

# **The TMJ Patient-Led RoundTable: A History and Summary of Work**

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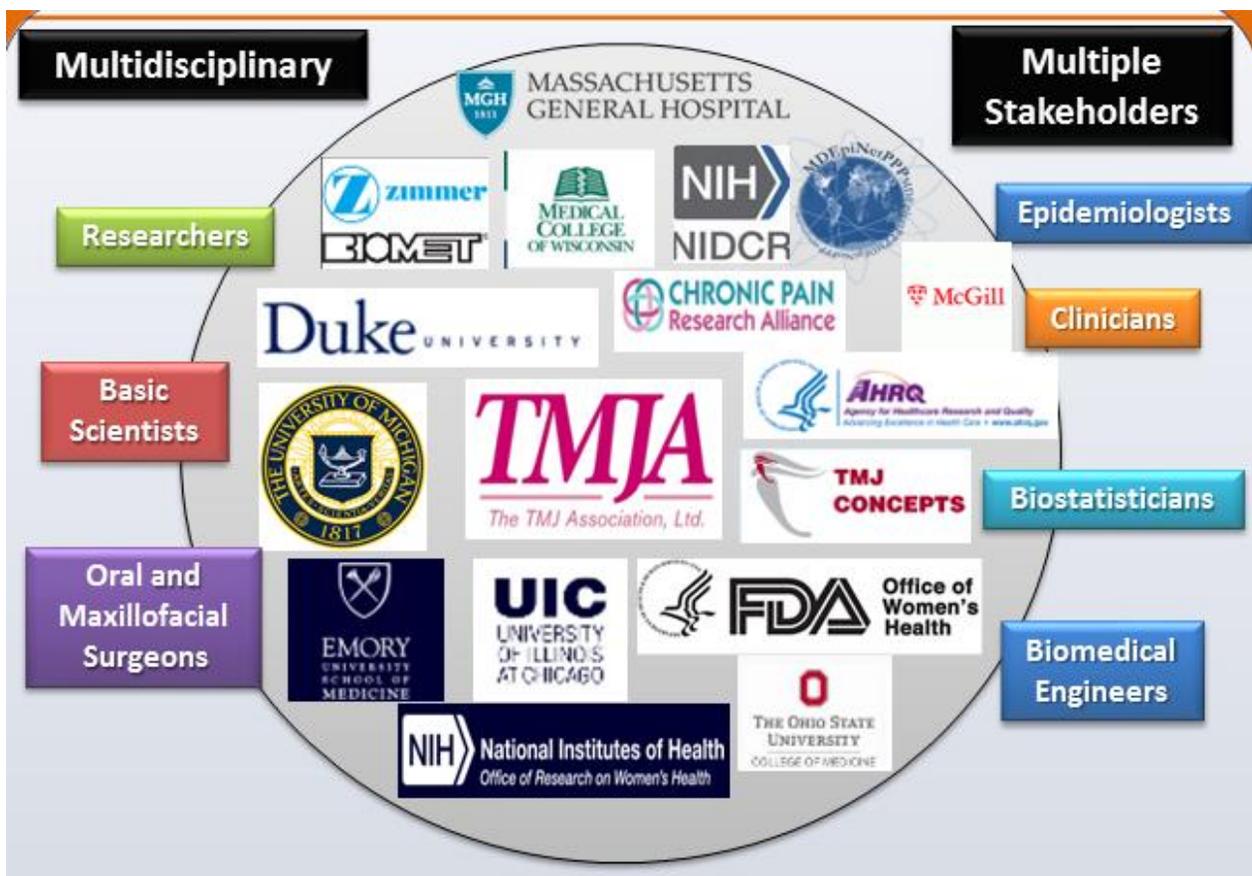
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This document summarizes how the TMJ Patient-Led RoundTable came about and evolved from a focus on determining which TMJ patients could benefit from implant surgery to recognition of the necessity of examining all aspects of Temporomandibular Disorders and its ecosystem. Included are reports of the work completed to date by the TMJ RoundTable Working Groups.

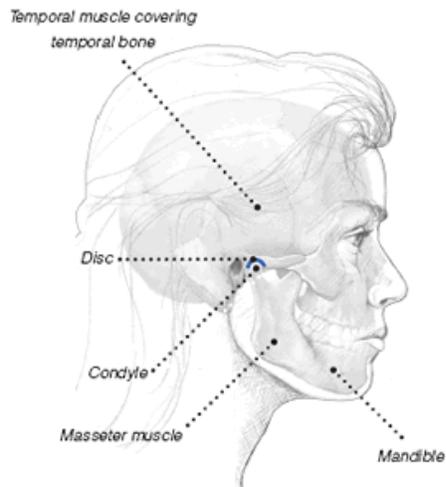


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## BACKGROUND ON TEMPOROMANDIBULAR DISORDERS

Temporomandibular disorders (TMD) are a diverse set of conditions characterized by pain and/or dysfunction of one or both jaw joints. These disorders affect the tissues of the joint including the muscles, bones, connective tissue, nerves, and vasculature.



Although many TMD symptoms affect individuals, pain is the factor that most motivates patients to seek care. Some patients have jaw dysfunction with or without pain, others pain without dysfunction, and others have both. With increasing severity, a person's ability to speak, chew, swallow, make facial expressions, and even breathe becomes compromised. [The disorders remain poorly understood and problematic to treat \(Yokoyama, Kakudate et al. 2018\).](#)

**Epidemiology.** Estimates in the literature of the prevalence of TMD in the United States range from 5 to 77 percent of all people. One study conducted in 1991 by Michael Von Korff, (Dworkin SF) found that 12 percent, or approximately 35 million people in the United States, have TMD. Other studies indicated that TMD resulted in more than 17 million lost workdays per year for every 100 million working adults in the U.S., at an annual cost of \$32 billion dollars (The Lewin Group) (Dworkin 1993, White, Williams et al. 2001, Janal, Raphael et al. 2008, Jussila, Kiviahde et al. 2017). An update of the incidence and prevalence of TMD, individual costs and economic burden on society, is clearly indicated.

Most acute TMD cases resolve on their own, either with time or conservative treatment, such as hot or cold compresses and a soft diet; however between 10 and 30 percent of cases become chronic. When conservative treatments fail to provide relief, many patients are led to invasive and often irreversible treatments.

**A Dental Focus.** Traditionally, the location of the temporomandibular joint in the orofacial region has made it the province of dentistry, with the result that historical and

current treatments for TMD have focused on the jaw joint, teeth and affiliated musculature. However, there is scant evidence of the safety and efficacy underlying more than 50 such treatments (Asa 1994, Reid and Greene 2013). These include, but are not limited to, “occlusal adjustment” (such as grinding down teeth, orthodontic treatment to change the bite, crown and bridge work, mandibular repositioning splints), local injections (such as Botox and steroids), and various surgical procedures.

**Siloes of Research.** The orofacial focus has also deeply affected biomedical research funding for TMD, given that the National Institutes of Health (NIH) is made up of 27 Institutes and Centers, each with a specific research agenda, often focusing on particular diseases or body systems. This division of research has resulted in the isolation of each institute into its own separate silo, overseeing and zealously directing the research toward “their” part of the body, thus serving primarily their own professional constituents. This is in direct contrast to the current [understanding of the body as an interdependent system \(Lee and Somerman 2018\)](#), with each part affecting and being affected by every other part. Over the years, the bulk of TMD research has been directed and funded by the National Institute of Dental and Craniofacial Research (NIDCR). There is tremendous potential for cross-institute collaborations among institutes whose mission and focus encompass relevant factors to TMD. There is a moral imperative to see that the best available science is directed toward TMD research.

## EVOLUTION OF THE PATIENT-LED TMJ ROUNDTABLE



One irreversible treatment for temporomandibular joint damage, degeneration and dysfunction is the implantation of a prosthesis, classified as a medical device by the U.S. Food and Drug Administration (FDA), and used to reconstruct the jaw joint and connect the device components to the mandible and skull.

The TMJ Association (TMJA) is a nonprofit patient advocacy organization founded in Milwaukee, Wisconsin in 1986. The TMJA advocates for research for solutions to TMD and the medical conditions that frequently

co-occur with it, as well as for the development of safe and effective diagnostics and treatments. For over 20 years the TMJA's advocacy efforts have resulted in [congressional report language](#) to advance TMD scientific research.

The TMJA submitted a statement detailing the history of temporomandibular joint (TMJ) devices to the U.S. Senate Special Committee on Aging on April 13, 2011 at a hearing titled, [A Delicate Balance: FDA and the Reform of the Medical Device Approval Process](#). Of particular note, in 1991 the FDA issued a Class 1 Recall of the Vitek Inc. TMJ implants because of what they termed "open communication to the brain." In June 1990 Vitek declared bankruptcy and moved its patents off shore and in 1992 Vitek's President fled the country for Switzerland, leaving the FDA to handle its first Class 1 recall.

In 2006 the TMJA asked for a U.S. General Accountability Office (GAO) investigation on how the TMJ implant devices received FDA approval. The [GAO report](#) revealed the problems associated with the FDA's approval of devices since 1999. It found there had been a general lack of transparency, a haphazard post-marketing surveillance system, a double standard in which small companies were treated more leniently than large companies, and approval of a device without clinical data. In part, FDA's problems with devices reflected overall issues in regard to agency operations.

**522 FDA Order.** Following the TMJA's request for the FDA to conduct an analysis of the MedWatch Reports for TMJ devices, [on February 7, 2011, the FDA issued a 522 order](#) to the three TMJ device manufacturers to conduct postmarket surveillance studies to determine the length of time before implants were removed or replaced due to pain or other reasons. [Among the reports it reviewed, the FDA found that 52% of the TMJ devices had to be removed less than three years after they were implanted.](#) Device problems included the need for removal or replacement, loosening, difficulty removing, noise, fracture and breaking.

**Conflicting Reports.** The need for the TMJ Patient-Led RoundTable grew out of conflicting reports on TMJ implant devices. Manufacturers, surgeons, and publications

claimed that patients improved after receiving implants. But comments from FDA's MedWatch system, as well as accounts circulating on social media and with information patients shared with the TMJA, told a different story. Many implant patients said that their pain and jaw dysfunction worsened after implants, and some reported developing infections and sensitivity to the implant materials. Patients often required multiple additional surgeries, replacement implants, and an array of other treatments. Many implant recipients reported the onset of new medical conditions, sometimes inexplicable, following device implantation. In more than a few cases, patients were rendered disfigured and totally disabled.

**RoundTable Members.** After Terrie Cowley, the TMJA President and member of the Medical Device Epidemiology Network (MDEpiNet), brought the TMJ implant issues to MDEpiNet colleagues, plans were developed for a TMJ Patient-Led RoundTable.

To address the array of issues experienced by implant patients, the TMJA proposed that the RoundTable comprise all key stakeholders as partners. These would include patients, the FDA, the National Institute of Dental and Craniofacial Research (NIDCR), the Agency for Health Care Research and Quality (AHRQ), the American Association of Oral and Maxillofacial Surgeons (AAOMS), TMJ device manufacturers, clinicians, scientists, advocacy organizations, and other experts, all under the auspices of MDEpiNet. The initial goal was to explore ways to improve TMJ implant treatment outcomes. However, in planning meetings it became clear that the scope of the meeting needed to expand to achieve meaningful results. Fundamentally, it was necessary to:

- Understand how a TMD patient's physiological systems interact with and affect responses to TMD treatments, and not just to total joint implants, as well as understand whether any specific physiological factors, present in implant patients experiencing adverse events, are absent in patients experiencing no adverse events.
- Learn if the patient's symptoms are a consequence of the patient's disease process instead of the treatment/device.

- Identify routinely recommended TMD treatments and their underlying scientific evidence, and determine whether which therapies may lead to more aggressive/invasive treatments, such as TMJ implants.
- Learn which treatment protocols, standards of care, guidelines and best practices are endorsed by the various professional societies whose practitioners treat TMD patients, and whether these practices are evidence-based and patient-centered, and whether practitioners comply with them.
- Examine the education of all health care professionals to determine whether academic curricula and post-graduate training are scientifically based and patient-centered.
- Understand the life cycle of both autologous and biomaterial implant devices and their impact on a patient's quality of life.
- Follow the implant patient throughout his/her lifetime to learn device sequelae.
- Perform implant retrieval analyses to assess performance and determine causes of failure.

**Meetings.** The [first RoundTable meeting was held on June 16, 2016](#), at the FDA headquarters in Silver Spring, Maryland. A large portion of the meeting featured the [personal stories of TMJ implant patients](#). Attendees heard patients' concerns about the state of current TMD treatments, the urgent need for more interdisciplinary research and a paradigm shift in TMD treatment. Non-patient stakeholders expressed their interest in hearing and learning from patients, and their hopes to find ways to "do better." The meeting led to the [formation of four working groups](#) to address specific areas of study, as well as a Steering Committee to coordinate and oversee the project as a whole. Importantly, the RoundTable was seen as a vehicle in which patients would play critical roles: as Steering Committee members, working group co-chairs, working group participants, and co-investigators in the project.

[The second RoundTable meeting took place on May 11, 2018, at FDA Headquarters.](#)

The objectives of the meeting were to:

1. Update participants on the status/results of the working group projects;

2. Identify gaps and next steps for achieving working group goals and establish a roadmap to achieve them;
3. Identify data collection needs to support working group activities and establish processes for the development of high quality, real-world evidence; and
4. Accomplish the above with a minimum burden to patients and caregivers.

## **WORKING GROUP 1 REPORT**

The charge for Working Group 1 is to *define the Natural History and Assess Biomarkers Associated with Outcomes in TMJ Implant Patients*. The objectives include:

1. Summarize knowledge related to the overall health of the TMJ patient based on the scientific literature, as well as physician and patient reported information. This includes reports of pain and other health conditions.
2. Summarize existing data on genetic, biochemical, immunological and physiological mechanisms that may collectively advance our understanding of how a patient may respond to implant procedures.
3. Assess existing phenotyping data and information needed to develop device/patient phenotyping classification.

The goal is to explore the multidisciplinary intersection of patient biology, anatomy, genetics, and physiology with TMJ medical devices and clinical patient-centered outcomes to better target therapies toward patients who are most likely to benefit from them.

### **Working Group 1 Findings.**

**A Paradigm Shift.** With completion of the most extensive research project on TMD conducted to date, the *Orofacial Pain: Prospective Evaluation and Risk Assessment (OPPERA)* study, supported by NIDCR, a clearer picture has emerged of the etiology of TMD. Essentially, the research has changed the paradigm by replacing the traditional way of thinking about the TMJ and its conditions as a dental problem confined to the

orofacial region, to seeing it as a medical problem involving multiple systems, and ultimately reflecting a dysfunction of the nervous system.

More specifically, the study unequivocally demonstrated that TMD is a complex disorder that is best envisaged within a biopsychosocial model of illness, which acknowledges the influence of genetic and environmental factors (Schrepf, Williams et al. 2018). It is a misnomer, and no longer appropriate, to regard TMD solely as a localized orofacial pain condition. For the majority of people with chronic TMD, it is a multisystem disorder with overlapping comorbidities (Maixner 2014). Although the underlying etiology of TMD is still poorly understood, as characterized in a recent review (Wilentz and Cowley 2017), findings point to a complex etiology centered on heightened central nervous system activity that contributes to TMD dysfunction and symptomology. As noted, onset of TMD appears to occur as a result of an individual's genetic makeup interacting with exposure to environmental risk factors. These would include injury, physical and psychological stressors, and negative life events — factors which influence the activity of biological pathways. However, much research is needed to understand the underlying genetic, epigenetic, other 'omic', biochemical, physiological, neurological, endocrine, and immune system mechanisms accounting for the pathological changes seen in TMD.

**Comorbidities.** Temporomandibular disorders are often associated with a number of [chronic overlapping pain conditions](#) including chronic low back pain, chronic migraine and tension-type headaches, endometriosis, fibromyalgia, interstitial cystitis/painful bladder syndrome, irritable bowel syndrome, myalgic encephalomyelitis /chronic fatigue syndrome, and vulvodynia. Non-pain conditions also associated with TMD include allergies, anxiety, depression, cardiovascular conditions, dysautonomia, fatigue, multiple chemical sensitivity, sleep disorders, and tinnitus.

One part of the OPPERA study, directed by Dr. William Maixner, was a prospective cohort study of adult volunteers who were initially TMD free. The study yielded new information regarding symptoms predictive of the onset of TMD. One of the strongest risk factors for developing TMD was the number of health conditions a patient had

reported from a checklist of 20 listed conditions, such as abdominal pain, depression, and tinnitus (Sanders, Slade et al. 2013). Also, participants who were symptom free when enrolled, but who exhibited high somatic awareness scores, had nearly twice the incidence rate of TMD as those participants with less frequent somatic symptoms. Patients with TMD and associated overlapping conditions commonly reported greater sensitivity to experimental pain compared to controls, even when pain sensitivity (pressure pain, heat, pinprick stimuli) was assessed at non-craniofacial sites (Greenspan, Slade et al. 2011, Greenspan, Slade et al. 2013). However, only a few of those associations were found to be predictors of TMD incidence, and effect estimates were weak (Greenspan, Slade et al. 2013).

**Replication and Increased Research.** More basic and clinical research, as well as independent replication and/or further confirmation of the risk factors for TMD identified in the OPPERA study are necessary before diagnostic and prognostic criteria can be established that would successfully differentiate TMD subtypes. This is critically important to enable selection of optimal TMD treatment regimens on an individual basis and prediction of possible clinical outcomes. While such profiling would be applicable to optimizing treatment approaches for all TMD patients, it would be especially beneficial for identifying best candidates for TMJ implant devices in order to avoid adverse outcomes. Nevertheless, sufficient knowledge is emerging of the biology and epigenetic aspects of TMD etiology, joint dysfunction, pain, and psychosocial abnormalities to permit some clustering of TMD patients. The result will be better diagnostic and prognostic criteria that can improve treatments and quality of life for all TMD patients.

The acquisition of this new knowledge on TMD is in part attributable to the eight biennial scientific meetings the TMJA has sponsored with co-funding from several NIH institutes and offices. The research reported at these international gatherings has ranged from the basic anatomy and physiology of the joint to exploring mechanisms underlying the presence of overlapping pain conditions in TMD patients. Each of these research conferences was notable for several reasons. First, they emphasized a multidisciplinary systems approach. Second, they focused on cutting-edge science, as supported by the

NIH, ranging from molecular genetics to current approaches in precision medicine. Third, they consistently incorporated patients into the program in meaningful and interactive ways. From each of these conferences, scientific recommendations were developed and published to advance the research and clinical needs of the field. Beyond recommendations for acceleration of research and funding for this entire field, it was repeatedly and strongly recommended that ways be sought to bring together the multidisciplinary areas of expertise needed to advance our understanding and management of this complex disorder. [NIH inter-Institute cross-disciplinary efforts](#) will be necessary to move this field forward; this includes expertise in neural and muscular biology, bone and joint biology, immunology, endocrinology, pain, psychology, genetics/genomics, and informatics. [Each meeting was summarized in TMJA's Scientific Journal, TMJ Science, and included the research recommendations developed by meeting attendees](#), which were distributed to NIH administrators and the research community.

**Psychosocial Factors.** Findings from the OPPERA study demonstrated that psychosocial measures, including somatic symptoms, psychological stress, and negative mood, were strongly associated with chronic TMD (Fillingim, Ohrbach et al. 2011). Moreover, pre-morbid, pre-diagnostic psychosocial functioning predicted future development of TMD (Fillingim, Ohrbach et al. 2013). Notably, these psychological variables often differ for females and males and may contribute to sex differences in pain (Fillingim, King et al. 2009).

The preceding paragraph summarizes what is known by the scientific community. There is, however, another, equally important data source that is relevant — the voices of the patients themselves, who are experiencing real-world situations that are not explored in the OPPERA study. These experiences include:

- Women treated in a male-dominated environment.
- Failure of health professionals to acknowledge or explain the severity and complexity of TMD in marketing to the public.

- Chaos and controversy that abounds in the TMD treatment arena where patients receive different diagnoses and treatment plans from different practitioners, risking patient healthcare decisions in the face of sometimes conflicting information.
- Patient abandonment when the treatments prescribed by the provider doesn't alleviate their condition or worsen it.
- Patients blamed when the treatments fail.
- Financial loss and bankruptcy due to the costs of TMD health care, unpredictable insurance coverage for TMD treatments, requirement by practitioners for patients to pay for services in cash in advance, encouraging patients to take personal loans, and sign contracts with financial companies affiliated with the dental practice.
- Harm from treatments that received FDA approval;
- Betrayal by and loss of trust in dentists and other practitioners with whom they have entrusted their well-being.
- Desperation to get relief trying any treatment, regardless of its scientific validity.
- The stigma of a condition that isn't readily obvious to friends, family, and the general public.
- Social isolation from friends and family leading to loneliness, anxiety, and depression.
- Dramatic changes in physical appearance resulting from the disorder, treatment, nutritional problems, and severe weight gain/loss. Facial deformities causing diminished self-esteem, shame and revulsion, the shock of no longer recognizing themselves when looking in the mirror, and the ultimate shame of being stared at in public.
- Social consequences such as: job loss; divorce; abandonment of career, educational, and personal ambitions; abandoning the idea of having children; inability to assume household and child-rearing responsibilities; and changed family roles.
- Physical inability for restaurant dining — society's way of interacting in a social or business setting Those who feel like going out suffer the embarrassment

imposed by their masticatory inadequacy, such as having food fall out of their mouths or choking.

- Loss of valuable friendships and inability to participate in daily experiences and pleasures normal people take for granted.
- The effect TMD on the sex lives of both the patient and partner — the once pleasurable sensations of being touched, hugged, kissed, having one's face stroked, and all the things that are an integral part of lovemaking and affection sharing, are, for many, excruciatingly painful.
- Thoughts and attempts of [ending one's life/suicide](#) (Bertoli and de Leeuw 2016).

To summarize, TMD patients often find their lives devastated in ways that are not easily quantified. Besides the obvious health concerns and accompanying pain, their lives are often diminished socially, financially, and emotionally, and they experience a loss in intimacy and their own sense of self-worth.

[The TMJ Association published an article titled, the “Unforgiveable Injury”, which describes these real-world situations in greater detail.](#)

This is a sampling of the realities shared by TMD patients. It is obvious that if TMD patients have comorbid anxiety, depression and other psychological issues, these issues may be magnified by TMD treatment and the many other affronts on the patient's psyche. These comorbid conditions, along with the psychological consequences of chronic TMD and the state of TMD treatment, must be included in the future biopsychosocial TMD studies.

**The Role of Genetic Variability in TMD.** Studies examining the genetic risk for TMD have begun to identify factors that can lead to pain chronicity and point to the need for more personalized treatment options. The genetic contribution to TMD has been estimated to be 27% (Plesh, Noonan et al. 2012) and is considered a major factor in explaining the large inter-individual variability in TMD pain and disability (Fillingim, Wallace et al. 2008). In part, this variability may also explain the differing responses to treatment modalities (Rollman, Visscher et al. 2013). Most of the knowledge gathered

on TMD genetics to date comes from candidate-gene studies. Investigators have sought associations between TMD and/or TMD-related phenotypes and genetic variants selected *a priori* based on their putative involvement in the phenotype being investigated. These studies have provided evidence for the involvement of genetic variants in the catecholaminergic, estrogenic, and serotonergic systems, as well as in cytokines, enzymes of the folate pathway, and other molecules associated with pain responses.

In these studies, TMD has been associated with single nucleotide polymorphisms (SNPs) in the: catechol-O-methyltransferase gene (*COMT*) (Meloto, Segall et al. 2015); beta adrenergic receptor genes (Diatchenko, Anderson et al. 2006); estrogen receptor alpha (*ESR1*) gene (Ribeiro-Dasilva, Peres Line et al. 2009); and serotonin transporter (*SLC6A4*) gene (Herken, Erdal et al. 2001). OPPERA researchers conducted a comprehensive candidate-gene study of chronic TMD patients by testing the association of 3295 SNPs spanning 358 genes known to be involved in systems relevant to pain perception (Smith, Maixner et al. 2011). Of the top nine SNPs showing nominal statistically significant association with chronic TMD, three are in the glucocorticoid receptor gene (*NR3C1*); one in the *HTR2A* gene (mentioned above); one in the muscarinic cholinergic receptor 2 gene (*CHRM2*); two in the calcium/calmodulin-dependent protein kinase 4 gene (*CAMK4*); one in the interferon-related developmental regulator gene (*IFRD1*); and one in the G protein-coupled receptor kinase 5 gene (*GRK5*). The putative association of these SNPs with TMD awaits confirmation in replication studies. A second candidate gene study performed by the OPPERA group identified genetic variants associated with the risk of developing TMD (Smith, Mir et al. 2013). No single SNP was associated with significant risk of TMD onset. However, many SNPs were associated with phenotypes known to be predictive of TMD onset. These genetic associations with TMD-related phenotypes may reveal genetic pathways that influence the risk of developing TMD.

In addition to the candidate gene studies, genome-wide association studies (GWAS) have also been undertaken to provide novel and unbiased insights into multiple aspects

of TMD (e.g. pathophysiology, chronicity, treatment targets). A recent TMD GWAS was completed by the OPPERA team on 999 TMD cases and 2,031 TMD-free controls (females and males) (Sanders, Jain et al. 2017). While preliminary, the results provide additional evidence that different molecular mechanisms underlie the pathophysiology of TMD in women and men and it is anticipated the results will suggest targets for investigations to explore novel therapeutic strategies.

Additional genetic research is needed to advance the field to a point where new precision medicine-based therapies can be derived and applied to precisely treat TMD patients with a high probability of success and minimal unwanted side effects.

**Sex Differences in TMD.** Based on general population data, the prevalence of TMD is greater in females, who also appear to be at a greater risk of first onset and persistence of the disorder (Drangsholt and LeResche 1999, Slade, Bair et al. 2011, Jussila, Kiviahde et al. 2017). Consistent with these and earlier observations (Macfarlane, Blinkhorn et al. 2004), OPPERA investigators also found that females were at somewhat greater risk for TMD onset and at significantly greater risk for persistence of symptoms (Slade, Bair et al. 2013).

There is evidence that females are also more likely to seek treatment for TMD, and this could be driven by more severe symptoms in women (Schmid-Schwab, Bristela et al. 2013). Females with TMD are also more likely to have multiple comorbid pain conditions, suggesting a more severe overall pain phenotype (Plesh, Adams et al. 2011, Visscher, Ligthart et al. 2015) (Dahan, Shir et al. 2015). An abundant literature demonstrates increased sensitivity to experimentally evoked pain among females across modalities and measures, which may contribute to increased TMD risk (Fillingim, King et al. 2009, Mogil 2012) (Cairns, Hu et al. 2001, Schmidt-Hansen, Svensson et al. 2006).

Sex differences in pain sensitivity are not restricted to the trigeminal system, as these differences have been observed across the body (Fillingim, King et al. 2009, Mogil

2012). Together, the data indicating more severe and persistent pain and the higher prevalence of multiple comorbid pain conditions among women may well explain observations of more treatment-seeking compared to males with TMD.

**Estrogen and TMD.** An important role of sex hormones in TMD pathophysiology is supported by observations of increased prevalence and severity of symptoms among women during the reproductive years. TMD symptoms also fluctuate across the female menstrual cycle, with peak pain occurring during the perimenstrual phase (LeResche, Mancl et al. 2003). Moreover, use of exogenous estrogens (but not progesterone) has been associated with increased risk and severity of TMD (LeResche, Saunders et al. 1997, Wise, Riley et al. 2000), the symptoms of which have also been found to decrease during pregnancy and increase again in the post-partum period (LeResche, Sherman et al. 2005). The mechanisms whereby sex hormones affect nociception and neural processing of pain have been studied in a number of laboratories, but it remains unclear the extent to which these hormonal influences upon pain processing and generalized pain sensitivity are peripherally and/or centrally mediated (Fillingim and Ness 2000, Craft 2007) (Cairns 2007) (Wu, Hao et al. 2015) (Fanton, Macedo et al. 2017).

**Role of Inflammation in TMD Pain.** Local and systemic inflammation can contribute to TMD pain by damaging peripheral structures, increasing afferent nerve activity and/or amplifying central pain sensitization. Local inflammation is indicated in the joints by excess pro-inflammatory cytokines in the synovial fluid, masseter muscles, and in plasma of TMD patients (Kellesarian, Al-Kheraif et al. 2016, Louca Jounger, Christidis et al. 2017). Such local inflammation could activate and sensitize nociceptors and their peripheral drive to the CNS. Systemic inflammation has also been observed in TMD patients with generalized chronic pain (Harmon, Sanders et al. , Slade, Conrad et al. 2011).

Although sex differences in immune and inflammatory responses are well recognized (Straub 2007, Manson 2010, Kovats 2015), the extent to which these relationships

contribute to chronic pain is just beginning to be explored. Several studies indicate that females exhibit a hyperinflammatory phenotype which is correlated with their clinical pain and is potentiated by estrogen (Sorge, LaCroix-Fralish et al. 2011, Karshikoff, Lekander et al. 2015). It has also been recently reported that microglia may be relevant to chronic pain only in male mice while the pain-producing functions of the male microglia may be performed instead in female mice by T cells of the adaptive immune system (Sorge, Mapplebeck et al. 2015).

**The TM Joint.** Recent research efforts are also underway on the biology and physiology of the TMJ itself. This joint is a modified hinge-type joint consisting of mandibular and temporal bones; an articular disc composed of fibrocartilage, several ligaments and muscles controlling motion and joint mechanics; and sensory innervation by the trigeminal nerve. Disc dysfunction is thought to be one of the early signs leading to joint pain. New research focused on the regeneration and repair of the TMJ is centered on engineering a disc complex and developing bone-cartilage interfaces, which will provide the basis for improved treatments of dysfunctional joints. To accomplish this, there is a need for a more detailed understanding of TMJ tissue mechanics, joint tissue interfaces, neurological control, inflammatory joint processes, and scaffold design.

**Working Group 1 Recommendations.** The following research approaches are needed:

- Human Studies
  - GWAS of TMD patients, patients with other chronic pain conditions/comorbidities, patients with multiple pain conditions
  - Patient-centered outcome trials
  - Mechanistic clinical studies
- Animal Studies
  - Utilize animal models for mechanistic studies
  - Elucidate mechanisms underlying genetic discoveries
  - For disease onset/progression and novel treatments

- Basic Biological Studies
  - Stem cell/IPS cell models of TMD patients
  - Molecular/biophysical studies
  - Molecular modeling of druggable targets
  - Temporomandibular joint mechanics
  - Scaffold and joint interfaces design and testing
- Bio-informatics/Digital Technologies Development
  - Advanced mathematical approaches to uncover genetic complexity of disease
  - Artificial Intelligence approaches for pattern recognition (genetic, biological, psychological, social traits, EHRs, PROs) to identify disease subtypes, develop individualized clinical decision support, and predict patient responses

It is evident that research in a number of areas needs to be expanded to achieve a meaningful level of precision medicine diagnosis and treatment of TMD patients. A deeper understanding is needed related to the:

1. Mechanisms of pain sensation;
2. Pathways and mechanisms responsible for the sex differences related to TMD;
3. Genetic and epigenetic contributions including the microbiome to TMD;
4. Identification and characterization of comorbidities in addition to chronic pain including other neurological, metabolic, and psychological disorders; and
5. Role of immune and inflammatory factors in peripheral and central pain mechanisms.

Numerous approaches will need to be applied to achieve these research goals. GWAS studies of large cohorts of TMD patients with a wider variety of chronic pain conditions and comorbidities are needed, including TMD patients with other chronic pain conditions and comorbidities. Animal disease models are needed to elucidate mechanisms underlying the observed genetic associations and to enable well-controlled studies

elucidating the onset and progression of these complex conditions. Basic biological studies on stem cell/IPS models of TMD patients, molecular/biophysical studies, and molecular modeling of druggable targets are needed. Underpinning this research is the need to develop a bio-informatics infrastructure that will enable the collection and analysis of genomic scale animal and human data. This digital infrastructure and information technology is essential for advancing precision medicine in this or any field of medicine.

## **WORKING GROUP 2 REPORT**

The charge for Working Group 2 is to *define Patient-Reported Outcome Evaluation*. The objectives are to:

1. Identify the scientific literature evaluating Patient Reported Outcomes (PROs) measures in TMD patients;
2. Specifically assess the methodological quality and the evidence related to psychometric aspects, and then synthesize these assessments into an overall rating of psychometric evidence for each PRO measure by using the Consensus-based Standards Measurement Instruments (COSMIN) criteria;
3. Evaluate PRO measures (PROMs) of TMD patients regarding the effects on quality of life (QoL); and
4. Provide recommendations whereby PRO measures can guide future decision-making based on COSMIN criteria for premarket and postmarket evaluation of TMJ medical devices.

The goals are to develop outcome assessment and reporting tools based on patient input, and to develop evidence to incorporate patient-centered data into clinical care.

**Working Group 2 Overview.** In recent years, patient reported outcomes (PROs) have been increasingly incorporated into the data gathering process for treatments, device performance, quality of life impact, and overall health care. The information from a patient's perspective is becoming an increasingly important component in the process of

obtaining FDA approval for new treatments and in post-marketing assessments of acceptability and safety. The TMD health care research community needs to develop PROMs that provide evidence-based information to inform patient and professional decision-making in pre- and post-marketing evaluations of drugs, biologics, devices and other therapies.

**Critical Path Research Project.** Working Group 2 has received an FDA Critical Path Research Project grant, titled, *Patient Engagement Interaction for Safety Evaluation in Patients with Temporomandibular Joint Replacement (TMJR)*.

**Justification.** The justification for this project is based on discussions with patient advocates which revealed a disconnect between the safety data reported from clinical trials for TMJ devices and patients' own experiences. Safety data from device manufacturer supported clinical trials appears to underreport the frequency of adverse events. To better understand the safety of TMJ devices, it is essential to listen to patients outside the clinical trial environment. Taking this first step will allow a better understanding of the TMJ safety profile that will serve as a basis for the development of meaningful patient assessment tools leading to improved treatment, care, and management of TMD.

The project is being conducted by means of a cross-sectional Office of Management and Budget approved online survey, using a validated, ad hoc self-administered questionnaire to gather the frequency of selected patients' reported outcomes regarding adverse events from TMJ implants. The results of this survey will be compared to 1) those reported in the scientific literature and 2) information stated in the labeling that appears in connection with the three FDA approved TMJ devices in the U.S. market. These comparisons will determine whether adverse events are underreported in the clinical trials and other clinical studies sponsored by TMJ device manufacturers. If underreporting is found, we will assess the magnitude of underreporting and investigate reasons for this discrepancy.

The study constitutes a first attempt to utilize an online self-administered questionnaire to collect real-world evidence for epidemiological surveillance. The standardized methodology can be an additional data gathering tool that may be included in the National Evaluation System for Health Technology (NEST), informing the process by which the FDA decides to approve a device. Also, the tool will strengthen patients' role in generating epidemiological surveillance data at the FDA's Center for Devices and Radiological Health. By demonstrating the utility of these methods in a high-profile area, the project will serve as a model that may be adopted in pilot studies of other medical devices.

**Working Group 2 Results.** Completed/In Process:

- All published peer-reviewed literature evaluating psychometric properties of self-administered questionnaires related to safety issues in patients with TMD have been identified and abstracted.
- [The domains and their operational definitions included in the literature have been identified.](#)
- To identify core domains, a Delphi survey has been designed to discuss the identified domains with stakeholders, including TMD patients, clinicians, FDA reviewers, and members of the device industry.

Next Steps:

- Present Delphi findings to focus groups of patients to discuss and refine domains.
- Determine which core domains, along with their operational definitions, are to be included in questionnaires and determine which validated instruments (or instrument subscales/questions) assess those domains and their level of validity, reliability and responsiveness.
- Use domains from existing psychometrically sound instruments to create the questionnaire.
- Pilot test the questionnaire with patients.

- Send to IRB the approved questionnaire to be installed in an online survey platform.
- Advertise the approved questionnaire for enrollment.
- Collect, process, and analyze the data.
- Write a final report and submit it for publication.

### **WORKING GROUP 3 REPORT**

The charge for Working Group 3 is to *examine treatment directives, educational criteria, and patient-centeredness*. The objectives are to:

1. Collect and compile currently available best practices, clinical practice guidelines, diagnostic and treatment protocols being used to direct clinical treatments of temporomandibular disorders. This information will be identified and collected from academia, research centers, private practices, scientific societies, professional organizations, and federal agencies.
2. Assess the scientific basis of these treatment directives, as well as the extent to which these guideline documents and treatment protocols include patient-centered preferences and guidance.

The goal is to develop evidence-based best practices, treatment protocols, and clinical practice guidelines which include patient-centered data.

**Working Group 3 Overview.** The treatment of temporomandibular disorders continues to be less than satisfactory, and most commonly recommended therapies are based on outdated beliefs. This is in spite of recent scientific progress demonstrating that TMD is a complex, multifactorial multisystem disorder with a complicated etiology and pathology. Outdated therapies that lack evidence of safety and efficacy continue to dominate TMD practice and can lead to irreversible changes in occlusal relationships and jaw positions. These treatments can have negative effects on the TM joints and exacerbate an existing TMJ problem or cause one. When conservative approaches fail to alleviate TMD, no currently available guidelines or therapeutic directives provide scientifically based next steps.

**Pathways to a Total Joint Replacement.** There are a number of clinical situations that can result in the need for total TMJ replacement. One situation concerns those with severe trauma resulting in unrepairable damage to the bony components of the TM joint. Similar situations can arise with benign or malignant diseases requiring removal of the bony components of the joint. Likewise, end stage osteoarthritis, rheumatoid arthritis, TMJ ankyloses, and craniofacial deformities are all pathological conditions that may require joint replacement.

Unfortunately, there are a number of iatrogenic causes that can lead to situations requiring joint replacement. These include among others:

- Prior treatment with oral appliances or major dental procedures that alter occlusal relationships and reposition jaw joints and affect surrounding tissues;
- Intracapsular procedures that fail to relieve symptoms of pain and dysfunction, or that produce severe degenerative changes in the bony components of the temporomandibular joint;
- Misdiagnosis of myofascial TMD pain, inappropriately managed by surgical procedures leading to other treatments and even further surgical procedures, including implants; and
- Multiple surgeries leading to severe and irreparable damage to the TMJ.

Treatments for TMD can range from:

**Non-surgical treatments (often in combination)**

- Acupuncture
- Behavioral modifications: stress reduction, work modifications, counseling, biofeedback, psychotherapy
- Hot and cold compresses
- Injections: Botox, corticosteroids, hyaluronic acid, anesthetics, prolotherapy, bio-oxidative ozone therapy, platelet rich plasma
- Low-level laser therapy

- Medications – antianxiety, anti-inflammatories, anticonvulsants, antidepressants, benzodiazepines, muscle relaxants, NSAIDS, Opioids  
*(Currently there are no drugs FDA labeled for TMD.)*
- Occlusal adjustments – grinding down teeth, braces
- Pain management clinics
- Physical therapy
- Soft diet, jaw rest
- Splint therapy – custom made flat plane and repositioning, all with multiple differing designs and materials

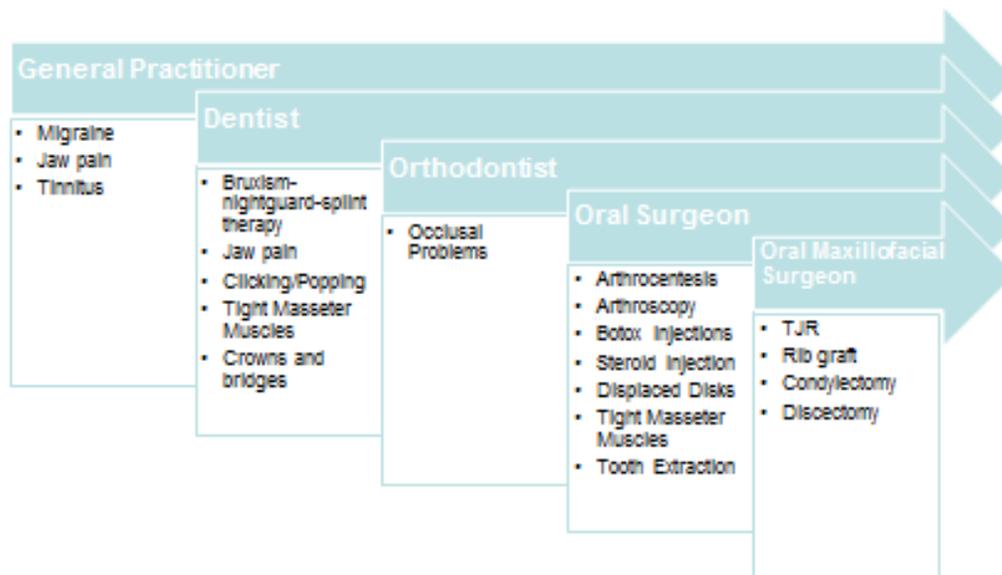
### **Surgical treatments**

- Arthrocentesis
- Arthroscopy
- Arthrotomy
- Condylectomy
- Condylotomy
- Discectomy/Disc repair or reconstruction
- Distraction osteogenesis
- Fat, tissue, and bone grafts harvested from various body sites for implantation into the TM joint
- Orthognathic
- Osteotomy

### **Joint Replacement**

- Partial replacement
- Total replacement
- Autogenous materials
- Biomaterials

# One Patient's TMD journey



**Is there a “Gold Standard” for TMD Management?** There are scientific statements and parameters of care, but no formal guidelines for TMD treatment formulated by professional groups for the management of TMD. The following information was gleaned from reviewing 24 professional organizations that profess to diagnose and manage TMD, by researching their websites to obtain information about their organizations’ theories and practices. The co-chairs of Working Group 3 contacted the organizations to obtain any published materials for diagnosing and treating TMD. Three organizations provided their information for treating TMD. These groups follow available scientific information to determine their strategies. These directives are freely available to the public.

1. **The American Association of Dental Research (AADR)** published a Science Information Statement in 2010 and reaffirmed in 2015 (Greene, Klasser et al. 2010) regarding the diagnosis and management of TMD. The AADR advocates

that a differential diagnosis of TMD should be based primarily on information obtained from the patient's history, clinical examination, and when indicated TMJ radiology or other imaging procedures. The statement endorses conservative, reversible and evidence-based therapeutic modalities to both diagnosis and treatment of TMD. <http://www.iadr.org/AADR/About-Us/Policy-Statements/Science-Policy/Temporomandibular-Disorders-TMD>

2. **The American Academy of Orofacial Pain (AAOP)** has developed treatment guidelines. The current directives are compiled in a book (sixth edition published in 2018) edited by Reny de Leeuw, DDS, PhD, MPH, and Gary Klasser, DMD, with contributions from several other AAOP members. They are consistent with the current view that TMD represents a biopsychosocial model of a complex disease. <http://www.quintpub.net/news/2018/04/orofacial-pain-management-in-dentistry-three-decades-of-the-aaop-guidelines/#.W182z8InaUk>
3. **The American Association of Oral and Maxillofacial Surgeons (AAOMS)** has developed parameters of care for surgical treatment of TMD. *Parameters of Care: AAOMS Clinical Practice Guidelines for Oral and Maxillofacial Surgery (AAOMS ParCare), Sixth Edition 2017*, reflects the contributions of many OMS opinion leaders and includes guidelines for treatment and outcome expectations for designated areas of oral and maxillofacial surgery, including TMJ surgery. Other TMJ surgical societies rely on these parameters for contemporary practice. <https://www.aaomsstore.com/p-137-aaoms-parameters-of-care-sixth-edition.aspx>

#### Other Professional Society Sources

- **The ECRI Institute**, a nonprofit organization for testing medical products, published a document in 2017 evaluating the strength of evidence for various TMD treatments (LINK: Hotline Response: Efficacy of Treatments for Temporomandibular Disorders). While not an official statement of ECRI, the report states that conservative approaches, such as self-management practices, medication, cognitive behavioral therapy, physical therapy and splinting, are the first-line options to relieve pain and improve function of the TMJ. It also states that TMJ surgery is a last resort when other conservative approaches fail to relieve pain or improve function. In addition, the report suggests that second-line

conservative therapies that relieve pain in some patients might include acupuncture and intra-articular injections. However, the report states that insufficient evidence is available regarding the efficacy of arthroscopy, autologous blood injection, botulinum toxin therapy, hypnosis/relaxation therapy, or ultra-low-frequency transcutaneous electrical nerve stimulation.

When conservative approaches fail to alleviate TMD, no currently available guidelines or therapeutic directives provide scientifically based next steps.

#### Sources with Little to No TMD Guidance

- **The American Dental Association (ADA)** is America's leading advocate for oral health. As a science-based organization, the ADA supports advancements in research, policy knowledge and international standards that improve the delivery of dental care and the oral health of all Americans. There are no official standards of care for TMD established by the ADA.
- Both the **American College of Physicians** and the **American Medical Association** lack statements, publications, or articles related to TMD.
- **American Academy of Family Physicians** posted an article on their website titled, *Diagnosis and Treatment of Temporomandibular Disorders*. This article serves as the association's recommended best practice guideline for TMD management by a general practitioner.  
<http://www.aafp.org/afp/2015/0315/p378.html>
- **The American College of Rheumatology** has a resource page accessible to members containing a letter template for use in influencing insurance companies to cover MRIs for TMJ arthritis patients (access is limited to members). TMD is also listed as a possible concomitant disorder presenting in patients with fibromyalgia. There are no statements or adopted articles on management of TMD and the profession does not claim to treat TMD.  
<https://www.rheumatology.org/I-Am-A/Patient-Caregiver/Diseases-Conditions/Fibromyalgia>

- **The American Academy of Neurology** lacks any statement or publication related to TMD in any capacity. The society’s page on chronic disorders does include TMD as a possible etiological factor associated with a chronic pain state. This is the extent of TMD-related publications of this Academy and they do not claim to treat TMD.
- **The American Academy of Orthopedic Surgeons** lacks any statement or publication related to TMD in any capacity. They do not claim to treat TMD.

#### Sources Stating TMD Etiology and Treatment Guidance

- **The American Academy of Otolaryngology-Head and Neck Surgery (AAO-HNS)** has a patient-centered health information page which describes TMJ function/location and associated symptoms. It also includes a brief anatomical overview of the joint, and etiologies for various pathologic conditions. Potential differential diagnoses, treatment modalities and home care remedies are also listed. The AAO states that because TMD symptoms often develop in the head and neck, otolaryngologists are appropriately qualified to diagnose TMJ problems. The information on this webpage is outdated in regard to the idea that dental occlusion is an important etiologic factor for TMDs, and that most TMJ pain is due to disc displacement. <https://www.entnet.org/content/tmj>
- **The American Academy of Craniofacial Pain (AACP)** produced *Craniofacial Pain: Guidelines for Assessment, Diagnosis and Management* in 2009 and although not publicly available, it advocates for irreversible (albeit nonsurgical) treatments for TMD. The common interest that binds this group of dentists together is the belief that dental occlusion plays a major role in predisposition, precipitation and perpetuation of TMD. Their directives advocate for a variety of mechanistic procedures involving oral splints, disc recapturing, occlusal changes, and irreversible mandibular repositioning.
- Members of the **American Osteopathic Association** utilize osteopathic manipulative treatment (OMT) and claim to be successful in the management of TMD. The academy published a video in 2015 illustrating a “therapeutic technique” for TMD management: <https://www.youtube.com/watch?v=wa->

[WI2EvrCU](#). The website lists some articles to support their viewpoint, and they state that there have been multiple publications from 1985-2011 in the *Journal of the American Osteopathic Association* and the *International Journal of Osteopathic Medicine* confirming the efficacy of OMT as a treatment modality for TMD.

- **The American Chiropractic Association** has little official information on TMJ/TMD. There are several “methods” of chiropractic treatment for TMD that have organized subgroups.
- **The American Craniosacral Therapy Association** is one of several groups utilizing the concepts of craniosacral therapy to treat a variety of conditions, including TMD.
- **The American Massage Therapist Association** has a publication from 2008 by Patricia O'Rourke & Michael Hamm which serves as a guide for massage therapists on how to evaluate and treat TMD.
- **The American Physical Therapy Association** website does not have any specific links to TMD or TMJ management. However, there is a subgroup of physical therapists who have dedicated themselves to the study and management of TMD and associated disorders, namely, the Physical Therapy Board of Craniofacial & Cervical Therapeutics ([www.ptbcct.org](http://www.ptbcct.org)). The Physical Therapy Board of Craniofacial & Cervical Therapeutics (PTBCCT) was founded in 1999 by an international group of physical therapists, many of whom are members of the **American Academy of Orofacial Pain (AAOP)**, to provide an ongoing educational venue within the Academy and assist the profession in the disbursement of evidenced based practice and research.

#### Complementary and Alternative Medicine Sources

- **The American Academy of Acupuncturists and Oriental Medicine** does not have any statement or publication related to TMD and does not claim to be able to manage TMDs in any capacity.

- **The American Association of Naturopathic Physicians** does not have any statement or publication related to TMD and does not claim to be able to manage TMDs in any capacity.
- **American Naprapathic Association.** Naprapathic medicine is a system of healthcare that employs manual medicine, non-invasive modalities, nutritional counseling, and therapeutic and rehabilitative exercise in the treatment of pain caused by connective tissue disorders. They do list TMD as one of the conditions they treat, but no specific information is available on related websites.
- **The American Institute of Homeopathic Physicians** lacks a statement or publication related to TMD in any capacity. They do not claim to treat TMD.
- **The Academy of Orofacial Myofunctional Therapy** (<https://aomtinfo.org/>) published an article in 2014 about myofunctional therapy's role in the management of TMD, written by an alternative medicine proponent, Dr. Joseph Mercola. <https://articles.mercola.com/sites/articles/archive/2013/04/07/orofacial-myofunctional-therapy.aspx> According to the article, TMD is managed most optimally through the neuromuscular re-education or re-patterning of the oral and facial muscles. This is accomplished by a myofunctional therapist through facial exercises and behavior modification techniques to promote proper tongue position, head and neck posture, as well as improved breathing, chewing, and swallowing. According to the article, these techniques can also be used to treat headaches, breathing problems, and dental-related parafunctional habits.

TMD patients seek treatment from a broad array of differing professionals. This is a result of the uncertainty and controversy that abounds in this field and the failure of therapies to address the pain and dysfunction that accompany this condition.

Additionally the complexity and multi-system aspects of TMD go beyond the jaw joint and requires the inclusion of the numerous medical disciplines/specialties, preferably through a team-based or medical home approach, to effectively diagnose and treat this condition.

In summary, the field lacks formal clinical practice guidelines for diagnosis and treatment of TMD ([Rosenfeld, Shiffman et al. 2013](#)). Guidelines translate best evidence into best practices and guidelines are particularly important when wide variations exist in managing a condition, such as TMD. A well-crafted guideline promotes quality by reducing healthcare variations, providing diagnostic accuracy, promoting effective therapy, and discouraging ineffective or potentially harmful interventions. Guidelines need to be developed with patients and consumers involved in the guideline panels. Guidelines should also include identification of risk factors and biomarkers with predictive value in terms of treatment outcomes. For this to be achieved in the field of TMD, well-controlled pragmatic and patient-centered, real-world trials with patient-reported outcomes are required.

**Education Related to TMD.** Many groups claim to provide continuing medical or dental education in some form, and some have developed a multi-course curriculum addressing TMD. Dental schools in the U.S. do not have a formal Commission on Dental Accreditation (CODA) requirement to teach about either orofacial pain or TMD at the predoctoral level. Education on these topics ranges from nearly zero to a few lectures and, in a few schools, extensive courses. There are 12 CODA-approved orofacial pain training programs at university dental schools. However, there also are many continuing education courses and programs available through several organizations, but there are no standards for teaching in this domain. [Effective education on TMD requires improvement at all levels.](#) The American Medical Education Association makes no reference to TMD on their website.

Today, dental and medical students are graduating with limited (or no) experience or competency in orofacial pain/TMD diagnosis and treatment. Serious changes in professional school curricula are needed that include sections on the complexity, comorbidities, and multi-systems character of TMDs (Ferracane, Garcia et al. 2017).

### **Working Group 3 Results:**

- 24 professional groups were contacted for practice guidelines.

- Only 5 had published directives
  - Several groups claimed to provide CE, only 3 provided multi-course curriculum (no standards for teaching)
  - There were almost no references to patient-centered treatment in the guidelines that were reviewed.
- Most dental schools do not have a formal requirement to teach OFP or TMD.
  - There are only 12 CODA approved 2-3 year advanced OFP training programs in the U.S.
  - No published Standards of Care established by the American Dental Association.
  - The American Association of Dental Research (AADR) has a Science Information Statement which is widely regarded as a contemporary “standard of care” in the TMD field and is in accord with the [NIDCR statement](#).

#### Patient-Centered Framework:

- Improve health care provider-patient communication
- Evaluate risk-benefit ratio, through a discussion of potential outcomes
- Employ shared decision making strategies to improve adherence and outcomes
- Develop a multidisciplinary team approach to care

### **WORKING GROUP 4 REPORT**

The charge for Working Group 4 is to *define Real-World Evidence and TMD Patient Data*. The objectives are to:

1. Assess the current availability of data and the ability of third parties to access, collect, and compile scientifically valid information related to selected aspects of TMD patient therapies.
2. Develop ways and means to collect such information from sources outside traditional clinical trials, such as prospective and observational studies, registry entries, retrospective database analyses, case reports, administrative and health insurance claims, electronic health records, and data from social media patient networks and patient advocacy organizations.

3. Develop the means to generate data that is sufficiently relevant and reliable to be used by TMJ roundtable partners, for example, by FDA in the review of medical devices, or by professional societies in developing practice guidelines.

These objectives will be achieved by incorporating results from Working Groups 1-3 into a coordinated data network that leverages existing data streams, while minimizing duplication, in order to develop patient-centered information.

**Working Group 4 Status.** Working Group 4 will start by developing a core minimum dataset to understand the TMD patient population, treatment parameters, concomitant medical conditions, and treatment outcomes. From this baseline, the group will examine existing data sources to determine where these data may already be stored, and determine additional data collection activities. The group will also help determine where an open-ended approach for data collection (e.g., registry) is appropriate, as opposed to a need for collection of data on a focused closed cohort. From the evaluation of data resources, the group will also determine the capabilities for linkage of patient records across different datasets to support a coordinated registry network (CRN) model.

The collection and evaluation of data will always be done with a focus toward evaluating specific, stated questions and analysis plans. Individual partners will be encouraged to perform analyses or collect additional data as needed to fulfill their individual missions, while the roundtable partnership remains focused on facilitating data collection for high-priority needs common to all partners.

**Working Group 4 Recommendations.**

- Establish a resource center for collecting fresh and frozen TMD tissues and TMJ device explants
- Establish an international database resource which would include critical information collected from both traditional and non-traditional sources, universal templates and common data elements relevant to TMD, and an analytical methods resource for evaluating and interpreting collected data.

## **SUMMARY**

There is an urgent need to accelerate biomedical research funding for TMD. Many uncertainties in the basic biological aspects of TMD, patient-centered data collection and analysis, and the scientific basis for treatments for TMD all need immediate attention and augmented support. Many patients continue to receive less than adequate guidance and treatment for their condition and suffer physically, socially, and economically. The activities of the TMJ Patient-Led RoundTable are leading the way in a new, evolving approach to improve the lives of TMD patients and their families by providing a forum for discussion, advocacy, and action to advance our understanding of this complex disorder.

It remains an open question at this time whether the data that is currently available may be used as the basis for identifying risks associated with TMJ implants and outcomes of pharmacological and biologics treatments. Patient reported outcomes, including quality of life and functional measures in real world settings, are emerging as important factors that must now be considered in post-market monitoring activities pertaining to medical devices and products. The FDA is responsible for ensuring the safety and efficacy of drugs, biological products, and medical devices. This responsibility includes both premarket approvals and postmarket surveillance. The FDA's MedWatch program, (FDA's Safety Information and Adverse Event Reporting Program) was established to collect, analyze, and disseminate data about adverse events associated with approved medical products. The FDA's Medical Device Epidemiology Network Initiative (MDEpiNet), a public-private partnership with FDA's Center for Devices and Radiological Health and the medical device industry, aims to establish new ways to study the safety and efficacy of medical devices throughout their life cycle. Leveraging both initiatives is important for developing new and effective treatments for TMD and improving the lives of individuals with chronic TMD. More specifically, FDA-led postmarket surveillance activities incorporate an evolving approach that focuses on patient-centeredness in the continuum of research and development so that all new

treatments coincide with patient preferences, public health improvement, and reduced costs of care.

This White Paper serves as a summary of input from numerous stakeholders in TMD research and care. It highlights current research directions, the current state of TMD treatment and educational efforts, and new approaches by regulatory and caregiver communities to improve the management of TMD. It is evident that in all of these areas, the integration of many areas of scientific expertise and clinical specialties that currently function independently will be required. This includes the various Institutes of the NIH and divisions of the FDA, the dental and medical communities, and the professional educational institutions involved in the training of dentists, physicians and surgeons. Much additional support is needed by stakeholders in order to reach the goal of precision therapies tailored to individual TMD patients. While most people who first develop TMD will recover with minimal or conservative treatments, those that transition to chronic TMD each represent a unique case requiring individual, precision treatments. A patient profile reflecting the individuality of each TMD patient is sorely needed.

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