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The path to personalized medicine in women's cancers: challenges and recent advances

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We are now two decades into the revolution of molecular biology in medicine, and it has been a little over 10 years since the human genome was cloned [1,2]. These advances have led to fundamental changes in our understanding of cancer biology and tumor heterogeneity, resulting in clinically meaningful advances for patients diagnosed with breast and gynecologic cancers [3]. Moreover, technical advances in the field of robotics, computer imaging, sentinel biopsies, and fertility preservation have further allowed us to tailor surgical treatments to the exact needs of an individual patient bringing us closer to the goal of truly personalized medicine. Although targeted therapy agents are increasingly available for breast and gynecologic cancers, many of the new promising drugs have produced disappointing results when tested in clinical trials, indicating that there are many challenges that must be addressed to advance this field. Progress is not as rapid as we would like. In this issue of *Current Opinion in Obstetrics and Gynecology* a series of articles highlight recent advances but also key challenges in our pursuit for personalized medicine in breast and gynecologic oncology.

Progress in the understanding of the molecular events in ovarian cancer has prompted the need for a revised International Federation of Gynecology and Obstetrics staging system that may provide more accurate prognostic information and more specific guidance on personalized management of ovarian cancer than the older staging system that was last revised in 1988. In this issue, Kandukuri and Rao [4] eloquently highlight the newly revised International Federation of Gynecology and Obstetrics 2013 staging system for ovarian cancer and exactly pinpoint how it better embraces our current and improved understanding of the overlap of histological features and molecular characteristics of ovarian, tubal and peritoneal cancers. This new staging system will allow a more accurate characterization of these tumors and their clinical behavior and could facilitate the development of new personalized treatments in the near future.

The rapidly increasing number of targeted therapies also provides a unique opportunity to improve treatment options for known rare gynecologic malignancies. However, their low frequency makes it difficult to test these new agents in randomized clinical trials. Ray-Coquard *et al*. [5] highlight in their article the need for international harmonization of medical practices and novel trial designs to speed up the clinical implementation of new treatments for known rare gynecologic tumors and the evolving rare molecular subtypes.

The developing fragmentation of traditional disease entities into molecular subtypes is best described for breast cancer. It is well recognized that breast cancer is now a heterogeneous entity that is composed of several clinically and molecularly distinct subtypes. About 10–15% of patients who are diagnosed with breast cancer are confronted with the diagnosis of triple-negative breast cancer (TNBC) defined by a lack of hormone receptor expression as well as lack of overexpression/amplification of HER2. Moreover, TNBC presents as a clinically and biologically heterogeneous entity itself and the low frequency of the resulting molecular subtypes makes it again very difficult to test new agents in randomized clinical trials. Despite these challenges, however, progress is being made and Liedtke and Rody [6] update us on new treatment strategies for TNBC including the optimization of chemotherapy or identification of novel therapeutic targets but also discovery of biomarkers that show promise for predicting response to therapy.

A key aspect to improving the efficacy of tailored treatments is understanding the mechanisms of drug resistance. For example, clinical benefits of antivascular endothelial growth factor therapy have been observed in ovarian cancer treatment trials; however, this use yielded only modest improvement

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in progression-free survival and development of resistance to antivascular endothelial growth factor therapy over time is inevitable. Adaptive resistance and escape from antiangiogenesis therapy is likely a multifactorial process, including induction of hypoxia, vascular modulators and the immune response. Yang *et al*. [7] describe new approaches to overcome adaptive resistance for drugs targeting tumor vasculature. To improve the therapeutic benefit and counteract compensatory escape mechanisms, it is likely that simultaneous targeting of multiple angiogenic pathways will be required to increase the efficacy of antiangiogenic therapies [7].

Traditionally, progress in the development of tailored treatments has been hampered by the fact that it can require up to 15 years to take a new drug from early testing in phase I studies to US Food and Drug Administration (FDA) approval for the treatment of early stage disease. In breast cancer, therefore, the FDA recently released a guidance for accelerated approval for therapeutics in the neoadjuvant setting. Under the new guidance, accelerated approval could be granted based on a surrogate endpoint that is reasonably likely to predict clinical benefit. Specifically, for neoadjuvant treatment of breast cancer, pathologic complete response may be such a surrogate endpoint. In this issue, Loibl [8] reviews recent developments in neoadjuvant treatment approaches and clearly shows how the use of pathologic complete response as surrogate marker has recently led to the rapid approval of a new tailored treatment approach for HER2 positive breast cancer.

The identification of women who are at risk of developing breast or gynecologic cancer is key to cancer prevention and preventive therapy in high-risk women is a major cornerstone of proper personalized medicine. In this issue, Sestak and Cuzick [9] report on recent findings that have shown that the inclusion of breast density and a panel of low penetrance genetic polymorphisms will improve risk estimation for breast cancer compared with previous models. Several agents may be useful for preventive therapy in the appropriately selected women including selective estrogen receptor modulators or aromatase inhibitors, but possibly also metformin, bisphosphonates, aspirin, and statins.

Three additional studies provide practical considerations in order to integrate the concept of a personalized surgical therapy into the treatment plan of patients diagnosed with gynecologic malignancies. In this issue, Cibula *et al*. [10] summarize the current knowledge and recent advances in the sentinel lymph node concept in the three most frequent gynecological cancers. They show that in addition to a reduction of the procedural radicality, the concept of sentinel lymph node biopsy can have other advantages such as more reliable detection of key nodes in atypical localizations, detection of small metastasis, and intraoperative triage of patients thanks to identification of key nodes for pathologic evaluation.

Future fertility is an important consideration in many young cancer patients. Anticancer treatments (surgery, cytotoxic, and endocrine therapy) may negatively impact gonadal function, inducing temporary or permanent premature ovarian failure and infertility. In this issue, Lambertini *et al*. [11] review both experimental and standard available strategies for breast cancer and ovarian cancer patients to individualize therapy and preserve fertility including oocyte or embryo cryopreservation, cryopreservation of ovarian tissue, ovarian suppression with LHRH analogs and conservative surgical therapies.

The concept of personalized surgical therapy is furthered by the development and implementation of robotic surgical strategies. The motivation to develop surgical robots is rooted in the desire to overcome the limitations of current laparoscopic technologies (absence of natural hand-eye coordination and dexterity, restricted degrees of motion, two-dimensional imaging, and ergonomic inadequacy) and to further expand the benefits of minimally invasive surgery. In this issue, Xie [12] critically reviews the current cost-effectiveness of robotic surgery in gynecology and gynecologic oncology. The wide adoption of robotic-assisted surgeries is surprising considering the high upfront and procedure costs. Moreover, studies show that robotic-assisted surgeries have similar outcomes to traditional laparoscopy, but at a higher cost. Xie concludes that under the current reimbursement climate, practicing physicians and hospitals should collaborate on identifying cost-effective uses of robotic systems and push manufacturers to lower purchase and procedure costs to a level that may be accepted by all stakeholders.

Progress in personalized cancer care has been strong in some parts of the world, but there remain daunting challenges in health equity for low-income and middle-income countries. For women, cancers of the breast and cervix are the most common causes of cancer deaths worldwide. Breast cancer is the most common cause in 99 countries, and cervical cancer the most common in 55 countries. In economically developed countries, there have been important advances in personalized medicine, including targeted therapies for breast and cervical cancers, development of new vaccines and the implementation of screening programmes. But we have been unable to make many of these methods

available globally [13]. In this issue, Kantelhardt *et al*. [14] illustrate the opposing reality of breast cancer care in East Africa and uncover wide gaps in the availability of affordable traditional treatments (not to mention targeted therapies) for patients diagnosed with breast cancer in other parts of the world.

The ultimate goal of personalized medicine in cancer care is to perform the right intervention in the right person at the right time in a patient's life. The assembled articles are testimony of the incredible opportunities that exist to move personalized cancer care forward but they also emphasize the need to do this in a financially sustainable way to help advance and secure global health equity.

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Conflicts of interest

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