

# NIH Research Plan on Vulvodynia



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## EXECUTIVE SUMMARY

Vulvodynia is the term used to describe chronic pain or discomfort of the vulva. Clinicians and patients trying to deal with vulvodynia are frustrated by the lack of scientific evidence to help assess causes, possible triggers, prevention, and treatment.

This *Research Plan on Vulvodynia*, developed by the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD) in collaboration with other federal, private, and non-profit agencies and researchers in the field, is designed to lay out an agenda for the rigorous scientific research needed to answer questions and fill in knowledge gaps about vulvodynia. The agenda not only builds upon ongoing vulvodynia research (supported by the National Institutes of Health [NIH] and other agencies and organizations), but also seeks to advance the field by enhancing capacity for conducting research related to vulvodynia. In addition, the plan aims to apprise the research community of scientific goals for vulvodynia research and to foster collaborations among agencies and organizations interested in the topic. To help develop the plan, the NICHD convened a scientific meeting in July 2011, interviewed leading scientists, assessed the size and scope of the research literature in vulvodynia, and reviewed NIH-supported grants related to vulvodynia.

To move toward better understanding the etiology, diagnosis, and treatment of vulvodynia, additional research capacity must be developed and research efforts must be expanded. Such an expansion is more than any one organization can achieve alone and is likely to take many years to accomplish. More scientists must join the existing small core group of researchers to build on current efforts. Scientists will need access to more sophisticated equipment, new models, and larger groups of patients to accelerate progress in basic, clinical, and translational research. Fortunately, a number of organizations, including the NIH, are eager to work together to expand the scientific infrastructure.

The plan identifies many scientific areas that need future emphasis within the field of vulvodynia research and presents a list of detailed research objectives. At the July 2011 meeting and in subsequent interviews, current vulvodynia researchers emphasized that more basic physiological research is required, both on vulvodynia specifically and in the broader context of

other pain disorders. As a result, several of the short-term objectives included in the plan are aimed at increasing scientific outreach efforts to the broader pain research community to encourage them to apply their scientific knowledge to vulvodynia research. In the longer term, it will also be important to develop animal models, in addition to the rat, to study the role of inflammation in pain disorders.

Scientists also stated that reliable, valid, and standardized measures for diagnosis and outcome measurement need to be developed to further both epidemiological and etiological studies. Consistency in evidence-based definitions and outcomes would allow for comparisons across studies and would enable the field to move forward more quickly. Supporting efforts of the scientific community to forge consensus on definitional issues is another important objective of the plan.

Treatment research in vulvodynia was also identified as a high priority, although thus far it has been hampered by methodological challenges. To address these challenges, several research objectives include identifying compounds that are effective in blocking central, peripheral, and mixed pain, and determining whether some of these compounds are suitable for testing in vulvodynia patients.

As detailed in a recent Institute of Medicine (IOM) report<sup>1</sup>, many people in this country continue to live with chronic pain. The NIH, partner organizations, and researchers should focus current efforts to help those living with chronic pain conditions like vulvodynia, while longer term research aimed at ameliorating these conditions proceeds. Disseminating evidence-based patient and provider education materials on vulvodynia could be an important contribution to this effort.

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<sup>1</sup> <http://iom.edu/Reports/2011/Relieving-Pain-in-America-A-Blueprint-for-Transforming-Prevention-Care-Education-Research.aspx>

## BACKGROUND

Vulvodynia is a term used to describe chronic pain or discomfort of the vulva. The nature of the pain may vary from woman to woman; vulvodynia can cause burning, stinging, irritation, or rawness. The pain may move around or always be in the same place; it can be constant, sporadic, or severe. Although it is difficult to determine how many women are affected by vulvodynia, studies suggest that many women may suffer from the condition. Researchers have estimated that 9 percent to 18 percent of women between the ages of 18 and 64 years may experience vulvar pain during their lifetime.<sup>2</sup>

Vulvodynia can have a significant impact on a woman's quality-of-life. Women who suffer from vulvodynia report that sex and many routine or daily activities such as tampon insertion, sitting, or even wearing underclothing can become difficult or impossible. A 2006 study reported that 42 percent of vulvodynia sufferers felt out of control of their lives, and 60 percent felt out of control of their bodies specifically due to their chronic vulvar pain.<sup>3</sup>

Obtaining a diagnosis of vulvodynia can be difficult and time consuming. Vulvodynia tends to be diagnosed only when other causes of vulvar pain, such as infection or skin diseases, have been ruled out. To diagnose vulvodynia, a health care provider may recommend that a woman have blood drawn to assess levels of estrogen, progesterone and testosterone. The provider may also perform a cotton-swab test, applying gentle pressure to various vulvar sites and asking the patient to rate the severity of the pain. If any areas of skin appear suspicious, these areas may be magnified or biopsied for further examination.

Because vulvodynia is often a diagnosis of exclusion, it can be difficult and time consuming to arrive at an actual diagnosis. The diagnostic process

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<sup>2</sup> Arnold L.D., Bachmann G.A., Rosen R., & Rhoads G.G. (2007). Assessment of vulvodynia symptoms in a sample of U.S. women: A prevalence survey with a nested case control study. *American Journal of Obstetrics and Gynecology*, 196(2), 128e1-128e6. Harlow B.L. & Stewart E.G. (2003). A population-based assessment of chronic unexplained vulvar pain: Have we underestimated the prevalence of vulvodynia? *Journal of the American Medical Women's Association*, 58(2), 82-88. Harlow B.L., Wise L.A., & Stewart E.G. (2001). Prevalence and predictors of chronic lower genital tract discomfort. *American Journal of Obstetrics and Gynecology*, 185(3), 545-550.

<sup>3</sup> Arnold, L.D., Bachmann, G.A., Rosen, R., Kelly, S., & Rhoads, G.G. (2006). Vulvodynia: Characteristics and associations with comorbidities and quality-of-life. *Obstetrics and Gynecology*, 107(3), 617-624.

can be especially problematic for women who lack health insurance because they may not have the resources to continue excluding possible causes of pain before a provider can arrive at a diagnosis of vulvodynia. Moreover, some women may be reluctant to discuss their pain or seek treatment.

A definitive root cause of vulvodynia remains unknown. Researchers speculate that one or more of the following may cause, or contribute to, vulvodynia:

- An injury to, or irritation of, the nerves that transmit pain and other sensations from the vulva;
- An increase in nerve fiber density in the vulvar vestibule;
- Elevated levels of inflammatory substances in the vulvar tissue;
- An abnormal response of vulvar cells to environmental factors;
- Altered hormone receptor expression in the vulvar tissue;
- Genetic susceptibility to chronic vestibular inflammation;
- Genetic susceptibility to chronic widespread pain;
- Genetic factors associated with an inability to combat vulvovaginal infection;
- A localized hypersensitivity to *Candida* or other vulvovaginal organisms; and/or
- Pelvic floor muscle dysfunction, weakness, or spasm.

The general lack of awareness of vulvodynia among clinicians and women across the age spectrum presents a particular challenge in the diagnosis and treatment of vulvodynia in teenage girls. Many health care providers may be reluctant to bring up the subject of vulvovaginal pain with teenage girls because of its perceived association with sexual activity, although vulvovaginal pain is not limited to sexually active females. Like adult women, teen girls may also be reticent to bring up issues of vulvovaginal pain with their health care providers or with their parents/caregivers. As a result, many teenage girls and adult women suffer vulvar pain in silence, with neither diagnoses nor treatments.

Although some treatments are successful for some women, there is currently no cure that works for all women, nor is there a standard panel of therapeutics known to reliably treat vulvodynia. A variety of treatment options may be presented to patients, including:

- Oral medications, such as pain medications, tricyclic antidepressants, anticonvulsants, or antihistamines;
- Biofeedback therapy, intended to help patients decrease pain sensation;
- Topical medications, such as lidocaine ointment or hormonal creams;
- Nerve block injections;
- Physical therapy to strengthen pelvic floor muscles;
- Surgery to remove the affected skin and tissue in localized vulvodynia;
- Diet modification;
- Neurostimulation and spinal infusion pump; and/or
- Complementary or alternative medicine.

## **SCIENTIFIC RESEARCH ON VULVODYNIA**

Currently, clinicians and patients have access to limited scientific information on what causes vulvodynia, what factors may trigger it, and how to prevent or treat its symptoms. These questions can be answered only with rigorous scientific research. The *Research Plan on Vulvodynia* is designed to build upon ongoing vulvodynia research (whether supported by the NIH or other organizations), to enhance capacity for conducting research related to vulvodynia, and to address key areas needed to move the science forward. The plan will also apprise the research community of scientific goals for moving forward in this area, and could potentially foster collaborations among federal, private, and non-profit agencies and groups.

To assist in the development of this plan, the NICHD:

- Held a scientific meeting in July 2011 to provide information about the current state of the science in vulvodynia, and to gather input for an agenda to guide the field of vulvodynia research.
- Interviewed leading vulvodynia investigators to collect their personal views on how to promote vulvodynia research and increase research capacity.
- Assessed the size and scope of the research literature in vulvodynia during the last 15 years to identify areas that need additional



research capacity, assess scientific opportunities, and identify potential research and training collaborators.

- Reviewed NIH-supported grants and projects related to vulvodynia to obtain data about NIH's past and current research, research training, and other efforts related to vulvodynia.

## **Scientific Meeting on Vulvodynia as a Chronic Pain Condition**

On July 11–12, 2011, the NICHD sponsored a scientific meeting entitled *Vulvodynia: A Chronic Pain Condition—Setting a Research Agenda* in Bethesda, Maryland (for more information about the meeting, visit <http://www.nichd.nih.gov/news/resources/spotlight/072111-vulvodynia-research-agenda.cfm>). The meeting brought together a diverse group of more than 80 scientists from the NICHD, the NIH Office of Research on Women's Health (ORWH), the National Institute of Dental and Craniofacial Research, the pharmaceutical industry, academic medicine, and patient and provider organizations. Although many of the leading scientists who conduct vulvodynia research were present, the meeting also included scientists whose research interests are related to chronic pain, but not specifically to vulvodynia. Clinicians who have treated vulvodynia patients and patient advocates also offered important perspectives. Participants discussed the need for additional research capacity in the field of vulvodynia, the relationship between vulvodynia and other chronic pain conditions, and specific research and knowledge gaps to be addressed in the field.

Meeting presentations focused on the history of pain and pain research; the recommendations of the then-recently published IOM report on pain research, [\*Relieving Pain in America\*](#); the need for consistent terminology, definitions, and diagnostic criteria for research and patient care; psychosocial aspects of vulvodynia, especially those related to sexual function and co-morbid pain conditions; appropriate ways to measure pain for research purposes; potential treatments for vulvodynia based on blocking the action of specific receptors; applying research results on the pathophysiology of fibromyalgia to vulvodynia; the potential for imaging- or biomarker-based technology to be applied to research on vulvodynia; and the possible role(s) of hormone balance/imbalance in vulvodynia.

The focus of the conference was on vulvodynia as a pain condition. Within that context, presenters and participants compared vulvodynia to other chronic pain conditions, such as temporomandibular joint disorders and fibromyalgia, and discussed the pathophysiology of vulvodynia pain. Researchers conferred about the challenges in assessing pain for clinical and research purposes. They also discussed a key challenge for scientists conducting clinical research in vulvodynia—that because pain measures are subjective to the individual, it is inappropriate to incorporate such measures into cross-sectional studies.

Participants at the conference agreed that the evidence base for vulvodynia research is sparse, and that there is insufficient scientific evidence to form a consensus on preferred methods of diagnosis and treatment. They also agreed that a much greater number of highly trained and dedicated investigators will be needed to move the field forward. Several participants suggested leveraging existing programs for research training and career development in gynecology to help expand the vulvodynia research field. Other individuals proposed funding young vulvodynia investigators through training and career development programs in neuroscience.

Participants noted that the need to re-invigorate the vulvodynia research field with new or young investigators is made more difficult by the complexity of the condition and the diversity of the disciplines required for significant scientific progress. Attendees strongly agreed that achieving progress in vulvodynia research would require the expertise of scientists in gynecology, neurology, dermatology, and pain research, among other disciplines. The participants acknowledged the many difficulties in bringing such a variety of disciplines to bear on a complex clinical problem. They agreed that too few investigators in all fields, but particularly in fields other than gynecology, were sufficiently knowledgeable and interested in vulvodynia. Participants suggested a variety of possible mechanisms to bring researchers from different fields together and to facilitate collaboration.

The problem of inconsistent definitions, terminology, and diagnostic criteria for vulvodynia was discussed extensively during the general sessions and the breakout groups. Even among the experts gathered for this meeting, there was some disagreement about the definition of vulvodynia, the validity and usefulness of current diagnostic methods, and the preferred terminology. Participants indicated that scientists have made limited

progress in identifying phenotypes that characterize vulvodynia because of this variation. In particular, researchers noted that subtypes of the condition have been difficult to identify and the phenotypic distinctions are difficult to determine. Moreover, clinician participants stated that differences in terminology cause confusion and make it more difficult for practitioners to apply research results.

Researchers agreed that the prevalence of vulvodynia is probably widespread, but that research on the prevalence of vulvodynia is limited in size and scope and is generally not population-based. In addition, the methods used to measure prevalence varied among studies, and it was difficult to determine the impact of varying definitions and diagnostic methods on the resulting statistics.

Conference participants expressed great interest in research on co-morbid conditions and quality-of-life in women with vulvodynia. Identifying co-morbidities with other urogynecological conditions (such as interstitial cystitis and pelvic floor disorders) and other chronic pain conditions (such as fibromyalgia) was of particular interest, and the conference attendees called for additional systematic research in this area. Scientists stated that sexual health measures were important, but that they were not sufficient by themselves to identify quality-of-life impact. Researchers also discussed the need to examine the relationships among psychosocial factors and the incidence and severity of vulvodynia symptoms.

Scientists agreed that although a variety of treatment approaches have been used in clinical practice to help vulvodynia patients, the evidence base for treatment is lacking. Some interventions, such as surgery, are thought to be effective in some patients, but there are challenges to establishing this effectiveness scientifically. Other approaches also required confirmation with clinical research testing. Conference participants stated that developing the evidence base for treatment will continue to be difficult until basic research on pathophysiology, outcomes measurement, and diagnosis have been satisfactorily addressed.

## Research Literature and Research Funding in Vulvodynia

To assist in developing a strategic plan for vulvodynia research, the NICHD gathered information about the size and scope of the research literature in vulvodynia. The analysis was designed to help identify specific areas where additional research capacity is needed, assess scientific opportunities, and identify potential collaborators in scientific research and training. The analysis addressed the whole of the vulvodynia research literature and was not limited to publications linked to research funded by the NIH as a way to maximize the results' usefulness.

*“When you look at our field, there’s a very small cadre of successful researchers and they do okay, but it’s hard to break into that [group].”*

*—NIH-funded scientist in the field of vulvodynia*

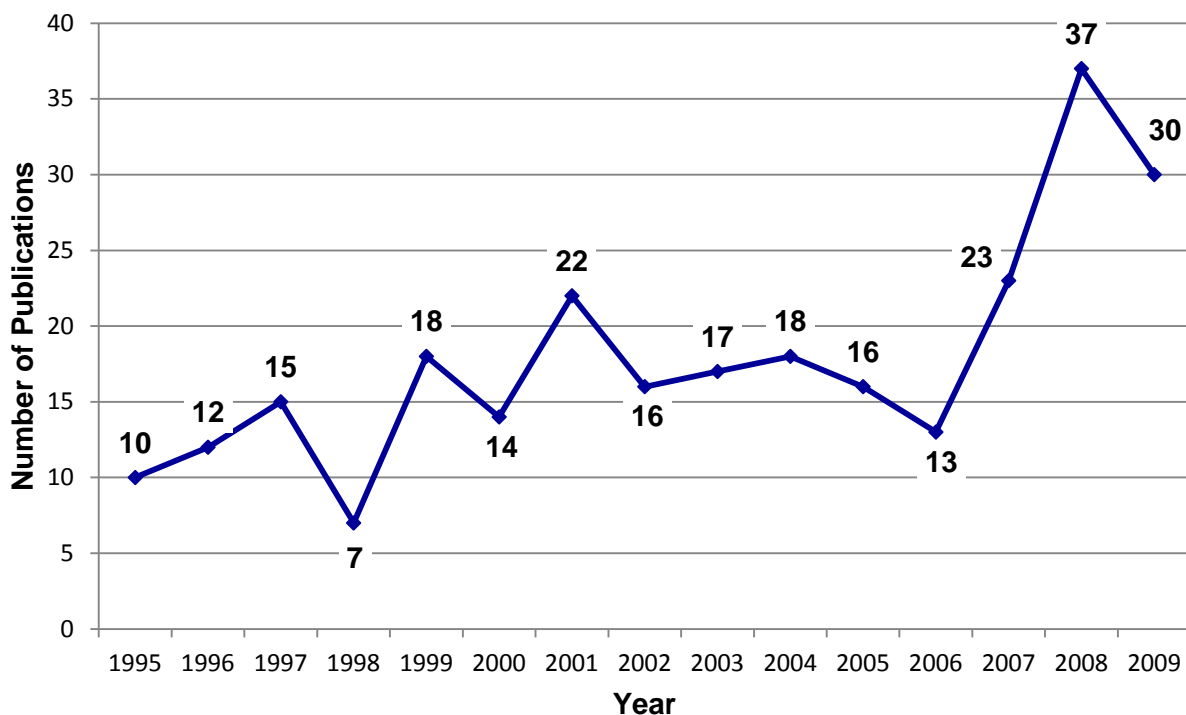
To identify the literature, a list of potential search terms was compiled based on the discussion at the July 2011 meeting on vulvodynia. This list was shared with a group of four scientific experts for additional input. Ultimately, 11 terms were included in the final literature search, encompassing the years 1995-2011.<sup>4</sup> Using a wide search strategy, a total of 2,536 distinct articles were returned, but the majority of these proved to be unrelated to vulvodynia. After further review, 755 articles clearly focused on vulvodynia were identified. About one-half of this body of publications on vulvodynia reported new, original research results (n=372); the remaining publications were reviews, editorials, case reports, and other publication types. A total of 296 publications represented new, original research results and were available in English. Each of these 296 publications was reviewed in detail.

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<sup>4</sup> The first round of searchers included 12 terms. However, one term returned no results relevant for vulvodynia; thus, it was dropped from the final analysis. The 11 final terms included: vulvodynia, vulvar vestibulitis, VVS, vulvovaginal disease, vestibulitis, vulvovaginal disorder, vulvar pain, vestibulodynia, vulvar dysesthesia, pudendal nerve pain, and dyspareunia.

The total number of original vulvodynia research publications for the years 1995 through 2009 is shown in Figure 1 below. (Although articles were retrieved through 2011, 2009 was the latest year for which complete data were available.) The results confirmed that, on average, 36 or fewer research articles on vulvodynia are published annually. A total of 794 scientists contributed to the overall research literature during this 15-year period. However, 75 percent of these researchers contributed to only one article during this time. A small cadre of 21 dedicated scientists published more than 5 original research articles each.

*FIGURE 1: ORIGINAL SCIENTIFIC RESEARCH PUBLICATIONS ON VULVODYNIA, 1995-2009, BY YEAR*



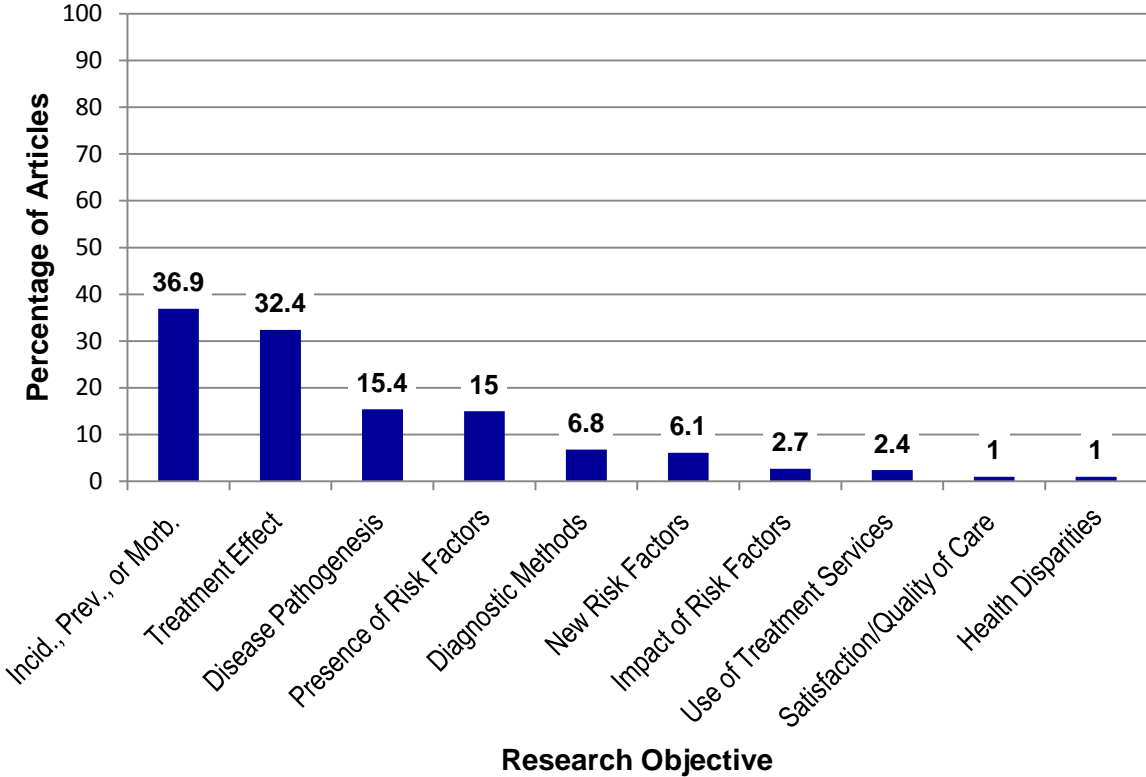
These findings are consistent with the response to recent NIH grant solicitations in the area of vulvodynia. Over the past 15 years, the NIH has published eight Funding Opportunity Announcements (FOAs) specifically related to vulvodynia. In response, the NIH received a total of 41 new applications and funded 10 awards. (An additional six awards in vulvodynia were funded from investigator-initiated grant applications during this period.) The majority of Principal Investigators (PIs) submitted only

one application to the NIH; of those who submitted more than one application, the majority submitted applications in research areas other than vulvodynia. Four trainees from institutional training programs in reproductive sciences supported by the NICHD went on to apply for vulvodynia-related grants. In addition to the limited response to the FOAs, of six grants eligible for renewal, only one PI applied for and received renewed funding. Taken together, the small number of original research publications and the limited response to NIH grant solicitations make it clear that many more investigators will be needed to establish a body of research sufficient to address diagnosis, etiology, prevention, and treatment of vulvodynia. These data demonstrate that increasing research capacity in vulvodynia is essential to future progress.

As discussed at the July 2011 meeting, vulvodynia research also requires multidisciplinary expertise. The vulvodynia research literature was published in many scientific journals, but more than three-fourths of the articles were published in obstetrics/gynecology journals. About 6 percent were published in pain research journals, while only a few were published in general interest clinical research journals. In discipline groups such as obstetrics/gynecology and dermatology, the majority of vulvodynia-related research articles were published in journals with relatively narrow foci, lower impact factors, and fewer average citations than the median journal within their specialty group.

As shown in Figure 2, about one-third (37 percent) of vulvodynia research publications reported results on the incidence, prevalence, or morbidity of vulvodynia. However, measures of prevalence were inconsistent across these studies: several studies measured self-reported pelvic pain; others used clinical diagnoses made on the basis of a “tampon test”; and others used different measures. These studies generally employed convenience or area samples instead of rigorously defined, randomized, population-based samples. Only two studies examined health disparities in vulvodynia, and neither was based on a broad population sample.

**FIGURE 2: ORIGINAL SCIENTIFIC RESEARCH PUBLICATIONS ON VULVODYNIA, 1995-2011, BY RESEARCH OBJECTIVE**

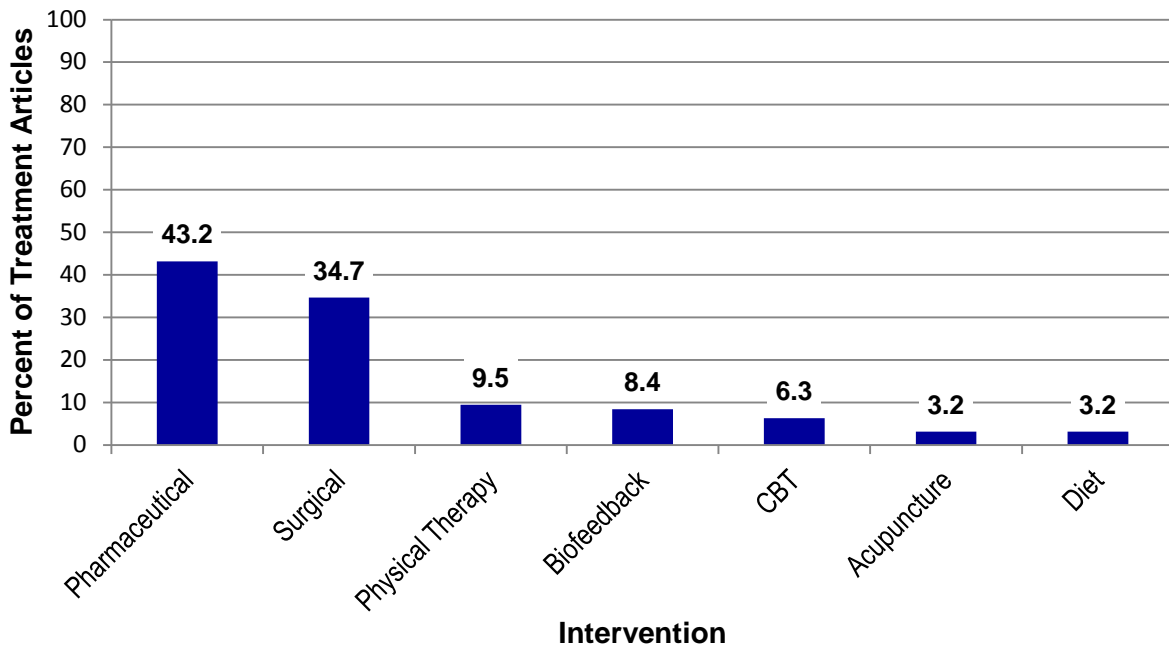


Notes: A minority of articles were classified in multiple categories.  
 Incid., Prev., or Morb.=Incidence, Prevalence, or Morbidity

A large number of studies described the symptoms and issues faced by women with vulvodynia. An important part of this segment of the research literature also described co-morbidities faced by many women with vulvodynia, including psychological and chronic pain conditions.

Treatment studies in vulvodynia accounted for slightly less than one-third of the research literature. As shown in Figure 3, surgery and pharmaceutical treatments—including pain medications and botulinum toxin type A (Botox) injections—were the most common treatment methods considered in the research. Other commonly used treatments, including physical therapy, biofeedback, diet, and cognitive behavioral therapy, were studied less frequently. Moreover, much of the treatment research in vulvodynia lacked scientific rigor. Randomized clinical trials were rare; when they were conducted, they were often underpowered, unmasked, and measured only limited outcomes, such as whether patients reported improvement.

*FIGURE 3: SCIENTIFIC RESEARCH PUBLICATIONS ON VULVODYNIA TREATMENT, 1995-2011, BY TYPE OF INTERVENTION*

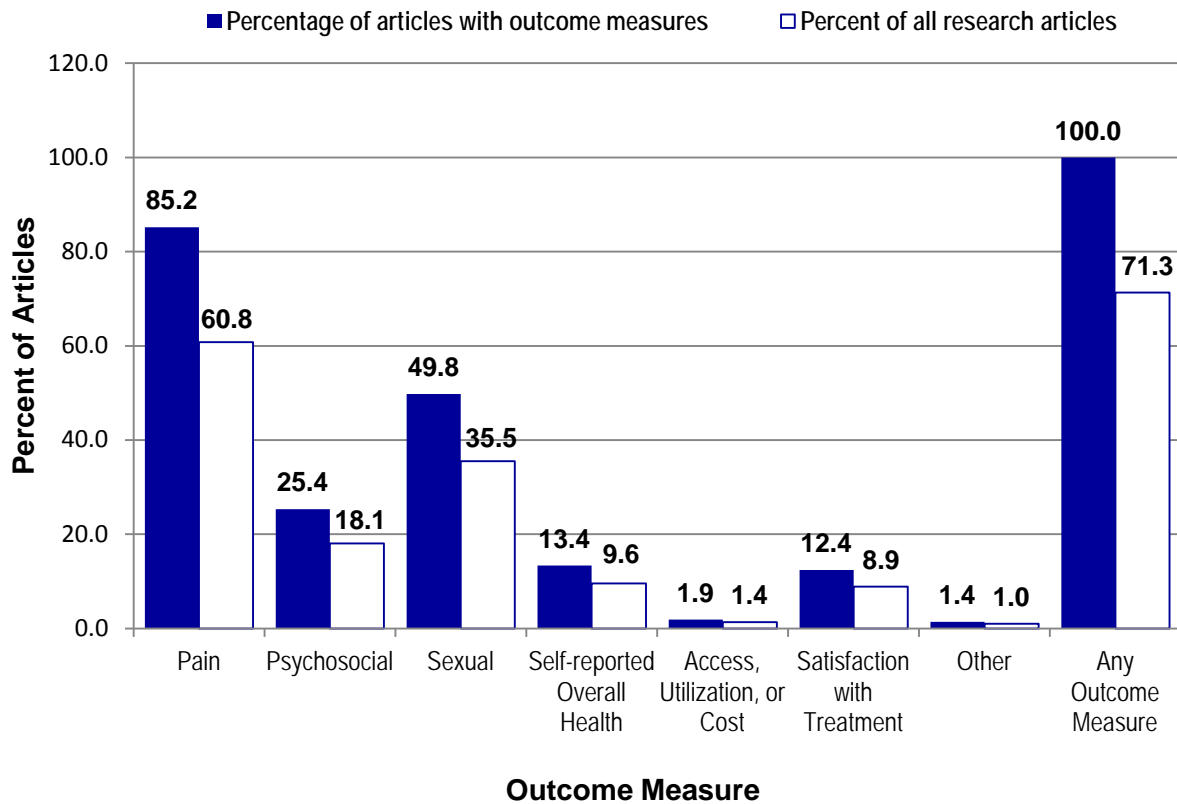


Note: A minority of articles assessed more than one treatment option.



Because pain is the primary presenting symptom in vulvodynia, it is not surprising that the most common outcome measure used in vulvodynia research was pain (see Figure 4). However, pain measures were frequently inconsistent across studies. Moreover, subjective pain measures were sometimes used in cross-sectional studies, where comparisons across individuals are inappropriate. Sexual outcome measures were also used in many studies. These measures included asking patients about the frequency of sexual activity, as well as the use of some standardized scale measures of sexual satisfaction and functioning.

*FIGURE 4: OUTCOME MEASURES USED IN RESEARCH PUBLICATIONS ON VULVODYNIA, 1995-2011*



Note: More than one-half of research articles included more than one outcome measure.

Since the late 1990s, the NIH has worked to increase research on vulvodynia. In the past several years, the NIH has attempted to improve the yield of vulvodynia FOAs. The NIH has created separate review groups for vulvodynia FOA applications to ensure that the review groups have the appropriate expertise. In addition, the NIH recently conducted Technical Assistance Workshops for potential grant applicants and added an array of grant mechanisms to the FOAs to provide investigators with opportunities to apply for funding without the need for extensive preliminary data. NIH-funded vulvodynia grants for fiscal year 2011 are shown in Table 5.

*TABLE 5: NIH GRANTS ON VULVODYNIA, FISCAL YEAR 2011*

<b>Funding Institute/ Center (IC)</b>	<b>Project Title</b>	<b>Recipient Organization</b>
NICHHD and NIH OD	A Controlled Trial of Gabapentin in Vulvodynia: Biological Correlates of Response	University of Tennessee Health Science Center
NICHHD	Longitudinal Population-based Study of Vulvodynia	University of Michigan, Ann Arbor
NINDS	Vulvar Vestibulitis Syndrome	University of North Carolina, Chapel Hill
NINDS	Phenotyping Core	University of North Carolina, Chapel Hill
NINDS	Sensory-based CNS Diagnostics for the Clinic	University of North Carolina, Chapel Hill
NCRR	Impact of Early Experience on Vulvovaginal Sensitivity in the Adult Mouse	University of Kansas Medical Center

Notes: NICHHD = *Eunice Kennedy Shriver* National Institute of Child Health and Human Development; NIH OD = National Institutes of Health, Office of the Director; NINDS = National Institute of Neurological Disorders and Stroke; NCRR = National Center for Research Resources.

Source: <http://Report.nih.gov>

The NIH, however, is not the only organization that supports research in vulvodynia. Of the 296 original research publications in English on vulvodynia, 39 percent acknowledged at least one source of external funding support. The most common funding sources for vulvodynia research are listed in Table 6. Government organizations in the United States, Canada, and Europe supported vulvodynia research, as did private non-profit groups, pharmaceutical companies, and other organizations.

*TABLE 6: MOST COMMON FUNDING SOURCES FOR VULVODYNIA RESEARCH, 1995-2011*

<b>Funding Source</b>	<b>Number of Research Articles Supported</b>	<b>Percent of Research Articles Supported</b>
All NIH Institutes combined (including ORWH)	34	11.6
NICHD	27	9.2
Canadian Institutes of Health	15	5.1
National Vulvodynia Association	10	3.4
Research Council of Canada	8	3.0
Mid Sweden Research and Development Centre, Sweden	5	1.7
Expo 2003 (Sweden)	4	1.4
McGill University	4	1.4
Ortho Inc.	4	1.4
Allergan Inc.	3	1.0
Fonds de la recherche en sante du Quebec	3	1.0
Health Research Council Sweden	3	1.0
Karolinska Institute, Sweden	3	1.0

<b>Funding Source</b>	<b>Number of Research Articles Supported</b>	<b>Percent of Research Articles Supported</b>
Social Sciences Research Council of Canada	3	1.0
Swedish Foundation for Health Care Sciences and Allergy Research	3	1.0
Swedish Medical Research Council	3	1.0
University of Michigan	3	1.0

Note: Some articles credited multiple funding sources.

## **RESEARCH GOALS AND OBJECTIVES**

To move toward better understanding the etiology, diagnosis, and treatment of vulvodynia, expanded research is required. Such an expansion is more than any one organization could accomplish alone and is likely to take many years to complete. Fortunately, the scientific meeting and analysis of the literature and NIH research grants showed that there are a number of organizations that could work together to promote vulvodynia research. In addition, the existence of the NIH Pain Consortium and the impetus of the IOM report can encourage more scientists to become involved within the NIH.

Many scientific areas within the field of vulvodynia research were identified for future emphasis, including a variety of areas that will provide the foundation for the translational and clinical studies needed to develop new interventions and improve current practice.

For purposes of this research agenda, goals and objectives are grouped into two areas:

- Building additional research capacity in vulvodynia; and
- Addressing research and knowledge gaps in vulvodynia.

Objectives are grouped by areas targeted for shorter term action, and those that can be addressed only once preliminary steps have been accomplished.

At the agenda-setting meeting and in follow-up interviews with NIH-funded vulvodynia investigators, scientists stated that additional research is needed on almost every aspect of vulvodynia; setting priorities is necessary, but difficult. Moreover, researchers acknowledged that it is unclear whether certain mechanisms to create capacity and promote research will be practicable in the area of vulvodynia, given the limited scientific base. Feasibility assessments and preliminary studies in some areas, with more extensive research and capacity building in others, will be required.

## **Building Additional Research Capacity to Support Scientific Research on Vulvodynia**

To expand vulvodynia research, it will be necessary not only to increase the number of investigators, but also to provide these investigators with the infrastructure needed to extend the scope and reach of vulvodynia studies. Scientists will need access to more sophisticated equipment, new models, and larger groups of patients to accelerate progress in basic, clinical, and translational research.

### *GOAL 1: BUILD AND STRENGTHEN THE SCIENTIFIC INFRASTRUCTURE TO INCREASE RESEARCH ON VULVODYNIA*

The published research on vulvodynia clearly indicates the need for expanded and stronger scientific research infrastructure; too many studies are too small, too narrowly focused, and do not take advantage of available scientific tools. In the shorter term, it is critical that efforts focus on strengthening current infrastructure, taking advantage of existing research organizations' capacities, and fostering collaborations of organizations already invested in vulvodynia research. In the longer term, new resources could be made available to facilitate collaboration among a growing cadre of researchers.

*“It just takes time, and it takes a group of people that are dedicated to making this work. We need to have more and more institutions get together and promote [vulvodynia research], that's the only way it's going to work.”*

*—NIH-funded scientist working in the vulvodynia field*

## SHORTER TERM OBJECTIVES

- Promote vulvodynia research within the NIH Pain Consortium by including a representative with knowledge of urogynecological pain conditions, suggesting related topics for inclusion in Consortium activities, and providing information to Consortium members on vulvodynia research and research opportunities;
- Investigate the feasibility of, in coordination with other NIH Institutes and Centers (ICs), to develop a patient registry and/or research database for pain conditions;
- Explore opportunities to expand vulvodynia researchers' access to advanced microscopy technologies (for examining pain in different physiological locations) and fluorescent imaging agents (for viewing nerves to permit potential targeting of therapeutic agents);
- Explore the feasibility of incorporating question(s) about chronic pelvic pain, and vulvodynia specifically, into national surveillance systems with population-based samples; and
- Explore new ways for small research projects on specific pain conditions to be appended as supplements to larger research projects on pain, and alert the research community to these opportunities.

## LONGER TERM OBJECTIVES

- Develop animal models, in addition to the rat, to study the role of inflammation in pain, and to screen for candidate therapeutic agents and prevention strategies for vulvodynia;
- Develop three-dimensional *in vitro* systems as models for studying pain syndromes;
- Create a model for studying conditions associated with vulvodynia, such as chronically macerated skin; and
- Assess the feasibility and utility of a tissue bank to study chronic pain conditions, such as vulvodynia, that could include tissue samples from both affected individuals and controls and link to a patient registry if feasible.

## GOAL 2: EXPAND OPPORTUNITIES FOR NEW INVESTIGATORS TO INCREASE SCIENTIFIC RESEARCH ON VULVODYNIA

Information gathered to date, including the literature analysis and the review of NIH grants, indicates that there is insufficient research to form a strong science base for understanding, diagnosing, treating, or preventing vulvodynia. More scientists must join the existing small core group of researchers to build on current efforts. These scientists must be properly prepared with knowledge of vulvodynia, and also with skills in research, training, mentoring, and career development.

*“The reality is that, if you really want to shift the field, start with your students, and in ten years this will result in having a lot more researchers looking at this topic.”*

*—NIH-funded scientist working in the vulvodynia field*

### SHORTER TERM OBJECTIVES

- Explore the feasibility of expanding and increasing the visibility of NIH Intramural Research Program efforts on vulvodynia to foster more extensive multidisciplinary interactions across NIH ICs that conduct research on chronic pain conditions;
- Design and implement a systematic, annual procedure to track scientific publications resulting from NIH grants related to vulvodynia, and share this information among partner organizations to help identify potential collaborations, promote mentoring, and design complementary research programs;
- Take advantage of existing NIH-funded programs by encouraging academic institutions that offer training and career development opportunities in the reproductive sciences to include vulvodynia in their curricula and training materials, involve vulvodynia researchers as mentors, and include scientific presentations and symposia on vulvodynia in the regular annual meetings of these programs;
- Consider establishing electronic systems, such as Web sites, blogs, Webinars, and other means, to support collaboration among researchers with an interest in vulvodynia;
- Provide grantsmanship training and assistance to young investigators at professional meetings or through Webinars; and

- With the help of the NIH Pain Consortium, increase scientific outreach efforts to the broader pain research community to encourage them to apply their scientific knowledge to vulvodynia research.

#### LONGER TERM OBJECTIVES

- Consider supporting additional new or young investigators from a range of appropriate disciplines who are interested in vulvodynia research by supplementing training, mentoring, and career development programs; and
- Create new or additional incentives for vulvodynia research within the context of existing reproductive sciences training and career development programs.

### Addressing Research Gaps in Vulvodynia

#### *GOAL 3: ADVANCE THE UNDERSTANDING OF VULVODYNIA AS A CHRONIC PAIN CONDITION*

Despite ongoing research efforts, vulvodynia remains a poorly understood set of disorders that have debilitating effects on women’s health and quality-of-life. The scientific community has not yet reached consensus on etiology, prevalence, diagnostic criteria, or treatment strategies. More baseline research is required, both on vulvodynia specifically and in the broader context of other pain disorders.

*“We need to look at how vulvodynia fits in the whole spectrum of pain syndromes. No doubt about it.”*

*—NIH-funded scientist working in the vulvodynia field*

Baseline information is necessary to help understand which women are subject to vulvodynia and other co-morbid pain conditions. Clinical findings suggest associations among various factors, giving rise to hypotheses about potential causes of pain disorders, including vulvodynia. Studies to test these hypotheses could lead to improved interventions.

The 2011 IOM report, [\*Relieving Pain in America\*](#), called for a personalized medicine approach to pain management. Such an approach requires more detailed information on the mechanisms that underlie specific pain



conditions. At the same time, some of these mechanisms, once identified, could lead to preventive measures or interventions across multiple pain conditions.

### SHORTER TERM OBJECTIVES

- Analyze existing published literature on vulvodynia to assess the evidence related to co-morbidity between vulvodynia and other chronic pain conditions; and
- Explore ways to create infrastructure for and design of epidemiological studies to help determine the prevalence of vulvodynia and its subtypes, including research to elucidate whether there are racial, ethnic, and socioeconomic disparities in vulvodynia and other chronic pain conditions.

### LONGER TERM OBJECTIVES

- Identify the neurological pain mechanisms that contribute to chronic pain conditions, including vulvodynia, and pinpoint the nerves involved in each type of pain;
- Identify the factors associated with normal tissue structure and tissue injury, and with rehabilitation of those tissues;
- Explore biological mechanisms, including inflammation, that are shared across co-morbid pain disorders;
- Explore which hormones and hormone-mimicking environmental agents may be involved in changes in pain levels, and the cyclic phase during which these agents influence outcomes, especially for different chronic pain conditions;
- Develop studies to consider a wide range of possible concurrent etiologies and/or co-morbidities that may contribute to vulvodynia; and
- Support population-based studies to explore what exposures (i.e., reproductive, gynecologic, environmental, or psychosocial), and what modifiers (i.e., microflora, viruses, genetic polymorphisms, and allergic susceptibility) may combine to result in an altered immune-inflammatory response that causes vulvar pain and/or other co-morbid chronic pain conditions (i.e., irritable bowel syndrome, interstitial cystitis, and fibromyalgia).

## GOAL 4: IMPROVE DIAGNOSIS OF VULVODYNIA

To date, vulvodynia research studies have used a wide range of inclusion and exclusion criteria, reportedly necessitated by cost constraints and by a lack of evidence-based consensus on the best criteria. The criteria researchers and practitioners often use vary by the woman's age, symptoms and their duration, and exact location of the pain, despite previous efforts to define the condition. Consistency in evidence-based definitions and outcomes would allow for comparisons across studies and would enable the field to move forward more quickly.

*"It's going to be very important, not only to promote the concept of multi-institutional collaborative efforts, but to define the condition in very concrete ways, to promote concrete outcome measures that can be used from place to place, that everybody agrees upon."*

*—NIH-funded scientist working in the vulvodynia field*

Confusion in terminology and about which factors should be included in the definition of "vulvodynia" continues to stifle growth in research because data cannot be compared across studies. Currently, there is no evidence-based, standardized method of diagnosing vulvodynia. In addition, researchers note the absence of standardized physical examination methodologies, including descriptions of normal response, to serve as a framework for understanding abnormal pain responses.

Because the etiology of vulvodynia-related conditions remains elusive and, to date, diagnoses have been made largely by exclusion, identifying biomarkers for the condition is challenging. However, the discovery of biomarkers to define subsets of vulvodynia could lead to significant improvements in management and treatment outcomes.

### SHORTER TERM OBJECTIVES

- Support efforts of the scientific community to forge a consensus on terminology, definition, and operational measures for vulvodynia and its subtypes;
- Establish partnerships between the NIH and the research community to collaborate on defining and measuring phenotypic information for

vulvodynia and its subtypes, while incorporating genetic, demographic, and psychosocial factors; and

- Support efforts of the scientific community to determine rigorously the reliability, validity, and standardization of existing diagnostic tests and tools.

#### LONGER TERM OBJECTIVES

- Design ways to improve inclusion/exclusion diagnostic criteria for vulvodynia, and standardize the criteria by subgroup factors such as a woman's age, symptom duration, location of pain (region of vulva), and treatment status;
- Develop both sensitive and specific biomarkers to test genetic, proteomic, or epigenetic characteristics that differentiate subsets of individuals with and without vulvodynia;
- Correlate these biomarkers with standard measures for vulvodynia (i.e., scales of sexual function and distress, histology, relationship impact); and
- Conduct natural history (longitudinal) studies of young girls before pain manifests to map the pathways that lead to the development of chronic pain, to identify which patients have a specific event that triggers chronic pain, and to understand the characteristics of patients who do not develop chronic pain.

#### GOAL 5: BROADEN THE RESEARCH BASE ON TREATMENT AND MANAGEMENT OF VULVODYNIA

Vulvodynia is a multidimensional set of pain conditions, often difficult to diagnose. Women may experience different levels of pain, or a range of relief from provoked or unprovoked pain. Because of the multidimensional nature of pain conditions, identifying effective treatments has posed a significant challenge. Treatment research in vulvodynia is hampered by methodological challenges, such as the subjective nature of pain, limited

*“Clearly, we've not been able to adequately study treatment efficacy in [vulvodynia], and I think that that's a really important area to do, but of course...I think it's also important for us to study the etiology.”*

*—NIH-funded scientist working in the vulvodynia field*

infrastructure for clinical research, and a dearth of reliable, valid, and standardized measures for diagnosis and outcome measurement.

### SHORTER TERM OBJECTIVES

- Encourage and support the strongest basic methodological research to help identify and standardize measures for treatment outcomes (e.g., less pain, improved sexual function, psychological status);
- Identify pharmaceutical compounds that are effective in blocking central, peripheral, and mixed pain, and determine whether some of these compounds are suitable for testing in vulvodynia patients;
- Explore, with the NIH Therapeutics for Rare and Neglected Diseases Program, whether off-patent drugs might be repurposed to treat pain conditions (including multimodal vulvodynia); and
- Encourage and support preliminary, small-scale, but rigorous clinical trials of existing therapies as a prelude to expanding the full range of multidisciplinary clinical research needed to establish an evidence base for treating vulvodynia.

### LONGER TERM OBJECTIVES

- Work with health care provider organizations and the NIH Pain Consortium to develop evidence-based protocols for multidisciplinary treatment (similar to the development of the fibromyalgia template) and to standardize data collection;
- Encourage and support rigorous clinical trials to examine systematically the efficacy of current treatment strategies (including surgical, medical, physical, or combination therapies such as pain modulators combined with cognitive psychotherapy), and compile available data on why some subsets of patients respond better than others to each type of approach (e.g., those patients who receive early diagnosis and treatment);
- Explore the role that inflammation plays in increasing pain and in lowering immune response and efficacy of treatments;
- Determine whether nerve blockers can obviate some types of pain, and allow nerves to grow back unaffected;
- Determine the role that chronic stress, early life trauma, and abuse play in increasing vulnerability to pain, including pain from vulvodynia;
- Examine partner/relationship factors in pain and sexual function; and
- Use stem cells to create neurons for studying the response of human cells to drugs under development that treat pain.

## GOAL 6: HELP WOMEN LIVING WITH VULVODYNIA AS A CHRONIC PAIN CONDITION

Like other chronic pain conditions, vulvodynia has a highly negative effect on quality-of-life. As detailed in the IOM report, many people in this country continue to live with chronic pain, and it is often resistant to treatment. For this reason, it is important for the NIH, partner organizations, and researchers to focus on ways to help those living with chronic pain conditions, while longer term research aimed at ameliorating these conditions proceeds.

*“[Women with vulvodynia] suffer at home, in silence, and they don't understand that the pain that they're experiencing is not normal.”*

*—NIH-funded scientist working in the vulvodynia field*

### SHORTER TERM OBJECTIVES

- Expand, update, and disseminate evidence-based patient and provider education materials on vulvodynia and related chronic pain conditions; and
- Establish, expand, evaluate, and update training for medical students, residents, and obstetrician/gynecologists to include relevant information from the fields of neurology, dermatology, and urology to assist in accurate diagnoses and targeted referrals for patients with vulvodynia and related pain conditions; and
- Support efforts by the scientific community to improve operational research measures related to quality-of-life for individuals with vulvodynia and related pain conditions, particularly improved comparisons of women's pain levels and sexual function.

### LONGER TERM OBJECTIVES

- Support additional research to study how living with someone with a chronic pain condition affects families; and
- Pursue research on the effective self-management of long-term chronic pain and adherence to pain management modalities, and disseminate results of these studies.

## **SUMMARY OF RESPONSES TO PUBLIC COMMENTS**

The NIH received nearly two dozen substantive comments on the draft *NIH Research Plan on Vulvodynia* during the open comment period. The majority of comments were submitted from clinicians whose patient populations include women who present with vulvodynia or other vulvar pain. Additional comments were submitted by researchers, patients, and members of professional societies. Most of the respondents agreed that having a plan in place will help to promote and advance research on the wide range of questions and resources needed to address vulvodynia as a chronic pain condition.

All comments were carefully considered. They are grouped according to topic and addressed as described below.

### **Improve Vulvodynia-Related Definitions/Terminology**

Many respondents agreed with statements in the plan about the need for clearer definitions and terminology related to vulvodynia, a necessity for comparable research results. Comments included a request that earlier efforts to develop such terminology be recognized, and an acknowledgement that vulvodynia may represent a spectrum of conditions, rather than a single disease entity. The NIH notes that even the proposed definitions offered in the comments were not uniform and agrees that another scientific meeting with relevant stakeholders may be required in the near future to come to some consensus on this subject and begin to move the field forward.

### **Identify Possible Etiological Factors**

By far the most comments on the draft research plan related to possible causes of vulvodynia. Although specific etiologies were meant to be included within the umbrella terms used in the plan, examples raised in the comments have been added to several of the goals for clarification; these include hormone use, psychosocial causes, and concurrent morbidities as examples of *potential* risk factors for vulvodynia. Several of the comments described clinical experience and/or theories for causes of vulvodynia,

demonstrating the need for sufficient research infrastructure to study these ideas.

### **Clarify and Emphasize Relationships Among Pain Conditions**

The concept that vulvodynia should be considered within the broader context of other chronic pain conditions, to look for common pathways and mechanisms, was thoroughly explored at the scientific meeting held in July 2011. Consequently, only a few comments addressed this topic, largely to point out that better understanding of the etiologies of vulvodynia would lead to more accurate diagnoses and, in turn, improved treatments. One respondent suggested adding supplements to current research grants as a way to obtain useful data in a cost-effective manner. The NIH believes that the research plan adequately incorporates the concept of vulvodynia as a chronic pain condition.

### **Foster Interdisciplinary Approach to Research and Care**

Several respondents shared their clinical experience in their comments on the plan, describing the need to address each patient's condition with a team of individuals who have different expertise. In particular, commenters noted that physical therapists are often brought in to relieve some of the pain and other symptoms of vulvodynia. In addition, some respondents noted that researchers from various disciplines (i.e., psychiatry, neuroscience) would be critical to vulvodynia research studies. Language was added to several of the plan's goals to clarify that a multidisciplinary approach to clinical and other research may help move the field forward.

### **Support Increased Clinical Research**

Clinicians who work with patients experiencing vulvodynia submitted comments on the research plan, mostly in support of the goal to broaden the research base regarding treatment and management of these conditions. Several offered their expertise in the design of clinical trials, and suggested types of expertise needed on any clinical research or care team, such as nurses, physical therapists, and cognitive behavioral therapists.

## **Improve Health Care Provider Education/Training**

A number of participants in the July 2011 meeting held by the NIH described some of the difficulties many women have in obtaining a diagnosis and treatment for vulvodynia. Several respondents submitted comments stating that reasons for these challenging situations include inadequate information for, and training of, the health care providers who are likely to see these patients. The commenters strongly recommended that improved educational materials be developed and disseminated. While the draft plan also emphasized this need, additional language was added to make the goal even stronger. In addition, the NIH notes that it frequently works closely with professional societies to ensure that new evidence is disseminated to the field once it is available.

## **CONCLUSION**

This plan, *The NIH Research Plan for Vulvodynia*, was developed by the NICHD with a significant amount of input from other NIH ICs, the scientific community outside of the NIH, and key organizations that include researchers involved in this area and advocates for individuals with vulvodynia and their families.

The research plan is intended to provide guidelines for prioritizing and coordinating future research related to vulvodynia, and to encourage scientists to consider vulvodynia within the larger context of pain research. The plan will also help NIH to communicate its priorities for research related to vulvodynia to the wider scientific community, hopefully encouraging the submission of new research applications.