Response to "Prognostic biomarkers in oral leukoplakia"

Villa, Alessandro; Celentano, Antonio; Glurich, Ingrid; Borgnakke, Wenche S; Jensen, Siri Beier; Peterson, Douglas E; Delli, Konstantina; Ojeda, David; Vissink, Arjan; Farah, Camile S

Published in:
Oral diseases

DOI:
10.1111/odi.13185

IMPORTANT NOTE: You are advised to consult the publisher's version (publisher's PDF) if you wish to cite from it. Please check the document version below.

Document Version
Final author's version (accepted by publisher, after peer review)

Publication date:
2019

Link to publication in University of Groningen/UMCG research database

Citation for published version (APA):

Copyright
Other than for strictly personal use, it is not permitted to download or to forward/distribute the text or part of it without the consent of the author(s) and/or copyright holder(s), unless the work is under an open content license (like Creative Commons).

Take-down policy
If you believe that this document breaches copyright please contact us providing details, and we will remove access to the work immediately and investigate your claim.

Downloaded from the University of Groningen/UMCG research database (Pure): http://www.rug.nl/research/portal. For technical reasons the number of authors shown on this cover page is limited to 10 maximum.
Title: Response to "Prognostic biomarkers in oral leukoplakia"

Running title: biomarkers in oral leukoplaki

Authors:
Alessandro Villa,1 Antonio Celentano,2 Ingrid Glurich,3 Wenche S. Borgnakke,4 Siri Beier Jensen,5 Douglas E. Peterson,6 Konstantina Delli,7 David Ojeda,8 Arjan Vissink,7 Camile S. Farah9

Affiliations
1Division of Oral Medicine and Dentistry, Brigham and Women's Hospital, and Department of Oral Medicine, Infection and Immunity, Harvard School of Dental Medicine, Boston, MA, USA
2Melbourne Dental School, The University of Melbourne, Melbourne VIC, Australia
3Center for Oral and Systemic Health, Marshfield Clinic Research Institute, Marshfield WI, USA

This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.1111/odi.13185

This article is protected by copyright. All rights reserved.
We thank Professor Warnakulasuriya for his letter (Warnakulasuriya, 2019) and comments in relation to our systematic review of prospective studies assessing the prognostic biomarkers of oral leukoplakia (Villa et al., 2019). We agree that identifying prognostic biomarkers for oral leukoplakia is an important topic for oral medicine specialists. Hence our commitment to addressing such a diverse and scientifically challenging area as a component of World Workshop of Oral Medicine VII.

We would like to clarify, though, that this first paper in a series of papers on the topic, examined prognostic biomarkers for oral leukoplakia in context of biomarker expression in human subject samples. Details of the search strategy, including potentially eligible studies, search terms, and strategy are detailed in our paper (Villa et al., 2019).

In relation to the putative biomarkers identified by Professor Warnakulasuriya, we would agree that many of these have been highlighted in the literature, some being more prognostic than others.
• However, several studies that discuss these biomarkers did not meet the inclusion criteria for our systematic review. For example, many studies did not specifically detail the oral leukoplakia cases, and this hampered inclusion of many papers and potential biomarkers, not only those raised by Professor Warnakulasuriya, but also some described by authors of the current systematic review.

• Additionally, as we reported in point “c)” of paragraph “2.1”, we did not include any review papers or those discussing meta-analyses, such as the publication by Alaizari et al. (2018). We only considered original studies for inclusion and excluded reviews or collective analyses of multiple studies. Detailed information of biomarkers identified, including prognostic information (when mentioned in the papers), are reported in the Supplementary data.

A recurrent confounder for development of our manuscript was imprecise description of the anatomical location of the lesions. As an example, several cases of not otherwise specified “oropharyngeal leukoplakias” could not be included for our analysis. In addition, many studies on putative biomarkers for oral leukoplakia actually describe them in terms of presence or absence of oral epithelial dysplasia without clear clinical information to warrant inclusion. As shown in Table 1 of our paper (Villa et al., 2019), exclusion category N3 captured 332 studies out of a total of 418 reports ineligible for inclusion due to lack of definitive clinical diagnosis and presentation of dysplasia data only.

We agree that the definition of oral leukoplakia in some studies may have affected the papers selected. However, this in an inherent limitation with the papers themselves, and the broader field of oral medicine, and not restricted to the inclusion criteria of our systemic review. We acknowledge that authors of some publications have included keratotic white lesions as potential leukoplakia, which complicates analysis of potential biomarkers for the latter condition. This issue is highlighted in a recent study by Villa and colleagues (Villa et al., 2019) which touches on the molecular profile of non-dysplastic leukoplakic lesions commonly reported histopathologically as benign keratosis in the literature, but identified as leukoplakia clinically. Unfortunately, without access to all details of studied cases, it is not possible to determine which cases could be validated for inclusion.

Rationale for study exclusion was clearly articulated in our paper. Although we agree that a table summarizing rationale could have been helpful, the sheer number of studies excluded precluded this from a practical point of view. We included an Appendix to this letter with all
the excluded studies for clarity (Appendix 1) Finally, we agree with Professor Warnakulasuriya that few, if any, of the prognostic biomarkers reported in the literature for oral leukoplakia are robust. Although some may hold more promise than others, including some omitted from our report, we could only report on those which met the inclusion criteria of the current systematic review.

Addressing the following issues in future studies (as we specified in Section 4.1 “Future directions” in the manuscript) would further strengthen the quality and clinical value of this line of research:

- Both clinical and histopathological details should be provided to allow analysis of clinical entities such as leukoplakia and corresponding histopathological entities such as dysplasia, in terms of identification of putative biomarkers. A recent paper by Farah and Fox (Farah and Fox, 2019) discusses this philosophical question by identifying the molecular profile of oral leukoplakia with and without dysplasia.
- A more concerted effort is required internationally to correctly define oral leukoplakia, as the current definition is not entirely helpful in a clinical sense.

Respectfully,

Alessandro Villa, Antonio Celentano, Ingrid Glurich, Wenche S. Borgnakke, Siri Beier Jensen, Douglas E. Peterson, Konstantina Delli, David Ojeda, Arjan Vissink, Camile S. Farah
References


