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The Evolution of Axial Spondyloarthropathies

Shannon Ghizzoni, MSEP, PA-C

Columbus Arthritis Center

Columbus, Ohio

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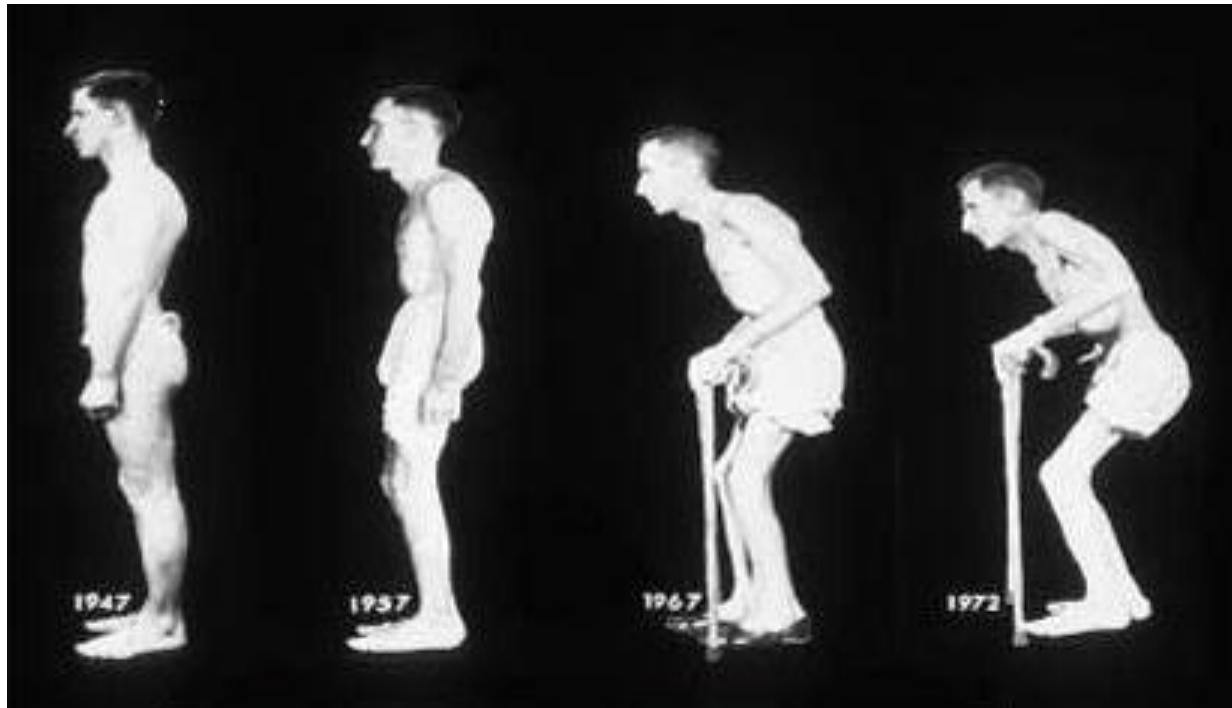
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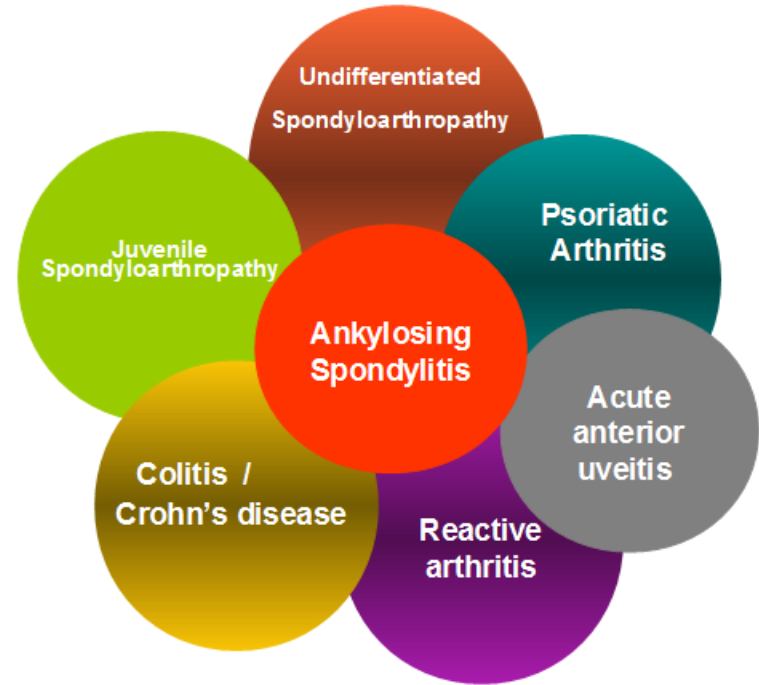
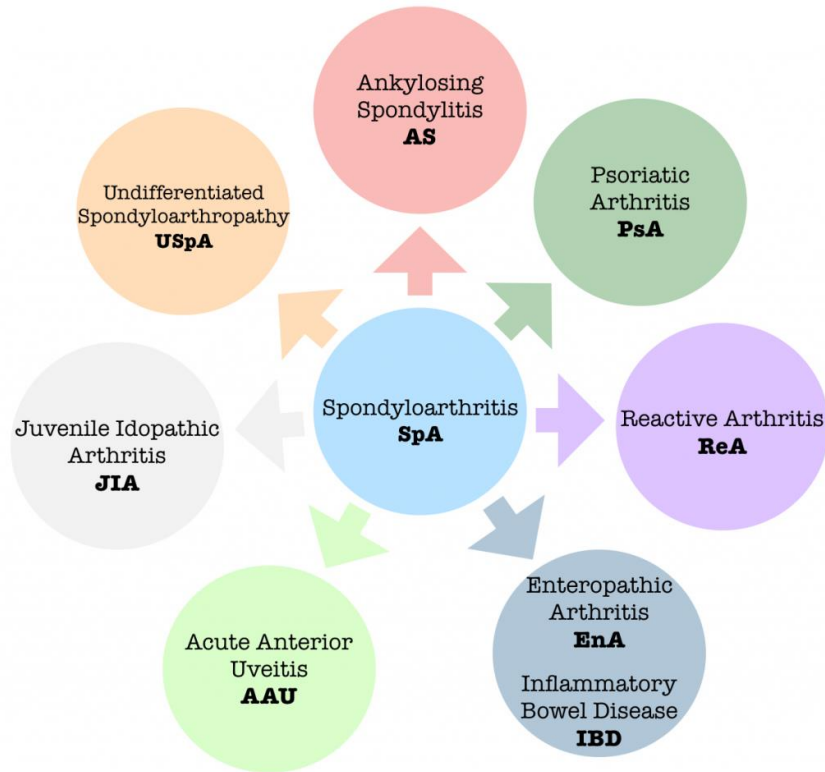
Objectives

- Review the 2009 Assessment of Spondyloarthritis International Society (ASAS) classification criteria for non-radiographical axial spondyloarthropathy (nr-axial axial SpA) and radiographical axial spondyloarthropathy (r-axial SpA)
- Understand key differences between nr-axial SpA and r-axial SpA
- Review findings from multiple cohort studies evaluating progression of nr-axial SpA to r-axial SpA (AS)
- Review the 2019 Updated non-radiological axial SpA and Ankylosing Spondylitis Treatment and Imaging Guidelines
- Discuss future needs and possible treatment options for axial SpA



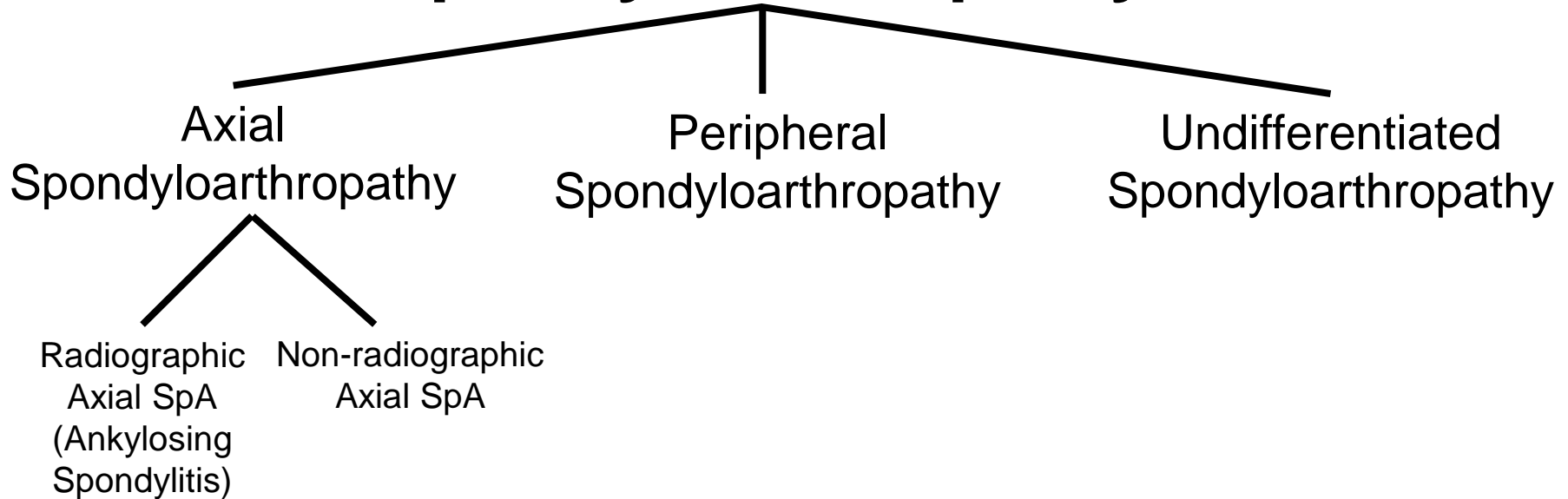
Little H, Swinson DR, Cruickshank B. *Am J Med.* 1976;60:279-285.

Spondyloarthritis



Terminology

Spondyloarthropathy



Classification Criteria

ASAS classification criteria for axial SpA
(in patients with back pain \geq 3 months and age at onset $<$ 45 years)

Sacroiliitis on imaging*

Plus

\geq 1 SpA feature**

**SpA features:

- Inflammatory back pain
- Arthritis
- Enthesitis (heel)
- Uveitis
- Dactylitis
- Psoriasis
- Crohn's disease/ulcerative colitis
- Good response to NSAIDs
- Family history for SpA
- HLA-B27
- Elevated CRP

HLA-B27

Plus

\geq 2 SpA features**

* Sacroiliitis on imaging:

- Active (acute) inflammation on MRI highly suggestive of sacroiliitis of associated with SpA

Or

- Definite radiographic sacroiliitis according to mod. New York criteria

Sensitivity 82.9%, specificity 84.4%; n = 649 patients with chronic back pain and age at onset $<$ 45 years.

Imaging arm (sacroiliitis) alone has a sensitivity of 66.2% and specificity of 97.3%.

**Note: Elevated CRP is considered a SpA feature in the context of chronic back pain.

Rudwaleit, et al. 2009.

Prevalence and Incidence

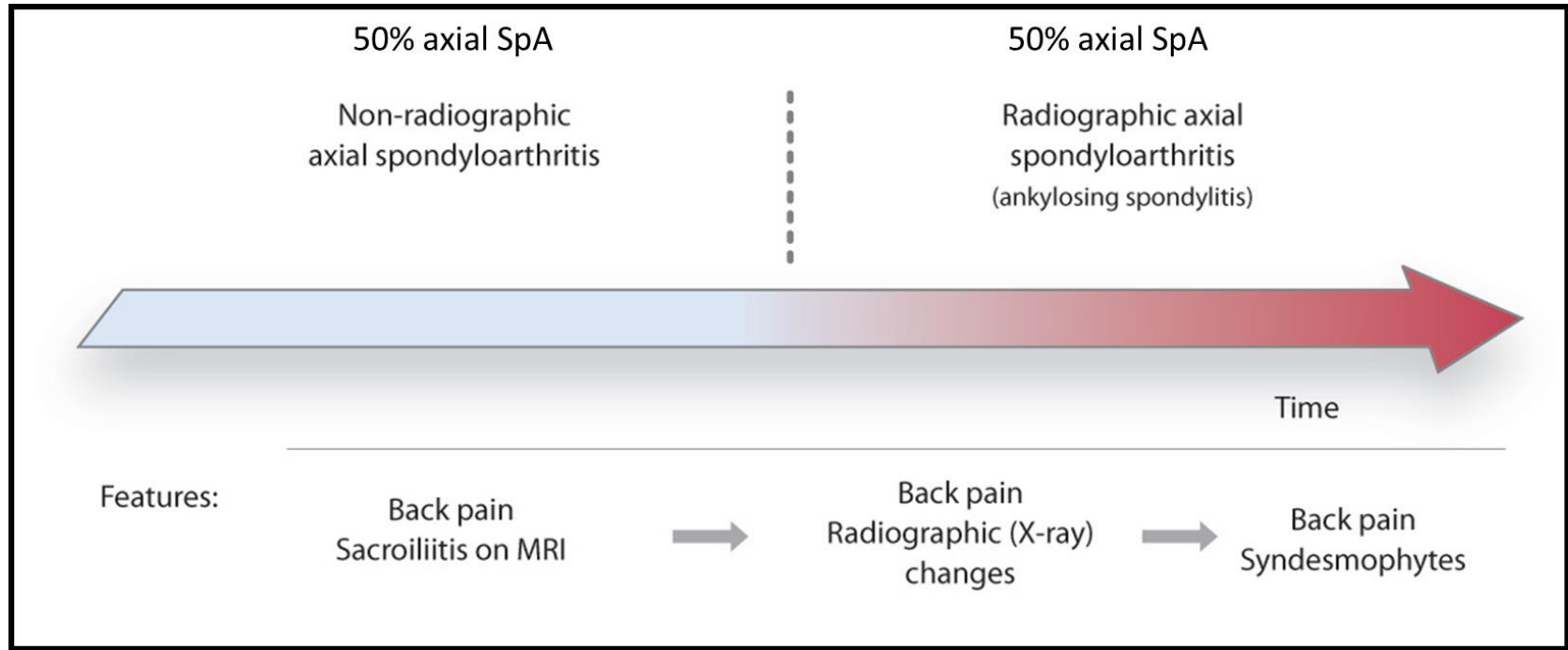
- Unclear, more investigation is needed
- Prevalence of axial SpA in general US population: 1% (0.9%-1.4%)
- Variance among regions and populations is associated with HLA-B27+ from region to region
- Both measurements can vary from study to study due to:
 - Classification criteria
 - When and where study was completed
 - Population studied
 - Screening method and who completed screening



Underdiagnosed and Delayed Diagnosis in Non-Radiographic Axial SpA > Ankylosing Spondylitis

- Reasons
 - Patients often not assessed for IBP
 - Patients initially see PCPs, chiropractors, etc
 - Lack of access to care including rheumatology providers
 - Lack of classic symptoms especially in women
- Consequences of delayed diagnosis
 - More functional impairment
 - Higher healthcare costs
 - Worse quality of life
- Mean diagnostic delay in AS is 8-10 years

One Disease, Different Timing



Differences in Nr-AxSpA vs R-AxSpA (AS)

- Overall, both have similar symptomology, disease burden, and treatment response. However, differences have been recognized (even when disease duration is the same)
- Male:female Prevalance:
 - **Nr-SpA: 1:1 vs AS: 3:1**
- Ankylosing Spondylitis patients have been shown to: (Baraliakos, X., Braun, J. 2015)
 - Have worse function and mobility
 - Have significantly higher CRP levels
 - Have a higher male:female ratio

Prevalence of Symptoms in Ankylosing Spondylitis vs Nr-axial SpA

	AS	nr-axial SpA
Peripheral Arthritis	29.7%	27.9%
Enthesitis	28.8%	35.4%
Dactylitis	6.0%	7.5%
Psoriasis	10.2%	10.9%
IBD	4.1%	6.4%
Uveitis	23.0%	15.9%

Gender Differences in Axial SpA

Male	Female
<ul style="list-style-type: none">• More radiographic changes• More lower back pain• Uveitis more common	<ul style="list-style-type: none">• Longer diagnostic delay• More cervical involvement• More extra-articular symptoms• Higher disease activity scores• Less responsive to TNF inhibitors• Lower drug adherence

Reasons for Gender Differences

- Different immunological, hormonal, and genetic responses:¹
 - Males may express TNAP haplotype which interplays with ANKH gene
 - May lead to more ossification in males
 - Different levels of TNF, IL-6, IL-17, and IL-18 between sexes
 - Males have shown higher levels of TNF and IL-17 (and TH17 cells)
 - ? Lower estrogen levels in pre-menopausal AS females vs controls
 - Estrogen may have an anti-inflammatory effect on AS manifestations

Gut Microbiome in Axial SpA

- Clinically evident IBD is observed in 6%-14% of AS patients, which is significantly more frequent compared to the general population¹
- Silent microscopic gut inflammation, is evident in around 60% in AS patients
- Axial SpA is more common in patients with Crohn's disease than those with Ulcerative Colitis
 - More chronic IBD, more likely to develop axial SpA²
- HLA-B27 positivity plays a role in gut intolerance³
- TNF inhibitors may “reset” abnormal gut flora in AS patients

Progression From Nr-Axial SpA to R-Axial SpA (AS)

- Not all nr-axial SpA patients will progress to AS
 - 10-40% of nr-axial SpA patients will progress to have radiographic signs of AS over 2-10 years¹
 - 5%-30% over up to 30 years.
 - 5.1% in 5 years and 19% in 10 years²
- Progression may occur quickly or take many years
- Patients may go through periods of relapse and remission

Progression From Nr-Axial SpA to R-Axial SpA (AS)

- REP Cohort (The Rochester Epidemiology Project Cohort)
- 1985-2010
- Used diagnosis codes and chart review
- Results:
 - 83 patients identified with new onset nr-axSpA
 - Over mean follow up of 10.6 years, 16 patients progressed to AS
 - Subjects in the radiographic arm progressed faster than subjects in clinical arm
 - A minority (26%) of patients with nr-axSpA progressed to AS when followed for up to 15 years

Progression From Nr-Axial SpA to R-Axial SpA (AS)

- **DESIR Cohort:** (Devenir des Spondyloarthropathies Indifférenciées Récentes Cohort)
- Radiographic vs non-radiographic axial SpA over a 5 year follow up
- 669 patients: 185 (27.7%) r-axial SpA and 484 (72.3%) nr-axial SpA
- Results:
 - R-axial SpA group had significantly higher amount of males
 - Over 5 years there was no difference in peripheral and extra-rheumatic manifestations of disease
 - Over 5 years there was no difference in patient reported outcomes and days of sick leave

Progression From Nr-Axial SpA to R-Axial SpA (AS)

- **The GESPIC Cohort** (German Spondyloarthritis Inception Cohort)
- 303 patients: 158 patients with AS and 145 patients with nr-axial SpA
- Average disease duration: <10 years for AS patients and <5 years for nr-axial SpA
- Patients DID NOT receive TNF inhibitors during 2 years of follow up
 - Cohort data started to be collected in 2000 before most TNF inhibitors were available to patients
- Results:
 - Patients in both groups demonstrated similar clinical disease course over 2 years
 - Patients with nr-axial SpA achieved a status of low disease activity more frequently than those with AS if outcome parameters that included CRP level were included

Progression From Nr-Axial SpA to R-Axial SpA (AS)

- **Pre-SpA Cohort**
- 51 seemingly healthy first-degree relatives of HLA+ AS patients
- Ages 18-40
- Results:
 - 33% of cohort could be classified as having axial SpA based on radiographic or clinical findings
 - 57% had back pain
 - 6% had low grade sacroiliitis
 - 20% had bone marrow edema at SI joints

Can We Stop Progression??



- TNF inhibitors
 - Meta analysis showing possible spinal progression inhibition in patients with radiographic evidence at baseline who took anti-TNF therapy >4 years compared to biologic-naïve patients¹
 - Literature review showing possible decreased progression in those with baseline syndesmophytes after 2 years of anti-TNF therapy²
- NSAIDs
 - Multiple studies showing possible disease progression inhibition
 - Effect seems more apparent in r-axial SpA vs nr-axial SpA

ACR 2019 Ankylosing Spondylitis and Non-Radiographic Axial SpA Guideline Update

- In adults with active AS, recommend continuous treatment with NSAIDs over on-demand treatment with NSAIDs (no particular NSAID is preferred)
- In adults with active AS, sulfasalazine, methotrexate, or tofacitinib should be used over no treatment and sulfasalazine, methotrexate should be considered only in patients with prominent peripheral arthritis or when tumor necrosis factor inhibitors (TNFi) are not available
- Do not recommend any particular TNFi as the preferred choice
- Recommend treatment with TNFi over treatment with secukinumab, ixekizumab, tofacitinib (but recommend secukinumab or ixekizumab over tofacitinib)

ACR 2019 Ankylosing Spondylitis and Non-Radiographic Axial SpA Guideline Update Cont...

- In adults with active AS despite treatment with the first TNFi used, recommend treatment with secukinumab or ixekizumab over treatment with a different TNFi in patients with primary nonresponse to TNFi
- In adults with AS and recurrent uveitis, recommend treatment with TNFi monoclonal antibodies over treatment with other biologic
- In adults with stable AS receiving an originator TNFi, strongly recommend continuing treatment with the originator TNFi over switching to its biosimilar
- In adults with AS and IBD, we conditionally recommend treatment with TNFi monoclonal antibodies over treatment with other biologics

ACR 2019 Ankylosing Spondylitis and Non-Radiographic Axial SpA Guideline Update Cont...

- Use of spinal MRI is recommended when degree of spinal inflammation is unclear and MRI findings may lead to treatment decisions
- Routine spinal radiographs are not recommended to monitor the progression of spinal fusion
- There should be caution when tapering or discontinuing biologics if patients are in remission

Biologic Axial SpA Treatment

TNF inhibitor	IL-17A inhibitor	IL-17A inhibitor
Etanercept Infliximab Adalimumab Golimumab Certolizumab*	Secukinumab*	Ixekizumab*

* Approved for non radiographic axial spondyloarthritis in US.

Prognostic Factors – Axial SpA

- Alcohol consumption → ↑ spinal structural progression in axial SpA
- + Smoking history → worse radiographic severity in AS patients
- Female sex and ?Older age at disease onset → worse functional outcome
- Male sex and younger age at disease onset → more radiographic findings
- Elevated ESR and CRP → more spinal progression
- Pregnant women with SpA have increased risk of adverse outcomes:
 - Higher risk of pre-term birth, emergency C-Section and epidural use

Looking Toward the Future

- Additional JAK inhibitor trials for Axial SpA
- Medications gaining more indications
 - Ex. nr-axial SpA, uveitis, AS
- Biomarkers for nr-axial SpA vs AS
- Effects of treatment on disease progression
- Targeting gut microbiota



What Is Needed?

- Faster diagnosis for patients, especially women
- Faster rheumatology referral for patients with IBP or other axial spondyloarthritis symptoms
- Reliable, cost effective biomarkers
- Personalized treatment for axial SpA patients
 - Nr-axial SpA vs axial SpA; axial symptoms vs peripheral symptoms; male vs female?

Nr-Axial SpA vs AS: Does it Matter??

- Diagnosis: Yes
- Treatment: Maybe, to be determined
- Prognosis: Unknown
- **MORE RESEARCH NEEDED**

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