The Science and Mystery of CRPS

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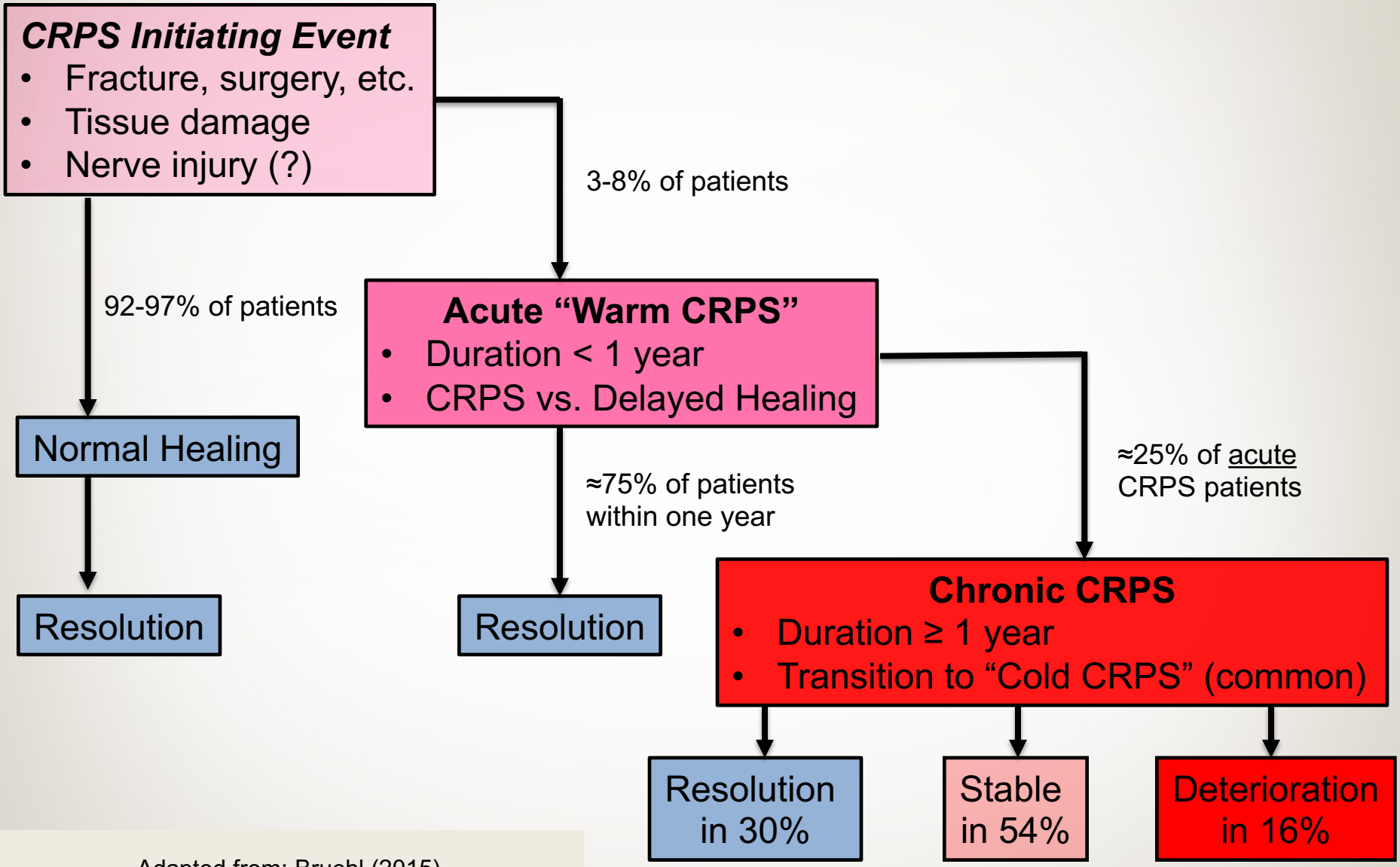
Natural History of CRPS



Adapted from: Bruehl (2015)

Is There a "Test for CRPS"?

- 2018 review paper:
  - No definitive CRPS test
  - Multiple potentially useful biomarkers
- 2019 Valencia Meeting – Possible biomarkers:
  - Degradation of Bradykinin (inflammatory mediator)
  - Osteoprotegerin (bone turnover marker)
  - IgG and IgM (immune marker)
  - microRNAs (miR-223, miR-338, and miR-548d)
  - NOT cytokines, bone scan, sensory testing, etc.

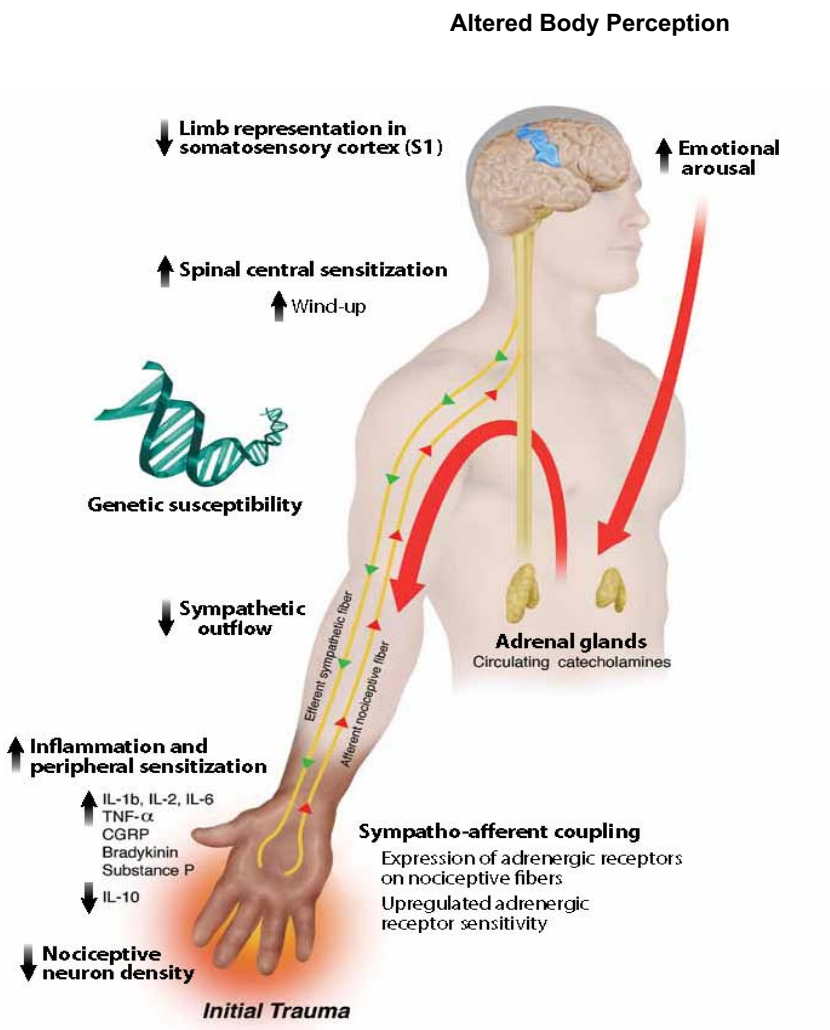
Who is At Risk for CRPS?

- "High CRPS risk" profile:
  - **High acute pain intensity following injury**
    - **Support from multiple prospective studies**
  - Female (3-4 times more common)
  - Middle-aged (≈50-70 years old)
  - Fracture (>40% of cases)

Who is At Risk for CRPS?

- Psychological factors are not a consistent predictor
  - CRPS is not a "psychogenic" condition
  - Theoretical model for psych-CRPS links
- Multiple studies show emotional distress has a stronger impact on CRPS pain than in other chronic pain conditions
  - Reflects physiology
  - Does NOT indicate pain is "all in your head"

CRPS Mechanisms Are Complex



<u>Big Question</u>:
***Cause* CRPS vs.**
***Associated with* CRPS?**

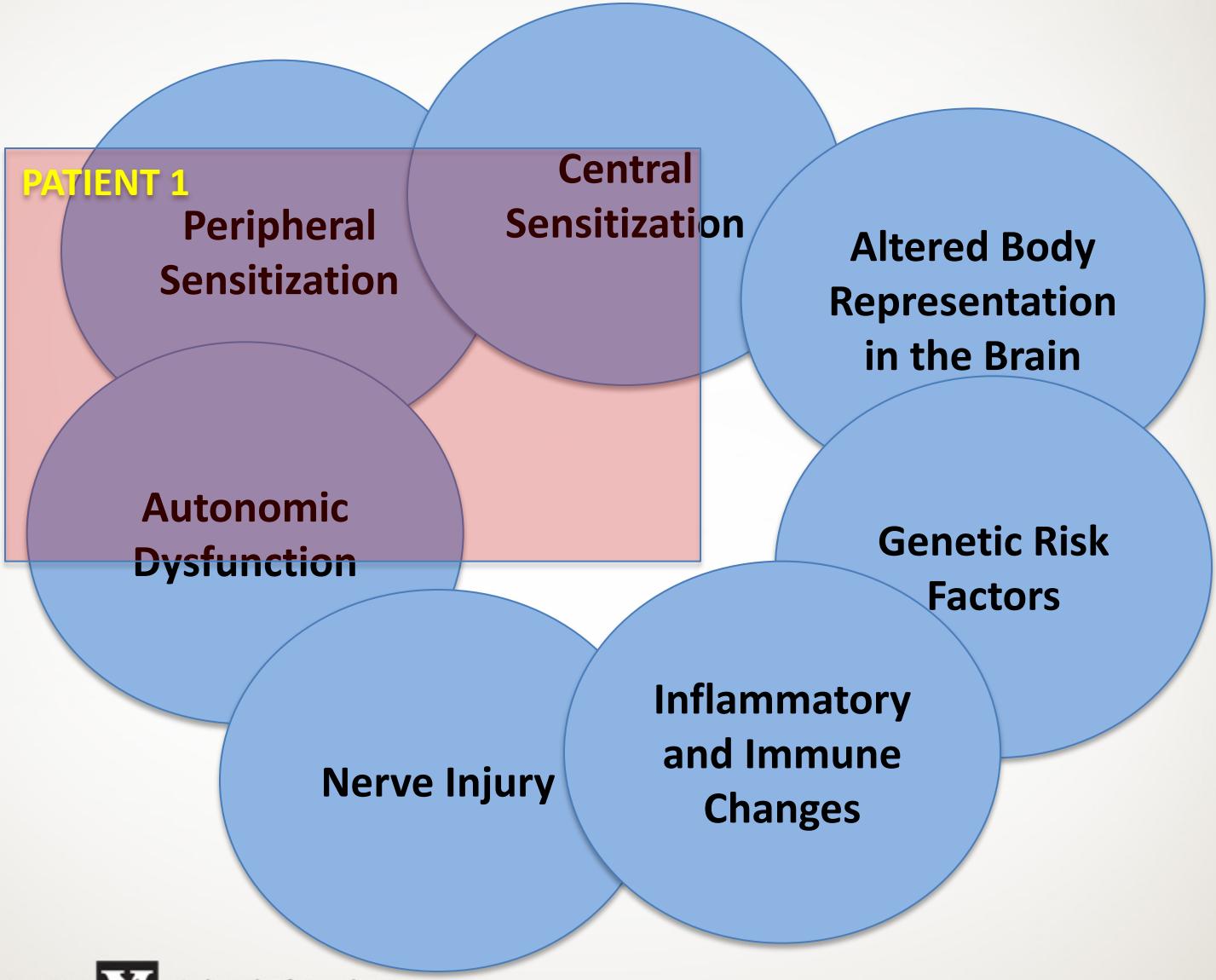
Animal models can address causation (e.g., support for inflammatory factors)

Bruehl, 2010; 2015

QUESTION:

Why is it so hard to make progress in treatment of CRPS?

Patient Meets Budapest Criteria…



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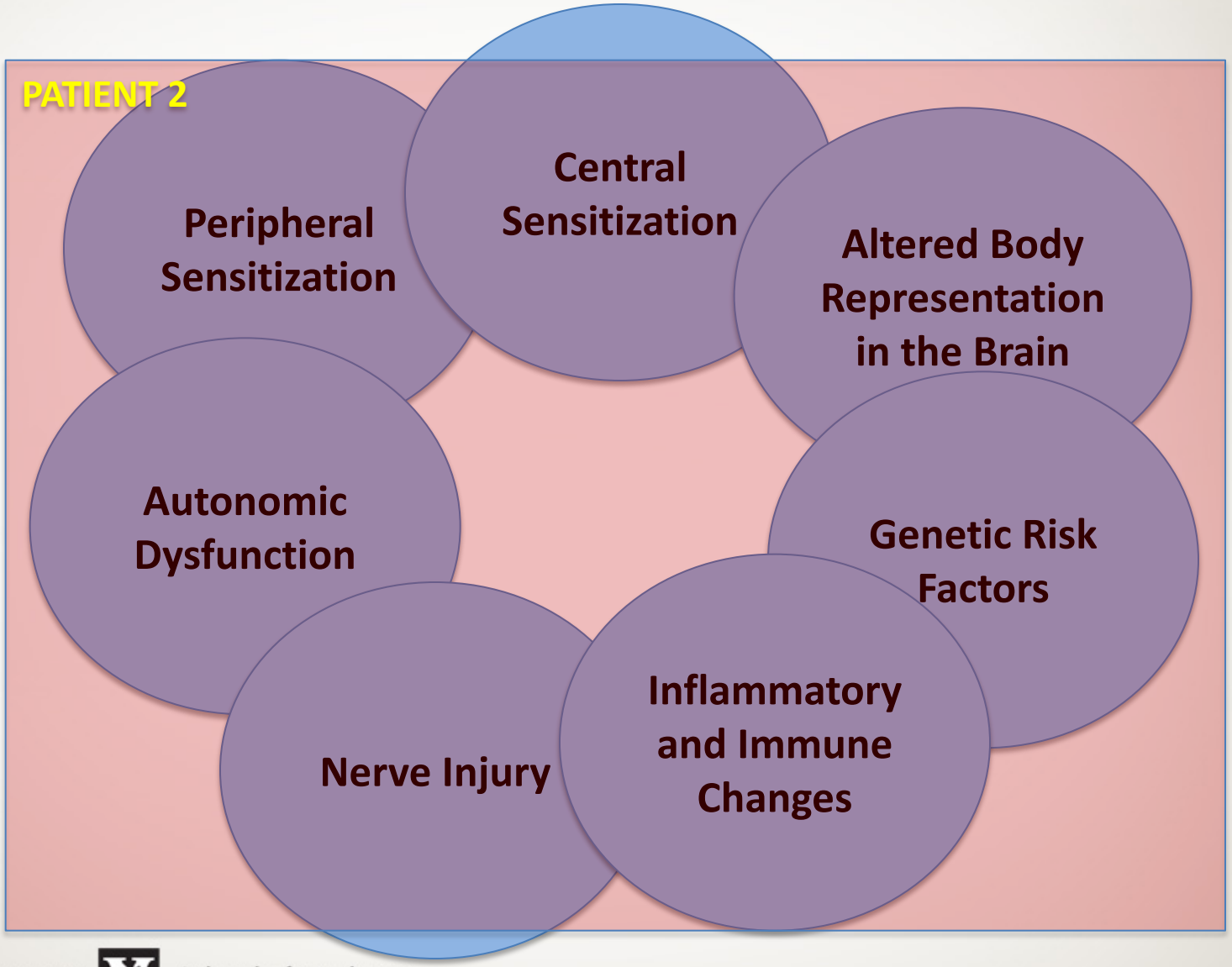

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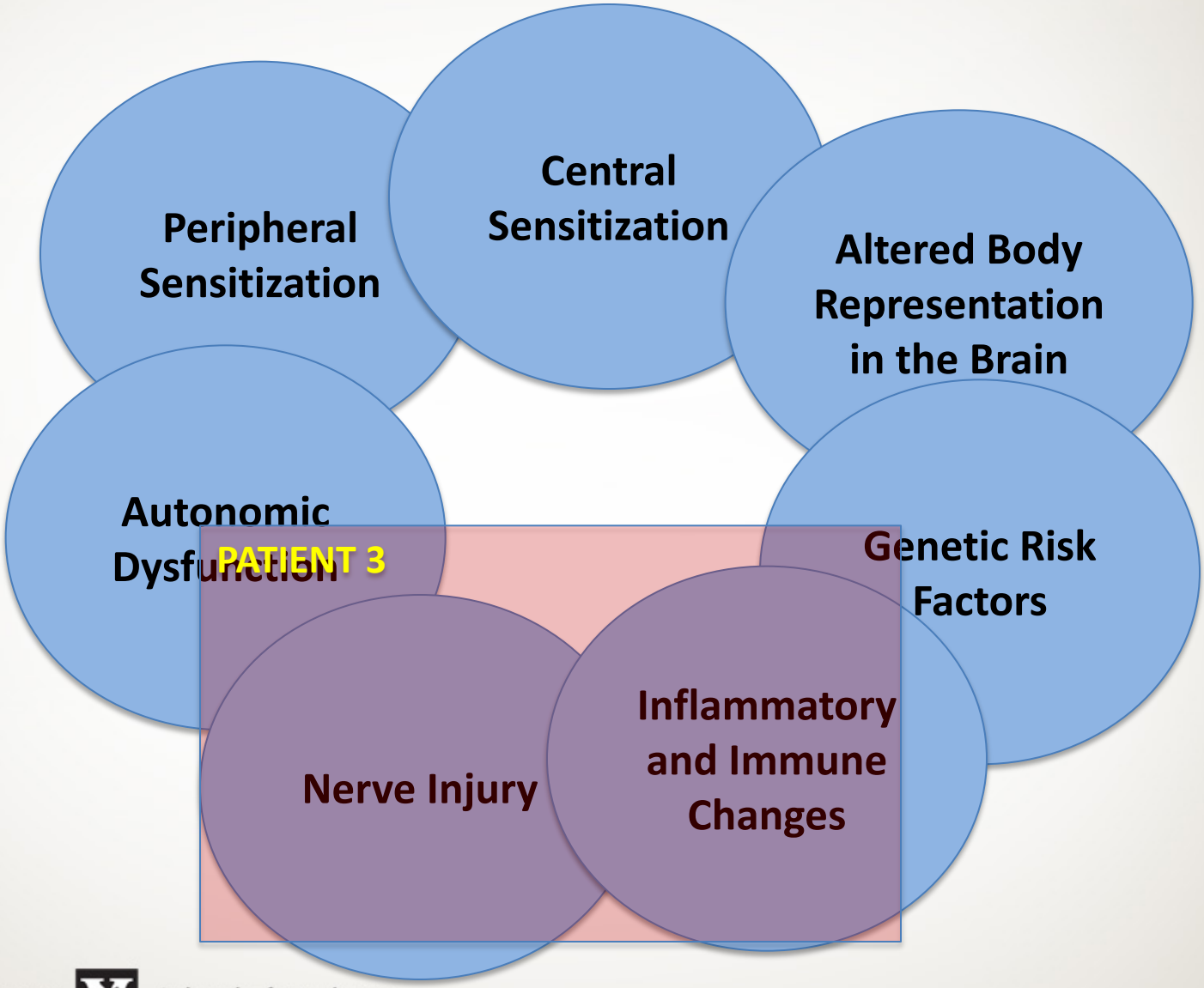

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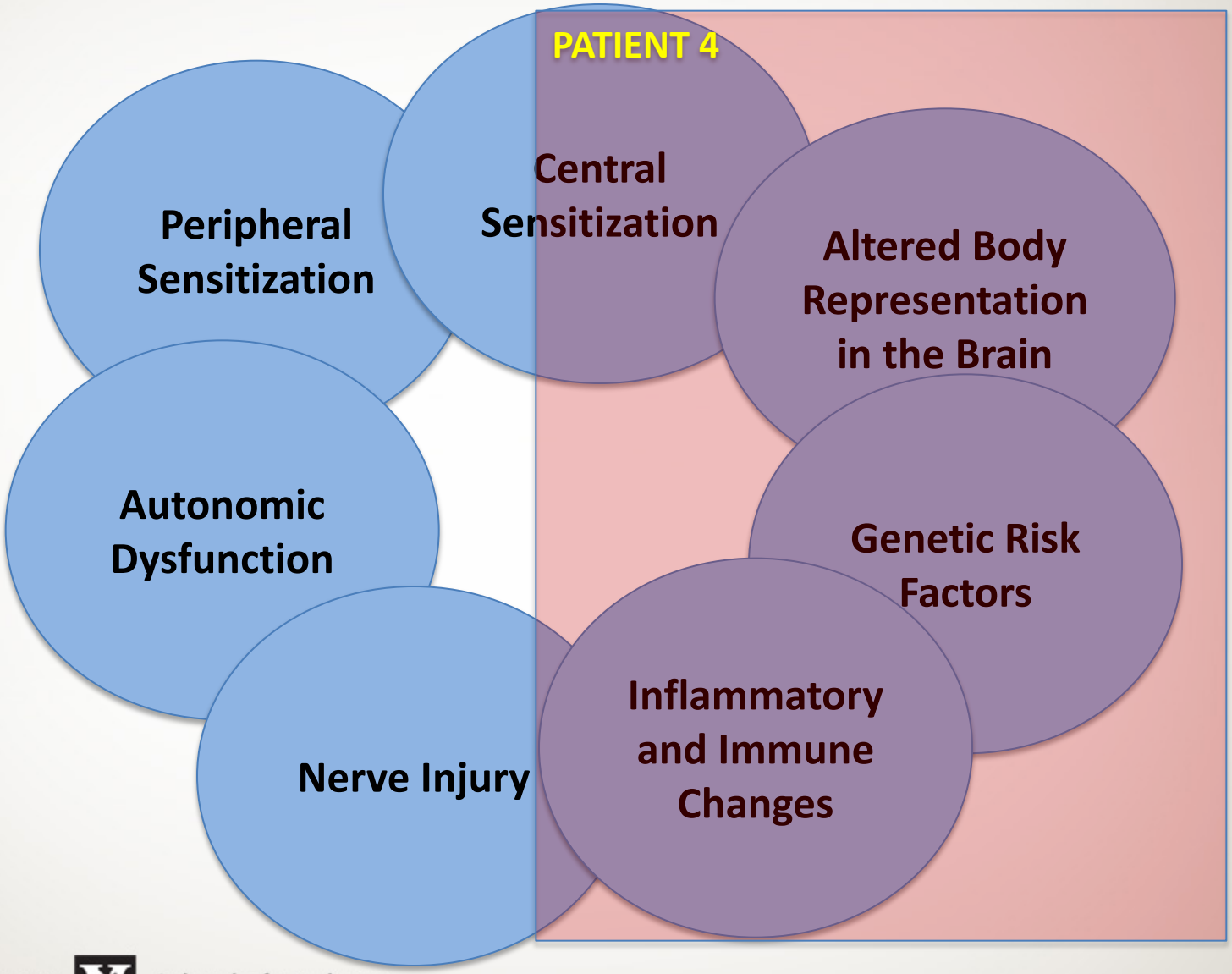


Inflammatory and Immune Mechanisms

Inflammation and CRPS

- Proinflammatory Cytokines and Neuropeptides
  - TNF-alpha, IL-1 beta, IL-2, IL-6
  - Substance P, calcitonin gene related peptide (CGRP), and bradykinin
  - Elevated in local blister fluid, circulating plasma, and cerebrospinal fluid in CRPS
  - Elevated in early CRPS, diminishes over first year
- Oxidative Stress (also can → inflammation)?
  - Animal model of CRPS-I (IR model)

Immune System and CRPS

- Inflammation and immune system linked
- Autoimmune role suggested in CRPS
  - Anti-neuronal antibodies significantly elevated in 30 -40% of CRPS patients
  - Autoantibodies sensitize pain receptors
- “Passive transfer model” and IgG

Immune System and CRPS

- Treatment Implications?
  - Plasma exchange?
  - IVIG?
  - Immune modulating drugs?
- Small studies show possible benefit
- Mycophenolate trial (Goebel et al., 2018)
  - Effective overall (with several dramatic responders)
  - BUT - 45% stopped taking drug due to side effects
  - Larger trial and related trials planned

Genomics and CRPS

Genomics of CRPS

- Genetics – Reflects the DNA we were born with and never changes.
  - Inherited variations in genes *may* increase CRPS risk
- Strongest support for genetic risk factors:
  - CRPS clusters within families
  - Genetic differences in the human leukocyte antigen (HLA) system (underlies the adaptive immune response)

van Rooijen et al., 2012; de Rooij et al., 2009; van de Beek et al., 2003; Vaneker et al., 2002

Genomics of CRPS

- Gene Expression – How genes are translated into forming the actual proteins in your body.
  - DNA ➔ RNA➔ Proteins
  - If you have a DNA signature that increases or decreases CRPS risk, actual risk only changes if that gene is turned on or off.

Jin et al., 2013; Tan et al., 2017

Genomics of CRPS

- Best evidence:
- Small study showing different gene expression in 4 CRPS patients compared to 5 non-pain controls
- Two of the top hits:
    - HLA gene (immune-related)
    - MMP9 gene (collagen-related)

Jin et al., 2013; Tan et al., 2017

Genomics of CRPS

- **Epigenetics** – Factors that can alter gene expression
- **DNA Methylation** – Can occur through genetic factors or environmental exposure. Alters gene expression. *These changes can be inherited and can impact on health even though the inherited DNA profile is unchanged*

Genomics of CRPS

- Best evidence:
- RSDSA-funded study of military traumatic limb injury patients (+amputation)
  - N = 9 with CRPS (Budapest criteria)
  - N = 38 with non-CRPS neuropathic pain
- 48 genetic locations between groups showed significant differences in methylation ($p<.001$) despite similar pain intensity
- Replication for 7 of these methylation sites

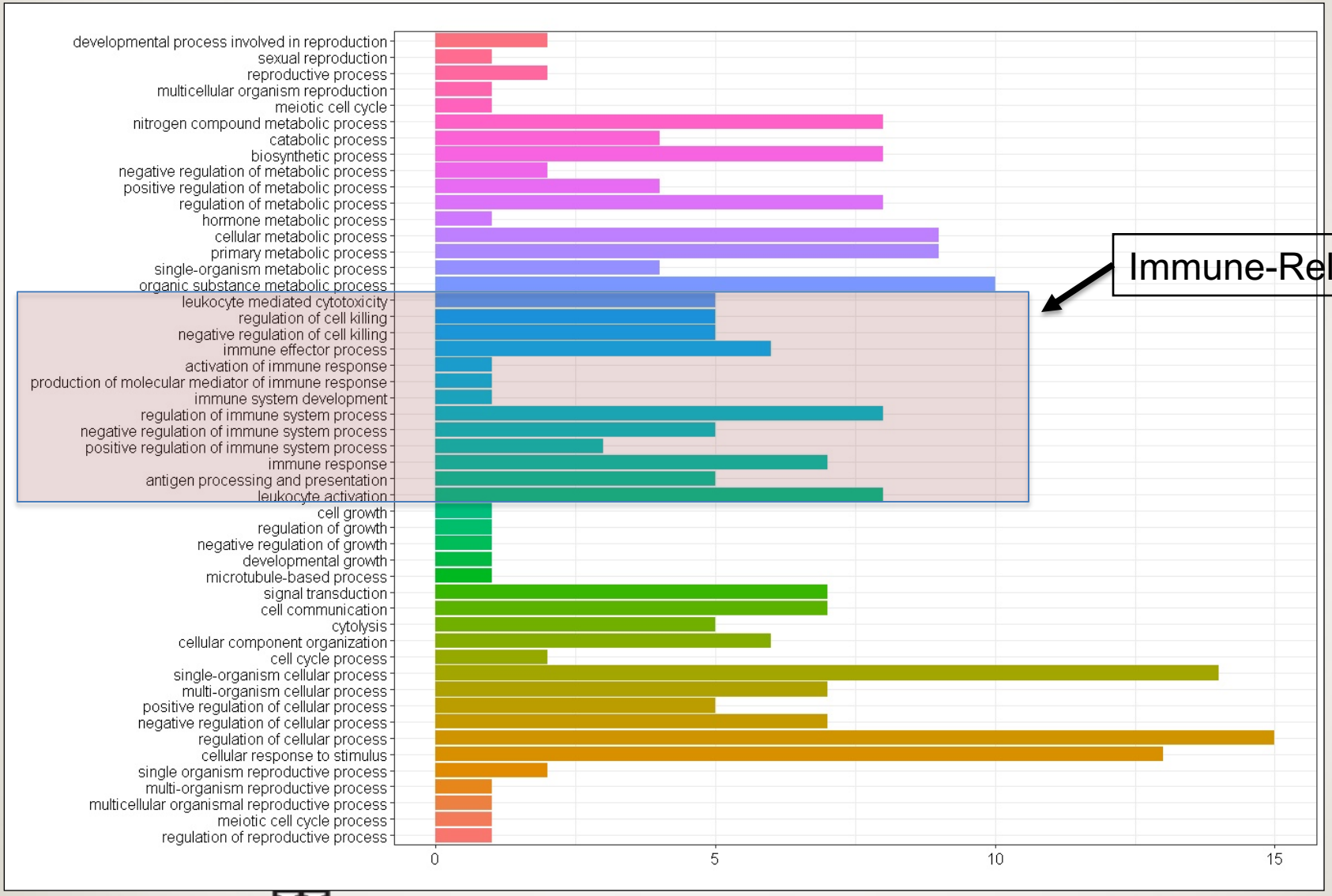
Bruehl et al., 2019

Genomics of CRPS

- Top 2 methylation sites were in the *COL11A1* and *HLA-DRB6* genes (both less methylation)
  - *HLA-DRB6* - immune-related
    - Same gene showed associations with CRPS in the only gene expression study
  - *COL11A1* - regulates collagen formation (e.g., skin)
    - The only gene expression study also showed collagen-related differences in CRPS

Bruehl et al., 2019

Functional Enrichment Analysis



Bruehl et al., 2019

Implications?

- Speculation:
  - HLA system involved in autoimmune diseases
  - Maybe differential DNA methylation influences risk for CRPS via HLA-mediated autoimmune mechanisms?
- Implications for treatment mechanisms

CRPS Stages and Subtypes

Are There Progressive Stages of CRPS?

- Early CRPS expert proposed 3 sequential stages with different symptom patterns that all CRPS patients move through
- Cluster Analysis (Pattern Recognition) Study:
  - NO sequential stages, but ID'd 3 CRPS subtypes:
    - Limited + mostly neuropathic pain/sensory symptoms
    - Limited + mostly vasomotor symptoms (skin color/temp)
    - Classic severe CRPS/RSD with a variety of symptoms
- Similar results in a large Dutch study

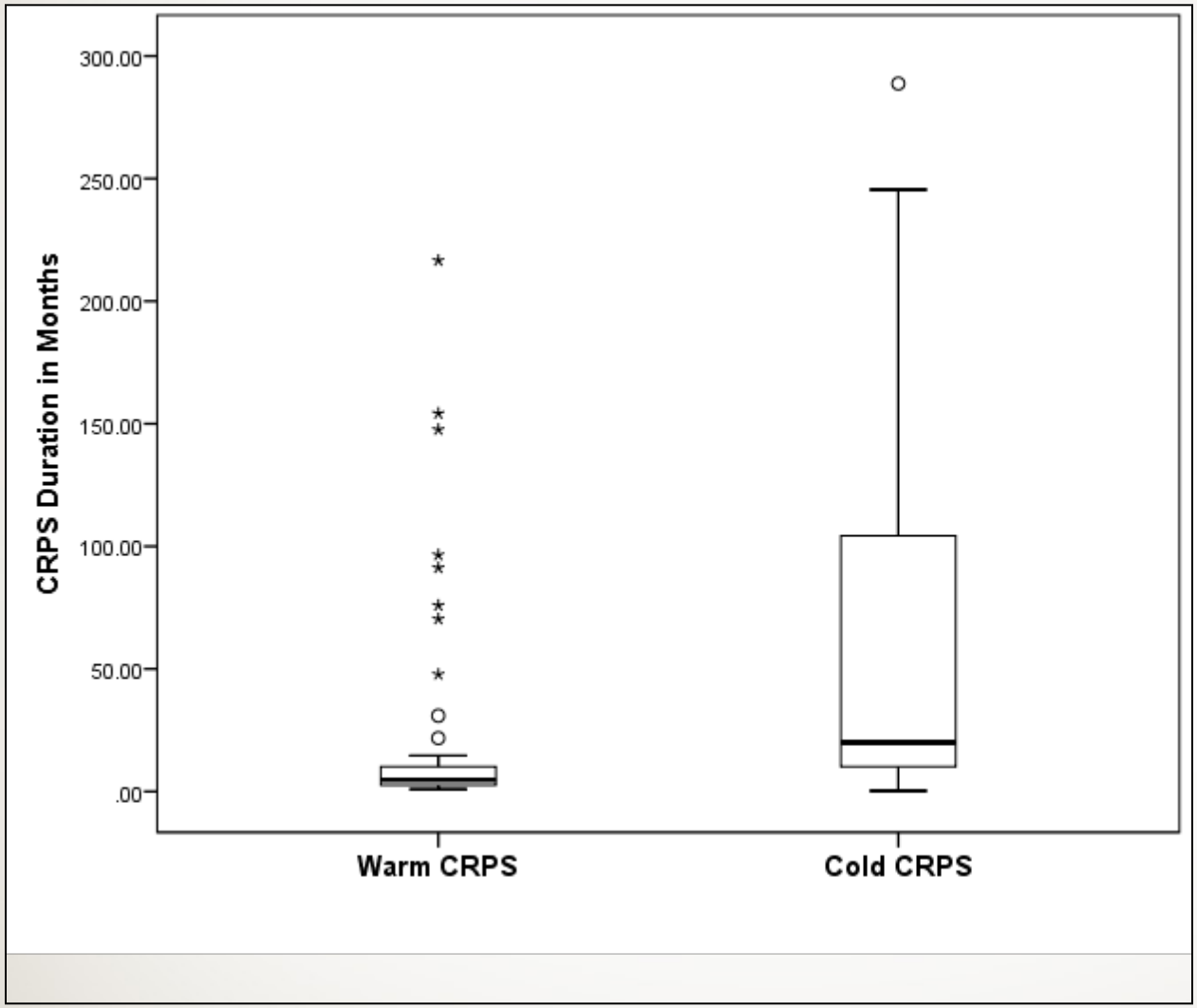
Bruehl et al., 2002; de Mos et al., 2009

CRPS Subtypes: Warm vs. Cold CRPS

- Budapest discussions
  - Warm vs. Cold CRPS Subtypes? "Unproven"
- Large clinical study of 152 acute and chronic CRPS patients followed over 3 months
- Cluster analysis (pattern recognition):
  - Warm CRPS = warm/red skin, sweaty, swelling
  - Cold CRPS = cool/blue skin, less swelling

Bruehl et al., 2016

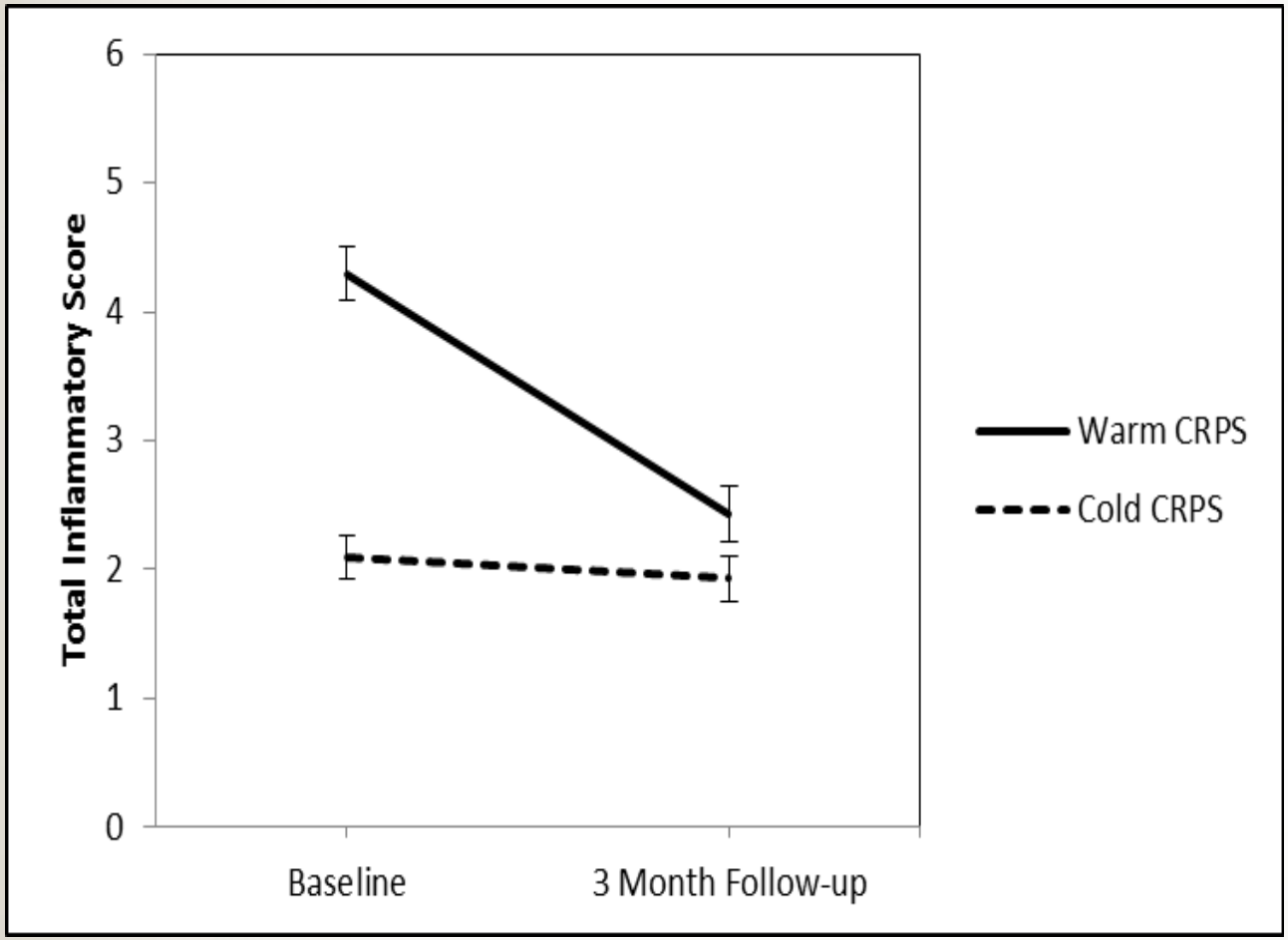
CRPS Subtypes: Warm vs. Cold CRPS



Warm = Acute
Cold = Chronic

Bruehl et al., 2016

CRPS Subtypes: Warm vs. Cold CRPS



Transition from warm to cold CRPS over time?

Bruehl et al., 2016

Treatment Implications

Drug Development Status

- Good News:
  - Orphan Condition status with FDA (and EMA)
  - Encourages drug development
- Bad News:
  - Multiple recent failed trials (1 still ongoing?)
  - Bisphosphonates, immune modulator

CRPS Complexity: TX Implications

- Problems:
  - Trials enroll “all CRPS patients”
  - Multiple CRPS mechanisms, and may differ between patients and over time
  - May be CRPS subtypes that respond and others that don’t (efficacy obscured by inclusion criteria?)
    - Recent trial results support this
  - Barrier to more CRPS trials = $$$$

Responses to Questions

For comprehensive CRPS overview, see:
Bruehl S. Complex regional pain syndrome. *British Medical Journal*. 2015; 351: h2730. [available free online]

Question

Problem with the Budapest (IASP) Criteria – Sometimes I meet criteria and sometimes I don't. Aren't these criteria most appropriate only for an initial diagnosis [before treatment improves symptoms]?

- Valencia meeting in September 2019
- New diagnostic category for ICD 11?:
  - "**CRPS with Remission of Some Features**"

Question

Physicians question spreading – any evidence?

- Yes - it occurs, but unclear how often
- Little available research (biased?)
- Definition issue:
  - Real spread (Budapest criteria) vs. secondary myofascial pain vs. widespread pain (CS?)
- Some bilateral mechanism changes are noted even before spreading of symptoms

Question

- Patterns of spread (descending frequency):
  - Mirror-image spread (e.g., left to right)
  - Upper to lower limb (and vice versa)
  - Diagonal spread
  - All 4 limbs
- Occurs on average 19 mo. after initial onset
- 37-91% of spreading cases occur after second injury

Question

Is CRPS in children different than CRPS in adults? Physicians seem to treat childhood CRPS as more of a psychological condition.

Question

Any evidence that CRPS and Fibromyalgia are related?

- "Central Sensitization Syndromes"
  - Fibromyalgia
  - IBS
  - Migraine
  - Bladder pain
  - Others

Question

CRPS and Gastrointestinal Symptoms – "It has been suggested that CRPS is 'doing something' to my vagus nerve which controls the digestive system. Is this possible?"

- Heart rate variability studies:
  - *Low* vagal tone in CRPS (and most pain conditions)
  - Low vagal tone linked to digestive disorders
  - Address via abdominal breathing practice:
    - **Breath in to count of 4, breath out to count of 6**

Question

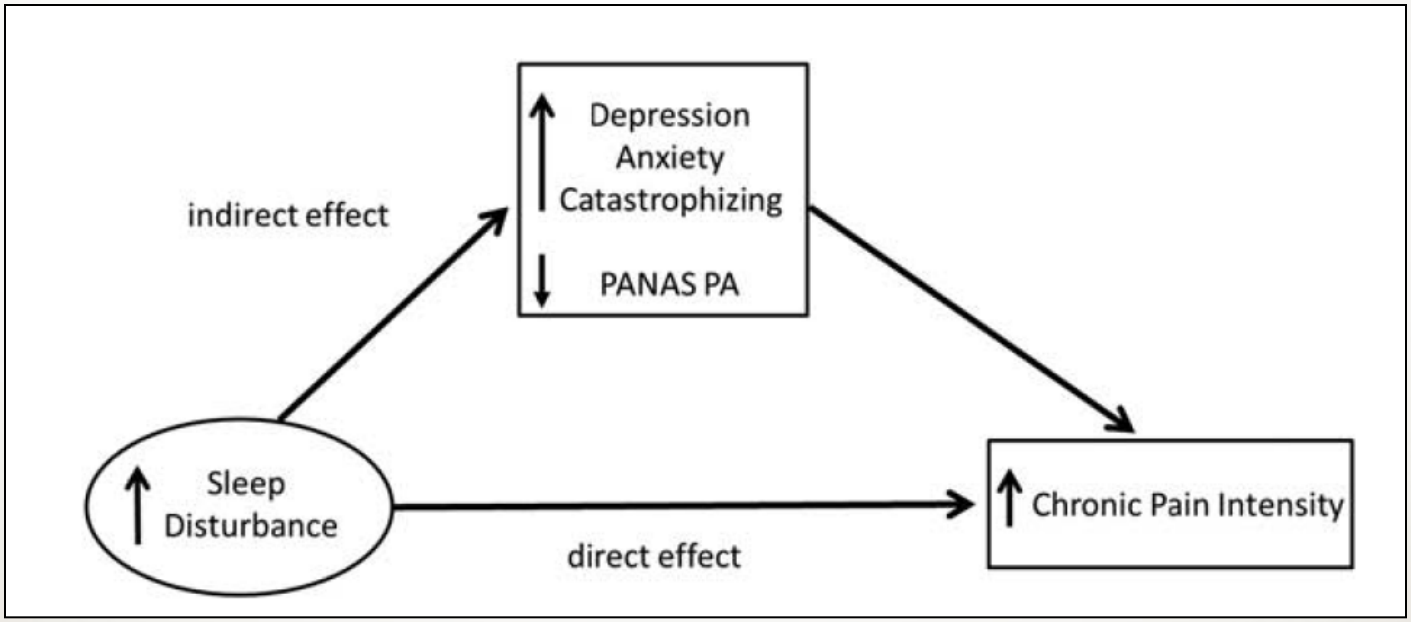
If CRPS occurs in the context of a nerve injury, and the nerve eventually regenerates, would CRPS be expected to improve?

- Specific nerve symptoms would resolve (numbness, tingling)
- Complex CRPS mechanisms, nerve injury only a small part (initial trigger?)

Question

Is CRPS associated with sleep problems? Are there any ongoing studies?

- Our study in chronic back pain patients:



Question

What should a newly diagnosed CRPS patient know about treatments?

- Caveat….
- Nothing proven highly effective for CRPS patients across the board (no cure)
  - Not many good studies to show what works
- CRPS is complex➔ multidisciplinary treatment
- SNS blocks used but no prolonged benefits

Question

- Best evidence for:
  - Antidepressant + Antiseizure medications
    - Low risk, moderately effective pain control options
    - Antidepressants improve sleep (= improved pain?)
  - Physical/Occupational Therapy and avoid disuse of affected limb in daily life
  - Corticosteroids (early CRPS only)
  - Stimulators: SCS and DRG (NOT first line TX)
  - Bisphosphonates?? (maybe early CRPS only)

Question

- Ketamine infusion may be effective
  - For evidence, see: Connolly SB, Prager JP, Harden RN. A systematic review of ketamine for complex regional pain syndrome. *Pain Med*. 2015;16(5):943-969.
- May help even in chronic CRPS due to its mechanism of action (central sensitization)
- Any form of ketamine (e.g., even sublingual) might work if adequate blood levels can be achieved
- More intensive protocols (repetition) better?
  - Benefits for 12 weeks?
- Need to balance benefits with risks (cognitive, liver)

Question

Any information on low dose naltrexone?

- No real clinical trials (one stuck in process)
- Small case report suggests may be effective
- Mechanism make sense
  - TLR4 receptor ➔ microglial inflammation
- Reflects problem in CRPS literature: Many experimental therapies with little evidence
  - Potentially waste money on ineffective treatments

Question

Are opioid analgesics useful for CRPS?

- One study in CRPS patients (negative results)
- Carefully weigh benefits vs. costs/risks
- Problem with "opioid-induced hyperalgesia"
  - Snake chasing tale (vicious cycle)…..
- Daily diary study: opioids used for mood control as well as pain control
  - Better options for mood control?

Question

Could CRPS increase the risk of a "cytokine storm" if I am infected with COVID-19?

- Possible, but hard to say for sure….