MS: Disease course and phenotypes

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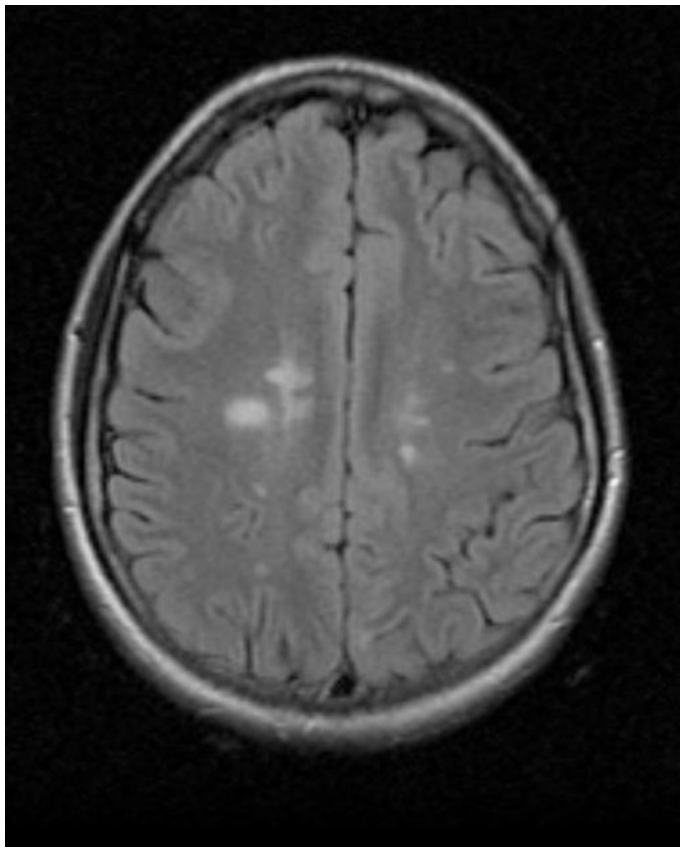
Patient 1

- 26 y/o female Medical student
- CC: blurred vision since 2 days ago
- PMH: Hypothyroidism
- Two cousins with MS
- Hyper-reflexia
- Babinski +/-



Personalization of MS care for women

Prognostication:
Disability
Genetic concerns
Pregnancy
Breast feeding

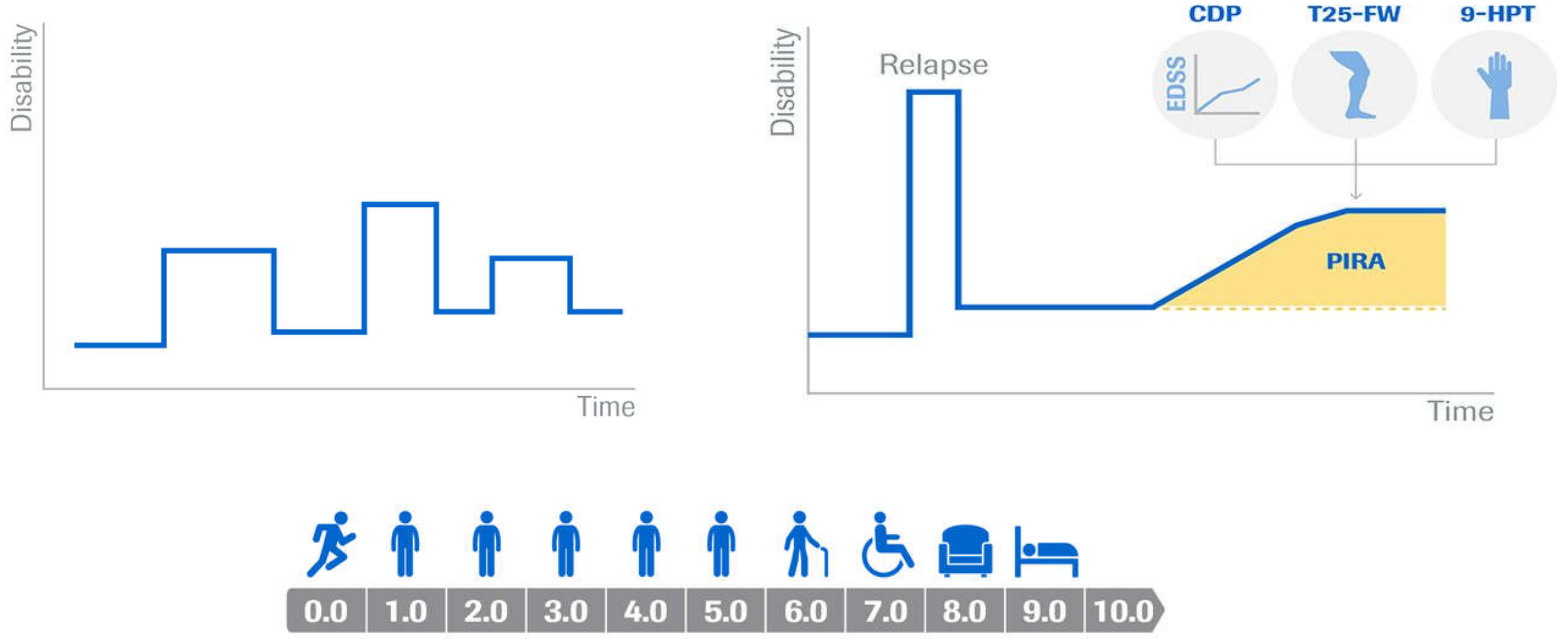
Treatment:
Start or wait
First line or second line

Monitoring:
Continue or stop
Escalation or switch

Caring for women vs men

- Differential Risk (3:1)
- Increasing sexual dimorphism
- Environmental and behavioral factors mediated differentially
- Differential disease course
- Mood
- Co-morbidities
- Pregnancy
- Child birth and breast feeding
- Menarche
- Hormone Use
- Menaupause

Relapse vs Progression



Progression in MS

- 15 years after the disease onset in RRMS (SPMS)
- In 15% of cases, primary progressive (PPMS)

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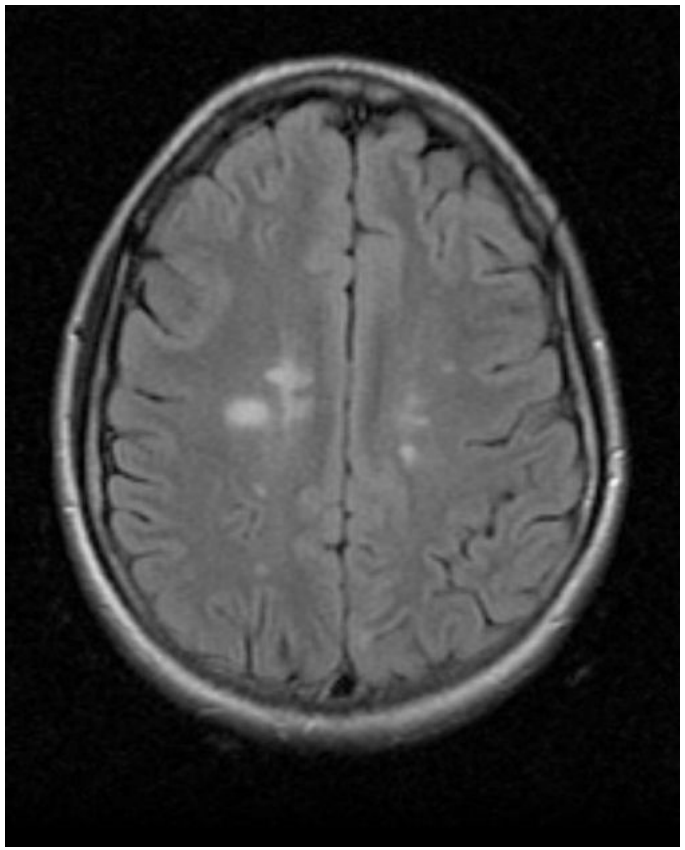
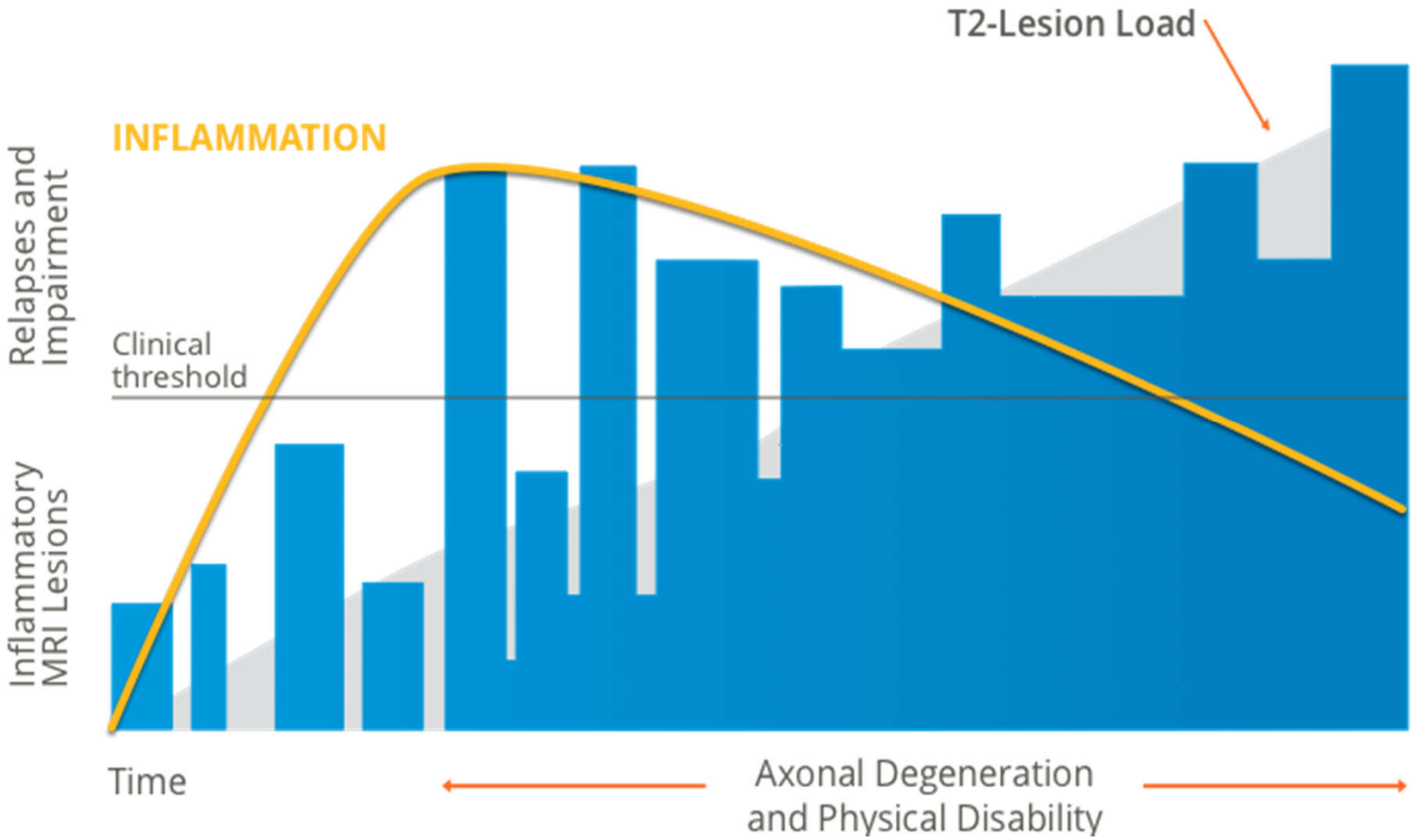
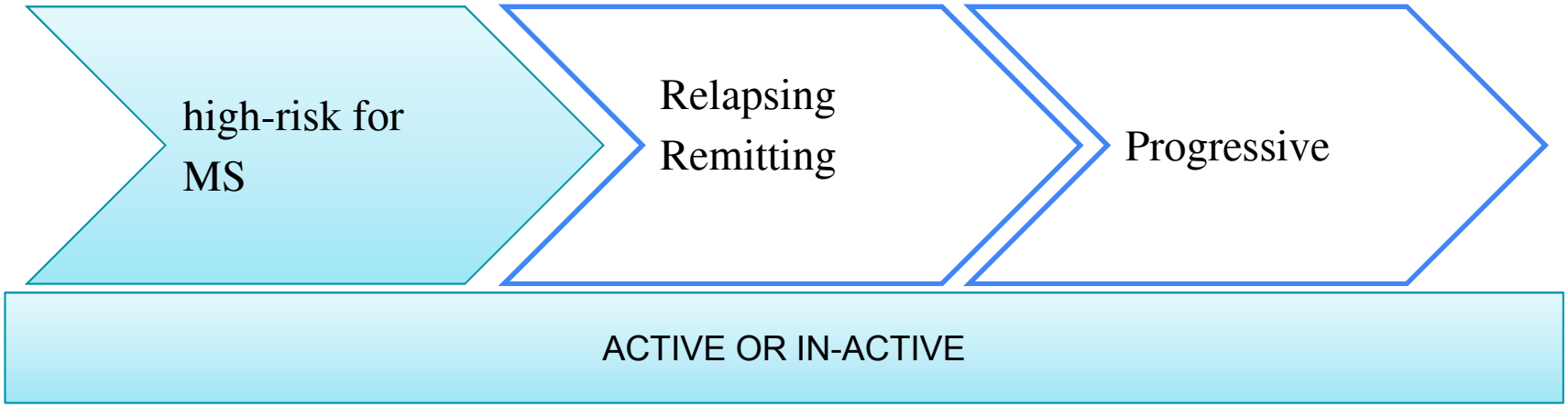


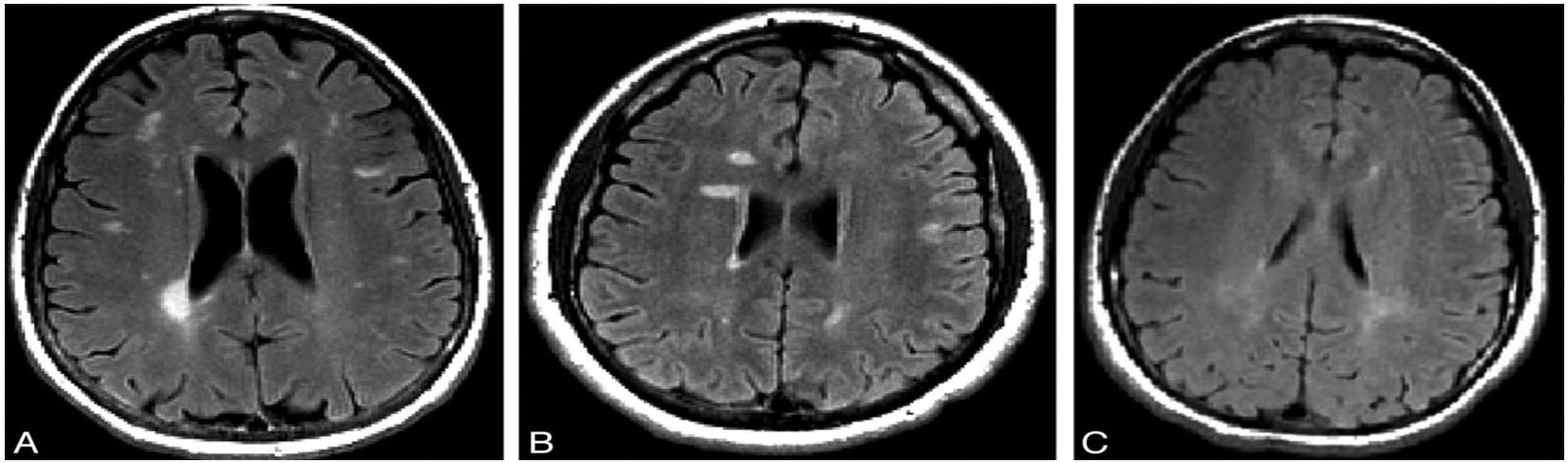

T2-Lesion Load
INFLAMMATION
Relapses and Impairment
Clinical threshold
Inflammatory MRI Lesions
Time
Axonal Degeneration and Physical Disability

- Immunomodulation: once the relapsing phase of MS is over
- Moderate to severe disability in MS: progressive disease
- the progressive gray matter and spinal cord atrophy started earlier than the clinical manifestations

Phases of the disease course



Radiologically Isolated Syndrome (RIS)



T. Gabelic et al. AJNR Am J Neuroradiol 2014;35:106-112

Radiologically Isolated Syndrome (RIS)

1) Symptoms not typical of MS
2) MRI fulfills the diagnostic imaging criteria

Evolution: 30% in 5 years ; faster in children (60% in 1-year)

RIS; MAGNIMS consensus recommendations-2018

Inclusion criteria

- DIS ($\geq$ 1 T2 hyperintense lesions) at least 2 of:
  1. Periventricular white matter
  2. Cortico-juxtacortical
  3. Spinal cord
  4. Infratentorial

Exclusion criteria

- Clinical evidence of neurological dysfunction suggestive of MS
- MRI explained by other disease process(aging, vascular, toxin)

Risk factors of RIS evolution to MS

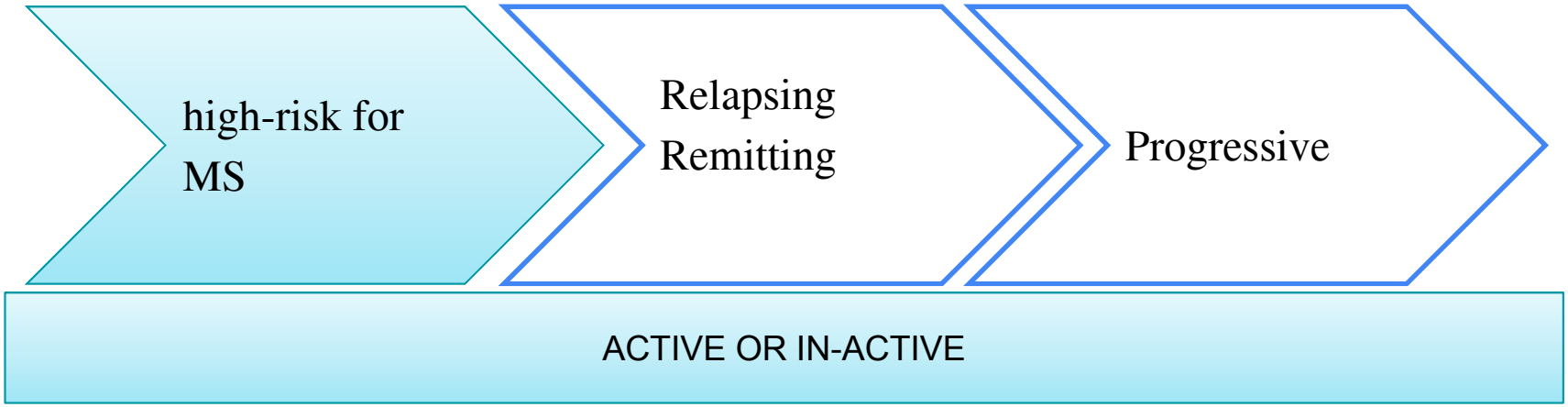
Strong evidence

1. Spinal cord lesions
2. Younger age < 37 years
3. Male gender

Weak evidence

1. OCB in CSF
2. Gd+ enhancing lesions
3. Cortical-juxtacortical lesions
4. High number of T2 lesions and brainstem/posterior fossa lesions
5. Abnormal VEP
6. Cognitive impairment
7. Brain volume loss
8. NfL

Phases of the disease course



2017 McDonald criteria for DIS & DIT

Dissemination in Space (DIS)

- ≥ 1 T2 lesion in at least two out of four areas of the CNS:
    - juxtacortical/intracortical
    - periventricular
    - infratentorial
    - spinal cord

Dissemination in Time (DIT)

- A new T2 and/or gadolinium-enhancing lesion on follow-up MRI, with reference to a baseline scan, irrespective of the timing of the baseline MRI ***OR***
- Simultaneous presence of asymptomatic gadolinium-enhancing and non-enhancing lesions at any time

Clinically isolated syndrome (CIS)

- a single episode of focal neurologic symptoms
- Disseminated in space but has yet to fulfill criteria of dissemination in ~~time~~.

- Any clinical or MRI activity, clinically isolated syndrome evolves into clinically definite relapsing-remitting MS

Risk of New Disease Activity in CIS and Early MS

Low risk: normal brain MRI

Medium risk: cord lesions

RRMS without activity over 2 years <u>while untreated</u>

High risk: ≥**1** relapse with ≥**2** lesions ≥**3** mm

smokers, younger than 30, low serum vitamin D levels

Very high risk: Single attack but meets 2017 diagnostic criteria

highest risk if ≥**2** enhancing lesions

CIS with new MRI activity

RRMS with ≥**2** or activities within 2–3 years

Follow up MRI:

- Brain MRI every 6–12 months
- Spinal cord MRI is not routinely recommended
- Use of gadolinium is not recommended
  - 3-6 Months for high-risk CIS (eg, ≥2 ovoid lesions)
  - 6–24 Months for low-risk CIS (normal MRI) and/or uncertain clinical syndrome with suspicious MRI features (eg, RIS)
  - follow up MRI for 3-5 years then until a new symptom

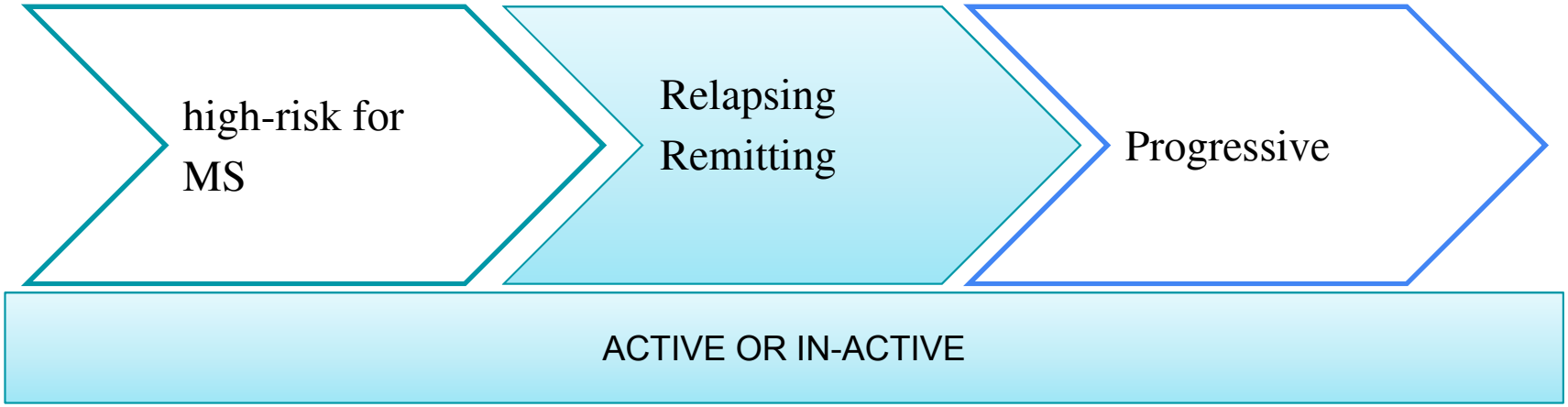
Management

- Identifying prognostic factors
- Education and support
- Management of modifiable lifestyle factors
- Unlikely to benefit from treatment:
  - with normal MRI scans
  - Untreated and no disease activity over the previous 2 years
- annual MRI monitoring for 5 years to confirm stability

Treatment

- All with two T2-hyperintense lesions on brain MRI (≥3 mm)
- only patients with ON who have a very low risk of future relapses and disability are those with a normal brain MRI

Phases of the disease course



Disease activity (symptomatic or asymptomatic)

Clinical activity:

Relapse

Progression

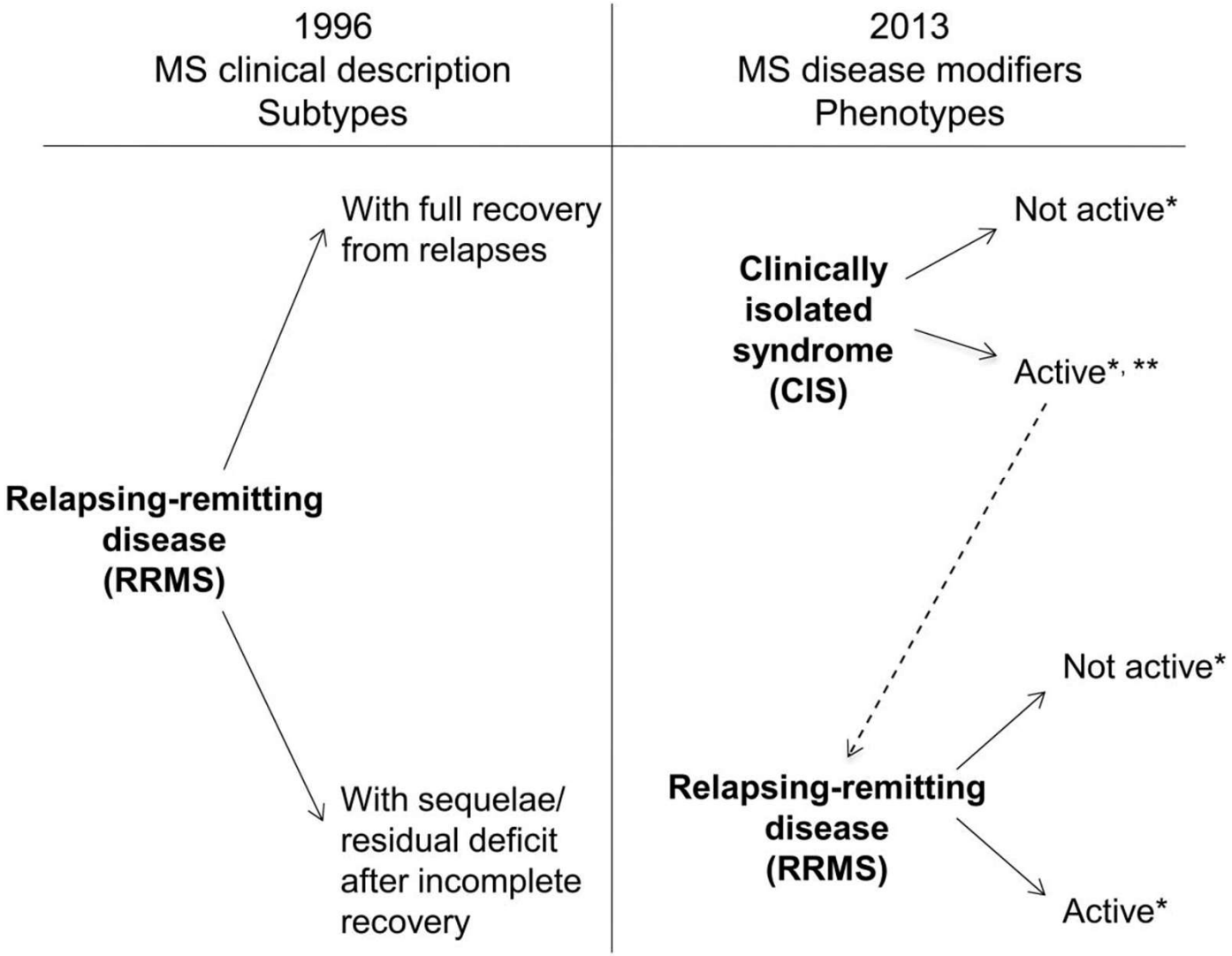
MRI activity:

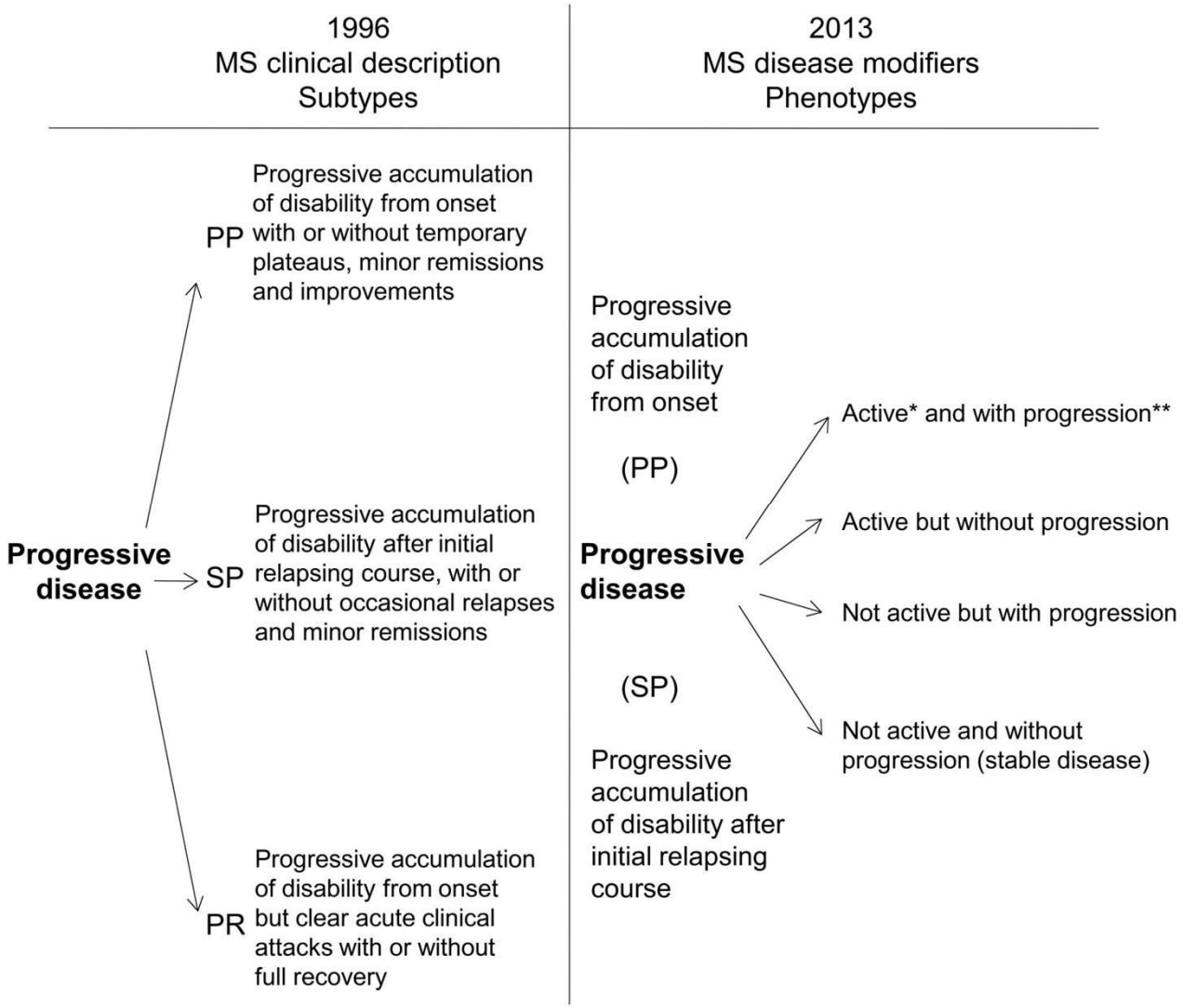
T2 lesion

new, enhancing or enlarging

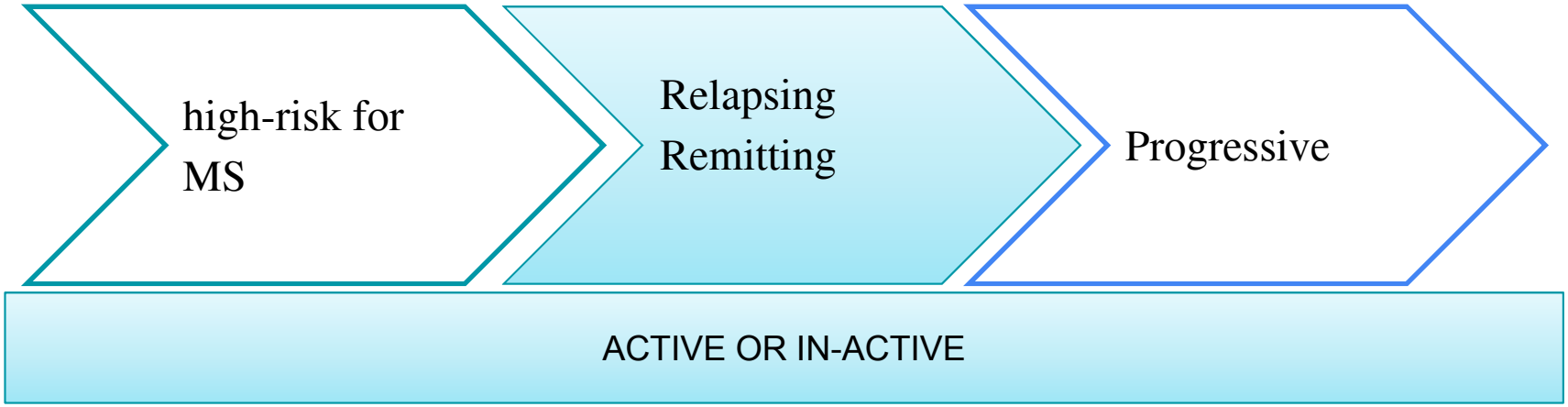
~~Atrophy~~

~~NAWM changes~~


1996
MS clinical description
Subtypes
2013
MS disease modifiers
Phenotypes
With full recovery from relapses
Relapsing-remitting disease (RRMS)
With sequelae/ residual deficit after incomplete recovery
Not active*
Clinically isolated syndrome (CIS)
Active*, **
Not active*
Relapsing-remitting disease (RRMS)
Active*


1996
MS clinical description
Subtypes
2013
MS disease modifiers
Phenotypes
Progressive accumulation of disability from onset with or without temporary plateaus, minor remissions and improvements
PP
Progressive disease
SP
Progressive accumulation of disability after initial relapsing course, with or without occasional relapses and minor remissions
PR
Progressive accumulation of disability from onset but clear acute clinical attacks with or without full recovery
Progressive accumulation of disability from onset
(PP)
Progressive disease
(SP)
Progressive accumulation of disability after initial relapsing course
Active* and with progression**
Active but without progression
Not active but with progression
Not active and without progression (stable disease)

Phases of the disease course



Risk Factors for Aggressive Multiple Sclerosis

Demographic Factors

- Male
- Onset after age 40
- Nonwhite race
- Smoking

Clinical Factors

- Relapse characteristics
  - Number of relapses
  - Short interval between relapses
  - Incomplete recovery from relapse
  - Unfavorable symptoms (pyramidal, cerebellar, sphincter, cognitive)
  - Multifocal presentation
- Disability
  - Rapidly worsening disability
- Phenotype of multiple sclerosis
  - Progression from onset

Risk Factors for Aggressive Multiple Sclerosis

MRI Characteristics

- T2 lesion burden
- Gadolinium-enhancing lesions
- T1-hypointense lesions
- Brain atrophy
- Infratentorial lesions
- Spinal cord lesions

CSF

- Oligoclonal bands

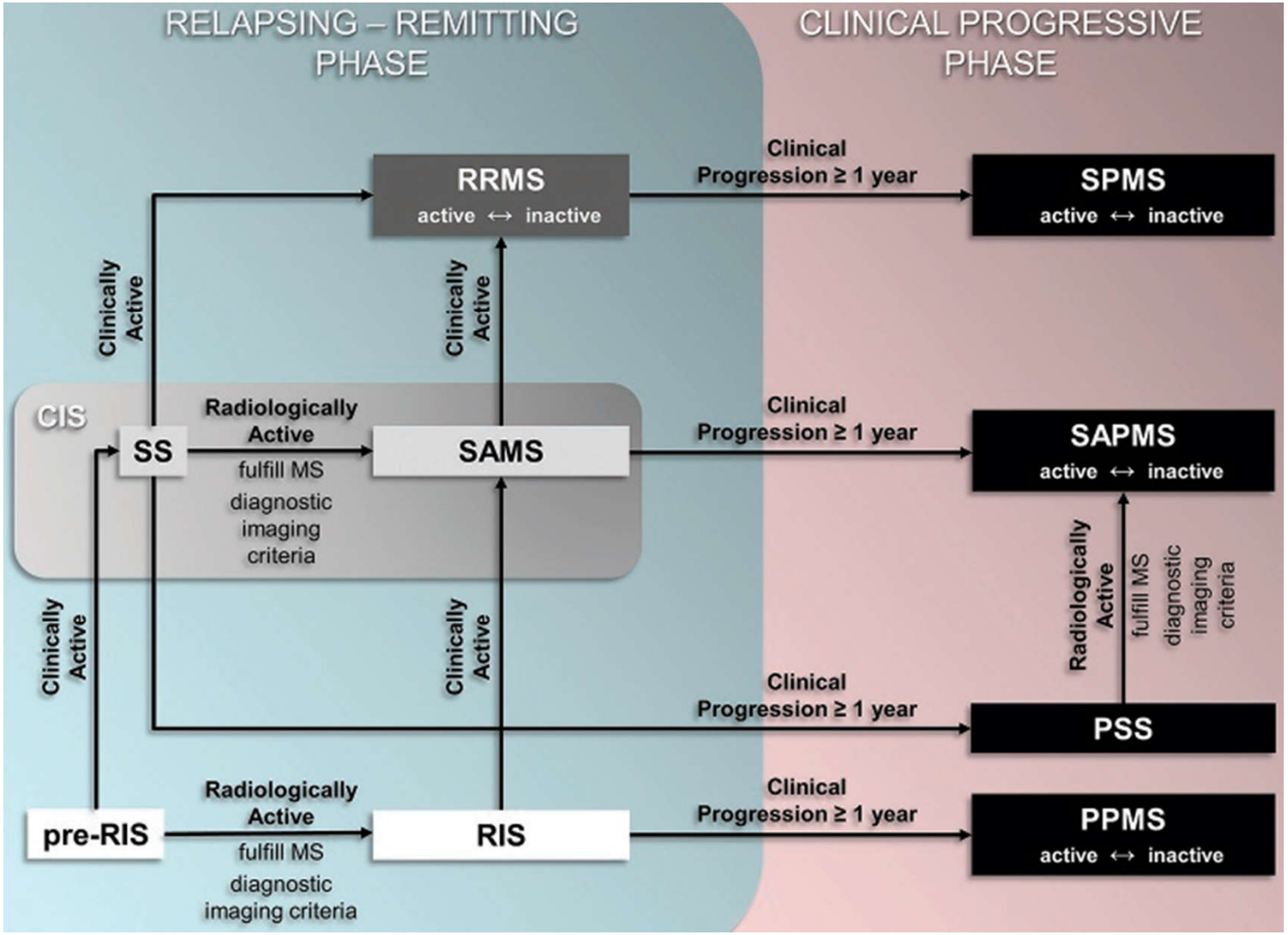
Biomarkers

- Neurofilament light chain (not commercially available

Highly active disease

- Relapse frequency in the previous year (≥2 relapses).
- Relapse severity (pyramidal/cerebellar systems involvement).
- Incomplete recovery from relapses.
- MRI with high T2 lesion load (≥10 lesions)
- Topography of spinal or infratentorial
- Enhancement of multiple lesions with Gadolinium

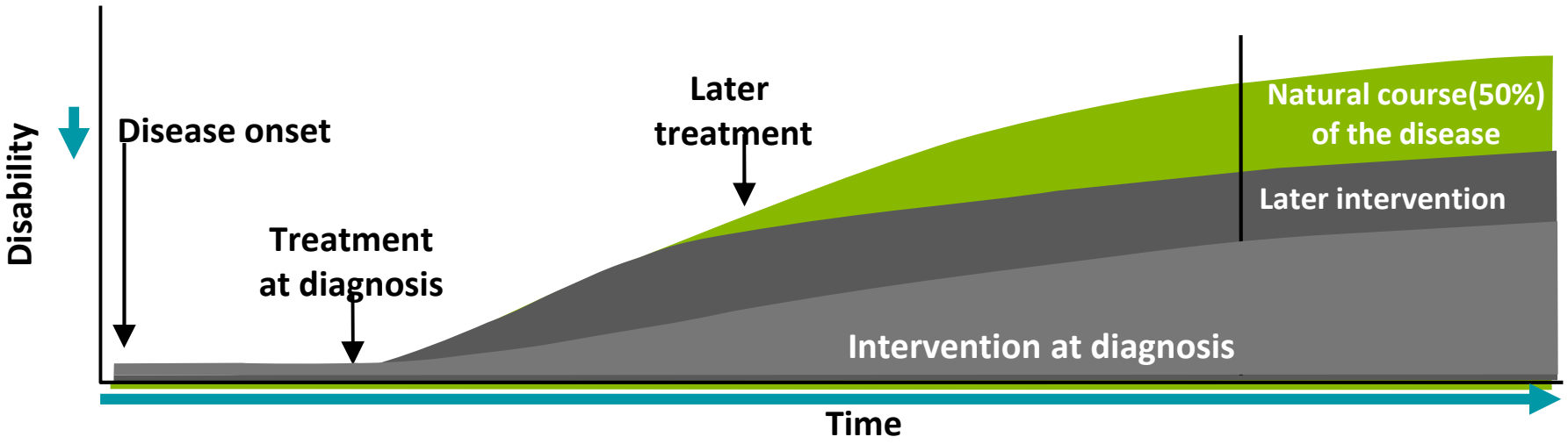
A subgroup of patients with high disease activity will follow a rapidly evolving aggressive course.


RELAPSING – REMITTING PHASE
CLINICAL PROGRESSIVE PHASE
RRMS
active ↔ inactive
Clinical Progression ≥ 1 year
SPMS
active ↔ inactive
Clinically Active
Clinically Active
CIS
SS
Radiologically Active
fulfill MS diagnostic imaging criteria
SAMS
Clinical Progression ≥ 1 year
SAPMS
active ↔ inactive
Clinically Active
Clinically Active
Radiologically Active
fulfill MS diagnostic imaging criteria
Clinical Progression ≥ 1 year
PSS
pre-RIS
Radiologically Active
fulfill MS diagnostic imaging criteria
RIS
Clinical Progression ≥ 1 year
PPMS
active ↔ inactive

Treatment modalities?

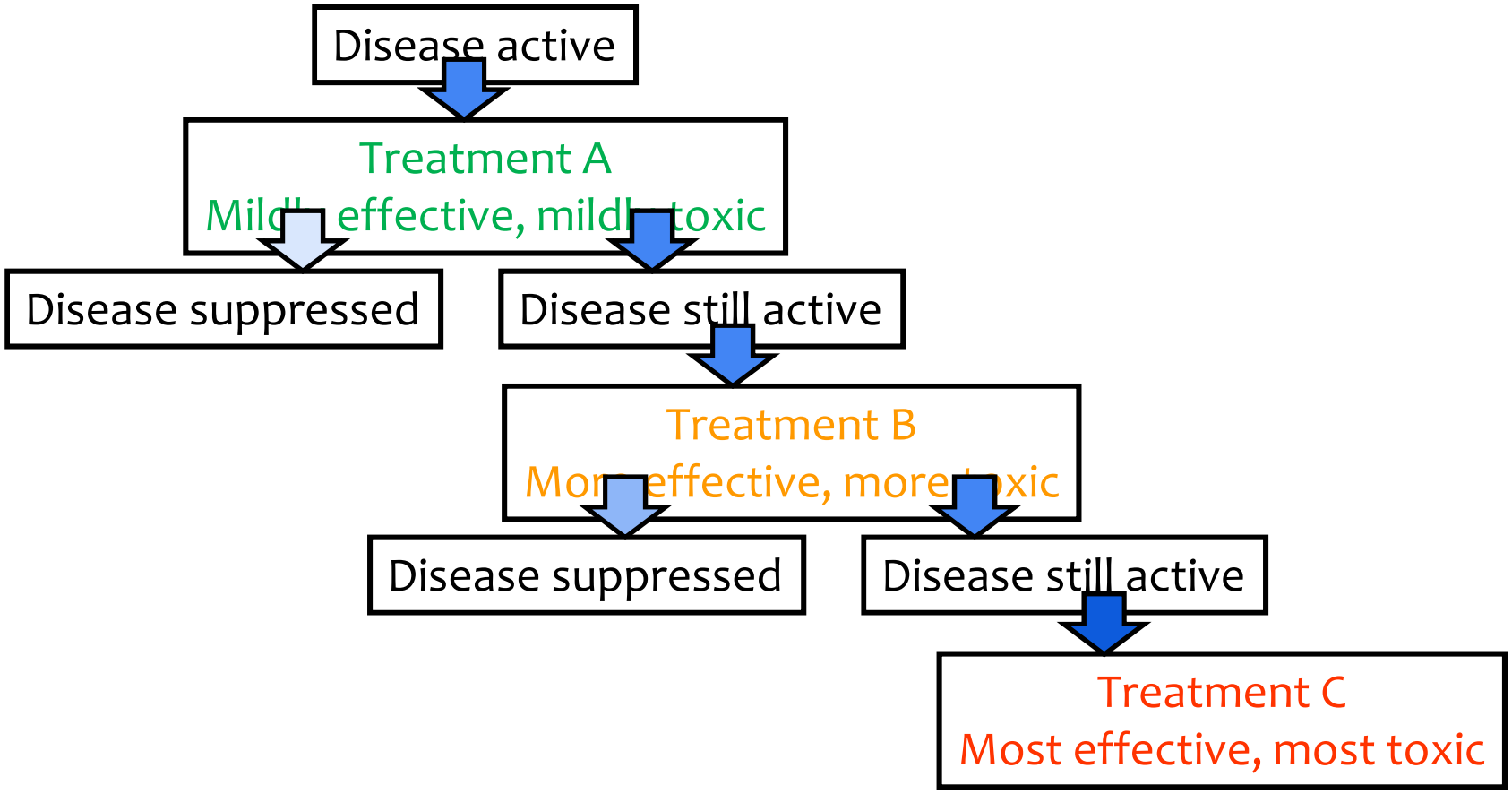
- Treatment of relapses
- Disease modification
- Symptom management
- Rehabilitation
- Psychosocial support

Time and Treatment



Miller JR. J Manag Care Pharm 2004;10(suppl S-b):S4-11.

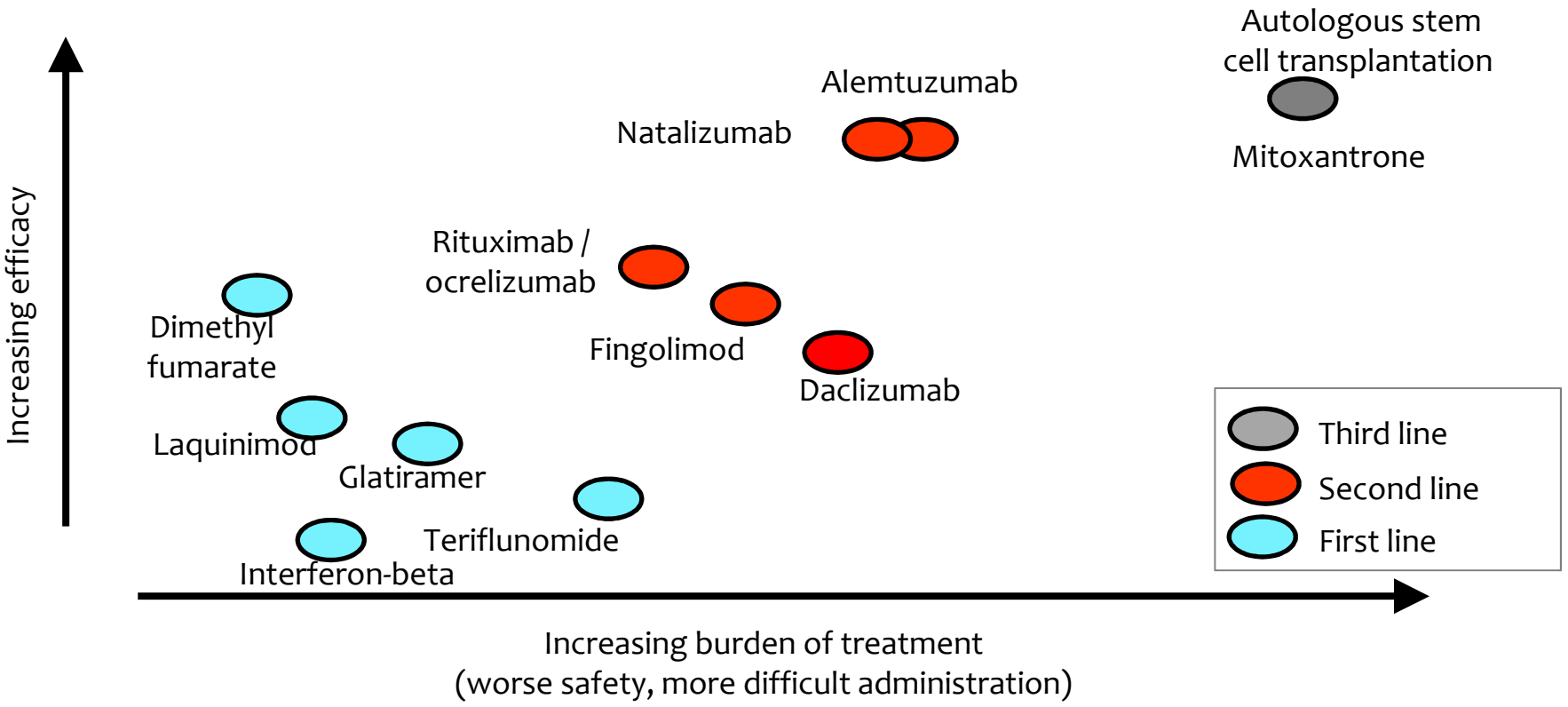
Escalation Strategy



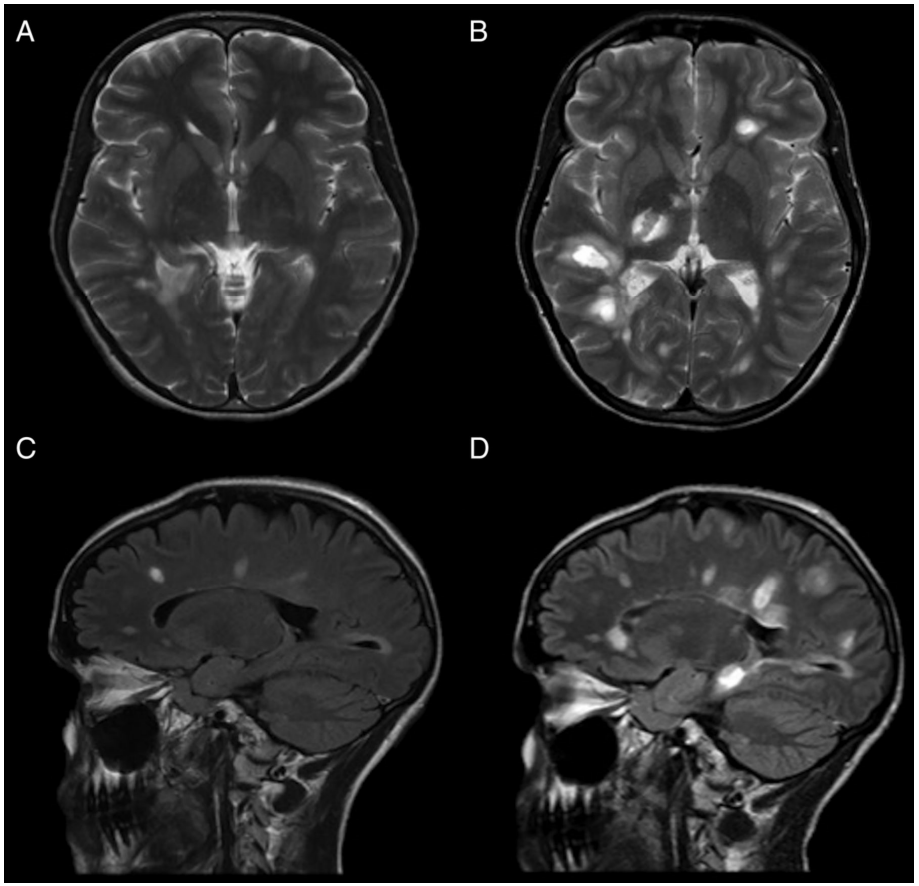
Available DMT's

- **Interferon beta-1a**
- **Interferon beta-1b**
- **Glatiramer acetate**
- **Dimethyl fumarate**
- **Teriflunomide**
- **Fingolimod**
- **Natalizumab**
- **Ocrelizumab**
- **Rituximab**
- **Alemtuzumab**

First, second and third line therapies



- Rebound due to impaired lymphocyte migration or trafficking :
  - fingolimod
  - siponimod
  - natalizumab



Washout

- current treatment
- future treatment
- the reason for the switch:
  - Lymphopenia
  - Activity
  - accelerated elimination
  - a limited or no washout period when switching from an injectable or oral agent to natalizumab, ocrelizumab, or alemtuzumab
  - if possible, to wait no more than 4 weeks to start another disease-modifying therapy after

Can we stop treatment?

no relapses for over 5 years:

- similar recurrence of relapse
- but more rapid onset of disease progression

QUESTIONS