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Cancer genomics and clinical practice: how can we close the gap more quickly?

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During his State of the Union address on January 12, 2016, President Barack Obama announced the establishment of a Cancer Moonshot to accelerate cancer research. The initiative – led by Vice President Joe Biden – aims to make more therapies available to more patients, while also improving our ability to prevent cancer and detect it at an early stage. A task force was charged with identifying key priorities some of which were accelerating our understanding of cancer and its prevention, early detection, treatment, and cure as well as encouraging the development of new cancer treatments. As of 2017, it is now fair to say that in oncology the concept of precision medicine, incorporating genomics into drug discovery and cancer treatment strategies, has finally been realized and is now firmly embedded in ongoing drug discovery programs and cancer treatments. This particularly holds true for diseases such as breast and nonsmall cell lung cancer or melanoma where multiple new-targeted therapies have been approved in the last decade. These new therapies refer to a new generation of cancer drugs that are designed to interfere with a specific molecular target that is believed to have a critical role in tumor growth or progression. This approach contrasts with the conventional, more empirical approach used to develop cytotoxic chemotherapeutics – the mainstay of cancer drug development in past decades. However, despite significant progress in the treatment of certain forms of cancer, it must be emphasized that very little progress has been made in the identification of novel targeted therapies for women diagnosed with gynecologic malignancies – cytotoxic chemotherapies are still the mainstay of treatment in 2017.

Consistent with this absence of progress for patients diagnosed with gynecologic malignancies survival rates for patients diagnosed with ovarian, endometrial or cervical cancer have at large remained unchanged or have only minimally improved over the last 30 years [1,2]. Needless to say that during this time the importance of tumor surgery and platinum/taxane-based chemotherapy as treatment for ovarian, endometrial and cervical cancer has been recognized, but the small survival gains have been predominately realized through prolonging the life expectancy of women with recurrent ovarian cancer, not through an increased cure rate.

This lack of progress in new drug development for women diagnosed with gynecologic malignancies is, however, astounding and in stark contrast to the recent revolution in our understanding of cancer biology and tumor heterogeneity. Clearly, cancer genomics stands as a critical foundation for novel pathway and drug discovery and given the limitations of current therapeutic standards for the treatment of gynecologic malignancies, there is little doubt that a better and quicker translation of cancer genomics into rational clinical trials could create real improvements for patients diagnosed with gynecologic cancers. In this issue of *Current Opinion in Obstetrics and Gynecology* a series of articles highlight recent advances but also key challenges in our pursuit to utilize cancer genomics for new drug discovery and personalized medicine in gynecologic oncology.

Bayer *et al.* (pp. 4–11) illustrated the power of a concerted large integrative cancer genomics effort to identify novel genes and proteins in cancer. This article beautifully illustrates how genomics can transform the path to drug discovery. In the 1990s, short expressed gene sequences were generated from cDNA libraries that were assembled from mRNA isolated from cells and tissues of interest. Full-length sequences were then overexpressed in transgenic mice and were subsequently screened for radiographical, biochemical, hematological, and histological differences from their wild-type littermates as a means of deciphering gene function. This effort led to the discovery of osteoprotegerin (OPG)

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and the receptor activator of nuclear factor kappa-B (RANK) and its ligand (RANKL) and their role in regulating bone metabolism. Further molecular genetics studies in mice confirmed the essential role of both RANK and RANKL in the development of osteoclasts, which led to the development of the fully human anti-RANKL antibody denosumab. In 2001, Amgen initiated clinical programs to establish the efficacy and safety of denosumab in patients with osteoporosis and cancer-induced bone destruction in advanced cancer; further studies were initiated to evaluate the potential of denosumab to delay or prevent the development of bone metastases in breast cancer. An overview of these programs is summarized in this issue in the article by Bayer *et al.* (pp. 4–11). The history of this translational effort is a case study for the successful conversion of a seminal genomics discovery into an innovative, first-in-class therapeutic.

In this issue, Barnato Giordano and Gradishar (pp. 12–17) illustrate how genomics has transformed the path to drug discovery in breast cancer and summarize recent clinical progress seen in the treatment of breast cancer patients. Importantly, they focus on the fact that our understanding of breast cancer continues to evolve through advances in molecular biology, allowing improved definition of target specific therapies. However, they are clear to point out that the precise role and sequence of conventional and targeted therapies, including immunotherapy, will require careful attention to the design of clinical trials with translational emphasis to allow the discovery, validation and implementation of predictive biomarkers into clinical care.

The integration of molecular testing and molecularly targeted therapy into the diagnosis and treatment of certain cancers, such as breast cancer, nonsmall cell lung cancer, melanoma, and chronic myeloid leukemia, has become part of the standard of care for patients diagnosed with these diseases. However, the adoption of comprehensive genomic profiling in gynecologic malignancies at both the academic and community level has been less robust than in other areas of oncology and molecularly targeted therapy for the treatment of these diseases, with the exception of BRCA1/2-directed therapy in ovarian cancer, remains investigational. In this issue Prendergast and Elvin (pp. 18–25) report on the current experience of molecular profiling in gynecologic malignancies and clearly demonstrate that targeted therapy directed against actionable mutations and identification of molecular subsets with distinct prognostic significance within gynecologic cancers is now feasible in clinical practice. Moreover, institutions with access to clinical trials investigating off-label therapies, and molecular-focused tumor boards are beginning to close this actionability gap much more quickly. The Targeted Agent and Profiling Utilization Registry (TAPUR) Study, for example, is a nonrandomized clinical trial that aims to describe the safety and efficacy of commercially available, targeted anticancer drugs prescribed for treatment of patients with advanced cancer that have a potentially actionable genomic variant. TAPUR will study Food and Drug Administration (FDA)-approved targeted therapies that are contributed by collaborating pharmaceutical companies. The purpose of this study is to learn from the real world practice of prescribing targeted therapies to patients with advanced cancer whose tumor harbors a genomic variant known to be a drug target or to predict sensitivity to a drug. A patient whose tumor shows a VEGFR mutation, amplification or overexpression would be given access to axitinib, with a Bcr-abl, SRC, LYN, LCK mutation to bosutinib, with an ALK, ROS1, MET mutation to crizotinib, with CDKN2A/p16 loss, CDK4, CDK6 amplification to palbociclib, with CSF1R, PDGFR, VEGFR mutations to sunitinib, with mTOR, TSC mutation to temsirolimus, with EGFR mutation to erlotinib, with a HER2 amplification to trastuzumab and pertuzumab, with a BRAFV600E mutation to vemurafenib and cobimetinib, with a PTCH1 deletion or inactivating mutation to vismodegib, with RET, VEGFR1, VEGFR2, VEGFR3, KIT, PDGFRβ, RAF-1, BRAF mutation/amplification to regorafenib, with a germline or somatic BRCA1/BRCA2 inactivating mutation or ATM mutation or deletion to olaparib, or with a POLE/POLD1 mutation access to pembrolizumab (ClinicalTrials.gov Identifier: NCT02693535).

Recent studies have shown that fallopian tube secretory epithelial cells (FTSECs) give rise to the most common form of ovarian cancer, high-grade serous ovarian carcinomas. In this issue, Kroeger and Drapkin (pp. 26–34) have summarized the recent evidence supporting the fallopian tube as the origin of ovarian cancer. Although it remains unclear what triggers neoplastic transformation of these cells, certain tumors exhibit loss of BRCA function or amplification of CCNE1. These alterations represent unique therapeutic opportunities in ovarian cancer. Kroeger and Drapkin (pp. 26–34) explore these new opportunities in light of our improved understanding of the exact origins of ovarian cancer.

Subsequently, Uppendahl *et al.* (pp. 35–39) summarize the changing landscape of endometrial cancer biology. As highlighted in this comprehensive review recent integrated genomic, transcriptomic and proteomic characterization of endometrial carcinomas using array-based and sequencing-based technologies has allowed the classification of endometrial cancers into four categories: POLE

ultramutated, microsatellite instability hypermutated, copy-number low, and copy-number high. Uppendahl *et al.* clearly illustrate how this new understanding will permit a reclassification that may affect treatment for women with aggressive tumors suggesting that genomic-based classification may lead to improved management of these patients.

Despite the global impact on women's health associated with endometrial cancer, there is not a screening test for it. However, the evolving knowledge of molecular changes involved in endometrial cancer carcinogenesis paired with sensitive and high throughput technological advancements now represents an unprecedented opportunity that can be leveraged to detect tumor DNA and proteins. Bagaria *et al.* (pp. 40–46) describe how these molecular biomarkers can now be identified in biospecimens collected via minimally invasive and noninvasive approaches. Knowledge of these genomic features preceding carcinogenesis could be utilized as biomarkers for the presence of disease and eventually in endometrial cancer screening.

Finally, Lee *et al.* (pp. 47–58) summarize recent clinical progress seen in the treatment of endometrial cancer. Importantly, this article emphasizes on the fact that our understanding of endometrial cancer continues to evolve through improvements in molecular biology, allowing the development of improved target specific therapies.

Without doubt, a Cancer Moonshot initiative would greatly facilitate efforts described in this issue to better understand how genetic factors impact the onset and outcomes of women diagnosed with breast and gynecologic malignancies. However, a Cancer Moonshot initiative still needs to be fully implemented and it is to be hoped that it can be sustained on a bipartisan basis and survive the turmoil of the recent election. Importantly, in order to secure the implementation of a Cancer Moonshot it will require a boost in funding from Congress and we as researchers and clinicians need to express continued support to turn it into legislation and help it become a reality.

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Conflicts of interest

There are no conflicts of interest.

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