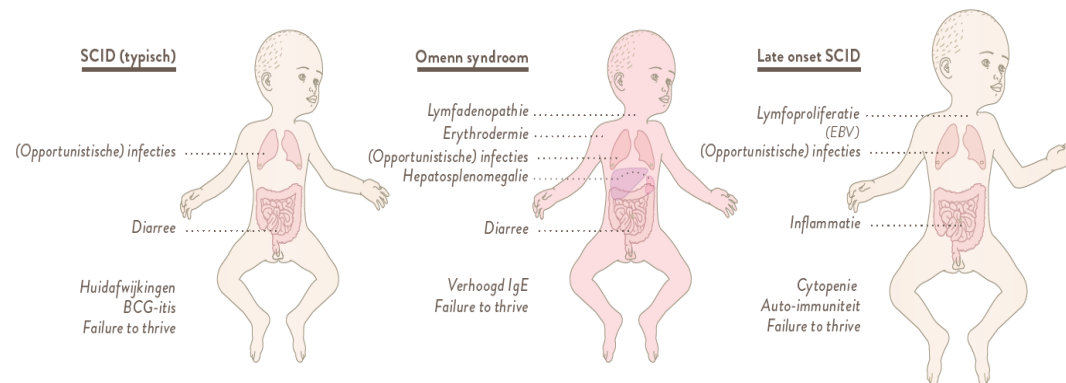
- Infecties
 - te veel
 - te lang
 - bijzondere plaatsen
 - bijzondere verwekkers
- Eczeem, lymfadenopathie, auto-immuniteit
- Diarree, slecht groeien (*failure to thrive*)
- Soms: dysmorfe kenmerken

Klassieke SCID

Overlijden < 12 maanden indien onbehandeld
Medical Emergency

Atypische varianten van SCID

Minder ernstige vormen van SCID
Lastige – late diagnose
Overlijden pas later, 2-20 jr

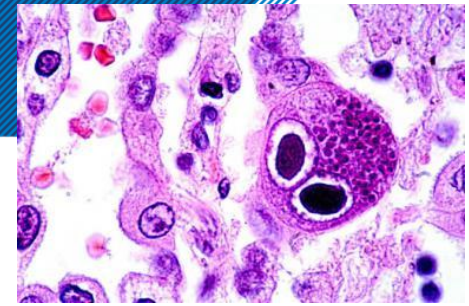


Welke diagnostiek wordt momenteel in NL verricht bij SCID verdenking?

1. Herkenning ...
2. Bevestiging diagnose:
 - Flow cytometrie van lymfocyten
 - Antistof metingen (specifieke immunoglobulines)
 - Functionele testen van lymfocyten, stralingsgevoeligheid
 - Genetica:
 - Er zijn > 20 genen oorzakelijk betrokken bij SCID
 - Losse gen bepalingen en NGS panel diagnostiek

Severe Combined Immunodeficiency (SCID) *pathogenen*

klinisch probleem	frequente verwekkers
persisterende virale gastro-enteritis	noro-, rota-, astro-, adenovirus
persisterende virale (lagere) luchtweginfecties	RS-, para-influenzavirus, CMV
pneumocystis jiroveci pneumonitis	
recidiverende/hardnekkige candidiasis	
achterblijvende groei	



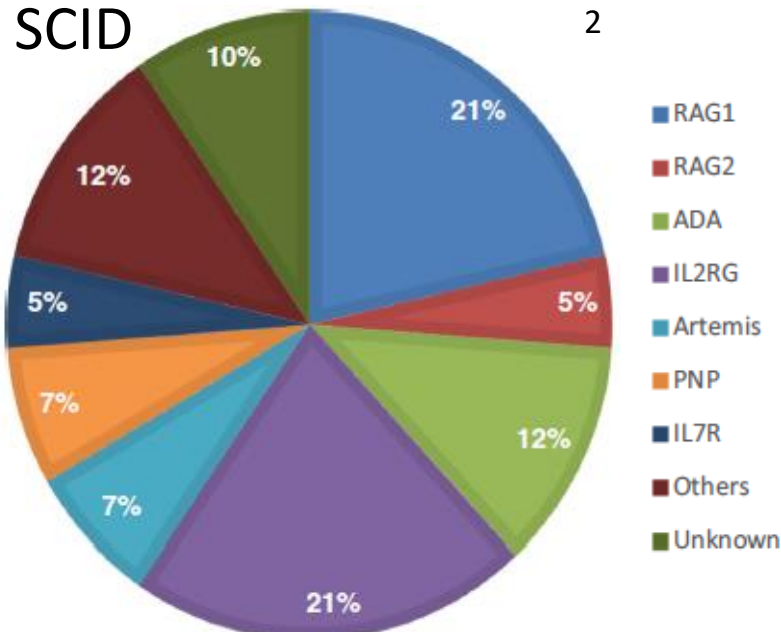
Severe Combined Immunodeficiency (SCID)

In NL: *incidentie - pathofysiologie*

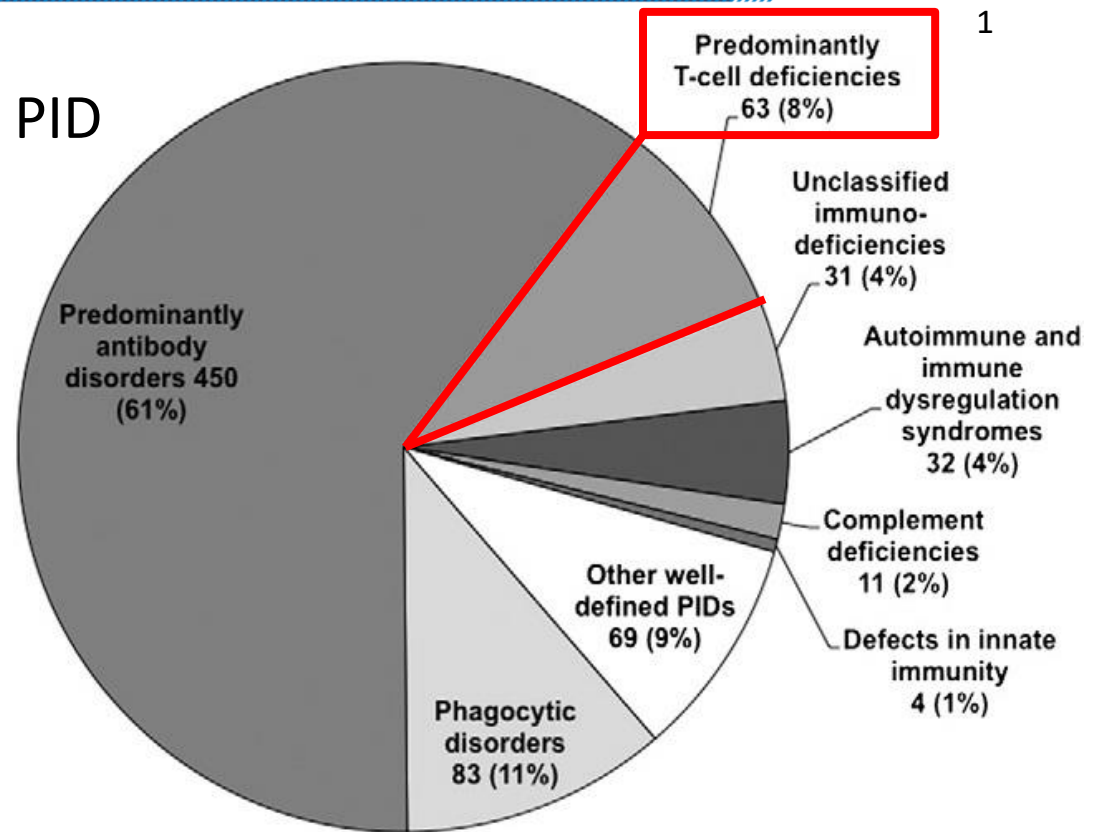
incidentie Nederland: ~1:63.000
(periode 1998 – 2013)²

meerdere gen defecten

SCID



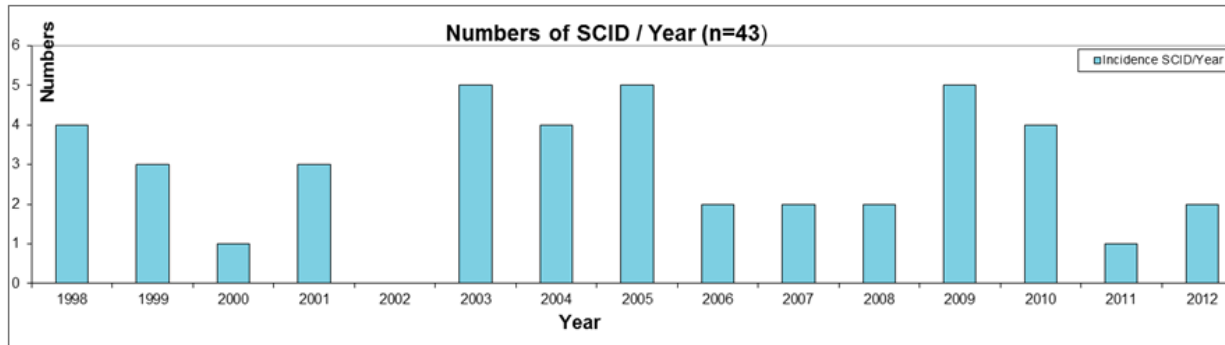
PID



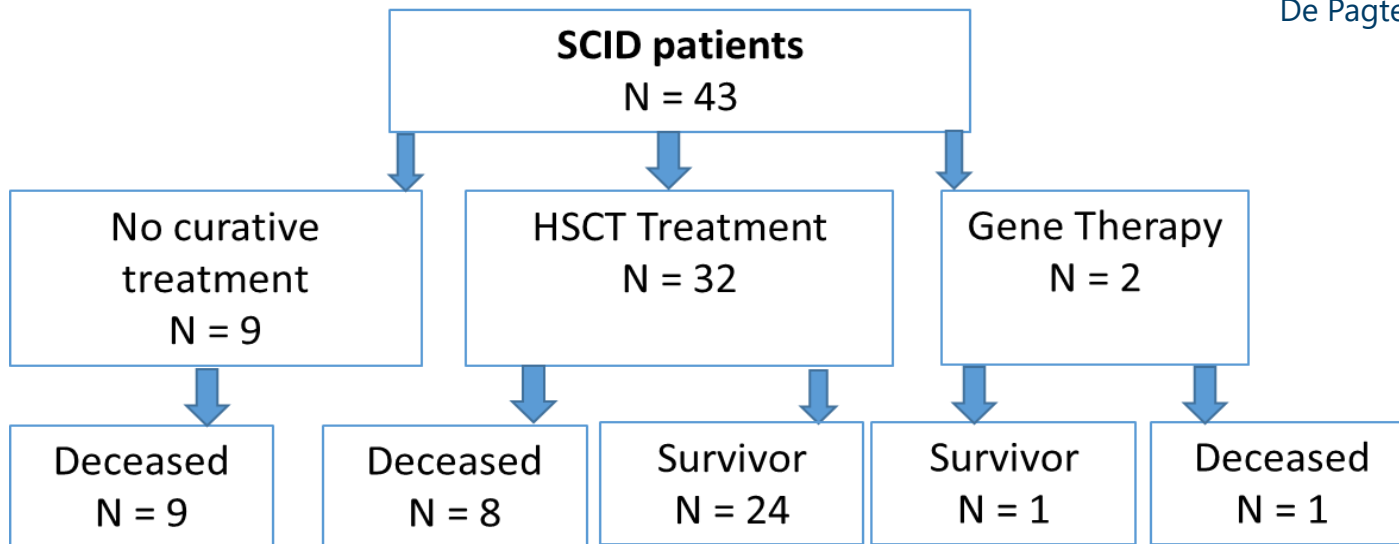
1. Jonkman-Berk et al. J Clin Immunol 2015

2. De Pagter et al. Eur J Pediatr 2015

Incidentie / outcome Nederland 1998 - 2012



De Pagter et al, *Eur J Pediatrics* 2015



- Overall mortaliteit: 18 / 43 patiënten
- Verhoogde mortaliteit vooral bij patiënten met infecties

Severe Combined Immunodeficiency (SCID)

behandeling - stamceltransplantatie

- curatieve optie = allogene hematopoietische stamceltransplantatie

HSCT hoe werkt dit?

Patiënt voorbereiden, cq. conditioneren (restant afweer verwijderen: met serotherapie en chemotherapie)

Stamcellen van gezonde donor toedienen aan patiënt

Stamcelbron: navelstrengbloed, beenmerg, bloed

Rijpen uit tot normaal functionerende afweer

Mainstay behandeling momenteel:

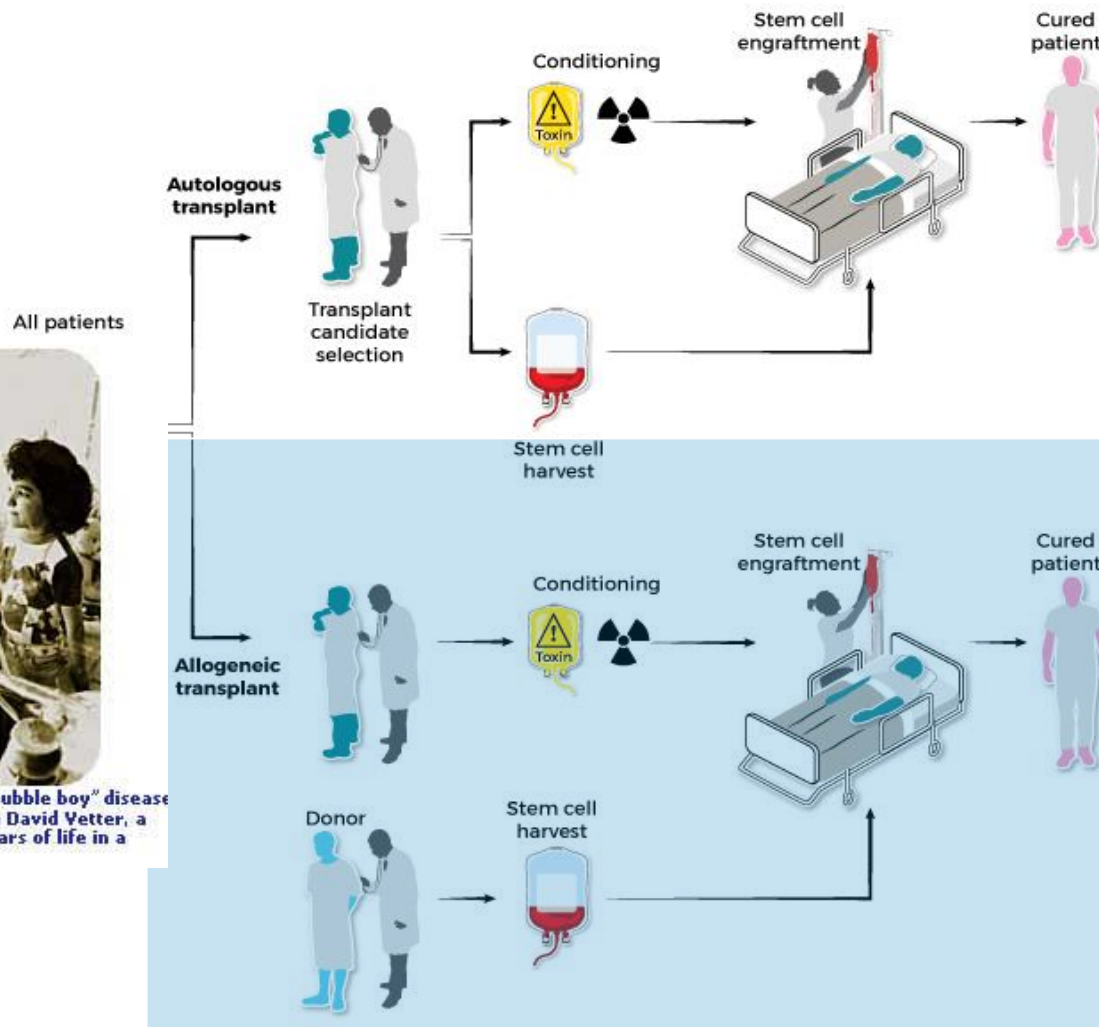
- Curatief
- Voor (bijna) iedereen beschikbaar

Severe Combined Immunodeficiency (SCID) behandeling - stamceltransplantatie

- curatieve optie = allogene hematopoietische stamceltransplantatie



Commonly referred to as "bubble boy" disease SCID, gets its moniker from David Vetter, a boy who lived out his 12 years of life in a germ-free plastic bubble.



Risico's en complicaties

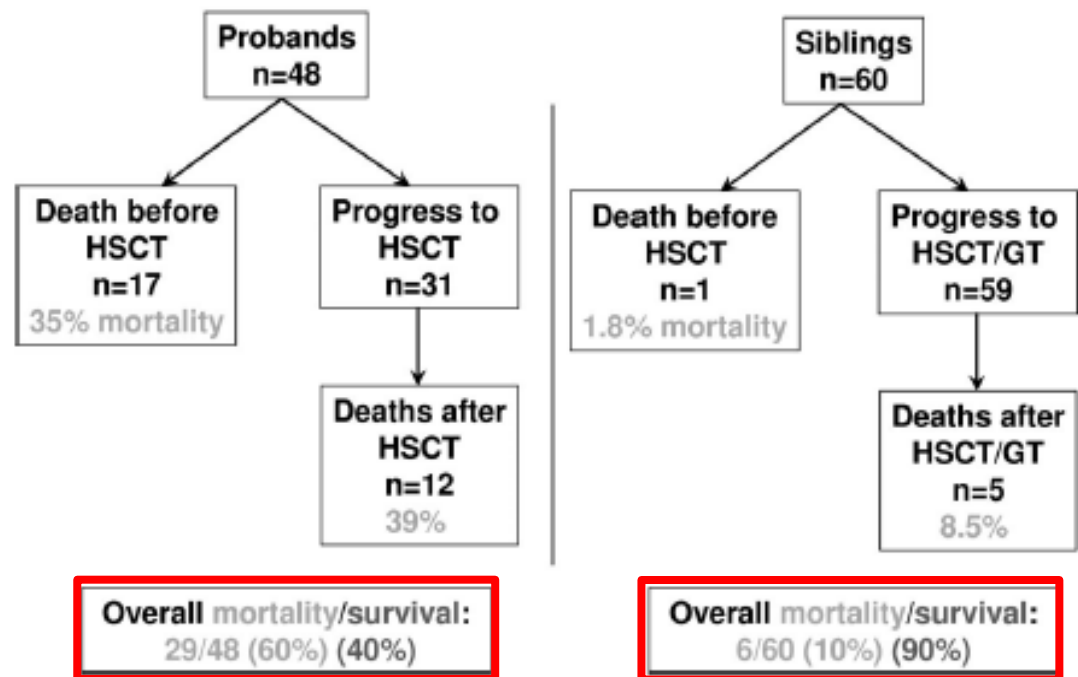
- infecties
- matching (HLA) – beperkte donorkeuze
- chemotherapie – toxiciteit
- graft versus host ziekte (GvHD)
- traag immuunherstel, langdurig verminderde afweer

Severe Combined Immunodeficiency (SCID)

behandeling - stamceltransplantatie

- curatieve optie = allogene hematopoietische stamceltransplantatie[^]
- behandeling van infecties (en andere problematiek)
- preventie: antibiotische profylaxe, substitutie immuunglobulines, leefregels
- vroege diagnose belangrijk!

Comparison of outcome in proband and sibling cohort



[^]voor ADA SCID evt enzymtherapie

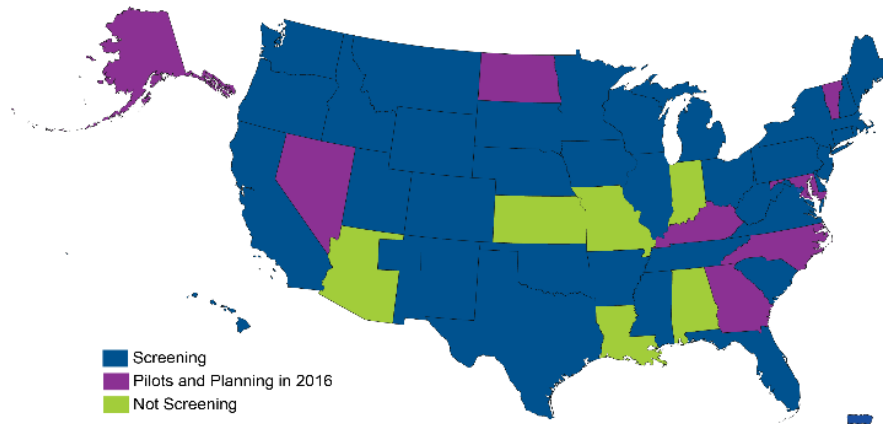
[^]voor sommige gendefecten evt. gentherapie

Severe Combined Immunodeficiency (SCID)

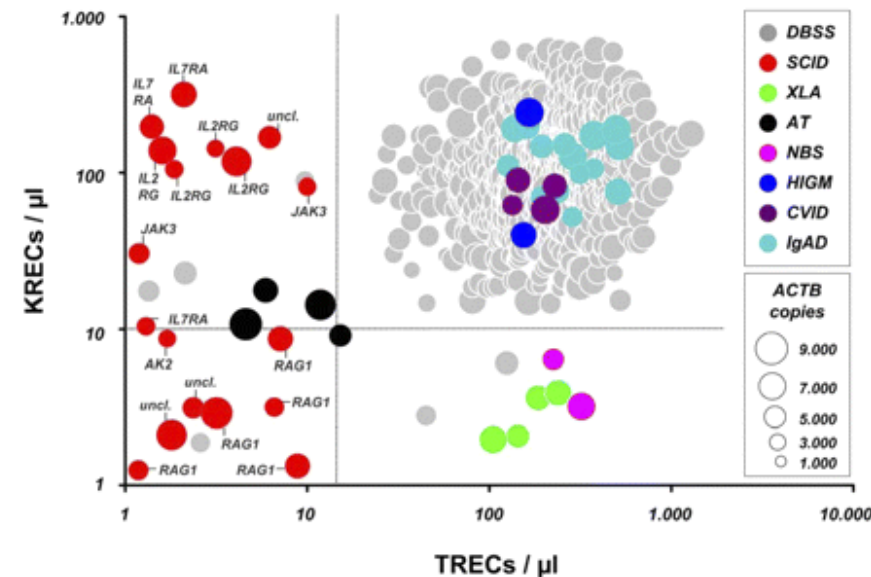
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- preventie: antibiotische profylaxe, substitutie immuunglobulines, leefregels
- vroege diagnose belangrijk!
- hieprikscreening – TRECs ('thymus output')

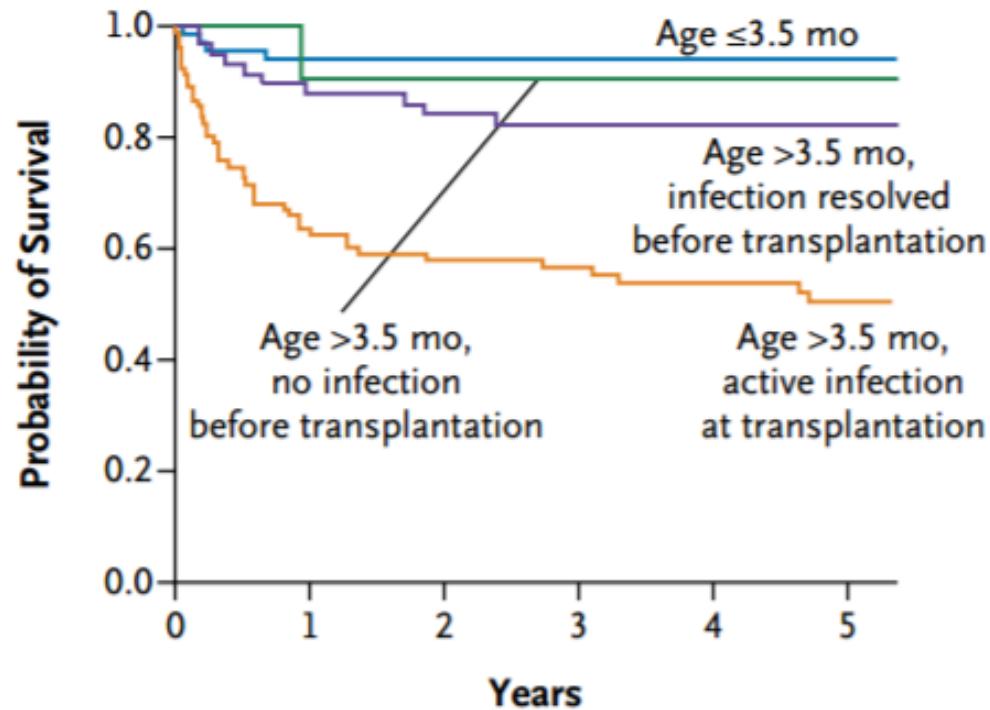
SCID Newborn Screening: Current Status of Implementation Map



As of March 3, 2016



Leeftijd waarop SCT & infectie ja/nee



Leeftijd van 3.5 maanden > betere overleving ten opzicht van stamceltransplantatie op oudere leeftijd

Pre-existente infecties > negatief effect op de overleving na stamceltransplantatie

Wat is de *outcome* van behandeling voor SCID?

3 opties:

- Overlijden ttv curatief traject (meestal aan infecties / graft vs host disease)
- Overleven met rest morbiditeit, zoals:
 - Chronische graft vs host disease
 - Orgaan, bv. longschade
 - Verhoogd risico op maligniteiten, infertiliteit
- Restloos genezen met goed functionerende afweer en goede kwaliteit van leven

Case presentaties: deel 2

- Sib 1 & Sib 2
- SCID diagnose bij geboorte
- HSCT op leeftijd 2 maanden
- Long term follow up:
 - Perfect

Wat zijn lange termijn perspectieven?

Korte termijn:

- Implementatie van NBS voor SCID en andere immuundeficiënties

Middellange termijn:

- “Genetics first approach” voor immuundeficiënties die niet met NBS zijn opgespoord

Langere termijn:

- Routine genoom analyse bij eerste presentatie
- Routine genoom analyse na geboorte

Vragen?

RIVM

Erasmus MC - LUMC

WID: werkgroep immuundeficiënties

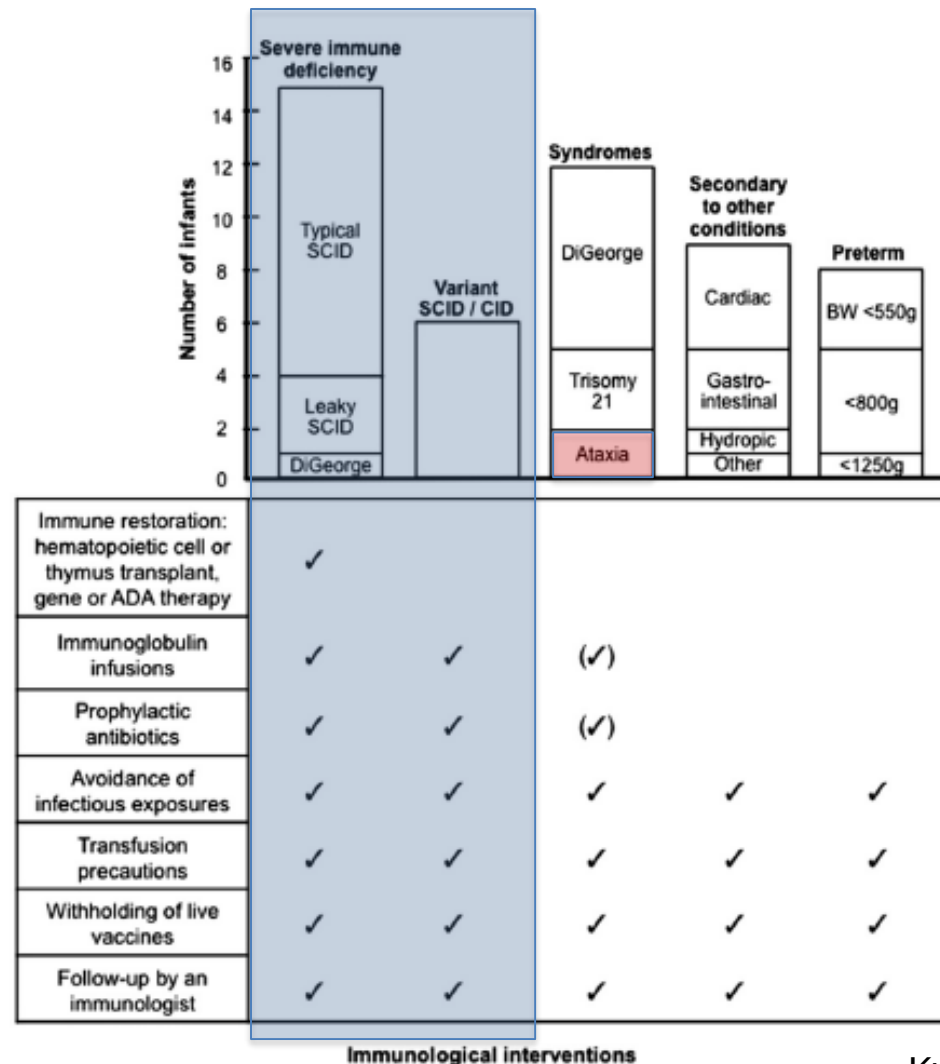
- *Mirjam van der Burg, EMC*
- *Gertjan Driessen, JKZ Den Haag*
- *Taco Kuijpers, AMC*
- *Joris van Montfrans, UMCU*
- *Robbert Bredius, LUMC*

SCID in vergelijking met andere hielprikscreening ziektes

TABLE E3. Birth prevalence of SCID and all cases of TCL in California: comparison with diseases in the Recommended Uniform Screening Panel

ACMG code	Disease	No. of cases*	Cases per 10,000 births	Notes
HEAR	Hearing loss	832 in 1 y†	15	
CH	Congenital hypothyroidism (includes transient and variant)	1390	5.14	Salt wasting: 112 cases; virilizing: 23 cases
CF	Cystic fibrosis	418	1.54	
Hb SS	Sickle cell anemia	248	0.917	
CAH	Congenital adrenal hyperplasia (all forms)	158	0.584	
GALT	Galactosemia (classical/Duarte)	156	0.577	Classical: 29 cases; Duarte: 127 cases
Hb S/C	Hb S/C disease	144	0.532	
TCL	TCL (<1500 T cells/ μ L and/or absent naive T cells)	50 in 2 y‡	0.503	SCID and non-SCID, including preterm alone (incidence 1/19,900)
MCAD	Medium-chain acyl-CoA dehydrogenase deficiency	126	0.466	
BIOT	Biotinidase deficiency (partial/profound)	84	0.310	Partial: 44 cases; Profound: 39 cases
Hb S/ β Th	HbS/ β -thalassemia (β^+ / β^0)	72	0.266	β^+ : 59 cases; β^0 : 13 cases
PKU	Phenylketonuria	69	0.255	
3-MCC	3-Methylcrotonyl-CoA carboxylase deficiency	67	0.248	
VLCAD	Very long-chain acyl-CoA dehydrogenase deficiency	41	0.152	
MUT	Methylmalonic academia (mutase deficiency) (mut^-/mut^0)	39	0.144	mut^- : 20 cases; mut^0 : 19 cases
SCID disorders	Requiring curative treatment by HCT, enzyme replacement (adenosine deaminase deficiency), gene therapy, or thymus transplantation	15 in 2 y‡	0.133	Typical and leaky SCID, Omenn syndrome, complete DiGeorge syndrome (incidence 1/66,250 births)
CUD	Carnitine uptake defect	34	0.126	
GA 1	Glutaric acidemia type I	32	0.118	
PA	Phenylalaninuria	24	0.087	

Immunologische interventies na abnormale TREC bevinding



Severe Combined Immunodeficiency (SCID)

behandeling - gentherapie

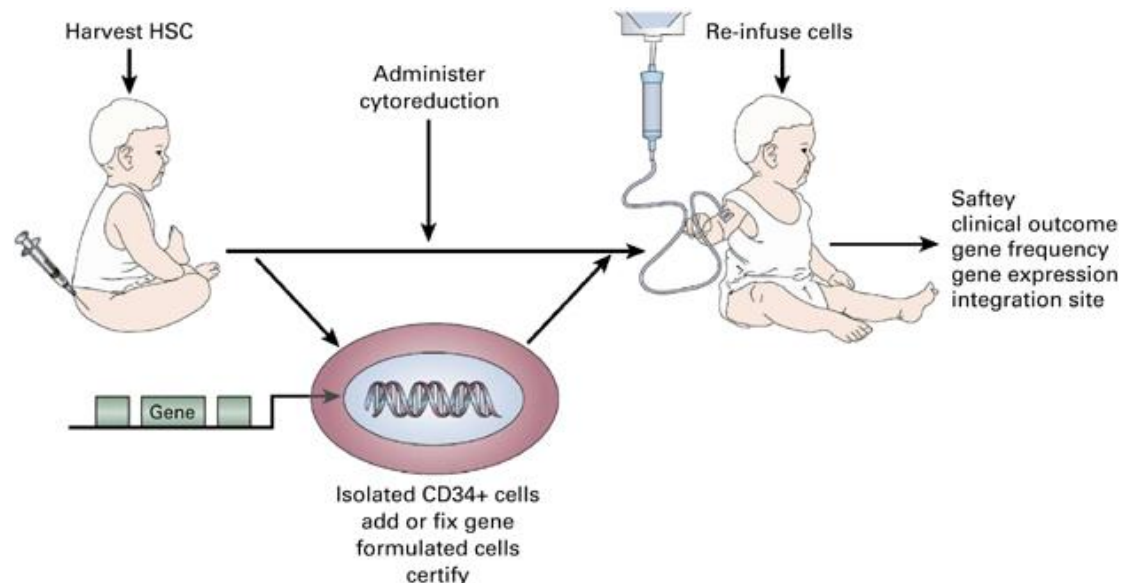
- curatieve optie = allogene hematopoietische stamceltransplantatie
- nieuwe ontwikkelingen: gentherapie
 - SCID: monogenetische aandoening
 - celpopulatie toegankelijk (hematopoietische stamcellen)
 - gen transfer middels virale vector mogelijk
 - procedure: stamceltransplantatie

Voordelen gentherapie

- autologe setting (mildere conditionering) – *bij ontbreken van gematchte donor*
- geen risico graft versus host ziekte

Nadelen gentherapie

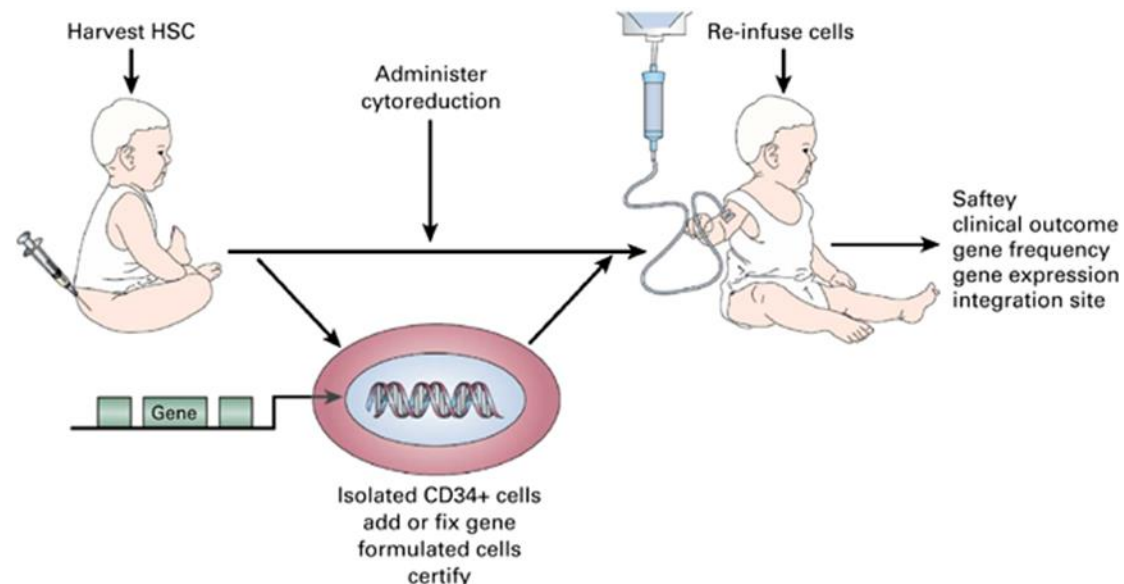
- Experimenteel
- Mutagenese
- Beperkt aantal 'genen' waarvoor dit kan

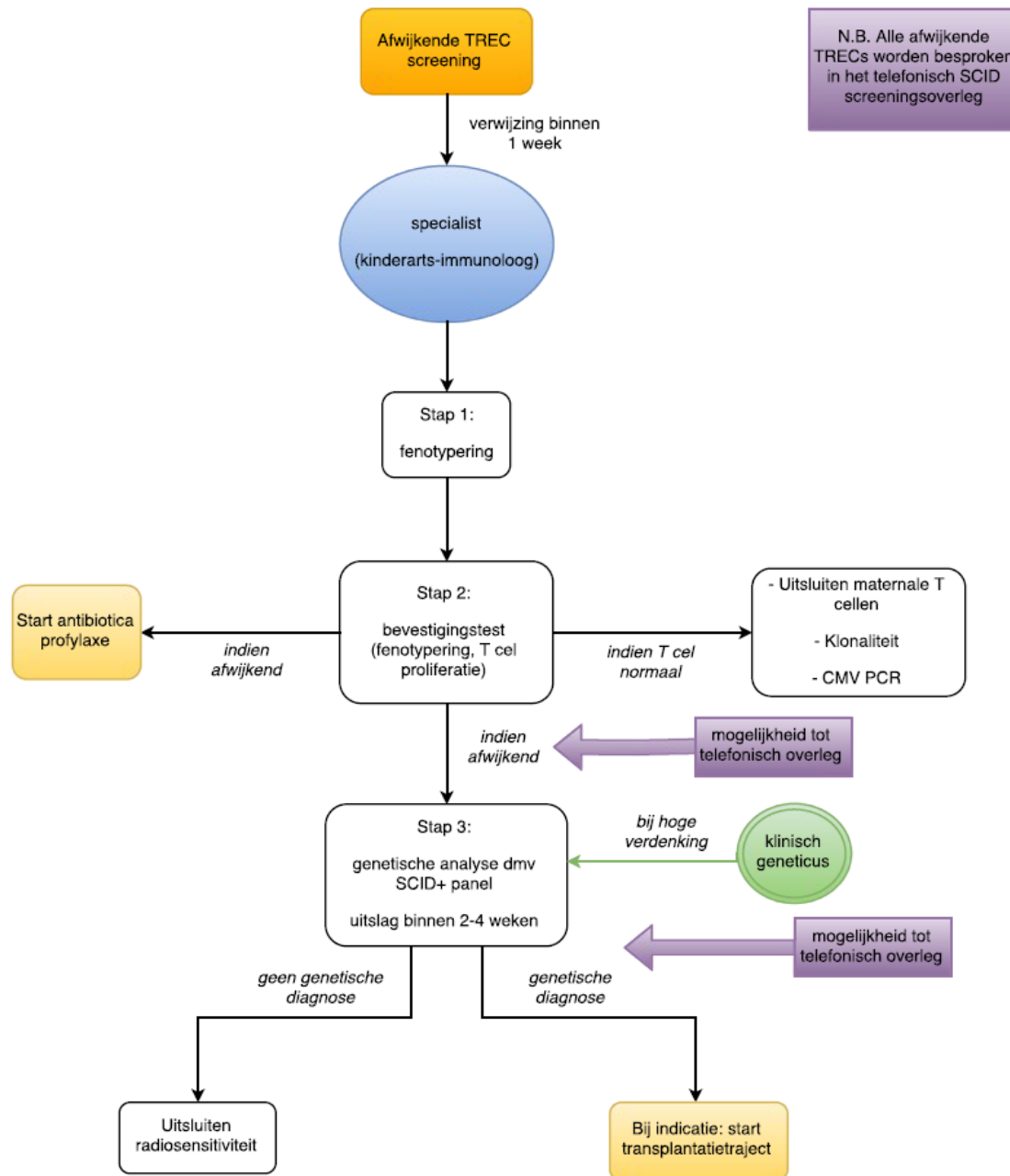


Severe Combined Immunodeficiency (SCID)

behandeling - gentherapie

- enige curatieve optie = allogene hematopoietische stamceltransplantatie
- nieuwe ontwikkelingen: gentherapie
 - voordelen
 - autologe setting (mildere conditionering) – *bij ontbreken van gematchte donor*
 - geen risico graft versus host ziekte





Why Does My Baby Need Another Newborn Screening Test?



The Newborn Screening Program was not able to test your baby's blood sample or get a valid result. Another specimen must be collected as soon as possible. This second blood test is called a "Newborn Screening repeat test."

California
Department of
Public Health

Newborn Screening Branch
Genetic Disease Screening Program
www.cdph.ca.gov/programs/nbs



Why Does My Baby Need A Newborn Screening Test?

Most babies are healthy when they are born. Some babies who look healthy at birth have certain diseases that can cause serious health problems without treatment. If we find this out early, we can prevent serious health problems like mental retardation, serious infections or death. Newborn screening can find many of these diseases.

Why Does My Baby Need A Repeat Test?

Before you left the hospital, a few drops of blood were taken from your baby's heel for testing. The blood sample was sent to a newborn screening lab. The lab was not able to get a valid result for all of the tests. Your baby needs to have a second specimen collected as soon as possible.

When Can I Get The Results?

Your baby's doctor will get the results about two weeks after the blood is drawn. If your baby needs more tests, you will get a letter or phone call. *If you move after the test is done, make sure your baby's health care provider or clinic has your new address and phone number.*

What Types Of Diseases Can Be Found By This Test?

Newborn screening tests for a variety of inherited diseases. This includes many different metabolic, endocrine, hemoglobin, and immune diseases, as well as cystic fibrosis. Early identification and treatment can help prevent the serious complications that these diseases can have.

Why Test for Immune Diseases?

The immune system protects the body from infections. Babies with this type of inherited disease can have little or no immune system. Early treatment can help prevent life-threatening infections in babies with this disease.

While newborn screening can identify some immune diseases, it does not test for HIV or AIDS.

To protect your baby's health, follow these important steps:

- Return to the doctor's office or hospital laboratory as instructed and have a second blood specimen collected from your baby as soon as possible.
- Continue to breastfeed or give infant formula that your doctor recommended while waiting for the results.

What If I Have Questions?

Call your doctor or the Newborn Screening Staff listed below if you have any questions or concerns about this repeat testing.



Why Does My Baby Need More Testing for Severe Combined Immunodeficiency (SCID)?



State law requires that all babies have newborn screening tests before leaving the hospital. A few drops of blood were taken from your baby's heel and tested for certain diseases. This testing is being expanded to include a rare disorder called SCID. Your baby had a positive or questionable result for the SCID test. Your baby now needs more testing as soon as possible.

California
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Why Does My Baby Need More Testing?

Your baby's screening test for SCID was positive or questionable. More testing is needed to find out if your baby has an immune problem related to SCID. Newborn Screening staff will work with you and your doctor to make sure the needed tests are done right away.

Babies can look healthy at birth and still have SCID or related disorders. If not recognized and treated, these diseases can cause severe health problems.

What Is SCID?

SCID stands for Severe Combined Immunodeficiency. It is sometimes called "bubble boy" disease. Babies with SCID are born with little or no immune system. This means that they cannot fight off infections. Babies with SCID do not usually have symptoms at first, since their mother's immune system protects them from infections for the first few weeks of life. Without treatment, even common infections can be life-threatening. For that reason, it's important that your baby have more testing as soon as possible. If your baby has SCID, a treatment plan can be started to help prevent the health problems it can cause.

What Other Immune System Problems Are Detected by Newborn Screening?

Other genetic disorders of the white blood cells called "T cells" may be found. These are not as severe as SCID, but are important to find out about and treat. Although these are immune diseases, they are not related to HIV or AIDS and are not infectious.

How Is SCID Treated?

Currently, the most effective treatment for SCID is a bone marrow transplant. It can cure babies of SCID and is most effective when done before a baby gets a severe infection. Other treatments can be used in some cases. Babies with less severe conditions may need to receive medication.

Is SCID Common?

Although not very common, about 8 - 12 babies are born with SCID each year in California.

How Will I Know My Baby's Results?

The Newborn Screening staff reports the results to your baby's doctor. The baby's doctor will let you know the results.

What Should I Do Right Now?

- Return to the doctor's office or hospital laboratory as instructed and have a blood specimen collected from your baby as soon as possible.
- Make sure your baby's doctor has talked to the Newborn Screening Staff before giving your baby any vaccines. The rotavirus vaccine or other *live* vaccines are not to be given to babies suspected of having SCID.

What If I Have Questions?

Call your doctor or the Newborn Screening Staff listed below if you have any questions or concerns about this testing.