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# The Role of Phenotyping in Chronic Prostatitis/Chronic Pelvic Pain Syndrome

**Brandon A. Mahal · Jeffrey M. Cohen · Stephen A. Allsop · John B. Moore · Salman F. Bhai · Gino Inverso · Jordan D. Dimitrakoff**

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**Abstract** Chronic prostatitis/chronic pelvic pain syndrome (CP/CPPS) is a chronic pain syndrome identified by the presence of noninfectious pelvic or perineal pain lasting longer than 3 months. Current diagnoses and treatments for the syndrome solely depend on and target symptoms, respectively. Thus far, the mechanistic disturbances responsible for the pathogenesis of CP/CPPS have remained largely elusive and treatments, and therefore, continue to be ineffective. To move toward successful management and treatment of CP/CPPS, it is necessary to elicit the underlying biological mechanisms responsible for the syndrome. Therefore, a phenotyping system that is able to bridge the gap between current symptom-based diagnosis and future mechanistic approaches to diagnosis and treatment is needed. In this article, we examine current CP/CPPS phenotyping systems, analyze their utility, and make suggestions for changes in clinical approaches to the syndrome that would both promulgate a mechanistic understanding and advance treatment approaches.

Brandon Mahal and Jeffrey Cohen contributed equally to this work.

B. A. Mahal · J. M. Cohen · S. A. Allsop · J. B. Moore · S. F. Bhai · J. D. Dimitrakoff
Harvard Medical School,
25 Shattuck Street,
Boston, MA 02115, USA

B. A. Mahal · J. M. Cohen · S. A. Allsop · J. B. Moore · S. F. Bhai · G. Inverso · J. D. Dimitrakoff (✉)
Beth Israel Deaconess Medical Center,
330 Brookline Avenue, Kirstein 316,
Boston, MA 02215, USA
e-mail: jdimitra@bidmc.harvard.edu

G. Inverso
Harvard School of Dental Medicine,
188 Longwood Ave,
Boston, MA 02115, USA

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## Introduction

Chronic prostatitis/chronic pelvic pain syndrome (CP/CPPS) is the most common urologic diagnosis in men under the age of 50 years. Population-based surveys have estimated the prevalence of CP/CPPS-like symptoms to be between 6% and 12% [1]. In addition, it has been shown that patients with CP/CPPS have a worse quality of life than patients with congestive heart failure, diabetes, and Crohn's disease [2]. However, despite years of diagnoses and empiric treatments, CP/CPPS remains a largely enigmatic disease.

CP/CPPS is a heterogeneous condition in terms of clinical manifestation and, most likely, underlying mechanism. This heterogeneity is evidenced by four critical observations: 1) the clinical presentation of patients varies from one patient to the next; 2) a single patient may have symptoms that fluctuate over time [3]; 3) varying etiological mechanisms (eg, infection, inflammation, and nerve damage) may account for the observed pathology in the same patient and between patients [4]; and, 4) the symptoms of CP/CPPS overlap with those of irritable bowel syndrome (IBS), fibromyalgia, chronic fatigue syndrome (CFS), and other chronic pain disorders [5].

## Mechanistic Insight into Chronic Prostatitis/Chronic Pelvic Pain Syndrome Through Phenotyping

There is a need for the development of a deeper mechanistic understanding of CP/CPPS etiology and

progression [6••]. Phenotyping is one way to address the knowledge deficit that exists, and will improve mechanistic understanding of the syndrome. Phenotyping research explores etiology and mechanisms of disease and fluctuations in symptoms and pathology over time [7].

A phenotyping system provides a platform through which associations can be made between genotypes and phenotypes. To make these associations, there must be a system for consistently defining and characterizing phenotypes. Thus, new genetic findings then can be placed into a preexisting system, and matched and associated with specific clinical presentations. The *Consortium for Neuropsychiatric Phenomics* successfully utilized this approach in systematically linking genomic variation to different psychological phenotypes [8]. Here, we review current CP/CPPS phenotyping approaches and discuss a more productive and predictive framework for future clinical and basic science research.

## UPOINT: Evaluation of a Novel Chronic Prostatitis/Chronic Pelvic Pain Syndrome Phenotyping System

### UPOINT as a Novel Approach

In 2009, Nickel and Shoskes [9••] introduced UPOINT, an original system that categorizes CP/CPPS symptoms in six domains: Urological, Psychosocial, Organ-specific, Infection, Neurological, and Tenderness of skeletal muscles. It accords broadly with the National Institutes of Health Chronic Prostatitis Symptom Index (NIH-CPSI) scale, which currently serves as the standardized symptom-severity questionnaire in CP/CPPS. However, it is important to note that CP/CPPS, by definition, is a chronic pain syndrome and, therefore, is encapsulated by the pain domain [10, 11]. Thus, a high total NIH-CPSI score may not necessarily reflect pain severity as captured by a high pain-domain score, but could result from a high voiding score (representing voiding dysfunction). In such a case, UPOINT is not a sensitive measure of chronic pain symptoms, a hallmark that defines CP/CPPS. Besides, in assessing UPOINT, the concordance of UPOINT domains with the NIH-CPSI score is most likely a by-product of the similarities in scope and approach between the two systems because UPOINT was created on the basis of NIH-CPSI–based studies.

In reality, the UPOINT system emerged because clinical trials (evaluating α-blockers, pentosan polysulfate, and pregabalin) failed to detect a significant difference between intervention and placebo, but significant differences were observed in secondary outcomes, such as quality of life [9••, 11]. Therefore, it appeared feasible to define cohorts based on secondary outcomes and to establish treatment guidelines for each group. However, due to the heterogeneity of CP/CPPS, it is unclear how helpful UPOINT can be for tailoring individual therapy.

### The Utility and Limitations of UPOINT

UPOINT strives to approximate etiology through clinical subgrouping and, thereby, inaccurately appears to be an upstream and predictive phenotyping system; the system postulates that the six domains reflect the disease state of CP/CPPS. In reality, this strategy does not attempt to capture underlying mechanisms (as does the DABBEC [Dimitrakoff, Allsop, Bhai, Brook, Erstad, Cohen] phenotyping system) and may artificially combine symptoms originating from discrete mechanisms or separate symptoms emerging from a common mechanism (Fig. 1). Specifically, the system is downstream (ie, symptoms emerge after pathological changes) and descriptive, rather than predictive, of mechanistic pathways that underlie the disease. Thus, UPOINT fails to create "evidence-based (biomechanistic) subcategories within domains" [9••] because the information captured by the UPOINT domains is at the end, rather than the beginning, of the causative pathway.

In a single-center nonblinded study, Shoskes et al. [12] treated CP/CPPS based on the multimodal domains of UPOINT. While UPOINT claims that it tailors treatment to domains, this study assigned treatments to patients regardless of their domains. Thus, it precluded comparisons between UPOINT domain-based and multimodal therapy–based efficacy, regardless of domain (except "organ-specific"). Furthermore, though UPOINT-directed multimodal therapy resulted in significant NIH-CPSI total score reductions, overlapping confidence intervals between the initial and final scores render UPOINT's effectiveness inconclusive [12]. Lastly, when UPOINT was applied retrospectively to a German cohort, there was no significant correlation between the number of positive UPOINT domains and NIH-CPSI-scored symptoms until an additional domain, sexual dysfunction (UPOINT[S]), was added [13].

Additionally, UPOINT promulgates the use of therapies that do not target specific mechanisms. Rather, the system focuses on alleviating symptoms, and thus, often dictates the use of therapies that previously have been shown to be ineffective [9••]. For example, although some subsets of men with CP/CPPS may benefit from $\alpha_1$-antagonist therapy, there was no statistically significant difference in the NIH-CPSI total and pain scores between patients receiving tamsulosin and those receiving placebo in an NIH-sponsored, multicenter, randomized control trial [11]. Often, prescribing practices in CP/CPPS are based on the individual clinician's preferences rather than hard evidence.

The use of quercetin (an anti-inflammatory, antioxidant, and antimicrobial agent) [14] for the UPOINT-guided multimodal therapy illustrates limitations of the system. UPOINT recommends quercetin for treatment of the "organ-specific" (prostate) domain [14]. Nevertheless,

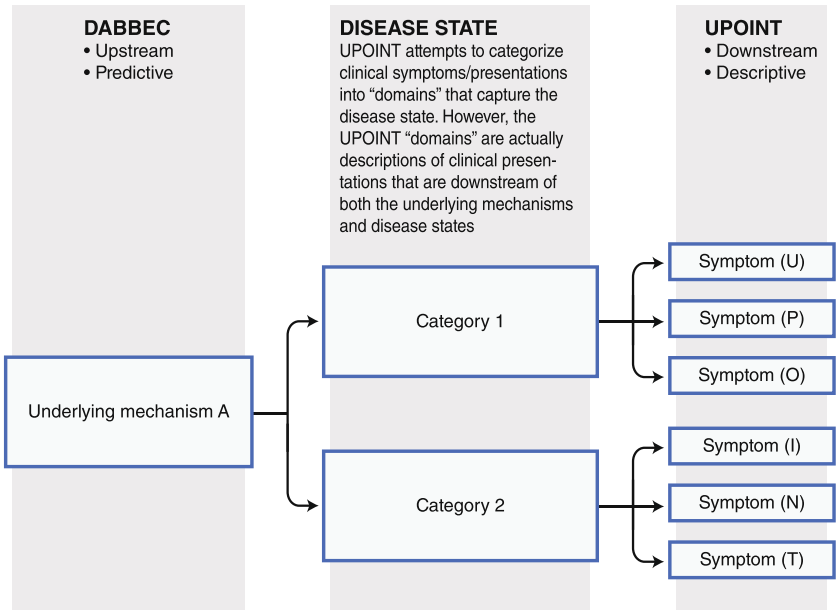


**Fig. 1** Spectrum of phenotyping systems for chronic prostatitis/chronic pelvic pain syndrome. Upstream: initial process resulting in disease state and eventually in the clinical presentation of symptoms. Downstream: final presenting event that results from mechanistic disturbances. Predictive: predicts the clinical presentation of symptoms. Descriptive: description of clinical presentation of symptoms (no predictive power). DABBEC is an upstream and predictive phenotyping system that strives to encapsulate the mechanistic underpinnings of CP/CPPS, while UPOINT is a downstream and descriptive phenotyping system that describes commonly seen clinical presentations associated with CP/CPPS. CP/CPPS—chronic prostatitis/chronic pelvic pain syndrome; DABBEC—phenotyping system proposed by Dimitrakoff, Allsop, Bhai, Brook, Erstad, and Cohen; UPOINT—Urological, Psychosocial, Organ-specific, Infection, Neurological, and Tenderness of skeletal muscles domain (phenotyping system)

patient symptoms as captured by this domain actually may reflect underlying inflammatory, pro-oxidant, and/or infectious etiologies, each of which is alleviated by quercetin. Thus, "UPOINT-defined" domains actually do not target the underlying disease state (Fig. 1).

UPOINT is commendable for seeking to phenotype CP/CPPS. However, its limitations restrict the mechanistic understanding of CP/CPPS and, consequently, prompted the development of a mechanistically sound system to bridge this lack of understanding.

## DABBEC: Moving Toward a Mechanistically Predictive Phenotyping System

To maximize diagnosis and management of CP/CPPS, a mechanistic understanding of its underlying pathophysiology must be obtained. The DABBEC Phenotyping System (DPS; Fig. 2) was designed to help guide a mechanistic understanding of CP/CPPS, and ultimately act as a tool for more precise diagnosis and mechanistic treatment. The individual parts of DPS can feasibly be incorporated into current clinical practice, but have not been used in concert thus far. We recommend two alterations in clinical practice to help move toward DPS and to help promote the understanding of the pathology and mechanisms of CP/CPPS.

### Hypothalamic–Pituitary–Adrenal Domain

The allostatic load is a measure of hypothalamic–pituitary–adrenal (HPA) axis function. Several lines of evidence suggest that patients with CP/CPPS have a dysfunctional HPA axis [15]. Anderson et al. [15] found that patients with CP/CPPS produce 30% less adrenocorticotropic hormones and have increased adrenal sensitivity as compared to normal control patients. A study by Lutgendorf and colleagues [16] found that women with painful bladder syndrome/interstitial cystitis, a condition that is closely related to CP/CPPS, had changes in the HPA axis that correlated with the severity of their symptoms. They found that women who had high cortisol levels early in the day were less likely to experience pain and urinary urgency throughout the morning. In contrast, women with low morning cortisol levels were 12.8% as likely to experience these symptoms in the early part of the day. Recently, CP/CPPS has been contextualized as part of a group of chronic pain conditions, including IBS, chronic fatigue syndrome, and fibromyalgia. Findings in those syndromes comprise a large body of research that suggests the involvement of HPA in symptom generation. [17••].

The HPA can have a complicated interaction with disease states that impact symptoms, disease progression, and management strategy. McEwen and Kalia [17••] report that the impact of HPA mediators of allostasis on the stress

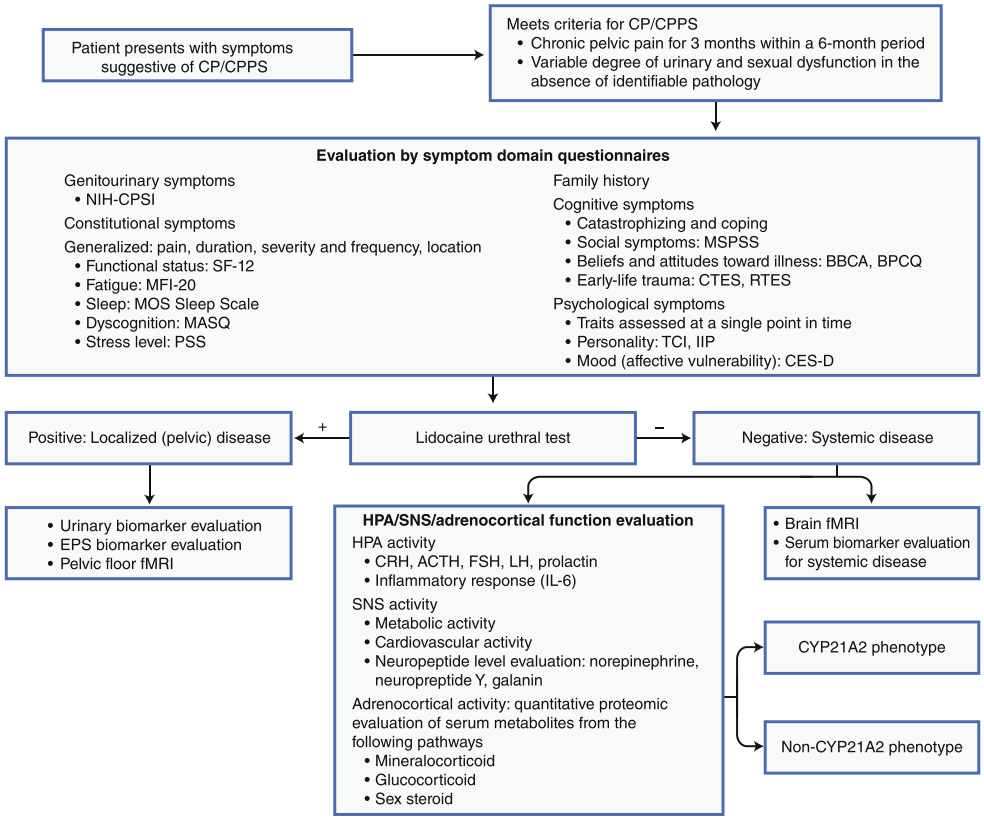


**Fig. 2** Design of the DABBEC Phenotyping System, a clinical phenotyping system for the diagnosis of CP/CPPS. This novel system mechanistically identifies phenotypic presentations of CP/CPPS by working through categorical evaluations to reach a specific pathophysiological cause. ACTH—adrenocorticotropic hormone; BBCA—Brief Beliefs and Coping Assessment; BPCQ—Beliefs about Pain Control Questionnaire; CES-D—Center for Epidemiologic Studies Depression Scale; CP/CPPS—chronic prostatitis/chronic pelvic pain syndrome; CRH—corticotrophin-releasing hormone; CTES—Childhood Traumatic Events Scale; CYP21A2—cytochrome P450, family 21, subfamily A, polypeptide 2; EPS—expressed prostatic secretions; fMRI—functional magnetic resonance imaging; FSH—follicle-stimulating hormone; HPA—hypothalamic–pituitary axis; IIP—Inventory of Interpersonal Problems; IL—interleukin; LH—luteinizing hormone; MASQ—Mood and Anxiety Symptoms Questionnaire; MFI-20—Multidimensional Fatigue Inventory; MOS—Medical Outcomes Study; MSPSS—Multidimensional Scale of Perceived Social Support; NIH-CPSI—National Institutes of Health/Chronic Prostatitis Symptom Index; PSS—Perceived Stress Scale; RTES—Recent Traumatic Events Scale; SF-12—Short Form 12; SNS—sympathetic nervous system; TCI—Temperament and Character Inventory

response is complex and nonlinear. Therefore, this leads to inconsistent results when treating such conditions with certain medications, such as steroids. Specifically, steroids have been found to produce paradoxical effects on pain. In some patients, the use of steroids alleviates pain, while in others, steroids can precipitate hyperalgesia. This seemingly contradictory finding is a result of the complex influence that HPA has on chronic pain conditions. The allostatic load has been used to predict a wide array of health outcomes.

Juster et al. [18••] suggested several biomarkers to measure to try to approximate allostatic load. The domains of allostasis that are likely to be most important in CP/CPPS are neuroendocrine and immune. These two domains include hormones like cortisol, epinephrine, norepinephrine, aldosterone, interleukin-6, C-reactive protein, and tumor necrosis factor-α (TNF-α). Potentially less important domains of their model are metabolic, cardiovascular and respiratory, and anthropometric. Juster and colleagues [18••] recommend that attention be paid to small, seemingly subclinical fluctuation in the levels of the biomarkers. The complexity of the interaction of HPA with the CP/CPPS disease state supports the notion that levels of one particular biomarker may be less important than the compound effect of small changes in levels of several biomarkers [18••]. Assessment of allostatic load will cause a significant advance in the diagnosis and classification of CP/CPPS. Currently, the only means by which CP/CPPS severity is quantified is by survey responses reported by patients. While this data is clinically useful, biochemical data will add to the understanding of CP/CPPS, providing an opportunity to objectively compare patients based on allostatic load, a value that reflects the levels of specific biomarkers. Furthermore, the addition of a biological parameter will advance the clinical evaluation of CP/CPPS. Currently, we do not know what the reference "normal" concentrations of these biomarkers are in the CP/CPPS patient population. This will present difficulty in interpreting

subtle differences in values and deciphering the relative clinical importance of small differences. Once enough data is collected from enough people, and the data is correlated with symptoms and disease state, the interpretation of biomarkers may prove to be instrumental in elucidating the mechanistic cause of CP/CPPS and essential to appropriate clinical care.

### *CYP21A2* Domain

Findings of altered HPA axis in CP/CPPS as described above provoked us to evaluate adrenocortical function/dysfunction as indicated by hormone levels produced by the adrenal gland. Our findings implicate decreased activity of the enzyme *CYP21A2* in the generation of symptoms in CP/CPPS. Therefore, *CYP21A2* is a candidate gene that is potentially mutated in CP/CPPS [19••]. This gene also is mutated in congenital adrenal hyperplasia, a disorder for which newborns are screened in 49 American states and at least 16 other countries. The screening can be done based on immunoassays of a dried blood spot collected for other newborn screening tests. The assay does not directly detect mutations in the *CYP21A2* gene; instead, it detects elevated levels of 17-hydroxyprogesterone (17-OHP). This metabolite accumulates because of a deficiency in the enzyme 21-hydroxylase, a product of the *CYP21A2*. The enzyme converts 17-OHP to 11-deoxycortisol and progesterone [20]. Therefore, increased levels of 17-OHP indicate a deficiency in 21-hydroxylase, which is a result of a *CYP21A2* mutation. The screening procedure, while not a direct test of *CYP21A2*, can help identify a population of patients with CP/CPPS who may be appropriate for direct gene sequencing and mutation analysis. This will help determine the role of *CYP21A2* in CP/CPPS. Symptoms and disease state can be correlated with *CYP21A2* status to elucidate the clinical significance of *CYP21A2* mutation in the CP/CPPS disease process. An advantage of introducing *CYP21A2* screening into the clinical assessment of CP/CPPS is the well-established average value that has been obtained from newborn screening data. Additionally, there is an accepted cutoff level of 17-OHP that signifies a *CYP21A2* mutation. If enough patients with CP/CPPS are screened for 17-OHP over time, an average 17-OHP can be established. This will allow clinicians to interpret 17-OHP levels in a way that is specific to the CP/CPPS patient population. Finally, the identification of a subgroup of patients with CP/CPPS with a specific mechanism would allow targeted therapeutic interventions.

## Future Directions for Chronic Prostatitis/Chronic Pelvic Pain Syndrome Phenotyping

The heterogeneous nature of CP/CPPS creates unique challenges in phenotyping the syndrome in the absence of any objective biomarkers. Discovery of the mechanistic underpinnings of CP/CPPS will allow physicians to make earlier and more accurate diagnoses and provide the basis for therapeutic clinical trials, which can potentially prevent disease progression [21•]. Objective quantitative patient parameters, such as messenger RNA levels, proteomic patterns (“proteomic signatures”), and signals derived from imaging methods (eg, magnetic resonance spectroscopy peaks) all have the potential of serving as biomarkers. Hewitt et al. [22] described the potential for biomarkers to be used as a tool to clearly define mechanisms of poorly defined diseases such as CP/CPPS. Furthermore, they discuss the power of a detailed understanding of a disease in the development of useful biomarkers, suggesting that early biomarker discovery in CP/CPPS could act as a catalyst for a better understanding and the identification of more biomarkers. [22]

Previous efforts at phenotyping CP/CPPS have done little in advancing the mechanistic understanding of the condition. A critical reason for the lack of mechanistic understanding of CP/CPPS is that researchers have continued to attempt to “categorize” clinical symptoms and presentations (as UPOINT does with its six “domains”). However, CP/CPPS would be better characterized as clinical symptoms and presentations that result from a number of unique mechanistic disturbances [21•]. Furthermore, these mechanistic disturbances may be responsible for multiple discrete symptoms. It is obvious that treating the underlying mechanism is not only more effective, but also more clinically and economically efficient (ie, treating a mechanistic disturbance alleviates several downstream symptoms). In this respect, DABBEC is designed to target the mechanistic underpinnings of CP/CPPS via biomarkers (such as *CYP21A2* and HPA axis) that need clinical validation, while UPOINT relies on the “categorization” of the clinical presentation of symptoms, a number of which develop from the mechanisms that DABBEC strives to describe (Fig. 1). In essence, treating the mechanistic disturbances afforded by DABBEC also would relieve multiple downstream symptoms, or “domains” as described by UPOINT.

We believe that the future of CP/CPPS diagnostic and therapeutic discovery lies in a comprehensive understanding of the mechanistic disturbances that underlie CP/CPPS pathogenesis. Thus, the basis of a mechanistic understanding of CP/CPPS lies in both the empiricism afforded by translational research and future biotechnological innovations in genomics, proteomics, and imaging. DABBEC will be used not only as a diagnostic tool, but also be used to aid these future advances [19••].

Previous studies have shown that extensive generation and compilation of genomic, proteomic, and metabolomic data provide the mechanistic basis for intricate networks

underlying the etiological basis of disease [23•]. These networks reveal the emergent properties of the most common forms of diseases, thereby eliciting etiological understanding and effective treatment. Furthermore, drug development has been largely dependent on the elucidation of linear mechanistic cascades in disease progression followed by identification of appropriate pathways, which can be pharmacologically modulated.

The success of network-based phenotypic screening is principally influenced by the development of networks that are mechanistically predictive rather than merely descriptive. Given the heterogeneous nature of the disorder and the numerous systems implicated in its presentation, understanding of the disease could potentially benefit from thorough network analysis. In delineating the differences between UPOINT and DABBEC, UPOINT description would not be able to provide a predictive framework for network models because the system focuses on providing "clinical descriptions" across the six UPOINT domains, while DABBEC is both predictive and forward looking as it accepts the complexity of CP/CPPS and relies on clinical and basic-science evidence (as is evidenced in the HPA and *CYP21A2* domains) as catalyzing agents in the development and refinement of CP/CPPS phenotyping. Therefore, it is evident that DABBEC provides promise in elucidating the intricate effects of candidate biomarkers on network effects.

To move the field toward successful and efficient treatment of CP/CPPS, it is necessary to establish a defined set of clinical phenotypes for CP/CPPS and to elucidate the underlying mechanisms of CP/CPPS. Advances will not be made using phenotypic approaches, such as UPOINT, that are designed to "allow us to understand our failure to discover a single cause or cure for CP/CPPS" [9••]. The heterogeneity of CP/CPPS is already well established and does little in providing new predictive information. Successful CP/CPPS phenotyping systems must be dynamic to incorporate advancements in biotechnology. Furthermore, they must provide a method for integrating evidence from translational research with improved technologies. Adapting a predictive and forward-looking phenotyping model, such as DABBEC, can accomplish these goals. The DABBEC Phenotyping System pushes for advancements in the understanding and treatment of CP/CPPS by providing a radically new way of characterizing and understanding the biology of the syndrome.

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