A National Interagency Temporomandibular Disorder Research Plan

This research plan was developed through the MDEpiNet TMJ Patient Led RoundTable, an interagency, multi-stakeholder initiative summarized here: http://mdepinet.org/tmj-patient-led-roundtable-crn/. The research priorities in this plan were established through two initiatives of the RoundTable. First, those research priorities identified as most important to patients and other stakeholder groups at a May 11, 2018 meeting of the Roundtable were included and second, additional research priorities were extracted from a Briefing Report prepared by the four Working Groups of the RoundTable. The briefing report summarizing the overall RoundTable initiative can be viewed at: http://mdepinet.org/wp-content/uploads/TMJ-Patient-RoundTable-Briefing-Report_9_25_18.pdf. The outcomes of the research results delineated by these recommendations will lead to a clear understanding of the biopsychosocial underpinnings of TMDs and accurate, precise treatment options for patients. Ultimately, these recommendations will lead to an improved quality of life for TMD patients and provide answers to the needs of patients expressed in the RoundTable meetings.

The proposed research will focus on two aspects of TMDs: 1, studies gathering information to assess the quality, safety and reliability of temporomandibular joint replacement implants, and studies to predict those subjects at greatest risk of harm from TMJ implant devices (mechanical failures, tissue reactions, etc.); and 2, studies collecting data on TMD subjects without implanted devices to determine the progression of pain, dysfunction, changes in quality of life, and the development of other co-morbidities stratified as:

a. those with no invasive or non-invasive procedures to the joints
b. those with non-surgical procedures to manipulate or realign the joints (e.g., stabilization splints, bite guards, etc.)
c. those with invasive procedures such as arthrocentesis, arthroscopy, condylotomy arthroplasty, reconstructive surgery, Botox injections, steroid treatments, etc.

A Priority Listing of Research Recommendations

Population/Epidemiological Science

Cross Sectional Study Design

     a. TMD patients with implants vs. TMD patients without implants vs. Control group with no TMD

     b. Chronic TMD vs no TMD

     c. Efficacy and harms of TMD treatments

        1. Patients receiving implants

        2. Patients without implants receiving all other current TMD treatments

Longitudinal Study Design

     a. Chronic TMD patients followed for 5 years

     b. Implant patients characterized at baseline and followed for 5+ years

- TMD and comorbidities, their development, risk factors,
    - Chronic pain conditions
    - Non-pain conditions
- Studies of disease progression, resilience, reversal
- Incidence, prevalence and risk factors for TMD
- Individual, economic, and societal costs of TMD
- Nutritional impact on oral disability
- Efficacy of physical therapy in all stages of TMD
- Palliative care of TMD patients
- Meta-analyses (multiple small cohorts exist)

Human Studies/Clinical Studies

- Clinical Treatment Trials
    - Efficacy trials
    - Pragmatic trials
- Patient Centered Outcomes Trials
    - Develop treatment guidelines
    - Develop best practices
    - Patient-reported outcomes
    - Predictors of treatment outcomes (success and failure) – individual, subgroups
- Neurological and psychological systems trials

- o Identify mechanisms by which psychosocial variables contribute to acute and chronic TMD and responses to implants and other TMJ treatments
- o Biopsychological factors impacting patients with TMD and loved ones/care-givers of TMD patients
- o Influence of psychological risk factors in TMD patients undergoing both successful and failed treatments
- o Identify individual, economic, and societal costs of TMD
- o Biobehavioral approaches to treat comorbidities (depression, anxiety, etc.) associated with TMD
- o Identify the influence of social and family environment and attitudes toward TMD treatment outcomes
- o The biological mechanisms by which psychosocial variables contribute to acute and chronic TMD and responses to implants
- Mining of insurance industry databases to identify patient characteristics regarding outcomes of TMD treatments

Basic Biological Science

- Molecular genomics.
  - o Integrated investigation of genetic polymorphisms, gene expression, epigenetic markers, nucleosome localization and genome interactions for cell populations and at the single-cell level in relevant tissue types of TMD subjects versus normal (next generation sequencing to characterize genome organization and chromatin status)
  - o Genomic/epigenomic/proteomic/immune profiling – including molecular immunophenotyping/metabolomic/biomic profiling
  - o Associations of novel genetic loci and non-coding mutations with well-defined phenotypes of TMD subjects, especially those loci considered most likely determinants rather than consequences of TMD
  - o Bioinformatic approaches that vertically integrate pathway analyses, polygenic risk scores, and immunoprofiles
  - o Concordance of phenotype groups or clusters with lifestyle exposures and stressors including invasive joint interventions
  - o Identification of potential diagnostic, prognostic, and therapeutic biomarkers
  - o Identify possible therapeutic targets and development of somatic cell genome editing tools to perform effective and safe genome editing in human patients
- Mechanisms underlying chronic TMD pain and joint specific pain
  - o Quantitative sensory testing

- - Mechanisms of peripheral and central sensitization mechanisms in localized and widespread chronic pain conditions in TMD subjects
- Sex differences
  - Effects of sex hormones upon disease initiation, progression and responses to drug treatments, surgical interventions and implants
- Neuro-endocrine system interactions
  - Stress induced mechanisms as causes of TMD progression (PTSD, social isolation, etc.)
- Immune/Inflammatory mechanisms
  - Role of the innate and adaptive immune system in the onset and progression of TMD and responses to surgical procedures and implant devices
  - Response to foreign substances including metals and plastics
  - Role of cytokines in disease onset, progression, regression, and resilience
- TM joint tissues and mechanics
  - Developmental biology of the joint and related tissues
  - Unique characteristics of jaw joint tissues and mechanics that distinguish them from other joints of the body
  - Unique characteristics of jaw joint tissues and mechanics that distinguish them from other biological structures, e.g., arteries, heart valves, and in conditions such as Ehlers-Danlos Syndrome, Marfans Syndrome
  - Cellular models of TM joint tissues
  - Cellular models of TM muscles
- Tissue engineering of TM joint and disk replacements
  - Novel materials
  - Regenerative medicine approaches

TMD and Data Science/Biomedical Informatics
- Advanced data analysis, artificial intelligence, machine learning, deep learning, novel clustering methods applied to TMD research at all levels
- eQTL analyses
- Polygenic approaches
- Pathway analyses
- Development of high risk/high reward, innovative approaches to data analysis for precise identification of TMD subtypes, disease risk, positive therapeutic effectiveness and outcomes