Patient Related Outcome Measures

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PERSPECTIVES

Engaging Stakeholders to Develop a Roadmap for Dry Eye and MGD PCORI-Funded Research

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Introduction: Although affecting an estimated 35% of the population, Dry Eye is not well understood by patients and the medical community. As a result, both in research and clinical settings, diagnostic and treatment protocols tend to be non-specific, ad hoc, and inadequate, with a narrow industry-driven focus. The purpose of this convening was to propose a research roadmap that orients Dry Eye researchers toward a comprehensive patient-centered approach to diagnosing and treating Dry Eye, Meibomian gland dysfunction (MGD), and related comorbidities with a goal of improving clinical outcomes for Dry Eye/MGD patients.

Methods: Sixteen participants, including Dry Eye/MGD patients, caregivers, and patient advocates together with a group of experts in Dry Eye, MGD and other fields identified gaps in research on Dry Eye and MGD diagnostic and treatment approaches (age range 20–80; male to female ratio of 7:11; patients: 7). During a 2-day virtual convening, participants were assigned to topic-specific focus-group sessions to discuss and develop research questions pertaining to Dry Eye and MGD. The research questions were compiled into a proposed patient-centered roadmap for Dry Eye and MGD research. Two additional participants contributed to the proposed roadmap following the convening.

Results: The focus groups identified over 80 patient-centered research questions important to patients and other stakeholders and compiled these into a proposed research roadmap.

Conclusion: The convened stakeholders aim to establish a cohesive and comprehensive patient-centered approach to treating Dry Eye, Meibomian Gland Dysfunction, and comorbidities. The research roadmap will serve as a reference for researchers, educational institutions, clinicians, and others evaluating diagnostic and treatment protocols in Dry Eye and MGD.

Keywords: dry eye disease, Meibomian gland dysfunction, patient-centered research, patient advocacy, ocular surface disease, patient care

Introduction

Dry Eye is a complex, multifactorial disease that often involves numerous comorbidities. These can cause severe pain, mental distress, suicidal ideation, suicide, and applications for euthanasia (Matt Borcina, personal communication, November 15, 2023). There are two Dry Eye variants – aqueous deficient Dry Eye (AD DE; prevalence 20%) and evaporative Dry Eye (EDE; prevalence 85%).[1] Both often coexist as mixed Dry Eye. Although affecting an estimated 35% of the population, Dry Eye is not well understood.[2] Diagnostic and treatment protocols tend to be non-specific, ad hoc, and inadequate, with a narrow industry-driven focus that largely ignores patients' actual symptoms and their etiology, the underlying cause of 90% of EDE (c), and other ocular surface comorbidities.[3]

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In three prior studies,[4–6] patient input on research priorities was either meager or nonexistent, a deficiency in study design given high prevalence.[2] In one of three studies, input was solicited from only one patient of 39 total participants.[4] In another study,[5] patients were asked to prioritize outcomes culled from a previous clinicians-only study.[6]

For this project which aims to amplify the patient perspective, a team of Dry Eye/MGD patients, caregivers, and patient advocates gathered with a group of experts in Dry Eye, MGD and other fields to identify gaps in research on diagnostic and treatment approaches. These research opportunities were compiled into a patient-centered roadmap for Dry Eye and MGD.

Methods

In December 2021, the Not A Dry Eye Foundation received a Stakeholder Convening Support grant from the Patient-Centered Outcomes Research Institute (PCORI) for a project titled "Engaging Stakeholders to Develop a Roadmap for Dry Eye and MGD-PCORI-Funded Research". [EASCS-23147]. The flow of the project is described in Figure 1.

Core Team

To assist in the design, development, and production of the event, the Project Lead (PL) assembled a core team with complimentary skills, engaging the services of an Instructional Systems Designer (ISD) and a Production Manager (PM) who would also serve as a Communication Manager (CM). The ISD's primary role was to ensure all participants were sufficiently familiar with the subject matter so that project goals would be met. This included: review and consultation on original and PCORI-provided training, developing background materials such as a guidebook on Dry Eye and MGD provided to participants prior to the convening, designing templates for guided activities during focus group sessions, pre- and post-convening communication with the participants, focus group assignments and roles. The PM managed both technical and non-technical aspects of the production, maintained participant lists, the pre-event and convening schedules, scheduled pre-convening video conferencing (Zoom) training, developed and maintained the pre-convening document lists, hosted and managed all Zoom general and focus group sessions during the convening, and identified technical equipment needs and requirements. The CM handled all participant pre-convening email communication and electronic signing of participant agreements.

Training

Project Training: Prior to the convening, each participant was individually briefed by the PL on the goals and methodology of the project. In addition, the PL reviewed the project objectives and its methodology during the required Zoom training sessions. Each convening participant was required to attend at least one training session hosted by the PM/CM on Zoom.

Zoom: To minimize technical issues that might interfere with the convening, Zoom training sessions were held several weeks prior to the convening. Participants were required to attend at least one Zoom training session, and several participants requested additional one-on-one training.

PCORI/PCOR: All participants were required to complete PCORI online training modules.[7–10] For participants regularly conducting research two PCORI training modules were optional.[9,10]

Guidebook: All convening participants received a guidebook[11] prior to the convening covering a variety of topics from an overview of the purpose of the project to links to PCORI online training modules[7–10] and information about Dry Eye and MGD. (See *Guidebook*.)

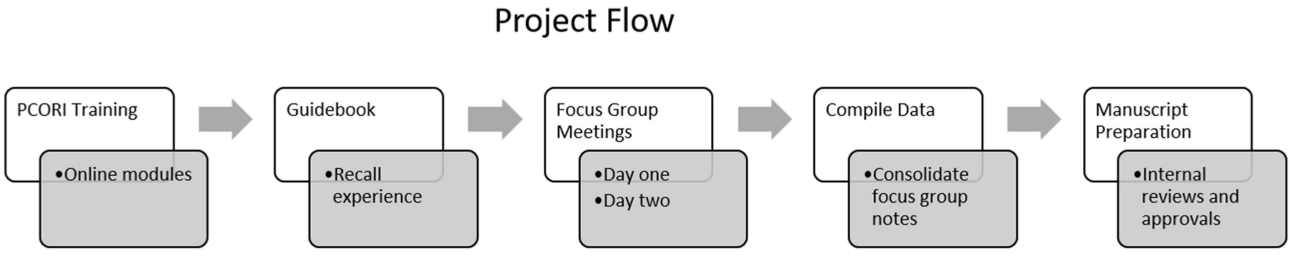

Figure 1 Phases and Project Flow. The phases of the project (white rectangles) and primary activity (grey rectangles).

Guidebook

The PL and ISD prepared a *Guidebook*[11] that covered a variety of topics pertinent to the convening and work product. A PDF version of the *Guidebook* was distributed to the participants several days before the convening along with instructions to review the contents and complete the included exercises. The exercises were designed to help participants recall prior to the convening their experience(s) with Dry Eye, MGD and common comorbidities via reflection, individual brainstorming, or other grounding methods. An introduction to PCORI principles and links to online PCORI training modules[7–10] were included as were instructions on how to pronounce medical terms such as *Meibomian* and *conjunctivochalasis* that may have been unfamiliar to some participants. (See *Guidebook* Table of Contents for a complete list of topics covered.)

The topics in the *Guidebook* largely mirrored the topics discussed in the convening focus group sessions. (See Focus Group Sessions Topics.) The *Guidebook* was also designed as a reference to be used by participants during the convening and later, during reviews of the work product.

Guidebook Table of Contents

1. Introduction
2. Goal of the project
3. Not A Dry Eye Foundation
4. PCORI
5. PCORI online training
   (a) The PCORI approach to patient-centered outcomes research
   (b) Engaging in stakeholder-driven research
   (c) Developing research questions
   (d) Designing the research study
6. The research framework at a glance
7. What is a research roadmap?
8. How do I pronounce?
9. Terms
10. Acronyms
11. Eye anatomy
12. Definitions of Dry Eye
13. Pathophysiology/causes of disease
14. Symptoms
15. Factors contributing to disease and symptoms
16. Diagnosis
17. Patient questionnaires
18. At-home/OTC therapies
19. Physician-prescribed and administered therapies
20. Patient, provider, regulatory agency awareness/education

Convening Participants

Each participating stakeholder was invited based on their professional expertise or personal experience with DE, MGD, and comorbidities, or, other relevant professional expertise; eg, information technology.

- Convening participants: n = 16
  - Additional stakeholders: n = 2
- Age range: 20 < n < 80
- Gender female: n = 11; male: n = 7

The following stakeholder groups were represented. In some cases, one participant represented more than one group (+ indicates post-convening contribution to roadmap).

Patient: n = 7
Patient advocate: n = 5
Caregiver: n = 3
Ophthalmic technician: n = 1
Administration: n = 2
Ophthalmology: n = 1 (+1)
Optometry: n = 1 (+1)
Other medical specialty: n = 1 (Internal medicine)
Research: n = 4 (+1)
Information Technology: n = 1
Instructional Systems Design: n = 1

Convening

The convening was held via Zoom video conferencing. Each focus group session lasted 1 hour followed by a 10- to 15-minute report-out to all participants and a 10- to 15-minute break.

Focus groups identified gaps in research and drafted proposed research questions to mitigate those gaps. Focus group topics included: comorbidities, factors contributing to disease and/or symptoms, diagnosis, patient questionnaires, disease definition and pathophysiology, psycho-social impact of disease on patients, training/education, OTC treatments, and prescribed treatments.

Participant Assignments

Generally, no less than 4 and no more than 7 participants were assigned to a single focus group session ensuring a high level of engagement by all. Patients were represented in each focus group. Three concurrent focus group sessions were held simultaneously throughout both days.

One member of each focus group was assigned the role of room leader. The room leader was tasked with facilitating the session process (eg, reading instructions out loud, maintaining the group's focus on its assignments) and ensuring the group completed its assignments on time. One other individual was assigned the role of scribe. This individual recorded video of the session, downloaded a discussion guide and template for taking notes, shared their screen, took notes, and filled out the templates provided (Table 1). Scribes were trained in using the note-taking and screen share tasks in the days prior to the convening.

Throughout both days, the PL and Host were available for content-related or technical questions respectively.

Focus Groups: Method

Through Zoom chat, the assigned scribe received a unique link to a document that outlined that focus group's assignments. The document included instructions for the Room Leader (driving discussion and time keeping), the Scribe (recording the session and taking notes), and all participants (prompts to identify gaps in research and developing research questions) as well as a template for note taking.

Documents were stored on a secure Google share drive where files were saved automatically and continuously, that is, as soon as a change was made to the file. All documents were also backed up automatically. The scribe typed notes on a continuous and ongoing basis directly into each template (Table 1) while sharing their screen so all participants could review and comment on the notes taken. Thereafter, at the close of each focus group session, the PL revoked access to the files so they could not be intentionally or accidentally altered, thus ensuring integrity of the work product.

Table 1 Research Question Template

Study Title	Briefly describes the study; may be posed as a statement, question or hypothesis
Significance	Why the study is important; how the study results will improve patient care
Study Type	Retrospective/prospective, survey, blind, controlled, etc.
Sample Size	Minimum sample size or ideal sample size
Parameters	Lists how subjects and/or study will be evaluated, ie, subject characteristics, tests, examinations, survey, etc., (See Notes, below)
Duration	How long the study will last eg, months, years
Info Tech (IT)	The role of IT in the study and beyond
Comments/References	Any additional comments or references if available or known

Notes: Unless otherwise noted in the tables, study parameters are defined as follows:

1. *.No exclusions*: All patients diagnosed with Dry Eye or MGD, regardless of symptoms or presence of other comorbidities, are eligible to be enrolled in the study
2. *Patient symptoms*: Chief complaint, symptom patterns, impact on quality of life (QOL)
3. *Visual acuity*: Snellen chart
4. *Aqueous tear status*: fluorescein clearance test (FCT) or other vital staining, serial Schirmer's test
5. *MG gland and meibum status*: tear break-up time (TBUT), meibography imaging, confocal microscopy imaging, lid tenderness evaluation to establish lid-MGD classification, lipid interferometry
6. *Ocular surface status*: comprehensive external and ocular surface disease exam, vital staining, includes eliciting symptoms for conjunctivochalasis and/or other surface tissue disease
7. *Comprehensive medical work-up*: comprehensive medical history; comprehensive family medical history; history of medication including hormone replacement therapy (HRT); screening for rosacea and other skin diseases; evaluation for risk or presence of autoimmune and non-autoimmune systemic diseases; previous exposure to toxins and/or particulate matter; lifestyle factors including climate, work/home/school environment, computer use, hobbies, etc.

Abbreviation: IT, information technology.

Results

Focus Groups: Comorbidities

Focus groups developed the following list of comorbidities. Proposed related research questions are listed in Table 2A. An additional research question, "How can MGD, ATD, conjunctivochalasis and other associated comorbidities be prevented?" was discussed but not included in Table 2A.

- Conjunctivochalasis
- ATD (Aqueous Tear Deficiency)
- Allergies (ie, environmental, drug- or preservative-induced)
- Autoimmune disease
- Bacterial infections (anterior blepharitis)
- Blepharitis
- Eyelash crusting, eyelashes stick together
- Demodex mite overpopulation
- Depression, psychiatric issues or mental health issues
- Dermatologic disease
- Distichiasis
- Epiphora
- Hormonal imbalances
- Lagophthalmos
- Lagophthalmos, nocturnal and blink
- Lashes getting stuck in eye
- Lid abnormalities, eg, Bell's palsy, ptosis
- Lid wiper epitheliopathy (added during review process)
- Map-dot-fingerprint dystrophy/anterior basement membrane dystrophy (ABMD)

- MGD
- Ocular immune disease/Grave's disease
- Post-viral Dry Eye/Post-COVID Dry Eye
- Prior ophthalmic surgeries where cornea is involved
- Reflex tearing
- Rosacea
- Sjogren's syndrome
- Superior limbic keratoconjunctivitis (SLK)
- Spontaneous corneal abrasion
- Systemic autoimmune disease
- Thyroid disease, causes and/or contributing factors
- Trauma history
- Trichiasis

Focus Groups: Symptoms

Focus groups developed the following list of symptoms. Proposed related research questions are listed in Table 2B.

- Awareness of eyes
- Blinking frequently
- Blurred vision
- Burning
- Constant unrelenting discomfort in the eyes
- Crawling on eye lashes
- Crusting
- Debris in eyes
- Debris in eye lashes
- Difficulty opening eyes
- Drippy eyes
- Dry eyes
- Epiphora (overflowing of tears)
- Eye pain
- Eyes feel exposed
- Eyes feel like open wounds
- Eyes feel like they are made out of wood (due to medications including steroids)
- Feels like crushed glass in the eyes
- Foreign body sensation
- Gritty, scratchy, or sandy
- Headache
- Heavy eyes, heavy eye lids
- Inflammation
- Itching
- Lashes falling out frequently, sticking to eyeball
- Lids stick to eyes
- Sensation of menthol, acid, or gasoline in the eyes
- Misdirected lashes
- Mucous discharge
- Pain or other discomfort when reading, driving, or doing other activities that requires focus
- Puffy eyelids

- Raw
- Red eyes and lid margins
- Redness
- Saponification, frothy tears
- Screwdriver in eye at waking
- Sensitivity to fumes and perfumes
- Sensitivity to light (photophobia)
- Sensitivity to many environmental factors
- Sensitivity to temperature
- Sensitivity to wind
- Sticky eyes
- Stinging
- Swollen eyes
- Tearing
- Tired eyes
- Tissues under eye lids
- Twitching eye lids
- Unable to take focus away from eyes, meaning that cognitive awareness is constantly on the eyes instead of no awareness of eyes.
- Watery eyes
- Wetness

Participants recognized the following as symptoms of interests, though did not propose related research questions

- Blurred vision
- Burning
- Debris in eye lashes
- Difficulty opening eyes
- Feeling of crushed glass in eyes
- Foreign body sensation
- Heavy eyes/eyelids
- Lids stick to eyes
- Menthol/acid/gasoline
- Misdirected lashes
- Mucous discharge
- Redness
- Stinging
- Tearing (when exposed to wind/environment)
- Tired/heavy eyes

Focus Groups: Factors

Focus groups developed the following list of factors that contribute to Dry Eye, MGD, and comorbidities, and proposed the research questions listed in Table 2C: age and stage of life (eg, pregnancy, menopause, andropause), binge-eating, climate, decreased/no social interaction leading to isolation and poor quality of life, environment, screen time, gender, genetics/heredity, sun exposure, hygiene (eg, cleansing methods and substances used), stress, use of cosmetics, exposure to particulate matter (eg, dust, smoke), exposure to toxins (eg, swimming in chlorinated pools without goggles, exposure to chemicals, occupational exposure), race, ethnicity, religion, diet and nutrition, blinking pattern, drying side effects due to medications/drugs (OTC or prescription), iatrogenic - exposure to medications (eg, anticholinergics, antihistamines,

Table 2 Research Questions on Comorbidities, Symptoms, and Factors

A. Comorbidities		
Allergies		
a	**Study Title**	The role of allergies in Meibomian gland dysfunction (MGD) and Dry Eye
	Significance	Difficult to pinpoint specific allergies and differentiate allergy symptoms from other ocular surface disease
	Study Type	Large, longitudinal, causal
	Sample Size	100 or more
	Parameters	• 1–7 • Comprehensive allergy testing (include patch testing for common and less common allergens, eg, metals) • Mucus production
	Duration	1–2 years, with annual follow-up
	Info Tech (IT)	Knowledge base of specific allergies associated with MGD and Dry Eye
	Comments/ References	May be one comorbidity in a larger comprehensive Dry Eye study
b	**Study Title**	Does reducing allergy symptoms have a secondary effect on MGD and Aqueous Tear Deficiency (ATD)?
	Significance	Allergies are a major comorbidity affecting patient comfort both directly and indirectly. Reducing allergy symptoms may improve status of Meibomian glands and watery tear secretions.
	Study Type	Prospective, randomized, blind
	Sample Size	50 or more
	Parameters	• 1–7 • Comprehensive allergy testing (include patch testing for common and less common allergens, eg, metals) • Mucus production
	Duration	1 week; 1 month; 3 months; 6 months; 1 year or more
	Info Tech (IT)	Knowledge base of existing causal connections between MGD, ATD to allergy symptoms
	Comments/ References	Assess the impact of inflammation due to allergies as well as impact of oral therapies directed toward control of allergies which can have a drying effect
c	**Study Title**	How can doctors be more specific about the general-term "allergies"?
	Significance	Patients are often told their allergies are affecting their eyes, but they are not told what they are allergic to or which allergens they need to avoid
	Study Type	Prospective
	Sample Size	50 patients or more due to variations in allergies, eg, 200 patients
	Parameters	Degree of symptoms among 50% of patients treated with allergy drops compared to 50% of patients that are referred to find the source and treatment for their allergies.
	Duration	1–2 years
	Info Tech (IT)	Knowledge base of allergy terms
	Comments/ References	Patients with suspected allergies according to their ophthalmologist/optometrist work collaboratively with an allergist or additional physician to determine the source of their allergies/sensitivities. Allergy drops can sometimes be recommended as a preventive measure, but most have preservatives that can worsen symptoms. Should everyone with Dry Eye be on an allergy drop, or should those with suspected allergies all be referred to an allergist?

(*Continued*)

Table 2 (Continued).

Aqueous Tear Deficiency		
d	**Study Title**	Is ATD hereditary?
	Significance	What role do genetics play in patients who develop ATD?
	Study Type	Family cohort
	Sample Size	25–100
	Parameters	• 1–7 • Identify patients (n = 25–100) then test siblings, parents, and children
	Duration	1–3 months to obtain samples
	Info Tech (IT)	Knowledge base of genetic risk factors
	Comments/ References	To what extent do genetics play a role in developing Dry Eye and MGD, and should family members of Dry Eye patients be observed more closely for developing asymptomatic or symptomatic disease?
Blepharitis		
e	**Study Title**	How does use of the term blepharitis, a confusing non-specific term, contribute to patient suffering?
	Significance	Without specific diagnoses and targeted treatments, patient-suffering can be prolonged while disease advances.
	Study Type	Survey
	Sample Size	50 or more in each group
	Parameters	• Patients diagnosed with "blepharitis" including: blepharitis, posterior blepharitis, anterior blepharitis. • Patients diagnosed with MGD, obstructive-MGD (o-MGD). • Prescribed treatments and their outcomes • Number of doctors seen • Health of lid margin • 2–6
	Duration	6 months
	Info Tech (IT)	Knowledge base containing the outcomes of: "blepharitis" diagnoses and prescribed treatments; MGD and diagnosis and prescribed treatments
	Comments/ References	Reliance on patient memories may be a limiting factor.
Conjunctivochalasis		
f	**Study Title**	What causes conjunctivochalasis? What is its etiology?
	Significance	Conjunctivochalasis is an often-overlooked comorbidity that can contribute significantly to symptoms and disease. The disease is increasingly being seen in younger patients.
	Study Type	Longitudinal, causal, prospective
	Sample Size	Large cohort (100 or more)
	Parameters	1–7
	Duration	3–10 years; with HRT 3–5
	Info Tech (IT)	Knowledge base on the causes associated with conjunctivochalasis
	Comments/ References	Multiple factors may contribute to etiology (screen time, environmental factors, etc.); aim to identify any and all contributing factors, including comorbidities that contribute to disease (eg, MGD, ATD).

(*Continued*)

Table 2 (Continued).

g	**Study Title**	Has increased screen time during COVID-19 contributed to conjunctivochalasis? Does computer use contribute to conjunctivochalasis?
	Significance	Conjunctivochalasis is being seen with increasing frequency in adolescents and young adults among whom computer use starts at an early age.
	Study Type	Retrospective
	Sample Size	50 or more
	Parameters	• Computer users • Degree of conjunctivochalasis • Age, impact on quality of life. • Control for contact lens use and allergy history • 2–6
	Duration	Compare pre-COVID 19 pandemic and post COVID-19 pandemic, 6 months, 1 year
	Info Tech (IT)	Causal relationships between computer use and conjunctivochalasis
	Comments/ References	Compare self-reported computer use per day before and after COVID-19. Investigate relationship between average computer usage time and change of the degree of conjunctivochalasis during the time of experiment.
h	**Study Title**	What is the current state of examination, testing, and diagnosis of conjunctivochalasis?
	Significance	Patients suffer when the disease is not diagnosed due to a lack of physician-awareness of the prevalence of disease or due to ineffective diagnostic methods. Younger patients with conjunctivochalasis are too often dismissed because of a general belief that the condition develops with increasing age.
	Study Type	Survey
	Sample Size	50 or more
	Parameters	• Patients with previously undiagnosed conjunctivochalasis who were later diagnosed and treated. • Identify the exams and tests previously administered. • Establish number of doctors seen prior to accurate diagnosis
	Duration	New patients seen in 12-month period
	Info Tech (IT)	Knowledge base on testing, examination and diagnosis of conjunctivochalasis
	Comments/ References	Reliance on patient memories may be a limiting factor.
i	**Study Title**	How can ocular surface exams be standardized to ensure all comorbidities are diagnosed?
	Significance	Patients suffer when ocular surface diseases are not diagnosed due to a lack of physician-awareness of the prevalence of disease or due to ineffective diagnostic methods.
	Study Type	Survey
	Sample Size	50 or more
	Parameters	• Patients with previously undiagnosed ocular surface diseases who were later diagnosed and treated. • Identify the exams and tests previously administered. • Establish number of doctors seen prior to accurate diagnosis
	Duration	New patients seen in 12-month period
	Info Tech (IT)	Knowledge base on testing, examination, and diagnosis of ocular surface diseases
	Comments/ References	Reliance on patient memories may be a limiting factor.

(*Continued*)

Table 2 (Continued).

Dry Eye, MGD, and Comorbidities: Causes		
j	**Study Title**	How does Dry Eye develop and progress? What role do comorbidities play in the development and progression of disease?
	Significance	Dry Eye and MGD are common diseases that are not well understood.
	Study Type	Large, longitudinal, causal, multiple sites
	Sample Size	100 or more. Model on Women's Health Initiative; include community centers and universities.
	Parameters	• Intervention: half of subjects are controls, the other half receive counseling on proper eye care, eg, wearing UVA/UVB protective glasses, proper lid hygiene, etc. • 2–7
	Duration	4 years
	Info Tech (IT)	Causal connections between comorbidities and disease progression
	Comments/ References	Additional objectives: • Understanding probability of developing Dry Eye, MGD, and comorbidities at various stages of life • Understanding which factors contribute to disease and why • Identify measures to prevent disease • Involve community centers and universities
Inflammation		
k	**Study Title**	Does diet contribute to inflammation and related symptoms?
	Significance	Patients are often instructed to follow anti-inflammatory diets to reverse disease or reduce symptoms.
	Study Type	Prospective, large, longitudinal, causal
	Sample Size	100 or more
	Parameters	2–7
	Duration	6 months −2 years
	Info Tech (IT)	Causal connection between diet and inflammation
	Comments/ References	May be one parameter in a larger comprehensive Dry Eye study
MGD		
l	**Study Title**	Is MGD hereditary?
	Significance	What role do genetics play in patients who develop MGD?
	Study Type	Family cohort
	Sample Size	25–100
	Parameters	• 1–7 • Identify patients (n = 25–100) then test siblings, parents, and children
	Duration	1–3 months to obtain samples
	Info Tech (IT)	Knowledge base of genetic risk factors
	Comments/ References	To what extent do genetics play a role in developing MGD, and should family members of MGD patients be observed more closely for developing asymptomatic or symptomatic disease?

(*Continued*)

Table 2 (Continued).

Recurring Pink Eye		
m	**Study Title**	What is the correlation between Dry Eye and recurring pink eye? Does aqueous deficiency or MGD increase risk of recurring pink eye?
	Significance	Evidence suggests some Dry Eye patients are prone to recurring pink eye.
	Study Type	Prospective, longitudinal
	Sample Size	50 or more
	Parameters	• Recurring pink eye status • 2–7
	Duration	6 months or longer
	Info Tech (IT)	Causal connection between pink eye, ATD, MGD
	Comments/ References	Patients who have had non-viral pink eye also suffer with severe Dry Eye. Are their eyes so aqueous deficient that they are unable to flush out microbes?
General		
n	**Study Title**	Is there a genetic marker for Dry Eye: ATD, MGD, common comorbidities?
	Comments/ References	Can genetic information be used to personalize medicine and provide preventative eye care to persons of a young age who may be at risk for developing disease?
B. Symptoms		
a	**Study Title**	What is the incidence of key symptoms?
	Significance	The length of a typical patient encounter (15-, 30-, 45-minutes is an impediment to collecting good data. Therefore, a robust patient questionnaire that covers a large set of key symptoms (including severity and frequency patterns) would expedite the diagnostic process while leading to both better diagnoses and more targeted treatment and more accurate study data.
	Study Type	Prospective, large, longitudinal, causal
	Sample Size	500 or more
	Parameters	1–7
	Duration	6 months −2 years
	Info Tech (IT)	Knowledge base of key symptoms associated with the study
	Comments/ References	May be part of a larger comprehensive Dry Eye study
Altered Blinking		
b	**Study Title**	What specifically is the impact of incomplete blinking, reduced blink rate, and increased blink rate on patient symptoms and disease?
	Significance	Incomplete blinks and a reduced blink rate are known contributors to Dry Eye and MGD.
	Study Type	Prospective, large, longitudinal, causal
	Sample Size	100 or more
	Parameters	1–7
	Duration	6 months −2 years

(*Continued*)

Table 2 (Continued).

	Info Tech (IT)	Causal connection between blink rate, symptoms, and disease
	Comments/ References	May be part of a larger comprehensive Dry Eye study
Epiphora		
c	**Study Title**	Prospective evaluation of the root cause of epiphora
	Significance	Successful therapy requires accurate diagnosis
	Study Type	Prospective
	Sample Size	100 or more
	Parameters	Test volume, tear break-up time (TBUT), tear clearance of identified subjects using fluorescein clearance test (FCT), identification of nasolacrimal outflow blockage - drainage to the nose
	Duration	1 month
	Info Tech (IT)	Knowledge base that gives information on source of excess tears and how to evaluate the cause
	Comments/ References	Eyelashes or other foreign body in the eye may be contributing factor 70% of the time versus 20% attributed to MGD.
Eye Pain		
d	**Study Title**	What is the source of eye pain?
	Significance	It is necessary to identify the source of eye pain to prescribe targeted therapy
	Study Type	Prospective
	Sample Size	50 or more
	Parameters	• Subjects: Baseline where pain is ruled out from other known non-surface sources; all surface infections and allergies are eliminated • Entry criteria: Chronic pain at least 2 weeks to 1 month • Confocal microscopy, meibography, diagnostic probing of MGs
	Duration	1 month or less
	Info Tech (IT)	Knowledge base of sources of pain; identification of MGD vs ATD vs foreign body (FB), etc.
	Comments/ References	There is always a source of pain and the source needs to be identified properly. Gender bias is endemic to the mistreatment of Dry Eye: men with Dry Eye may not accept that they have Dry Eye and may resort to alcoholism or other destructive coping mechanisms; women may be labeled "neuropathic" and may be treated with medicine that may exacerbate disease and symptoms.
Gritting, Gravely, Scratchy, or Sandy		
e	**Study Title**	Which comorbidities do the different FB sensations gritty, gravely, scratchy, and sandy indicate and what is the most effective approach to a specific diagnosis for each symptom?
	Significance	Different FB sensations indicate different comorbidities but diagnostic approaches do not always aim toward a specific comorbidity, which can delay targeted and effective treatment.
	Study Type	Prospective
	Sample Size	50 or more
	Parameters	1–7

(*Continued*)

Table 2 (Continued).

	Duration	1 month
	Info Tech (IT)	Knowledge base of the comorbidity and associated effective treatment
	Comments/ References	Improve the accuracy of diagnosing ATD, MGD, and other comorbidities.
Photophobia		
f	**Study Title**	How long does it take symptoms of photophobia to resolve after amniotic membrane transplant (AMT) surgery for conjunctivochalasis?
	Significance	Photophobia impacts quality of life.
	Study Type	Retrospective
	Sample Size	50 or more
	Parameters	Severity and duration of photophobia pre-surgery; return of symptoms post-surgery; improvement in degree of symptom post-surgery; duration of improvement in symptoms post-surgery
	Duration	Per subject, length of time after surgery to feel improvement in photophobia
	Info Tech (IT)	A decision support system to help set expectations regarding post-surgery outcome
	Comments/ References	Patients have reported that symptoms of photophobia stopped or gradually subsided after AMT surgery.
Puffy Eyelids		
g	**Study Title**	What causes puffy eyelids?
	Significance	Successful therapy requires accurate diagnosis
	Study Type	Prospective
	Sample Size	100 with puffy eyelids for more than 2 weeks prior to enrollment.
	Parameters	• Patients with chronic puffy lid • Flaking of lid • Redness of lid • Allergy evaluation • Evaluate for history of eye rubbing, toxic exposure, burning wood, other environmental exposure • 2–7
	Duration	1 month
	Info Tech (IT)	Knowledge base that provides information on etiology of puffy eyelids; decision support system for clinicians to evaluate the patients more accurately
	Comments/ References	No objective measure for eyelid puffiness. Puffiness can be accompanied by various other symptoms like itching. Puffiness can be due to systemic diseases such as skin disorder, or eye makeup.
General, Relating Comorbidities with Symptoms		
h	**Study Title**	Which specific comorbidity does each individual symptom indicate?
	Significance	Correlating each specific symptom with a specific comorbidity is an important part of the diagnostic process and begins with the technician. Trained technicians will be better equipped to ask patients the right questions and, in particular, the kinds of questions that will help patients describe their symptoms very specifically.
	Study Type	Retrospective

(*Continued*)

Table 2 (Continued).

	Sample Size	100 or more from 10–20 different clinics
	Parameters	• Control group - no change in current patient intake practice • Test group – using a streamlined questionnaire to discuss symptoms and history with patients • Duration of symptom relief • 1-7
	Duration	6 months or longer
	Info Tech (IT)	Causal connection between comorbidity and individual symptom
	Comments/ References	Asking patients the right questions will help doctors and technicians hone in on an accurate diagnosis, eg, allergy commonly presents as itching or burning. This study would help to standardize the process of taking patient histories and reviewing symptoms.
C. Factors		
Computer Use/ Screen Time		
a	**Study Title**	Frequency and duration of computer use as a risk factor for MGD and Dry Eye
	Significance	High rates of extensive screen time in all populations
	Study Type	Prospective
	Sample Size	100 or more
	Parameters	• Age groups, eg, a<18, 18<a<30, etc. • 1–7
	Duration	3–5 years
	Info Tech (IT)	Knowledge base that provides recommendations/information on risk factors associated with computer use leading to MGD and Dry Eye
	Comments/ References	Create a roadmap for ocular surface health in non-adult (<18 years old) populations
b	**Study Title**	Does childhood screen time cause or contribute to Dry Eye later in life?
	Significance	Provide evidence to establish the importance of managing screen time in non-adult (<18 years old) populations
	Study Type	Retrospective
	Sample Size	50 or more
	Parameters	• Pre-K to high school • Screen time • 2–7
	Duration	10–15 years
	Info Tech (IT)	Knowledge base on screen-time use for non-adult population
	Comments/ References	Establish Meibomian gland imaging as part of the standard Dry Eye consult
c	**Study Title**	How does screen exposure impact blinking patterns that can ultimately lead to Dry Eye, MGD, and related comorbidities?
	Significance	Complete spontaneous blinking, and the correct rate, is an integral component of ocular surface health, but its importance is underappreciated.

(*Continued*)

Table 2 (Continued).

	Study Type	Prospective
	Sample Size	50 or more
	Parameters	Measure patient's screen exposure time and their blinking patterns in relation to their symptom severity and signs of disease.
	Duration	1 year
	Info Tech (IT)	Knowledge base containing causal connection between screen time and Dry Eye and MGD
	Comments/ References	Blink exercises can improve the formation of complete blinks.
d	**Study Title**	Why does eyelid surgery result in incomplete blinking?
	Significance	Plastic surgery is becoming more accessible and patients are having eyelid tissue removed, which can lead to inability to make complete blinks.
	Study Type	Retrospective
	Sample Size	100 or more
	Parameters	• New onset Dry Eye symptoms after surgery • Degree of symptoms
	Duration	1 year
	Info Tech (IT)	Knowledge base describing reason for causal connection between eyelid surgery and incomplete blinking
	Comments/ References	None
Dietary or Nutritional Factors		
e	**Study Title**	Effect of caffeine on Meibomian glands and aqueous tear production
	Significance	High rates of caffeine consumption (eg, coffee, other caffeinated beverages, chocolate) and theoretical adverse effects on the eye
	Study Type	Double blinded prospective randomized study using placebo
	Sample Size	50 or more
	Parameters	• Caffeine dosage and placebo • Lid fissure width • Blink rate • Eyelid tenderness • 2–7
	Duration	6–12 months
	Info Tech (IT)	Knowledge base that indicates what amount of caffeine will adversely affect eyes and contribute to MGD and ATD.
	Comments/ References	Worth prioritizing since this is something patients can control
f	**Study Title**	The impact of controlling Dry Eye-related nutritional issues through anti-inflammatory and other dietary programs
	Significance	Evidence suggests that removing nutritional insults to the tear and ocular surface structures improves or supports ocular health, reverses diseases, and improves symptoms
	Study Type	Prospective, randomized, blind

(*Continued*)

Table 2 (Continued).

	Sample Size	50 or more
	Parameters	1–7
	Duration	1 week; 1 month; 3 months; 6 months; 1 year
	Info Tech (IT)	Knowledge base on Dry Eye and anti-inflammatory dietary recommendations
	Comments/ References	Empowering to patients: gives patients a measure of control over their own bodies and puts patients in charge of their own destiny; self-regulated by patients not by physician. Aim to prove or disprove anecdotal insight with evidence-based research.
g	**Study Title**	How do inflammatory foods impact DED? Can changing diet significantly change DED symptoms?
	Significance	Patients may be motivated to change dietary habits if provided evidence of negative effects of inflammatory foods
	Study Type	Prospective
	Sample Size	100 or more
	Parameters	• Determine patient diet; correlate with Dry Eye symptoms • 1–7 • Food challenge tests; food sensitivity tests
	Duration	6 months or more
	Info Tech (IT)	Knowledge base of inflammatory-food impact on DED
	Comments/ References	Study the effects of commonly consumed foods known to be inflammatory such as sugars, carbohydrates, caffeine, dairy, gluten, different protein sources (vegan, vegetarians). Note: vegetarian and vegan diets may lack omega-3 fatty acids intake due to refraining from eating fish
h	**Study Title**	How does vitamin deficiency impact DED?
	Significance	Patients often do not consume sufficient quantities of vitamins and other nutrients. Identifying and addressing vitamin/ nutrient deficiencies could provide patients with a holistic alternative to prevent or reduce DED symptoms. Patients may be more willing to take "natural" supplements than prescription medications.
	Study Type	Prospective
	Sample Size	100 or more
	Parameters	• Blood serum vitamin levels • 2–7
	Duration	1 year or more
	Info Tech (IT)	Knowledge base of vitamin deficiency impact on Dry Eye
	Comments/ References	Patients may be deficient in vitamins A, D, B12, or nutraceuticals (eg, omega-3 fatty acids). Patients may require a life-long supplement, as opposed to daily prescription medications. Nutritional supplementation may be especially important for younger patients diagnosed with, or who are at risk for developing, Dry Eye, and who may need intervention for the rest of their lives.
Hereditary Factors		
i	**Study Title**	Hereditary factors of developing Dry Eye
	Significance	Is Dry Eye familial, hereditary? Are family members of patients with Dry Eye predisposed to developing disease?
	Study Type	Prospective
	Sample Size	50 or more

(*Continued*)

Table 2 (Continued).

	Parameters	• Family history of disease • 1–7
	Duration	2 years or more
	Info Tech (IT)	Knowledge base of hereditary factors that may indicate Dry Eye or comorbidities
	Comments/ References	The study would help raise the awareness of the risk of developing Dry Eye disease among young patients; the study would aid clinicians in evaluating young children for risk factors and consider early preventative measures, eg, limiting screen time, developing good eye and eyelid hygiene habits.
Hormones		
j	**Study Title**	Impact of hormonal changes on Dry Eye.
	Significance	Higher incidence of Dry Eye disease among women than men
	Study Type	Large, longitudinal, causal
	Sample Size	Large cohort (100 or more)
	Parameters	• Young women/middle-aged/older women (periods of transition) • 2–7
	Duration	5–10 years
	Info Tech (IT)	Knowledge base of impact of hormonal changes on Dry Eye
	Comments/ References	May be one study in a larger comprehensive Dry Eye study that may include questions such as: does hormonal imbalance affect Meibomian glands? How? Is anemia associated with Dry Eye? How does the menstrual cycle affect Dry Eye?
Toxic Exposure		
k	**Study Title**	What is the impact of exposure to toxins on the ocular surface? Does exposure to toxins contribute to ATD, MGD, and related comorbidities? How?
	Significance	Many toxins are ubiquitous and therefore difficult to avoid for patients with Dry Eye and MGD.
	Study Type	Retrospective
	Sample Size	50 or more
	Parameters	• Degree of exposure to toxins • 2–7
	Duration	Years TBD
	Info Tech (IT)	• Knowledge base of impact of toxins on Dry Eyes • Knowledge base that provides recommendations and insights on high-risk factors of toxins leading to, or contributing to, MGD, Dry Eye and/or comorbidities
	Comments/ References	Long term exposure to the sun, smoke stacks, wildfire events, swimming in chlorinated pools without goggles, cooking fumes, etc.
Particulate Matter		
l	**Study Title**	What is the impact of environmental particulate matter and toxins on Meibomian glands, and symptoms of MGD, Dry Eye, and comorbidities
	Significance	Particulate matter is ubiquitous and therefore difficult to avoid for patients with Dry Eye and MGD.

(*Continued*)

Table 2 (Continued).

	Study Type	Retrospective or survey
	Sample Size	100 or more
	Parameters	1–7
	Duration	1 year
	Info Tech (IT)	Knowledge base that provides recommendations and insights on high risk factors of toxins and particulate matter leading to, or contributing to, MGD, Dry Eye and/or comorbidities
	Comments/ References	Select communities with high risk factors and low risk factor communities and compare the symptoms of eye irritation. 2nd arm to the study: physicians examine patients for signs and symptoms of disease using identical examination protocol.
m	**Study Title**	Comparing Dry Eye symptom severity between people who work inside with those who are outside where they are prone to exposure to particulate matter
	Significance	Particulate matter is ubiquitous and therefore difficult to avoid for patients with Dry Eye and MGD.
	Study Type	Retrospective
	Sample Size	100 or more
	Parameters	• People who work outdoors or in environments with high levels of particulate matter; control: people who work indoors in environments with low levels of particulate matter. • 2–7
	Duration	1 year
	Info Tech (IT)	Knowledge base on outdoor and indoor working environments and their impact on Dry Eye, MGD, and comorbidities
	Comments/ References	Indoor work also poses environmental risk factors, such as nearby perfume, cologne, dust in the AC or on surfaces, low humidity in the air, strong air currents from AC, screen exposure, and mold. Pollen, dirt, fumes, and even sweat can all impact one's environment while working. Particulate matter that may be present in one's hair or on clothing and can transfer to pillows/bedding when sleeping.
n	**Study Title**	Study to determine and quantify how various environments contribute to Dry Eye, MGD, and comorbidities. Include a variety of climates and regions across the country: inland, coast, mountains, deserts, temperate, subtropic, seasons, weather patterns, etc.
	Significance	Knowledge that certain regions or environments impact DED differently would equip patients with information which may help them improve their quality of life.
	Study Type	Retrospective
	Sample Size	100 or more
	Parameters	• People living and working in various climates and regions • 2–7
	Duration	1 year
	Info Tech (IT)	Knowledge base indicating how various environments affects Dry Eye
	Comments/ References	Results of study may support a lifestyle modification approach to addressing signs and symptoms of DED.

Abbreviations: MGD, Meibomian gland dysfunction; o-MGD, obstructive- Meibomian gland dysfunction; HRT; hormone replacement therapy; ATD, aqueous tear deficiency; TBUT, tear break-up time; FCT, fluorescein clearance test; FB, foreign body; AMT, amniotic membrane transplant; DED, dry eye disorder.

isotretinoin (ie, Accutane), retin-A cream), iatrogenic - surgeries/procedures (eg, LASIK, photorefractive keratectomy (PRK), cataract, pterygium, Botox injections, ptosis repair), eyelid tattoo.

Focus Groups: Diagnosis

Focus groups developed the following list of tests and exams: single Schirmer's with topical anesthetic; serial Schirmer's test with topical anesthetic; slit lamp exam including eversion of the upper lid; stimulation inside the nose; fluorescein clearance test (FCT); tear break-up time (TBUT); Meibomian glands expressibility; meibum clarity, fluidity, color, presence of particulate matter, volume; lid tenderness; meibography; confocal microscopy; tear osmolarity; MMP-9 enzymes; Meibomian gland probing (findings during treatment); bacteria test; demodex test; lissamine green staining; fluorescein staining; tear meniscus height; lipid layer thickness; facial skin evaluation; corneal sensation. The proposed research questions are listed in Table 3A.

One focus group considered the accuracy of two Dry Eye questionnaires[12,13] frequently administered to patients in both clinical and research settings. The group discussed potential issues with the questionnaires in severe cases or occult cases when signs and symptoms do not align, and developed an associated research question (Table 3B).

Focus Group: Definition and Pathophysiology

Definition

One focus group with 7 participants discussed the definition of Dry Eye and disease pathophysiology.

First the group reviewed the DEWSII 2017 definition of Dry Eye:

> Dry eye is a multifactorial disease of the ocular surface characterized by a loss of homeostasis of the tear film, and accompanied by ocular symptoms, in which tear film instability and hyperosmolarity, ocular surface inflammation and damage, and neurosensory abnormalities play etiological roles.[14]

The group agreed that the disease is multifactorial but did not agree that a) osmolarity was specific to Dry Eye, b) patients are always symptomatic (they are often asymptomatic) and c) neurosensory abnormalities, being exceedingly rare, always play etiological roles.

Although the DEWSII Committee developed the 2017 definition of Dry Eye by consensus, the focus group believed there was a potential for bias due committee members' reported conflicts of interest[14–16] as well as the fact that patients were sparsely represented on the project overall.[16]

Pathophysiology: Inflammation

The focus group discussed the commonly aired commercials for RESTASIS 0.04%[17] which state, Dry Eye is caused by "reduced tear production due to inflammation".

The group made the following comments:

- The statement is too narrow
- Lack of redness does not mean there is no inflammation or an organic cause

Pathophysiology: Ocular Neuropathic Pain

The focus group discussed ocular neuropathic pain, called "pain without stain" because patient symptoms are not indicated by clinical signs.

The focus group made the following comments:

- Many conditions can lead to "pain without stain" including: uncorrected refracted error, sinusitis, migraine, occipital neuralgia, and diseases that are missed, misdiagnosed or incorrectly evaluated such as ATD, MGD, conjunctivochalasis, pinguecula, etc. In all cases, a specific diagnosis should be sought.
- Doctors should not be satisfied if they find a single disease and make a single diagnosis because of the high prevalence of comorbidities that lead to ocular surface pain.
- Even with an accurate diagnosis, if treatment is not targeted, patient symptoms will persist.

Pathophysiology: Models of MGD

The focus group discussed 5 models describing the proximate cause of MGD:

1. Hyperkeratinization: keratin covers the orifice and excretory duct
2. Thickened meibum: meibum does not flow out of the glands
3. Stress: leads to thickened meibum and hyperkeratinization
4. Solutes in tear film: flow onto the lid margin causing damage at the orifice that leads to inflammation
5. Periductal fibrosis: invades and disrupts the glands

The group made the following comments:

- Models 1–4, hyperkeratinization, thickened meibum, stress, and solutes lead to model 5, periductal fibrosis
  - Periductal scar tissue chokes off the duct
  - The flow of oil is blocked increasing the pressure behind the blockage leading to atrophy of the glands
  - The underlying cause of obstructive MGD is not fully realized
- Commercial interests of large entities impact the dissemination of information about the proximate cause of MGD.
- More information is needed to validate the model; use of repeatable experiments can help
- Study disease as it develops in young adults or teenagers
- Comorbidities can lead to Meibomian gland disease

Proposed research questions are detailed in Table 3C. Participants noted the importance of definitively determining the proximate cause of MGD.

Focus Group: Impact

One focus group discussed the impact Dry Eye, MGD, and related comorbidities had on patient quality-of-life (QOL). The group was presented with a list of emotions experienced and behaviors displayed by Dry Eye patients (Table 4), instructed to identify gaps in the list, and develop associated research questions (Table 3D).

The group noted that although the lists they developed were long, if given more time, they might be even longer. Regardless of length, the group agreed that the reported impact of disease on Dry Eye patients illustrates the importance of early treatment, before psychological impact becomes severe and the patient's QOL declines.

While brainstorming possible research questions, the focus group noted that many items listed merit both further discussion and dedicated research projects, such as assessing incidence and impact on QOL. Three proposed research questions are listed in Table 3D.

Focus Groups: At-Home and OTC Therapies

Three concurrent focus groups discussed at-home and OTC therapies typically used by patients with or without medical supervision.

Participants were presented with a list of at-home and OTC therapies organized by disease, and life-style changes, asked to list any additional OTC or at home treatments, and write associated research questions (Table 3E).

Following is a list of at-home and OTC therapies for various conditions (*indicates added by Focus Group):

- ATD
  - Lubricating eye drops, with preservatives
  - Lubricating eye drops, preservative-free
  - Lubricating eye drops with varying degrees of viscosity
  - Lubricating eye drops, emulsions*
  - Lubricating sprays and mists

- Lubricating gels
- Lubricating ointments
- Wrap-around glasses

- Nocturnal lagophthalmos
  - Lubricating ointments
  - Moisture-chamber goggles
  - Taping eyes closed: SleepTite/SleepRite*, amblyopia patch*, EyeLocc patch*

- MGD
  - Warm compresses
  - Lid scrubs and washes
  - Lid expression
  - Lid/lash hygiene

- Demodex Mites
  - Tea tree oil wipes: Cliradex, Blephadex, Eyeeco products*, lip balm with tea tree oil*
  - Zocular
  - OcuSOFT cleanser*

- Supportive Nutritional Therapy
  - Omega-3 fatty acids
  - Various oral supplements
  - Eliminating caffeine
  - Treating food sensitivities
  - Water and hydration
  - Limiting/eliminating alcohol*

- Allergies
  - Topical allergy drops
  - Oral allergy medications
  - Cold compresses or ice

- Life-Style Changes
  - Reduce gazing activity
  - Avoid winds and drafts
  - Avoid dry environments
  - Avoid cold
  - Avoid fumes
  - Limit exposure to allergens, toxins, and other potential irritants
  - Sleeping

- Other Therapies
  - Blinking exercises
  - Blink reminder app
  - Irrigation with sterile preservative free saline or buffered saline solution*

Focus Groups: Physician-Prescribed Treatments

Three concurrent focus groups discussed physician-prescribed treatments. Participants were presented with a list of treatments organized by disease, and life-style changes, asked to identify any gaps, and write associated research questions (Table 3F).

Following is a list of physician-prescribed therapies for various conditions (* indicates added by Focus Group):

- Allergies
  - Prescription eye drops
  - Prescription oral medications
  - Desensitization therapy
  - Irrigation with sterile preservative-free saline or buffered saline solution*
- ATD
  - Amniotic membrane transplant surgery
  - Autologous serum tears
  - Cevimeline (Evoxac®) and Pilocarpine (Salagen®)
  - Cyclosporine-based treatments: RESTASIS® 0.04%, Cequa 0.09%
  - Contact lenses that are very wet, eg, Dailies Total1 One-Day Contact Lenses (Alcon)
  - LACRISERT inserts (if aqueous tear volume is sufficient for dissolving plugs)
  - Narrowing the opening between the eye lids
  - Punctal cautery (thermal and other methods)
  - Punctal plugs
  - Scleral lenses
  - Nasal spray that triggers tear production (Tyrvaya)
  - Weights or springs in eye lids
  - Wet contact lenses
  - Lifitegrast ophthalmic solution 5% (Xiidra™)
- Blepharospasm
  - Botulinum toxin (Botox)
- Conjunctivochalasis/SLK
  - Amniotic membrane transplant (AMT)
  - Other ocular surface reconstruction methods
  - Prokera*
- Delayed Tear Clearance
  - 0.9% sterile saline wash
- Demodex
  - Ivermectin, oral
  - Ivermectin, topical
  - Exfoliation
- Infections
  - Antibiotic drops and ointments
  - Antifungal medications

- Inflammation/Inflammation Unspecified Source
  - Cyclosporine-based treatments
  - Corticosteroid drops and ointments
  - Doxycycline, minocycline
  - Lifitegrast ophthalmic solution 5% (Xiidra)

- Lateral Canthal Crowding
  (a common cluster of comorbidities that includes dermatochalasis, entropion, trichiasis, and conjunctivochalasis.)
  - Treatments as noted elsewhere

- Ocular Neuropathic Pain
  - Autologous serum tears
  - Pain medications
  - Scleral lenses
  - Gabapentin, pregabalin
  - Antidepressants

- MGD
  - Antibiotic drops and ointments
  - Azithromycin ophthalmic (Azasite)
  - Expressing Meibomian glands
  - Heat (MiBoFlo®)
  - Heat and lid massage (LipiFlow®)
  - Intraductal Meibomian gland probing (Maskin® Probing)
  - Intense Pulsed Light (IPL)
  - Lid margin debridement (manual, Blephex)
  - Lid massage
  - LLLT photobiomodulation (low level light therapy)*
  - Other devices that apply heat and massage to eyelids
  - Stem cell therapy (currently experimental)
  - Heating lids with radio frequency waves generated by electrical currents*
  - TearCare*

- Trichiasis
  - Epilation

Focus Group: Awareness and Education

One focus group considered research focused on raising awareness and educating patients, providers, and other stakeholder groups. Participants were asked to share their personal experience with patient or personnel training materials provided by treating physicians, pharmaceutical and medical device companies, government or regulatory agencies, medical-focused websites, or other sources where they have sought information on Dry Eye, MGD, or related comorbidities.

The focus group then brainstormed feasible ideas for improving awareness/education among the various stakeholder groups, and projects or research questions associated with these ideas (Table 3G).

Table 3 Research Questions on Diagnosis, Questionnaires, Definition and Pathophysiology, Impact, at-Home and Over-The-Counter (OTC) Therapies, Physician-Prescribed Treatments, and Awareness and Education

A. Diagnosis		
a	**Study Title**	How many cases of ATD are being missed when not performing serial Schirmer's tests?
	Significance	ATD is being missed when administering single Schirmer's test
	Study Type	Prospective
	Sample Size	25 or more
	Parameters	• 2 • Serial Schirmer's
	Duration	1-time evaluation
	Info Tech (IT)	Knowledge based that provides information on the components of performing the Schirmer's test
	Comments/ References	Is the test being performed properly? Administer test at different times of day to check for circadian rhythm in tear production.
b	**Study Title**	What is the incidence of conjunctivochalasis (superior and inferior) in younger populations?
	Significance	Conjunctivochalasis is known to be very common among older adults, but the incidence in younger adults and children, although believed to be low historically, may be increasing.
	Study Type	Prospective
	Sample Size	150 (50, <20 y/o; 50, 20–29 y/o; 50, >30) or more
	Parameters	Slit lamp exam, advancement of superior conjunctivochalasis, existing scale for severity of inferior conjunctivochalasis according to number of folds on lid margin
	Duration	1-time evaluation
	Info Tech (IT)	Knowledge base to optimize quality of care
	Comments/ References	Conjunctivochalasis is increasingly observed in patients in their 20s. Compare incidence with one-way analysis of variance (ANOVA).
c	**Study Title**	At what age should meibography be performed as a baseline?
	Significance	MGD often progresses occultly, without obvious signs or symptoms. Determine at what age MGD can first be clinically detected.
	Study Type	Prospective
	Sample Size	Starting at 10 y/o, every 2 years, 20 or more at each age
	Parameters	• Meibography analysis • 2–7 (note severity of symptoms)
	Duration	1-time evaluation
	Info Tech (IT)	Recommendation engine to provide information on when meibography tests need to be performed
	Comments/ References	Potential to establish meibography as part of initial eye exam in adolescents to evaluate for early onset asymptomatic MGD and to prevent progression; meibography can be done on children as young as 6 years of age if cooperative and is recommended in setting of corneal scar tissue or chronic red eyes.
d	**Study Title**	Correlation between MG probe findings and meibography findings
	Significance	Findings of fixed obstruction from periductal fibrosis may reflect gland drop-out and atrophy on meibography
	Study Type	Retrospective

(*Continued*)

Table 3 (Continued).

	Sample Size	50 or more
	Parameters	Meibography analysis and probe findings form
	Duration	No follow-up needed
	Info Tech (IT)	Causal network providing information on the MG probe findings to the findings of the meibography analysis
	Comments/ References	Gland by gland analysis
e	**Study Title**	Is Meibomian gland atrophy (as see on meibography) an early diagnostic indicator for autoimmune disease?
	Significance	Potential for early indication of subclinical autoimmune disease; initiate preventive measures or treatment of morbidity; prevent mortality.
	Study Type	Prospective
	Sample Size	100 or more
	Parameters	• Meibography analysis and probe findings form • 7
	Duration	3–5 years
	Info Tech (IT)	Causal network on meibography findings
	Comments/ References	Gland by gland analysis
f	**Study Title**	What causes a doctor to stop diagnostics before finding the root cause of a disease?
	Significance	The high incidence of misdiagnosis
	Study Type	Survey, interviews
	Sample Size	100 or more
	Parameters	Cornea/external disease ophthalmologists and optometrists whose patients were misdiagnosed
	Duration	2 years
	Info Tech (IT)	Not applicable
	Comments/ References	Identifying doctors who have misdiagnosed patients and who are also willing to participate in study may not be feasible.
g	**Study Title**	How to successfully diagnose asymptomatic ATD, MGD, and related comorbidities, and symptomatic but occult disease.
	Significance	The frequent misdiagnosis of patients leads to avoidable suffering
	Study Type	Prospective, longitudinal
	Sample Size	100 or more
	Parameters	• Compare patients who are evaluated routinely and receive maintenance treatment to those who only seek care later in life when they are symptomatic • 2–7
	Duration	10 years or more
	Info Tech (IT)	A recommendation engine leading to successful diagnosis

(*Continued*)

Table 3 (Continued).

	Comments/ References	All too often doctors miss comorbidities or misdiagnose comorbidities when patients are asymptomatic or disease is symptomatic but occult.
h	**Study Title**	Assess the accuracy of Schirmer's and other tests for aqueous tear deficiency
	Significance	Rates of missed disease and misdiagnosis may be higher than anticipated; evaluate accuracy and specificity of tests
	Study Type	Prospective
	Sample Size	50 or more
	Parameters	1–7
	Duration	1 year or more
	Info Tech (IT)	A recommendation engine leading to successful diagnosis
	Comments/ References	How accurate are Schirmer's or other tests for aqueous tear deficiency if tear production fluctuates throughout the day? If tests are not properly administered?
i	**Study Title**	Compare accuracy, repeatability, and specificity of fluorescein staining to tear osmolarity for ATD evaluation
	Significance	Quantify accuracy, specificity, and repeatability of diagnostic approaches
	Study Type	Prospective, double blind.
	Sample Size	50 participants
	Parameters	Measure ATD pre and post-treatment
	Duration	6 months
	Info Tech (IT)	Recommendation engine for ATD tests
	Comments/ References	Reduce incidence of misdiagnosis or inadequate diagnosis.
B. Questionnaires		
a	**Study Title**	With a patient-centered approach, re-assess the validity of patient questionnaires commonly used in research and clinical settings. Develop a new patient-centered questionnaire that encompasses ATD, MGD, and common comorbidities.
	Significance	Patients have different objectives than the medical industrial complex that includes pharmaceutical companies, medical device manufacturers, medical providers, insurers, and research centers.
	Study Type	Not applicable
	Sample Size	TBD
	Parameters	Experienced researchers and informed patient groups collaborate on patient-centered, comprehensive, and unbiased questionnaire.
	Duration	1–2 years
	Info Tech (IT)	Knowledge base that encompasses ATD, MGD, and common comorbidities.

(*Continued*)

Table 3 (Continued).

	Comments/ References	• Take into account different scenarios for different patient-groups and different applications, eg, clinical setting vs research setting, extremely debilitating symptoms vs manageable symptoms, recent onset vs years-long, etc. • Consider non-numerical scale eg, red/yellow/green or other, to indicate non-emergent/emergent status quickly (to indicate need for prioritized aggressive treatment) • Reflect the fluctuating nature of symptoms over time • Reflect the psycho-social impact on patient; QOL rating • Reflect the patient's physical experience; nature and severity of symptoms, and as importantly, the burden of the physical experience • Provide patients with self-assessment tool to chart symptoms continually and over time • If driving to a "single number" algorithmic result, make absolutely sure that the single number does not exclude 20% of the population which may need emergent care. • Ensure questionnaires lead physicians to accurately diagnose and prescribe targeted treatment (eg, "just because the patient is a woman, it does not mean she is wearing makeup and the treatment is to tell her to stop wearing makeup"). • Any questionnaire must accurately reflect patient status (specific diagnoses) as well assist doctors to prescribe targeted therapy rather than one-size-fits all therapy.
C. Definition and Pathophysiology		
a	**Study Title**	Establish an accurate, patient-centric definition of Dry Eye.
	Significance	The current definition of Dry Eye is imprecise and its development by DEWSII, which lacked significant patient input, may have been subject to bias. The term minimizes the actual patient experience, consequently patients are taken less seriously by their doctors and also their families and friends.
	Study Type	Not applicable
	Sample Size	Not applicable
	Parameters	Not applicable
	Duration	Not applicable
	Info Tech (IT)	Not applicable
	Comments/ References	Consider term for advanced Dry Eye that impacts quality of life significantly versus "Dry Eye that can be simply managed with drops".
b	**Study Title**	How does saponification occur?
	Significance	Can cause severe symptoms and chronic discomfort
	Study Type	Prospective
	Sample Size	50 or more
	Parameters	Analyze patient's tear chemistry and the interlinked components leading to saponification.
	Duration	6 months – 1 year
	Info Tech (IT)	Knowledge base on the causes that lead to saponification
	Comments/ References	Identify tear chemistry issues: oils, electrolytes, etc. With disease, tears have an imbalance of "ingredients" and altered chemistry. Quantify the imbalance. Conjunctivochalasis may misdirect tears and inefficiently lubricate the surface of the eye.
c	**Study Title**	Explore the role of LASIK surgery in Dry Eye and ocular surface disease
	Significance	Reveal the causal link between LASIK surgery and Dry Eye, Dry Eye related comorbidities.
	Study Type	Prospective

(*Continued*)

Table 3 (Continued).

	Sample Size	100 or more
	Parameters	Comprehensive pre-surgery evaluation; number of patients complaining of Dry Eye or worsening symptoms after corneal surgery. Two groups: treated prior to surgery, not treated prior to surgery.
	Duration	6 months – 1 year
	Info Tech (IT)	Recommendation engine on LASIK surgery for persons suffering from Dry Eye and ocular surface disease
	Comments/ References	Many patients complain of Dry Eye symptoms after corneal surgeries including LASIK. (More prevalent as more patients opt to be free of eyeglasses and contact lenses). What percentages of LASIK patients have Dry Eye? Raw data required for comparison. Identifying variables which would be confounding "causality".
D. Impact		
a	**Study Title**	Compare Dry Eye patients who go through treatment with psychological support of a group of peers, patients who receive professional counseling, and patients who have no psychological support.
	Significance	Addressing psychological impact could reduce trauma of Dry Eye on patients.
	Study Type	Prospective
	Sample Size	25 or more for each group
	Parameters	• Patient symptoms and level of pain • Psychological counseling and support
	Duration	6 months – 1 year
	Info Tech (IT)	A recommendation engine that provides answers to key questions on Dry Eye to relieve the patient from anxiety associated with the disease
	Comments/ References	It has been observed and reported anecdotally that the trauma of living with severe Dry Eye that leads to suicidal ideation and attempted suicide can cause PTSD-like symptoms; impact on QOL can be significant causing psychological distress; patients with severe symptoms may be unable to function and may withdraw from everyday life
b	**Study Title**	Are primary care physicians (PCP) who receive Dry Eye training better able to assist patients with Dry Eye disease management, speed and accuracy of diagnosis, management of symptoms, and psychological support than their peers who do not receive training?
	Significance	PCP is a patient's first line of defense. An informed PCP may be more likely to refer patients to doctors able to accurately diagnose Dry Eye and comorbidities, and prescribe targeted and effective treatments, thus preventing the onset of severe psychological distress. Alternatively, if PCP is aware of the potential for psychological distress among Dry Eye patients, could refer patients to support groups or professional counseling that could ease or prevent severe psychological distress.
	Study Type	Prospective
	Sample Size	25 or more for each group (with and without PCP who received DED training)
	Parameters	PCP with patients 1–7
	Duration	6 months – 1 year, plus physician training
	Info Tech (IT)	Not Applicable
	Comments/ References	Recruiting PCP physicians may be a challenge
c	**Study Title**	How does Dry Eye impact a patient's daily life (QOL) and mental health
	Significance	Many Dry Eye patients have a reduced QOL; lack of community support due to lack of awareness of impact on patients

(*Continued*)

Table 3 (Continued).

	Study Type	Prospective, survey, interview
	Sample Size	100 or more
	Parameters	• 1–7 • Offer support group with every exam of symptomatic patients • Survey patients on mental health at initial exam and each follow/up
	Duration	2–5 years
	Info Tech (IT)	Knowledge base on the subject matter
	Comments/ References	High incidence of suicidal patients; patients often report decline in mental health and QOL.
d	**Study Title**	Primary: establish incidence/prevalence of suicidal ideation among patients with Dry Eye, MGD, and related comorbidities. Secondary: evaluate directionality between suicidal ideation and disease.
	Significance	Patients with unresolved symptoms of Dry Eye, MGD, and comorbidities, may experience suicidal ideation indicting urgent/emergent need for effective, targeted treatment to rapidly reduce symptoms.
	Study Type	Prospective
	Sample Size	100 or more
	Parameters	• 1–7 • Severity and duration of symptoms; number and type of treatments administered • Frequency/duration of suicidal ideation
	Duration	2–5 years
	Info Tech (IT)	Knowledge base on suicidal ideation among Dry Eye patients
	Comments/ References	High incidence of suicidal patients; patients often report decline in mental health and QOL.
E. At-Home and Over-The-Counter (OTC) Therapies		
Lubricating Eye Drops		
a	**Study Title**	Why are some patients unsuccessful using eye drops and require additional intervention?
	Significance	Severe cases of Dry Eye are rarely resolved with OTC eye drops. Some patients may be more sensitive to drops. Specific diagnoses are often missed
	Study Type	Prospective
	Sample Size	50 or more
	Parameters	• Degree of symptoms • Compare efficacy of drops with various active ingredients (eg, hyaluronic acid) • 1–7
	Duration	1–2 year
	Info Tech (IT)	Knowledge base on eye drop therapy; recommendation engine for treatment
	Comments/ References	Pharmaceutical companies are promoting eye drop use. Patients are sometimes directed to use eye drops every hour. This remedy only worsens symptoms in the long run. Doctors rarely assess MGs properly and recommend drops as a "band-aid". Initial eye exam needs to be more comprehensive before recommending eye drops.

(*Continued*)

Table 3 (Continued).

Warm Compress		
b	**Study Title**	Comparing effectiveness of warm compresses to facial steamers/humidifiers
	Significance	Patients are often told to use warm compresses. However, they may have a better experience using facial steamers/humidifiers for relief.
	Study Type	Prospective
	Sample Size	50 or more: 50% use warm compress, 50% use facial steamer daily
	Parameters	• Compare degree of symptoms; length of relief • 1–7
	Duration	3, 6, 9 and 12 month follow ups
	Info Tech (IT)	Recommendation engine for treatment
	Comments/ References	Are facial steamers more effective at bringing relief than warm compresses? Is the expense justified?
Moisture Chamber Goggles		
c	**Study Title**	How well do moisture-chamber goggles improve a patient's symptoms?
	Significance	Some patients suffer from nocturnal lagophthalmos (sleeping with their lids not completely closed)
	Study Type	Prospective
	Sample Size	25 or more
	Parameters	• Degree of symptoms • Duration of relief • 2–6
	Duration	6 months
	Info Tech (IT)	Recommendation engine for treatment
	Comments/ References	Justify the expense and use of moisture chamber goggles when sleeping
Lid/Lash Hygiene		
d	**Study Title**	Are there safe ways to wear eye makeup without worsening Dry Eye symptoms?
	Significance	Use of eye makeup can improve a patient's QOL. Wearing makeup may be feasible for patients with proper cleansing; with safe, non-irritating ingredients.
	Study Type	Prospective
	Sample Size	50 or more
	Parameters	• 1–7 • Degree of symptoms of patients who do and do not wear makeup daily; compare the ingredients of the makeup being worn; compare placement of makeup; compare cleansing routines.
	Duration	6 months
	Info Tech (IT)	Knowledge base on causality between eye makeup and Dry Eye, MGD, and comorbidities; evidence-based recommendations for using makeup
	Comments/ References	Doctors often tell patients that they cannot wear any sort of eye makeup, but do hypoallergenic products, organic products pose less of a risk?

(*Continued*)

Table 3 (Continued).

e	**Study Title**	Comparative study of cleanser used in lid hygiene. Which product is the most effective for eliminating all lash debris/discharge and lid margin biofilm without excessive desiccation of the lid margin?
	Significance	Important to find pathway for therapeutic treatment that is not toxic; this study would find that "sweet spot"
	Study Type	Prospective
	Sample Size	50 or more
	Parameters	• Color photography of the lid margin and lashes; evaluate resilience of demodex and bacteria thru culture of lid margins and examination for mites; meibography to look for impact on Meibomian glands, eg, excessively dry lid margins • 2, 5, 6
	Duration	3 months (to be able to track change with meibography)
	Info Tech (IT)	Recommendation engine for lid hygiene
	Comments/ References	Many Dry Eye patients over-use lid cleansers and scrubs to their own detriment. Ingredients in products, including seemingly safe products that are preservative-free or organic, can penetrate into the stem cells at the lid margin. This study would provide patients with evidence-based advice about products and frequency of use.
Topical Allergy Drops		
f	**Study Title**	Efficacy of topical allergy drops versus lubricant drops or sterile saline in patients with itchy and burning eyes who test negative for allergens
	Significance	Reduce cost; reduce toxicity
	Study Type	Prospective
	Sample Size	75 or more (25 or more in each group)
	Parameters	1–7
	Duration	1 month or more
	Info Tech (IT)	Knowledge base on effects of allergy and other drops; recommendation engine for treatment
	Comments/ References	Support patient self-care
g	**Study Title**	Determining if patients who test negative and have itchy and burning eyes may still benefit from topical or systemic allergy treatments.
	Significance	Allergy tests are often used to determine pathways of treatment but the tests are not necessarily comprehensive; would highlight an overlooked therapy that may prove to be effective
	Study Type	Prospective
	Sample Size	50 or more (25 or more in each group)
	Parameters	1–7
	Duration	1 month
	Info Tech (IT)	Knowledge base on effects of allergy treatments; recommendation engine for treatment
	Comments/ References	Because testing of allergens is limited in scope (not all allergens are tested), doctors may rule out treatment for allergies to the detriment of patients.

(*Continued*)

Table 3 (Continued).

Supportive Nutritional Therapy		
h	**Study Title**	Compare the effectiveness of omega-3 fatty acid supplements, eg, fish oils vs flax seed oils, for improving Dry Eye symptoms.
	Significance	Patients are often bewildered by the best and most effective way to supplement with omega-3 fatty acids.
	Study Type	Prospective
	Sample Size	50 or more (25 or more in each group)
	Parameters	1–7
	Duration	1–2 months
	Info Tech (IT)	Knowledge base capturing the results of the study; recommendation engine for treatment
	Comments/ References	Many options available
i	**Study Title**	Effect of alcohol on tear film and Dry Eye; dose-specific
	Significance	Alcohol is commonly consumed
	Study Type	Controlled study
	Sample Size	25 or more in each group
	Parameters	1–7
	Duration	1–2 months
	Info Tech (IT)	Recommendation engine to provide recommendation on alcohol use for patients with Dry Eye and MGD
	Comments/ References	Test after the participant has had alcohol; control could be the patient themselves, consuming and not consuming alcohol.
j	**Study Title**	Impact of identifying and eliminating food sensitivities on Dry Eye parameters
	Significance	Food sensitivities are thought to have an effect on ocular surface health
	Study Type	Prospective
	Sample Size	50 or more
	Parameters	1–7
	Duration	6 weeks or more
	Info Tech (IT)	Knowledge base containing the results of the study; recommendation engine for treatment
	Comments/ References	• Would require compliant patients; would be guided by the test results rather than eliminating a set grouping of foods. • Comparative component: once patient has identified sensitivity, compare patient's treatment outcomes when they are consuming the food versus when they are not consuming the food. • Must be controlled for other comorbidities and co-factors, like climate, time of year.
Night Time Treatments		
k	**Study Title**	Compare effectiveness of night-time treatments
	Significance	Not all night-time treatments have the same effectiveness for all patients
	Study Type	Controlled study
	Sample Size	25 or more in each group

(*Continued*)

Table 3 (Continued).

	Parameters	1–7
	Duration	1 month or more
	Info Tech (IT)	Recommendation engine for treatment
	Comments/ References	Use of different tools at night time, patient could be control, placebo group does nothing at night
Blinking Exercises		
l	**Study Title**	How effective are blinking exercises in changing a partial blink to a complete blink?
	Significance	Determine if blinking exercises transform into a more effective blink habit
	Study Type	Prospective, controlled study
	Sample Size	25 or more in each group
	Parameters	LipiView blink assessment
	Duration	6 weeks
	Info Tech (IT)	Recommendation engine for blinking exercises
	Comments/ References	• Quality of blink is an important and often overlooked problem for Dry Eye patients. Incomplete blinks may be due to a variety of factors such as cosmetic surgery, reduced corneal sensitivity, and Parkinson's disease; often occur during gazing activities; present but without a primary cause. Converting partial blink to complete blink would have a significant and positive impact. • Compare 3 groups: 1st group has partial blinks and does not receive blink training; 2nd group has partial blinks and receives blink training; 3rd group has a healthy complete blink. Compare results of all three groups.
F. Physician-Prescribed Treatments		
ATD		
a	**Study Title**	Compare benefits/efficacy of punctal plugs vs punctal cautery
	Significance	Patients are not often aware of the difference between these therapies
	Study Type	Prospective
	Sample Size	50 or more
	Parameters	• ATD • 2–4
	Duration	3–6 months using temporary plugs or cautery
	Info Tech (IT)	Knowledge base on the results of the study; recommendation engine for treatment
	Comments/ References	Permanent plugs can become an irritant to the surface of the eye and harbor bacteria on the plug itself. Do plugs achieve a complete closure?
b	**Study Title**	Comparative analysis of treatments for the remediation of ATD
	Significance	ATD contributes to patient symptoms significantly. While patients need rapid relief of symptoms, they are often prescribed therapy, eg, RESTASIS, which does not offer rapid relief of symptoms and for which there is limited independent patient-centered research on its effectiveness. The result is prolonged patient suffering while disease advances.
	Study Type	Prospective, randomized, controlled, blinded
	Sample Size	50 or more

(*Continued*)

Table 3 (Continued).

	Parameters	1–7
	Duration	1 week; 1 month; 3 months; 6 months; 1 year if possible
	Info Tech (IT)	Knowledge base containing the results of the study; recommendation engine for treatment
	Comments/ References	Rapid reduction of symptoms is often patient's primary goal.
c	**Study Title**	Comparative analysis of punctal cautery methods: superior punctum vs inferior punctum, partial superficial vs total deep cautery.
	Significance	ATD contributes to patient symptoms significantly. Punctal cautery is a simple and effective in-office procedure that gives rapid relief of symptoms. Studies have not compared these methods.
	Study Type	Prospective, randomized, controlled, blinded
	Sample Size	50 or more
	Parameters	1–7
	Duration	1 week; 1 month; 3 months; 6 months; 1 year
	Info Tech (IT)	Knowledge base containing the results of the study; recommendation engine for treatment
	Comments/ References	Rapid reduction of symptoms is often patient's primary goal.
Inflammation		
d	**Study Title**	Do RESTASIS and Xiidra effectively treat Dry Eye? Specifically, which underlying conditions do these medications treat?
	Significance	Reported efficacy rates for the two topical treatments are relatively low, but they are widely prescribed. Determine which specific comorbidities each treatment targets; determine which treatment shows most efficacy.
	Study Type	Prospective, double blind
	Sample Size	75 or more: 25 or more use RESTASIS, 25 or more use Xiidra, and 25 or more control (placebo)
	Parameters	1–7
	Duration	1 year
	Info Tech (IT)	Recommendation engine for treatment
	Comments/ References	These treatments often cause burning pain. However, patients may experience improved tolerance with extended use. Although patients are desperate for relief, treatment may need to last as long as 3–6 months before it takes effect. Patients may spend this time in pain, yet hopeful for relief, only to be disappointed if treatment is ineffective. Effective treatments are delayed for many months, prolonging patient suffering while untreated disease advances and symptoms worsen.
MGD		
e	**Study Title**	Compare MGD treatments (Probing, Radio Frequency (RF) Therapy, Intense Pulsed Light (IPL) Therapy, and combination of two or all three).
	Significance	Identify the most effective treatment of MGD
	Study Type	Prospective, double blind with sham treatments
	Sample Size	75 or more (25 or more in each group)
	Parameters	1–7

(*Continued*)

Table 3 (Continued).

	Duration	1 year
	Info Tech (IT)	Knowledge base on MGD treatments; recommendation engine for treatment
	Comments/ References	To evaluate whether these treatments would work best when combined or alone. Based on the patient's self-evaluation before and after treatment.
f	**Study Title**	Effectiveness of LipiFlow after Meibomian gland probing in the treatment of MGD
	Significance	Can LipiFlow be a helpful maintenance tool after MG probing?
	Study Type	Prospective
	Sample Size	50 or more
	Parameters	• Compare patients with and without LipiFlow after probing; lipid layer; MG gland expression • 1–7
	Duration	1 year
	Info Tech (IT)	Knowledge base encompassing the results of the study; recommendation engine for treatment
	Comments/ References	To evaluate if Lipiflow is an effective maintenance treatment after MG probing. Based on the patient's self-evaluation before and after treatment.
g	**Study Title**	Compare the efficacy of Cequa vs Xiidra for the treatment of MGD
	Significance	Compare the long term-effects of each treatment
	Study Type	Prospective
	Sample Size	50 or more (25 or more in each group)
	Parameters	1–7
	Duration	6 months
	Info Tech (IT)	Knowledge base encompassing the results of the study; recommendation engine for treatment
	Comments/ References	Determine which treatment offers patients more comfort; some patients experience burning with Xiidra.
h	**Study Title**	Compare the post-probing efficacy of adjunctive lavage therapies on Meibomian glands for maintaining patency and/or promoting growth of gland tissue: compare effectiveness of autologous serum drops, platelet-rich plasma (PRP) drops, cord blood serum drops, corticosteroid, or other therapies to each other and placebo
	Significance	• Meibomian gland retention and patency • 1–7
	Study Type	Prospective
	Sample Size	125 or more; 25 or more control, 25 or more in each adjunctive treatment group
	Parameters	• Lipid layer thickness, TBUT, meibography • Confocal microscopy • 1–7
	Duration	1–1.5+ years or more
	Info Tech (IT)	Knowledge base encompassing the results of the study: recommendation engine for treatment
	Comments/ References	MG probing establishes and maintains patency, promotes gland growth

(*Continued*)

Table 3 (Continued).

i	**Study Title**	Compare effectiveness of therapy targeting the proximate cause of obstructive MGD, namely periductal fibrosis: intraductal Meibomian gland probing, IPL, LipiFlow, etc.
	Significance	Assess effectiveness of therapy to reduce patient suffering
	Study Type	Prospective, randomized control; blinded
	Sample Size	75 or more: 25 or more in each treatment group
	Parameters	• Presence and location of periductal fibrosis assessed with post-treatment intraductal Meibomian gland probing • 1–7
	Duration	1 week, 1 month, 3 months, 6 months, 1 year
	Info Tech (IT)	Knowledge base encompassing the results of the study; recommendation engine for treatment
	Comments/ References	Obstructive MGD accounts for over 85% of cases with ocular irritation and discomfort. Assess effectiveness of therapies with post-treatment diagnostic probing of glands to evaluate for presence and location (proximal, distal) of periductal fibrosis.
j	**Study Title**	Compare effectiveness of Meibomian gland probing methods: depth of probing (length of probe used), diameter of probe, frequency of treatment.
	Significance	Assess effectiveness of probing methods in reducing patient symptoms and signs of disease
	Study Type	Prospective, randomized control; blinded
	Sample Size	75 or more: 25 or more in each treatment group
	Parameters	• Presence and location of periductal fibrosis assessed with post-treatment intraductal Meibomian gland probing • 1–7
	Duration	1 week, 1 month, 3 months, 6 months, 9 months, 1 year; for 3 consecutive years or more.
	Info Tech (IT)	Knowledge base encompassing the results of the study; recommendation engine for treatment
	Comments/ References	Obstructive MGD accounts for over 85% of cases with ocular irritation and discomfort.
G. Awareness and Education		
a	**Study Title**	Evaluate the accessibility of educational materials on Dry Eye
	Significance	How common is it for doctors to have Dry Eye educational materials available for their patients and staffs. Are available materials accurate and patient-focused or industry-focused?
	Study Type	Market survey, interviews
	Sample Size	100 or more
	Parameters	Ophthalmology and optometry practices: sole provider, group practice, institutional settings
	Duration	< One year
	Info Tech (IT)	Knowledge base encompassing the results of the study
	Comments/ References	Step 1: Is material available? What is the prevalence? Step 2: What is the quality of the materials? Is it evidence-based, industry-focused, other?
b	**Study Title**	Evaluate the need for community awareness training in Dry Eye, MGD, and related ocular surface comorbidities
	Significance	Quantify the level of awareness of Dry Eye to justify the funding for educational tools
	Study Type	Survey, interviews

(*Continued*)

Table 3 (Continued).

	Sample Size	100 or more
	Parameters	Different age groups
	Duration	1 year
	Info Tech (IT)	Knowledge base encompassing the results of the study
	Comments/ References	Identify information deserts so that these areas of need can be targeted appropriately
c	**Study Title**	Conduct cost-effectiveness analysis of various diagnostic and treatment approaches and payment models to evaluate financial burden and/or benefit to patients, providers, and payers.
	Significance	Ensure patients receive quality care that is beneficial to them while ensuring providers are adequately compensated for the care they provide.
	Study Type	Cost-effectiveness, retrospective
	Sample Size	As available
	Parameters	Medical records, claims data
	Duration	5–10 years retrospective
	Info Tech (IT)	Knowledge base encompassing the results of the study, with clear and comprehensive cost/benefit analysis.
	Comments/ References	Address financial burden on patients
Rename the Term Dry Eye		
d	**Study Title**	Rename the term Dry Eye to better communicate the significance and complexity of disease
	Significance	The term Dry Eye connotes a mild, easily treatable condition when in fact, patients can experience severe and extremely debilitating symptoms.
	Study Type	Prospective, survey, interview
	Sample Size	100 patients, 100 ophthalmologists/optometrists
	Parameters	Survey patients and ophthalmologists/optometrists to determine how they identify their DED experience with current and alternative definitions; determine the preferred representative definition.
	Duration	6 months (or acquisition of adequate responses)
	Info Tech (IT)	Not Applicable
	Comments/ References	The term *ocular surface disease* may be too general, but is more representative of a patient's suffering.
e	**Study Title**	Evaluate the effect of rebranding the general term Dry Eye with more specific terms that describe specific modalities. Is perceived importance of disease increased? Is focus on disease increased?
	Significance	Raising awareness of disease and the risk it poses to the general public; increase insurance coverage and funding for diagnosis and treatment
	Study Type	Survey, interview
	Sample Size	50 or more
	Parameters	Survey patients, non-patients, ophthalmologists/optometrists and others involved in patient care, eg, caregivers, PCP
	Duration	6 months

(*Continued*)

Table 3 (Continued).

	Info Tech (IT)	Knowledge base encompassing the results of the study
	Comments/ References	Too often symptoms/disease are minimized
Awareness of Comorbidities		
f	**Study Title**	Raising physician awareness of the many treatments that can contribute to Dry Eye and related comorbidities.
	Significance	Many patients are prescribed systemic medications that can contribute to or worsen ATD, MGD, and related comorbidities, but doctors are not always aware of these side effects.
	Study Type	Prospective, survey
	Sample Size	TBD, based on number of specialties and subspecialties targeted
	Parameters	PCP, various specialties and subspecialties including dermatology, psychology, etc.
	Duration	6 months
	Info Tech (IT)	Recommendation engine to increase physician awareness
	Comments/ References	• Treatments that can contribute to Dry Eye, MGD, and related comorbidities: oral antihistamines, aspirin, ibuprofen, medications for depression and anxiety, hormonal medications, pain medications, gabapentin, Accutane (used to shrink sebaceous glands on the face in acne patients, also shrinks Meibomian glands). • Patients need to receive a screening that reviews a thorough list of current medications. • Physicians need to understand how these treatments may play a role in Dry Eye, MGD, and comorbidities. Inform PCPs and dermatologists in addition to optometrist/ophthalmologist
g	**Study Title**	Raise awareness among doctors that unidentifiable eye irritation is often due to missed diagnosis of occult disease, misdiagnosis and/or inadequate or untargeted treatment; establish incidence/prevalence of true ocular neuropathic pain
	Significance	The diagnosis ocular neuropathic pain is incorrect because eye irritation is more often real, due to identifiable causes
	Study Type	Prospective, survey
	Sample Size	50
	Parameters	Ophthalmologists and optometrists
	Duration	1 year
	Info Tech (IT)	Recommendation engine to increase physician awareness
	Comments/ References	Goal is accurate diagnosis of specific comorbidities

Abbreviations: MGD, Meibomian gland dysfunction; MG, Meibomian gland; HRT; hormone replacement therapy; ATD, aqueous tear deficiency; QOL, quality of life; TBUT, tear break-up time; FCT, fluorescein clearance test; DED, dry eye disorder; RF, radio frequency; IPL, intense pulsed light.

Discussion

Dry Eye/MGD patients, caregivers, patient advocates, clinicians managing Dry Eye and MGD cases, researchers, and other stakeholders convened to identify gaps in Dry Eye and MGD research. One prior study prioritizing aspects of Dry Eye research had almost no patient representation.[4] A second study solicited patient input,[5] but only from a list of priorities previously generated by clinicians.[6] In contrast, this convening incorporated the patient perspective from its inception through the preparation of this manuscript. We considered gaps in Dry Eye and MGD research and propose here research questions to fill those gaps. This extensive list of research questions can serve as a guide, or roadmap, for researchers considering the current status of Dry Eye and MGD care. Our overarching goal is to motivate independent researchers to undertake studies that incorporate Dry Eye and MGD patient-centered outcomes.

Table 4 Impact

List of Emotions and/or Behaviors Presented to Patients	List of Additional Emotions and/or Behaviors Listed by Patients
• Anger • Anxiety • Avoiding light • Depression • Desperation • Disappointment • Fear of being in public because eyes look bad • Fear of getting a haircut • Fear/terror • Frequent cold compresses • Frequent use of eye drops • Frequent warm compresses • Frustration • Hopelessness • Keeping eyes closed • Loss of social contacts and friends • Panic, panic attacks • Post-traumatic stress disorder (PTSD) • Seeing many eye doctors • Skepticism, thinking no one can help • Staying indoors during the day • Thinking about enucleation (removing eyes) • Thoughts of suicide to end pain • Thoughts of suicide to end emotional distress • Unable to drive • Unable to read • Unable to scan grocery and other store shelves • Unable to use a computer • Unable to work • Withdrawal from normal daily activities	• Avoidance of situations that might involve exposure to particulate matter or fumes • Being dismissed by doctors; being invalidated by doctors, then family members siding with these doctors • Delaying non-Dry Eye-related time sensitive medical decisions and maintenance (eg, pregnancy, mammogram, dental visits) • Doubting self • Dread of waking up in the morning • Experiencing being victim of sexism and ageism in medicine; being made to feel it's your fault, eg, "it's your makeup", even when female patient does not wear makeup • Existential fear of the future • Fatigue, emotional and physical • Fear of blindness • Fear of crying • Fear of forced air and fans • Fear of regression into severe symptoms • Fear of someone breathing in your face • Fear that treatments may make eyes irreversibly worse • Fear that treatment that was administered is not going to work; fear of regression • Fear of what's going to happen when treating physician retires; fear of needing to finding a new doctor • Feeling of abandonment by medical system and doctors • Feelings of loss of control over healthcare choices • Financial struggles; fear of insurance companies refusing to cover treatments • Frustrations • Hesitancy to hug and have close physical contact with people • Hyper-observant of other people's eyes; envy and insecurity over bright white eyes; spotting people with Dry Eye symptoms/signs • Increased attention to/concern over shampoos, cosmetics, skincare • Increased stress that can lead to more issues with health (seeing a chiropractor for neck and back pain; teeth grinding) • Limiting duration of time spent in forced air environments, eg, museums, grocery stores, sports games, movie theaters. • Limiting the possibilities of work • Mistrusting doctors • Poor sleep • Strain on personal relationships • Struggle to communicate severity of symptoms and what patient has gone through–emotionally and physically • Taking on emotional/time burden of becoming a sounding board for friends and family with eye struggles; re-traumatizing • Wariness of misdiagnosis; dealing with expense and lingering trauma of misdiagnosis • Wearing sunglasses (or glasses with wide sides) in unusual situations/all the time; concern over looking strange • Yawning

Over the course of two days, 16 participants, including 7 patients, 5 patient advocates, and 3 caregivers (some participants belonged to more than one group, eg, patient and patient advocate) identified gaps in research and produced ideas for research questions important to Dry Eye patients and stakeholder groups. During the convening held via Zoom, participants were assigned to focus groups that considered one of the following topics: comorbidities, factors contributing to disease and/or symptoms, diagnosis, patient questionnaires, disease definition and pathophysiology, physical and

psycho-social impact of disease on patients, training/education, OTC and at-home treatments, and physician-prescribed treatments. Each group discussed the current state of research on that topic and potential research questions. One member of each focus group served as a scribe and another as a group leader and time keeper. Scribes shared their screens while taking notes in Microsoft Word, and notes were saved to a secure Google drive.

In total, the focus groups produced over 80 research questions that were compiled into a list, or proposed research roadmap (Table 2 and Table 3). The expansive roadmap illustrates the many gaps in current research and offers a rich source of potential topics for future research important to improvement in patient care. The focus groups found that commonly used questionnaires did not appear to reliably identify patients with severe symptoms and did not capture the episodic nature of symptoms.[12,13] One participant noted that even less-than-severe symptoms that last for a long time can be extremely debilitating, potentially leading to suicidal ideation, but the questionnaires do not provide a mechanism for the collection of information about this type of physical distress. Furthermore, because the questionnaires are often used in research studies, the groups expressed concern that countless Dry Eye and MGD-related studies may be flawed because they drew conclusions based on data collected from flawed questionnaires.

One focus group considered the definition of Dry Eye as proposed by the Tear Film and Ocular Surface society in its Dry Eye Workshop II (DEWS II) report:[14]

> Dry eye is a multifactorial disease of the ocular surface characterized by a loss of homeostasis of the tear film, and accompanied by ocular symptoms, in which tear film instability and hyperosmolarity, ocular surface inflammation and damage, and neurosensory abnormalities play etiological roles.

Although participants generally agreed that Dry Eye is multifactorial, they noted that hyperosmolarity is non-specific, and that patients may be asymptomatic. They recommended further work on the definition while also disagreeing with the focus on neurosensory abnormalities, noting that severe symptoms are to be expected in highly innervated and chronically irritated tissues.

Research questions for comorbidities, symptoms, and other factors contributing to Dry Eye and MGD, focused on allergies, ATD, blepharitis, and conjunctivochalasis individually as well as their comorbid effect on disease status. One focus group proposed a study to standardize ocular surface examinations so all comorbidities, including conjunctivochalasis, are evaluated and correctly diagnosed noting too often patients are not properly evaluated for many comorbidities, leading to diagnoses of ocular neuropathic pain. Other research question topics ranged from the roles of screen time and genetics to diet and inflammation on disease pathophysiology.

While brainstorming research questions about symptoms, participants noted the episodic nature of symptoms. Proposed research questions focused on the meaning of specific symptoms (which specific disease a symptom indicates), the incidence of common symptoms, and the value of identifying a specific underlying cause of pain and treating the underlying cause of the symptom versus treatment that focuses only on pain regardless of cause.

Regarding factors contributing to disease, screen time among adults and children, was a common theme. Additionally, participants suggested conducting research on factors that patients can control themselves, like diet, screen time, and nutritional supplements, versus genetics and aging, or previous exposure to toxins or particulate matter, which are not controllable by the patients.

In addition to research on questionnaires, on the topic of diagnosis, participants suggested research questions about the Schirmer's test and other tests for ATD, meibography, and Meibomian gland probing as a diagnostic approach in addition to treatment of MGD. Participants suggested a study to determine why doctors do not look for root causes of disease and a related study regarding the best approach to diagnosing asymptomatic or occult disease.

On the topic of impact on patients and their loved ones, research questions focused on the psycho-social aspects of disease. One focus group proposed a primary study to determine the incidence and prevalence of suicidal ideation among patients with Dry Eye with a secondary study evaluating directionality between suicidal ideation and disease. A second focus group suggested evaluating the association of patient outcomes with participation in peer support groups, professional counseling, and with psychological support as a control.

Over-the-counter or at home treatments topics focused on efficacy and included lubricating drops, warm compresses, moisture chamber goggles, lid and lash hygiene, topical allergy drops, supportive nutritional therapy, alcohol and coffee

consumption, night-time treatments, and blinking exercises. Similarly, physician-prescribed treatment topics focused on efficacy of punctal plugs, punctal cautery, topical anti-inflammatory drops, a range of treatments for MGD, and several studies to evaluate Meibomian gland probing methods.

One focus group proposed research studies for raising awareness of disease and improving patient and physician education. The group suggested a study to evaluate cost-effectiveness of treatments and various payment models to improve access to care as well as a study to determine if primary care physician awareness of Dry Eye and MGD causes and treatments can improve patient outcomes.

There was general consensus among all participants that the term Dry Eye is wholly inadequate in describing a disease that can have devastating impacts. To illustrate the potential magnitude of the impact of Dry Eye, MGD, and comorbidities, patients expanded on a list 30 emotions or behaviors displayed by Dry Eye patients bringing the total to 64. The patients noted that had they had more than the one-hour allotted time to expand on the list, it would have become even longer. We present the list here to underscore the importance of the research topics suggested by participants (Table 4. Impact).

Overwhelmingly, stakeholders attending the convening and those who served as non-attendee reviewers expressed strong support for the project in post-convening surveys. Of particular note was a comment about increased awareness of the impact disease may have on patients, particularly in severe symptomatic cases.

This study has several limitations. Although participants were instructed to consider research gaps, the views are limited to those individuals participating in the convening rather than a larger group if the project had been conducted as a survey. More participants may have emphasized different research gaps and proposed different studies to address those gaps. However, research questions proposed by participants were not ranked or prioritized to minimize the potential for bias. Moreover, only 1.5 hours was allotted for each focus group session. More allotted time may have yielded additional questions.

Finally, because patient questionnaires underpin clinical and research activities and this convening revealed the potential inadequacies of two commonly used questionnaires, development of reliable and meaningful Dry Eye and MGD symptom and severity questionnaires may rise in priority.

Conclusion

Over the course of two days, Dry Eye and MGD patients, clinicians and others representing various stakeholder groups met virtually via Zoom to assess gaps in Dry Eye and MGD research and develop a list of research questions to fill those gaps with the aim of improving the care Dry Eye and MGD patients receive. Participants received training in Dry Eye and MGD prior to the meeting in the form of a guidebook[11] that included information about Dry Eye, MGD, and related comorbidities and questions designed to help participants recall their experiences via reflection, individual brainstorming, or other grounding methods. The participants also reviewed four PCORI on-line modules[7–10] about research methods and the benefits of conducting clinical comparative effectiveness research that includes patient-centered outcomes. During the meeting, participants were divided into smaller focus groups where they discussed topics and brainstormed research questions. The research questions were recorded and compiled into a research roadmap (Table 2 and Table 3) that can serve as a source of inspiration to independent researchers interested in conducting research in Dry Eye, MGD, and related topics. Participants identified over 80 research questions and noted that incorporating a better understanding of the patient experience with disease and developing less biased and more accurate questionnaires or other symptom and status assessment tools may rise in priority as these provide the raw data that underpins the clinician's practice and drives the Dry Eye and MGD industry and research.

Ethics Approval and Informed Consent

This research has received a "Not Human Research Determination" from the Institutional Review Board at the University of Central Florida.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Disclosure

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