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Ethical, Legal, and Regulatory Issues for the Implementation of Omics-Based Risk Prediction of Women's Cancer: Points to Consider

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Abstract
Background and Objective: Advances in omics open new opportunities for cancer risk prediction and risk-based screening interventions. However, implementation of risk prediction in clinical practice may impact the ethical, legal, and regulatory aspects of current cancer screening programs. In order to support decision-making, we analyzed the ethical, legal, and regulatory issues and developed a set of Points to Consider to support management of these issues. ***Methods:*** We analyzed the legal and policy frameworks applicable to breast and cervical cancer screening programs in 7 European countries. We identified the most relevant issues to be considered, and we developed considerations for their management, based on the literature, the legal and policy frameworks, and our experience with similar issues. ***Results:*** The considerations focus on five topics: (A) health services planning, (B) information and invitation, (C) consent and data/sample collection, (D) risk calculation and communication of results, and (E) storage of data and residual samples. ***Conclusion:*** Current frameworks might not be adequate to implement a risk prediction approach using omics factors due to the different characteristics of such approaches.

Background

Advances in omics (e.g., genomics, epigenetics, metagenomics) open new opportunities for risk prediction and risk-based screening interventions [1, 2]. Omics-based risk factors (e.g., genetic mutation, genetic and epigenetic variations) could be combined with personal and environmental risk factors (e.g., body mass index, age, lifestyle) to predict the risk of developing certain cancers. Such individualized prediction of the risk of cancer would then support risk-adapted screening and prevention strategies. For instance, a woman identified at higher risk of breast cancer could be advised to start mammography screening earlier or more frequently than the general

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Fig. 1. Steps for implementing risk prediction for women's cancers.

population and consider taking medication for preventive purposes [3]. Targeting those most likely to benefit from screening would increase the benefits of screening (e.g., earlier diagnosis) and decrease potential harms (e.g., overdiagnosis).

Several major research projects on women's cancer risk prediction are ongoing (e.g., WISDOM [4], BRIDGES [5], MyPeBS [6], PROMISE [7], and FORECEE [8]), and so, this approach could soon be implemented in current practice, and complement national screening programs. However, implementation of a risk prediction approach in clinical practice impacts the ethical, legal, and regulatory aspects of current tests, strategies and programs related to cancer screening. For instance, proposing a reduction in the screening frequency for women at lower risk or addressing the particular nature of results derived from epigenetic factors may raise new ethical, legal, and regulatory considerations. Adequate management of the ethical, legal, and regulatory issues related to the implementation of a risk prediction approach is essential to ensure optimal translation of science into clinical practice. In this paper, we present our analysis of these ethical, legal, and regulatory issues and a Points to Consider to support the management of these issues.

Methods

As we are involved in the "Female cancer prediction using cervical omics to individualise screening and prevention" (FORECEE) project, our work is based on the contextual background particular to this project. FORECEE was funded in 2015 by the European Commission Research and Innovation program Horizon 2020 [8] and by the charity The Eve Appeal. This project aims to develop a new risk prediction approach for women's cancers, based on omics, microbial, and clinical factors. With this model, clinical data will be processed in combination with the results of the analysis of a sample of cervical epithelial cells (i.e., cervical smear), using an algorithm, to provide an individualized estimation of the risk of developing breast, ovarian, endometrial, and cervical cancers. Individualized risk estimation is expected to help tailor both screening and prevention for these four cancers, with measures recommended according to a woman's risk level [9].

First, we reviewed current cancer screening frameworks that could be applicable to a risk prediction model. We examined the legal and policy frameworks applicable to breast and cervical cancer screening programs in 7 countries involved in the FORECEE project (UK, Germany, Sweden, Austria, Norway, Italy, and the Czech Republic). Most of these countries have developed implementation frameworks (via legislation, policy, or guidance) for cancer screening programs. However, these regulatory frameworks do not systematically address the implementation of novel screening techniques (such as omics-based risk prediction tests). The implementation of such tests within a clinical context may in some cases fall under the scope of more general clinical care legislation, regulations on medical devices/tests, or quality standards. Thus, our research included any provisions related to the use of new screening tests or approaches (involving either a change to an existing screening program or the implementation of a new program).

An overview of the European-level policy framework was also done, in order to provide the background context for the adoption and implementation of screening strategies at the national level.

Our review was undertaken based on documents available in English, and publicly accessible on the web between April 2017 and October 2017 (see Table 1). Resources used to conduct the search included the following: general web searches (Google) for each jurisdiction, Google Scholar searches for relevant literature (general, and jurisdiction-specific), regulatory databases, specialized websites (National Institutes of Health, PHG Foundation, World Health Organization, etc.), and jurisdiction-specific governmental websites.

A broad summary of the ethical, legal, and regulatory issues surrounding the possible implementation of the risk prediction approach was developed based on the examination of several frameworks governing the implementation of cancer screening (in the 7 countries identified) and from the literature on this topic. We regrouped these issues in relation to the implementation step they belong to. Figure 1, represents the core implementation steps we identified for risk prediction of women's cancers, at the population level.

For each implementation step, we identified the most relevant issues to be considered with respect to: their recurrence in the documents consulted (laws, policies, and literature), the importance of their impact on end-users (women, health-professionals, and health authorities), their likelihood of arising under the risk prediction approach, and the complexity required to appropriately address them. For each issue identified, we also developed considerations for their management, based on the literature consulted, the legal and policy frameworks examined, and our experience with similar issues.

Table 1. Documents on screening frameworks examined to develop the Points to Consider

Jurisdiction	Author, *Document title*	Year
USA	National Cancer Institute (National Institutes of Health (NIH)), *International Cancer Screening Network, Breast Cancer Screening Programs* (https://healthcaredelivery.cancer.gov/icsn/breast/screening.html)	2012
USA	National Cancer Institute (National Institutes of Health (NIH)), International Cancer Screening Network, *Cervical Cancer Screening Programs* (https://healthcaredelivery.cancer.gov/icsn/cervical/screening.html)	2012
Europe	European Commission, *Cancer Screening in the European Union (2017) – Report on the Implementation of the Council Recommendation on Cancer Screening* (https://ec.europa.eu/health/sites/health/files/major_chronic_diseases/docs/2017_cancerscreening_2ndreportimplementation_en.pdf)	2017
Europe	Cancer Control Joint Action (CanCON), *European Guide on Quality Improvement in Comprehensive Cancer Control* (https://cancercontrol.eu/archived/uploads/images/Guide/pdf/CanCon_Guide_FINAL_Web.pdf)	2017
Europe	European Commission, Directorate-General for Health and Food Safety, *European Guidelines for Quality Assurance in Cervical Cancer Screening* (http://bookshop.europa.eu/en/european-guidelines-for-quality-assurance-in-cervical-cancer-screening-pbND7007117/)	2008
Europe	European Council, *Council Recommendation on Cancer Screening* (2003/878/EC) (http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2003:327:0034:0038:EN:PDF)	2003
UK	National Health Services (NHS), *NHS Population Screening Explained – Ethics of Populational Screening* (https://www.gov.uk/guidance/nhs-population-screening-explained)	2018
UK	National Health Services (NHS), *Service Specifications for Implementation of Screening Programmes*, *Breast Cancer Screening Service Specification* (https://www.england.nhs.uk/wp-content/uploads/2017/04/service-spec-24.pdf)	2017
UK	National Health Services (NHS), *Service Specifications for Implementation of Screening Programmes*, *Cervical Cancer Screening Service Specification* (https://www.england.nhs.uk/wp-content/uploads/2017/05/serv-spec-25.pdf)	2017
UK	Annual Report of the Chief Medical Officer, *Easton et al., Chapter 10: Risk-Stratified Cancer Screening* (https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/631043/CMO_annual_report_generation_genome.pdf)	2017
UK	PHG Foundation, *Genetic Screening Programmes – An International Review of Assessment Criteria* (http://www.phgfoundation.org/file/17371/)	2015
UK	*Health and Social Care Act (2012),* c.17 (http://www.legislation.gov.uk/ukpga/2012/7/contents)	2012
UK	*National Health Service Act (2006)*, c.41 (http://www.legislation.gov.uk/ukpga/2006/41/contents)	2006
UK	National Health Services (NHS), Public Health England (PHE), *NHS Breast Cancer Screening Program* (https://www.gov.uk/topic/population-screening-programmes/breast)	NA
UK	National Health Services (NHS), Public Health England (PHE), *NHS Cervical Cancer Screening Program* (https://www.gov.uk/topic/population-screening-programmes/cervical)	NA
Germany	The German Guideline Programme in Oncology (German Cancer Society, German Cancer Aid, AWMF): *Diagnosis, Treatment, and Follow-Up of Women with Breast Cancer* (https://www.senologie.org/fileadmin/media/documents/pdf/Leitlinien%20der%20Deutschen%20Gesellschaft%20f%C3%BCr%20Senologie/s3_leitlinie_en.pdf)	2008
Germany	German Federal Joint Committee (G-BA), *Code of Procedures* (http://www.english.g-ba.de/legalmandate/procedures/methods/evidence/)	NA
Germany	Institute for Quality and Efficiency in Health Care, *The Breast Cancer Screening Program in Germany* (https://www.ncbi.nlm.nih.gov/pubmedhealth/PMH0087094/)	2016
Sweden	National Screening Programs, *A Model for Assessment, Introduction and Follow-Up*	2014
Austria	AGES, *Quality Control Guidelines – Reference Center for Technical Quality Assurance (RefZQS)* (https://www.ages.at/en/topics/radiation-protection/breast-cancer-early-detection-programme/#)	NA
Norway	Norwegian Ministry of Health and Care Services, *Together against Cancer – National Cancer Strategy 2013–2017* (https://www.regjeringen.no/contentassets/444d08daf15e48aca5321f2cefaac511/mammografirapport-til-web.pdf)	2012
Norway	Research Council of Norway, *Research-Based Evaluation of the Norwegian Breast Cancer Screening Program* (https://www.regjeringen.no/contentassets/444d08daf15e48aca5321f2cefaac511/mammografirapport-til-web.pdf)	2015
Italy	Italy, Ministry of Health (Italy), *Report on the Health Status in Italy during the years 2009–2010* (http://www.rssp.salute.gov.it/rssp/documenti/Summary_of_report.pdf)	2010
Czech Republic	Organization for Economic Co-operation and Development (OECD), *OECD Reviews of Health Care Quality: Czech Republic (Chapter 3: Screening and Prevention Programmes in Czech Republic)* (http://www.keepeek.com/Digital-Asset-Management/oecd/social-issues-migration-health/oecd-reviews-of-health-care-quality-czech-republic-2014_9789264208605-en#page8)	2014

Points to Consider for Future Implementation of Omics-Based Risk Prediction

The most relevant ethical, legal, and regulatory issues of cancer risk prediction implementation which were identified are presented below, along with the suggested considerations for their management. However, a broad range of additional local considerations would need to be examined before proposing a specific solution for a given country (including a detailed review of domestic legislation, the health system, the regulatory requirements, and the specificities of the population). Since this detailed assessment of local specificities was beyond the scope of the current review, our Points to Consider only provide a primer on the broad range of issues to be addressed prior to implementation of the risk prediction approach in a given country.

Health Services Planning

Planning health services involves adopting policy and strategic directions, as well as setting the course of action to achieve the expected objectives with regard to population health, and to existing and anticipated resources. Implementation of the risk prediction approach would require thorough planning, especially considering the specificities of its omics component.

Legal, Regulatory and Policy Frameworks Should Adequately Support Implementation and Be Adapted if Necessary

Because of their mandatory nature, the existing legal, regulatory, and policy frameworks might have major impact on achieving implementation of the risk prediction approach. These frameworks might need to be appropriately adapted to the specificities of this approach. They can apply either directly (e.g., policy on disease screening) or incidentally (e.g., regulation pertaining to medical records management) to prediction and screening of cancer in women.

The legal, regulatory, and policy frameworks directly targeting cancer screening aim to regulate the most important aspects of the delivery of services at the national level. Current frameworks can pose barriers to the changes that would arise when implementing a risk prediction approach. For example, this approach might require the addition of different diseases to be covered by screening, the use of omics-based tests, or a modification to the population subgroups targeted by risk prediction. Furthermore, these frameworks can also mandate criteria specifically relevant to risk prediction, such as the obligation to demonstrate the social and ethical acceptability of a new screening program, and implementation of a method to select and review the genetic variants of a new test [10]. For instance, the EU regulation for in vitro diagnostic medical devices requires that patients be "provided with relevant information on the nature, the significance and the implications of the genetic test" and appropriate counseling should be offered to them [11].

Legal, regulatory, and policy frameworks which incidentally affect the prediction of cancer or screening could also impact implementation. For instance, regulatory provisions applicable to the duties of health professionals might limit who can prescribe and interpret the omics test. Laws governing linkage of data may also pose significant hurdles considering that risk prediction often relies on linking data from different sources (e.g., environmental databases, registries, and medical records). Similarly, the software used to calculate the predictive risk of cancer may also have to comply with performance and safety standards pertaining to the EU regulations on medical devices [12].

Measures to Mitigate the Potential Creation or Reinforcement of Social Inequities Should Be Anticipated

Careful attention should be paid to the potential social inequities that could incidentally be created or reinforced by the implementation of a new risk prediction approach. For instance, potential discrimination, or barriers to equitable access to the new health services, should be taken into account.

Discrimination and stigmatization by insurers and employers based on omics characteristics is a form of inequity that could occur with the implementation of a risk prediction assessment. Risk prediction allows classification of individuals into risk groups (e.g., high risk, intermediate risk), leading to the potential for discrimination of individuals in such groups, and possibly also for their biological family members [13]. For instance, insurance companies could use results on cancer risk as a basis for setting higher premiums [13]. Having anti-discrimination legislation in place, or other means of adequate protection (e.g., restricting access and use of results by insurers [14, 15]), can help protect individuals [16].

Other barriers (low literacy/numeracy, language comprehension, etc.) may also prevent certain subgroups from fairly benefiting from the risk prediction approach. Approaches based on genomics may exacerbate current inequities related to socioeconomic status, education, or ethnicity [17, 18]. The complexity of information involved in genomic-based approaches is a major challenge when communicating with people with low health literacy or numeracy [19]. The complexity of the results pro-

vided to women could be exacerbated by patients' misperception of information related to cancer risk and cancer screening [20]. This could reinforce social inequities when inviting individuals, obtaining informed consent or providing tests results. The European Council Recommendation on cancer screening recognizes that equal access to screening should be ensured and highlights the possible need to target particular socioeconomic groups.

Information and Invitation

Providing information about the health services offered and an invitation to take part in these services are key steps to ensuring that the policy and strategic directions adopted as part of the previous step (Health Services Planning) are extended into the provision of services. Informing women about cancer risk prediction will first require targeting the relevant groups and, second, making them aware of the services offered. Although information provided at this step is part of the consent process continuum, it does not necessarily include all of the detailed information that must be provided before an expression of consent.

The Risk Assessment Process and the Omics Test Should Be Clearly Explained

The risk calculation process and the use of an omics test will likely be new or unfamiliar for both the population invited to risk prediction and the health professionals. The risk prediction approach will likely involve more steps than the current breast/cervical cancer screening programs (see Fig. 2).

The communication strategy for the introduction of this new method should provide explanations as to the process involved in the new approach implemented, including the role of the omics factors. If the risk prediction approach is offered as a public health, population-based program, the medical community will also need to be aware of its general process as well as the specificities related to the use of omics technologies. Given the complexity of an omics-based approach and the lack of genomics expertise of primary care providers [21], the health professionals likely to be involved with women of the targeted age group will need to be educated on the implications of this approach.

Consent and Data/Sample Collection

Once women are informed of the cancer risk prediction approach, a more individualized step will follow: obtaining informed consent and collecting the data and samples required.

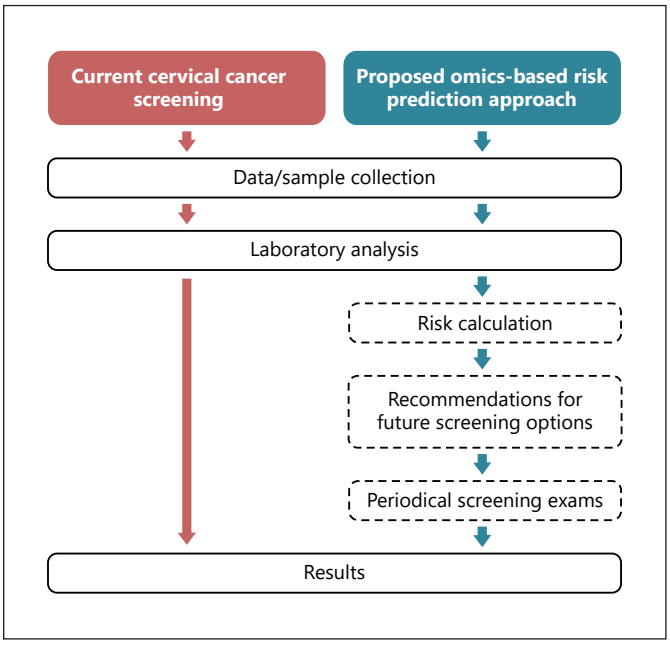

Fig. 2. Differences in steps between the current cervical cancer screening and the future risk prediction approach.

Information Provided Should Be Adapted to the Specificities of Omics-Based Risk Prediction

In general, providing sufficient information to patients to support consent is seen as an ethical, policy, and/or regulatory requirement, and can often be found listed as a criterion for the assessment of new screening methods. At the European level, member states must ensure that predictive genetic testing is preceded by provision of information to the patient about the nature, the significance, and the implications of the test.

Background information provided to women would need to be tailored to a risk prediction assessment involving omics factors. The specificities to consider could include: the probabilistic nature of the results, the limits of both the omics test (e.g., exclusion of some mutations) and the risk assessment (e.g., difficulty to interpret omics results from individuals of non-European ancestry [22]), the preventive and/or medical treatment options that would be offered, the potential for unsolicited (incidental) findings, and the potential disadvantages of such findings (e.g., impacts of results on insurability, epigenetic findings that may be related to lifestyle/environmental factors). Indeed, the capacity of health-care providers to provide adequate information and answers on these topics will be a key factor in obtaining informed consent. New informed consent models and patient decision aids

could be needed to structure information in order to support informed decision-making.

Risk Calculation and Communication of Results

In the risk calculation step, information generated from sample and data analysis is calculated with an algorithm in order to predict cancer risk. The communication of the cancer risk level will be followed by recommendations appropriate to the woman's risk level, but might also involve management of unsolicited findings.

Consideration Should Be Given as to whether the Omics Test Will Reveal any Unsolicited Findings and, if So, How They Will Be Handled

Depending on the scope of the omics analysis used for risk prediction, certain actionable unsolicited findings related to the health condition of the patient (e.g., a predisposition to heart disease) could be revealed. This gives rise to significant ethical considerations given their unexpected nature and the uncertain outcome related to such results for the individuals [23, 24].

Therefore, a strategy to handle potential unsolicited findings should be adopted, including the criteria to decide which of them will be communicated to the patient [25]. For instance, the possibility of taking preventive measures, or whether the condition is treatable, will be key criteria in the decision to offer or not this information to women [24, 26, 27]. If such unsolicited findings are expected to be found through risk prediction testing, a clear explanation of the implications of these findings should also be provided as part of consent information before the test is administered [17].

Potential Impacts of the Results (or, Where Applicable, Unsolicited Findings) on Family Members Should Be Assessed and Managed

In some cases, the results of risk prediction testing based on omics analysis (or, where applicable, unsolicited findings), could be relevant to biological family members, and by extension, to future offspring. This would for instance be the case when a hereditary mutation that greatly increases the risk of breast cancer is uncovered (e.g., in the BRCA1/2 genes). But some results and unsolicited findings might not be transposable to family members: results pertaining to cancer risk which rely on combinations of hundreds of genomic variants and several individual factors that each increase cancer risk moderately or slightly, will not be transposable to other family members.

The potential benefits (e.g., health improvement) and disadvantages (e.g., anxiety) of communicating information to family members raise significant ethical, legal (e.g., duties of health professionals), and organizational issues [28–30]. Where applicable, women should be informed of the possibility that they could be asked to share some results with family members and whether results may have an impact on their future reproductive choices.

Clear Information on Appropriate Follow-Up Measures and Available Health Services Should Be Provided

As the ultimate goal of risk prediction is to offer follow-up measures to those at higher risk, the appropriate measures for each risk level should be established in the clinical community and clearly provided to the patients. In particular, patients should be informed whether the intensity of subsequent screening or medical examinations may be modified (e.g., more or less frequent mammography screening), and what additional health services may be available for individuals with similar risk levels. Finally, risk prediction may raise the issue of distributive justice with respect to individuals deemed to be in the lowest risk level of developing the disease (low-risk group) following testing [17]. Indeed, attention must be paid to any reduction in the health services offered to those at low risk (e.g., change in screening intervals). Careful planning of the strategy and clear communication with the population should be adopted to avoid any perception that low-risk individuals are being withheld health services [17].

Specificities of Epigenetic Results (where Applicable) Should Be Taken into Account

Changes in the genome that do not alter the DNA sequence but can modify genomic expression are called epigenetic modifications [31]. Because epigenetic modifications might be involved in the development of some cancers, their analysis could be of great interest for risk prediction. For instance, assessment of epigenetic modifications associated with susceptibility to cervical cancer could be integrated into public health programs [32]. However, the use of epigenetic risk factors also raises additional questions.

The plasticity of the epigenome in response to environmental factors (e.g., prenatal exposures, nutrition, childhood adversities, climate) [33] might raise potentially stigmatizing associations with many characteristics, for instance socioeconomic status, gender, ethnicity, or living conditions (e.g., childhood maltreatment, substance abuse, smoking, physical inactivity, exposure to sexually transmitted diseases, body weight, etc.). Furthermore, the possibility that some epigenetic changes are inherited

from previous generations may also amplify such issues: association with a socioethnic background could lead to discrimination of groups [34], and the revelation of the living conditions of ancestors could also have familial impacts when this information is new for the offspring (e.g., childhood maltreatment). Public health policies should take into account inequity with regard to exposures to adverse epigenetic risk factors [35, 36].

In a populational risk prediction approach, the extent to which epigenetic factors are used as part of the risk calculation, and the type of information revealed by epigenetic results (if any), are relevant. In particular, there should be careful consideration as to whether epigenetic factors would exacerbate all of these issues and potentially reveal community-level risk factors.

The evolving nature of the epigenome, including its reversibility, is another specificity that could have an impact on risk prediction. Due to the evolution of the epigenome over time and in relation to exposure to environmental factors, repeating a risk assessment calculation may be necessary in some situations [9, 37]. If periodical reassessment is required, health professionals using risk prediction results should understand the difference between the nature of genomic factors and the evolving nature of the epigenetic factors. Women should be aware that risk assessment may need to be repeated.

Storage of Data and Residual Samples

The risk prediction approach yields datasets that are richer and contain more types of data than those from traditional screening. Resulting data could include genomic variants, epigenetic data, lifestyle information, environmental data, and other types of rich data. Given the scientific potential regarding the use of such data, some jurisdictions will be interested in storing it and possibly biobanking residual samples for future research purposes.

Storage of Data and Residual Samples for Research Purposes Should Be under a Clear and Ethically Acceptable Framework

To support population trust in medical and scientific practices, storage for future research purposes requires a clear and ethically acceptable framework. In addition to the usual steps for establishing research biobanks (e.g., ethics approval, legal authorization, informed consent), attention should be paid to some specificities arising from the risk prediction approach. One is the difficulty of ensuring clarity on storage issues considering the complexity of the information provided to women within the risk prediction process, and the differences in communication of results that women should expect (e.g., whether or not the biobank returns results to participants). However, a secondary goal of risk prediction, namely supporting future scientific research, should not impinge on its primary goal, which is to improve the health of women assessed. Accordingly, storage of data and samples for scientific purposes should remain optional.

Conclusion

A risk prediction approach aims to improve early detection or prevention of cancer by adding more personalization to the current programs. Our work indicates that the ethical, legal, and regulatory issues discussed could occur across the full spectrum of implementation, from health services planning to the storage of data and results.

Although cancer risk prediction is promising, its implementation within population screening programs raises ethical, legal, and regulatory issues for decision-makers. Carefully planning the implementation of such a new health approach – especially one that is expected to reach a large population – is key to enhancing the success of translation into clinical practice, and to instigate a public debate.

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Disclosure Statement

The authors declare no conflicts of interest.

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