# The Evidence-based Vulvodynia Assessment Project

## *A National Registry for the Study of Vulvodynia*

**Georgine Lamvu, M.D., M.P.H., Ruby H. N. Nguyen, Ph.D., Lara J. Burrows, M.D., Andrea Rapkin, M.D., Kathryn Witzeman, M.D., Richard P. Marvel, M.D., David Hutchins, M.D., Steven S. Witkin, Ph.D., Christin Veasley, B.S., Roger Fillingim, Ph.D., and Denniz Zolnoun, M.D.**

*OBJECTIVE: To create a national registry for the study of vulvodynia in order to enhance classification of vulvodynia based on multiple phenotypic domains such as pain characteristics, clinical examination, sexual function, psychological functioning, and distress.*

*STUDY DESIGN: Methodology for this prospective cohort registry was institutional review board approved and implemented at 8 enrollment sites starting in 2009. Women underwent gynecologic evaluation and pressure sensory testing for assessment of pain sensitivity in the vaginal mucosa and vaginal muscles. Psychometric questionnaires were used to assess self-described pain, distress, sexual function, and quality of life.*

***…women with vulvodynia should also be routinely evaluated for musculoskeletal dysfunction, comorbid pain conditions, and emotional distress…***

*RESULTS: More than 300 women were enrolled and 176 charts were analyzed. This cohort had a median age of 29 years and median pain duration of 25.5 months. A total of 84% of participants were previously or currently sexually active in spite of pain. The most common pain comorbidities reported by the women were migraines (34%), chronic pelvic pain (22%), and irritable bowel*

From the Division of Advanced Minimally Invasive Surgery and Gynecology, Florida Hospital, Orlando, Florida; the Division of Epidemiology and Community Health, University of Minnesota, Minneapolis; the Center for Sexual Health, Akron, Ohio; the Department of Obstetrics and Gynecology, David Geffen School of Medicine at the University of California–Los Angeles; the Pelvic Pain Clinic, Denver Health Medical Center, Denver, Colorado; the Center for Pelvic Pain at Annapolis, Annapolis, Maryland; the Center for Vulvar Disorders, University of Arkansas for Medical Sciences, Little Rock, Arkansas; the Department of Obstetrics and Gynecology, Weill Cornell Medical College, New York, New York; National Vulvodynia Association, Silver Spring, Maryland; Pain Research and Intervention Center of Excellence, University of Florida, Gainesville; and the Pelvic Pain Unit, Department of Obstetrics and Gynecology, University of North Carolina, Chapel Hill, North Carolina.

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Data and methodology from the National Vulvodynia Registry has been presented at the Annual Meeting of the Society for Gynecologic Investigation, Orlando, Florida, March 20–23, 2013; the Annual Meeting of the International Pelvic Pain Society, Orlando, Florida, October 17–19, 2013; and the 33rd Annual Scientific Meeting of the American Pain Society, Tampa, Florida, April 30–May 3, 2014.

Address correspondence to: Georgine Lamvu, M.D., M.P.H., Division of Advanced Minimally Invasive Surgery and Gynecology, Florida Hospital, 2415 North Orange Avenue, Suite 300, Orlando, FL 32804 (georgine.lamvu@flhosp.org).

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*syndrome (20%). Anxiety affected 41% of the cohort. More than 90% presented with localized vestibular pain, and 90% had muscular examination abnormalities.*
*CONCLUSION: A national registry for the study of vulvodynia was established with successful enrollment of participants at 8 sites. In addition to the cotton swab evaluation for vulvar allodynia, women with vulvar chronic pain should also be routinely screened for musculoskeletal dysfunction, emotional distress with specific emphasis on anxiety, and comorbid pain conditions.* (J Reprod Med 2015;60:223–235)

**Keywords:** chronic pain, musculoskeletal pain, registry, vestibulitis, vulva, vulvar pain, vulvodynia.

Vulvodynia is a condition characterized by chronic vulvar pain that affects >14 million women in the United States. Of the millions who have these symptoms, half do not seek medical care for their pain.[1] Among those who seek help, 60% will see 3 or more doctors at some point in their lifetime for vulvar pain symptoms.[1] Women with vulvodynia suffer on average >5 years without receiving a definite diagnosis, and <1.4% of those seeking care actually receive an appropriate diagnosis.[1] Despite the burden of this condition on women's health, little progress has been made in its treatment since this disease was first described more than 100 years ago.[2,3]

In general, vulvodynia is a diagnosis limited to patients without an obvious identifiable cause for their pain, such as infection (*Candida* or herpes), neoplasia, neurologic disorder (e.g., herpes neuralgia, spinal or peripheral nerve compression), or dermatologic conditions (such as lichen planus or lichen sclerosis). Vulvodynia is often further characterized based on (1) whether it is localized to one area of the vulva or generalized, (2) provoked by contact (such as with intercourse or tampon insertion) or not provoked, and (3) whether pain began with first vulvovaginal contact (primary) or whether it began after a pain-free period of time (secondary).[4-6] Since its description by Friedrich[7] in 1980, there has been little advancement in the clinical techniques to classify women with chronic vulvar pain. Besides the presence of pain during a vulvar examination using a non-painful stimuli such as a cotton-tip swab applicator, there is no other evidence-based method for differentiating subtypes of vulvodynia.

Rather than a homogeneous group representing a single disease entity, vulvodynia (like headache) is now recognized to display considerable variability in clinical symptoms, physical findings, and extragenital pain sensitivity, indicating a probable substantial heterogeneity in the mechanisms underlying this disorder. Current diagnostic approaches based on onset, location, and pain during cotton swab evaluation are insufficient to describe this phenotypic heterogeneity. The inability to consistently classify phenotypes of vulvodynia patients may partially explain the limited effectiveness of currently available treatments.[8,9]

In 2004 and 2012 the National Institutes of Health convened state-of-the-art consensus meetings on vulvodynia research in which one of the primary recommendations was that researchers should establish a national registry to collect baseline and follow-up data from vulvodynia patients treated in multiple practice settings.[10] Clinicians and researchers agreed that there is an immediate "need for consistent terminology definitions, and diagnostic criteria for research and patient care" that include "psychosocial aspects of vulvodynia, especially those related to sexual function, comorbid conditions, and appropriate ways to measure pain."[11]

To address the insufficient diagnostic criteria for the phenotyping of vulvodynia, our initial objective was to create a national registry for the study of vulvodynia. The aim of the National Vulvodynia Registry (NVR) was to develop multidimensional assessment tools that reflect routine clinical practice and to include in-depth exploration of patient characteristics before and after the treatment of vulvovaginal pain. Features considered important to the registry included collaboration between multiple clinicians and researchers and development of data collection questionnaires and examination tools that can be standardized across all sites. In an effort to further elucidate the etiology and natural history of vulvodynia, the NVR also aimed to identify immune and genetic biomarkers that will allow classification of women with vulvodynia into therapeutically relevant subtypes. The future objective of the methodology developed in this registry is to enhance classification of vulvodynia by subtyping patients across multiple phenotypic domains such as pain characteristics (e.g., duration, temporal features, pain qualities), clinical examination (e.g., skin inflammation, muscular dysfunction), genital and extragenital pain sensitivity, psychological functioning and distress, and sexual function.

The overarching goal of our research is to move toward a mechanism-based classification by determining the clinical and pathophysiologic validity of these phenotypic subtypes. This registry represents the most comprehensive approach to phenotyping vulvodynia patients to date, and we expect that in the future these biopsychosocial phenotypes will serve not only to diagnosis but also to help create more effective targeted therapies. The primary purpose of this article is to describe in detail the methodology developed for the registry while briefly presenting some characteristics of the study population. Additional specifics on pain and psychometric, immunologic and genetic characteristics of women enrolled in the NVR will be fully described in subsequent publications.

## *Methods*

From 2008 through 2009 clinical and research experts on chronic vulvovaginal conditions were invited to form a collaborative study group and establish a national registry. Consensus on the primary objectives for the registry was achieved and are as follows: (1) to objectively measure baseline patient characteristics such as self-reported symptoms, pain levels, physical function, sexual function, and pain-related psychological distress, (2) to objectively measure skin and muscle sensitivity and document the visual appearance of vulvar and vaginal tissue, (3) to investigate the potential for distinct subtypes of disease based on patient characteristics and measures of skin and pelvic floor muscle dysfunction, (4) to determine which patient characteristics or clinical examination measurements are better predictors of treatment outcomes, and (5) to define genetic, immune, and infectious biomarkers and their association with specific phenotypes.

### *Development of the Clinical Assessment*

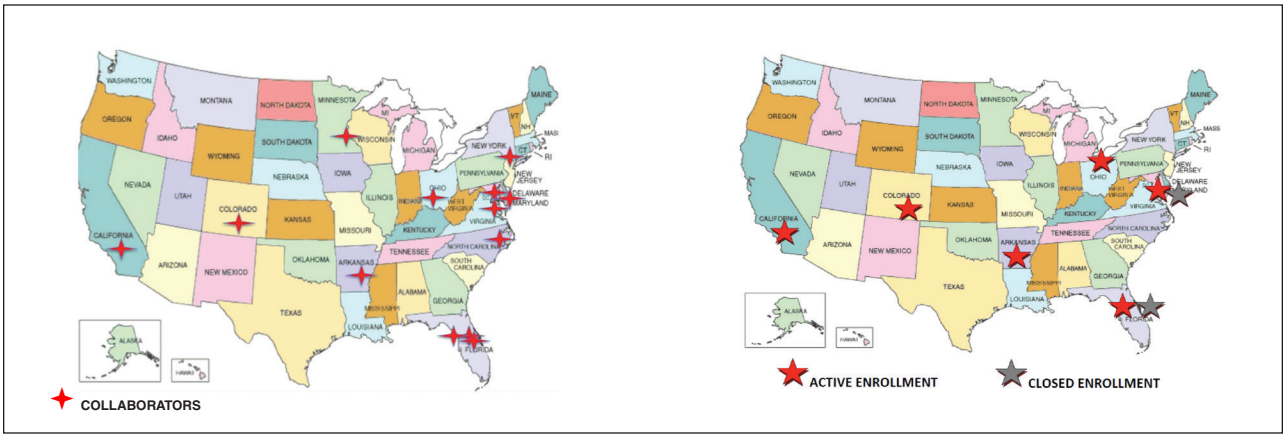
An extensive review of the literature (MEDLINE, EMBASE, and Cochrane Database) and consensus among collaborators was used to develop protocols for clinical evaluation of the vulva and vaginal muscles. The initial methodology for the physical examination of vulvar mucosa and muscular sensitivity was tested and validated under a previous grant funded by the National Institutes of Health (NIH) (K23 HD053631 01).[12] Similar consensus based on expertise and literature review was used to select psychometric questionnaires for evaluation of patient self-described quality of life, depression, anxiety, coping, partner relationships, sexual function, and presence of other chronic pain diagnoses.[13-22] An additional general medical and treatment history questionnaire was developed to collect information on pain history, previous medical comorbidities, surgical history, sexual history, and medical and surgical treatments for vulvodynia.

We anticipated that adapting a single standardized methodology across all clinical sites would pose significant challenges. For example, interindividual variation and site limitations were encountered during the early stages of protocol development. Thus, prior to formal initiation of the protocol we focused on attaining reliable and reproducible measures within and between examiners and ensuring that procedures could be carried out consistently within and between sites. The investigators underwent formal training sessions specifying testing technique, instrument calibration, and data collection to ensure that all mucosal and muscular measures were collected in a comparable manner. Seven clinical site investigators who participated in enrollment (Figure 1) attended 1 training session lasting 1–2 hours before starting enrollment and another session after the first 1–5 participants were enrolled (1–2 hours). Investigators also attended an annual meeting (4–6 hours), where they were retrained and measurement issues were addressed. All registry sites were provided with written protocols, instructions, and mechanical algometers (Wagner Instruments Pain Test, Greenwich, Connecticut). Institutional review board approval was obtained in writing at each clinical site before enrollment began.

Once standardized protocols were employed across 8 enrollment sites (Figure 1), the cohort of patients was followed for a period of 12 months as detailed in Figure 2; for some participants, follow-up is ongoing. Data analysis was performed using Stata Statistical Software v.10 (Stata, College Station, Texas).

### *Inclusion/Exclusion Criteria*

The registry was limited to patients with vulvodynia (including vestibulitis) and normal, pain-free patients as controls. Vulvodynia was defined as vulvar pain (often described as burning) occurring in the absence of obvious pathology (infectious or inflammatory, neoplastic or neurologic). Vestibulitis was defined as pain on vestibular touch (tampon insertion) or intercourse and physical findings limited to erythema.[4,23] Any woman reporting these




| Collaborator | Location | Role |
|---|---|---|
| Georgine Lamvu, M.D., M.P.H. | Division of Advanced & Minimally Invasive Gynecology, Florida Hospital, Orlando, FL | National Vulvodynia Registry Director<br>Leadership/Administration<br>Primary Clinical Investigator and Patient Enrollment Site<br>Scientific Oversight and Analyses |
| Lara Burrows, M.D. | Center for Sexual Health, Akron, OH | Clinical Investigator and Patient Enrollment Site |
| Andrea Rapkin, M.D. | Department of Obstetrics and Gynecology, David Geffen School of Medicine at UCLA, Los Angeles, CA | Clinical Investigator and Patient Enrollment Site |
| Kathryn Witzeman, M.D. | Pelvic Pain Clinic, Denver Health Medical Center, Denver, CO | Clinical Investigator and Patient Enrollment Site |
| Richard Marvel, M.D. | Center for Pelvic Pain at Annapolis, Annapolis, MD | Clinical Investigator and Patient Enrollment Site |
| David Hutchins, M.D. | Center for Vulvar Disorders, University of Arkansas for Medical Sciences, Little Rock, AR | Clinical Investigator and Patient Enrollment Site |
| Lori Boardman, M.D. | University of Central Florida, Orlanda, FL | Clinical Investigator and Patient Enrollment Site |
| Steven Witkin, Ph.D. | Department of Obstetrics and Gynecology, Weill Cornell Medical College, New York, NY | Scientific Oversight and Analyses<br>Biological Specimen Analysis |
| Roger Fillingim, Ph.D. | Pain Research and Intervention Center of Excellence, University of Florida, Gainesville, FL | Scientific Oversight and Analyses<br>Pain Assessment Methodology |
| Denniz Zolnoun, M.D. | Pelvic Pain Unit, Department of Obstetrics and Gynecology, University of North Carolina, Chapel Hill, NC | Scientific Oversight and Analyses<br>Vaginal Exam Standardization |
| William Ledger, M.D. | Department of Obstetrics and Gynecology, Weill Cornell Medical College, New York, NY | Scientific Oversight and Analyses<br>Vulvar Cross Polarized Light Imaging |
| Ruby Nguyen, Ph.D. | Division of Epidemiology & Community Health, University of Minnesota, Minneapolis, MN | Scientific Oversight and Analyses<br>Epidemiology Data Analysis |
| Christin Veasley | National Vulvodynia Association, Silver Spring, MD | National Vulvodynia Association, Director<br>Leadership/Administration |

**Figure 1** Registry collaborators and enrollment sites.

complaints for longer than 3 months was eligible for screening and evaluation. *Because the causes of vulvodynia and vestibulitis are poorly understood, and the definition is controversial, the inclusion criteria were*

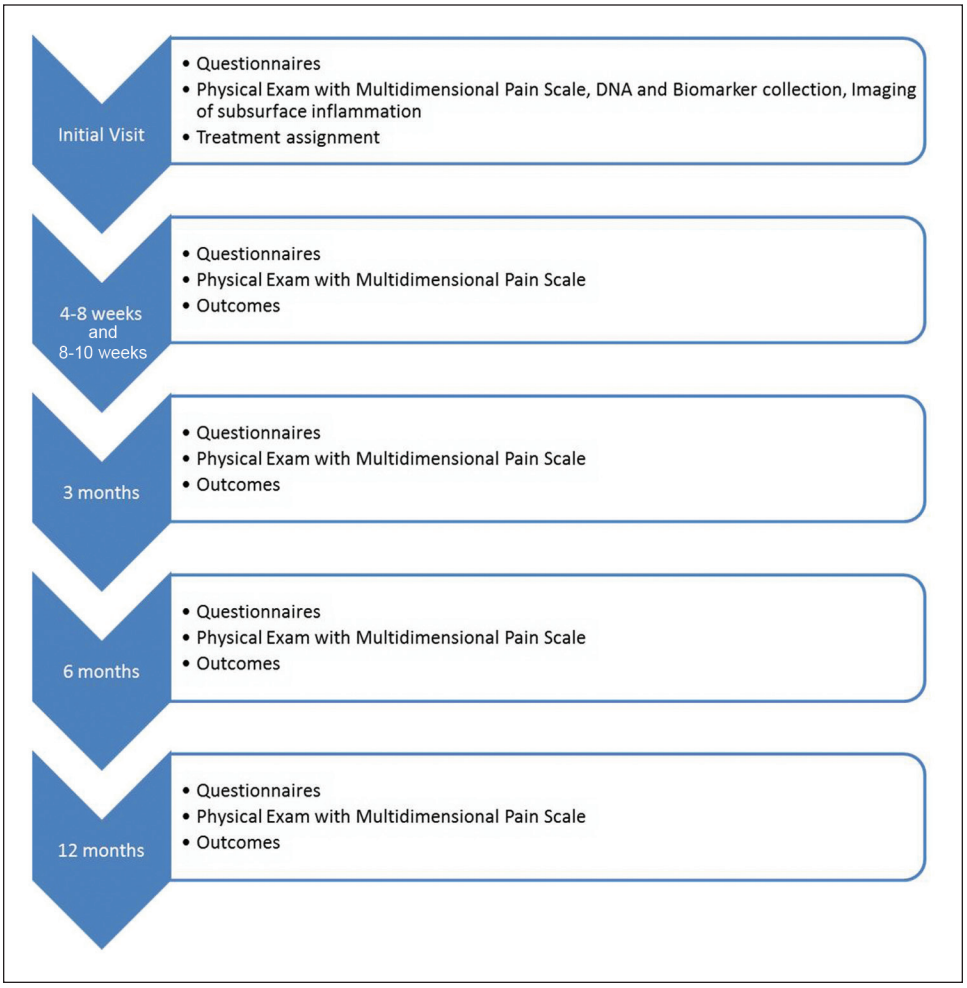



**Figure 2**
NVR participant flow.

*purposely left broad.* Pain or discomfort had to be subjectively described as severe enough to cause impaired sexual function and quality of life. All participants were screened for chronic vulvar pain using the standardized questionnaire by Harlow and colleagues.[3]

Women were excluded if they met any of the following criteria: (1) non–English speaking, (2) aged < 20 years, (3) inability to provide consent, (4) history of recent psychiatric hospitalization, current illicit drug abuse, current uncontrolled seizure disorder, (5) history of reproductive tract malignancy or post-chemotherapy or radiation therapy, (6) pregnant or breast-feeding, (7) presence of acute pelvic pain that required immediate evaluation and treatment, or (8) any of the following findings upon gynecologic screening examination: vaginismus preventing examination, vulvar dermatitis such as lichen planus or lichen sclerosis, and pelvic mass.

### *Participant Flow, Treatment and Subsequent Follow-up*

After providing informed consent, all participants completed the General Medical History questionnaire, which collected demographic information as well as pain, medical, reproductive and surgical history. Specifically, we gathered data on gravidity, parity, duration of intercourse-related pain, past treatments, past surgeries, number of physicians seen to date, current medications (e.g., hormonal contraceptive, antidepressants, anticonvulsants, and anxiolytics), and a detailed pain history. Participants were then educated about the pain measurements, descriptors of pain, and study protocols. When the education was completed, providers began the gynecologic examination in sequential order as described in Table I: (1) visual inspection of the vulvar region to rule out dermatoses and vulvovaginitis, (2) inspection of the vulva and vestibule

using cross-polarized light, (3) assessment of the internal vaginal mucosa for allodynia and collection of 2 vulvar and vaginal swab samples, (4) sensory neurologic examination of the vulva and perineum, (5) vestibular pain mapping (testing for static and dynamic allodynia) and collection of 2 vestibular samples, (6) internal musculoskeletal examination of single digit palpation, (7) speculum examination, measurement of vaginal pH, wet prep, potassium hydroxide (KOH), (8) bimanual examination (to minimize risk of including women with pain secondary to deep dyspareunia, pelvic mass, or other pelvic pathology), (9) testing pain sensitivity at extragenital sites (bilateral deltoids and shins), and (10) obtaining a buccal swab for DNA analysis (Epicentre, Madison, Wisconsin) if the participant consented to biospecimen collection for genetic testing.

Patients were treated according to the clinician's recommendation. Participation in the registry did not modify any medical management recommended as provided by the woman's healthcare team. However, all enrolled patients were asked to return at 3, 6, and 12 months after the initial visit. All treatments prescribed were recorded in detail including type of therapy, dosing, timing of use, and compliance with recommended therapy.

During each visit, participants were also asked to complete a Gracely Box Pain Scale, a questionnaire that evaluates sensory (severity of pain) and affective (emotional response) components of pain.[13,14] For the purposes of our research the Gracely Box Pain Scale was modified to specifically assess components of pain associated with intercourse. Psychometric and quality of life questionnaires were completed at the end of the initial visit and at 6 and 12 months. Questionnaires also screened women for sexual or physical abuse. Completion of questionnaires was conducted in a private setting in-clinic or at home with the requirement that they be returned to the clinic within 2 weeks of the visit (via mail or in person).

### *Assessment of Vulvar and Muscular Pain*

Perineal, vaginal mucosa, and pelvic muscle testing was conducted using a technique previously developed by Zolnoun and colleagues[12] and modified for use by registry investigators. The procedure is fully described in Table I. Briefly, the examination began by first educating the participant on the cotton-tip examination such that baseline is established as "cotton ball" when she is touched with the cotton portion of the applicator or "pin prick" when she is touched with the wooden portion. Participants were also instructed that if they feel a painful sensation, the pain should be quantified using a visual analog scale (VAS) (0–10), where 10 is the "worst imaginable pain."[24] Investigators were taught to distinguish between mechanical allodynia and hyperalgesia.[25] Mechanical allodynia was characterized as pain in response "to a stimulus that does not normally provoke pain."[25] That is, a participant

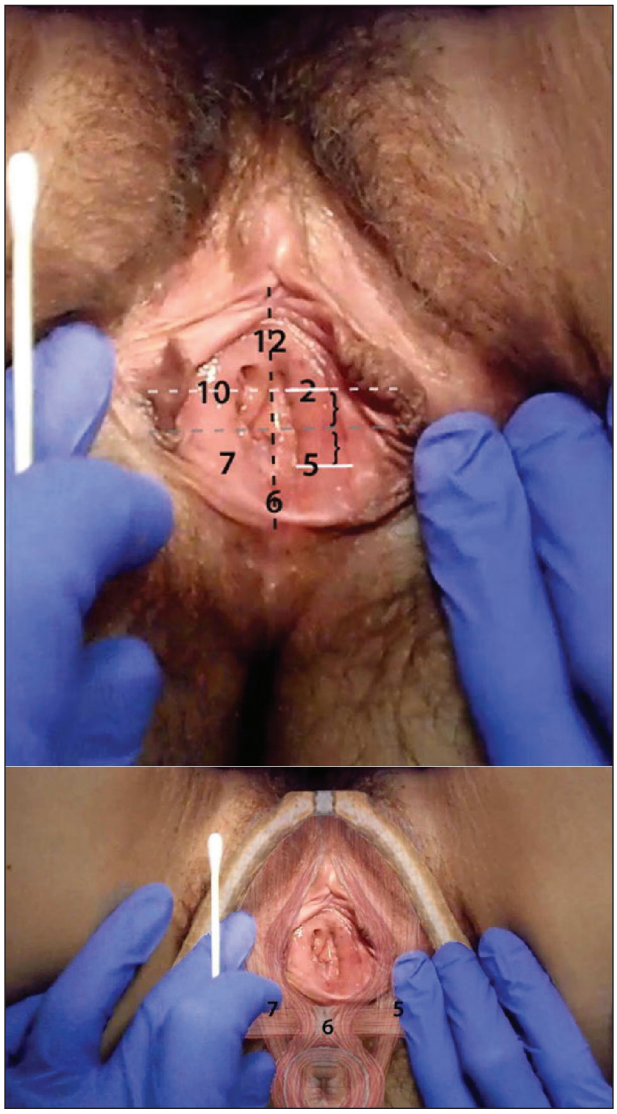



**Figure 3** Anatomical sites of vestibular and muscular testing. Measurements of vulvar proportions and size are in relation to Hart's line, the point where keratinized hairy skin transitions to mucosa. Images of anatomical sites courtesy of Denniz Zolnoun, M.D.

would report "pain" instead of "cotton ball" when touched with the cotton portion of the applicator. Mechanical allodynia was further differentiated as static when it occurred in response to light pressure or dynamic if it occurred in response to light brushing. Conversely, hyperalgesia was characterized as increased sensitivity to a painful or noxious stimulus.[25] In this case the participant would report "pain" instead of just a "pin prick" when touched with the wooden portion of the applicator. For all reports of pain the investigators were asked to record a corresponding VAS score threshold.

After ensuring that the participant was comfortable in a neutral lithotomy position, the examiner first looked for abnormalities and abrasions of the vulvar skin. To assess for vaginal allodynia, a wet cotton-tip swab was inserted into the upper 2/3 of the vaginal canal (taking care to avoid the vestibule) and moved back and forth while asking 3 questions: (1) "Is the movement neutral or unpleasant?" (2) "Do you feel pressure, pain, or neither with the movement of the cotton-tip swab?" (3) "If painful, is the pain similar to the pain you experience with intercourse?"

Then a brief neurosensory examination of the vulva was done by gently stroking (upwards) the sensory dermatomes T12, L1, S2/S3, S4/S5, and S1 with a cotton swab. This examination was repeated with the sharp wooden portion of the cotton swab using static pressure. With these 2 examinations the provider determined if the participant had allodynia, hyperalgesia, hypersensitivity, or normal sensation. Participants were also asked to describe if the sensation was equal on both sides and, if there was pain, to provide the severity using the VAS and McGill descriptor for the pain.

The examiner then proceeded to sensory examination of the vulvar vestibule (Table I). Six anatomical sites on the vestibule were determined with reference to the conventional "clock face," with 12 and 6 o'clock positions corresponding to the anterior and posterior position on the midline, respectively (Figure 3). The vestibule was examined using both static and dynamic touch with the cotton-tip to identify allodynia. Next the examiner assessed pelvic floor muscle function and sensitivity. The participant was educated on which muscles the examiner would test, which sensations to focus on, and which to ignore (i.e., skin irritation, bone sensation, and the sensation of flatulence). Initially, the examiner calibrated his/her finger to 2 kg of pressure (using a 15 kg digital pressure algometer) and then slowly inserted 1 lubricated digit into the vagina while avoiding the vestibule. After that, the examiner went through a sequence assessing the presence or absence of pelvic floor contracture and the ability to voluntarily contract the pelvic floor. The patient was then allowed to relax and maintain a relaxed pelvic floor for about 5 seconds before the examiner proceeded to internally applying around 2 kg of pressure, for approximately 2 seconds, to the superficial muscles of the vaginal entrance: bulbocavernosus at 5 o'clock and 7 o'clock and the perineal body at 6 o'clock. Lastly, with similar internal pressure, the examiner palpated the levator complex on the right and on the left (Figure 3). With each pressure location the examiners asked the patient to rate and describe her pain.

The gynecologic assessment was completed with a speculum examination where the examiner obtained a vaginal sample using a cotton swab, measured the pH, and prepared a wet prep and KOH slide, all to rule out other conditions that may contribute to vulvar pain.

### *Assessment of General (Extragenital) Pain Sensitivity and Collection of Genetic and Immune Biomarkers*

Biomarkers were selected based on the best available evidence indicating a potential link to development of chronic vulvovaginal pain or chronic pain[26-41] and on financial and technical resources available for the registry. The list of immune and genetic biomarkers evaluated in body samples (buccal cells or vulvovaginal fluid) of registry participants included (1) herpes virus, *Candida albicans*, environmental allergen, and seminal fluid antibodies, (2) bacterial heat shock proteins produced in the setting of immune responses generated during chronic vaginal infections, (3) hyaluronan and gelsolin analysis that provide evidence for exaggerated immune responses, and (4) polymorphisms for genes associated with chronic pain such as manganese superoxide dismutase (MnSOD) and catechol-O-methyltransferase.[42,43]

Extragenital pain sensitivity was assessed as it is an established marker of abnormal central nervous system pain processing.[44] The testing was conducted using a 15 kg pressure algometer. For this technique the examiner applied pressure with the algometer at each of the following 2 paired points: skin over deltoid muscle (right and left), and shin 5 cm below the patella (right and left). The maximum pressure tolerated was recorded along with a VAS score rating the level of discomfort.

**Table I** *Detailed Description of the Physical Examination*

| | Method | Reporting |
|---|---|---|
| Visual inspection | Examination of the vulvovaginal area first with *unaided eye*, subset of 100 also evaluated with the Syris v600 device (a cross-polarized light to identify subsurface inflammation). | Abnormalities or abrasions on vulvar skin (erythema and dryness) reported using Farage et al Standard Scoring Scale for Erythema and Dryness[52] for 3 locations: (1) vestibular glands, (2) entire area of vestibule, (3) beyond the vestibule and into the cornified epithelium of the labia (physician reported). |
| Vaginal allodynia assessment | Cotton-tip into vaginal canal and moves smoothly back and forth 3 times with light pressure, making certain not to touch vaginal wall. | Classified 3 ways: (1) neutral or unpleasant, (2) pain or pressure, (3) familiar pain, i.e., whether pain is familiar to that experienced with intercourse (patient reported). |
| Vaginal and vestibule secretion samples (subset of 100 patients and 100 controls) | Two samples obtained by rotating 2 cotton-tip swabs against the posterior vaginal wall called the *vaginal sample*. A separate sample collected by rotating 2 cotton-tip swabs over the vestibule called the *vestibular sample*. | |
| Neurosensory examination of the vulva and perineum | (1) Gentle upwards strokes at sensory dermatomes (T12, L1, S2/S3, S4/S5, S1). Repeated bilaterally with similar pressure.<br><br>(2) Both sides repeated again with wooden end of cotton swab with light pressure for 1 second over each dermatome. | Three variables reported for each location bilaterally: (1) sensation (normal, allodynia, hyperalgesia or hyposensitivity), (2) if pain is present, VAS for level (0–10), (3) McGill descriptor (normal, sharp, shooting or radiating to another site). (Patient reported.) |
| Sensory examination of the vulvar vestibule* | Six anatomical sites on the vestibule are determined with reference to the conventional clock face with 12 and 6 o'clock positions corresponding to the anterior and posterior position of midline, respectively. Punctuate ("static") pressure is used to collect pain levels at 12, 10, 7, 6, 5, and 2 o'clock sites. Repeat the examination using an upward stroke motion ("dynamic") at 11 to 1, 5 to 2, 7 to 10, and 7 to 5 o'clock sites. | Static pressure reported variables: (1) VAS levels (0–10), (2) pain descriptors (burning, shooting, dry, and itching) are reported by the patient, and (3) gross visual abnormalities (erythematous and edematous, etc.) are described by the physician.<br><br>Dynamic pressure reported variables: (1) VAS levels (0–10) and (2) pain descriptors (burning, shooting, dry, and itching) are reported by the patient. |
| Pelvic floor muscle function and sensitivity* | Contract and release of pelvic floor muscles. Examiner calibrates his/her finger to 2 kg pressure using digital pressure algometer and inserts lubricated digit into the vagina, avoiding the vestibule; request to contract pelvic floor muscle repeated, with no deep palpation of muscle. Five seconds to rest before proceeding to internally apply ~ 2 kg pressure for approximately 2 seconds to the superficial muscles of the vaginal entrance: bulbocavernosus (5 and 7 o'clock), perineal body (6 o'clock). With similar internal pressure the examiner palpates the levator complex on the right (7 o'clock) and left (5 o'clock). | Presence of pelvic floor contracture and ability to voluntarily contract the pelvic floor. The physician reports strength of the 2 muscle groups' contractions as "normal" or "low" and tone at each pressure point as "normal" or "high."<br><br>Patient reports the VAS (0–10) pain score for each pressure point. |
| Speculum examination | Cotton swab for vaginal sample, measures pH and prepares wet prep and KOH slide. | Vaginal pH, wet prep whiff test, clue cells and Trichomoniasis are determined "positive" or "negative." During the KOH test, hyphae or budding yeast is reported "positive" or "negative."<br><br>Vaginal Maturation Index to report percentage of parabasal cells, white blood cells and epithelial cells (physician reported). |

**Table I** *Detailed Description of the Physical Examination (Cont'd)*

| | Method | Reporting |
|---|---|---|
| Pain sensitivity at extragenital sites | Technique is performed with a 15 kg pressure algometer, where the examiner applies pressure using the algometer at the following 2 paired points: skin over deltoid muscle (right and left), and shin 5 cm below the knee cap. | Maximum pressure tolerated is recorded at each site along with a VAS (0–10) score rating the level of discomfort reported by the patient. |
| DNA samples | A catch-all sample swab is rotated on the inside of the cheek, back and forth, several times on each side. Sample then is allowed drying time of 15–30 minutes at room temperature and stored in a laboratory refrigerator until DNA analyses are performed. | Immune and biomarkers evaluated include (1) herpes virus, *Candida albicans*, environmental allergen and seminal fluid antibodies, (2) bacterial heat shock proteins produced in setting of immune responses generated during chronic vaginal infections, (3) hyaluronan and gelsolin analysis that occur in exaggerated immune responses, and (4) genetic polymorphisms for genes associated with chronic pain such as manganese superoxide dismutase (MnSOD) and catechol-O-methyltransferase.[42,43] |

VAS = visual analog scale, KHO = potassium hydroxide.
*Based on the procedure first reported by Denniz Zolnoun in methodology developed for research funded by the National Institutes of Health, K23 HD053631-01: *Refining Diagnosis Criteria of a Pain Disorder: Vulvar Vestibulitis Syndrome*.

### *Psychometric Questionnaires*

After consent and full evaluation, registry participants completed the following questionnaires: Short-Form McGill Pain Questionnaire,[16] Coping Strategies Questionnaire,[17] Female Sexual Function Index (FSFI),[18] Revised Dyadic Adjustment Scale (DAS-4),[19] Beck Depression Inventory,[20] Spielberger State-Trait Anxiety Inventory,[21] and Short Form–12 questionnaire of health-related quality of life.[22,45] Participants completed these questionnaires at the initial visit and at 6 and 12 months after initial evaluation. In addition, the Gracely Box Pain Scale,[13-15] which uses a numeric scale (0–100) and verbal descriptors of pain, was completed at each examination.

## *Results*

Of 15 experts who were invited to join the Evidence-based Vulvodynia Assessment (EVA) Project, 13 agreed to participate in our network (8 as enrollment sites and 5 as advisors; 2 declined to participate). Collaborators, their roles, and registry sites are listed in Figure 1. Methodology for examination of genital skin and muscle was tested and retested over a period of 1 year beginning in 2009. We found that cotton-tip swab examination of the vaginal mucosa was easily performed with reproducible results by all investigators. However, methodology for the assessment of pelvic floor muscle dysfunction in vulvodynia was not previously well studied and required more in-depth experimentation. We considered several methods, including single digit palpation, surface electromyography, vaginal algometry,[46] or computerized pressure algometry.[12] Previous research had shown that normal controls could tolerate up to 1.52 kg/cm (SD = 0.62) of pressure applied intravaginally to the pubococcygeus and iliococcygeus muscles without reporting pain.[46] A more recent study on assessment of pressure pain sensitivity in the vagina confirmed that the 5, 6, and 7 o'clock positions corresponding to the bulbocavernosus, pubococcygeus, and iliococcygeus muscles were reliable testing sites in discriminating cases from controls.[12] For the purposes of our research we utilized this data to create a muscle testing protocol that used single digit calibration (with a Wagner pressure algometer) to apply 2 kg/cm pressure to these vaginal muscles. This method was reliable, reproducible at all enrollment sites, and more cost effective (data not shown) than computerized methods.

Registry participants were enrolled in 8 sites across the U.S. starting in 2009. Over 3 years more than 930 women were screened, 323 women were enrolled, 21 were lost to follow-up, and 64 completed 1 year of follow-up. Six sites are actively enrolling in 2013 (Figure 1), and 250 women are currently being followed. At the time of this manuscript preparation 176 charts were finalized and available for analysis.

Initial univariate analysis of demographics (Table II) demonstrated that the registry cohort

had a mean age of 32.7 years (SD ± 11.4, median 29, range 20–72 years), and the racial distribution was > 86.9% (n = 153) Caucasian. A total of 86% of participants (n = 152) were privately insured, 77.3% (n = 136) were employed, and 97.2% (n = 171) had completed high school or a higher level of education.

Nearly 67% (n = 117) described being married or in a stable relationship longer than 2 years, and 58.5% (n = 103) of participants reported being sexually active in spite of pain. The average pain duration of the cohort was median 25.5 months and range from 1–360 months. Prior to enrollment 47.2% (n = 83) experienced onset of pain beginning with the first act of insertional intercourse. A total of 84% had been sexually active in the past in spite of feeling pain during intercourse.

Of the 148 women who completed the comorbidity section of their questionnaire, nearly 20% reported some type of pain comorbidity. Chronic pain comorbidities included migraine headaches in 34% (n = 50), chronic pelvic pain in 22% (n = 32), irritable bowel syndrome (IBS) in 20% (n = 30), interstitial cystitis (IC) in 9% (n = 13), temporomandibular joint disorder (TMD) in 7% (n = 10), and fibromyalgia in 4% (n = 6). Psychiatric comorbidities were reported as follows: anxiety in 41% (n = 61) and depression in 40% (n = 60). A history of abuse was rare in this population, with 7% reporting a history of sexual abuse (n = 10) and 3% reporting a history of physical abuse (n = 5).

Evaluation of the vestibule by cotton swab was completed in 176 cases. Of that cohort 100% had a VAS score ≥3. Ninety percent had pain localized to the vestibule, 10% had generalized pain extending beyond the vestibule to the vulva, and 90% had musculoskeletal pain. Mean vestibular pain levels using the VAS were 4.2 (SD ± 2.7) static at 10 o'clock and 3.4 (SD ± 2.6) dynamic at 7 to 10 o'clock, 5.0 (SD ± 2.9) static at 7 o'clock and 3.8 (SD ± 2.8) dynamic at 7 to 5 o'clock, 4.8 (SD ± 2.8) static at 6 o'clock, 4.2 (SD ± 2.8) static at 2 o'clock and 3.2 (SD ± 2.7) dynamic at 5 to 2 o'clock, and 5.1 (SD ± 2.9) static at 5 o'clock. Of the 176 participants 173 (98.3%) also reported pain during examination of the pelvic floor muscles. Mean musculoskeletal VAS pain levels were as follows: (1) bulbocavernosus at 5 o'clock: 3.1 (SD ± 3.0), (2) bulbocavernosus at 7 o'clock: 3.1 (SD ± 3.0), (3) perineal body: 2.7 (SD ± 3.0), (4) levator at 7 o'clock: 3.2 (SD ± 3.1), (5) levator at 5 o'clock: 3.2 (SD ± 3.1). The highest abnormal elevated muscle tone was reported in 65.6% of levator muscle assessments, and abnormally lower strength was reported in only 38.1% of women. The most common descriptors used by participants to describe the character of their pain during the cotton-tip examination were *burning* or *sharp*; only 2 women reported *dryness*. The severity of the pain was described mostly with words like *moderate*, *mild*, *intense*, *slightly intense*, and *very mild*.

**Table II** *Demographic Characteristics of the Study Population*

| Variable | Total sample (n = 176)* |
|---|---|
| Age (y) | 32.7 ± 11.4 |
| | 29 (20–72) |
| Racial distribution | |
| Caucasian | 153 (86.9) |
| African American | 2 (1.1) |
| Latino/Hispanic | 13 (7.4) |
| Native American | 1 (0.6) |
| Asian/Pacific Islander | 2 (1.1) |
| Other | 4 (2.3) |
| Missing | 1 (0.6) |
| Insurance status | |
| Privately insured | 152 (86.4) |
| Uninsured | 5 (2.9) |
| Medicare | 7 (3.9) |
| Medicaid | 1 (0.6) |
| Other | 7 (3.9) |
| Missing | 4 (2.3) |
| Education | |
| Completed college | 74 (42.1) |
| Postgraduate study | 53 (30.1) |
| Some college | 35 (19.9) |
| Completed high school or GED | 9 (5.1) |
| Missing | 5 (2.8) |
| Relationship status | |
| Married | 88 (50.1) |
| Single | 35 (19.8) |
| Stable relationship ≥ 2 years | 29 (16.4) |
| Stable relationship < 2 years | 15 (8.5) |
| Separated/divorced | 4 (2.3) |
| Widowed | 1 (0.6) |
| Other | 3 (1.7) |
| Missing | 1 (0.6) |
| Employment | |
| Employed | 136 (77.3) |
| Unemployed | 15 (8.5) |
| Other | 24 (13.6) |
| Missing | 1 (0.6) |
| Income | |
| < $20,000 | 10 (5.7) |
| $20,000–$50,000 | 44 (25.1) |
| $50,000–$100,000 | 58 (32.9) |
| > $100,000 | 54 (30.6) |
| Missing | 10 (5.7) |

*Data are given as mean ± standard deviation, median (range), or n (%) unless otherwise specified.

### *Discussion*

To improve our overall understanding of vulvodynia, the NVR was used to extensively pilot the necessary components for research: (1) recruitment of participants from the community, (2) research protocols for use within the clinical setting, and (3) data management tools.

Over the last 3 years the NVR screened more than 930 women and enrolled 323 participants who presented with pain complaints to clinics. In a population-based study Harlow et al reported a cumulative incidence of vulvodynia ranging from 3–16% among Caucasians and African Americans and 23% among Hispanics.[1,3] However, as in other publications, our data showed that women receiving specialized care in our treatment centers were more likely to be married, Caucasian, insured, and to have higher income, suggesting a potential disparity in access to care.[2,47,48] Similar disparities were found in 2012 by Reed and colleagues.[49] Their research showed that when identifying women with vulvodynia from the general population using screening questionnaires, survey respondents who identify themselves as having vulvodynia are more likely to be white, married, and educated than are nonrespondents.[49] This data emphasized the need to educate women of all ethnicities about vulvodynia. Further research will have to clinically define this syndrome in diverse populations in order to determine if this is a disease mostly prevalent in Caucasians or whether minorities experience the condition but fail to seek treatment.

Only 10% of registry participants presented with generalized vulvar pain, suggesting that the burden of disease is carried by women with localized pain (90.1%). Pain during intercourse was the most common complaint (i.e., provoked pain), and similar to previously published reports, 84% of the women described being sexually active in the past in spite of pain.[1,50] The median duration of pain was 25.5 months (range, 1–360 months). Although this reflects shorter pain duration compared to the findings of Reed et al,[1] we confirmed that women with vulvodynia spend a significant amount of time in pain and seeking treatment. The lengthy duration of pain, and the fact that women continue to have intercourse in spite of pain, indicates that the negative emotional impact of pain and the mechanisms that allow women to cope are important factors that need to be further understood.

Comorbid pain conditions such as IBS (20%), IC (9%), migraines (34%), TMD (7%), fibromyalgia (4%), and chronic pelvic pain (22%) were frequently reported in our sample. Twenty percent of the women in the registry stated they had at least 1 additional comorbid pain condition. This finding is consistent with previous studies showing that chronic pain syndromes are significantly associated with vulvodynia.[50] In the population-based study published by Reed and colleagues,[49] 19.1% of the cohort (1,890 women surveyed) reported having one of the chronic pain conditions that included IC (7.5%), IBS (9.4%), and fibromyalgia (11.8%). However, women with vulvodynia were 2–3 times more likely to have a comorbid pain condition than were controls.[49] A similar large population-based study (1,457 women surveyed) conducted at the University of Minnesota found that among women with self-reported vulvodynia, 26.8% had at least 1 pain comorbidity (including IC, TMD, IBS, fibromyalgia, endometriosis, and chronic headaches), 17.9% reported at least 2 comorbidities, and 27.1% had 3 or more comorbidities.[51] The NVR differs from the above-described studies in that NVR participation was limited to only women with clinically-confirmed vulvodynia. Thus it was expected that our cohort would report a similar or higher level of associated chronic pain syndromes although the distribution of comorbid pain conditions was not necessarily the same.[49,51]

In registry participants the prevalence of anxiety and depression was high at 41% and 40%, respectively, yet past or current sexual abuse or physical abuse was quite infrequent. This data suggests that women with vulvodynia may need to be routinely screened for symptoms of other chronic pain conditions and for various psychological impairments that include not only depression but also anxiety. Although the interplay between altered pain processing and psychological distress has been documented in a variety of chronic pain syndromes, including vulvodynia, much research needs to be done to determine how these findings can be incorporated into diagnosis, treatment, and outcomes.

When we used reliable methodology for examining the musculature in the vaginal region,[12] >90% of patients enrolled in the registry had an abnormal muscular examination. This was surprising given that abnormal muscle function was not part of the screening or enrollment criteria. Our findings support previous work done by Zolnoun and colleagues,[12] demonstrating that compared to controls, vestibulodynia patients report lower muscular pain thresholds and higher pain sensitivity

during muscular examination. However, we are limited in our ability to determine whether musculoskeletal involvement leads to increased mucosal pain sensitivity or whether musculoskeletal pain is secondary to a process that initiates with referral from an abnormal mucosa. Regardless, given the high prevalence of abnormal muscular findings in our population, we can safely conclude that a musculoskeletal vaginal evaluation should be routinely performed in all patients with vulvodynia.

Additional limitations of the registry study design include the inability to evaluate data for women who declined participation, loss to follow-up over the 12-month study period, and unequal enrollment at multiple sites. Nonetheless, as recommended by the NIH, a national vulvodynia registry and database was successfully created and tested. Examination and patient assessment questionnaires were developed and implemented for use across all sites. A network for the development of research protocols for improving the diagnosis and treatment of vulvodynia is achievable. Our research demonstrates that, in addition to evaluation with a cotton-tip applicator, women with vulvodynia should also be *routinely* evaluated for musculoskeletal dysfunction, comorbid pain conditions, and emotional distress with specific emphasis on anxiety. We believe that this type of multidimensional evaluation may be the key to potentially improving management of this complex disorder.

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