Challenges in the Development of Pain Therapies – A Patient's Perspective

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www.ChronicPainResearch.org

Many Treatments

But … what works for whom? At what risk? At what cost?

"Unfortunately, the field of chronic pain treatment is strikingly deficient in high-quality scientific evidence."

Former FDA Commissioner Dr. Robert Califf
NEJM 2016;374:1480-5

Susan:
A “Success” Story

History:

- Some Gene x Environment Risk
- Trigger – accident, surgeries
- 1 year later - neck/back pain started, but manageable with self-care, PT & chiropractic care
- 2 years later, cascade of chronic pain conditions began

… 4 years ….

hydrocodone

gabapentin

nortriptyline

cyclobenzaprine

duloxetine

milnacipran

propranolol

pregabalin

tizanidine

self-care

ice/heat

injections

physical therapy

chiro-practor

TENS

yoga

massage

Susan Today – 20 years later

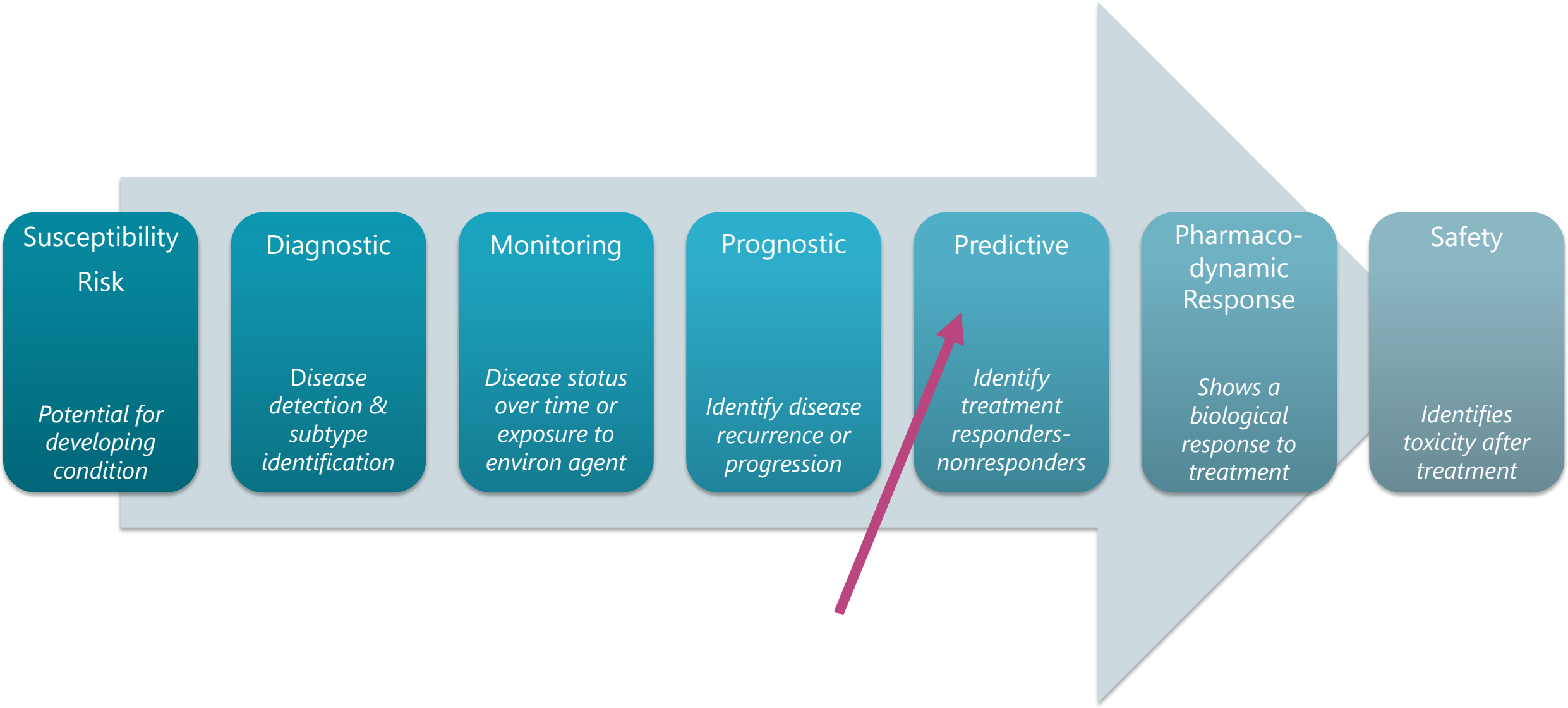
Occipital Neuralgia
Chronic Migraine
Temporomandibular Disorder
Myofascial pain syndrome
Chronic pelvic pain
Chronic back pain
Endometriosis
Pelvic Congestion Syndrome
Inflammatory Bowel Disease
Painful Bladder Syndrome
Premenstrual Disorder
Depression
Chronic Fatigue

still has moderate, sometimes severe, daily pain
↓works part-time, stopped volunteer activities
cannot exercise w/o flare, but can tolerate "activity in moderation"
significant impact on mood, sleep, cognition, energy & social function

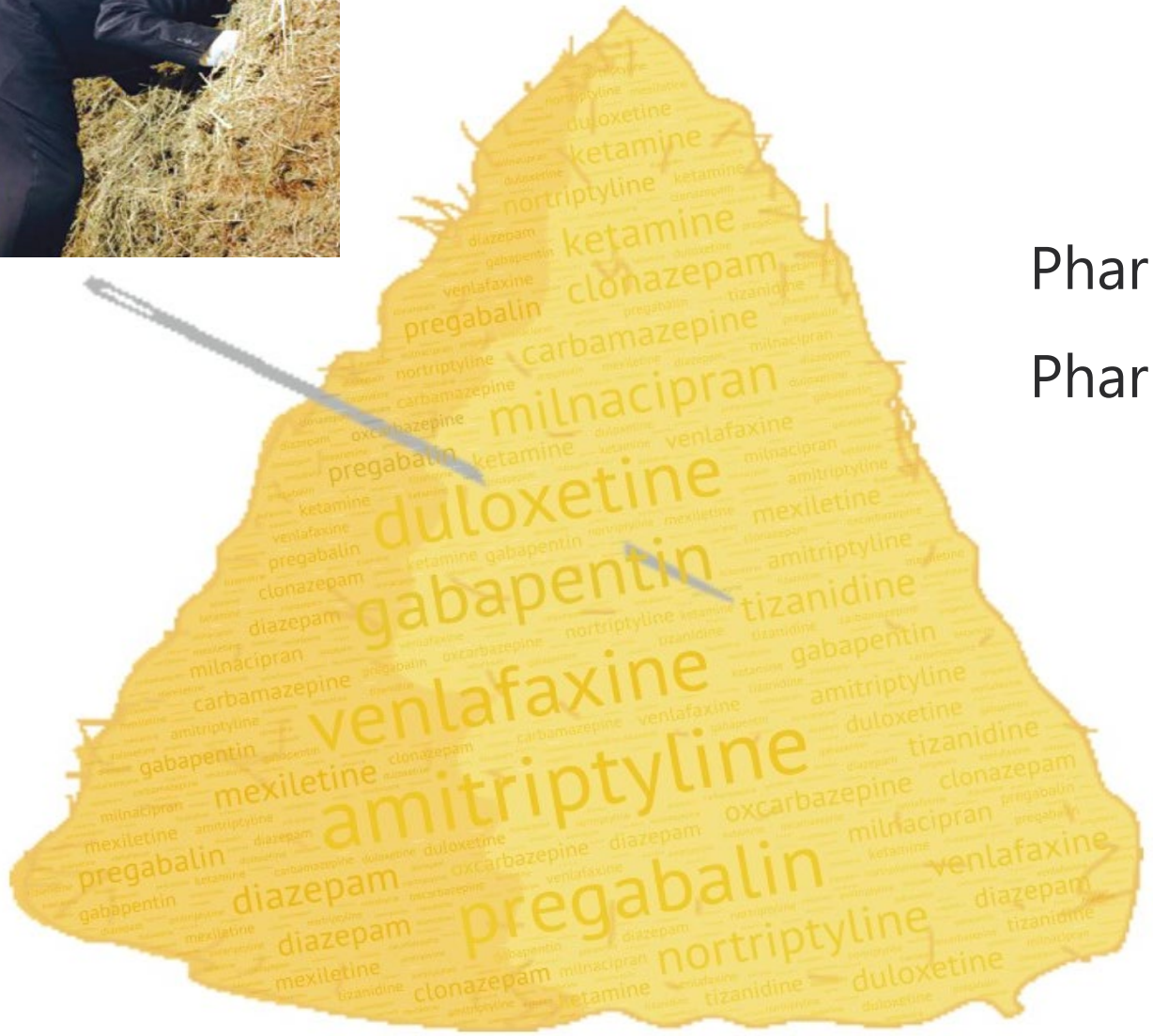
Success?

Biomarker Types & Potential Uses in Chronic Pain

FDA "BEST": Biomarkers, EndpointS and other Tools

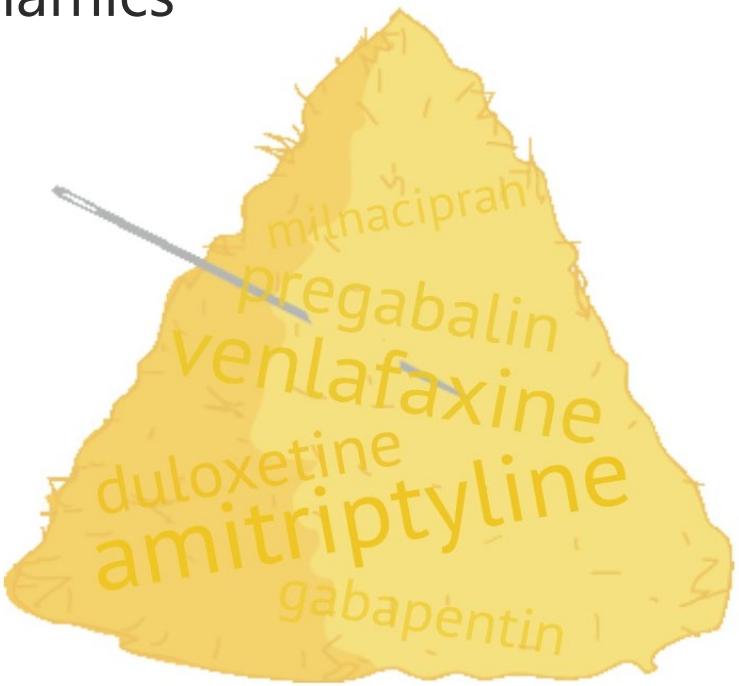


An Example … Pharmacogenetic Testing



Pharmacokinetics

Pharmacodynamics



Pharmacogenetic Testing

ANTIDEPRESSANTS

USE AS DIRECTED
desvenlafaxine (Pristiq®)
levomilnacipran (Fetzima®)
selegiline (Emsam®)

MODERATE GENE-DRUG INTERACTION	
sertraline (Zoloft®)	1
vilazodone (Viibryd®)	1
bupropion (Wellbutrin®)	1,6
mirtazapine (Remeron®)	3,7
trazodone (Desyrel®)	3,7
duloxetine (Cymbalta®)	3,7,8
fluvoxamine (Luvox®)	3,7,8

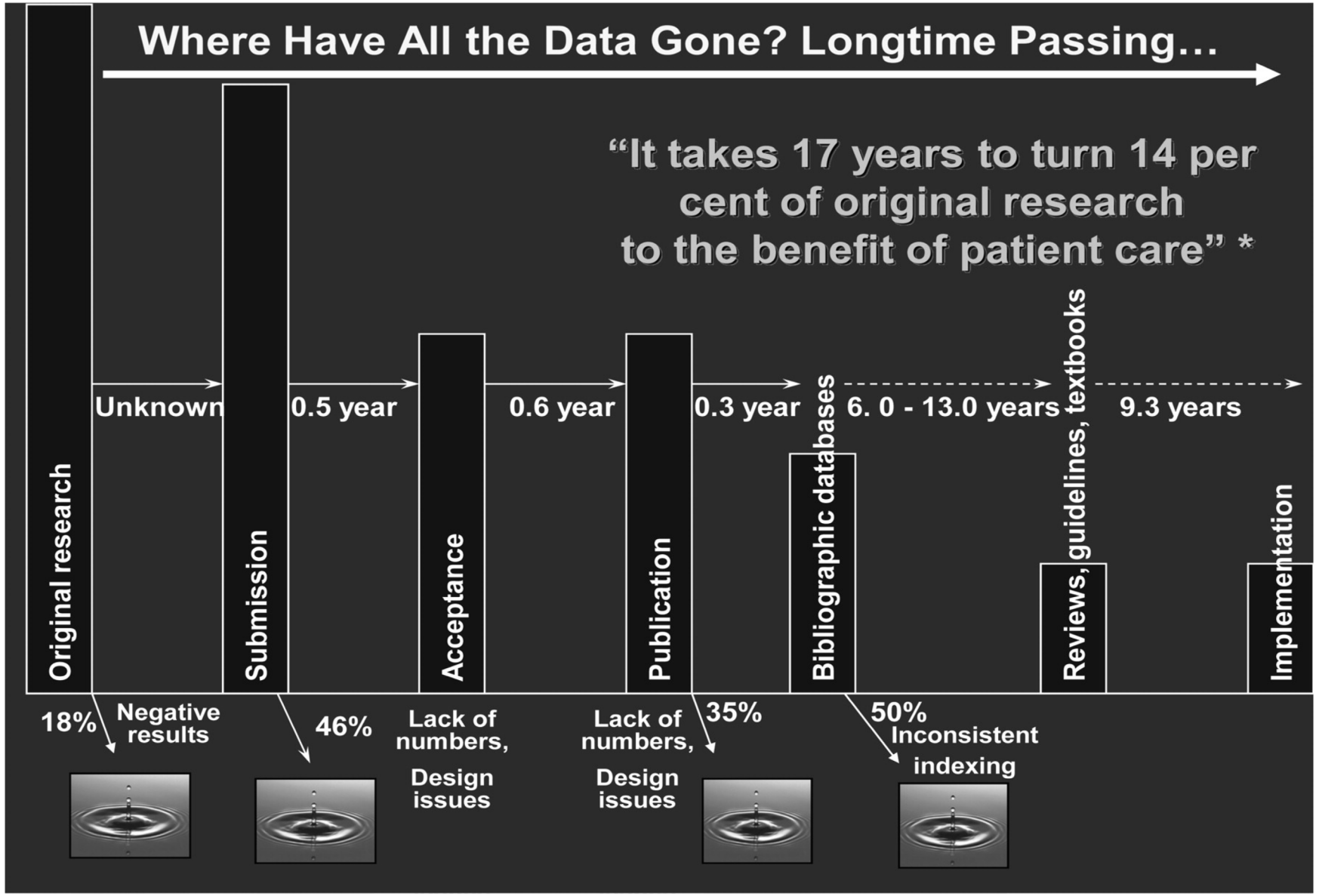
SIGNIFICANT GENE-DRUG INTERACTION	
citalopram (Celexa®)	1,6
escitalopram (Lexapro®)	1,6
fluoxetine (Prozac®)	1,6
venlafaxine (Effexor®)	1,6
amitriptyline (Elavil®)	1,6,8
clomipramine (Anafranil®)	1,6,8
desipramine (Norpramin®)	1,6,8
doxepin (Sinequan®)	1,6,8
imipramine (Tofranil®)	1,6,8
nortriptyline (Pamelor®)	1,6,8
paroxetine (Paxil®)	1,6,8
vortioxetine (Trintellix®)	1,6,8

CLINICAL CONSIDERATIONS

1. Serum level may be too high, lower doses may be required.
3. Difficult to predict dose adjustments due to conflicting variations in metabolism.
6. Use of this drug may increase risk of side effects.
7. Serum level may be too low in smokers.
8. FDA label identifies a potential gene-drug interaction for this medication.

Knowledge Translation

When science advances and produces clinically useful tools, why aren't they being used?

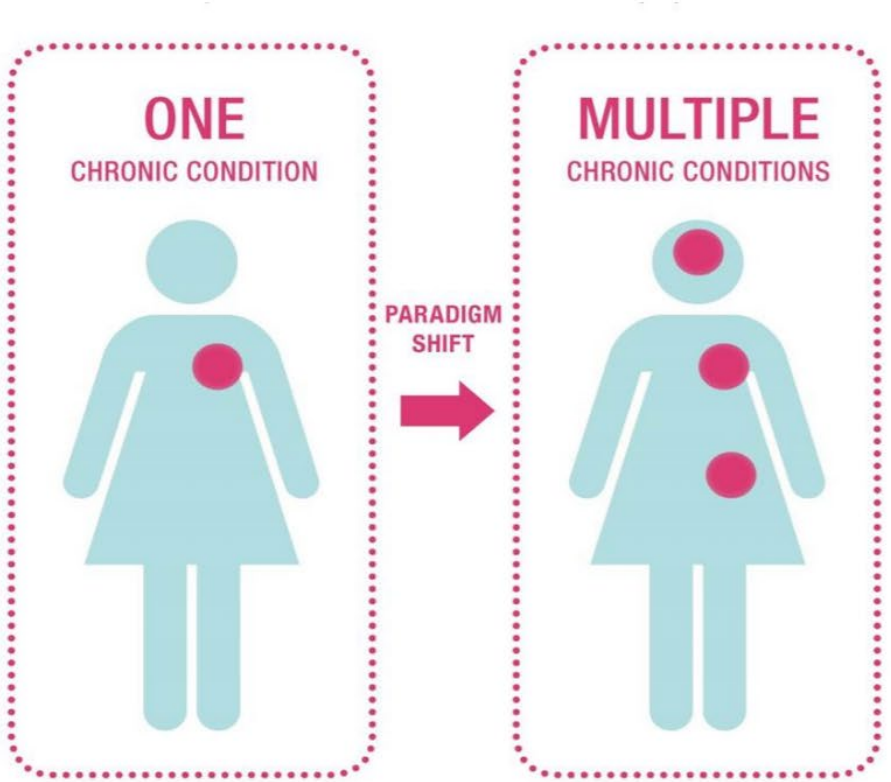


Balas EA, Boren SA. Yearbook of Medical Informatics 2000: Patient-centered Systems. 2000: 65–70. Green L. Fam Pract. 2008;25(suppl_1):i20-i24.

Plans for Implementation Need to Start Now & Include All Necessary Stakeholders

Multimorbidity

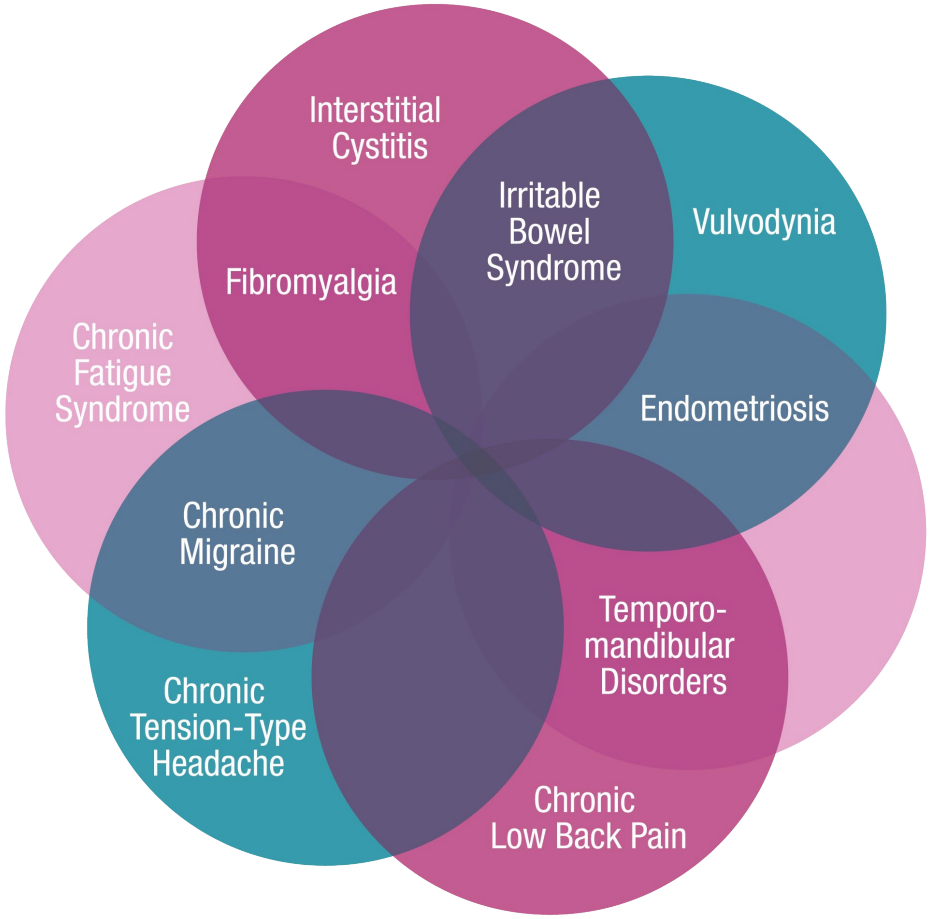
"The most common chronic condition experienced by adults is multimorbidity, the coexistence of multiple chronic diseases or conditions."

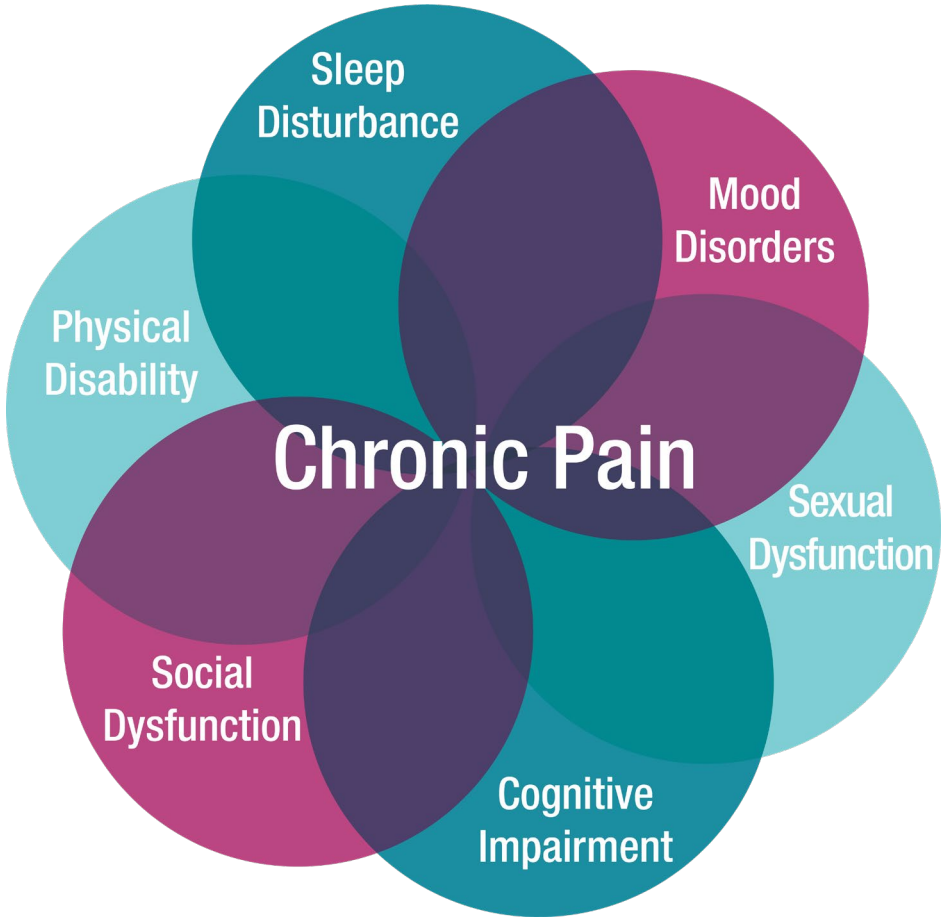


Tinetti et al. JAMA, 2012
HHS Multiple Chronic Conditions Initiative

Multimorbidity

- Approximately 1 in 4 Americans has MCC, including 1 in 15 children
- In those >65 years, 3 in 4 have MCC
- Increased risk for mortality and poorer functioning
- 66% of the total health care spending associated with MCC





Pain Comorbidity

Notable Findings Related to Comorbidity

As # of pain diagnoses (or body sites of pain) increase:

- But, most RCTs enroll patients with more than 1 pain condition, but only track the index condition
- Existence of multiple disorders ↓ likelihood of effect?
- Could "flares" in non-index pain condition(s) create a "false negative" outcomes?
- Sleep, mood & other factors have known deleterious effect on pain severity. These are often not tracked – or tracked but not analyzed
- Do other comorbid chronic diseases impact outcomes?

Literature reviewed in: Veasley C, et al., Impact of COPCs on public health and the urgent need for safe and effective treatment:. CPRA. 2015. http://cpralliance.org/public/CPRA_WhitePaper_2015-FINAL-Digital.pdf

Comorbidity | Clinical Trials

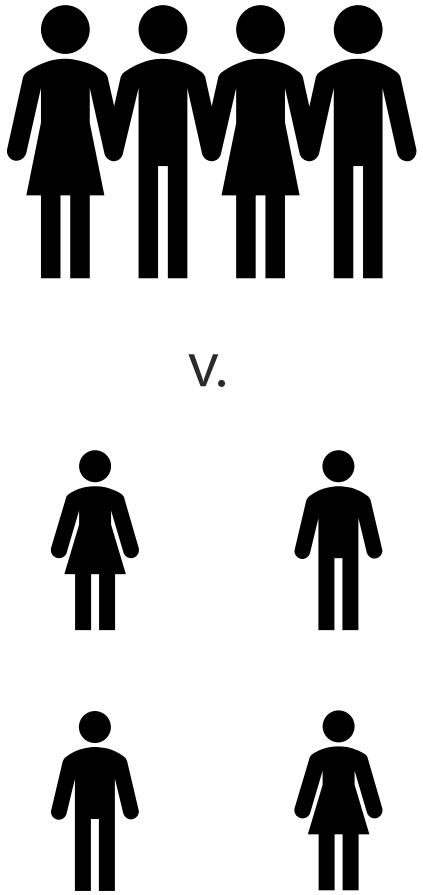
EFFECTS OF POLYPHARMACY?

EFFECTS OF COMBINATION DRUG & NON-DRUG TREATMENTS?

Classification of Pain, Lumping v. Splitting & Phenotyping

"The classification of most chronic pain disorders gives emphasis to anatomical location of the pain to distinguish the disorder from another, or to define subtypes. However, anatomical criteria overlook etiology, potentially hampering treatment decisions."

Bair E, et al. Pain. 2016 Jun;157(6):1266-78.

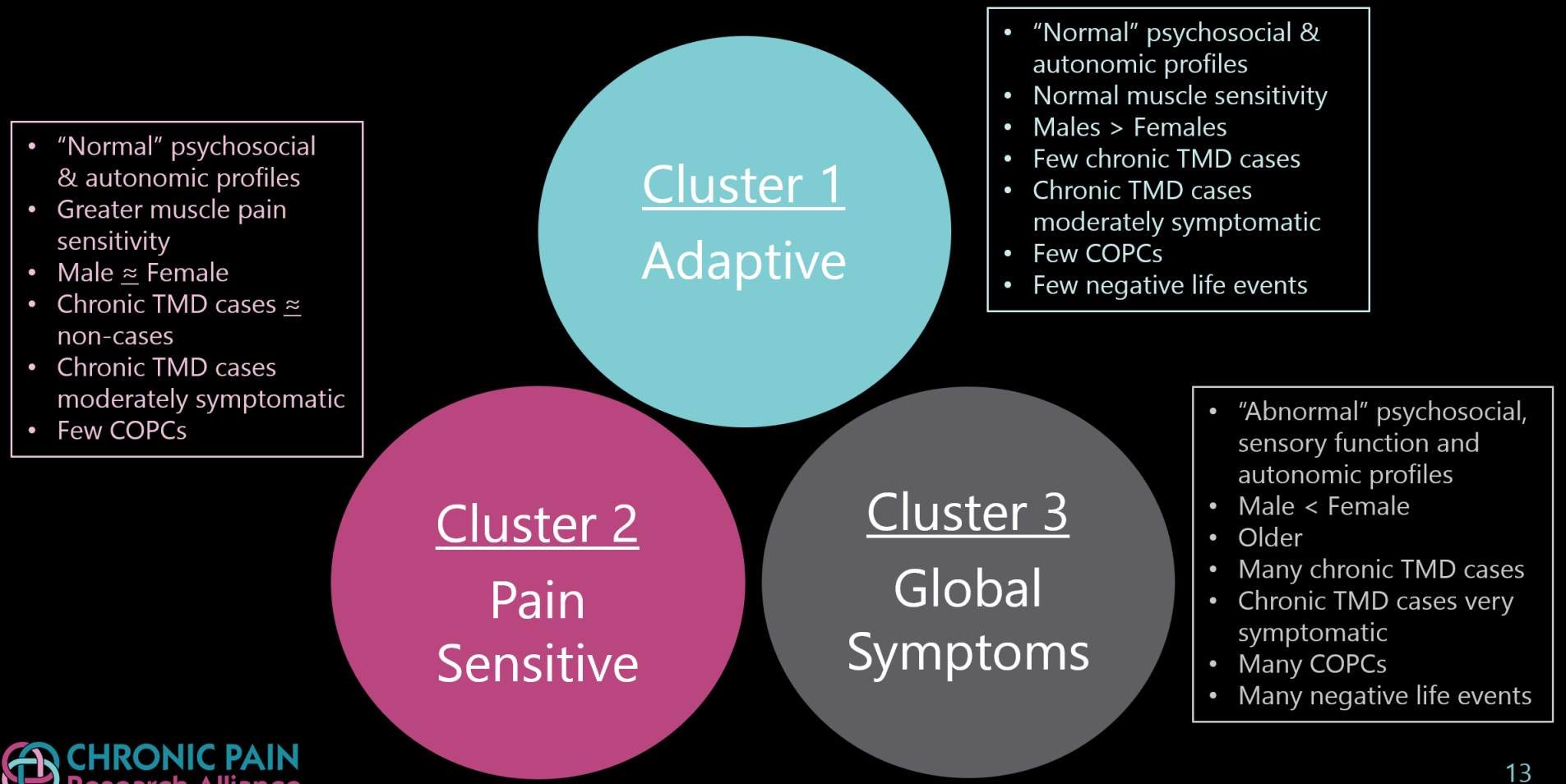


"EPPIC-Net will incorporate innovative designs to accelerate therapy development in <u>well-phenotyped subpopulations of patients with well-characterized pain conditions.</u>"

COPCs Cluster Analysis

Orofacial Pain Prospective Evaluation & Risk Assessment (OPPERA) Study

- Prominent NIH-funded longitudinal TMD study. Comorbidity assessed as important disease modifier.
- Cluster analysis of 1031 chronic TMD cases & 3,247 TMD-free controls



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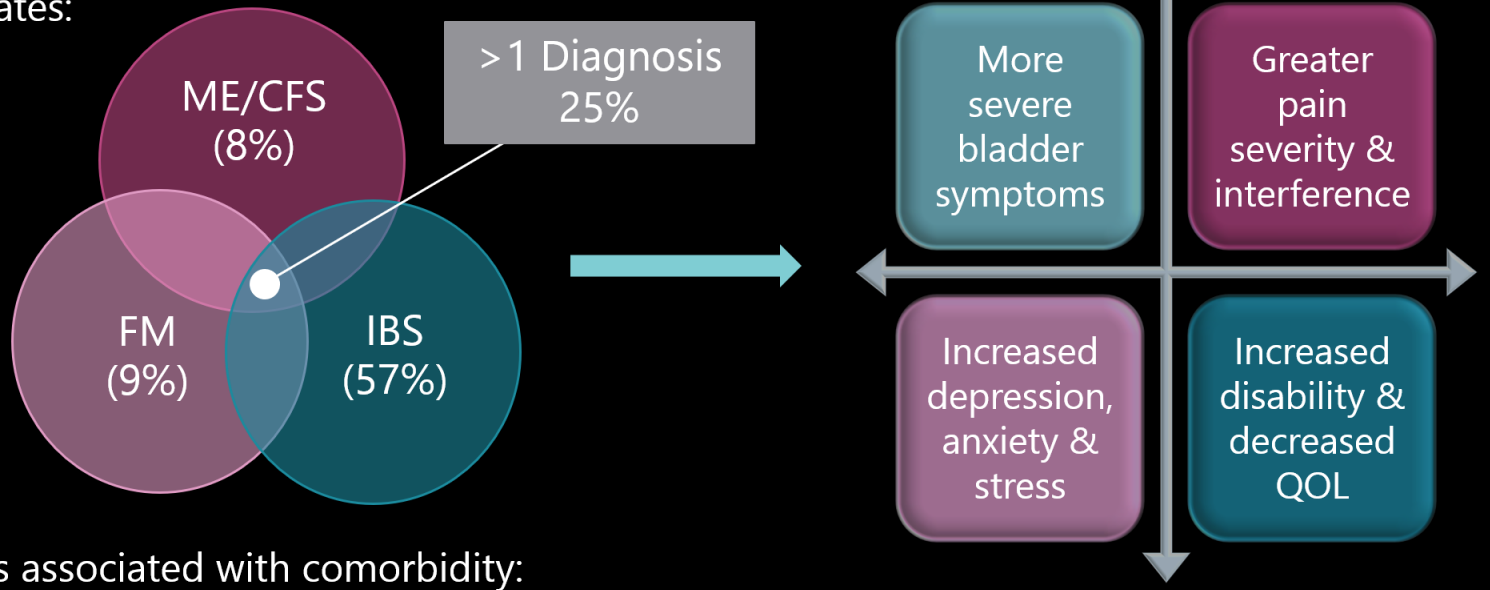
Slade GD, et al. J Pain. 2011;12:T12–26; Bair E, et al. Pain. 2016 Jun;157(6):1266-78.

COPCs Co-Prevalence Rates & Major Findings

Multi-Disciplinary Approach to the Study of Chronic Pelvic Pain (MAPP)

- Prominent longitudinal NIH-led, IC/PBS study. Comorbidity assessed as important disease modifier.
- Of 424 participants, 38% reported at least 1 comorbid pain syndrome (44% female vs. 31% male)
- Co-prevalence rates:



- Two constructs associated with comorbidity:

Generalized Sensory Sensitivity (GSS)
+ increased sensitivity to *external* stimuli across multiple sensory modalities
+ Increased sensitivity to *internal* symptoms/sensations (somatic awareness)
+ Hyperalgesia/allodynia in multiple body regions

S.P.A.C.E.	
S	Sleep disturbance
P	Pain (widespread)
A	Affect (negative)
C	Cognitive dysfunction
E	Energy depletion/fatigue

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Krieger JN et al. J Urol. 2015;193(4):1254-62; Schrepf A, et al. Pain. 2018 May 28; Williams DA. J Appl Behav Res. 2018;23:e12135.

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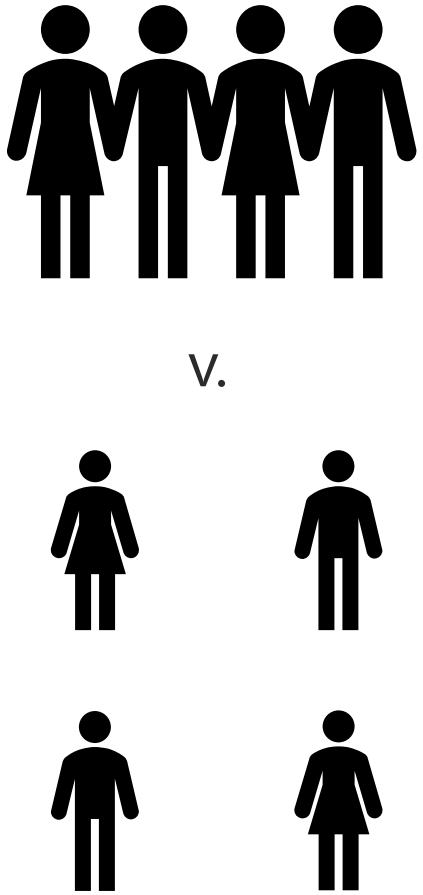

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