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LETTER TO THE EDITOR

A response to "Personalised medicine and population health: breast and ovarian cancer"

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Introduction

Based on Dr. Narod's assessment of the premise of personalized medicine in his review *"Personalised medicine and population health: breast and ovarian cancer"*, we invite him to learn more about the critical studies that are changing the landscape in screening and prevention. As a group of leaders of personalized medicine initiatives in breast cancer, we feel that it is critical to counter Dr. Narod's pessimistic view of the opportunities for personalizing screening and prevention. In the neoadjuvant breast cancer treatment setting, we are making tremendous strides by understanding and tailoring treatment based on tumor risk, biology, and a better understanding of what can reduce risk using early endpoints. We have the same opportunity to revolutionize breast cancer screening by integrating the concepts of risk stratification, prevention, and early detection. We need an adaptive framework that facilitates continuous learning to maximize benefit, reduce costs, and, importantly, to reduce morbidity.

Screening

Dr. Narod's negative views on personalized screening would likely change if he was aware of the primary aims of the randomized trials and cohort studies underway. In the WISDOM study (Women Informed to Screen Depending on Measures of risk), a large pragmatic trial funded by the Patient Centered Outcome Research Institute (PCORI),

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we are testing the proposition that a personalized approach incorporating comprehensive risk assessment, including density as well as sequencing of targeted genes and SNPs, is as safe, less morbid, preferred by women, promotes prevention, and is of higher healthcare value than annual mammography in the US (Esserman 2017). We are generating the evidence; we are not yet promoting it as policy. The goal is not to "save lives", but to deescalate and reduce the unintended consequences of screening (false-positive tests and overdiagnosis) for the vast majority of women, and at the same time, identify those at highest risk for cancer—that small but high impact group with a > 40% chance of developing breast cancer. While we agree that the number of these women is small (indeed, that is what personalization implies!), we should not discard the opportunity to do the most good for those at highest risk who can consider both prevention as well as more intensive surveillance. There is an additional critical effort, the randomized European MyPeBS (My Personalized Breast Screening) trial, which has a significant support from the EU and is implemented across several countries (UNICANCER 2018). WISDOM and MyPeBS will share data to increase the chance for insight.

The Canadian study (PERSPECTIVE I&I—Personalized risk assessment for prevention and early detection of breast cancer: Integration and Implementation) is focused on improving the genetic counseling process, and allowing healthcare providers to make more informed decisions about the use of multi-gene panel testing for individualized risk prediction (Genome Canada 2018). On a population basis, this project will assemble a large prospective cohort to generate novel evidence on acceptability and feasibility of risk-based screening, uptake of genetic testing for risk assessment, screening behaviours, and outcomes by risk category. International collaborations, such as the joint effort of PERSPECTIVE and the European B-CAST (http://www.b-cast.eu) and BRIDGES (http://www.bridges-research.eu) projects, will continue to generate and validate the improved risk prediction models for women at high risk that can then be integrated into the risk stratification models that drive the randomized and implementation studies.

Prevention

Dr. Narod asserts that there are no markers indicating benefit from breast cancer chemoprevention. Reduced mammographic density has consistently been shown to be associated with benefit (Cuzick et al. 2011; Li et al. 2013; Nyante et al. 2015). In addition, the elements of breast density that drive risk are being further elucidated and the tools for measurement are improving and should be rapidly put into trials. Additional biomarkers are emerging, such as background parenchymal enhancement, measured by MRI. Screening trials of new modalities in the high-risk setting will yield additional insights and help us to refine mutable markers of risk. New interventions that reduce risk are on the horizon, and the feasibility of testing them and of women using them will dramatically improve when we have ways to a better identify those at high risk—ongoing platform trials provide the framework for rapidly demonstrating the benefit of the intervention. Reducing the use of combined hormone replacement is the first example of a high impact intervention that has actually lowered the incidence of breast cancer (Chlebowski et al. 2003; Ravdin et al. 2007). This finding has both individual as well as societal benefit. If a woman is aware of her risk, she can make better choices. If we push to develop the tools to implement the prevention studies for the high-risk population, we will further improve our chance to decrease the incidence of breast cancer. The low computed number of breast cancer diagnoses averted in Dr. Narod's calculations is not a failure of personalized medicine—on the contrary, it is an argument for greater use of it. For prevention, we are getting to the stage of understanding the risks for specific subtypes (at least estrogen receptor positive and negative), for example B-CAST, which should facilitate more targeted chemoprevention. As these advances emerge, they are being seamlessly integrated into trials like the WISDOM study, to assess their impact on the uptake of prevention interventions. There is an emerging consensus that the massive effort around screening should evolve to include and emphasize prevention (UK Department of Health & Social Care 2018). In addition to driving decisions about prevention, risk may very well be an efficient and effective way to direct downstream use of resources for screening. That is what is being tested in the WISDOM study as well as the MyPeBS study.

Cost and implementation

The author also states that no one will pay for a more personalized approach and that women will not participate in such efforts. Fortunately, there is no truth to that statement. Advances in legal constructs and next-generation sequencing have brought the cost of testing to that of a having a mammogram. The success of and demand for direct-to-consumer DNA testing, such as that offered by 23 and me, demonstrates there is a clear willingness on behalf of the public to pay for such services. For healthcare payors, the case is sufficiently compelling that this industry has chosen to join the effort to generate modern era data that will allow us to improve our approach to screening and prevention. Blue Cross/Blue Shield of California as well as Blue Cross/Blue Shield National are partners in the WISDOM study and are covering the cost of the genetic testing and targeted prevention counseling using a coverage with evidence progression

framework (Rosenberg-Wohl et al. 2017). Modeling demonstrates that there could be a significant reduction in cost from less frequent screening (Pashayan et al. 2018) which could then free up health care resources to spend on genetic testing, getting to Dr. Narod's goal of universal screening for BRCA1 and 2 and beyond. A key goal is better outcomes at less cost. The EU is funding the MyPeBS trial for the same reason. To date, 20,000 women have enrolled in WISDOM and MyPeBS is just starting enrollment. One of the aims of the PERSPECTIVE study is to develop a strategy to guide organizational implementation and management solutions for health authorities. As we refine our ability to predict risk and assign the frequency and use of screening, we will further reduce morbidity and cost, and improve outcomes by focusing interventions (screening and prevention) on those who benefit most.

Summary

Dr. Narod has painted a picture of the status quo today in screening and prevention as if it is an acceptable state. There are many opportunities to improve screening, to integrate screening with risk assessment and prevention, and to put frameworks in place to allow continuous improvement. Therefore, we invite Dr. Narod to learn more about the many initiatives going on around the world to better understand risk, how to reduce risk, what factors are mutable and useable as early endpoints, and how best to prevent consequential cancers. The future is bright, but it can only be reached by changing the status quo, and that requires taking the first step forward. We invite him to join us in making this bright future a reality.

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