IV CONGRESSO NAZIONALE

SOCIETÀ ITALIANA
G.U.I.D.A.
PER LA GESTIONE UNIFICATA E INTERDISCIPLINARE
DEL DOLORE MUSCOLO-SCHELETRICO E DELL'ALGODISTROFIA

Antimo Moretti

Low Back Pain: biomarker del rischio di cronicizzazione

Centro Congressi Unione Industriali

TORINO 11-13 MAGGIO 2023

Low back pain: epidemiology

- Main cause of disability worldwide
- Most common MSK painful condition
- In over 80% of individuals at some point in their lives
- **15% develop chronic pain and disability**

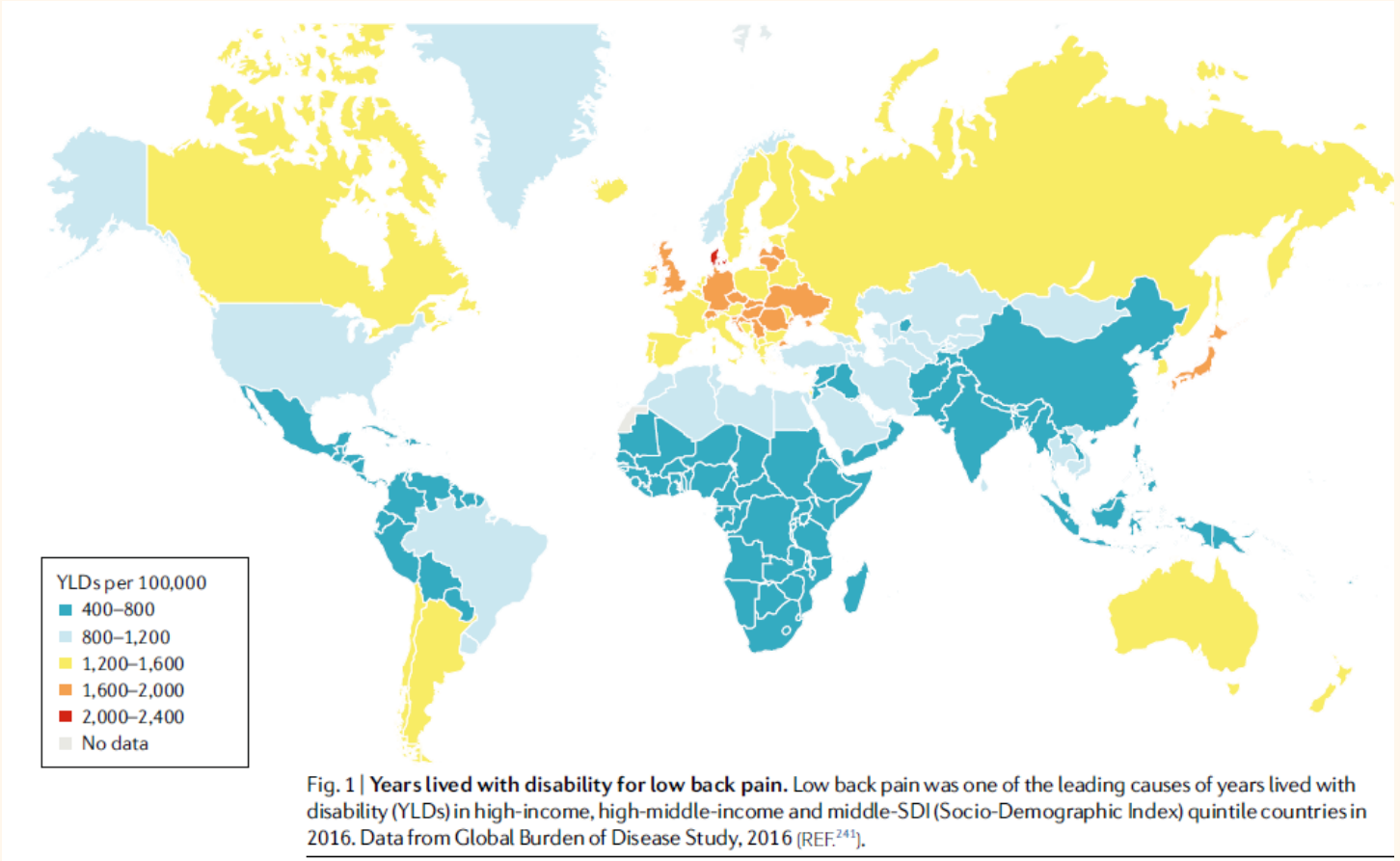
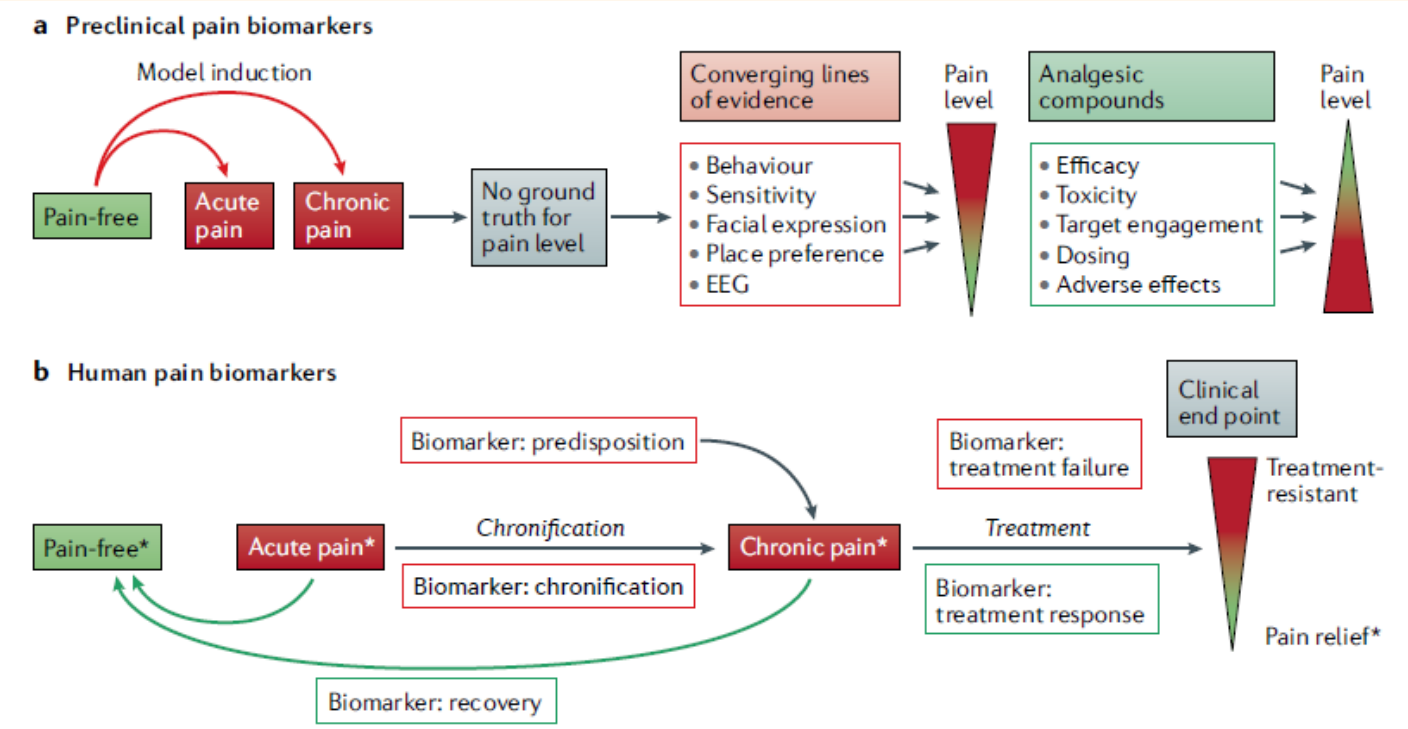


Fig. 1 | **Years lived with disability for low back pain.** Low back pain was one of the leading causes of years lived with disability (YLDs) in high-income, high-middle-income and middle-SDI (Socio-Demographic Index) quintile countries in 2016. Data from Global Burden of Disease Study, 2016 (REF.[241]).

Hartvigsen J et al. Lancet. 2018
Vlaeyen JWS et al. Nat Rev Dis Primers. 2018

Low back pain: Biomarkers

- A defined characteristic that is measured as an indicator of
  - Normal or pathological biological processes
  - Responses to an exposure or intervention
- Molecular, histological, radiographic or physiological characteristics



FDA Biomarkers, EndpointS and other Tools (BEST) glossary
Davis KD et al. Nat Rev Neurol. 2020

Transition from Acute to Chronic LBP: Biomarkers

- Prognostic: identify likelihood of a progression in patients with a disease
- Pain biomarker panel more likely encompass biological, psychological, social, emotional, and environmental factors.
- Top research priority for Federal Pain Research Strategy (USA)

Type of Biomarker	Definition	Pain Examples (present; future)
Diagnostic	To detect or confirm the presence of a disease or condition.	QST; EEG; intra-epidermal nerve fibre density;
		microneurography; neuroimaging, Genetics
Monitoring	To assess status of a disease or condition or effect of a medical product by any biomarker that is measured serially.	QST; compound levels in plasma, CSF;
		Neuroimaging; EEG; intra-epidermal nerve fibre density
Pharmacodynamic/ Response	To show that a biological response occurs in an individual exposed to a medical product.	QST; neuroimaging; EEG; Changes in cytokines
		Specific mechanistic/biochemical pain drivers; intra-epidermal nerve fibre density
Predictive	To identify individuals more likely than individuals without the biomarker to experience a favourable or unfavourable effect from exposure to a medical product.	Genetics
		Neuroimaging; EEG; intra-epidermal nerve fibre density
Prognostic	To identify likelihood of a clinical event, disease recurrence or progression in patients with disease of interest.	Genetics
		Neuroimaging; EEG; intra-epidermal nerve fibre density
Safety	Measured before or after an exposure to a medical product to indicate likelihood, presence or extent of toxicity.	Treatment related e.g. sedation, tolerance, constipation, respiratory depression
		Neuroimaging; EEG
Susceptibility/Risk	Potential for developing a disease or medical condition	Genetics
		Neuroimaging; EEG

Tracey I et al. et al. Neuron. 2019
SZ George et al. Pain Rep 2020

Low back pain: risk factors

- Traditionally considered as a consequence of an injury ("injury model"): simplistic
  - Prolonged orthostasis, lifting heavy objects not close to the body, awkward postures, being distracted during an activity
- Modest association of mechanical load - structural degenerative changes of the spine (pathological findings in asymptomatic)
  - >1/3 of acute LBP episodes with no inciting event

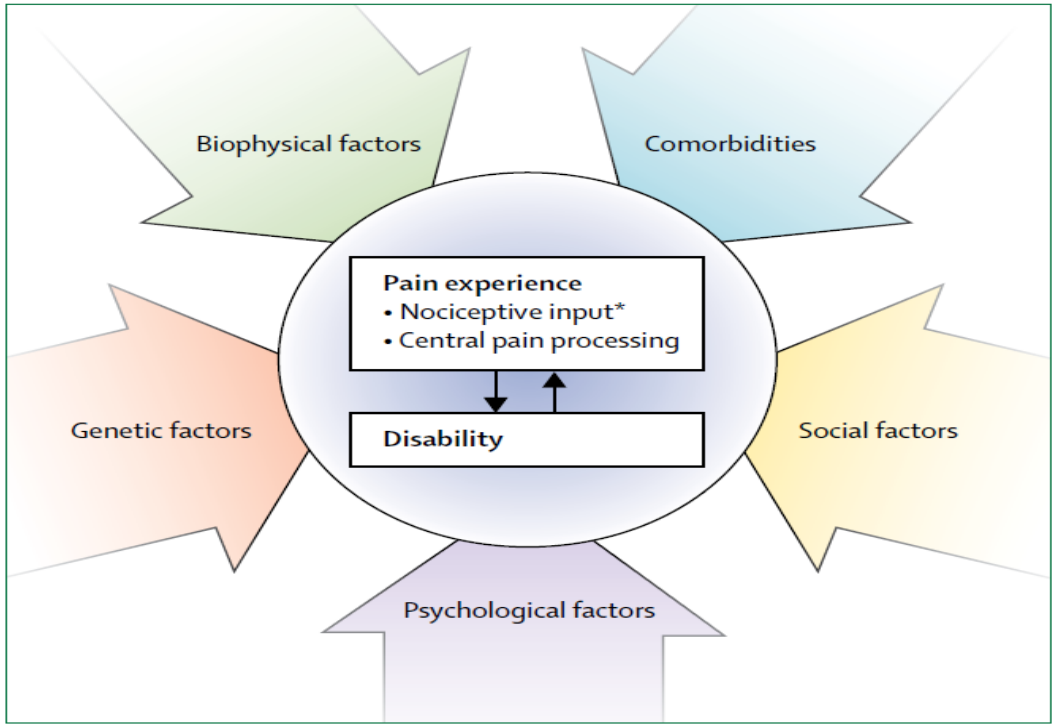
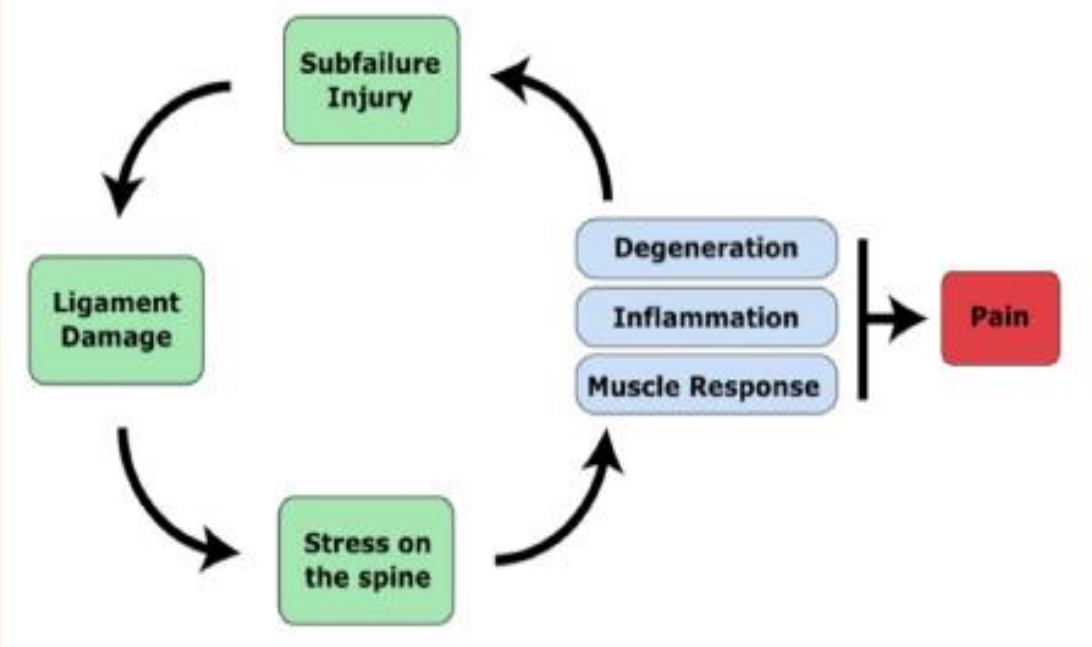


Figure 1: **Contributors to low back pain and disability**
The model includes key contributors to low back pain and disability but does not attempt to represent the complex interactions between different contributors. *Nociceptive input includes non-identifiable sources in non-specific low back pain, neurological sources (eg, radicular pain) and specific pathology (eg, fractures).

Hartvigsen J et al. Lancet. 2018

Chronic Low back pain: pathophysiology

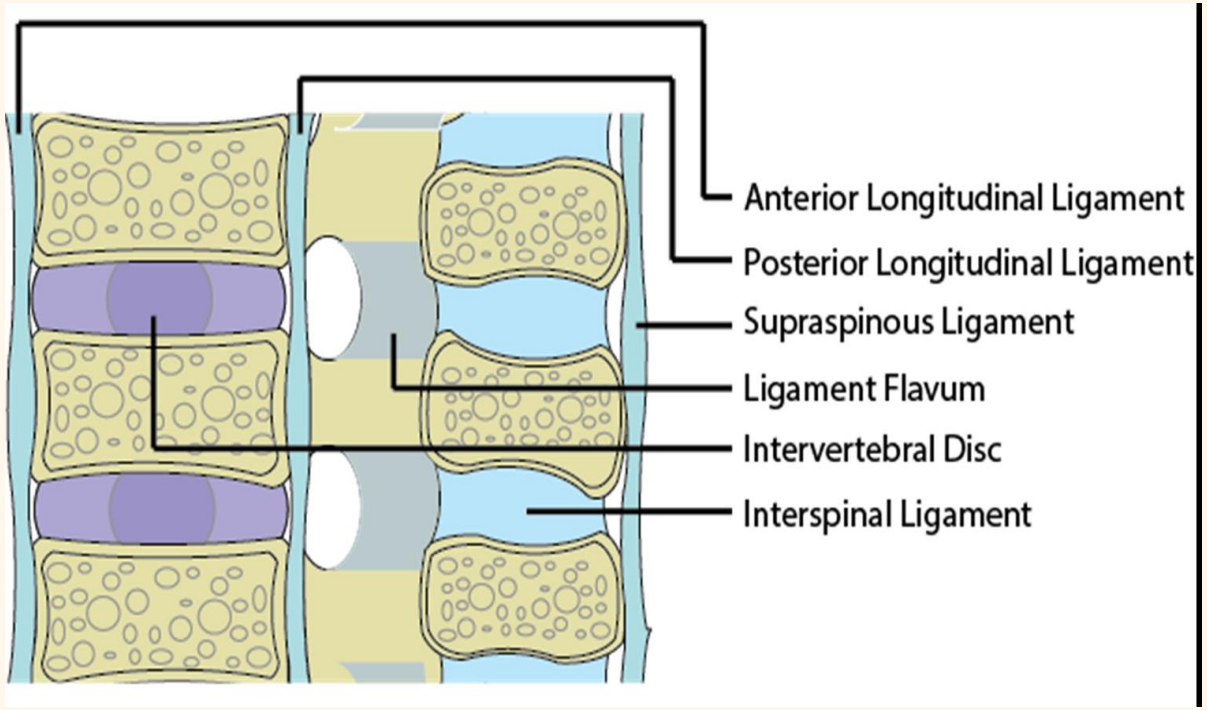
- Begins due to spinal injury/micro-trauma that contribute to degeneration of different structures
- 3 main sources
  - Muscle/ligament strain (myofascial pain)
  - IVD degeneration (discogenic pain)
  - Degenerative joints (FJ, SI, spinal stenosis)



Mosabbir, A. Life 2023

Chronic Low back pain pathophysiology: Ligamentous concept

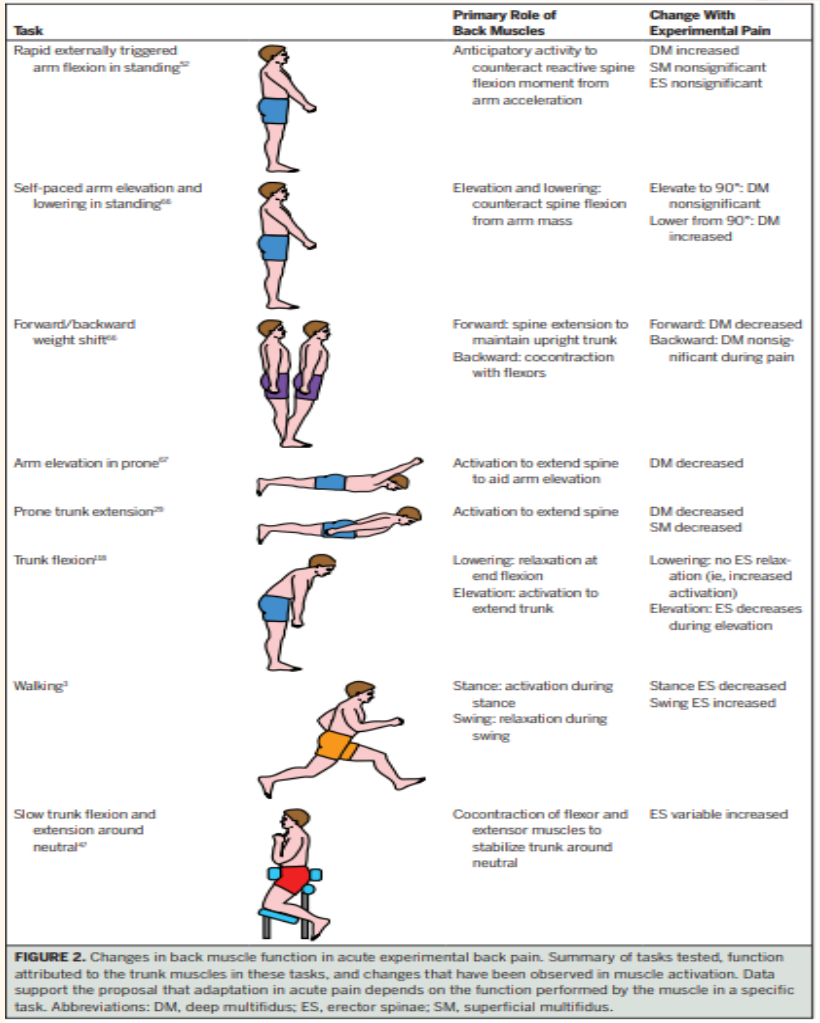
- Major components that passively stabilizes the spine and maintain alignment: ligaments, joint capsules and IVD
- Ligaments damage (trauma/microtrauma) leads to spinal misalignment.
  - Ligament: painful sensation if disturbed by mechanical/chemical irritation
- Misaligned spine impose axial load on vertebrae, disc and FJ that initiates degenerative and inflammatory responses that lead to pain.



Li, W et al. J Pain Res. 2021

Chronic LBP pathophysiology: Myofascia and Spinal Muscles

- Thoracolumbar fascia (TLF): external layer of support above the ligaments, stabilizes the spine
  - Transmits external loads from spine to pelvis, legs and arms
  - Mechanoreceptors: info on spinal position
- Lumbar multifidus and erector spinae: changes from acute to cLBP, atrophy, fat infiltration and connective tissue accumulation (disuse and deconditioning)



Task	Primary Role of Back Muscles	Change With Experimental Pain
Rapid externally triggered arm flexion in standing[52]	Anticipatory activity to counteract reactive spine flexion moment from arm acceleration	DM increased SM nonsignificant ES nonsignificant
Self-paced arm elevation and lowering in standing[66]	Elevation and lowering: counteract spine flexion from arm mass	Elevate to 90°: DM nonsignificant Lower from 90°: DM increased
Forward/backward weight shift[66]	Forward: spine extension to maintain upright trunk Backward: cocontraction with flexors	Forward: DM decreased Backward: DM nonsignificant during pain
Arm elevation in prone[67]	Activation to extend spine to aid arm elevation	DM decreased
Prone trunk extension[29]	Activation to extend spine	DM decreased SM decreased
Trunk flexion[118]	Lowering: relaxation at end flexion Elevation: activation to extend trunk	Lowering: no ES relaxation (ie, increased activation) Elevation: ES decreases during elevation
Walking[3]	Stance: activation during stance Swing: relaxation during swing	Stance ES decreased Swing ES increased
Slow trunk flexion and extension around neutral[47]	Cocontraction of flexor and extensor muscles to stabilize trunk around neutral	ES variable increased

FIGURE 2. Changes in back muscle function in acute experimental back pain. Summary of tasks tested, function attributed to the trunk muscles in these tasks, and changes that have been observed in muscle activation. Data support the proposal that adaptation in acute pain depends on the function performed by the muscle in a specific task. Abbreviations: DM, deep multifidus; ES, erector spinae; SM, superficial multifidus.

Hodges, P.W. et al. J. Orthop. Sports Phys. Ther. 2019

Chronic LBP pathophysiology: Spinal Muscles

- Fat infiltration in paraspinal muscle more relevant than IVD degeneration in generating cLBP
- Fat infiltration in multifidus and erector spinae highly associated with IVD degeneration
- Greater stress on the spine

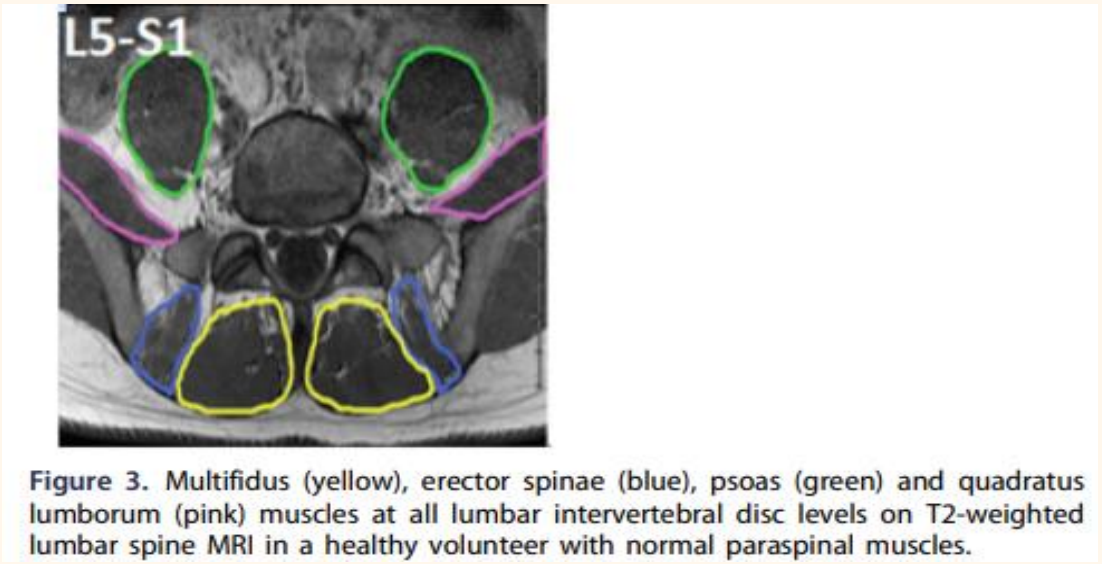
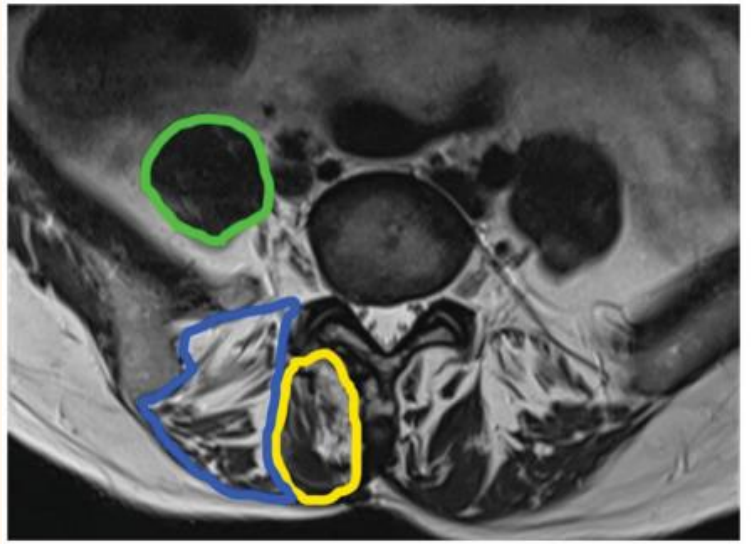


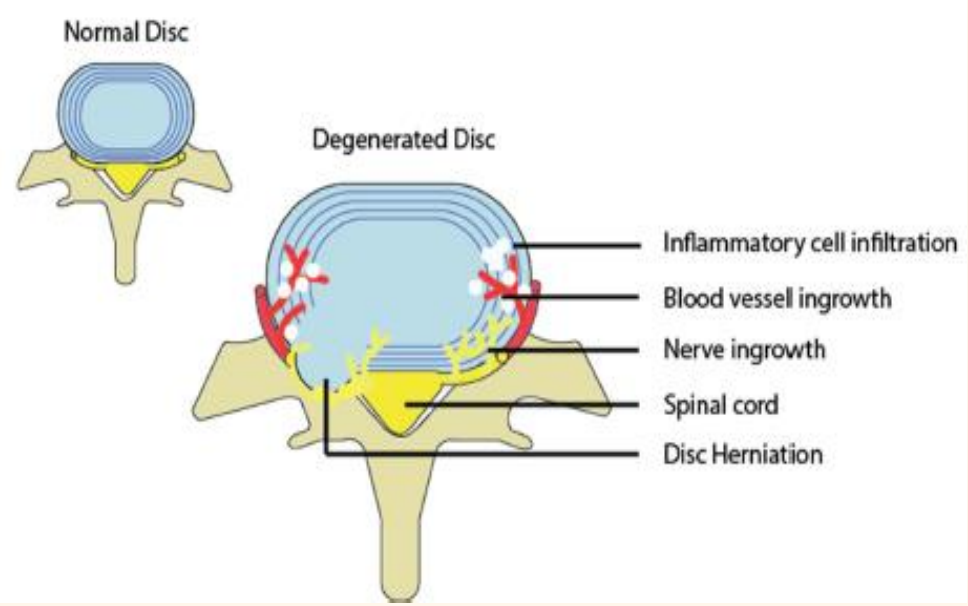
Figure 3. Multifidus (yellow), erector spinae (blue), psoas (green) and quadratus lumborum (pink) muscles at all lumbar intervertebral disc levels on T2-weighted lumbar spine MRI in a healthy volunteer with normal paraspinal muscles.



Özcan-Eksi et al. Br. J. Neurosurg. 2021

Chronic LBP pathophysiology: IVD Degeneration

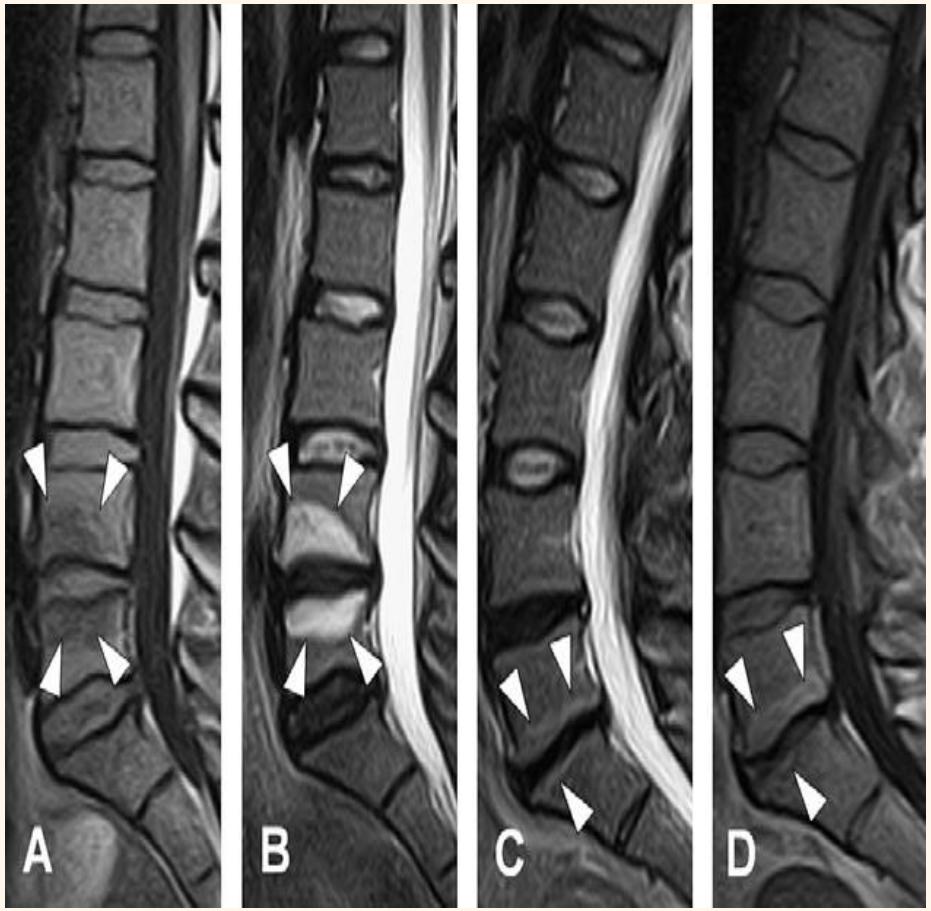
- Irreversible process: matrix degeneration, NP proteoglycan and hydration loss, destructuration and reduced disc height
- Bending loads (by ligament damage and misalignment) put extra pressure on endplates and annulus → disc prolapse and cell-mediated degenerative changes.
- Further mechanical load can lead to calcification of endplates
- Structural and material changes induce ingrowth of nerves and blood vessels within the disc, which produces painful nerve signals
- Modest association between IVD and LBP



Mosabbir, A. Life 2023

Back pain and bone edema: what relationship?

- Vertebral subchondral bone edema common in LBP (18-58%)
- Pathogenetic hypotheses: mechanical and bacterial
- Modic
  - Type 1 (hypoT1, hyperT2): fibrovascular tissue (bone edema) – painful, can evolve into type 2 or decrease
  - Type 2 (hyperT1-T2): Yellow (adipose) marrow, usually shrinks
  - Type 3 (hypoT1-T2): vertebral plate osteosclerosis



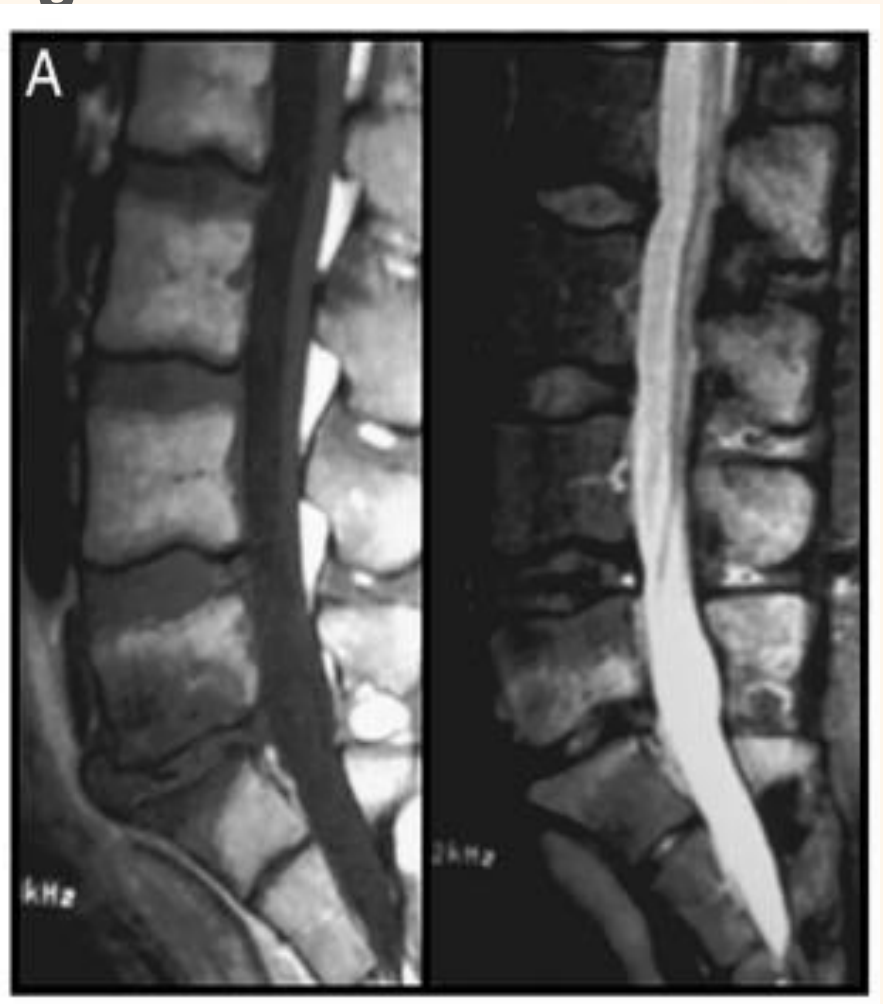
Albert HB et al. Med Hypotheses 2008

Serum biomarkers in cLBP and Modic 1 changes

- Late 1980s: changes of vertebral endplate subchondral bone adjacent to degenerative disc disease on MRI
- Modic 1 changes associated with clinical and laboratory signs ("active discopathy" – inflammatory-like)

Table 1 Modic classification: MRI changes and associated pathological features

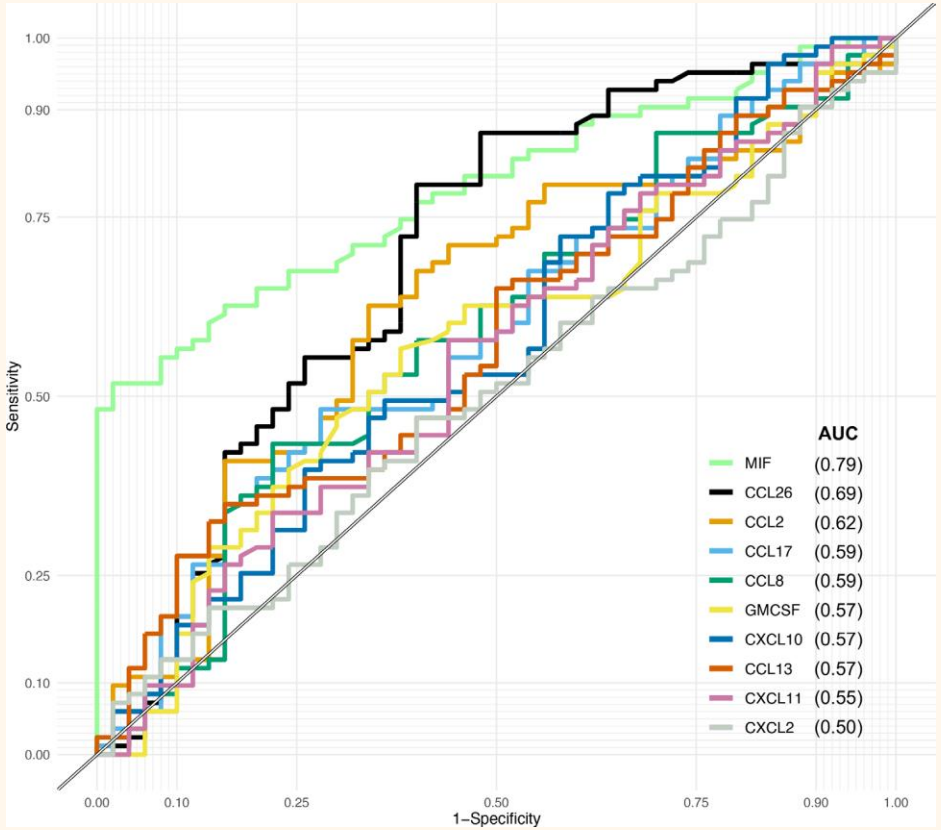
Vertebral endplates	T1-weighted sequences	T2-weighted sequences	Histopathology
Modic 1	Hyposignal	Hypersignal	Oedema, inflammation
Modic 2	Hypersignal	Isosignal or hypersignal	Fatty changes
Modic 3	Hyposignal	Hyposignal	Fibrous process



Nguyen C. et al. Ann Rheum Dis 2015

Serum biomarkers in cLBP and Modic 1 changes

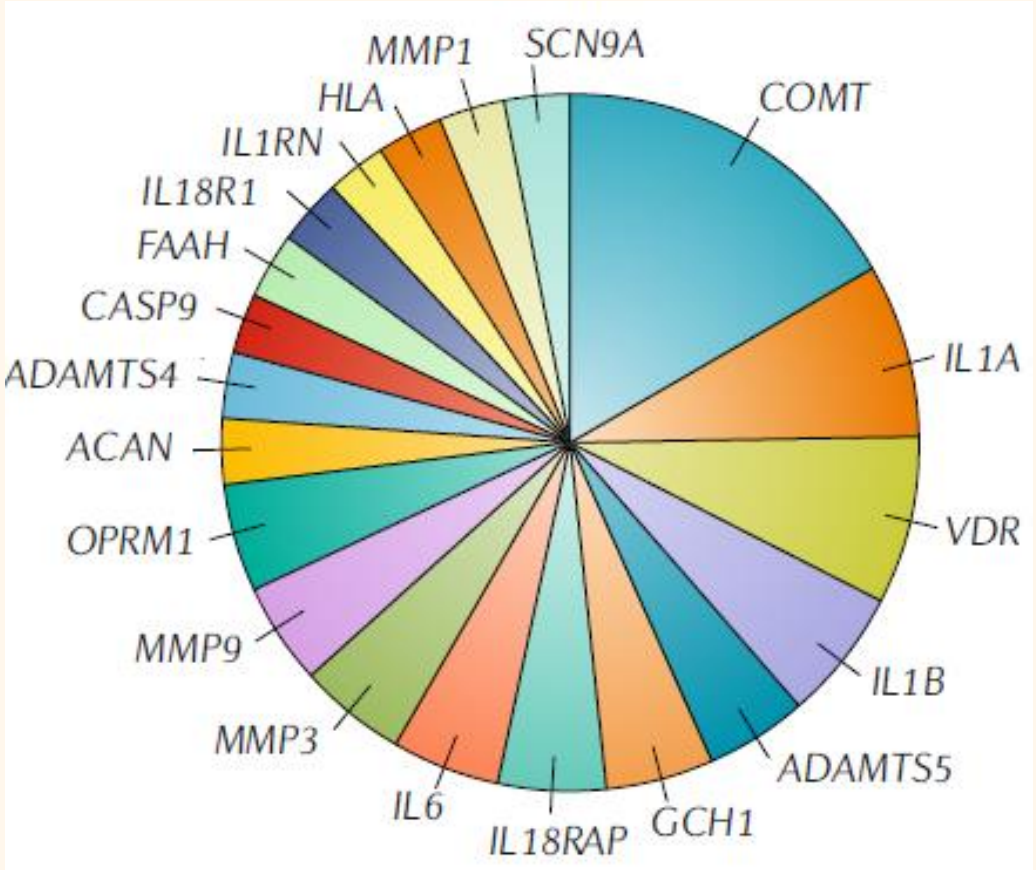
- No significant contribution of cytokines except for Macrophage migration inhibitory factor (MIF) as promising biomarker of LBP subgroups with Modic type 1



Boisson et al. Sci Rep 2019
Gjefsen E et al. RMD Open 2021

Low back pain: genetics

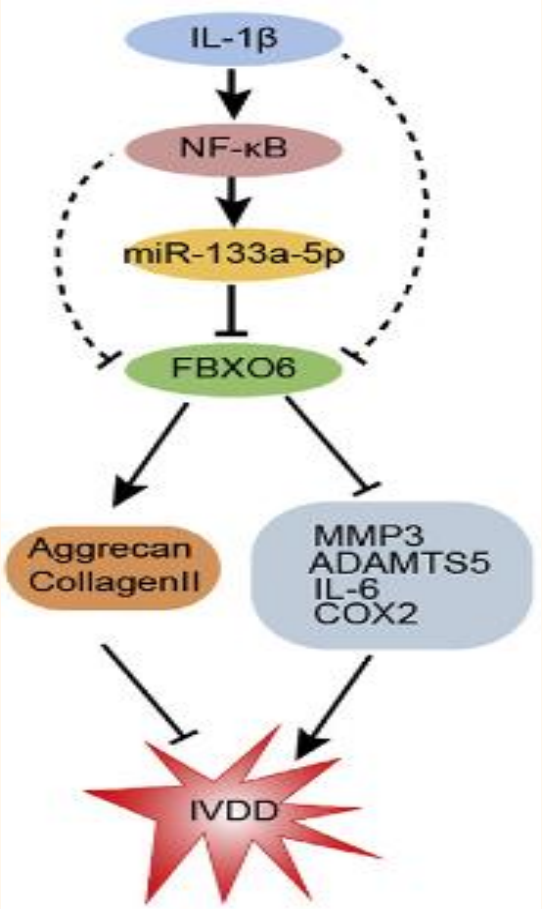
- Inheritance 32-44% from twin studies, associated with Modic (endplate) changes
- Heritability based on genetic variants drops to 7%, linked to IVD degeneration
- Group of genes associated with pain intensity and disc degeneration do not overlap (distinct pathophysiological mechanisms?)



Vlaeyen JWS et al. Nat Rev Dis Primers. 2018

From acute to cLBP: Epigenetics miR-regulated

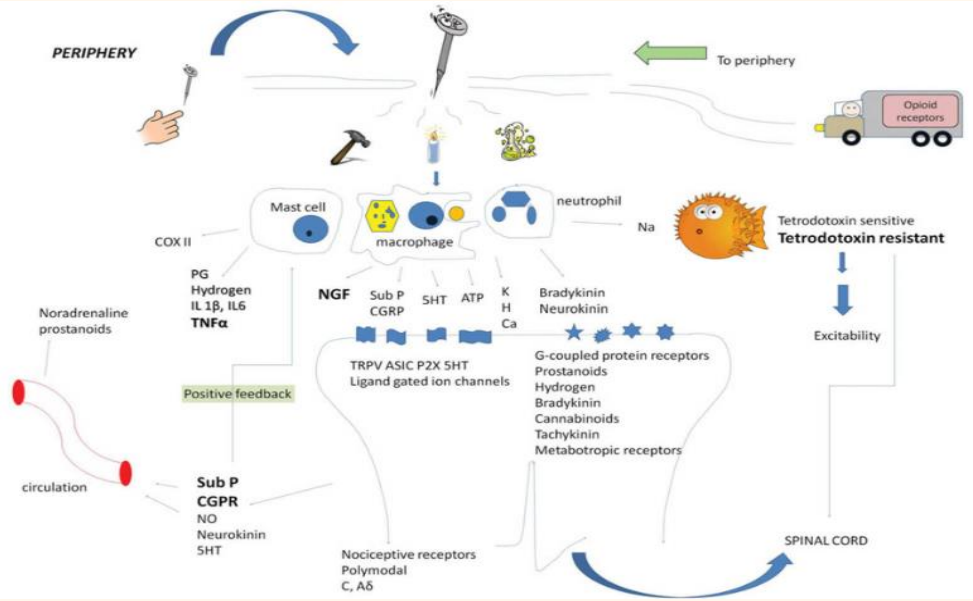
- miR-133a-5p expression aggravates IVD degeneration inhibiting FBXO6, highly expressed in healthy discs
- miR124 putative biomarker: upregulation associated with therapy response (multidisciplinary)
  - Involved in synaptic plasticity
  - One of most important miRNAs regarding psychological disorders
  - "Negotiator" between nervous and immune system (alterations of neuroglia and brain-peripheral signaling)

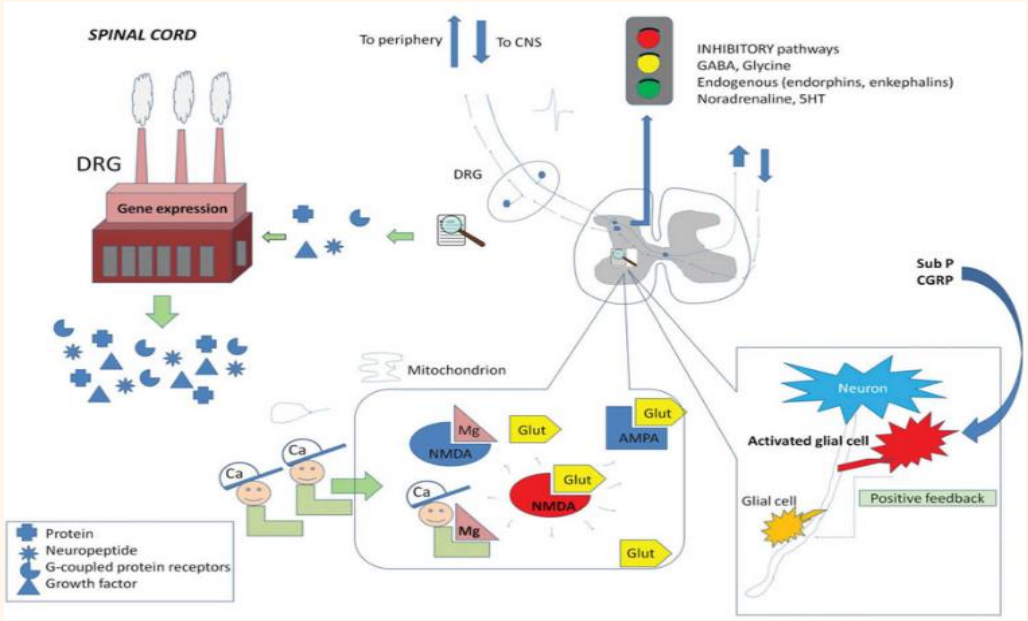


Luchting, B. et al. Spine 2017
Du, X.F. Et al. J. Orthop. Transl. 2021

Transition from Acute to Chronic Pain

- Morphology and function of CNS changes
- Begins due to acute persistent nociceptive stimulation with chronic inflammation of peripheral nerves (peripheral sensitization)
- In spinal cord, changes in DRG, dorsal horn neurons and glial cells (more excitable - 'wind-up'- central sensitization)



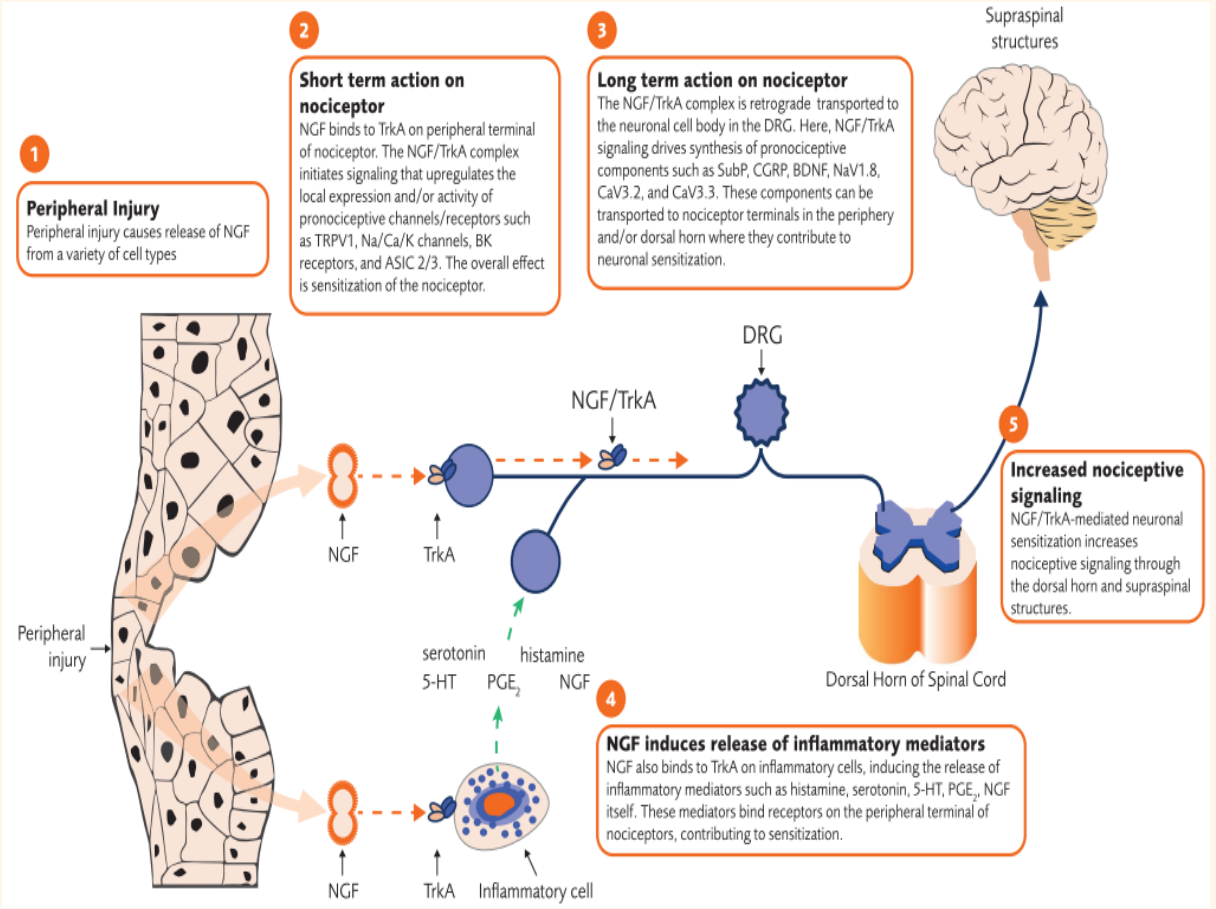


Feizerfan, A. et al. Contin. Educ. Anaesth. Crit. Care Pain 2015

Transition from Acute to Chronic Pain

Table 3 | Potential pain biomarkers used in clinical trials

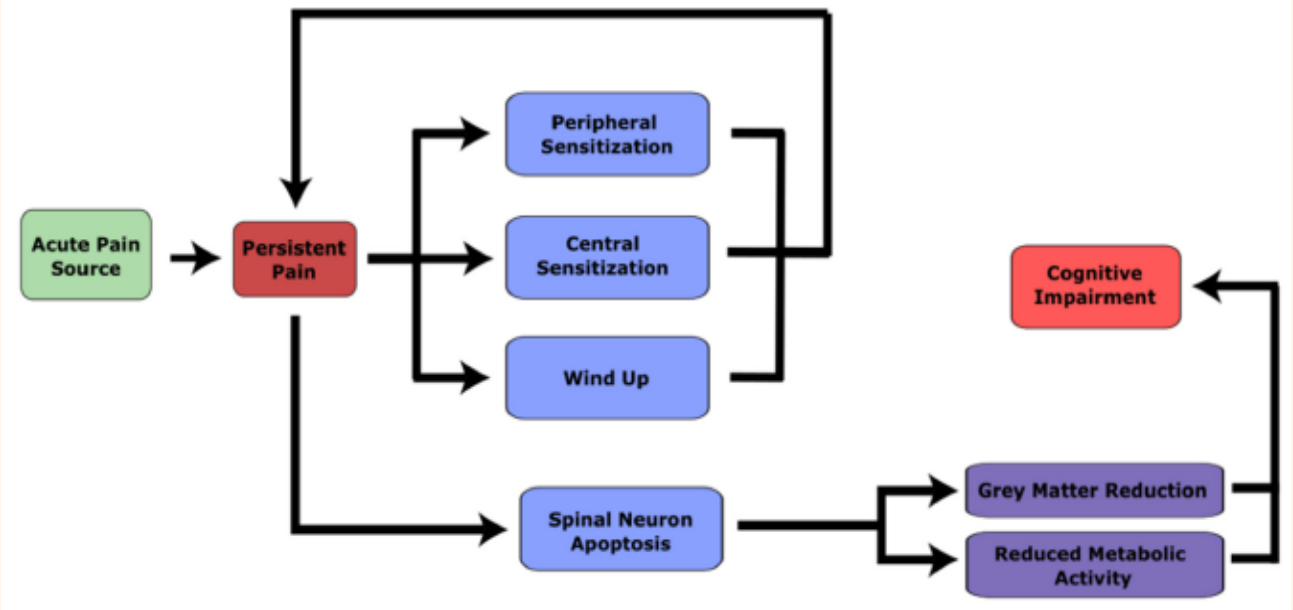
Pain disease state	Biomarker	Correlation to disease	Correlation with pharmacodynamic outcome	Correlation with pain state	Clinical efficacy shown
Rheumatoid arthritis and neuropathic pain	CCL concentration in cerebrospinal fluid and plasma	CCL in neuropathic pain	Highly efficient antagonism of CCR2	No	No[236,237]
Inflammatory pain	TRPV expression	TRPV elevated	TRPV antagonism leads to reduction in inflammation	Yes	No[238,239]
Chronic back pain	Nerve growth factor	High	High	Yes	Yes[240]
Migraine	CGRP concentration	Elevated in disease state	Yes	Yes	Yes[241]
Neuropathic pain	Resting-state functional connectivity, temporal summation of pain	No specific correlation	Unknown	Yes	Yes[148]
Painful diabetic neuropathy	Conditioned pain modulation	No specific correlation	Yes	Yes	Yes[242]
Migraine, fibromyalgia (nociplastic pain)	Conditioned pain modulation	Poor conditioned pain modulation capacity	Yes	Yes	Yes[183,243–245]



Davis KD et al. Nat Rev Neurol. 2020
Schmelz M et al. Pain. 2019

Transition from Acute to Chronic LBP: Neurodegenerative changes

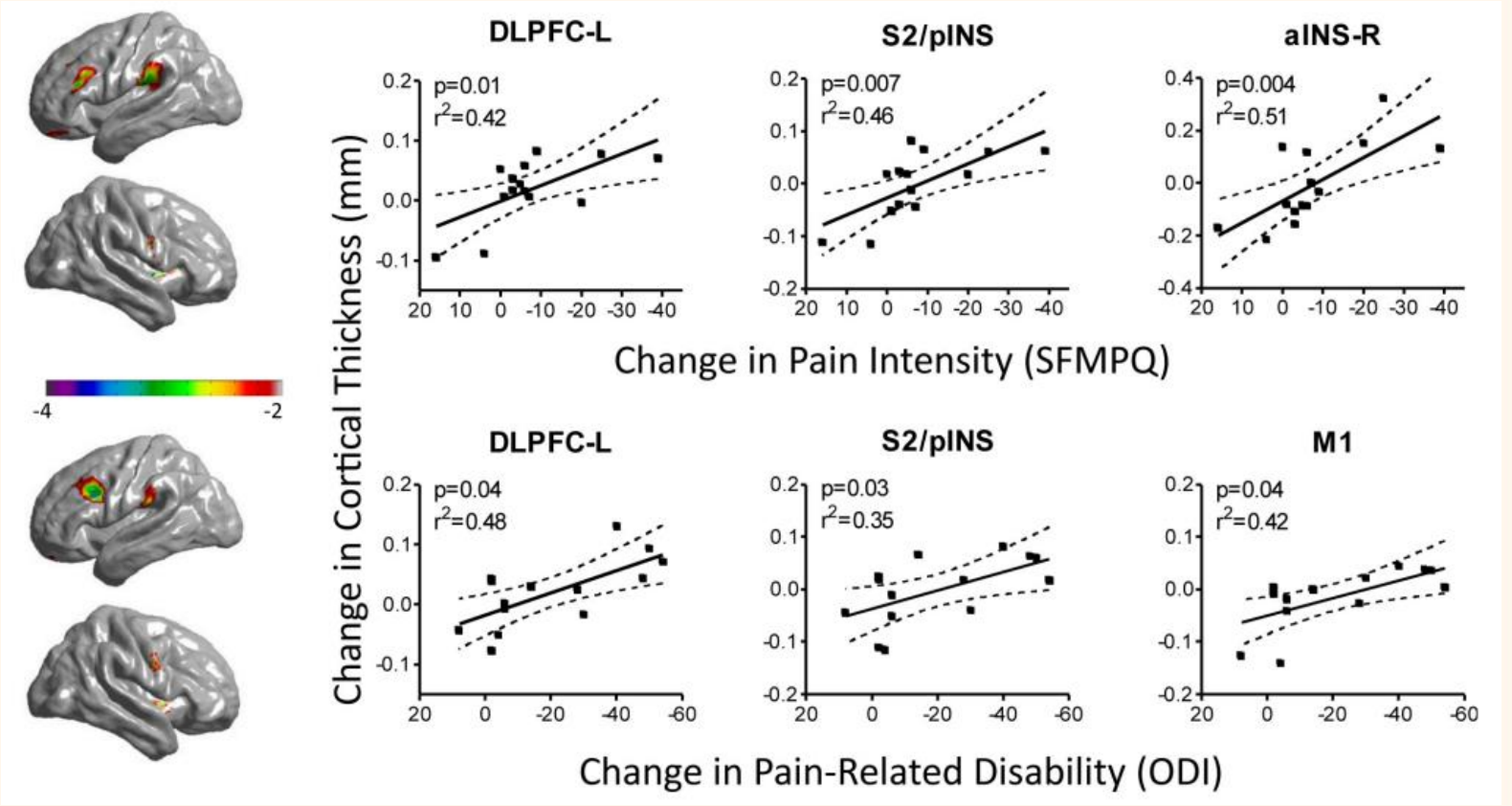
- Abnormal oscillatory activity in thalamo–cortico–thalamo loops (thalamocortical dysrhythmia) hallmark for chronic pain
- Reduced NAc and functional connectivity between mPFC and NAc biomarkers of "chronification"
- Amygdala morphology biomarker of resilience to persisting pain (larger in resilient)
- Total volume of grey matter negatively correlated with years lived with cLBP (cortical volume loss by 1.5 cm^3 vs that aging-associated) - Accelerated brain aging and cognitive impairment



Zhang Z et al. Front. Neurol. 2022
Asada M et al. Pain 2022

Chronic LBP as neurodegenerative disorder?

- Grey matter reduction potentially reversible with successful treatment.
- After 6 months of treatment of FJ injections, patients with pain relief showed greater cortical thickness in DLPFC and motor cortex



Seminowicz, D.A et al. J. Neurosci. 2011

Low back pain: key issues

- Majority of patients have NSLBP (unidentified underlying disease/nociceptive stimulus)
- Initial intensity, spread across multiple locations, and psychological distress increase the risk of disability
- Biopsychosocial model: Biological factors with modest effects interact with other RFs contributing to chronicity
  - ➢ Nonbiological RFs: Negative expectations about pain, emotional responses, pain-related behaviors, impaired perception of the relationship between pain, health, work, and social barriers.

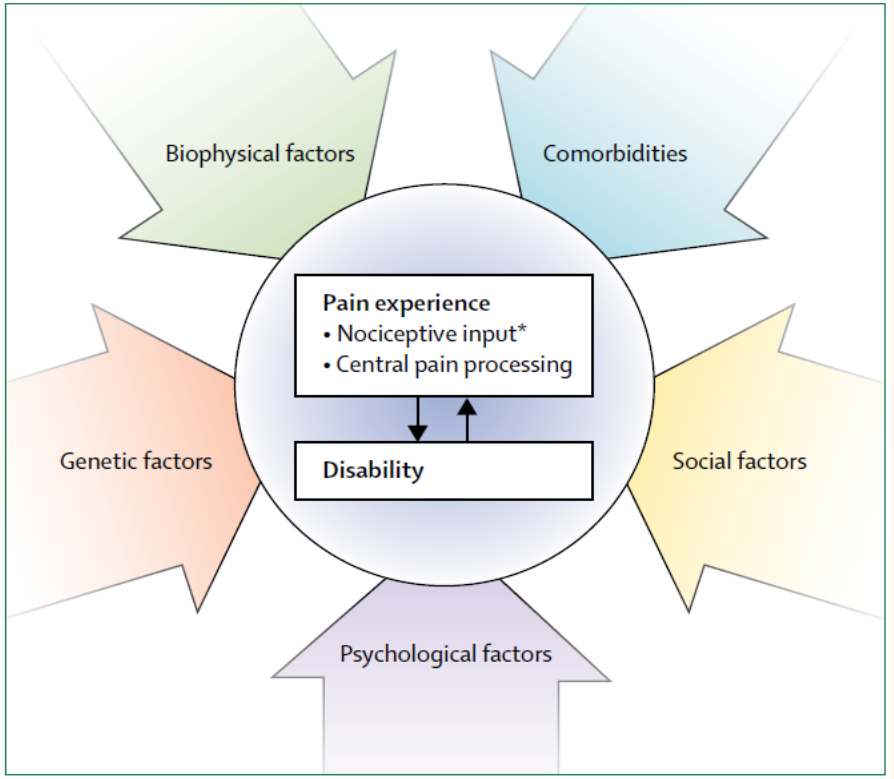


Figure 1: **Contributors to low back pain and disability**
The model includes key contributors to low back pain and disability but does not attempt to represent the complex interactions between different contributors. *Nociceptive input includes non-identifiable sources in non-specific low back pain, neurological sources (eg, radicular pain) and specific pathology (eg, fractures).

Hartvigsen J et al. Lancet. 2018

Low back pain: diagnostic pitfalls and risk factors for chronicization

- In addition to red flags, other prognostic factors to consider:
  - Orange Flag (psychiatric) – Mood disorders
  - Yellow (cognitive-behavioral, emotional-affective) – unhelpful beliefs about pain
  - Blue (work related) – too onerous and workmates unsupportive
  - Black (related to social context) - litigation
  - White (future?): Recommendations from healthcare professionals that reflect their own expectations of LBP, not necessarily the patients' clinical and occupational conditions

Table 1 | **'Flag' model of low back pain**

Flag	Nature	Examples
Red	Alerting features that when present raise suspicion of serious pathology	• New bladder or bowel dysfunction (possible cauda equina syndrome) • Intravenous drug use, fever or recent infection (possible spinal infection) • Previous history of cancer (possible vertebral metastases)
Orange	Psychiatric symptoms	• Clinical depression • Personality disorder
Yellow	Beliefs, appraisals and judgements	• Unhelpful beliefs about pain: indication of injury as uncontrollable or likely to worsen • Expectations of poor treatment outcome • Delayed return to work
	Emotional responses	• Distress not meeting criteria for diagnosis of mental disorder • Worry • Fears • Anxiety
	Pain behaviour (including pain coping strategies)	• Avoidance of activities due to expectations of pain and possible re-injury • Over-reliance on passive treatments, such as hot packs, cold packs and analgesics
Blue	Perceptions about the relationship between work and health	• Belief that work is too onerous and likely to cause further injury • Belief that workplace supervisor and workmates are unsupportive
Black	System or contextual obstacles	• Legislation restricting options for return to work • Conflict with insurance staff over injury claim • Overly solicitous family and health-care providers • Heavy work, with little opportunity to modify duties

Flags refer to potential risk factors for the development of persistent pain and associated disability: these are suspicion of serious biological pathology (red flags); psychiatric symptoms that probably require specialist mental health referral (orange flags); psychological risk factors, such as fears and unhelpful beliefs (yellow flags); workers' perceptions that their workplace is stressful, unsupportive and excessively demanding (blue flags); and observable characteristics of the workplace and nature of the work as well the insurance and compensation system under which workplace injuries are managed (black flags). Adapted with permission from REF.[116], Oxford University Press.

Vlaeyen JWS et al. Nat Rev Dis Primers. 2018

Low back pain: validated screening tools for chronicization

- To be administered during the first visit for acute LBP
- Örebro Musculoskeletal Pain Screening Questionnaire (ÖMPSQ) and STarTBack tool
  - ➢ Assess psychological and social factors, pain duration, emotional distress, fear avoidance beliefs, self-perceived functioning, and expected return to work
- ÖMPSQ: Risk of future work absenteeism due to pain (>50/100)
- STarTBack (NICE): function
  - Stratification into low, medium, and high risk of pain-related disability

Örebro Musculoskeletal Pain Screening Questionnaire (Short)

Name: _____ **Date of Birth:** _____

Are you: ☐ Male ☐ Female

1. How long have you had your current pain problem? Tick (√) one.
☐ 0-1 weeks [1] ☐ 1-2 weeks [2] ☐ 3-4 weeks [3] ☐ 4-5 weeks [4] ☐ 6-8 weeks [5]
☐ 9-11 weeks [6] ☐ 3-6 months [7] ☐ 6-9 months [8] ☐ 9-12 months [9] ☐ over 1 year [10]

2. How would you rate the pain that you have had during the past week? Circle one.
0 1 2 3 4 5 6 7 8 9 10
No pain *Pain as bad as it could be*

Please circle the one number which best describes your current ability to participate in each of these activities.

3. I can do light work for an hour. 10-x
0 1 2 3 4 5 6 7 8 9 10
Can't do it because of the pain problem *Can do it without pain being a problem*

4. I can sleep at night. 10-x
0 1 2 3 4 5 6 7 8 9 10
Can't do it because of the pain problem *Can do it without pain being a problem*

5. How tense or anxious have you felt in the past week? Circle one.
0 1 2 3 4 5 6 7 8 9 10
Absolutely calm and relaxed *As tense and anxious as I've ever felt*

6. How much have you been bothered by feeling depressed in the past week? Circle one.
0 1 2 3 4 5 6 7 8 9 10
Not at all *Extremely*

7. In your view, how large is the risk that your current pain may become persistent?
0 1 2 3 4 5 6 7 8 9 10
No risk *Very large risk*

8. In your estimation, what are the chances you will be working your normal duties in 3 months 10-x
0 1 2 3 4 5 6 7 8 9 10
No chance *Very Large Chance*

Here are some of the things which other people have told us about their pain. For each statement please circle one number from 0-10 to say how much physical activities, such as bending, lifting, walking, or driving affect your pain.

9. An increase in pain is an indication that I should stop what I'm doing until the pain decreases.
0 1 2 3 4 5 6 7 8 9 10
Completely disagree *Completely agree*

10. I should not do my normal work with my present pain.
0 1 2 3 4 5 6 7 8 9 10
Completely disagree *Completely agree*

SUM:

Strumento di screening Keele StarT Back (www.keele.ac.uk/sbt)

Nome e cognome del paziente:_____
Data:_____

Pensando alle **ultime due settimane**, metta una crocetta alle risposte delle seguenti domande:

	Non d'accordo 0	D'accordo 1
1. Il dolore alla schiena **si è diffuso nella/e gamba/e** nelle ultime 2 settimane	☐	☐
2. Talvolta, nelle ultime 2 settimane, ho percepito dolori alla **spalla** o al **collo**	☐	☐
3. Ho **camminato solo per brevi distanze** a causa del dolore alla schiena	☐	☐
4. Nelle ultime 2 settimane, mi sono **vestito/a più lentamente** del solito a causa del dolore alla schiena	☐	☐
5. Per una persona nelle mie condizioni, non è molto sicuro essere attivo fisicamente	☐	☐
6. Spesso mi sono venuti in mente **dei pensieri preoccupanti**	☐	☐
7. Ho la sensazione che il **dolore alla schiena sia insopportabile** e che **non migliorerà mai**	☐	☐
8. In generale, **non provo piacere** a fare le cose che di solito mi piacevano	☐	☐

9. Complessivamente, quanto è stato **fastidioso** il suo dolore alla schiena nelle **ultime 2 settimane**?

Per niente	Un poco	Moderatamente	Parecchio	Estremamente
☐ 0	☐ 0	☐ 0	☐ 1	☐ 1

Punteggio totale: **Sub punteggio:**

Basso= punteggio totale 0-3

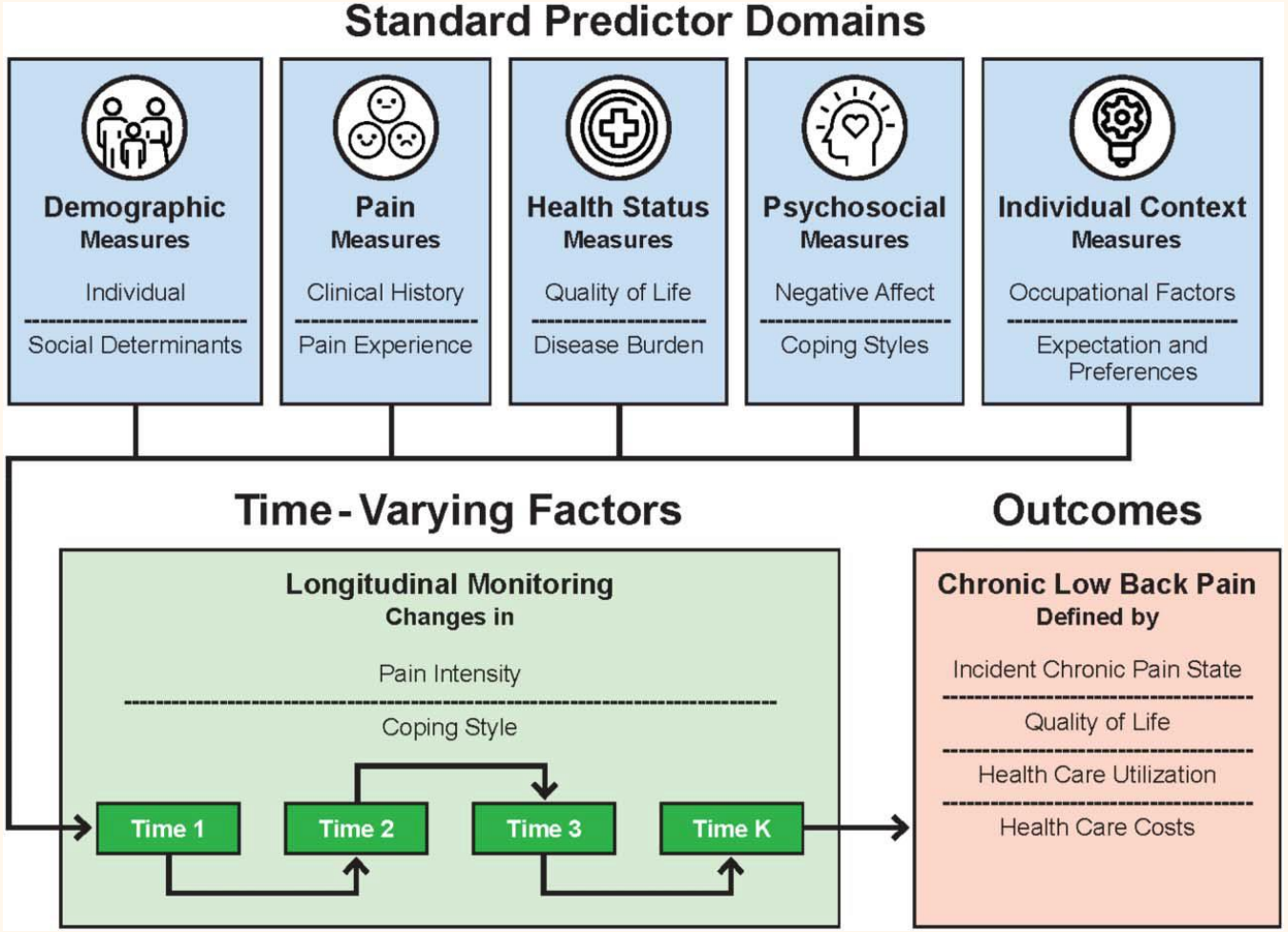
Alto= punteggio totale 4-5

Medio= il resto

Vlaeyen JWS et al. Nat Rev Dis Primers. 2018

Transition from Acute to Chronic LBP: framework for prediction

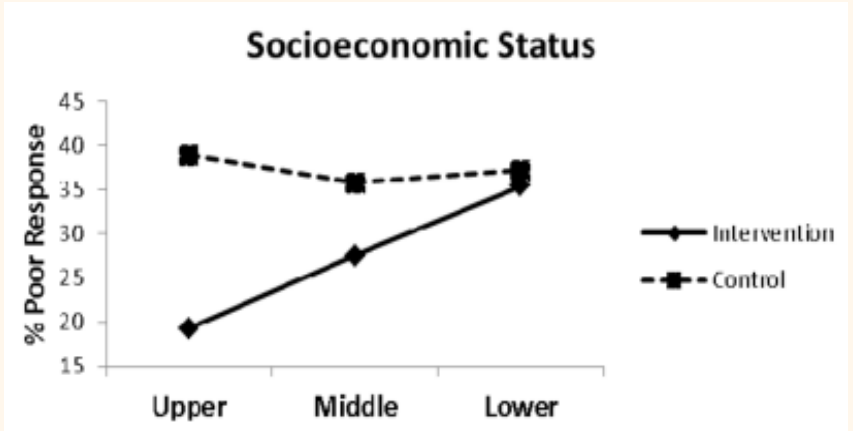
- Both modifiable (and direct treatment targets, e.g., baseline pain intensity), as well as nonmodifiable factors for treatments tailoring (e.g., age, gender)
- Must be pragmatic for capture using electronic health record, and not greatly increase patient or provider burden.
- Minimum set of variables for each domain

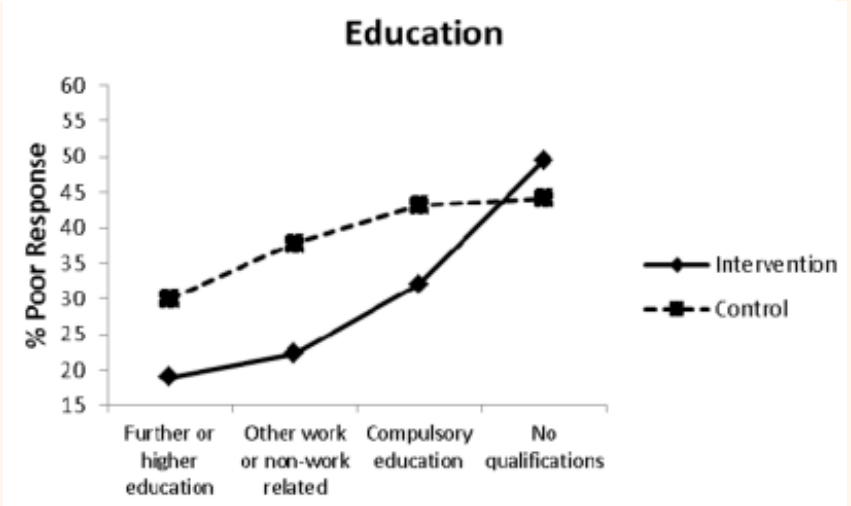


SZ George et al. Pain Rep 2020

From Acute to Chronic LBP: framework domains

- Social
  - Medicaid coverage predicts poor LBP outcomes
  - Lower education and income decreased efficacy of psychological interventions for LBP
- Pain
  - Multiple sites predictor of poor LBP outcomes
- Health status
  - Lower comorbidity protective vs persistent pain at 1-year after physical therapy
- Psychosocial: negative (eg, fear avoidance, catastrophizing) and positive (eg, self-efficacy, acceptance) coping
- Individual context: occupational factors (eg, job satisfaction, perceived work stress).





SZ George et al. Pain Rep 2020
Katzan IL et al. Spine J 2019

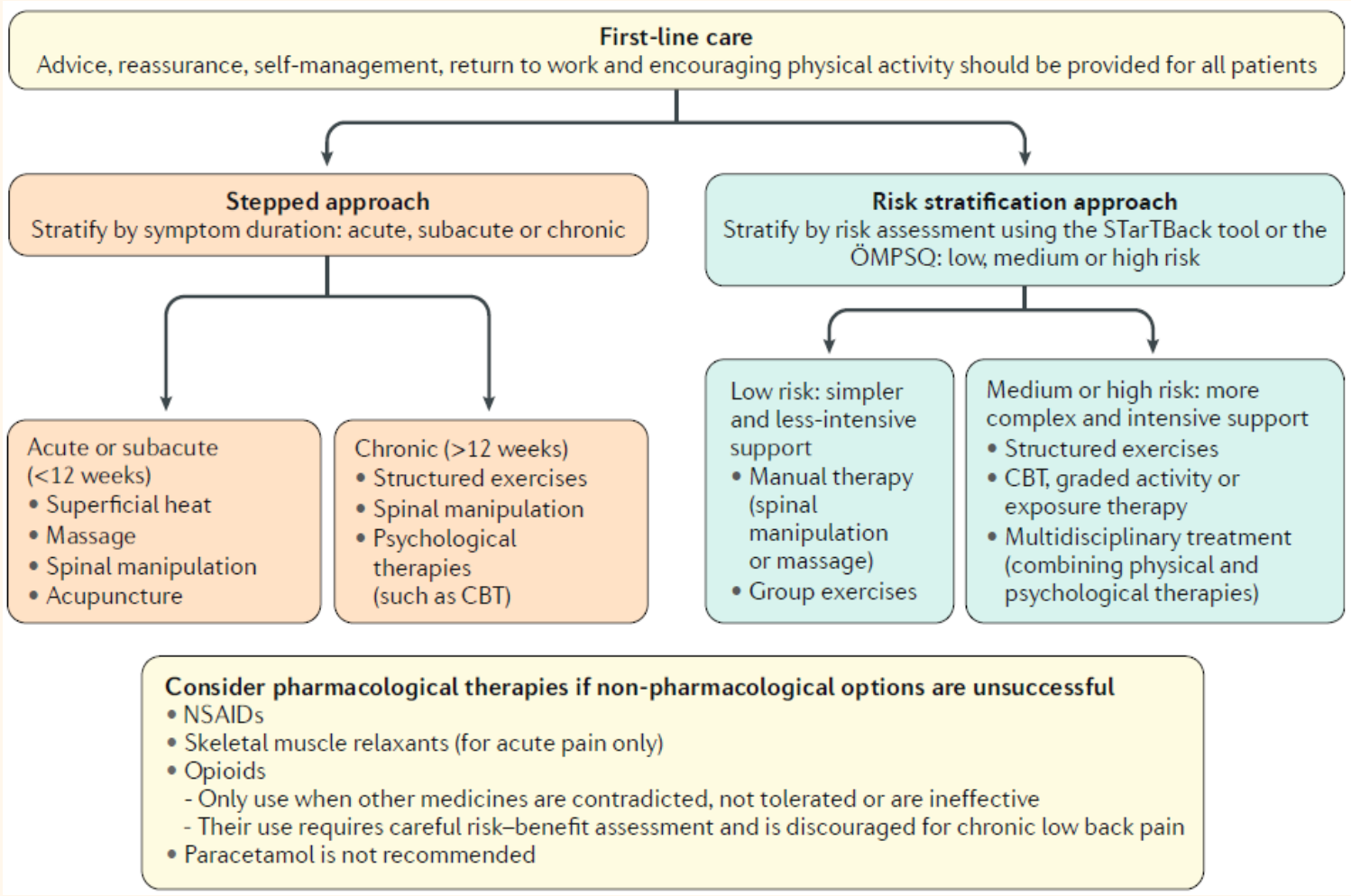
From Acute to Chronic LBP

- 40 items (many derived from validated questionnaires, STarTBack tool)
- Time-varying factors (longitudinal monitoring): more accurately determine risk status, with care options adjusted in real time.

NIH LBP task force	Predictor domains					Outcome domains			
Minimal data set item	Demographic	Pain	Health status	Psychosocial	Context	Pain states	Quality of life	Care utilization	Care costs
1. How long has low back pain been an ongoing problem for you?		X				X			
2. How often has low back pain been an ongoing problem for you over the past 6 months?		X				X			
3. In the past 7 days, how would you rate your low back pain on average?		X				X			
4. Has back pain spread down your leg(s) during the past 2 weeks		X							
5. During the past 4 weeks, how much have you been bothered by…			X						
6. Have you ever had a low back operation?		X						X	X
7. If yes, when was your last back operation?		X						X	X
8. Did any of your back operations involve a spinal fusion? (also called an arthrodesis)		X						X	X
9. In the past 7 days, how much did pain interfere with your day-to-day activities?			X				X		
10. In the past 7 days, how much did pain interfere with work around the home?			X				X		
11. In the past 7 days, how much did pain interfere with your ability to participate in social activities?			X				X		
12. In the past 7 days, how much did pain interfere with your household chores?			X				X		
13. Have you used any of the following treatments for your back pain? (Check all that apply)		X						X	X
14. I have been off work or unemployed for 1 month or more due to low back pain.					X				
15. I receive or have applied for disability or workers' compensation benefits because I am unable to work due to low back pain.					X				
16. Are you able to do chores such as vacuuming or yard work?			X						
17. Are you able to go up and down stairs at a normal pace?			X						
18. Are you able to go for a walk of at least 15 minutes?			X						

From Acute to Chronic LBP: management

- Early and accurate prediction allow for efficient distribution of health care resources at the initial point of care
  - ➢ Dramatic effects on downstream pain-related outcomes, health care utilization, and costs
  - ➢ Could reduce uncertainty on optimal LBP management strategies (pharmacological and nonpharmacological options very similar treatment effects)



Vlaeyen JWS et al. Nat Rev Dis Primers. 2018

Take home message

- Biomarkers play an important role in decision-making for many conditions, including cLBP
- Ability to predict the transition from acute LBP is limited by current understanding of the underlying mechanisms and its complexity (unlikely to be a single biomarker for cLBP development)
- Clinically useful tools are more likely to be composite biomarkers that consist of several measurements.
- More complex testing (MRI or EEG) provides specific information about the pathways involved in cLBP, but application to everyday practice is limited and confounded by other factors