Dag van de Huid
PSO & HS
(H)erken risico’s en grijp op tijd in

Dr. Ewout Baerveldt IJsseland Ziekenhuis & Sint Antonius Ziekenhuis

Ewout Baerveldt

Dermatoloog

- Domeingroep Inflammatoire Dermatose
- **Psoriasis** richtlijn voorzitter
- ZI Zinnige Zorg: **Psoriasis** en Eczeem
- ZI Uitkomstgerichte zorg Psoriasis
- PhD EMC **Psoriasis** 2013

Huidscreening bij hoog risico (beroeps)groepen

Derma inzichten en educatie voor 1e lijn

Disclosures

(Potentiële) belangenverstrengeling	
Research grants	Geen
Educational grant/fee	Novartis, BMS
Honorarium tbv adviesraad, presentaties, congres-verslag	Abbvie, Johnson&Johnson, Novartis, UCB Pharma, Takeda
Aandeelhouder	SkinTwin

Natalie Fletcher, Artist – Body painter, Psoriasis patient
https://www.novartis.com/stories/body-painter-captures-anguish-those-who-suffer-from-psoriasis

‘Leer er maar mee leven’ hebben velen te horen gekregen na de diagnose, want HS is nog niet te genezen. Het leven met HS bestaat uit ongemak, pijn, verdriet en (vaak dagelijkse) verzorging van ontstekingen of wonden. Bovendien kan HS ingrijpend zijn op verschillende levensgebieden, als sociaal leven, werk, relatie of mentaal welzijn.

https://hidradenitis.nl/leven-met-hs/

Red Bull
Mobil 1

Agenda vandaag

- **PSO & HS: Risico's?**
- **Cumulative Life Course Impairment Mini Workshop**
  - Definieer CLCI
  - Schets lange termijn impact
  - Hoe & Wanneer grijp je in?

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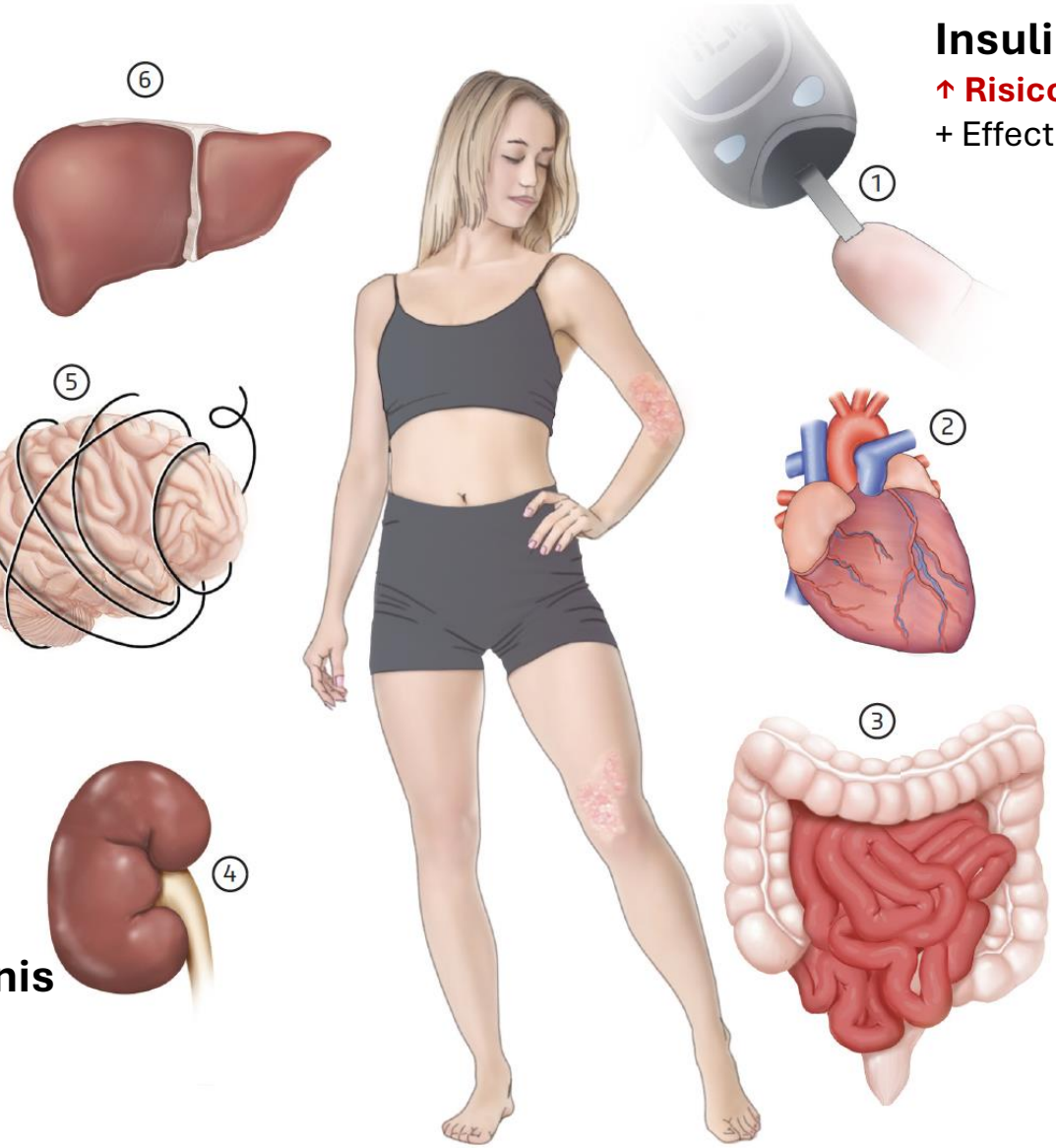
PSO & HS = Gedeelde Risico's



Insulinresistance
↑ Risico op DM2
+ Effect van GLP-1 agonisten op HS & PsO

Smoking
↑ Risico op HS & PSO + viceversa
↑ Ziekte ernst

Cardiovasculair risico
↑ Risico bij HS & PSO
↑ Hypertensie
↑ Risico stijgt met ziekteduur en onstekingsactiviteit

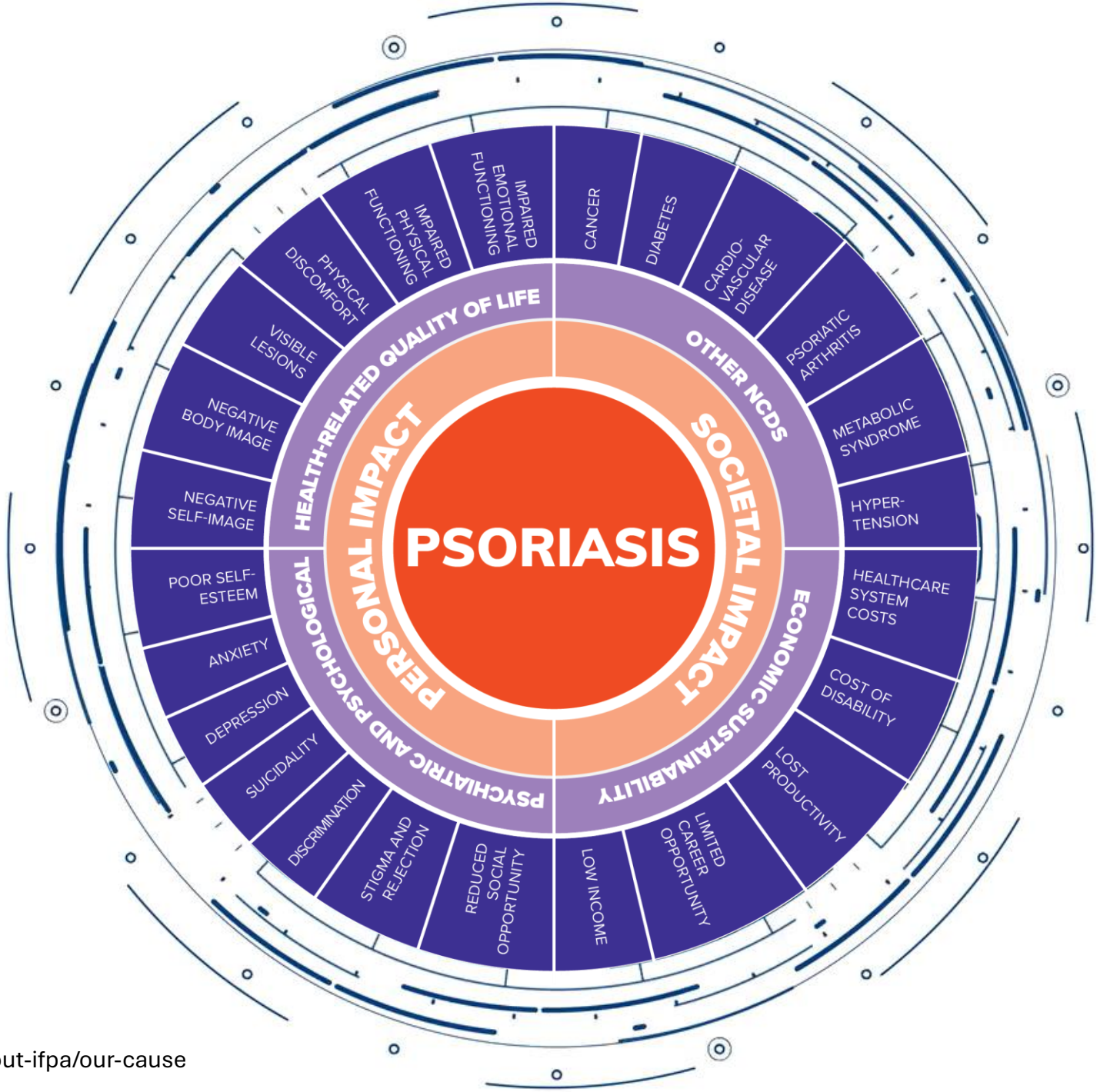
Gastrointestinaal
↑ Prevalentie IBD
Δ Microbioom

Nierfunctiestoornis
↑ Prevalentie

Genetics
TNF-α genvarianten
IL23R, IL12B
NOD2, CARD14, TNFAIP3, KRT, LCE
Trisomy 21

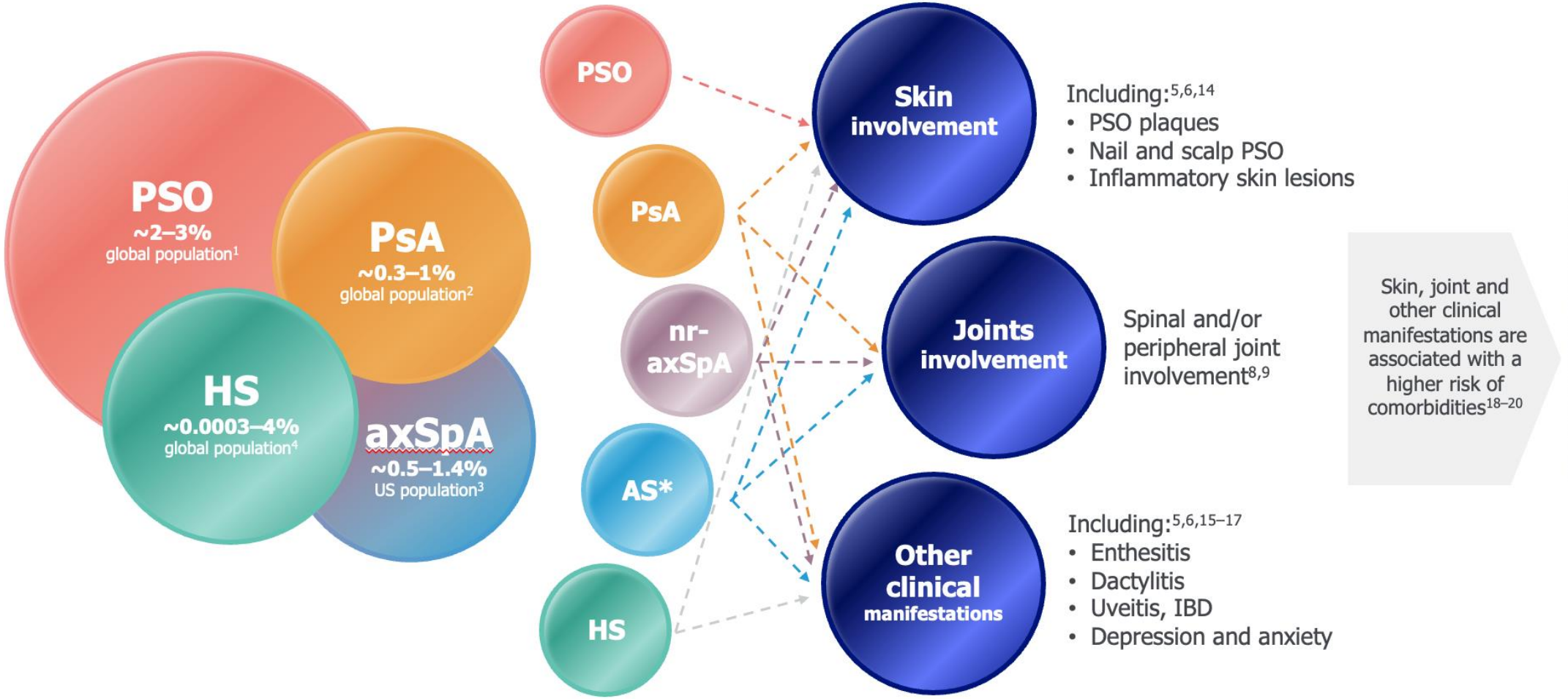
Psychiatric
↑ Risico suicide
Angst, depressie
Slaapstoornis
Kans op verslaving

Obesity
↑ Risico PSO & HS
Metabolic syndroom
NAFLD



Adapted from https://ifpa-pso.com/about-ifpa/our-cause

PSO & HS = Gedeelde ziekte manifestaties

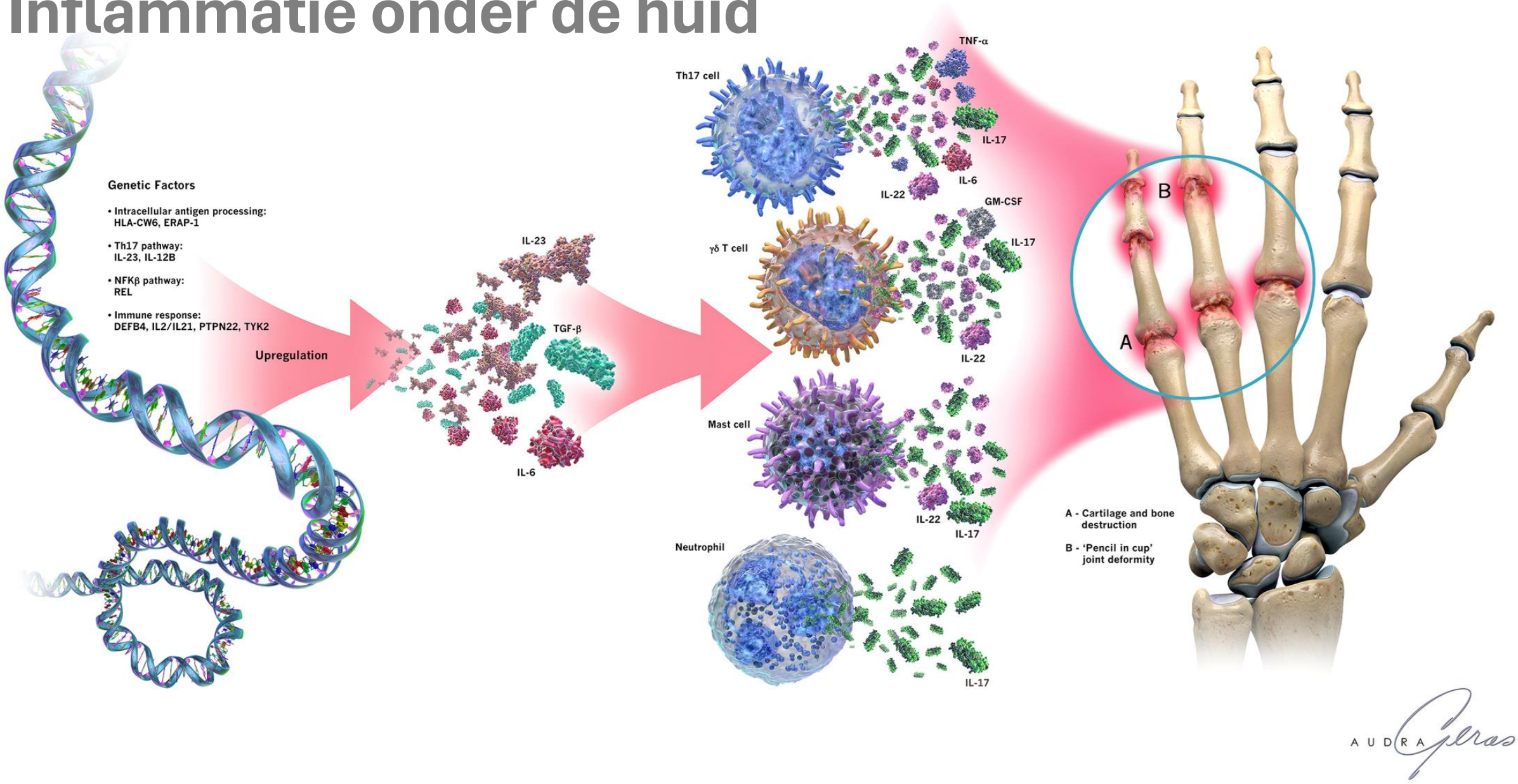


*Also known as r-axSpA. AS, ankylosing spondylitis; axSpA, axial spondyloarthritis; HS, hidradenitis suppurativa; IBD, inflammatory bowel disorder; nr-axSpA, non-radiographic axial spondyloarthritis; PsA, psoriatic arthritis; PSO, psoriasis; r-axSpA, radiographic axial spondyloarthritis.

1. National Psoriasis Foundation. Statistics. Available at: https://www.psoriasis.org/content/statistics. Last accessed: July 2024. 2. Gladman DD, et al. Ann Rheum Dis. 2005;64(suppl 2):ii14–7. 3. Reveille JD, et al. Am J Med Sci. 2013;345:431–6. 4. Alotaibi HM. Clin Cosmet Investig Dermatol. 2023;16:545–52. . 5. Dopytalska K, et al. Reumatologia. 2018;56:392–8. 6. Pittam B, et al. Rheumatology (Oxford). 2020;59:2199–206. 7. van Straalen KR, et al. Br J Dermatol. 2020;183:763–5. 8. McInnes IB, et al. Lancet. 2023;401:25–37. 9. van der Heijde D, et al. Ann Rheum Dis. 2023:ard-2022-223595. 10. Maroof A, et al. 2022. SHSA. Poster 3776. 11. Braun J and Coates LC. RMD Open. 2023;9:e003063. 12. Rondags A, et al. Semin Arthritis Rheum. 2019;48(4):611–7. 13. Patel M, et al. J Am Acad Dermatol. 2015;73(4):701–2. 14. Kimball AB, et al. 2023. AAD. Late-breaking presentation. 15. Fioravanti A, et al. Indian J Dermatol Venereol Leprol. 2011;77:74–6. 16. Lee DJ, et al. Ocul Immunol Inflamm. 2021;29(7-8):1318–23. 17. Caccavale S, et al. Life (Basal). 2023;13:189. 18. Tzellos T and Zouboulis CC. Dermatol Ther (Heidelb). 2020;10:63–71. 19. Gupta S, et al. Rheumatol Int. 2021;41:27–84. 20. Zhao SS, et al. Rheumatology (Oxford). 2020;59:iv47–57.

PSO & HS

Inflammatie onder de huid



AUDRA Geras

Als behandelaar voel ik me vertrouwd met het signaleren van PSA

A. Ja, ik voel me bekwaam in het screenen van diagnose PSA
B. Ja, ik voel me bekwaam in stellen diagnose, maar overleg met reumatoloog in kader van dubbel-check en behandeling
C. Nee, ik voel me niet bekwaam maar gebruik daarom vragenlijsten
D. Nee, ik vrees dat ik dit mis

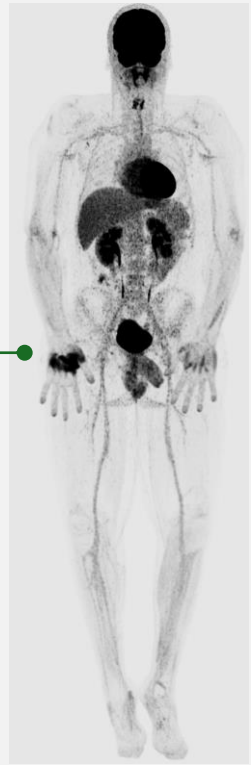
PSO & HS

Inflammatie onder de huid

Total Body PET/CT with ^{18}F-FDG radiotracer provides evidence of inflammation and identifies the extent and the nature of joint, spine, entheses and nail involvement in PsA:

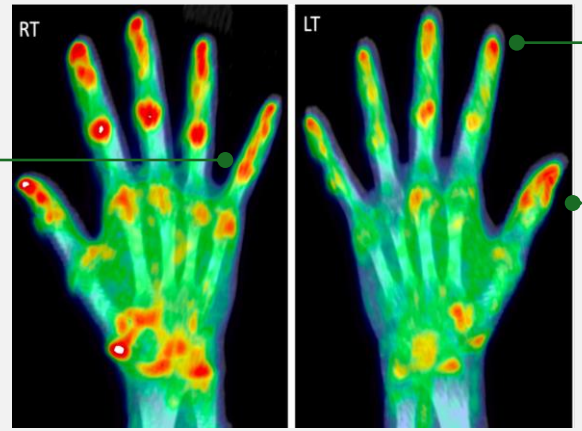
Asymmetric polyarthritis

Predominant involvement of **wrists** and **small joints of hands**



Asymmetric involvement of small joints of the hands, including the wrists

Inflammation of the extensor tendon on the right little finger

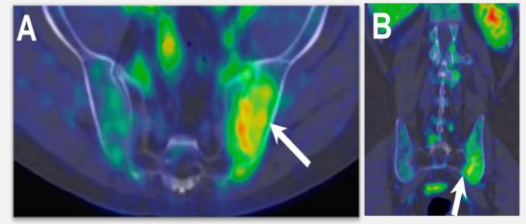


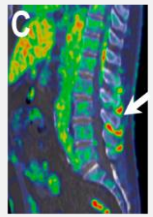
Nail matrix inflammation

Dactylitis of the left thumb evidenced by **swelling and inflammation** of the soft tissue compared to the right thumb

Axial involvement in PsA

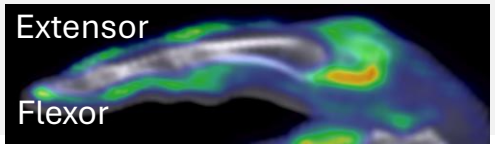
Sacroiliitis

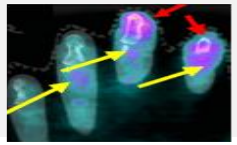




Involvement of inter-/supra-spinous ligament and **facet joints**

Nail matrix involvement, enthesitis and **inflammation** of the flexor/extensor tendons of fingers





Nail matrix/bed

Enthesitis

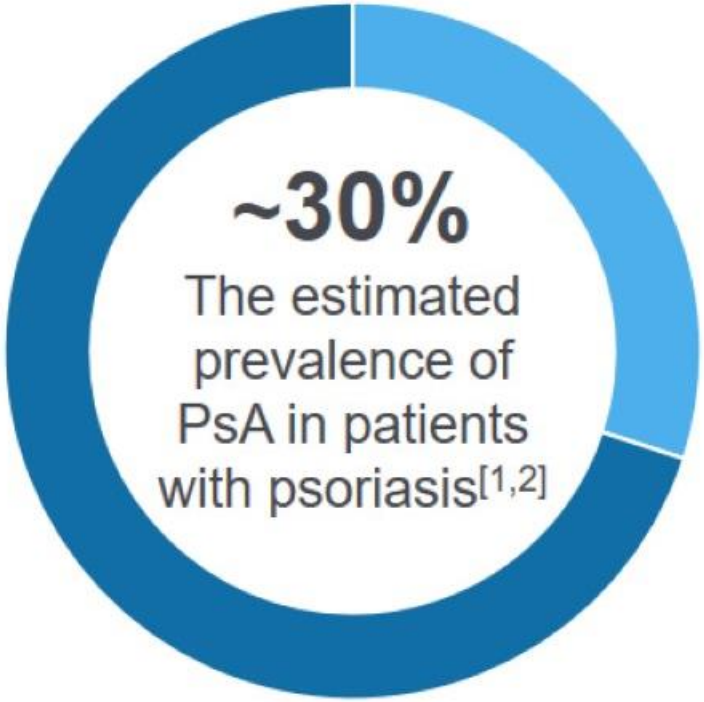
Images and descriptions provided with permission from Dr Siba Raychaudhuri and Dr Abhijit J. Chaudhari. University of California Davis

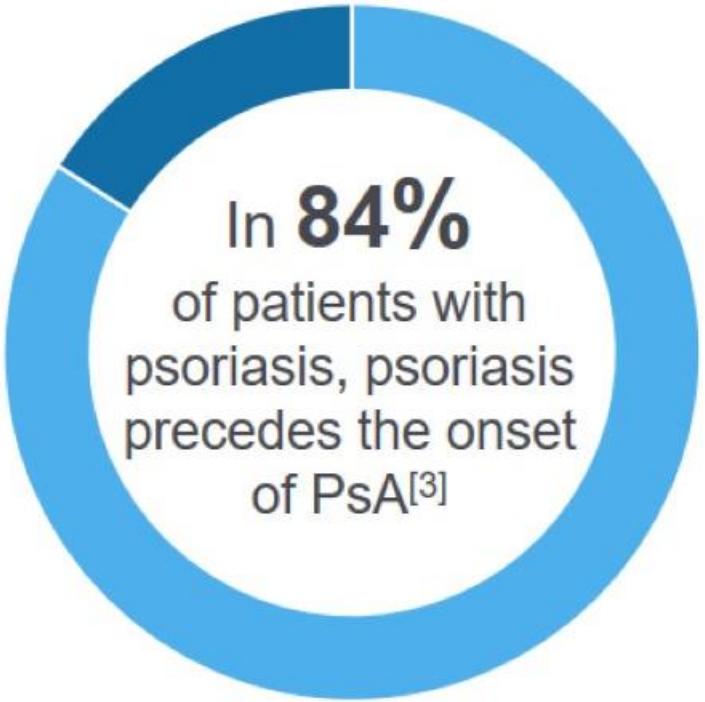
PET/CT is not a commonly used tool in practice. 18F-FDG: 2-deoxy-2-[fluorine-18]fluoro-D-glucose; DIP: distal interphalangeal; MCP: metacarpophalangeal joint; PET/CT: positron emission tomography/computed tomography; PIP: proximal interphalangeal.

Raychaudhuri S, et al. Arthritis Rheumatol. 2021;73(Suppl 10). Abstract 0452.

Inflammatoire Artritis

Rol voor dermatoloog (en 1e lijn) in screening



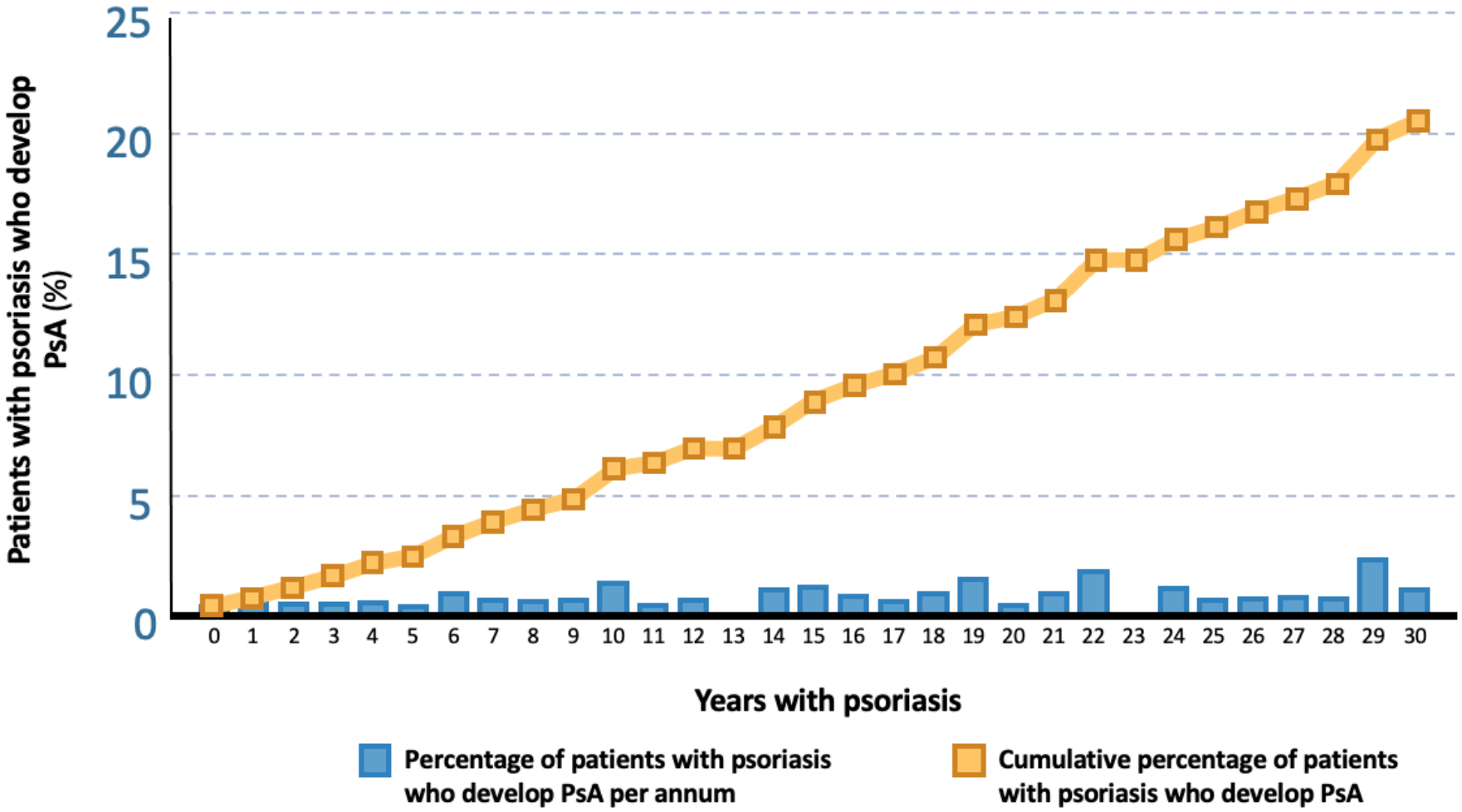


Door vroege alertheid en opsporing van PsA in PsO patienten, kunnen dermatologen de ziekteprogressie tegen gaan en de QoL positief beinvloeden.

1. Ritchlin CT, et al. N Engl J Med. 2017;376:957-970; 2. Coates LC, et al. Psoriatic arthritis. In: Watts RA, et al, eds. Oxford Textbook of Rheumatology. 4th ed. Oxford; 2013:890-900; 3. Villani AP, et al. J Am Acad Dermatol. 2015;73:242-248; 4. Gottlieb A, et al. J Dermatol Treat. 2020;31:663-679; 5. Acosta Felquer ML, et al. Ann Rheum Dis. 2022;81:74-79.

Risico PSA

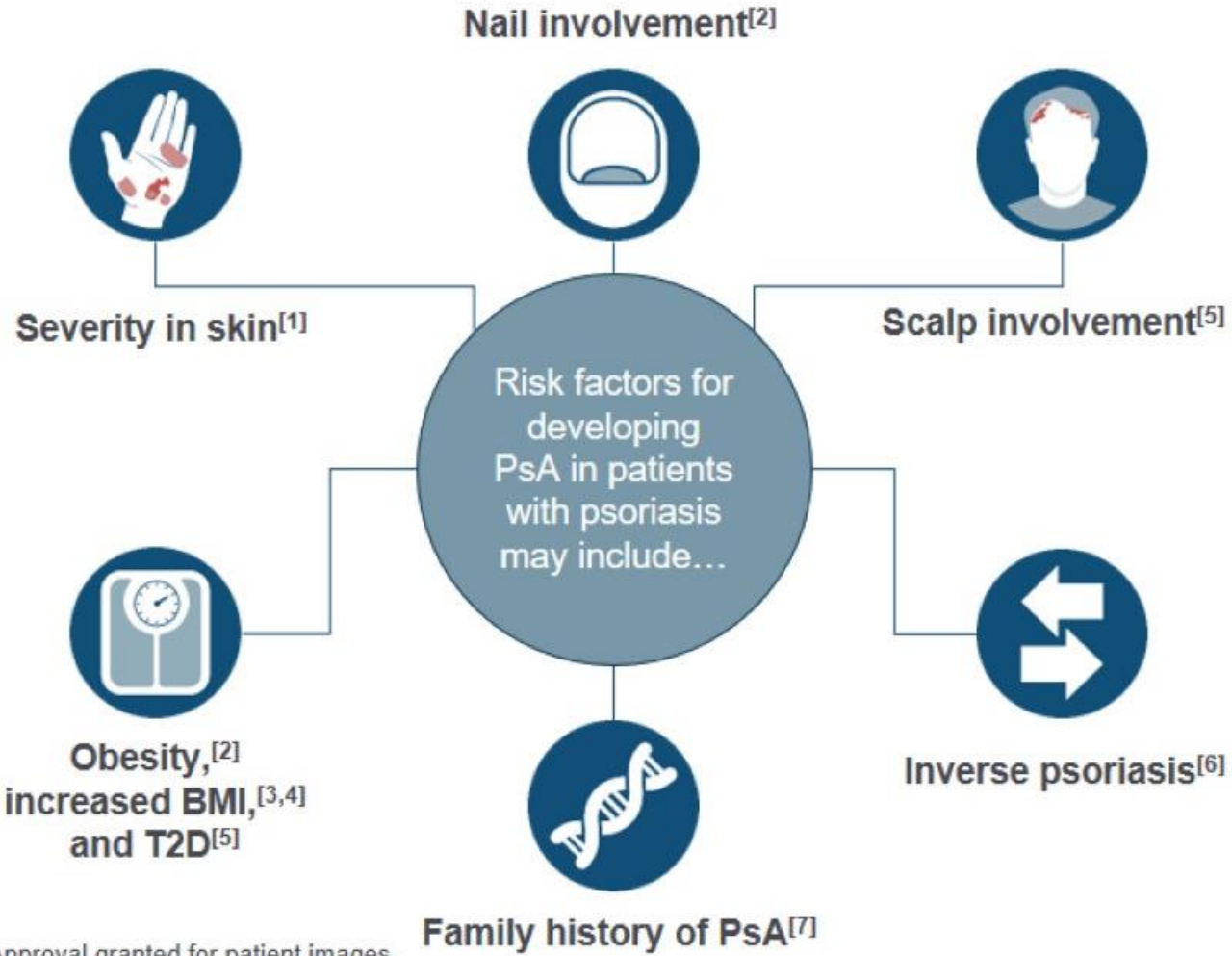
Jaarlijks 3% = constant na diagnose PsO

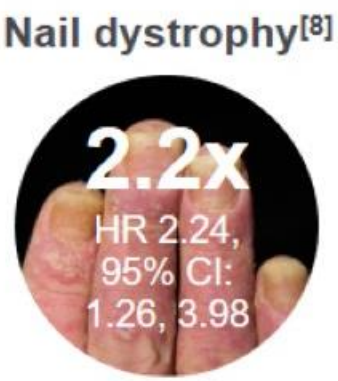


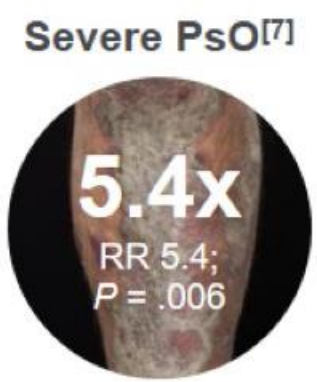
Merola J.F. et al, JAAD 2022 ; Christophers E, et al. J Eur Acad Dermatol Venereol. 2009;24(5):548-54.

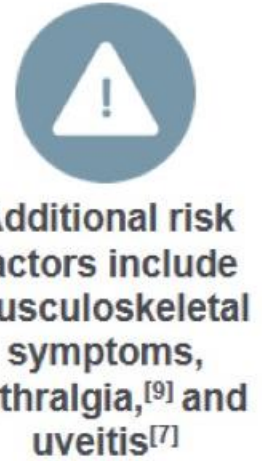
Risico PSA

Risicofactoren









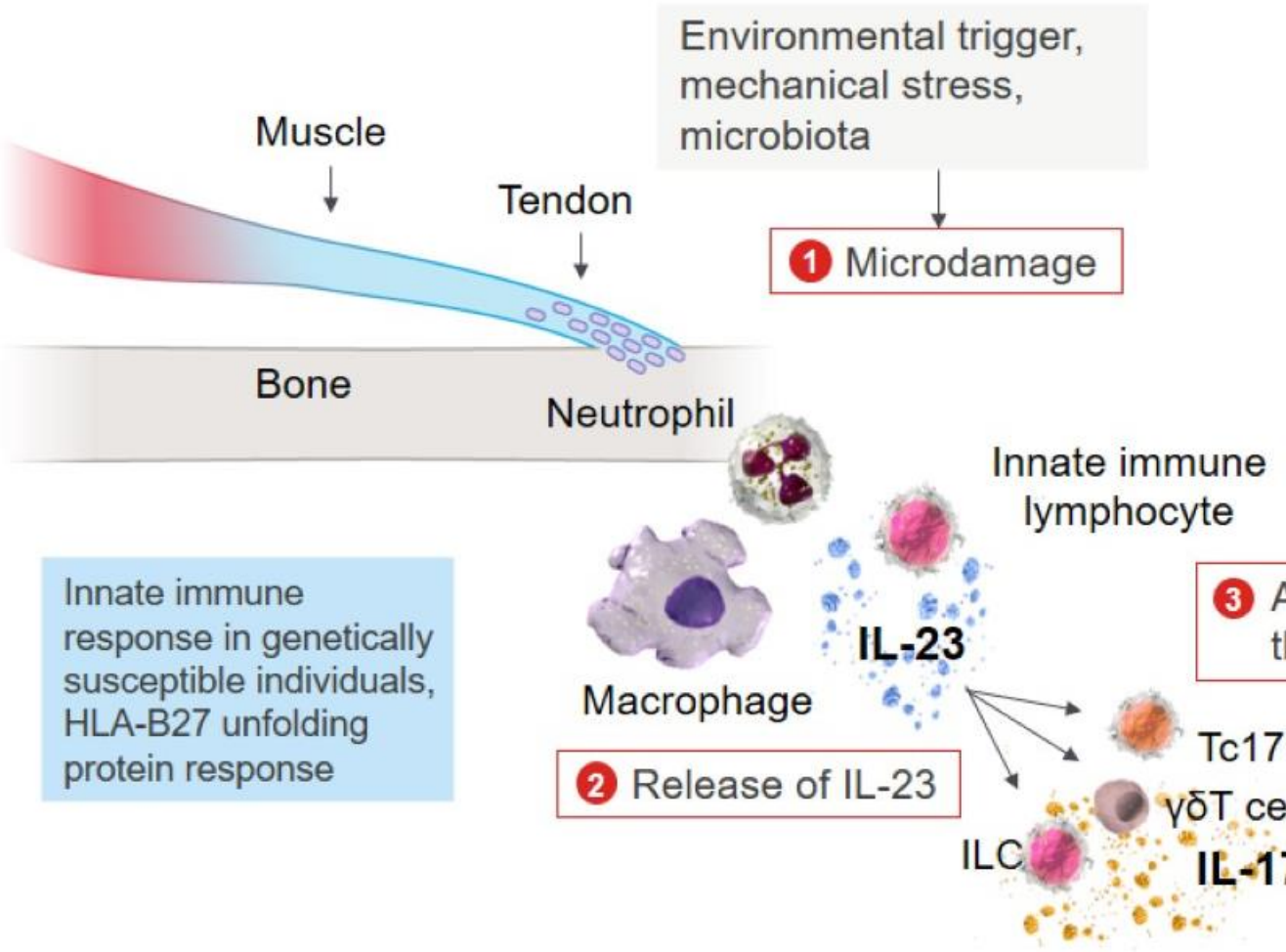
Approval granted for patient images.

BMI, body mass index; HR, hazard ratio; T2D, type 2 diabetes; RR, risk ratio.

1. Merola JF, et al. J Am Acad Dermatol. 2022;86:748-757; 2. Ogdie A, et al. Curr Rheumatol Rep. 2015;17:64; 3. Li W, et al. Ann Rheum Dis. 2012;71:1267-1272; 4. Green A, et al. Br J Dermatol. 2020;182:714-720; 5. Yan D, et al. Dermatol Ther (Heidelb). 2018;8:593-604; 6. Gottlieb AB, et al. J Dermatolog Treat. 2022;33:1907-1915; 7. Eder L, et al. Arthritis Rheumatol. 2016;68:915-923; 8. Wilson FC, et al. Arthritis Rheum. 2009;61:233-239; 9. Zabotti A, et al. Rheumatol Ther. 2021;8:1519-1534.

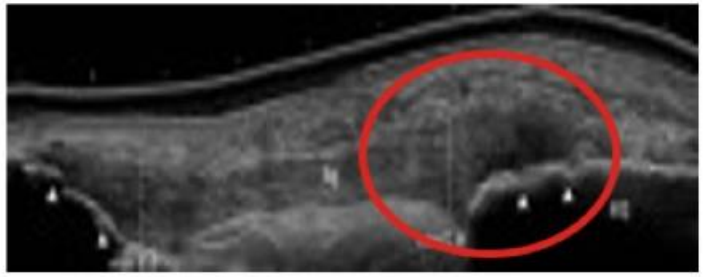
Transitie PSO naar PSA

Enthesitis: vroege fase PSA



Microscopic damage from high levels of mechanical stress occurs at the enthesis
Microdamage may be a trigger for IL-23-dependent entheseal inflammation involving innate and adaptive immune cells
Absence of normal immune regulation leads to chronic inflammation
Akin to a deep Koebner response in genetically predisposed patients

Innate immune response in genetically susceptible individuals, HLA-B27 unfolding protein response



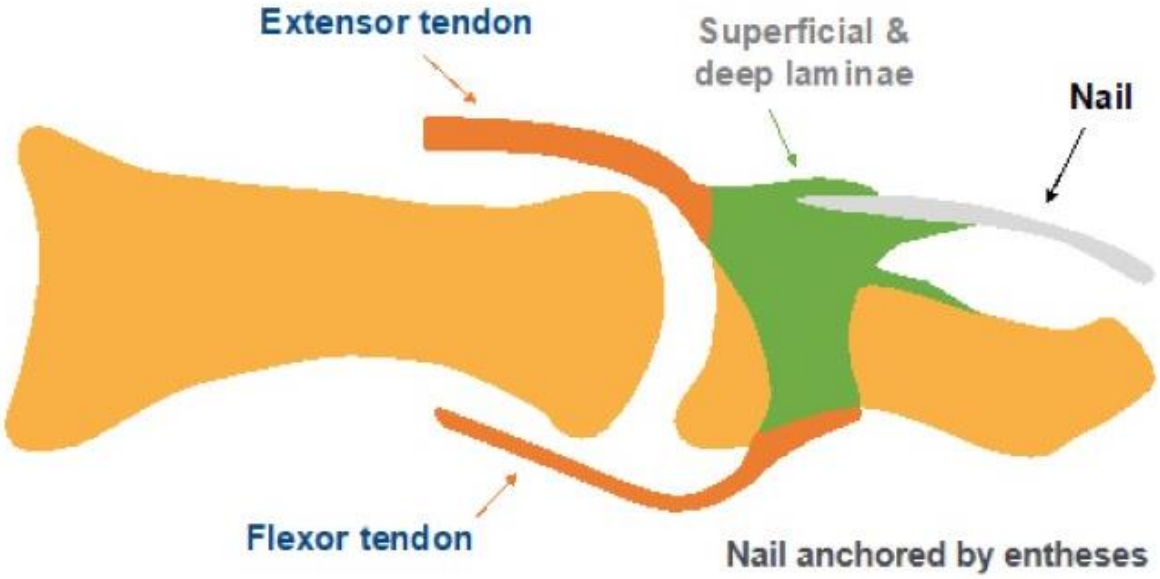
HLA, human leukocyte antigen; ILC, innate lymphoid cell; Tc, T cytotoxic.

1. De Vlam K, et al. Acta Derm Venereol. 2014;94:627-634; 2. Mease P, et al. EMJ Rheumatol. 2015;2:55-64; 3. Kehl AS, et al. Arthritis Rheumatol. 2016;68:312-322; 4. McGonagle D, et al. Ann Rheum Dis. 2011;70(Suppl 1):i71-i76; 5. Sherlock JP, et al. Nat Med. 2012;18:1069-1076; 6. Raychaudhuri SP, et al. Arthritis Res Ther. 2017;19:51.

PSA

Nagel = uniek screeningstool

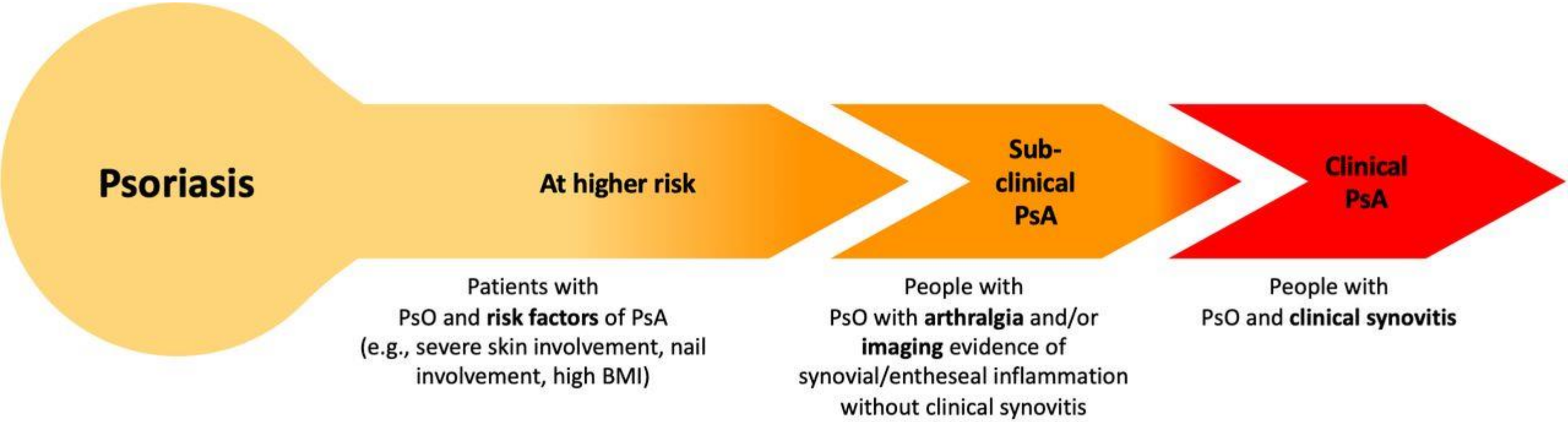
- Nagelpsoriasis = bio-link tussen Pso en PsA
- Enthesitis Dip gewricht = hoge incidentie in vroege PSA
- Nagelpsoriasis kan 1e klinische manifestatie van PsA zijn
- Huid PsO >> bij patienten met nagelpsoriasis



1. McGonagle D, et al. Dermatology. 2009;218:97-102; 2. Langenbruch A, et al. Br J Dermatol. 2014;171:1123-1128; 3. Radtke MA, et al. J Dtsch Dermatol Ges. 2013;11:203-219; 4. Scarpa R, et al. J Rheumatol. 2006;33:1315-1319; 5. Hallaji Z, et al. J Am Acad Dermatol. 2012;66:e12-e13.

EULAR

Clinical and imaging features suspicious for progression from PSO to PSA



https://ard.bmj.com/content/82/9/1162

Artritis psoriatica

Richtlijn psoriasis screening module

- **PSA Screenings-Vragen**
  - Spontane aanhoudende pijnlijke zwelling gewrichten
  - of stijfheid van een of meerdere gewrichten en nabijgelegen ligamenten en pezen
  - of chronische rugklachten die ten minste drie maanden dagelijks aanwezig zijn
  - èn ontstaan zijn voor het 45ste levensjaar.
- Het gebruik van een screenende vragenlijst voor PSA kan praktisch houvast bieden.
- Verwijs patiënten met een verdenking op PSA naar de reumatoloog.
- Zie voor de onderbouwing van het bovenstaande & verdere aanbevelingen
- Artritis psoriatica – Richtlijn Psoriasis – Richtlijnendatabase.

NVDV
Nederlandse Vereniging voor Dermatologie en Venereologie

Federatie Medisch Specialisten

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54%

of the employed patients surveyed feel their condition has affected their professional life.

84%

of the total sample report having experienced discrimination or humiliation because of their psoriasis.

43%

of patients surveyed say that psoriasis has affected their relationships.

1. Novartis. Clear about Psoriasis survey. Available at novartis.gcs-web.com/static-files/30bdd3da-1971-4dcb-aae9-339096dcc583. Accessed July 2022;
2. McCormick HL. *Am J Manag Care* 2016;22:S104–7.

PSO

Impact op Wellbeing

Stigma[1]

84% of patients with psoriasis suffer discrimination or humiliation

34% have been stared at in a swimming pool

16% of people with psoriasis have been refused service at a beautician, hairdresser, or barber's shop

Psychological[2]

>50% of people with psoriasis report that the disease interferes with their enjoyment of life

Up to **30%** of patients suffer from anxiety/depression

88% of family members report the same level of depression and anxiety as those with psoriasis

Social[1]

16% of patients with psoriasis hide themselves away from the world

43% feel psoriasis has affected their relationships

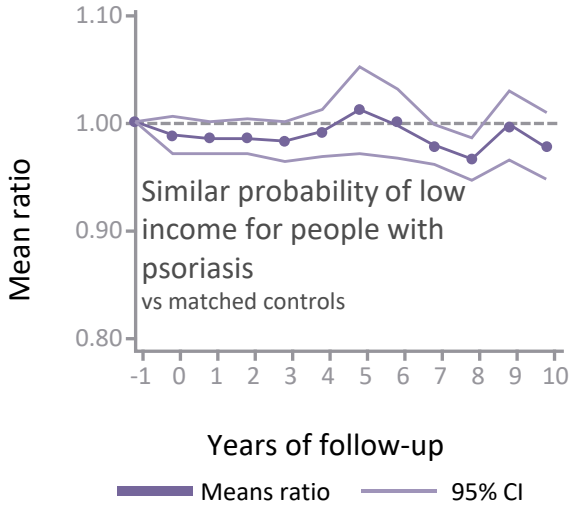
Of those,
50% avoid having sex or intimate relationships

1. Novartis. Clear about Psoriasis survey. Available at novartis.gcs-web.com/static-files/30bdd3da-1971-4dcb-aae9-339096dcc583. Accessed July 2022;
2. McCormick HL. *Am J Manag Care* 2016;22:S104–7.

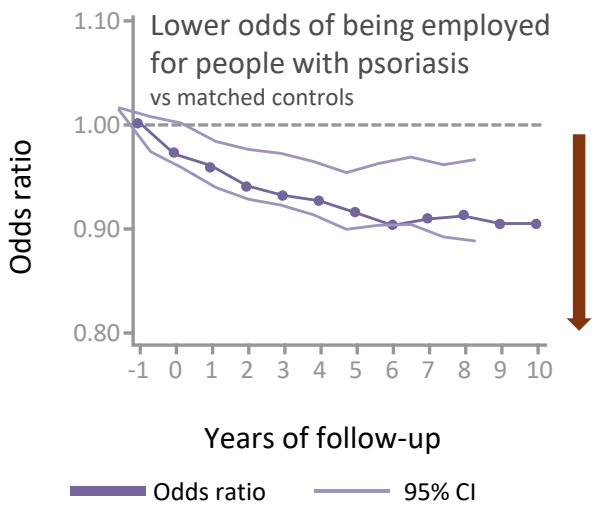
PSO

Impact op arbeid & relatie

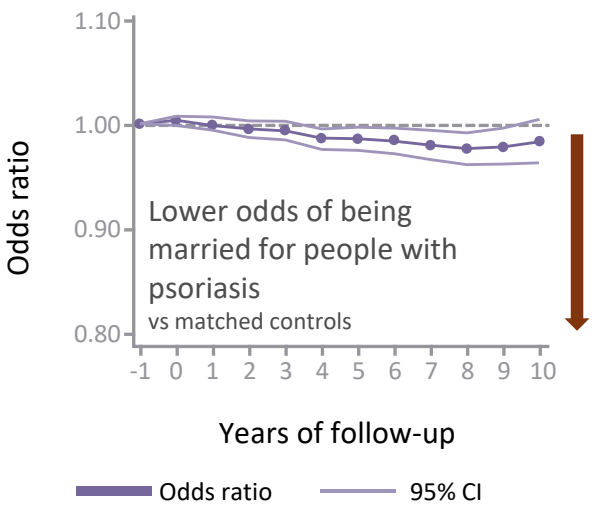
Individual income



Employment status



Marital status



10% fewer patients with psoriasis were employed 6 years after first diagnosis, versus matched controls[1]

Study of 109,803 patients with psoriasis versus 1.08 million matched controls in the Swedish national registry from 2002 to 2013.
CI, confidence interval. 1. Häbel, et al. *J Am Acad Dermatol* 2021;3:63–75.

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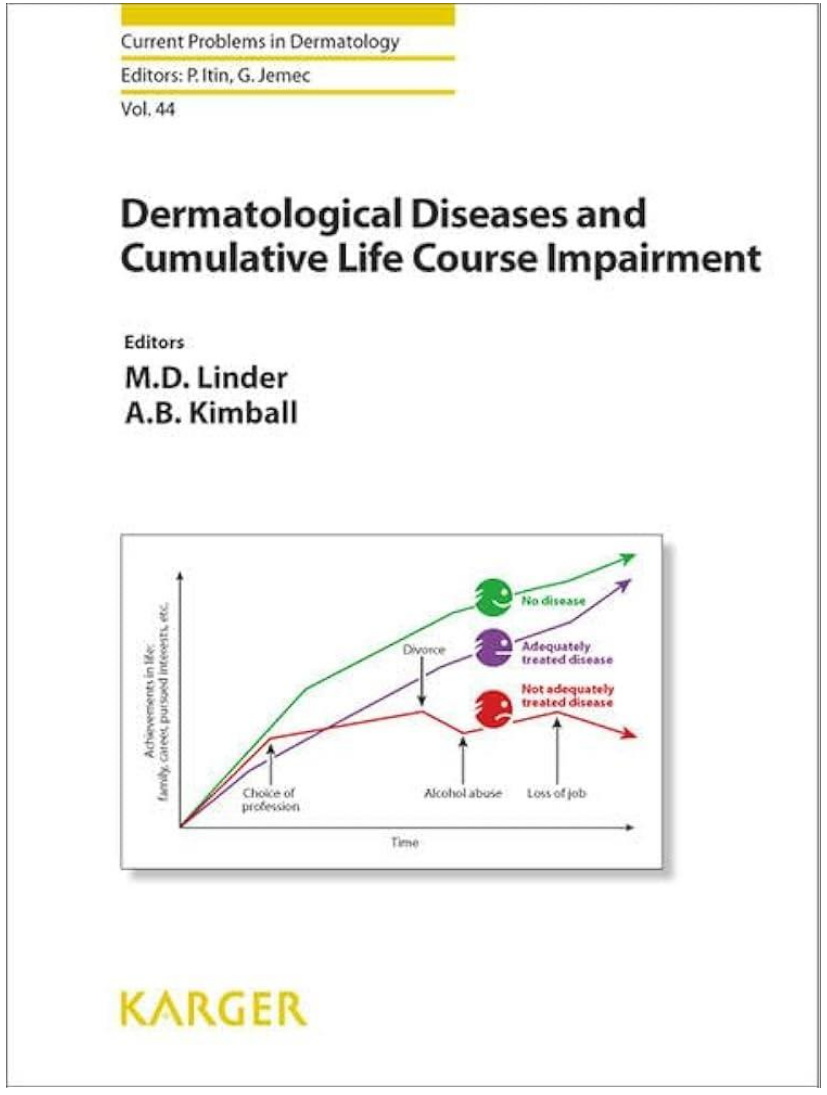
PSO & HS

Concept CLCI



Cumulative Life Course Impairment (CLCI)
CLCI is een concept dat de lange termijn impact van chronische aandoeningen op de kwaliteit van leven, carrière en sociale interacties van patiënten beschrijft.
Het is een maat voor de cumulatieve ziektelast in de loop van de tijd.

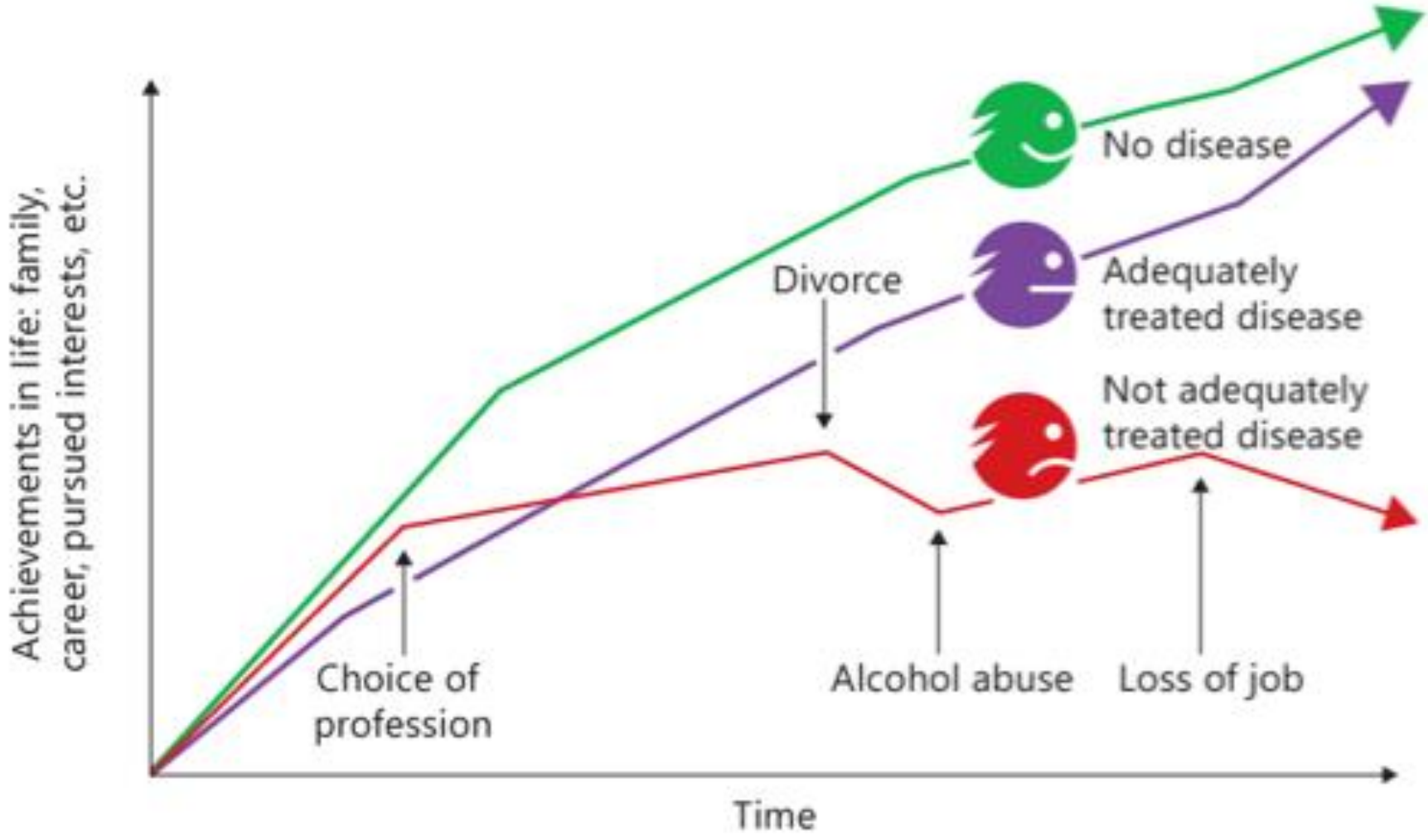
Components of CLCI
De componenten van CLCI omvatten:

- Lichamelijke symptomen
- Psychische problemen
- Sociaal isolement
- Werkgerelateerde beperkingen.

Elk onderdeel heeft een unieke impact op het welzijn van patiënten op de lange termijn.

PSO & HS

Concept CLCI



PSO

CLCI = Belangrijkste pilaren

PHYSICAL COMORBIDITIES

- PsA
- CV disease
- Metabolic syndrome (obesity, diabetes, hypertension, ischaemic heart disease)
- Crohn's disease
- High risk of other immune-related conditions
  - **HS**
  - Obstructive Pulmonary disease
  - Gastric Reflux

STIGMA

- Perception
- Overt public reaction
- Rejection behaviours
- Self-image
- Confidence

PSYCHOLOGICAL COMORBIDITIES

- Anxiety
- Social phobias
- Depression
- Suicide ideation
- Alexithymia
- Addiction/ substance abuse

SOCIAL SUPPORT

- Family
- Friends
- Colleagues
- Patient support groups
- Healthcare professionals

COPING

- Maladaptive coping (avoidance)
- Limited activity
- Disengagement
- Denial
- Helplessness
- Sense of coherence
- Adherence to therapy

Adapted from Kimball AB, et al. J Eur Acad Dermatol Venereol 2010;24:989–1004.

1. Wu Y, et al. J Drugs Dermatol. 2008;7(4):373-7. 2. Mrowietz U, et al. Arch Dermatol Res. 2006;298(7):309-19. 3. Gottlieb AB, et al. J Dermatolog Treat. 2008;19(1):5-21.
4. Ludwig RJ, et al. Br J Dermatol. 2007;156(2):271-6. 5. Gisondi P, et al. J Hepatol. 2009;51(4):758-64.
6. Gisondi P, et al. Dermatology. 2009;218(2):110-3. 7. Kourosh AS, et al. Skin Therapy Lett. 2008;13(1):1-5. 8. Boehncke W-H, et al. BMJ. 2010;340:200-3.
9. McGonagle D. J Eur Acad Dermatol Venereol. 2009 Sep;23 Suppl 1:9-13. 10. Brockbank J, et al. Ann Rheum Dis. 2005;64:188-90.

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- **Cumulative Life Course Impairment Mini Workshop**
  - Definieer CLCI
  - Schets lange termijn impact
  - Hoe & Wanneer grijp je in?

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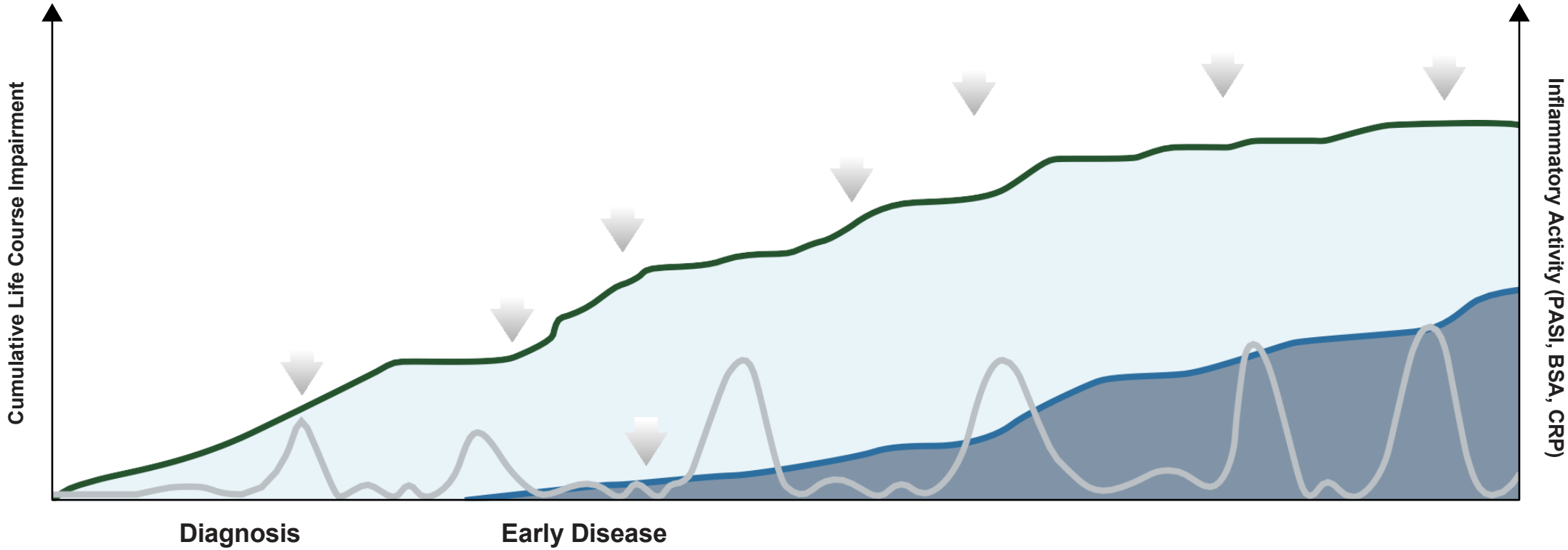
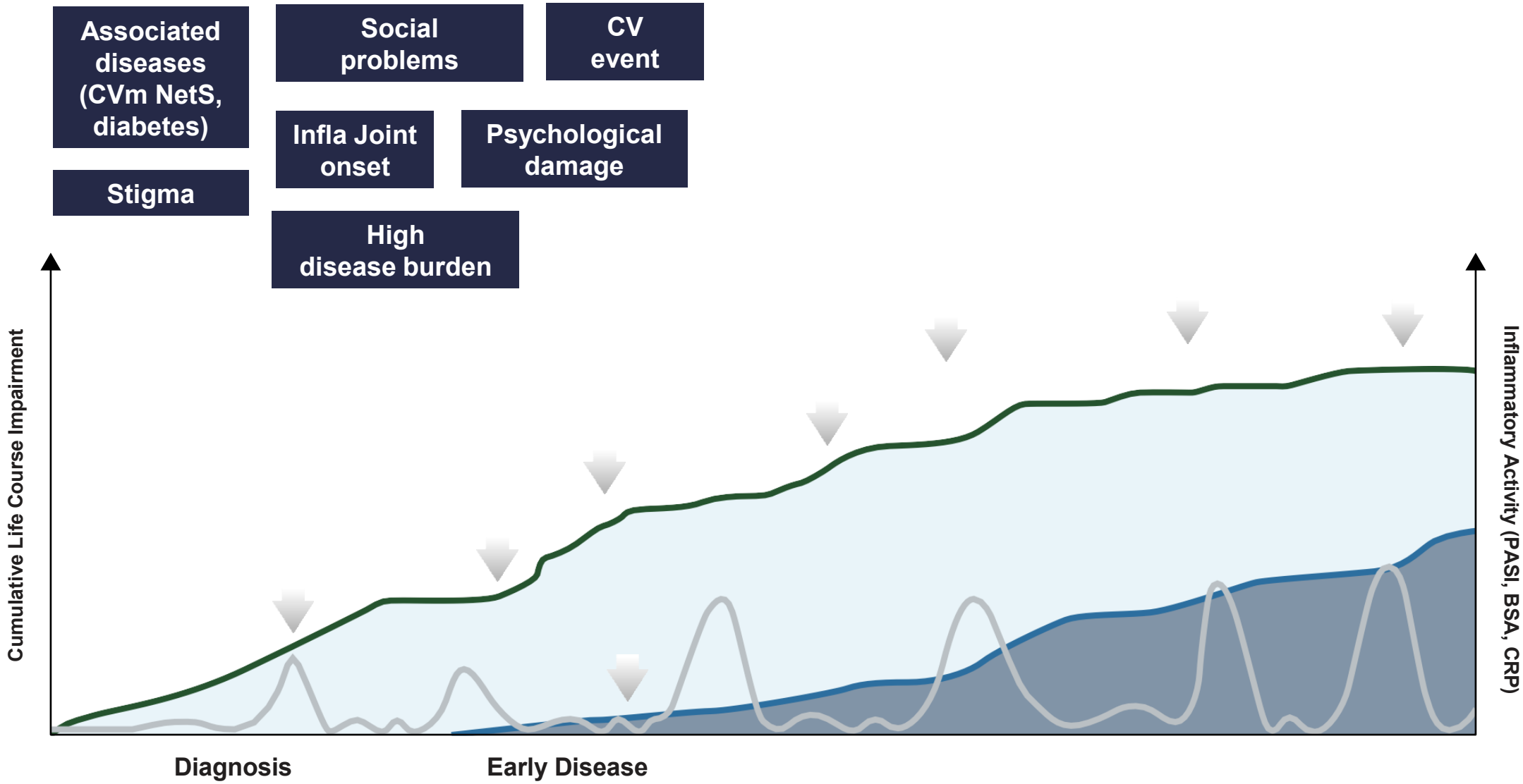


Illustrative model created based on the progression model in Crohn disease.[1]
CLCI, Cumulative Life Course Impairment; CRP, C-reactive protein; CV, cardiovascular; MetS, metabolic syndrome.
1.Sandborn WJ, et al J Crohns Colitis 2014;8:927-935; 2. Linder MD, et al. Acta Derm Venerol. 2016;96:102-108.



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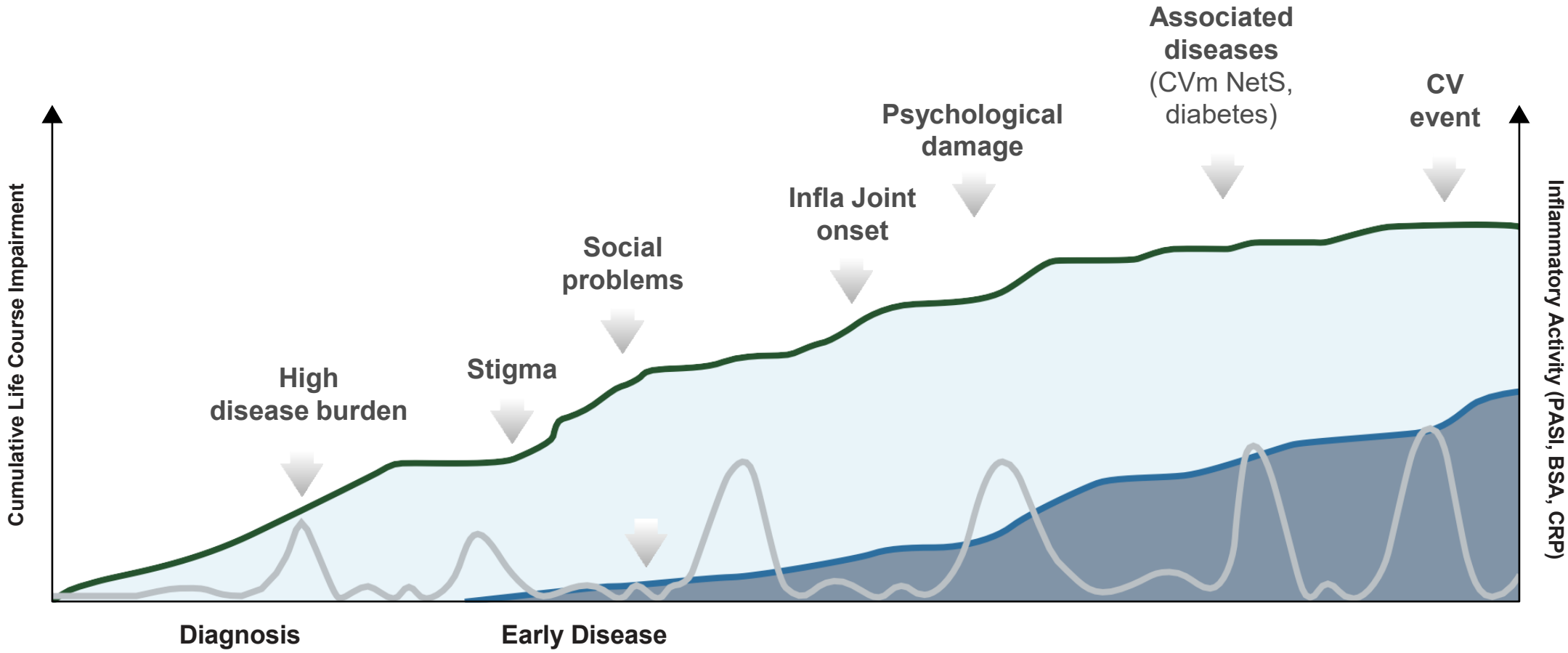
1.Sandborn WJ, et al J Crohns Colitis 2014;8:927-935; 2. Linder MD, et al. Acta Derm Venerol. 2016;96:102-108.

CLCI

Ziektelast accumuleert en leidt tot erger



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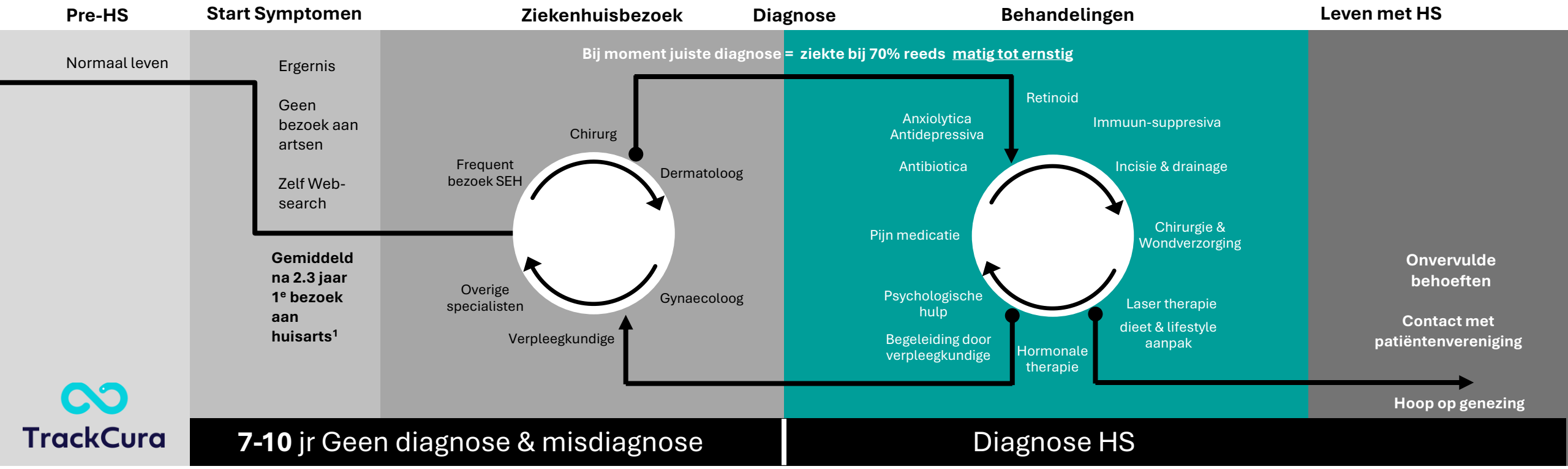
CLCI HS

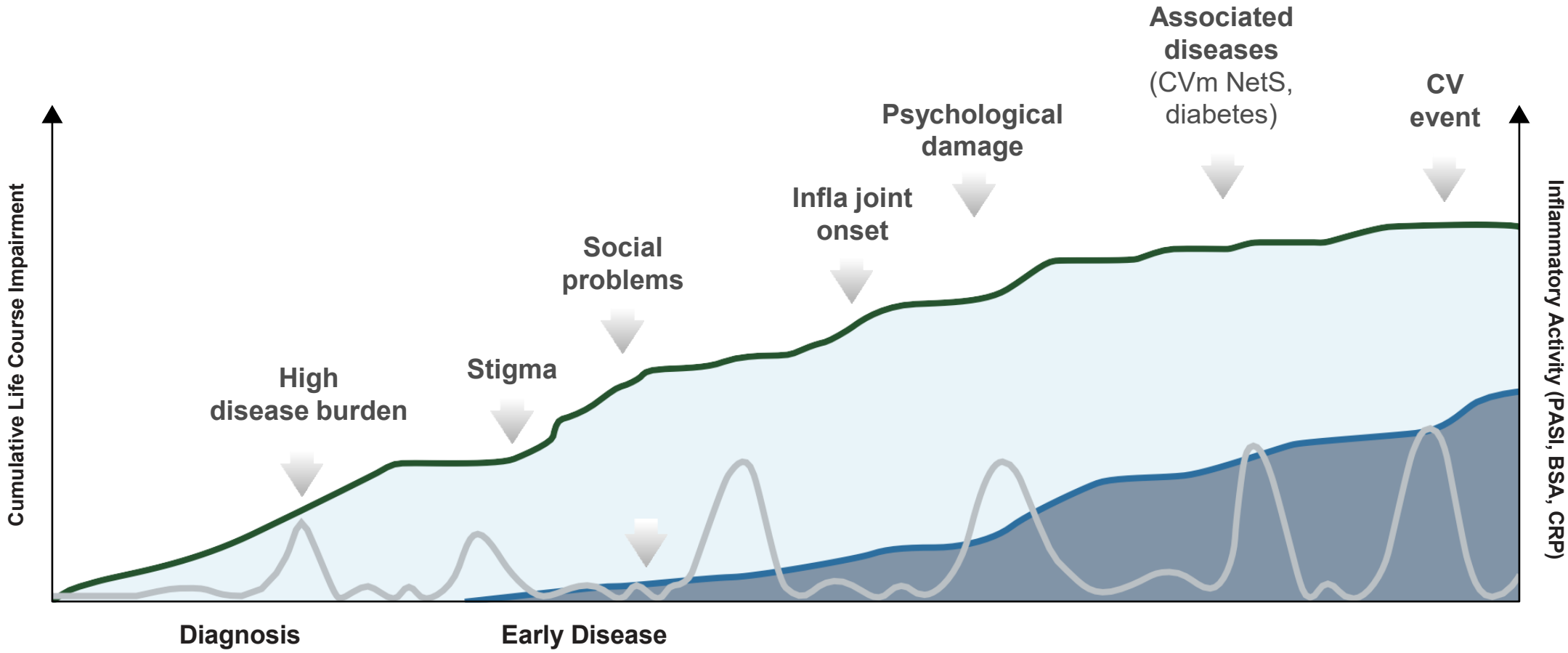
Ziektelast accumuleert bij onjuiste en niet tijdige diagnose èn leidt tot erger



TrackCura

CLCI

Wanneer ingrijpen?



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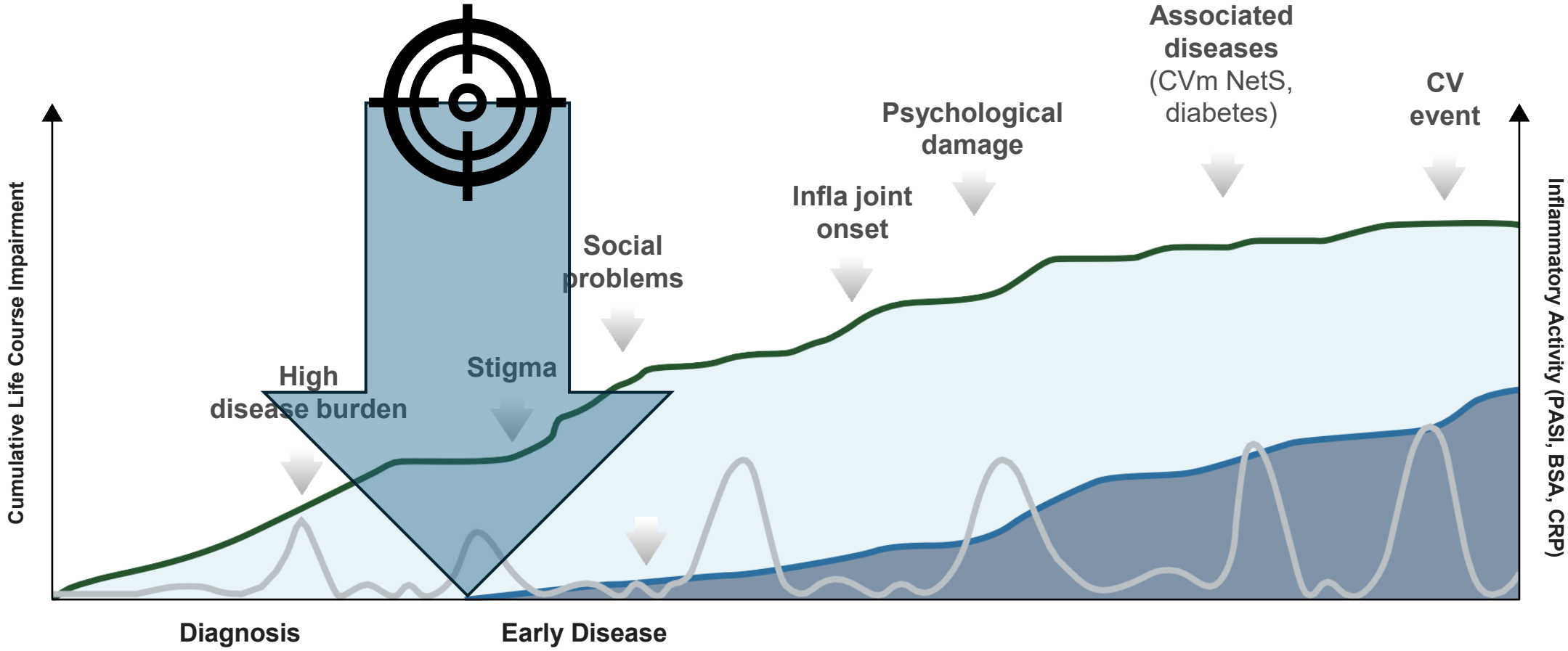
CLCI

Wanneer ingrijpen?



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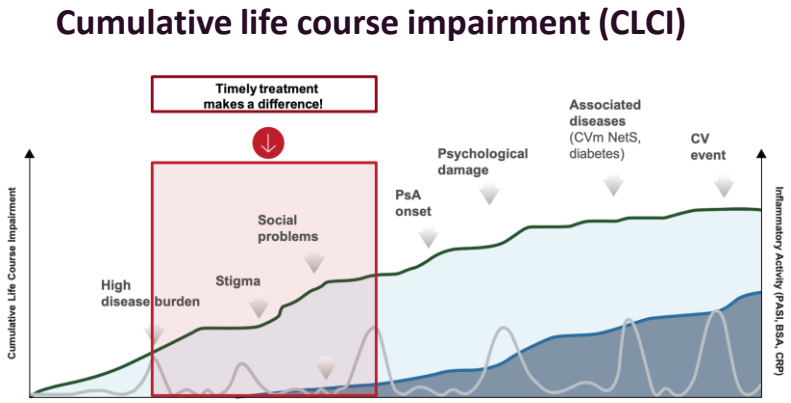
CLCI

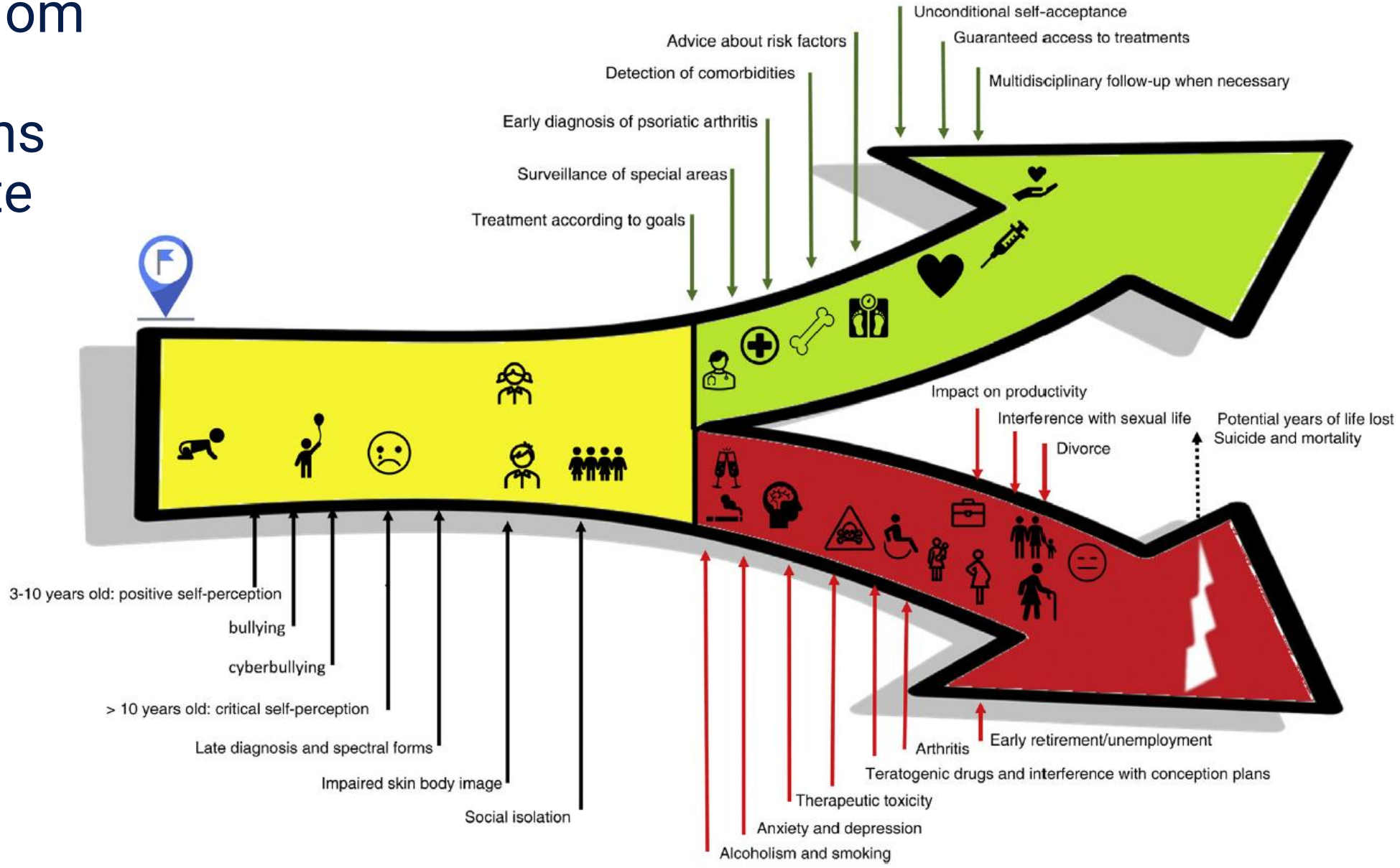
Prospectief impact voorspellen aan hand van

- Age
- Early disease onset
- Severity
- Low education
- Disease duration
- Sex
- Early cutaneous symptoms
- Smoking
- Systemic treatment
- Bad coping
- Impaired general health
- Hospitalisations
- Comorbidities
- Other psychosocial domains?



BSA, body surface area; CLCI, cumulative life course impairment; CV, cardiovascular; MetS, metastases; PASI, Psoriasis Area and Severity Index; PsA, psoriatic arthritis. 1. Augustin M, *Curr Probl Dermatol* 2013;44:74–81; 2. von Stülpnagel CC, et al. *J Eur Acad Dermatol Venereol* 2021; published May 14, 2021. DOI: https://doi.org/10.1111/jdv.17348.

Mogelijkheden om cumulatieve ziektelast tijdens de levensloop te beperken



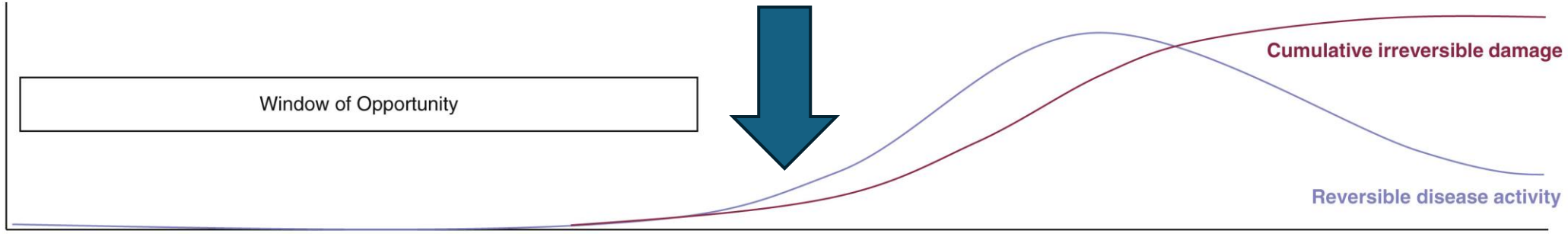
Romiti R, et al. *An Bras Dermatol*. 2024;99(2):269-76.

Early intervention in psoriasis – Window of opportunity?

Genetic Risk → Asymptomatic At-Risk → Preclinical target organ disease → Symptom onset → Diagnosis → Established disease → Severe postinflammatory second organ damage

Pathogenic Processes

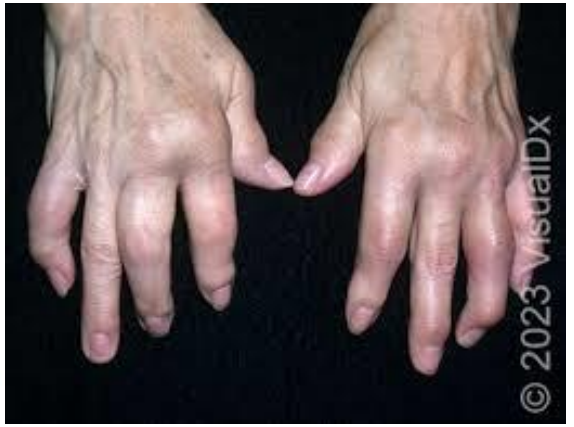
Normal clinical and immune phenotype	Generation of auto-antigen and local response in sites that may be distant from target organs of established disease Adaptive immune response and autoantibodies	Asymptomatic inflammation in target organs of established disease	Target organ inflammation causes symptoms less specific than established disease	Increasing inflammatory changes in target organs Epigenetic regulation of inflammation Secondary lymphoid changes in target organs	Symptom burden dominated by accumulated irreversible processes: Organ damage Glucocorticoid toxicity Burden of chronic disease on quality of life and productivity



Potential Diagnostic and Therapeutic Strategies

Identify individuals at risk and stratify for likelihood of progression Potential novel prevention therapies that may not require immunosuppression	Earlier diagnosis Early immunosuppressive intervention aiming to alter long-term trajectory of disease	Predict worst outcomes and stratify more intensive therapies Potential for evolution of most appropriate therapeutic targets over course of disease

Target tissue homeostasis → Target Adaptive Immunity



Adapted from: Carter LM et al. J Invest Dermatol. 2022; 142:944-950

Waarom vroeg behandelen?

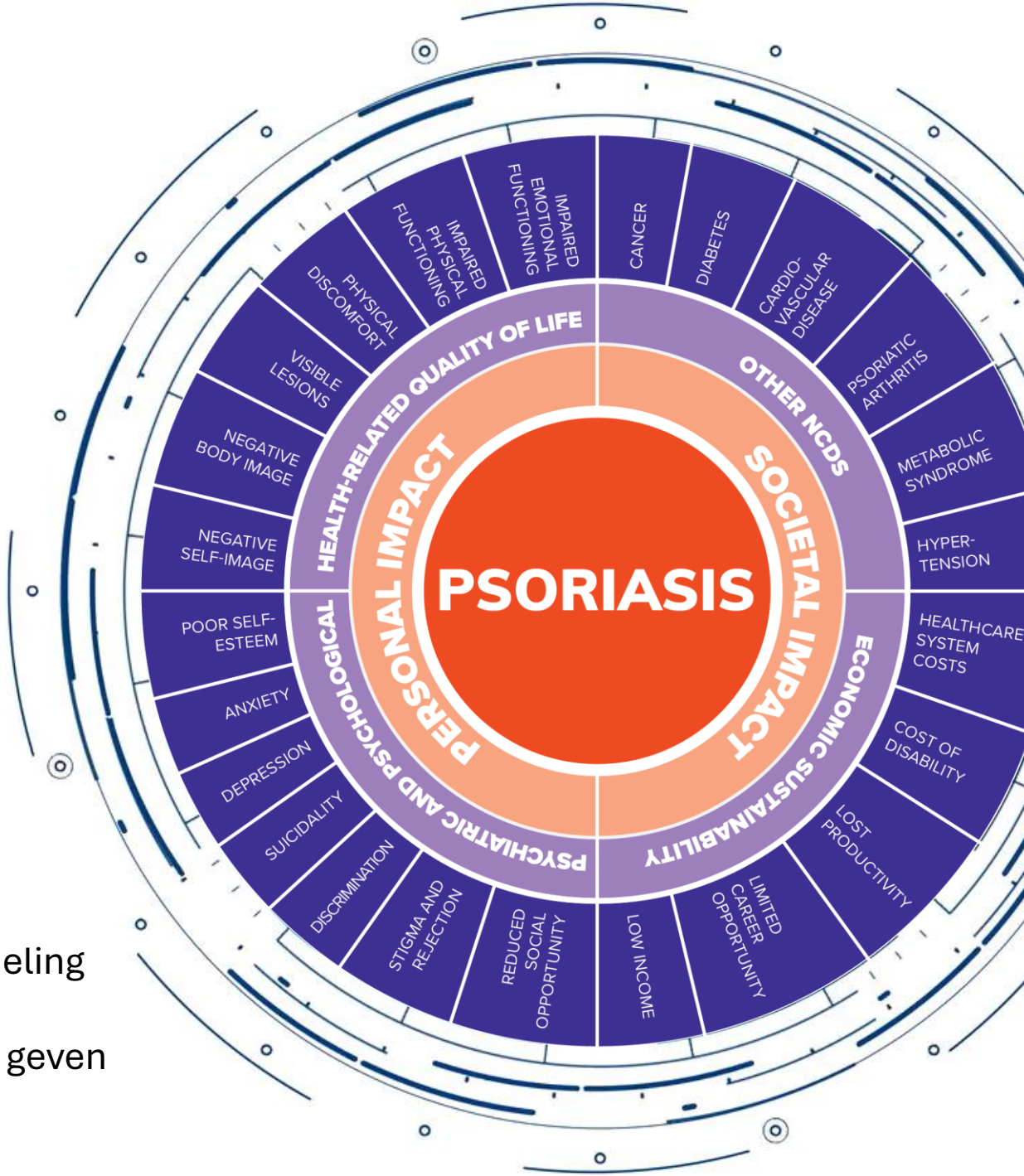
- Onderbreek cumulatieve impact op de kwaliteit van leven
- Impact op ontwikkeling/progressie van comorbiditeiten
- Impact op het beloop/de progressie van huidziekte

Toekomst inzake therapie

- **Eerder ingrijpen** om tot een betere respons te komen
- Orale versus biologische therapie
- Biologic-dosering met langere tussenpozen
- **Preventie** van **comorbiditeiten**
- Nadruk op high-impact spots ondanks lage % BSA

Behoefte aan herclassificatie?

- Het naleven van BSA of PASI alleen leidt tot onderbehandeling
- Hoge noodzaak van behandeling van ‘hoge impact’ spots
- Richtlijnen aanpassen om deze klinische realiteit weer te geven



Adapted from https://ifpa-pso.com/about-ifpa/our-cause

Agenda vandaag

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  - Hoe & Wanneer grijp je in?
  - Bonus = Heeft het ook zin?

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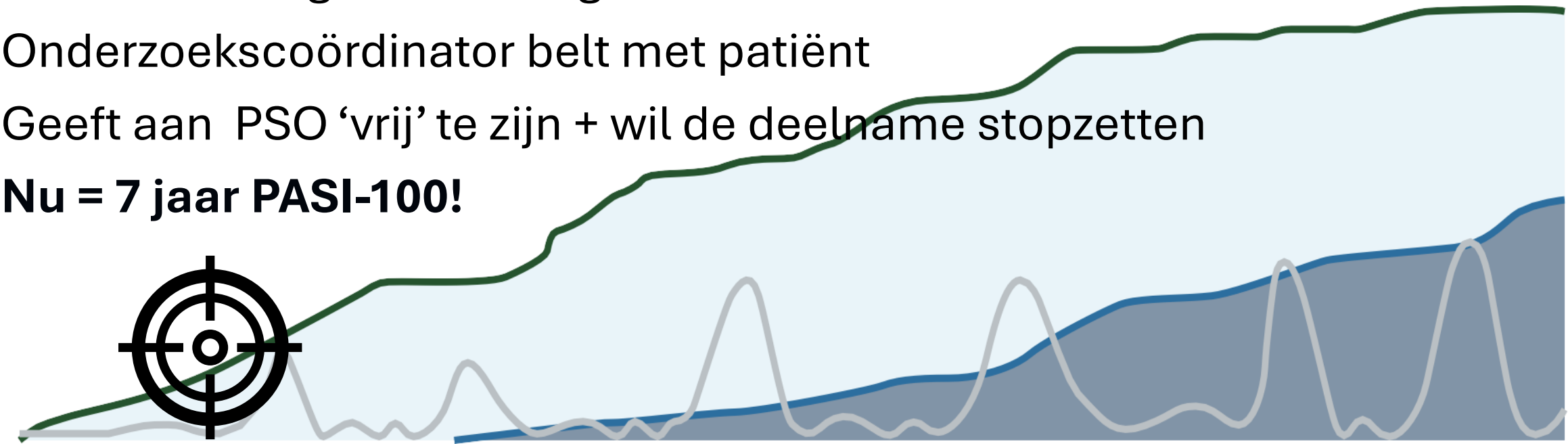
Heeft vroeg behandelen ook zin?

- **19-jarige man 1 jaar PSO (35% BSA, PASI = 2)**
- Mislukte pogingen met smeren en UVB therapie
- Deelname trial Rinzankizumab 150 mg op **dag 0**
- Komt niet terug voor vervolgbezoek!
- Onderzoekscoördinator belt met patiënt
- Geeft aan PSO ‘vrij’ te zijn + wil de deelname stopzetten
- **Nu = 7 jaar PASI-100!**



See related commentary on pg 2614

PERSPECTIVE

Curing Psoriasis

Su M. Lwin[1,2,7], Shir Azrielant[2,3,7], Juan He[2,4] and Christopher E.M. Griffiths[2,5,6]

As medicine advances, cures are being found for diseases that were previously considered incurable, as is the case for some types of cancer. Traditionally, the term cure is reserved for resolution of disease, both at a clinical and a molecular level, which continues after cessation of treatment. Biologic therapies have revolutionized the definition of remission in severe psoriasis, with some patients achieving long-lasting disease suppression, but the disease nearly always relapses on withdrawal of the drug. Our improved understanding of the pathomechanisms of psoriasis, coupled with anecdotal reports of long-term clearance of the disease after cell-based therapies, leads us to the hypothesis that psoriasis is curable. We propose that cure of psoriasis can be achieved by restoring immune homeostasis through a combinatorial, personalized medicine approach encompassing early intervention to include biologics, advanced therapeutics, and lifestyle modification.

Keywords: Advanced therapies, Biologics, Cure, Lifestyle modification, Personalized medicine, Psoriasis

Journal of Investigative Dermatology (2024) **144,** 2645–2649; doi:10.1016/j.jid.2024.09.012

Curing Psoriasis

‘ We propose that cure of psoriasis can be achieved by **restoring immune homeostasis** through a combinatorial, personalized medicine approach encompassing **early intervention** to include **biologics, advanced therapeutics, and lifestyle modification**’

Take Home boodschappen 1

Psoriasis is een systemische ziekte met belangrijke comorbiditeiten

Onthoudt dat huidverschijnselen vaak onderdeel zijn van bredere ontstekingsprocessen die artritis, cardiovasculair risico, metabool syndroom, depressie, angst en vermoeidheid kunnen omvatten.

Optimaliseer behandeling zodat systemische ontsteking zo vroeg en effectief mogelijk wordt onderdrukt; dit kan het risico op comorbiditeiten verminderen.

Vroegtijdige opsporing voorkomt onomkeerbare schade

Screen vroeg en regelmatig op deze co-morbiditeiten;

vroeg ingrijpen beperkt functieverlies en cumulatieve levensschade.

Actieve aandacht voor leefstijl als co-behandeling

Adviseer + faciliteer interventies voor **stoppen met roken**, **gewichtsreductie**, **beweging** en **slaapverbetering**; *leefstijlinterventies verminderen comorbiditeitsrisico's en verbeteren therapierespons.*

Monitor en optimaliseer systemische ontstekingscontrole

Take Home boodschappen 2

Train en betrek het hele zorgteam en de patiënt

Zorg voor korte praktische en heldere protocollen, triagetools en patiënteducatie; empower patiënten met herkennings-vaardigheden voor symptomen van comorbiditeiten en wanneer te verwijzen.

Multidisciplinaire zorg verkleint cumulatieve life course impairment

Organiseer directe lijnen tussen 1e lijn, dermatologie, reumatologie, cardiologie, maar ook diëtetiek en geestelijke gezondheidszorg voor gezamenlijke beslissingen en snelle doorverwijzing.

Personaliseer behandeling en behandeldoelen op levenskwaliteit

Formuleer **samen met de patiënt** doelen gericht op symptoomcontrole, functioneren en participatie;

Behandelkeuze moet comorbiditeiten + levensfase meenemen!

Dag van de Huid
PSO & HS
(H)erken risico’s en grijp op tijd in

Dank voor uw aandacht!

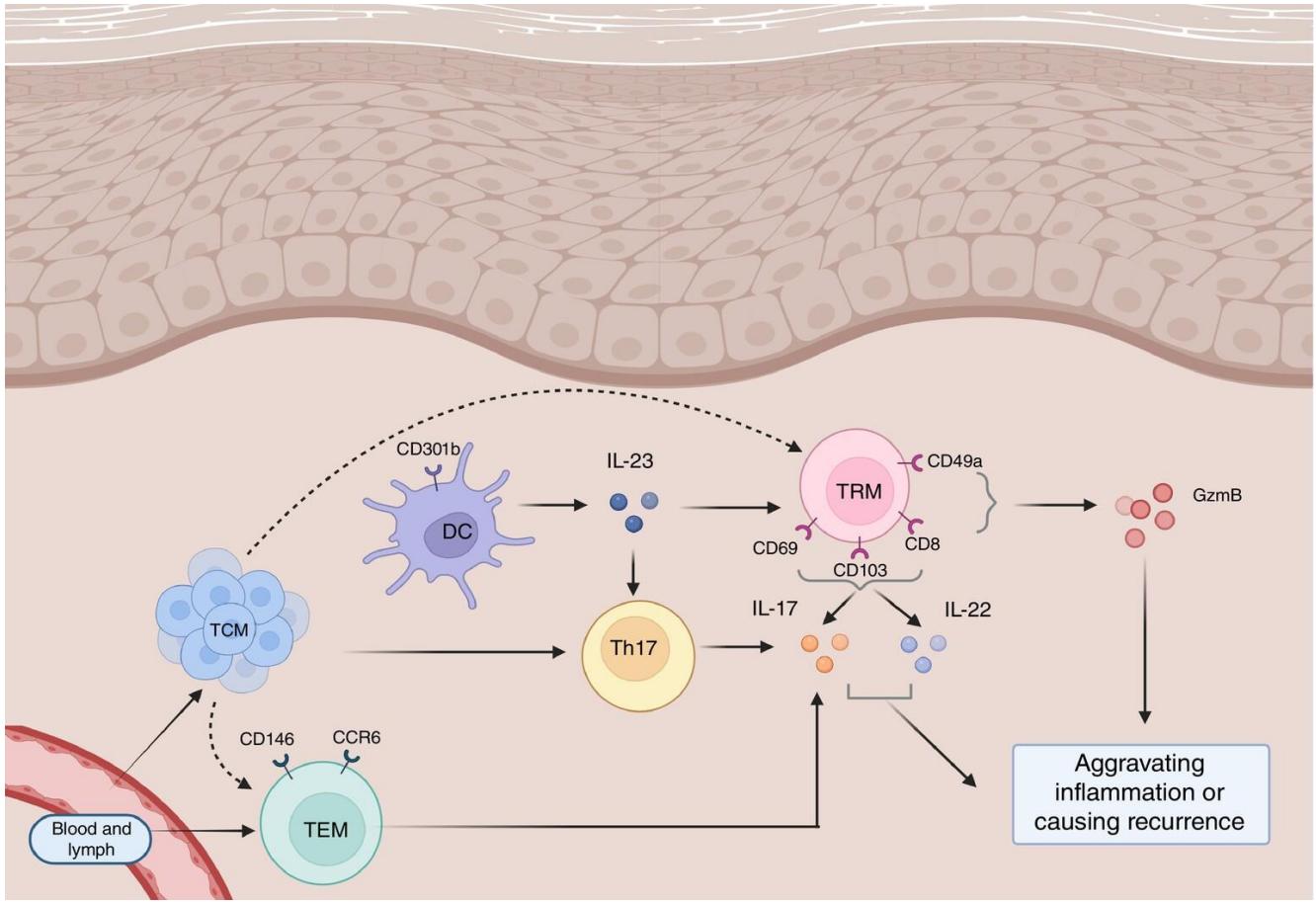
“HIT HARD, HIT EARLY”

- Can work in other autoimmune inflammatory diseases, like rheumatoid arthritis, Crohn’s disease (high initial IV dose of Ustekinumab utilized), and Multiple Sclerosis
- May decrease ability of resident memory T cels (TRM) from **’setting up shop’** in skin affected by psoriasis

Iversen et al, J Eur Acad Dermatol Venereol, 2018

What are Tissue-Resident TRM cells?

- Develop in pathogen-specific manner within tissues in response to infection
- Long-lived; protect tissue from reinfection with original pathogen
- Found in healed psoriasis skin; responsible for psoriasis recurrences at same site as previous disease
- When reactivated , TRM amplify immune response by recruiting effector T cells (TH17 and TC17) from blood
- Local IL-23 is required for proliferation and retention of TRM in skin



Immunology, 2024 Volume: 173, Issue: 3, Pages: 470-480

Current memory Tcell-based treatments

Mem T cells	Intervention	Observation	Origin of evidence
Treatments	Calcipotriol/betamet	Reduces biomarkers of TRM cells and inflammatory response	Patients
	MTX, ADA, Secu, Ixe	Reduces biomarkers of TRM cells and inflammatory response	Patients
	Guselkumab	Reduces freq of CD8+CD49a+CD103+TRM cells	Patients
	FeN402-SACs	Reduces number of CD8+CD103+TRM cells	Mice
	Dihydroartemisinin	Downreg EOMES and BCL-6 of CD8+ T cells and reduces freq of CD8+ TRM cells	Mice
	Alefacept	Reduces number of CD4+ and CD8+ TEM cells	Patients
	PAP-1	Reduces biomarkers of Kv1.3+ TEM cells	Patients, Mice
Therapeutic target	IL-23 Receptor	Reduces number of TRM17 cells, inflammatory reponse	Patients, Mice

Immunology, 2024 Volume: 173, Issue: 3, Pages: 470-480

KNOCKOUT: METHODS

Key eligibility

Patients (≥18 years) with moderate-to-severe plaque psoriasis were enrolled

- Psoriasis onset ≥6 months
- BSA ≥10
- PASI ≥12
- No prior risankizumab use

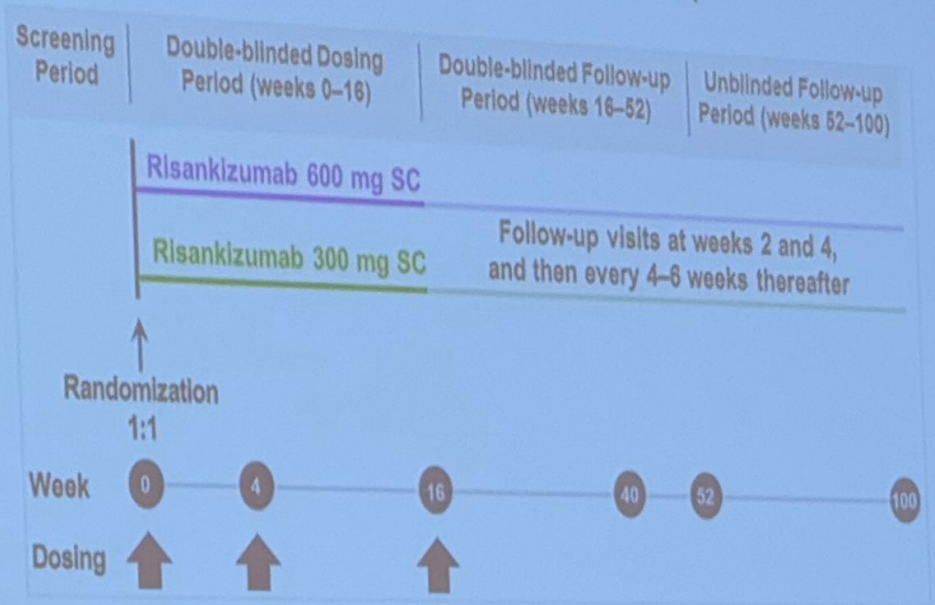
Treatment

Patients were randomized (1:1) to receive either risankizumab 300 mg or 600 mg SC at Weeks 0, 4, and 16, with no further treatment

Analysis of T_{RM} cells

Skin biopsies of lesional and non-lesional skin were obtained at Weeks 0 and 52 and processed for immunohistochemical staining and single-cell RNA sequence analysis

Study design of KNOCKOUT (NCT05283135)



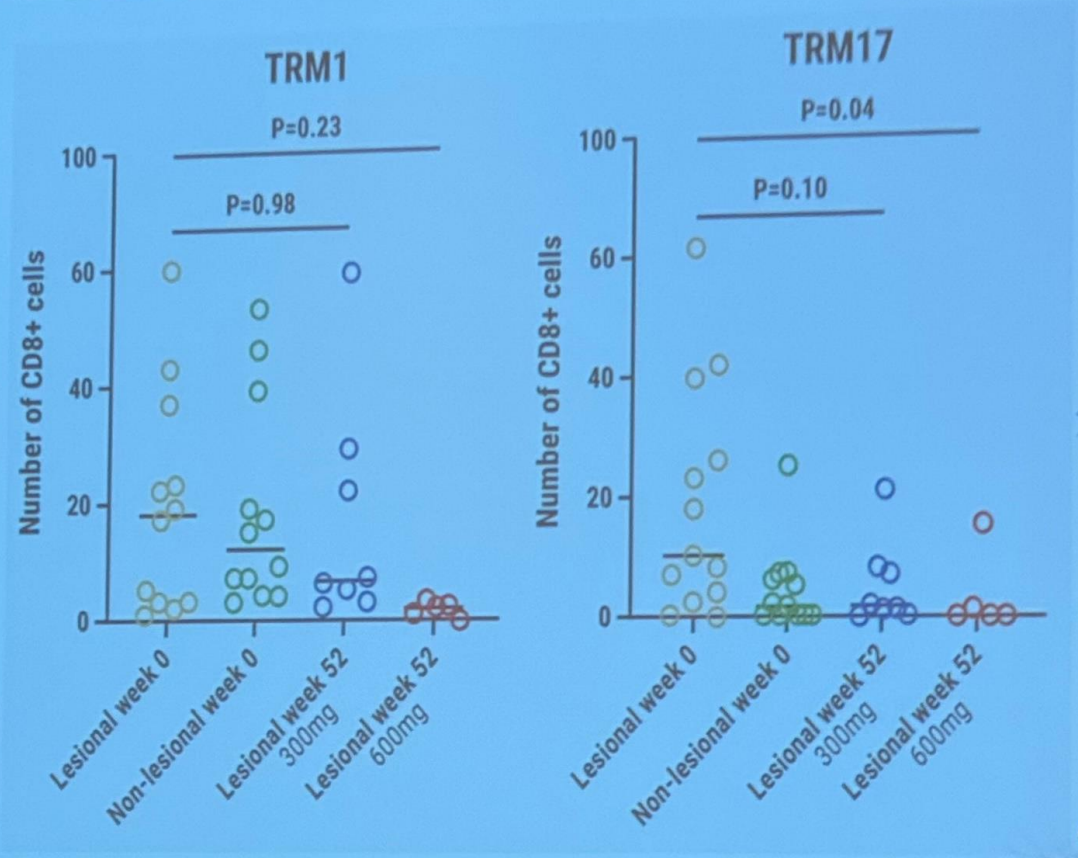
Key endpoints

- *Primary*: Change in T_{RM} cell number from baseline to Week 52
- *Secondary*:
  - PASI 100 at Weeks 28, 40, and 52
  - Safety at Week 52

KNOCKOUT Study

- Doubleblinded single-center
- Risankizumab 1:1 300 or 600 mg at Weeks 0, 4, and 16, with no further dosing, and monitored through Week 52
- RNA seq was performed on lesional and non-lesional skin to assess TRM levels

- Week 52: High induction doses of risankizumab
  - High levels of skin clearance
  - Prolonged disease remission
  - Reduction in TRM



Blauvelt A et al. AAD

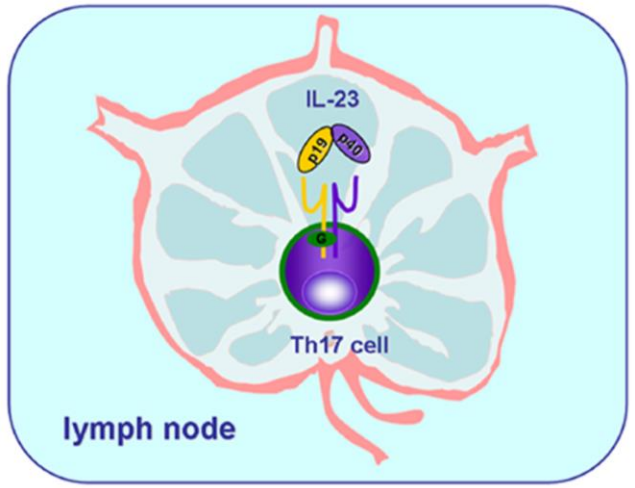
IL23R Polymorphism protects from developing psoriasis

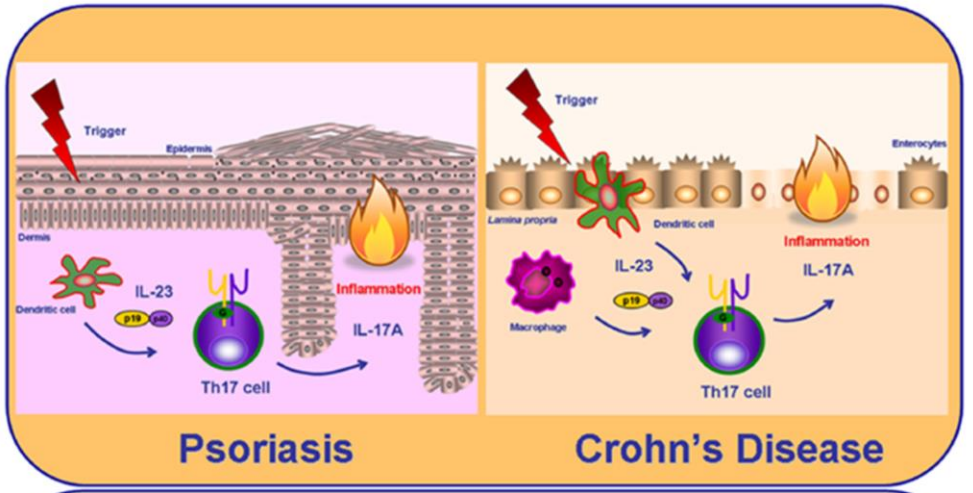
Common G allele

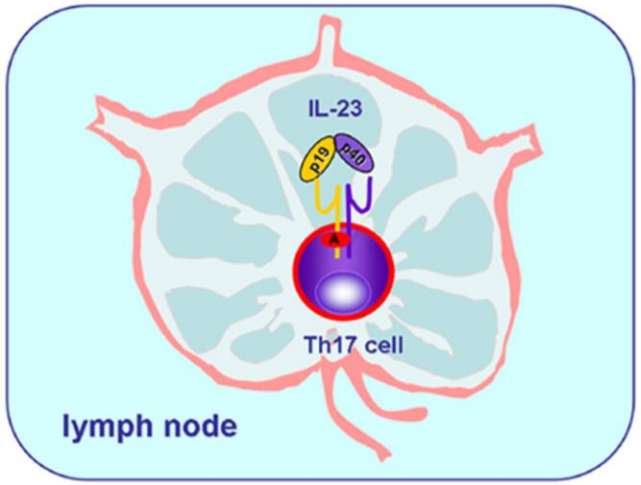
(susceptibile to PsO and Crohn's)

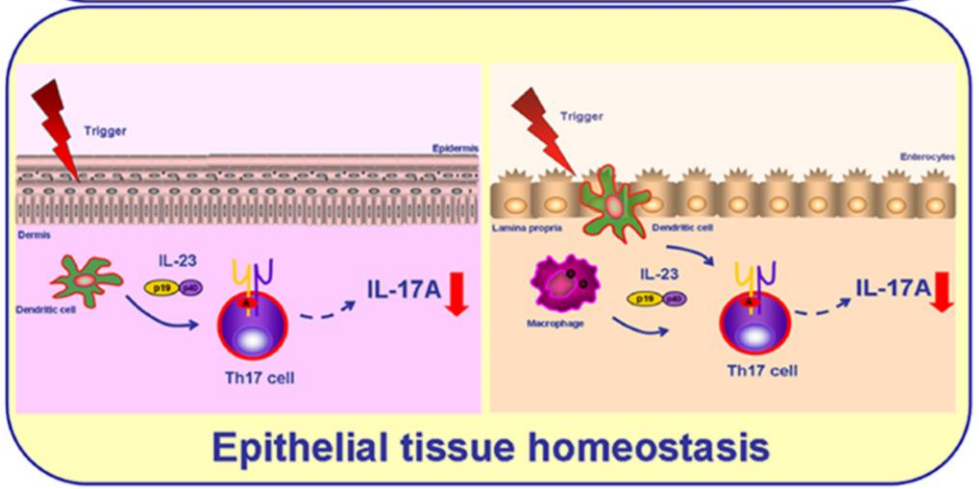
Variant A allele

(protective of psoriasis and Crohn's)



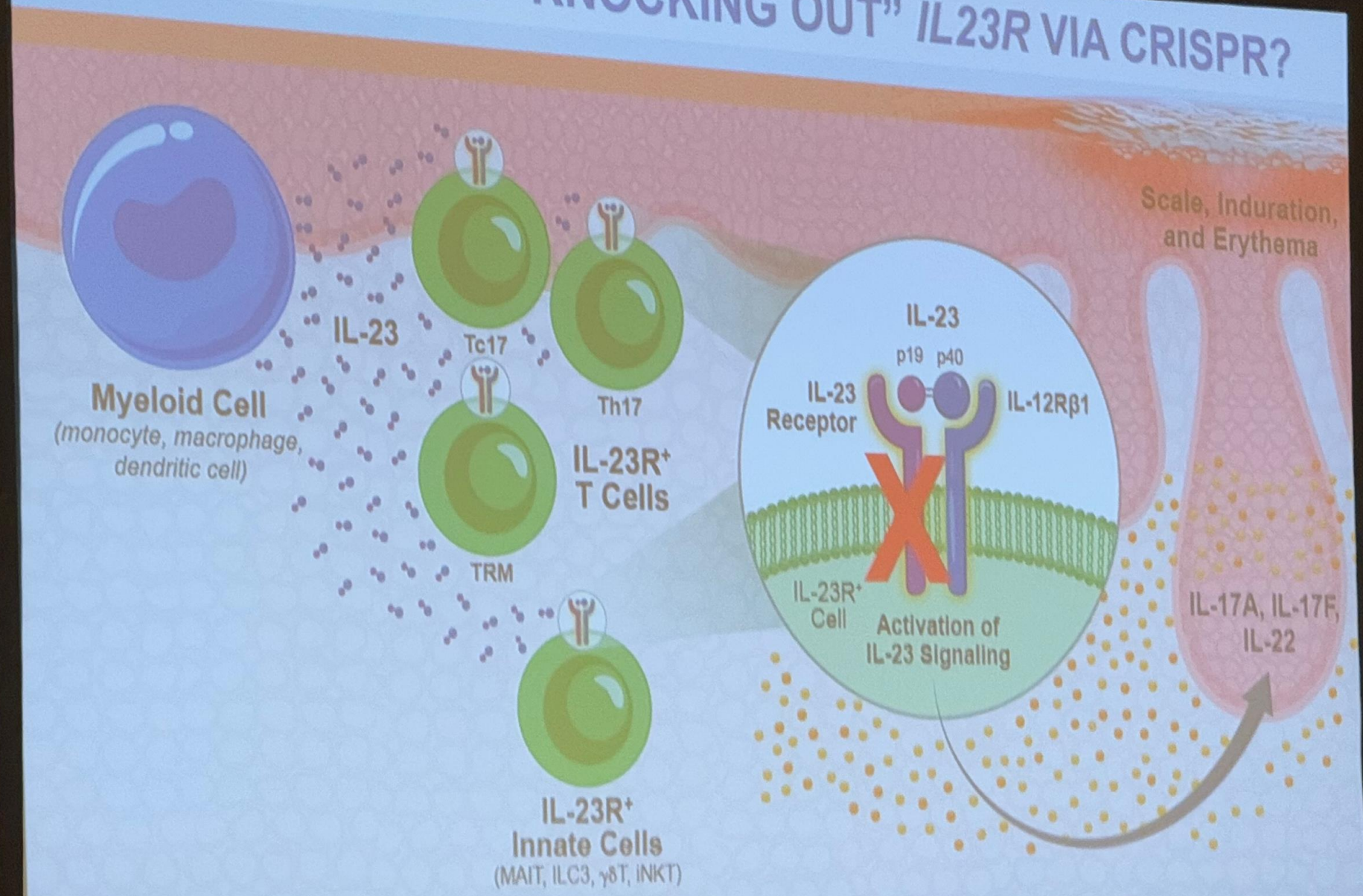




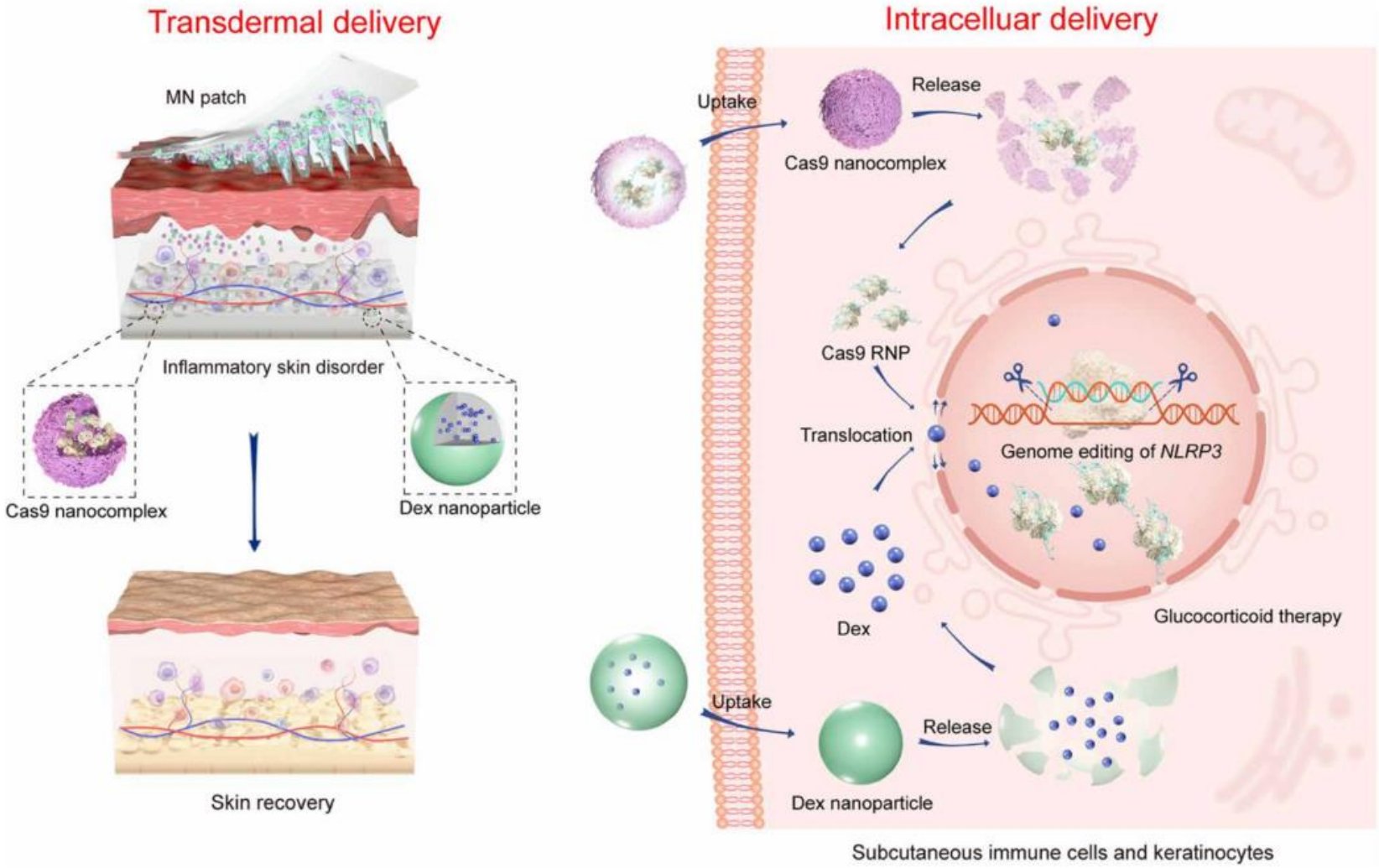


Di Meglio et al, PLoS One, 2011

GENE THERAPY: "KNOCKING OUT" *IL23R* VIA CRISPR?



CRISPR Delivery To The Skin With Microneedles



https://crisprmedicinenews.com/news/crispr-delivery-to-the-skin-with-microneedles/

CURING PSORIASIS: SUMMARY

- Hitting hard (with high-dose IL-23 inhibition) and early (less than 1 year disease duration) may lead to prolonged remissions and cure in some patients
- Cell-based therapies may offer the best approach to cure, and are just beginning to be studied in the clinic
- Gene therapy (via CRISPR) is a promising future approach to curing psoriasis