Urinary Biomarkers for Chronic Pain Management

Meeting Date & Time:	June 22, 2023, 4:00-5:00 p.m. EST
Facilitator:	Dr. Meredith Loveless, CMD
Location:	Teleconference
Topic Discussion:	DL39616 Urinary Biomarkers for Chronic Pain Management

Dr. Loveless: Urinary Biomarkers for Chronic Pain Management, Biomarkers are developed to help diagnose, aid in prognosis and evaluation of treatment response and help inform decision making for drug development and treatment. At this time, there's no specific biomarkers for chronic pain.

There is a currently available test called the Foundation Pain Index, or FPI, developed by Ethos Laboratory in Newport, KY, and this test evaluates multiple different biomarkers in order to create a panel of biomarkers for evaluation of chronic pain.

This is collected via a urine sample and then an algorithm is used to report a pain index score and the likelihood of atypical biochemical function associated with pain.

At this time, this test is non-covered.

The basis of this test is that there are nutritional deficiencies, metabolic abnormalities and oxidative stress that can be treated with dietary modification or supplementation.

The challenge is that there is a lack of evidence to support the treatment of chronic pain through dietary modification or supplemental pathways.

And this route of management is not part of the management pathways included by the American Society of Anesthesiologist, American Academy of Pain Medicine, Institute of Clinical Symptoms improvement, or the NIH guidelines.

Nor do they include urinary biomarkers as part of the management pathways for chronic pain.

There are three studies that were published to support the Foundation Pain Index, urinary biomarker test, and I'll review each of these studies, but in summary, there's a retrospective study that concludes 11 biomarkers are abnormal and chronic pain patients as compared to pain free control and observational study designed for clinical validity to determine a discriminatory value for the FPI test and then a randomized controlled trial that was non-blinded to establish clinical utility looking at primary care physicians treatment if they receive the results of the FPI test and if they and the algorithms for those treatment pathways as compared to providers who did not receive this information.

The challenge with this literature is that there are significant limitations. This is included in the study design. There is confounding risk of bias, lack of clear definition of chronic pain, the role of pain and comorbid conditions, and quantification of pain is not clearly established as well as a lack of value validation of the individual biomarkers. And finally, the effect of other medications from the biomarker test results is not established. There is also a lack of validation using comparison to standard of care.

The retrospective study was analyzed using grade analysis and due to these risk factors, was determined to be very low quality. This includes the lack of blinding randomization method and risk of bias, and this is the randomized control trial, not retrospective, and I apologize for the error.

Currently there is not established evidence to support a role of urinary biomarker test for management of chronic pain, which led to CGS's Administration's decision to consider the urinary biomarker test for chronic pain, experimental and non-covered at this time.

We do have one presentation, so I'll be turning the floor over to our presenter, but prior to turning that over, I do want to explain that this policy is currently in the open comment period.

That means we can receive comments from providers, stakeholders, any other interested parties. Our preferred way to receive those comments is for them to be sent through the electronic form that's located on our website and submit that form to cmd.inquiry@cgsadmin.com.

We will respond to all received comments in a published response to comment article for all comments that are received.

We encourage submission of peer reviewed supporting literature for those comments. Our comment period is open through July 9th, 2023.

This slide does provide the direct website for the PDF form for the comments and the email box for comments. Draft LCD Comment Submission Form (A/B MAC Jurisdiction 15): https://www.cgsmedicare.com/pdf/j15/j15_draft_lcd_Comment_submission_form.pdf.

And now I'm going to turn the floor over to our presenter and we will pull up your slides.

Dr. Gunn: Good afternoon, this is Josh Gunn. I'm the Chief Scientific Officer and Co-founder of Ethos Research and Development.

I'd start by disclosing that my company was directly involved with the development of Foundation Pain Index and the clinical studies demonstrating its clinical validity and utility.

Ethos Research and Development now licenses this technology to Ethos Laboratories.

So firstly, thank you for the opportunity to present today and apologies again for the other check complications.

I'd like to first make mention of the fact that the proposed LCD, in its current form, did not include reference to or review of an important piece of peer reviewed literature supporting the clinical validity of FPI.

The proposed LCD may have been prepared prior to this publication, but I did want to point out that we would like to submit in its full form the manuscript here entitled, “Cross Validation of Foundation Pain Index with PROMIS- 29 in Chronic Pain Patients.

This manuscript was published in the Journal of Pain Research in August of 2021, and we would ask that the committee include this publication in its review and summary of evidence, in addition to the three manuscripts described here this afternoon. And we will provide this in the public comments.

So, a little detail on this study, this study was designed to further investigate the relationships between the objective biomarkers of the FPI and the validated patient reported outcomes. As you may recall, FPI was initially validated against the short form 36 or the SF36 Questionnaire, which is arguably the most widely used measure of health related QoL in chronic pain research.

In the clinic, however, many physicians utilize the PROMIS-29 to evaluate chronic pain and its impact on quality of life and several of our physician collaborators suggested that by cross correlating FPI with the PROMIS-29, we would not only further establish the clinical validity of FPI, but also provide more direct relevance to many trading physicians.

And I’ll just make a point here that when it comes to clinical validation of biomarker assays for subjective states like chronic pain, where obviously without a gold standard criterion, if you will, such as a biopsy or an unequivocal test.

And so, it's become very commonplace and widely accepted to establish criterion validity of these biomarker assays against validated clinical assessments of pain and hence our efforts to validate against the SF36 and the PROMIS-29 briefly.

However, PROMIS-29 scores and FPI scores were obtained from 298 subjects with chronic pain.

And as was the case in our first validation study, FPI, scores were found to correlate significantly with multiple PROMIS-29 domain and overall PROMIS-29 scoring, which further supports the role of deranged biochemistry in the etiology of chronic pain.

Specifically, FPI scores correlated most strongly with domains of paying fatigue, depression and physical functioning. And again, we will submit this manuscript in its full form.

The proposed LCD indicates on several occasions that there are no specific biomarkers for pain.

This is a true and fair statement and actually an important part of FPI messaging, because pain is and always will be a subjective experience and as such can't be objectively measured, and other leading researchers in the field stated, pain is a subjective sensory experience that can mostly be reported but cannot be directly measured or quantified.

And they go on to say that instead, the goal of biomarker work should be to utilize objective measurable correlates of the pathophysiological processes involved in different chronic pain conditions. And I would just say that this statement is the principal basis for foundation pain Index. FPI does not claim to detect the presence of pain.

It doesn't claim to refute or confirm the claim of pain. It doesn't claim to quantify one's experience with pain. Instead, it utilizes measurable correlates to determine what role, if any, biochemical processing maybe responsible for driving painful symptoms.

Foundation Pain Index is indeed a panel of mechanistic pain biomarkers. And by this, I mean that each biomarker in this panel is well characterized as a marker of a particular biochemical pathway. And each of the biochemical pathways represented is well characterized as being pain relevant. By definition. however, a mechanistic pain biomarker will only be present or abnormal when that biochemical pathway it represents is perturbed or abnormal.

So therefore, mechanistic pain biomarkers can never be validated as being pain biomarkers by the FDA because they won't be abnormal in every single pain patient.

However, when they are found to be abnormal, that provides incredibly valuable insight for that given patient, and I'll illustrate my point in the simplest form.

Elevated methylmalonic acid, which is indicative of an intracellular vitamin B12 deficiency, will never be validated by the FDA as a pain specific biomarker because not all chronic pain patients have vitamin B12 deficiencies.

But if a particular patient presents with idiopathic peripheral neuropathy or paresthesias and is found to have an elevated level of methylmalonic acid, then that indeed is a pain biomarker for that patient.

And that's the distinction I'd like to make between pain perception biomarkers and mechanistic biomarkers.

Just to provide or illustrate further the impact of these mechanistic biomarkers. I wanted to present a little bit of real-world data very, very briefly.

In the 10-month period between July of 22 and April of 23 physicians employing FPI testing have been able to identify the following: 3,147 vitamin B12 deficiencies.

I would note that many of these patients present with pain related symptoms consistent with B12 deficiency according to their ICD 10's and elevens. Common ICD 10s include those of chronic fatigue and idiopathic peripheral neuropathies.

Without FPI testing, these symptoms may be regarded as idiopathic, moving forward and left to worsen. But with FPI testing, physicians are able to identify the biochemical processes driving these symptoms and therefore can treat or counsel accordingly.

6,308 vitamin B6 deficiencies. Again, many of these patients present with peripheral neuropathy or idiopathic neuropathies.

Finding a specific biochemical abnormality which is documented to drive symptoms consistent with patient presentation means that FPI not only provides answers as to why, but also facilitates decision making when evaluating treatment options.

The last thing I'll mention here just for the purpose of time, testing also identified more than 15,000 patients with elevated markers of systemic inflammation.

These markers have been shown in the literature to correlate with pain, which we will provide in the public comments, but also drive the development of the pressive symptoms through their direct action on NMDA receptors. And we all understand the importance of these common behavioral and mental health tone in pain.

I I'd also like to make points that recently a group of leading physicians developed a clinical guidelines document, which outlines best practices for the implementation and utilization of Foundation Pain Index.

This document is full of peer-to-peer guidance on medical necessity, test utilization, how to address abnormal findings and what to expect when initiating FPI testing.

These best practices will be published as a white paper and made available to physicians employing FPI, and we will also present at national meetings and conferences.

Additionally, a large prospective study employing biomarker guided therapies and longitudinal FPI testing is scheduled to begin recruiting on August 1st of this year.

This study, known as FPI 001, has been designed to evaluate the impact of targeted interventions on chronic pain subjects who exhibit abnormal FPI results at baseline.

This will be the largest study ever conducted exploring the relevance and utility of biomarker guided interventions in chronic pain and we feel very strongly that any concerns raised in the proposed LCD regarding the efficacy of such interventions will be sufficiently addressed during this study.

We will conclude, by simply saying that we would, we would ask CGS Administrators to review and consider not only the information presented today, but also the peer reviewed publication that was not included in their initial analysis.

I would also note that we are preparing, and we'll submit additional peer review support via the public comment mechanism prior to the July 9th deadline.

And I would just say that without Medicare coverage, it's very unlikely that physicians will have the ability to identify and address the neurobiological underpinnings of chronic pain.

And our team feels very strongly that pain is in great need of novel objective tools as we continue to battle our way out of the opioid epidemic.

Thank you for your time and consideration today.

Dr. Loveless: Thank you very much for your presentation and we will look forward to receiving the additional literature and written comments during our open comment period.

We do not have any additional presentations, so that is going to conclude today's open meeting and the and the information on how to submit comments has already been presented. So, if there's any questions on that, you're welcome to reach out to us and otherwise have a wonderful evening.

Thank you everyone for your time.