FDA/CDRH Epidemiology Grand Rounds Program, May 18, 2017

Overview of TMD and History of TMJ Replacement

Terrie Cowley - President & Co-founder

The TMJ Association, Ltd.

www.tmj.org

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FDA
Center for Devices and Radiological Health

MDEpiNet

NIH National Institute of Dental and Craniofacial Research

AHRQ
Agency for Healthcare Research and Quality
Advancing Excellence in Health Care • www.ahrq.gov

The TMJ Association

- A non-profit patient advocacy organization
- Mission is to improve the quality of health care and life for everyone affected by TMD
- Founded in 1986 based in Milwaukee, WI

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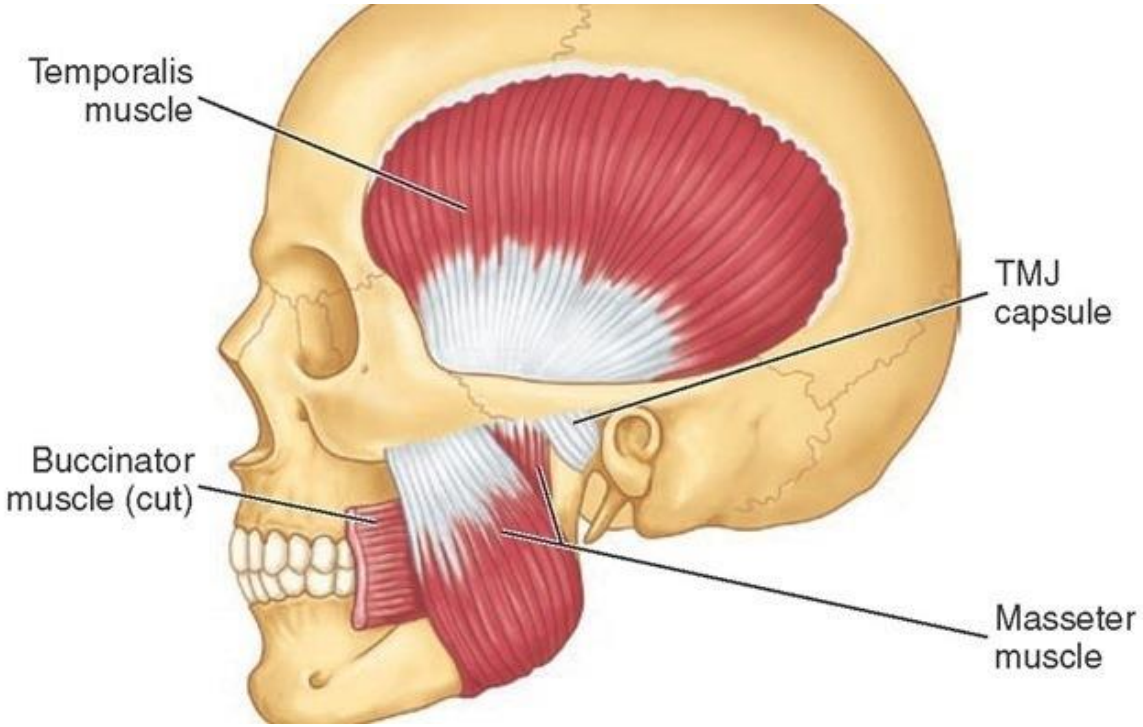
Manifestation of TMD



Pain in the chewing muscles of the face

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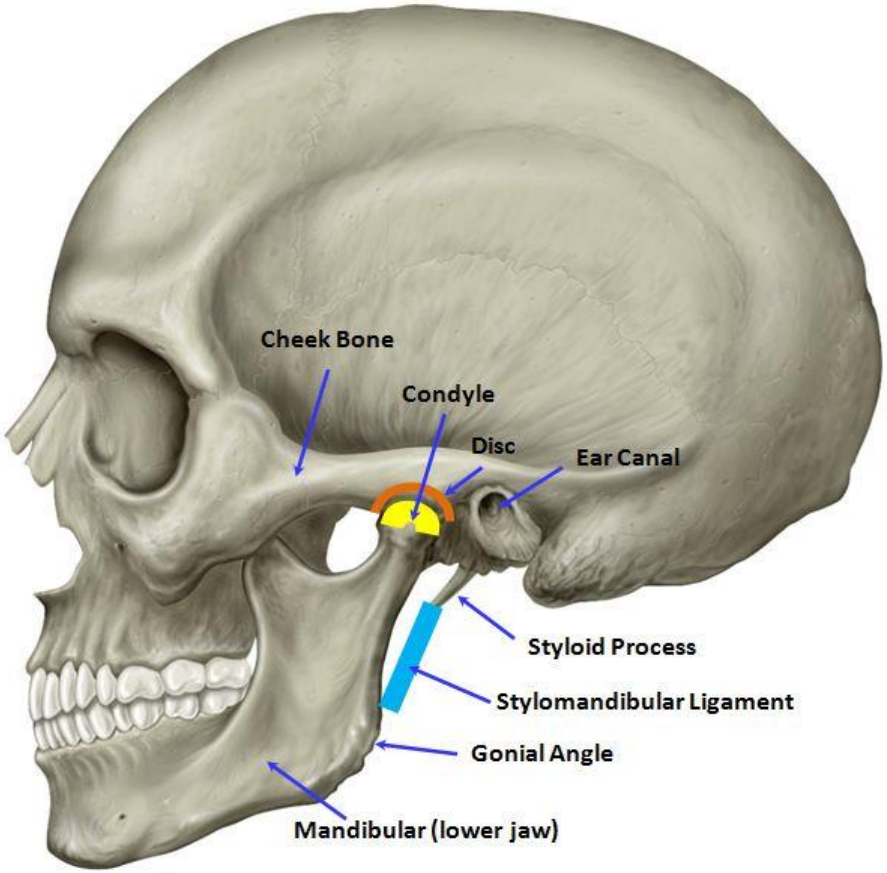
Manifestation of TMJ



Same conditions that affect other joints in the body affect the TMJ

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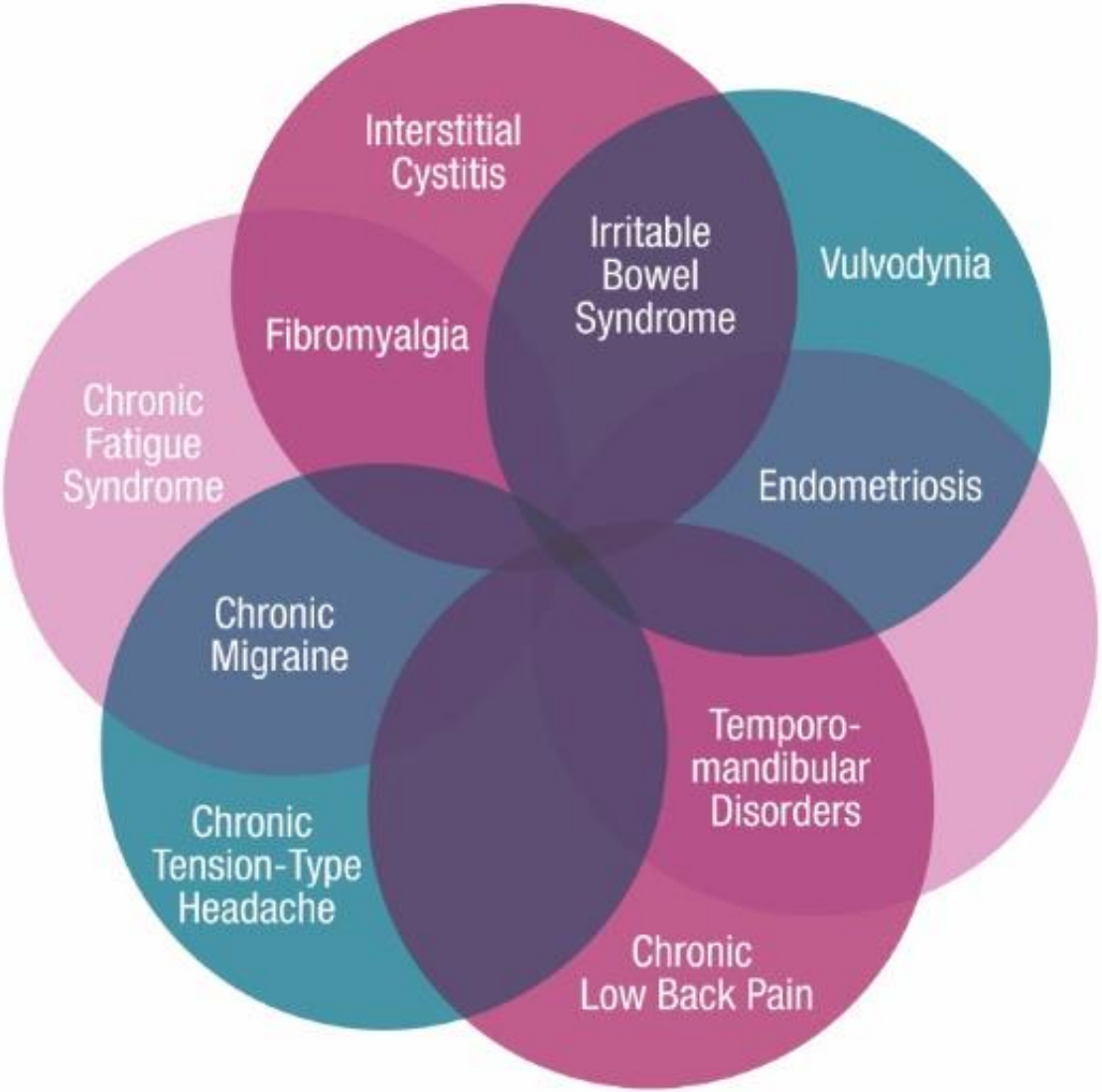
TMD Does Not Exist Alone



Chronic TMD is a complex medical condition–a multisystem disorder with overlapping comorbidities mediated by genes, sex, age, behavioral, environmental/epigenetic triggers

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CHRONIC PAIN Research Alliance

TMD Does Not Exist Alone

Approximately 36 million Americans have some degree of TMD. The majority are women in their child bearing years.

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TMJ Treatments

There are a multitude of treatments available to TMD patients–most without scientific evidence of safety or efficacy.

There is not one drug or biologic labeled for TMD.

A 1992 study estimated the annual cost of TMJ treatments to be $32 billion. (J. Fricton et al. 1992)

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Interpositional Implants

Throughout the 1980s two materials were used to replace the disc between the skull and jaw bone.

- Dacron reinforced Silastic Sheeting (Dow Corning)
- Telfon coated Proplast (PTFE) Vitek

Some Implant Reactions

- Open communication to the brain
- Numerous new medical conditions
- Inflammatory and/or immunological responses
- Foreign body giant cell reactions
- Severe reactive synovitis, bone resorption
- Silicone-related lymphadenopathy
- Avascular necrosis of the condyle and condylar neck = severe changes in occlusion
- Severe pain
- Swelling

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PTFE – Silastic

- FDA recalled Vitek implant in 1990 and seized all products.
- Vitek President moved patents off shore, fled to Switzerland, and resumed business.
- FDA became responsible for conducting its very first recall.
- 1993 Dow Corning discontinued labeling Silastic sheeting for TMJ trismus. Still used off label.

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assessing the dangers of destinations, Routh said, noting that the travel and rising fuel prices from the Middle East crisis.

Harley-Davidson recalls bikes

Harley-Davidson Inc., the nation's lone motorcycle manufacturer, has recalled 43,000 motorcycles because of a brake caliper defect that could cause front wheels to lock while driving.

Models affected are all of the FXR and XLH cycles sold between 1987 and 1990, the National Highway Traffic Safety Administration said.

The problem is that the upper mounting bolt on the calipers might fracture, while the motorcycle is in use. If that happens, the front brakes would remain functional, but a bushing could move out of position and into the front spokes, causing the front wheel to lock up, the agency said.

Anyone owning one of the motorcycles should take it to any Harley dealer for repair.

Harley spokesman Dan Klemencic estimated the recall would cost $150,000 and said the company was unaware of any injuries related to the defect.

ANSWER LINE
CONSUMER WATCH

Jaw implants

Implants used to treat a painful joint condition have been recalled by the manufacturer, Vitek Inc. of Houston because they may cause bone degeneration.

The devices, marketed between 1983 and 1988, were used to treat temporomandibular joint syndrome — commonly referred to as TMJ — a condition of the joint connecting the jaw bone and skull.

Anyone who has or thinks he may have one of these so-called interpositional implants should contact the dentist who performed the surgery, the Food and Drug Administration said.

The implants were made with a Teflon composite coating that can break down under pressure, producing particles that cause the body to reject them, the FDA said.

tures Forum Action Committee.

■ Chairman of the Arizona Strategic Planning for Economic Development project.

■ President of the Arizona Innovation Network.

■ A mentor for a new business program sponsored by America Telephone & Telegraph Co. and the Phoenix Chamber of Commerce.

ARE FDA AND NIH IGNORING THE DANGERS OF TMJ (JAW) IMPLANTS?

HEARING

BEFORE THE

HUMAN RESOURCES AND INTERGOVERNMENTAL RELATIONS SUBCOMMITTEE

OF THE

COMMITTEE ON GOVERNMENT OPERATIONS HOUSE OF REPRESENTATIVES

ONE HUNDRED SECOND CONGRESS

SECOND SESSION

JUNE 4, 1992

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GLOBE READER'S TALE OF TRUE COURAGE

iel-artist Amy Marks, 38, had surgery to
ace a joint in her jaw. But the Teflon-based
lant shattered, and so did her life. After
ly 30 operations, Amy remains disfigured
in gut-wrenching pain. Here is her story.

MY 17 YRS OF TMJ HORROR

Amy was a model with a beautiful face – & had an upbeat personality to match

Deformed by her TMJ nightmare, pain-wracked Amy now leads a shattered life

Bed-ridden Amy relies on hubby Barry for almost everything. And romance is out, too

have faces so distorted by repeated surgery that even old friends don't recognize them.

I went to Washington in 1992 to tell my story to a congressional subcommittee hearing on the implant controversy.

The hardest thing, I found, is some people don't see any obvious physical problems. I once was told I merely suffered psychosomatic pain – you know, only in my mind – and two weeks later they removed a huge bone spur, which had been ripping into my jaw muscles every time I opened my mouth.

There's no painkiller that's ever been strong enough, even though I've received nearly lethal doses of narcotics.

I can't eat real food anymore. My chin and lower lip are paralyzed, so chewing is messy and embarrassing. I'm down to 69 pounds on a diet of nothing but mush.

Vitek introduced the implants in 1983. By 1988, liability insurance woes forced the Houston firm to pull its product – which, according to the FDA, hadn't been properly tested – from the market. Vitek went bankrupt in 1990.

It all goes back to damage done by residue from the first implant. After that, everything else was doomed. The doctors kept trying to rebuild my jaw joint with two of my ribs and a collarbone. One implant even bulged out of my head.

Before my last implant – this time with metal joints – I lived with no jaw at all, which was extremely painful and disfiguring. I have scars all over my body where bones and skin grafts were taken. There's a constant re-

HELP IS A PHONE CALL AWAY

THE WALL STREET JOURNAL.

TUESDAY, AUGUST 31, 1993

Medical Mess

Implants in Jaw Joint Fail, Leaving Patients In Pain and Disfigured

Teflon-Coated Disk Seemed A Boon for TMJ at First But Had Little Testing

'Surgical Merry-Go-Round'

By Bruce Ingersoll and Rose Gutfeld
Staff Reporters of The Wall Street Journal

Robbyn Ruggles is weeping. "This isn't my face," she says. "I used to be real pretty."

Eight oral-surgery operations have left her disfigured, without jaw joints, her mouth permanently agape. She can't bite into a sandwich. She can't purse her lips for a kiss.

And alone at night, she can hardly bear the muscle spasms and the pain. "It never goes away; it's God-awful pain," says the onetime nurse, who lives in Cuyahoga Falls, Ohio. "I have to pretend it's something else to hold onto my sanity."

Ms. Ruggles, 37 years old, is a victim of biomaterials engineering gone awry, caught up in a medical catastrophe that is claiming new casualties almost every day. *The cause of her pain and disfigurement: synthetic jaw implants aggressively marketed by Charles Homsy, founder of Vitek Inc., without adequate premarket testing.* Hundreds of oral surgeons embraced the so-called interpositional implants as a breakthrough of sorts in the 1980s. One prominent surgeon, John Kent, lent his name to Vitek products and served as Dr. Homsy's clinical consultant.

An Unfolding Disaster

More than 25,000 patients afflicted with the same jaw disorder as Ms. Ruggles – temporo-mandibular joint syndrome, or TMJ – received Vitek implants before liability-insurance problems forced the small Houston company to take them off the market in mid-1988. In 1990 the Food and Drug Administration forced the company to issue a safety alert and eventually seized its products.

But for thousands of patients, the implant affair is far from over. Medical experts now expect a high percentage, if not all, of the implants to break up into microscopic fragments and beget a biochemical reaction in patients that erodes jaw bone, creating many other painful complications. Says Larry Wolford, a Dallas oral surgeon: "This is the worst disaster our specialty has ever faced."

It is one with many contributing factors. Federal regulation of the medical-devices industry was lax when the device was introduced in 1983. Vitek was headed by a zealous entrepreneur who, according to the FDA and experts in biomechanics, neglected to run a critical test of the implant's durability. The company was quick to discount adverse findings in animal experiments – all done after the implant was in widespread use – and was slow to accept the implications of early implant failures.

TMJ disorders can produce arthritis, jaw and facial pain, headaches, earaches, clicking sounds in the jaw, and restricted jaw movement. The temporomandibular joint is terribly complicated: It lets the lower jaw, or mandible, move up and down, side to side, forward and back, and in many combinations as a person speaks, bites, chews, swallows, smiles, laughs, grimaces. It is an exquisite network of nerves and muscles, and it isn't well understood. No one knows, for instance, why TMJ disorders afflict women more than men, 90% of the Vitek implant recipients are women.

Charles Homsy

Treatment of TMJ disorders has long occupied a medical gray area. Orthopedic surgeons have stayed away from it, fearful of slipping up in an area so close to the brain, ear and facial nerves. But oral and maxillofacial surgeons have been more aggressive in treating TMJ, and when the Vitek implant came on the market, many turned to it enthusiastically.

Compounding the tragedy, new research in the Netherlands suggests that the best treatment for TMJ may be none at all, because most TMJ disorders abate in a few years. Some experts in the U.S. also say there is no justification for surgical intervention in TMJ cases. "The worst post-surgical cases are far worse than the worst cases in their natural, pre-surgical states," says Joseph Marbach of Columbia University's school of public health.

Blaming Surgeons

Dr. Homsy, a chemical engineer who was president and majority owner of now-defunct Vitek, blames surgeons for putting his products in the wrong patients or for botching the procedure. The implants, he asserts, "weren't at fault; poor surgical judgment and technique were." If there were any gaps in testing, he says, it is the fault of Dr. Kent.

Dr. Kent, head of oral and maxillofacial surgery at Louisiana State University, blames Dr. Homsy for inadequate testing. "The ultimate responsibility for testing in the manufacturer's," says Dr. Kent. Counters his erstwhile friend, who contends that he urged Dr. Kent to conduct the appropriate tests: "I'm a scientist. I can't

Please Turn to Page A8, Column 1

THE WALL STREET JOURNAL.

FRIDAY, OCTOBER 1, 1993

Letters to the Editor

Ethical Dilemma of Jaw Implants

* * *

The TMJ Association as a national nonprofit advocacy group for people with TMJ disorders hears tragic stories daily of pain and suffering. We are appalled and outraged at the senseless devastation wreaked upon the lives of thousands of TMJ sufferers in this country—all because profit and greed are put before the welfare of patients.

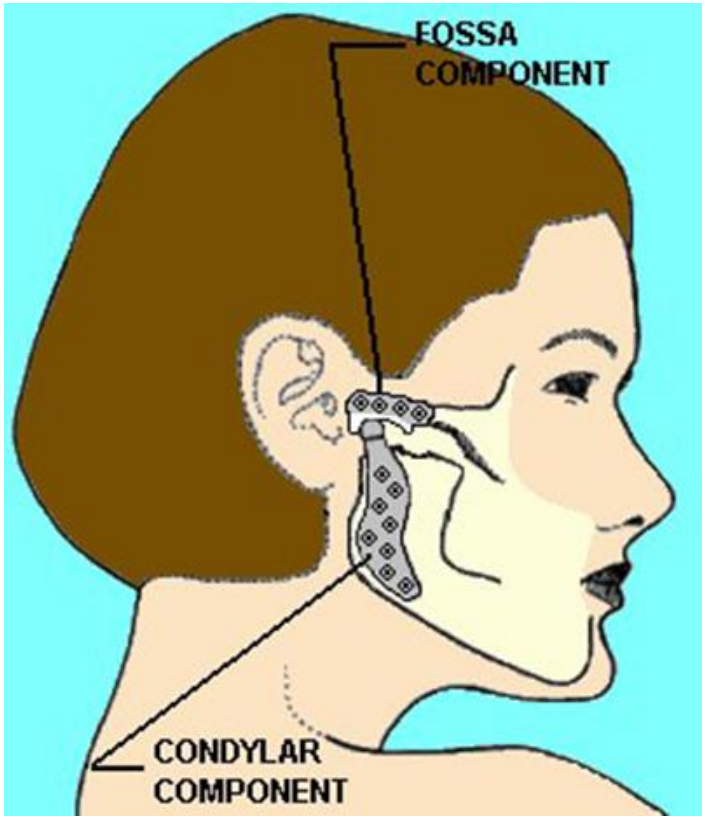
You outline the scenario of how governmental agencies, health care professionals and device manufacturers—by actions of commission or omission—fail to protect the temporomandibular joint patients of this country. However, the American Dental Association, the National Institutes of Health and the medical community, who were spared criticism, should also share the blame. The ADA has neglected to make TMJ a specialty with educational criteria and, even worse, has ignored the blatant quackery being practiced by American dentists. The NIH has spent a mere .07% of its total budget on research of a disorder that affects about 20% of the population, 90% of whom are women. And the medical community has completely avoided temporomandibular joint disorder, although most aspects of the disorder are non-dental.

What we have is a disorder with no consensus on definition, cause, diagnosis, or treatment—in other words, a virtual lack of science, with the end result a huge "medical mess." Isn't it time this disorder is given the scientific respect it deserves?

Terrie Cowley
President
The TMJ Association
Milwaukee

* * *

TMJ Total Joint Devices



1999 FDA approves TMJ Concepts device

2001 FDA approves TMJ Implants, Inc. device (MoM)

2002 FDA approves Biomet/Walter Lorenz device

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TMJ Implant Issues

The following information was gathered from The TMJ Association's interactions with patients and MedWatch reports.

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Adverse Events at the Time of Surgery

- Transient ischemic attack (TIA)
- Stroke
- Traumatic brain injury (TBI)
- Facial paralysis
- Tachycardia, bradycardia
- Death

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Post-surgical Adverse Events Related to Device Material or Design

- Perforations of device into the skull, ear or skin
- Loose or broken screws
- Fractured device materials parts embedded in surrounding tissue and/or migrating in the general circulation

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Post-implant Complications

- abnormal thyroid function
- allergy – hives, rashes itching
- bite changes
- bladder dysfunction
- bone degeneration
- Chronic Fatigue
- chronic, continuous headaches – migraine, tension-type, other
- chronic respiratory, urinary tract, pelvic, or gastrointestinal infections
- cognitive dysfunction and memory issues
- cold extremities
- constant low-grade fever
- decreased jaw range of motion
- device materials leaching into tissues & blood stream
- dizziness, balance issues
- drooling
- dyslexia
- dystonic tremor
- ear pain, diminished or hearing loss, hyperacusis
- eye lid paralysis necessitating gold leaf implant or suturing eye lids together
- face unrecognizable after surgery
- Fibromyalgia, Myofascial Pain Dysfunction, muscle aches and various types of pain in the head, neck and upper back.
- flu-like symptoms
- foreign body giant cell reaction
- harvest site issues (butt, abdomen, rib, ear cartilage, muscle, rib, toe, etc.)

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Post-implant Complications (cont.)

- heterotopic bone growth and ankyloses
- hoarseness
- infections not responsive to antibiotics
- intolerance to heat and/or cold
- lymphadenopathy
- MS-like symptoms
- metal sensitivity and allergies
- metalosis
- muscle atrophy
- muscle spasms
- night sweats
- numbness that does not alleviate over time
- paralysis that does not recover over time
- parotid gland cysts, stones
- pelvic gastrointestinal infections
- post-traumatic stress syndrome
- seizures
- Sjogren's; dry eyes and dry mucous membranes
- skin discoloration
- sleep apnea or sleep disorders
- snow blindness, blurred vision, dyslexia
- speech difficulty
- stroke
- swallowing difficulties
- swelling that does not subside
- traumatic brain injury
- teeth breaking during and after the procedure
- urinary tract issues

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2007 GAO Report FDA Concerns

- Inadequate measurement or inaccurate clinical study results
- Lack of patient history data
- Original sample size of study too small
- Lack of patient follow-up
- Inadequate wear testing
- Inadequate fatigue testing
- Inadequate other engineering testing
- Inadequate device labeling
- Unaddressed microbiology, packaging, and shelf-life issues
- Incomplete sponsor manufacturing inspections

“FDA management indicated that the clinical data was not expected to be of high quality because the sponsor was a small manufacturer.”

“Either good engineering data or good clinical data was acceptable to approve a device - not necessarily both.”
Both later found to be inadequate

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522 Order

On February 7, 2011 the FDA issued a 522 order following an analysis of MedWatch complaints from 2004 to 2010 in which ***52% of the devices had to be explanted before three years.***

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State of All Treatments

Patients can improve.

Patients can be unaffected.

Patients can be worsened.

Patients can acquire TMD.

We call this TMJ lotto.

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Chaos and Controversy Abound in TMD

- Dentists, oral surgeons and device manufacturers tell us that we only hear from the “bad ones.” They have many successes.
- A chasm exists between what the patients are experiencing and what professionals claim the patients are experiencing.
- Patients report to The TMJ Association, FDA MedWatch, and discuss in TMJ chatrooms the many problems they are experiencing.
- Publications by professionals on TMJ device results include no mention of the adverse events patients are experiencing.
- Patients who experience adverse events are often left abandoned, isolated and hopeless with no good treatment options.

Who Can the Patient Trust?

- We have no independent registry to verify what is actually occurring
- Treatments are without validated safety and efficacy
- No specialty in medicine or dentistry
- No educational criteria
- Medical doctors do not understand what is happening to the patients
- No standards of care/protocols
- Haphazard insurance coverage

“We need a comprehensive approach, a combined effort, a coming together or meeting of the minds of all stakeholders to address every aspect of this disorder.”
Adriana V.

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A Solution…
TMJ Patient RoundTable

- First-of-its-kind collaboration in the TMD/FDA area bringing together all stakeholders–patients, industry, surgeons, regulators, academia, government agency representatives, researchers and policymakers.
- A unique feature is the patient centered approach. Patients have a vital role and discussions will address their experiences and problems.
- This transparent and respectful venue will hopefully breakdown the barriers that currently allow the continuation of rumors, blame, and suspicion that is detrimental to all involved.

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June 16, 2016 Meeting

- Held at FDA headquarters.
- Each stakeholder provided their perspective.
- A Steering Committee was formed and working groups developed to address the issues raised.

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Working Group 1
Dr. Torosyan

The TMJ Patient: Natural History and Assessment of Biomarkers Associated with Outcomes in TMJ Implant Patients

Their charge is to define biological and other characteristics of the patient, patient reported outcomes as risk factors to identify success/failure of implants and other treatments.

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Working Group 2
Dr. Alvarez-Garriga

Patient-Reported Outcome Evaluation and Real-World Evidence and Patient Data

Their charge is to identify patient reported outcomes which include patient quality of life, for the evaluation of TMJ treatments, such as implants and develop instruments for patient reported outcomes.

They will also summarize current recommended therapies and identify adverse events due to implants through patient reported surveys outside of the clinical trial reporting environment with input from other Working Groups.

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Working Group 3

Education, Patient-Centered Treatment

Their charge is to compile currently available best diagnostic tests and practice guidelines and identify those that need to be developed.

Coordinate with Working Group 1 and identify risk factors to be included in diagnostics and guidelines for implants and other TMJ therapies.

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Expected Project Outcomes

- Patient-preferences will be included in premarket applications and post-market surveillance efforts for all TMD treatments.
- Provide a roadmap for the development of precision medicine algorithms that predict individual outcomes from TMJ therapies.
- Evidence-based protocols, guidelines and best practices will be developed and included in professional health care curriculum.
- Collaborative and individual research projects will incorporate the needs and concerns of patients.

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Acknowledgements

TMJ Patients
Food and Drug Administration/CDRH
National Institute of Dental and Craniofacial Research
Agency for Healthcare Research and Quality
TMJ Device Manufacturers
American Association of Oral and Maxillofacial Surgeons
MDEpiNet
Others lending their expertise to this project

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FDA U.S. FOOD & DRUG ADMINISTRATION

Patient-Reported Outcome Evaluation & Real-World Evidence & Patient Data

Carolina Alvarez-Garriga
Epidemiologist

FDA U.S. FOOD & DRUG ADMINISTRATION

Background

- Patients with TMD have been diagnosed and treated with a variety of non-specific tests and pain scales that do not address endpoints that are important to patients.

- The three TMJ implant devices are under 522 study orders to address their questionable benefit-risk profiles, including reports of multiple revisions, migration, and extreme facial scarring resulting in depression, opiate abuse, and suicides related to chronic pain.

U.S. FOOD & DRUG ADMINISTRATION

Background

- Discussions with patient advocates have revealed a disconnect between the safety data from clinical trials for TMD device treatments (TMJ) and patients' experience.

- Safety data from manufacturers supported clinical trials seem to under-report the frequency of adverse events.

FDA U.S. FOOD & DRUG ADMINISTRATION

Background

- To better understand the safety of TMJ devices, it is important to first listen 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 development of meaningful patient assessment tools leading to improved treatment, care, and management of TMD.

Background

- The U.S. Food and Drug Administration (FDA) defines a *patient-reported outcome* (PRO) as “any report of the status of a patient’s health condition that comes directly from the patient, without interpretation of the patient’s response by a clinician or anyone else”.

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Patient-Reported Outcome Evaluation

Co-chairs:

Joel Gagnier, Assistant Professor, Department of Orthopaedic Surgery, Department of Epidemiology, School of Public Health, University of Michigan.

Tricia Kalinowski, TMJ Patient

Goals:

(1) to develop outcome assessment and reporting tools based on patient input, and

(2) to develop evidence to incorporate patient-centered data into clinical care

Responsibilities:

(1) identify available validated PRO instruments that include patient quality of life for the evaluation TMJ treatments, such as device implants, and

(2) to develop valid instruments to gather PROs as needed

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Patient-Reported Outcome Evaluation

The Patient Engagement Interaction for Safety Evaluation in Patients with TMJ project was recently awarded by Critical Pathway funding.

This study will be conducted by means of a cross-sectional online survey using a validated *ad hoc* self-administered questionnaire to gather the frequency of selected PROs regarding adverse events from TMJ implanted subjects.

The results of this survey will be compared to those of the literature and the labeling of the three FDA approved TMJ devices in the US market to determine whether or not adverse events are under-reported in the clinical trials and other clinical studies sponsored by TMJ manufacturers. If under-reporting is found we will assess the magnitude of under-reporting and provide potential explanations.

U.S. FOOD & DRUG ADMINISTRATION

Real-World Evidence & Patient Data

Co-chairs:

Carolina Alvarez-Garriga, Division of Epidemiology, CDRH

Michele Kaseta, TMJ Patient

Goal:

to develop evidence based best practices, treatment protocols and clinical practice guidelines which will include patient-centered data

Responsibilities:

(1) summarize current recommended therapies and identify adverse events due to implants through patient reported surveys outside of the clinical trial reporting environment, and

(2) coordinate with input from the other three TMJ working groups

Regulatory and public health impacts

- The development of PROs will allow better communication between FDA, manufacturers, doctors, and patients about patient's expectations for TMD treatment options.

- Agreement upon outcomes between patients, physicians and FDA, will promote:
  - better patient's acceptance of trial results
  - more suitable evaluation of new products, and
  - provide more solid basis for regulatory assessments

FDA U.S. FOOD & DRUG ADMINISTRATION

Thank you!

Epidemiology Grand Round

May 18, 2017

Overview of TMD / TMJ Replacement Research Area (3):

In silico research opportunities

Lisa Torosyan, MD, PhD

Division of Epidemiology,
DEPI/CDRH/FDA

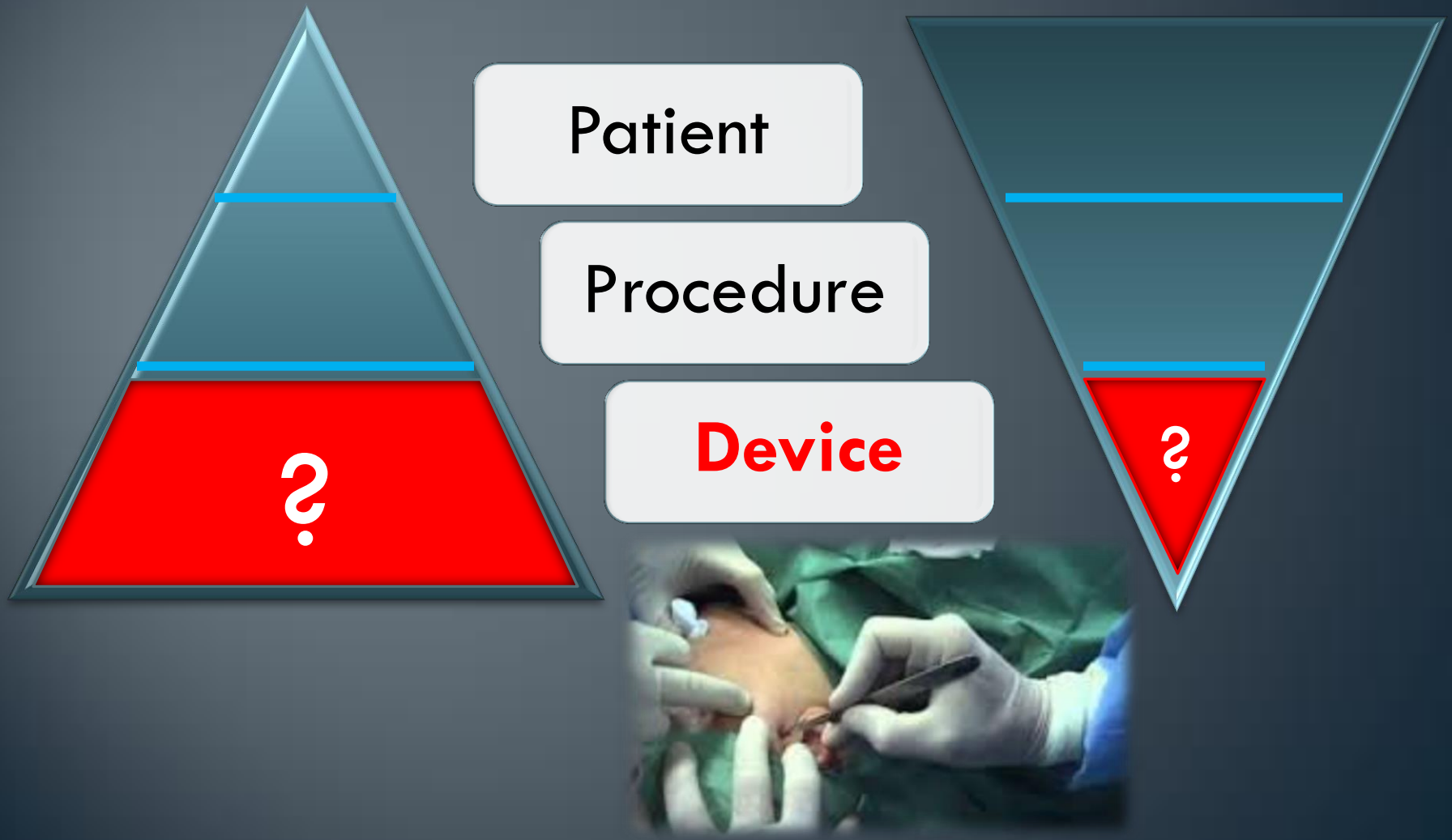
Narrowing the gap between currently available and urgently needed

- Enhanced susceptibility and modifying factors (e.g., sex):
  - Variability in clinical manifestation and disease severity
  - Variability in treatment responses and outcomes

- The need for diagnostic and prognostic biomarkers:
  - Intention-to-Treat population with **degenerative and ankylotic TMD** conditions to be treated with TMJ replacement
  - Predictive assessment of real-world device performance
  - Prevention and diagnostic/therapeutic management of adverse events

- *In silico* research and evidence integration for developing TMD-related Precision/Stratified Medicine applications

Patient-Procedure-Device:
the role of treatment modifying effects in TMD/TMJA



Promise of 'Omic Research for elucidating the causes for susceptibility and inter-individual variability

Oral Dis. Author manuscript; available in PMC 2013 Oct 2.
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Oral Dis. 2013 Mar; 19(2): 111–120.
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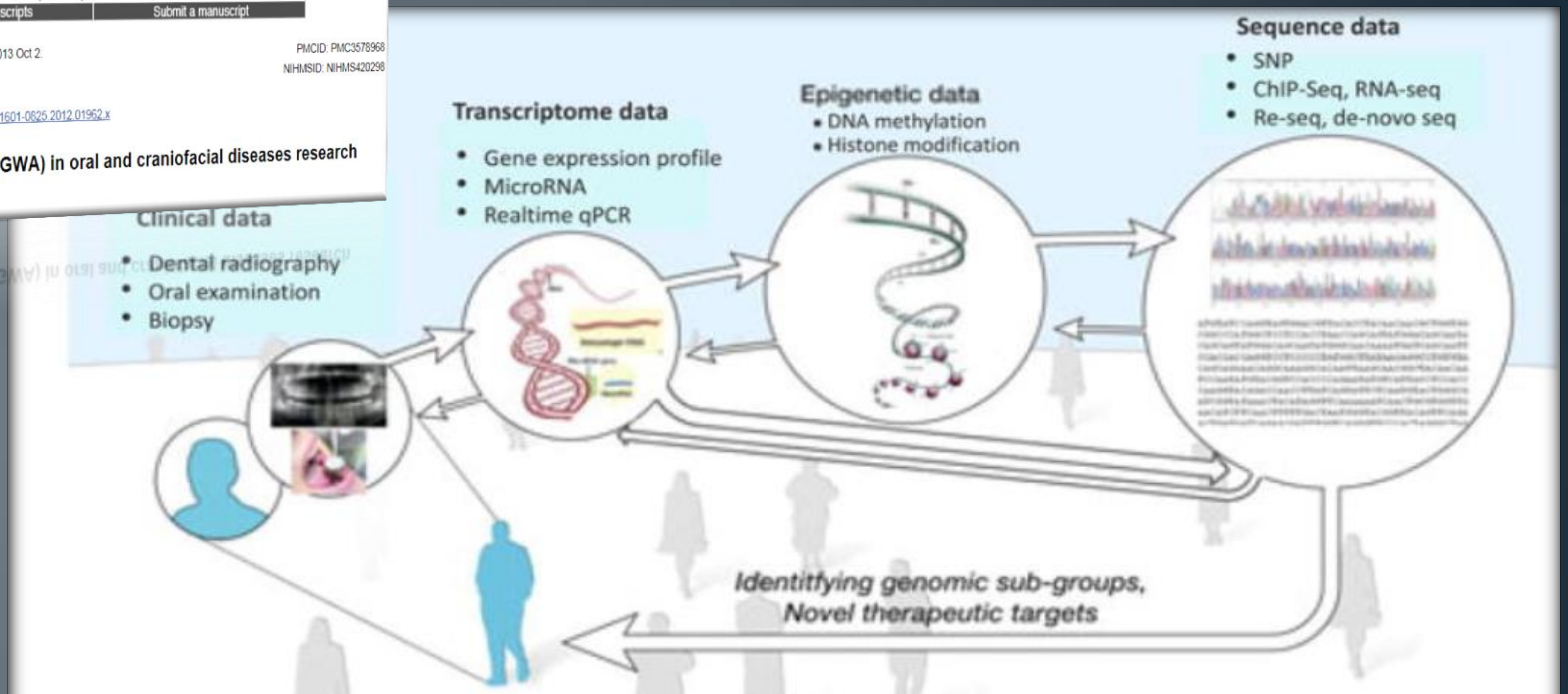
PMCID: PMC3578968
NIHMSID: NIHMS420298

Genome-wide approaches (GWA) in oral and craniofacial diseases research

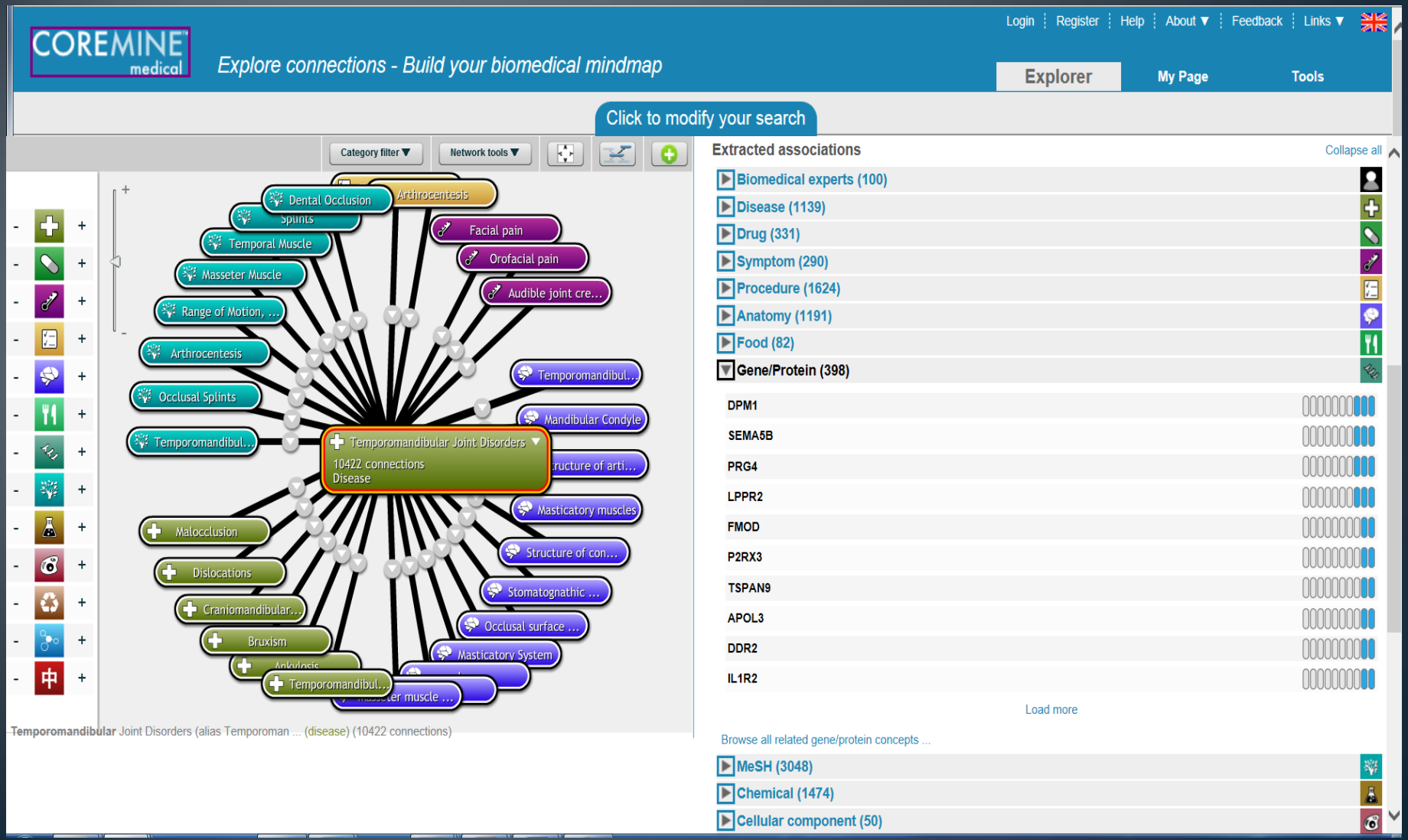
H Kim,[1] S Gordon,[2] and R Dionne[1]



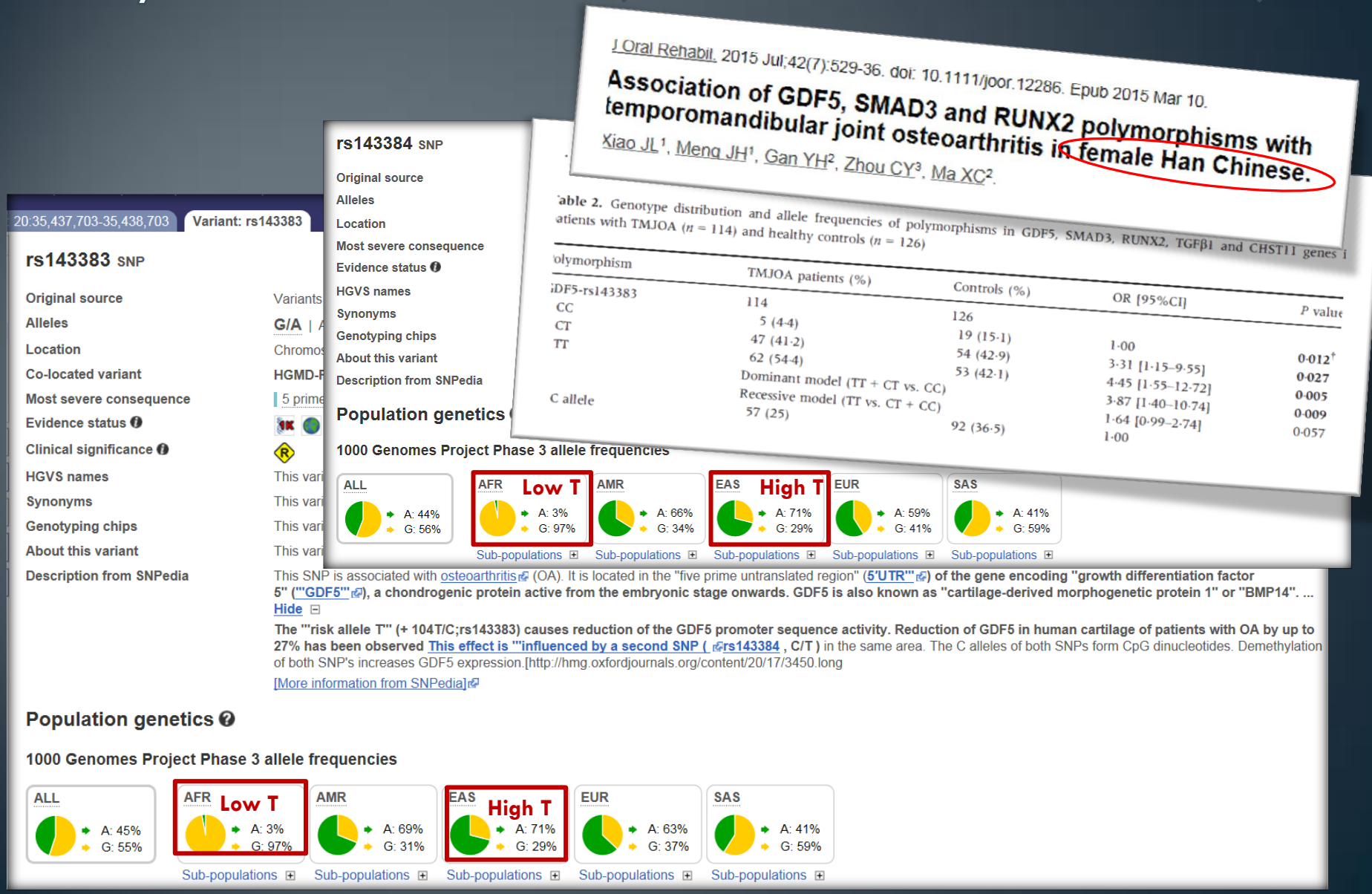
- GWAS hold great promise for advancing our understanding of the genetic contributions …, risk factors for susceptibility and prognosis, and the development of individualized dental [and craniofacial] medicine.
- **…however, we are still in the early stages of the translation of genomics to clinic [and regulatory] practice.**

Contributions of molecular genetic approaches to the study of oral and craniofacial diseases

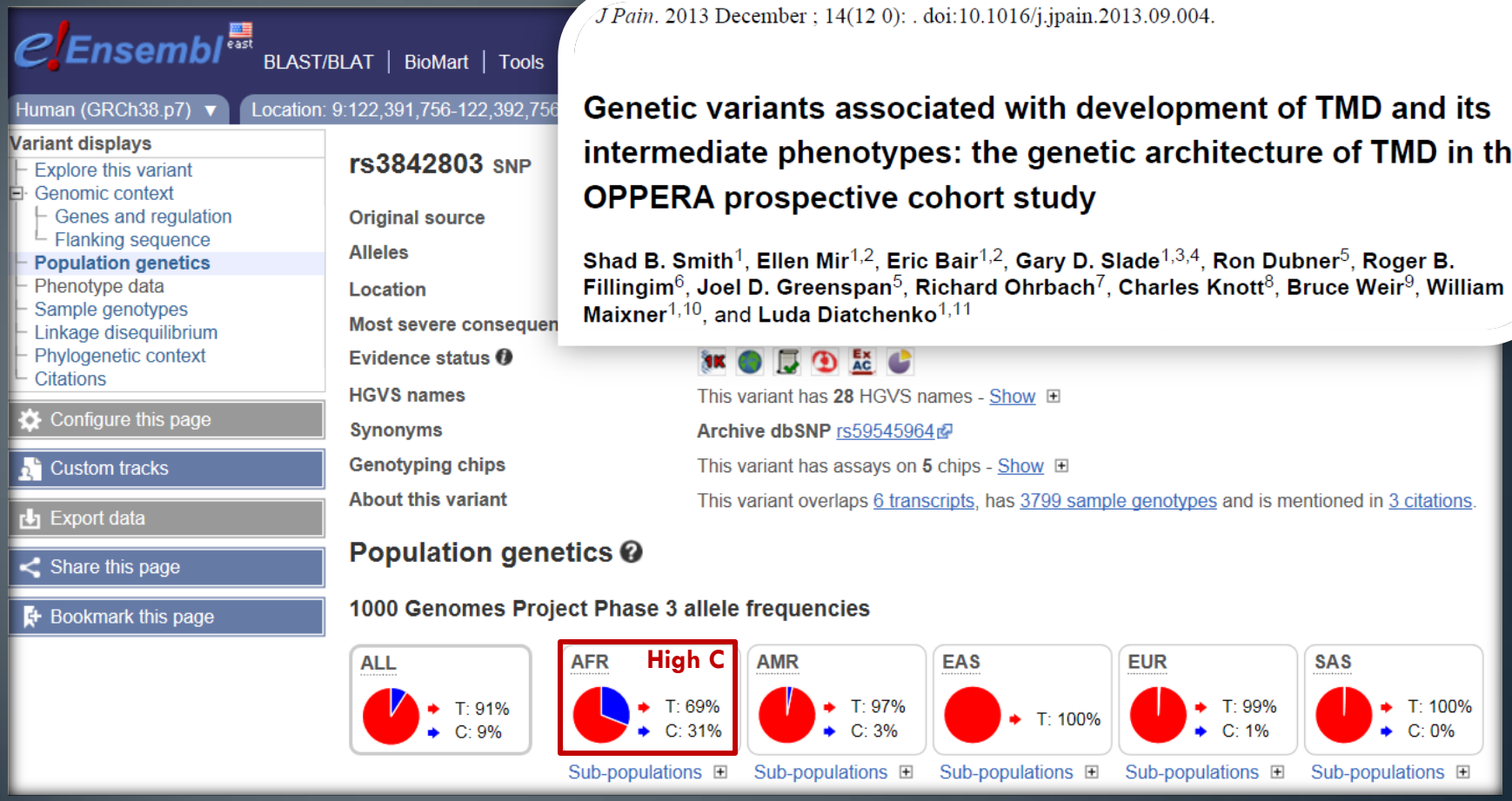
TMD in Coremine knowledgebase:
>10,400 connections, including ~400 genes/proteins



Example of potential sex/race-related variability in utility of TMD biomarkers (*Xiao et al 2015; 1000 Genomes*)



Example of a TMD biomarker limited to one racial subgroup (*Smith et al 2013;* 1000 Genomes)



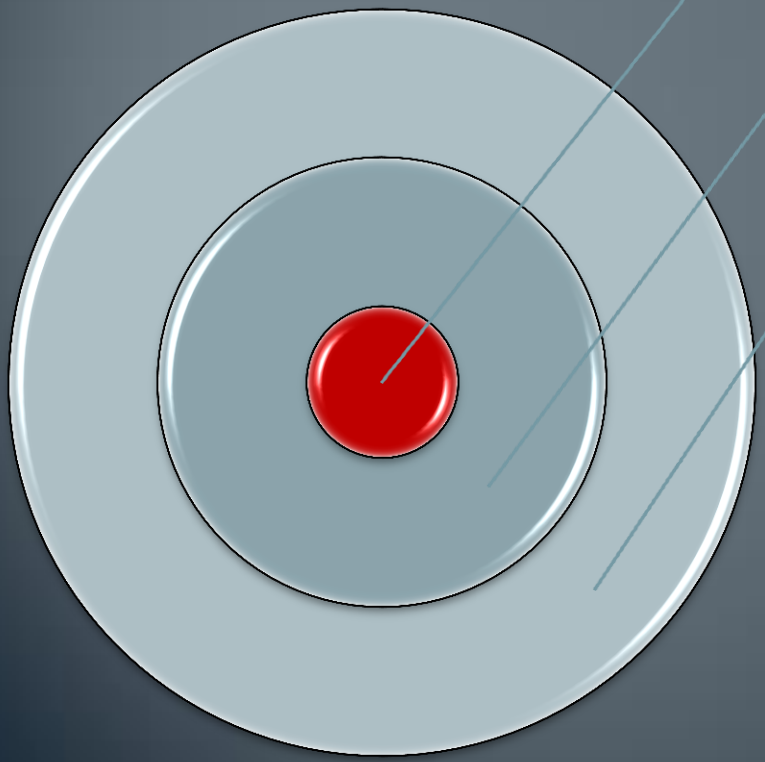
J Pain. 2013 December ; 14(12 0): . doi:10.1016/j.jpain.2013.09.004.

Genetic variants associated with development of TMD and its intermediate phenotypes: the genetic architecture of TMD in the OPPERA prospective cohort study

Shad B. Smith[1], **Ellen Mir**[1,2], **Eric Bair**[1,2], **Gary D. Slade**[1,3,4], **Ron Dubner**[5], **Roger B. Fillingim**[6], **Joel D. Greenspan**[5], **Richard Ohrbach**[7], **Charles Knott**[8], **Bruce Weir**[9], **William Maixner**[1,10], and **Luda Diatchenko**[1,11]

- *"A SNP in PTGS1 (rs3842803) showed the strongest association with global psychological symptoms. However, as this SNP is very rare in Caucasians/Europeans, but fairly common in African populations, the SNP remained strongly associated only in African-Americans."*

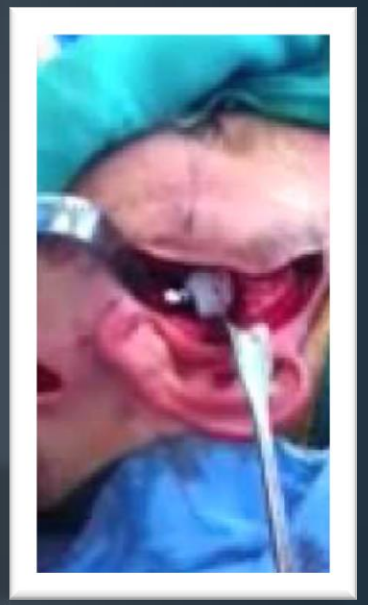
TMD complexity complicating treatment choices



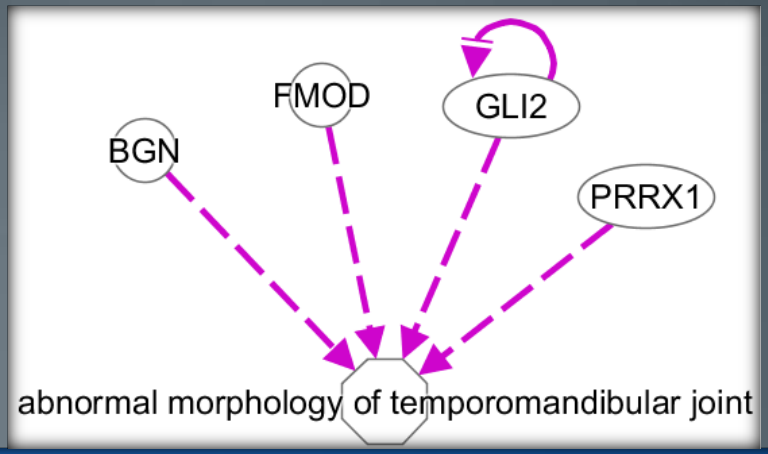
Degenerative and ankylotic TMDs as indications for TMJ REPLACEMENT

TMJ OA

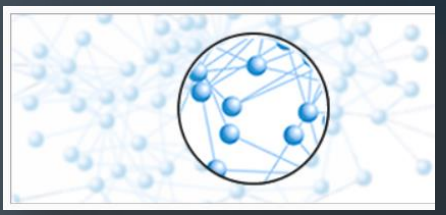
TMDs
(eg, chronic pain – nociceptive, neuropathic, etc.)



Ingenuity Knowledgebase (1): Genes involved in abnormal TMJ morphology



INGENUITY



Provide Feedback | Support Dr. Torosyan Close IPA

Genes and Chemicals | Diseases and Functions | Pathways and Tox Lists

temporomandibular SEARCH Advanced Search

QIAGEN

Search

ADD TO MY PATHWAY | ADD TO MY LIST | ANNOTATIONS | SHOW FINDINGS | EFFECT ON FUNCTION | SHOW FUNCTIONS | EXPAND FUNCTIONS | BIOPROFILER

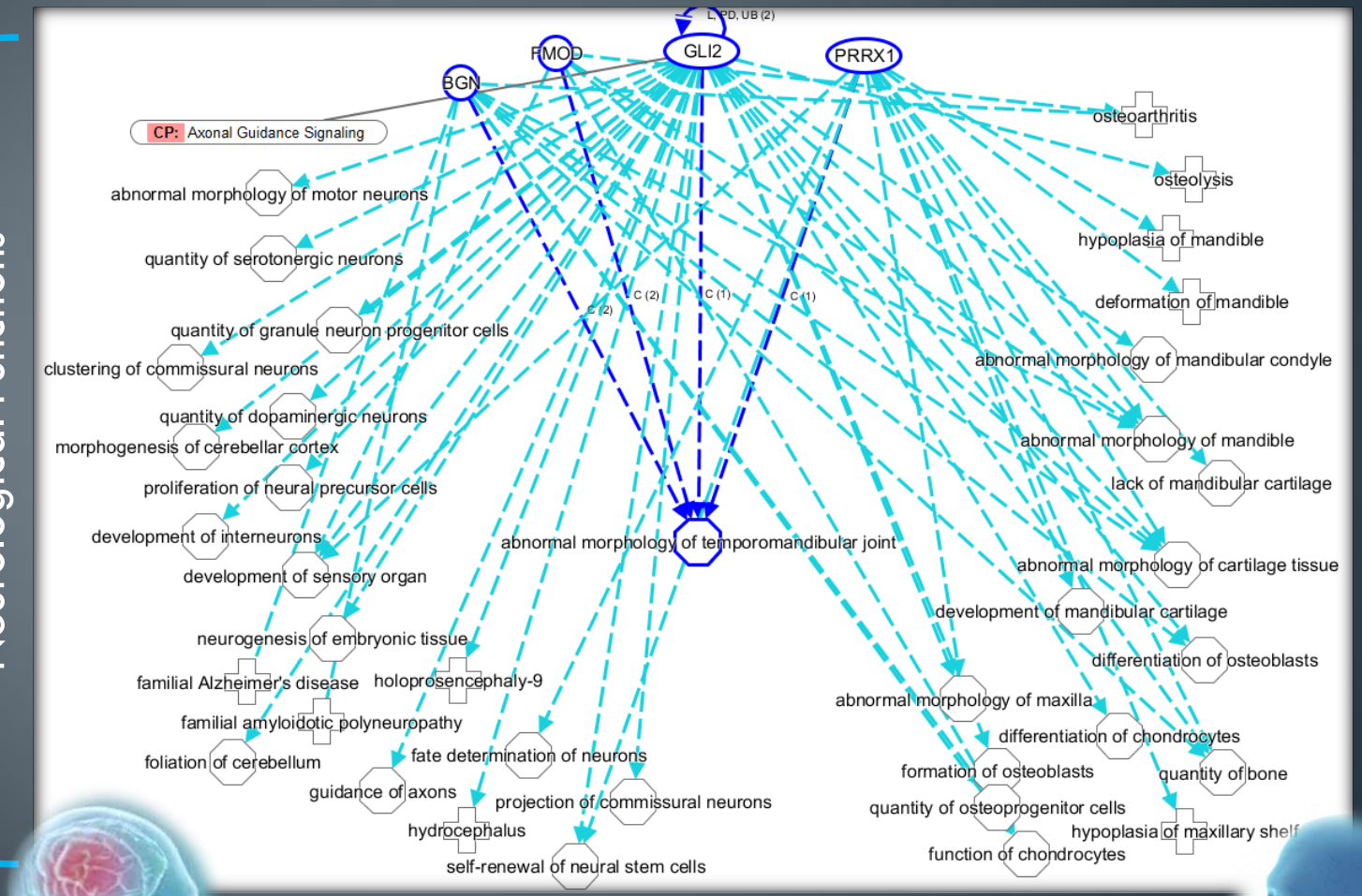
The search for temporomandibular matched 1 diseases and functions.

Diseases & Functions	Associated Molecule
Matching Diseases & Functions	4
Skeletal and Muscular System Development and Function	4
abnormal morphology	4
abnormal morphology of temporomandibular joint [abnormal morphology of temporomandibular articulation,abnormal morphology of articulatio temporomandibularis]	4
BGN, FMOD, GLI2, PRRX1	

Ingenuity Knowledgebase (2):

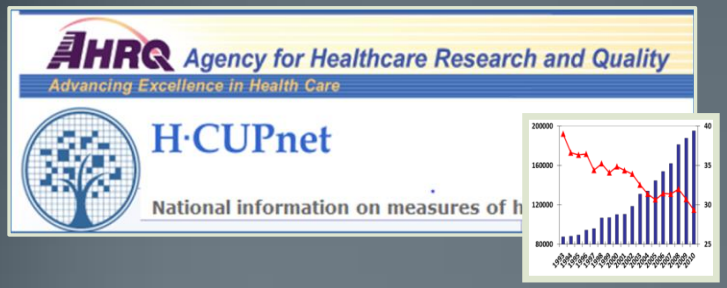
genes that are associated with Abnormal TMJ Morphology and Osteoarthritis can be also involved in Neurological Functions

Neurological Functions



TMJ Morphology & Inflammation

In silico Framework for Integrating Epidemiological and Genetic Evidence



EPIDEMIOLOGICAL EVIDENCE
from different sources (eg, RCT, EHR, registries)

Discovery of Biomarkers and Risk Predictors Based on In Silico Generated Epi-Gen Evidence

GENETIC EVIDENCE
from open-source and other available 'omic databases (eg, NCBI/GEO)

In silico research: *going beyond conventional evidence integration*

- Apply *Systems Biology/Medicine* approach
- Integrate *multidisciplinary* evidence
- Extract new information by reanalyzing *raw pre-existing* data
- Integrate amassed device/biomaterial-related knowledge
  (*eg, biomedical, clinical, epidemiological, population genetics, etc*)
- Promote translational research by incorporating *pre-clinical* findings
- Data analysis and interpretation using *computer modeling and simulation*:
  - Elicit and test new hypotheses
  - Cross-validate the results from different sources

Data repurposing and reutilization:
the gift that keeps on giving

What can be expected from *in silico* evidentiary approaches to the TMD area

- ✓ **Biological and clinical plausibility of TMD study endpoints and biomarkers based on:**
  - ✓ Better understanding of molecular/mechanistic underpinnings
  - ✓ Improved pre-selection for further qualification, validation and implementation steps
- ✓ **Clinical and regulatory relevance :**
  - ✓ New druggable targets for different types of TMDs
  - ✓ Well-categorized TMD biomarkers (*eg,* diagnostic, monitoring, predictive, prognostic, *etc*)
  - ✓ Well-defined target subpopulations (eg, ITT for TMJ Replacement)
  - ✓ *Proactive* surveillance using new study endpoints (eg, biomarkers) for early detection and monitoring of adverse (clinical and subclinical) events in TMD/TMJ arthroplasty
  - ✓ Less burdensome and more ethical - *in vitro* and *ex vivo* – TMJ device/biomaterial testing
- ✓ Cost/time-efficient solutions for TMD-related Precision Medicine applications

Thank you!

Questions ?

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