Foreword: Biomarkers and Surrogate Endpoints in Ophthalmic Clinical Research

This special issue collects original research, reviews, scientific, and regulatory perspectives focusing on biomarkers and surrogate endpoints in ophthalmic clinical research.

Biomarkers and surrogate endpoints provide an essential set of tools needed to translate scientific concepts into diagnostic and therapeutic approaches and technologies. These tools have significant potential for accelerating basic science, drug discovery, medical product development, and for improving clinical care.[1]

The first essential effort to improve the use of biomarkers and surrogate endpoints should aim to get effective and unambiguous communication. For this reason, since 2015 the FDA-NIH Joint Leadership Council developed the BEST (Biomarkers, EndpointS, and other Tools) glossary.[2]

In order to improve communication and understanding of the conceptual framework, we felt that it would be important to share with the readership of this special issue some contents of the BEST Resource.

The currently accepted definition of the term *biomarker* is "a defined characteristic that is measured as an indicator of normal biological processes, pathogenic processes, or responses to an exposure or intervention, including therapeutic interventions. [...] A biomarker is not an assessment of how an individual feels, functions, or survives."[2] Categories of biomarkers are summarized in the Table.

Another central concept is the endpoints' surrogacy. A surrogate endpoint is defined as "an endpoint that is used in clinical trials as a substitute for a direct measure of how a patient feels, functions, or survives. A surrogate endpoint does not measure the clinical benefit of primary interest in and of itself, but rather is expected to predict that clinical benefit or harm based on epidemiologic, therapeutic, pathophysiologic, or other scientific evidence."[2]

Correlation with the clinical endpoint is a necessary but not sufficient condition for surrogacy. A validated surrogate endpoint must be "supported by a clear mechanistic rationale and clinical data providing strong evidence that an effect on the surrogate endpoint predicts a clinical benefit."[2]

As elegantly theorized in 1996 by Fleming and DeMets,[3] in the ideal setting for surrogacy, "the surrogate is in the only causal pathway of the disease process, and the intervention's entire effect on the true clinical outcome is mediated through its effect on the surrogate" (Fig. 1).

In the last few years, the role of biomarkers and surrogate endpoints, together with the efforts needed for their validation and the concerns related to their misuse, has become a hot topic in ophthalmology (Fig. 2).

TABLE. Biomarkers' Categories and Definitions Reported in the FDA-NIH BEST Resource[2]

| Biomarker Category	Definition	Notes
Diagnostic biomarker	A biomarker used to detect or confirm presence of a disease or condition of interest or to identify individuals with a subtype of the disease.	The limitations of a diagnostic biomarker test are related to the clinical sensitivity and specificity of the biomarker and to the analytical performance of the measurement method.
Monitoring biomarker	A biomarker measured serially for assessing status of a disease or medical condition or for evidence of exposure to (or effect of) a medical product or an environmental agent.	The serial nature of the measurements focuses attention on change in the biomarker's value.
Pharmacodynamic/ Response biomarker	A biomarker used to show that a biological response has occurred in an individual who has been exposed to a medical product or an environmental agent.	Pharmacodynamic/response biomarkers do not necessarily reflect the effect of an intervention on a future clinical event (they may not be accepted surrogate endpoints).
Predictive biomarker	A biomarker used to identify individuals who are more likely than similar individuals without the biomarker to experience a favorable or unfavorable effect from exposure to a medical product or an environmental agent.	Prognostic biomarkers and predictive biomarkers cannot generally be distinguished when only patients who have received a particular therapy are studied. To identify a predictive biomarker, there generally should be a comparison of a treatment to a control in patients with and without the biomarker.
Prognostic biomarker	A biomarker used to identify likelihood of a clinical event, disease recurrence or progression in patients who have the disease or medical condition of interest.	Prognostic biomarkers are often identified from observational data and are regularly used to identify patients more likely to have a particular outcome.
Safety biomarker	A biomarker measured before or after an exposure to a medical product or an environmental agent to indicate the likelihood, presence, or extent of toxicity as an adverse effect.	Ideally, a safety biomarker would signal developing toxicity (e.g., drug induced organ injury) prior to clinical signs and before any irreversible damage occurs.
Susceptibility/Risk biomarker	A biomarker that indicates the potential for developing a disease or medical condition in an individual who does not currently have clinically apparent disease or the medical condition.	Susceptibility/risk biomarkers may be detected many years before the appearance of clinical signs and symptoms. Susceptibility/risk biomarkers do not describe a relationship to any specific treatment.

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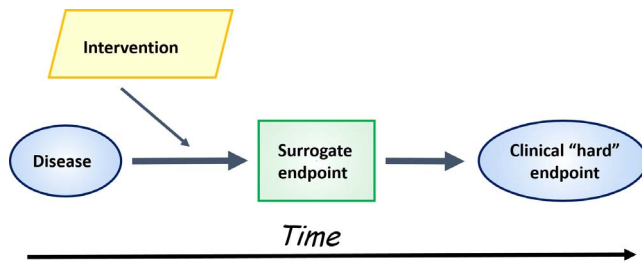
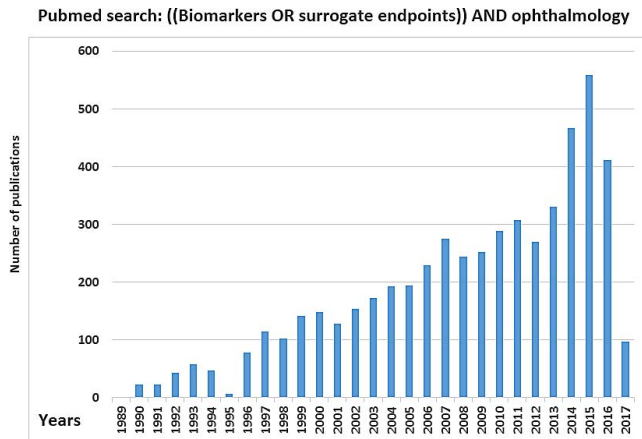**FIGURE 1.** Conceptual model of valid endpoint surrogacy.

FIGURE 2. Biomarkers and surrogate endpoint publication volume in ophthalmology, from PubMed abstract search performed on April 1, 2017.

This special issue is a great opportunity to take stock of this important and complex topic. The invited and unsolicited reviews provide precious information and novel updates on scientific and regulatory issues. The original research report new advances in biomarkers and surrogate endpoints development, validation and usage in different areas of ophthalmic clinical research and care.

We would like to thank all the reviewers for their fundamental and anonymous work and all the researchers who have contributed to this special issue.

We would also like to thank Thomas Yorio, Editor-in-Chief of *IOVS*, for having shared our enthusiasm for this project and for his invaluable guidance, and Marco Stoutamire, Gayle Claman, and Debbie Chin, *IOVS* staff, for their work and their kind and constant support in managing the submissions.

We hope that this special issue will help to increase awareness and to focus attention on the implications of this important topic and will be an incentive for addressing the several open challenges.

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References

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Investigative Ophthalmology & Visual Science