Diagnosis, Computational Phenotypes and Pre-Clinical Rounds for the OFP Specialist

[A.K.A. Finding and Teaching Disease Phenotypes relevant in OFP]

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TOPIC #1: Diagnosis vs Misdiagnosis

Q: Does Misdiagnosis often happen?

A: Yes, far too often. See the IOM study.

An Institute of Medicine 2015 report highlighted that physician diagnostic error is common and suggested that <u>computers</u> may eventually be able to make accurate clinical diagnoses.^{1,2}

Q: Can you show me examples of medical misdiagnosis?

A: Yes, see the figures cited below

- Autopsies: Major unexpected discrepancies that would have changed the management are found in 10–20% [Shojania K, et al, 2002; Sonderegger-Iseli K, et al, 2000].
- **Patient surveys: 33%** of patients relate a diagnostic error that affected themselves, a family member, or close friend [Blendon RJ, et al, 2002]
- **Standardized patients:** Internists misdiagnosed **13%** of patients presenting with common conditions to clinic (COPD, RA, others) [Peabody JW, et al, 2004]
- Imaging Errors: 10–30% of breast cancers are missed on mammography [Beam CA, et al; 1996]
- **Biopsy Errors: 1–2%** of cancers are misread on biopsy samples [Raab SS; 2005]
- ER Cases: 12–51% of patients with subarachnoid haemorrhage are misdiagnosed in the emergency department. [Kowalski R, et al. 2004]
- Hospital Case Reviews: 5% of 1000 hospital deaths considered preventable, and most frequent etiology was diagnostic error. [Hogan H, et al. 2012]

Q: Why do medical misdiagnoses happen?

A: Here is a quote from John Halamka MD, chief information officer at Beth Israel Deaconess Medical Center, who served on the EHR standards committees under both George W. Bush and Barack Obama.





"In America, [physicians] have 11 minutes to see a patient, and, you know, you're going to be empathetic, make eye contact, enter about 100 pieces of data, and never commit malpractice. It's not possible!"

Q: How often do we find OFP/TMD/HA Misdiagnosis?

PubMed Search Results - August 14, 2018

A: Unknown, but if you go to PubMed and search for the word misdiagnosis and a specific disease you can get a hint.

Oral cancer misdiagnosis	890
Maxillofacial misdiagnosis	826
Headache misdiagnosis	669
Cluster misdiagnosis	659
Temporomandibular misdiagnosis	398
Salivary cancer misdiagnosis	318
Orofacial pain misdiagnosis	262
Facial pain misdiagnosis	245
Migraine misdiagnosis	232
Sinusitis misdiagnosis	192
Odontogenic tumor misdiagnosis	85
Trigeminal Neuropathy misdiagnosis	70
Trigeminal neuralgia misdiagnosis	58
Facial anesthesia misdiagnosis	51
Salivary infection misdiagnosis	32
Oral candidiasis misdiagnosis	28
Toothache misdiagnosis	28
Trigeminal nerve cancer misdiagnosis	24
Salivary stone misdiagnosis	16

Q: Can you reduce the # of Misdiagnoses?

A: Yes, we can, but it takes time

Why are errors made?

Failure to collect enough information	Sloppy
Accepting a Pre-existing Diagnosis	Lazy
Accepting a diagnosis before it is fully verified	Overconfident
Lack of knowledge of disease criteria	Undertrained
Persistent Biases or Holding onto a diagnosis even after receiving contradictory	Stubborn
information	
Overreliance on diagnostic testing	Timid
Suboptimal weighing of critical pieces of information	Inexperienced

The bottom line is: Too much to know and too little time to find it!



Q: As an expert in OFP, how many diseases, disorders and dysfunctions do you have to know? A: Approximately 100 not counting Psychological Diseases

Table 1: A Partial list of Orofacial Pain related diseases, disorders and dysfunctions

Acute Malocclusion [Lateral Pterygoid	Familial Migraine	Peri-menstrual Migraine
Acute Mechanical Cervical Disease	Fibrous Ankvlosis	Periodontal Infection
Anomaly of Dental Arch (various types)	Frequent Migraine	Posterior Disk Displacement
Arthralgia/Capsulitis	Frequent TTHA	Primary Cough Headache
Atypical Burning Mouth Disorder	Glossopharyngeal Neuralgia	Primary Exertion Headache
Bell's Palsy	Gout related TMJ Arthritis	Primary Idiopathic Stabbing Headache
Bony Ankylosis	Hemicrania Continua	Primary thunderclap headache
Burning Tongue Syndrome	Hypnic headache	Psoriatic TMJ Arthritis
Cervical Myalgia/Myofascial Pain	latrogenic Bite Change (NOS)	Psychogenic Hypertonicity of Jaw Muscles
Cervical Nerve Impingement	latrogenic Dental Occlusion Anomaly	Pulpal Infection
Cervical Osteoarthritis	Idiopathic Condylar Resorption	Pulsatile Tinnitus
Cervicogenic Headache	Intracapsular Adhesions	Radiation Fibrosis
Chronic Daily Headache (Chronic Migraine)	Lyme Disease related TMJ Arthritis	Salivary Gland Infection
Chronic Daily Headache (Med. Overuse)	Malignancy [Trigeminal Sensory Disorder]	Secondary BMS (mucosal disease)
Chronic Daily Headache (NOS)	Mandibular Hyperplasia	Secondary Otalgia
Chronic Jaw Muscle Trismus	Masticatory Muscle Hypertrophy	Severe Sleep Bruxism
Chronic Trigeminal Neuropathy	Masticatory Myalgia/Myofascial Pain	Sinus Headache
Cluster Headache	Medication Induced Jaw Muscle Hyperactivity	Sinusitis
Complicated Migraine	Medication Overuse Headache	SUNA Headache
Condylar Hypertrophy	Nerve Injury with Sensory Deficit	SUNCT Headache
Connective Tissue Disorder [Paresthesia]	New Daily Persistent Headache (NDPH)	Systemic Sclerosis
Continuous DDNR	Numbness (NOS)	Temporal Arteritis
Contracture of Masticatory Closers	Occipital Neuralgia	Tensor Tympani Syndrome
Coronoid-Zygoma Impingement	Open Jaw Dislocation	TMJ Headache
Cracked/Broken Tooth	Open Jaw Locking	TMJ Neoplasia (NOS)
Disk Displacement with Reduction	Ophthalmic Migraine	TMJ Osteoarthritis
Dysesthesia NOS	Oral Infection (NOS)	TMJ Rheumatoid Arthritis
Dysgeusia (various)	Orofacial Dyskinesia	Traumatic Dental Arch Anomaly
Episodic DDNR	Orofacial Dystonia	Trigeminal Neuralgia
Episodic Migraine	Osteochondroma	Trigeminal Neuritis
Episodic TTHA	Other Facial Asymmetries (NOS)	Trigeminal Neuropathic Headache
Facial Nerve trauma	Paroxysmal Hemicrania	

Q: Which of these diseases, disorders and dysfunctions are common, uncommon or even "rare"? A: 20 – 40 – 40. But this is an estimate not a data-based number. My criteria are:

Very Common = 1/20 Uncommon = 1/200 Rare = 1/1000 *Of course, the disease incidence will vary depending on the location and nature of your clinic's advertising and referrals.*

Q: Which of the OFP diseases have useable & definitive biomarkers?

A: Currently none, but maybe some in the future. There is a remarkable book on this published a few years ago.

Goulet JP., Woda A. (2017) Orofacial Pain: Classification and Road Map to Clinical Phenotypes. In: Goulet JP., Velly A. (eds) Orofacial Pain Biomarkers. Springer, Berlin, Heidelberg.

Review: This chapter reviews how OFP disorders are categorized

- 1. There are several categorization systems: IASP, IHS, AAOP, AACP
- 2. These systems have various deficiencies and inconsistencies.
- 3. A new multiaxial classification system using ontology is needed!

4. Need to identify and include biomarkers in any new system to optimize it.

[MY CONCLUSION: Hopefully biomarkers will soon exist!]

Q: What progress has been made since 2017 on biomarkers?

A: See the article on this topic 2021. BTW: There conclusion was "**"In painful TMD, the role of biomarkers is still elusive"**.

International Journal of Oral Science





www.nature.com/ijos

REVIEW ARTICLE OPEN A comprehensive review on biomarkers associated with painful temporomandibular disorders

Mayank Shrivastava¹, Ricardo Battaglino^{2™} and Liang Ye^{2™}

Pain of the orofacial region is the primary complaint for which patients seek treatment. Of all the orofacial pain conditions, one condition that possess a significant global health problem is temporomandibular disorder (TMD). Patients with TMD typically frequently complaints of pain as a symptom. TMD can occur due to complex interplay between peripheral and central sensitization, endogenous modulatory pathways, and cortical processing. For diagnosis of TMD pain a descriptive history, clinical assessment, and imaging is needed. However, due to the complex nature of pain an additional step is needed to render a definitive TMD diagnosis. In this review we explicate the role of different biomarkers involved in painful TMD. In painful TMD conditions, the role of biomarkers is still elusive. We believe that the identification of biomarkers associated with painful TMD may stimulate researchers and clinician to understand the mechanism underlying the pathogenesis of TMD and help them in developing newer methods for the diagnosis and management of TMD. Therefore, to understand the potential relationship of biomarkers, and painful TMD we categorize the biomarkers as molecular biomarkers, neuroimaging biomarkers and sensory biomarkers. In addition, we will briefly discuss pain genetics and the role of potential microRNA (miRNA) involved in TMD pain.

International Journal of Oral Science (2021)13:23

; https://doi.org/10.1038/s41368-021-00129-1

Q: What to do about biomarkers?

A: Keep hoping for serologic, genetic, histologic, advanced imaging biomarkers, but in the absence of quality disease biomarkers, we must rely on its clinical features (a.k.a. phenotype) to recognize it!

Q: Do you know the 5-10 critical clinical features for all 100 of the "OFP conditions"?

A: Some of our experts will, but not our novices!

TOPIC #2: Computational Phenotyping

Q: Computers never forget so is IOM correct, will an Artificially Intelligent EMR be the solution? A: Not without unlimited funds and years and years of failures! See the IBM Watson Story below.

M.D. Anderson Partners with IBM Watson:

Photo: A leukemia doctor at M.D. Anderson, Courtney DiNardo, used IBM's Watson system while consulting with a patient in 2013.

A Reality Check for IBM's AI Ambitions

David H. Freedman June 27, 2017; MIT Media Lab

The M.D. Anderson Cancer Center in Houston and IBM partnered in 2012



with a plan was to combine genetic data, pathology reports with physicians' notes and relevant journal articles to help doctors come up with diagnoses and treatments. In February 2017 M.D. Anderson announced it had shuttered the project after investing \$39 million. After four years it had not produced a tool for use with patients that was ready to go beyond pilot tests. In theory, machine learning systems are supposed to continually readjust their data algorithms to produce the highest possible percentage of correct answers. Unfortunately, training a ML system is extremely difficult when no experts have sifted through and properly organized the data. Specialized domains of medicine need experts trained for decades to label what data you feed to the computer.

Q: Should we?



A: This is not the Devine Comedy and we are not at the gates of hell so, no, no, no!!

GTC: While I am sure with unlimited resources, a true A.I.-EMR can be built that will process all types of data including:

- interview physical examination imaging
- serologic biopsy/histopathology/immunopathology
- genetic testing and relevant medical literature
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If it existed, such a system could correctly diagnose and recommend the best treatment methods. This system does not exist now!!!

Q: Will the EPIC's EMR & NIH's \$1.5B "AllofUS" research project help us achieve precision Medicine in OFP? A: It is a beginning so "Maybe", [but probably not]. Here are 3 dental schools using EPIC!



Columbia

Univ. Mississippi

UCSF

Q: What is the click/keystroke burden an EMR causes?

A: Here is a quote from *James Allen, MD is a Professor Emeritus of Internal Medicine at the Ohio State University and former Medical Director of Ohio State University East Hospital*]

"My average encounter note has 7,369 characters **[~1040-1830 words with spaces]** although most of those characters are automatically imported from templates. As a percentage, 20% of the content of my notes are copy/paste, **15% are manually typed in**, and 65% are imported via templates/SmartTools. **[~400 clicks]**"

Death By 1,000 Clicks: Where Electronic Health Records Went Wrong

The U.S. government claimed that turning American medical charts into electronic records would make health care better, safer and cheaper. Ten years and \$36 billion later, the system is an unholy mess. Inside a digital revolution that took a bad turn.

By Fred Schulte and Erika Fry, Fortune • MARCH 18, 2019



Q: Is the SmartText features of EPIC or other EMRs the solution?

A: EPIC allows you to create a moderately structured note that can be text mined easily. Unfortunately, structuring also increases dramatically the EMR's click burden.

Q: How much time does a physician spend on documenting the patient in an EMR?

A: Of course, everyone is different and it also depends on the type of diagnosis that must be documented. Here is a reasonable quote from Dr. James Allen MD. *"On average, I spend 2 extra hours doing EMR work for every 4 hours spent in the clinic." James Allen, MD*

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Q: Yes, we all hate EMRs but if you could mine the data to create data-based phenotypes in OFP would this help us diagnose better?

A: It's a big task but most certainly it would. I have taken on this task and while it is a long-term project, a preliminary publication was published in the Journal of the American Medical Informatics Association where we created classification algorithms for our 5 most common disorders achieving an accuracy rate between 83 and 97%.

Q: Tell me more of how machine learning helps to create a data-based phenotype?

A: There are several ways to achieve a "computational phenotype" for a specific disease. One method is to collect a large set of cases in a dataset. Machine learning can then be used on this dataset if you have enough examples of the disease you want to define. In our AMIA article we mostly used Random Forest Classification modeling to identify the variable of importance that define a specific disease. This is a common method but it does require that the data set have about 100 or more examples of the disease you are examining.

AMIA Annu Symp Proc. 2020; 2020: 943–952. Published online 2021 Jan 25.	PMCID: PMC8075456 PMID: <u>33936470</u>
Building an Automated Orofacial Pain, Headache Disorder Diagnosis System	and Temporomandibular
Luciano Nocera, PhD, ¹ Anette Vistoso, DDS, MS, ¹ Yuya Yoshida, DDS, Ph Chukwudubem Nwoji, MS, ¹ and Glenn T. Clark, DDS, MS ¹	D, ² <u>Yuka Abe</u> , DDS, PhD, ²
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This article has been <u>cited by</u> other articles in PMC.	
Abstract	Go to: 🕑
Physicians collect data in patient encounters that they use to diagnose needed data is not collected or if physicians fail to interpret the data. I has automated diagnosis from encounter notes and pre-encounter diag	patients. This process can fail if the Previous work in orofacial pain (OFP)

In solutions contect data in parton one one of the discussion of the data. Previous work in orofacial pain (OFP) has automated diagnosis from encounter notes and pre-encounter diagnoses questionnaires, however they do not address how variables are selected and how to scale the number of diagnoses. With a domain expert we extract a dataset of 451 cases from patient notes. We examine the performance of various machine learning (ML) approaches and compare with a simplified model that captures the diagnostic process followed by the expert. Our experiments show that the methods are adequate to making data-driven diagnoses predictions for 5 diagnoses and we discuss the lessons learned to scale the number of diagnoses and cases as to allow for an actual implementation in an OFP clinic.

Q: How does ML identify which variables are important and should be included in the phenotype?

A: With classification ML modeling you end up with importance scores for those variables (also called features) that are most associated with the diagnosis. With a RF model, you will need at least 100 case examples to find important variables. The number of trees defines how robust the training is and how accurate the model is. Usually, training requires at least 100 cases. For testing, 10 is enough.

Q: You mentioned that that are other methods beyond ML modeling, can you explain?

A: First you must have a dataset that contains all the variables collected during a history and examination, and all the various diagnoses you must differentiate. With this dataset you can determine which variable are consistently present for any diagnosis. These would be the high frequency variables. These variables then be examined to see if they are present in multiple diagnoses or are unique to the diagnosis under consideration. **High Frequency Variables:** Defined as any variable occurring at or above a designated percent (i.e. ~67%) of the time for a specific diagnosis.

Variable "Uniqueness" Weighting Factor: Defined as the reciprocal of the number of times the specified variable is found to be an HFV for the other all of the other diagnoses being differentiated.

Q. What are the variables for Masticatory Myalgia/MFP? N= 555

A: See the table below High Frequency Variable for MM % Weighting Uniqueness Importance Rank Factor* Scores (% x 1/W) N = 555 (total dataset has 1020 cases) occurrence Factor = 1/#Location: Extraoral Jaw Muscle 0.94 17 0.059 0.055 2 Location: Extraoral TMJ Joint 0.75 18 0.056 0.042 6 23 0.043 5 CC: Pain 0.98 0.043 CC: TMJDysfunction 0.67 13 0.077 0.052 4 3 HPI – Pain-Character: Dull aching 0.87 16 0.063 0.054 HPI-Pain-ExtraQs: Very sore jaw 0.85 13 0.077 0.065 1 muscles? (+) Age: Mean±StDev 40.62 N.A. N.A. N.A. MAO: Mean±StDev 45.70 N.A. N.A. N.A. 5.55 N.A. N.A. N.A. NRS10- (Pain): Mean±StDev

[*Problem: Myalgia does not have "unique" variables as the weighting score is high. This means that myalgia will be co-morbid with multiple other diagnoses!]

Q. What is the "computation phenotype that is created from these data?

A: To create a CP you take the variables in the table and order them by their importance score. You can also include the Mean±St.Dev. values of the continuous variable, but these are non-critical. See the example below. Masticatory Myalgia Key Variables

-----Critical Variables-----

- 1. ExtraQ's: (+) Very Sore Jaw Muscles?
- 2. Location: Jaw Muscles/TMJ
- 3. Character: Dull Aching
- 4. CC: Pain/TMJ

-----Non-Critical Variables-----

- 1. Mean Age: 40.9
- 2. Sex: 77.2% Female
- 3. MAO = 45.7 mm
- 4. Exam R+L Masseters: 4.7/6 (0-3)
- 5. NRS10 Pain: 5.5

Q. What else can be done with this data?

A: Computational phenotypes are the beginning but eventually you will want to look for diagnostic subsets. These subsets might occur because there is a different mechanism for the diagnosis. The mechanism clusters are potentially "Endotypes". A subset of a CP might occur because there is a different response to a treatment. This additional analysis begins with computational phenotyping of disease. See the example of two groups of myalgia cases. The top group has masticatory myalgia and a Disc Displacement with Reduction (DDWR). The bottom group are myalgia without DDWR diagnoses. Do these two groups or clusters represent different mechanisms for masticatory myalgia?



Q: O.K. I now believe that Computational Phenotypes are needed, but how do we get them?

A: To get GOOD data we need a GOOD note taking system with:

- 1. Low click burden
- 2. Branching (= fewer clicks)
- 3. Hybrid (for odd cases needing narrative note)
- 4. Check box based (therefore ML compatible)
- 5. Designed specifically for OFP
- 6. High Key Variable Compliance!!!

Q: Can you explain this branching, check-box note taking system in more detail?

A: Yes, below is a diagram that illustrates how the system works. It is also explained in the Nocera 2020 paper.



Q: Why do you need branching in a note taking system?

A: Branching allows you to focus on the chief complaint and reduce the click/keystroke count. With the system we have in our clinic, it takes approximately *150 clicks/keystrokes* to record a patient data [with a very short narrative note]. If you write a lot of notes in our hybrid system, this will double or triple the keystroke count. In comparison, a typical narrative note has between 400-500 keystrokes. See an example of the final note!

Yes
Yes
5
Yes
45
46
47
8
8
2
Yes
Yes
Yes
Yes
Yes
Yes
Yes
Yes
3

Q: Will finding the data-driven clinical phenotypes be the end of our journey to diagnostic expertise? A: No, we need Genotypes, Biologic Markers and Endotyping must follow.

TOPIC #3: Rounds

Q: what are "pre-clinical rounds"?

A: This is a pre-clinical meeting where the residents in OFP learn and demonstrate their knowledge to the faculty. It is essentially a session where the resident present what the known about each case they will be seeing in the clinic.

Q: How is the session structured?

At USC we review every patient who is on our schedule to visit our clinic (8-9AM). This involves each resident briefly presenting their assigned cases. As they present the faculty ask questions (see list of sample questions).

- If it is a first visit [with only a CC or referral letter]:
- 1. What are the DDx's they should consider?

If it is a follow-up visit:

- 2. What diagnoses apply in this case?
- 3. Name the diagnosis defining variables?
- 4. What medications were used (known ADRs)?
- 5. What outcomes are you looking for today?
- 6. What are Social Determinants effecting this case?
- 7. What is their plan A for treatment of the Dx?
- 8. What is their plan B if plan A is not working?

Q: Can you name the most frequently occurring variables for [xxxx] diagnosis?

A: Knowing the clinical features [a.k.a. phenotype] in OFP is key to Dx. Let me take a single diagnosis (burning mouth disorder) and illustrate this process.

Q: What are the variables that define a Burning Mouth disorder.

- 1. Character: burning
- 2. Pattern: Continuous
- 3. Side: Bilateral
- 4. Exam: No visible tongue lesions
- 5. Mean Age: 66.94 (oldest of all Dx)
- 6. Sex: female (81.3% Female)

Q: What, if any, diagnostic tests are needed for this Dx?

- 1. Clinical features are key to the diagnosis
- 2. There is no definitive practical biomarker
- 3. General physical exam + serology with PCP
- 4. Rule out mucosal/other causes of Burning
- 5. Rule out vitamin deficiencies
- 6. Rule out neurotoxic medications
- 7. Treatment is a Quasi-Diagnostic Test
- 8. Frequent recall is critical for the first year

Q: What Rx's are most commonly used for this Dx, including MOA, use instructions, dosing & side effects?

- 1. Clonazepam (topical application to tongue)
- 2. ADR: dizziness
- 3. Binds to GABA-A receptors on taste buds
- 4. Physical Addiction if swallowed
- 5. Disturbs sleep onset or return to sleep at 3:00 AM

Q: What are the questions you need to ask at follow-up for this Dx?

- 1. Medication use protocol review
- 2. Q's about dizziness
- 3. Q's about sleep onset disturbance when you stop medication
- 4. Q's about duration of effect

Q: What are the most common reasons your treatment isn't working?

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- 1. Failure to follow instructions
- 2. Misunderstanding about NPP prognosis
- 3. Misunderstanding (fear) about medications
- 4. Too low a dose
- 5. Wrong diagnosis

Q: What do you do if plan A truly doesn't seem to work?

- 1. Reinforce medication use protocol
- 2. Educate and clear up any misunderstandings
- 3. Raise the dose
- 4. Add a second medication
- 5. Start over (re: diagnosis)
- 6. Examine for "Pain induced Brain change" and deal with it if present.

Q: How have others used clinical rounds to teach?

A: Yes, there is literature on this. See article below

DeSipio J, et al., Use of Real Patients and Patient-Simulation-Based Methodologies for Teaching Gastroenterology to Pre-Clinical Medical Students. Healthcare (Basel). 2018 Jun 12;6(2):61.

Study: Examine use of Patients (real+virtual) to teach medical students

- 1. Goals: demonstrate bio-psychosocial aspects of clinical practice,
- 2. Goals: demonstrate commonality of gastrointestinal ailments
- 3. Goals: help understand complex gastroenterology concepts.
- 4. Methods:

(1) students given brief, pre-prepared questions;

- (2) patient participation
- (3) virtual patients
- (4) fast Q+A sessions before lecture

Results

- 1. Faculty report using these tools improved the teaching effectiveness
- 2. Survey of students provided very positive feedback



Survey of student attitudes



Q: How do you do pre-clinical rounds if you are a solo practitioner?

A: Organize Weekly Zoom-based Rounds with other OFP practitioners [just be careful of HIPAA]

Weekly Zoom-based OFP case based study clubs (be very careful of HIPAA)!



Q: When will you have 100 computational phenotypes?

A: This is a long-term process so talk to me after we have 5,000 cases in our Database and we have a web app for collecting PGHD and taking clinical notes in OFP in 3 years).



A: "The Road Goes On Forever and the Party Never Ends"



Not The End, but The Beginning