Genomics in Gynecological Cancer: Future Perspective

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Abstract

All cancers arise as a result of dynamic changes in the cancer genome. Cancer cells show diverse biological capabilities that are conferred by numerous genetic and epigenetic changes. Over the past years, comprehensive genomic studies using next-generation sequencing technology have resulted in an increasing wealth of the understanding of molecular mechanisms with respect to the genomic features of gynecological malignancies, including ovarian, endometrial, and cervical cancers. These studies can be exploited to develop and improve cancer classification, new diagnostic methods, and novel therapeutic strategies.

In this chapter, we review the principles of our current understanding of cancer genomes in gynecological malignancies, particularly ovarian, endometrial, and cervical cancers. Furthermore, a vision for the future of genomics in gynecological cancer has been discussed. We hope that cancer genomic research will ultimately guide clinical decision-making in association with the development of novel therapeutic strategies and biomarker-based clinical trials, affecting the clinical outcome of cancer patients.

Keywords

Cancer genome • Gynecologic cancer • Ovarian cancer • Endometrial cancer Cervical cancer

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2.1 Introduction

After a quarter of a century of rapid advances, comprehensive genomic studies have generated a complex body of knowledge, demonstrating cancer to be a disease involving dynamic changes in the "cancer genome" [1]. A cancer genome harbors numerous alterations at the level of the nucleotides, chromatin, and chromosomes [2, 3]. These alterations comprise irreversible aberrations in the DNA structure and in the number of particular sequences, genes, or chromosomes. Additionally, they include reversible changes, such as epigenetic modifications in the DNA and histone proteins. These reversible and irreversible changes collectively induce the activation or inhibition of various biological molecular pathways, affecting cancer pathophysiology, including invasion, metastasis, immune evasion, angiogenesis, or cell death [4].

Integrated genome-wide sequencing has recently demonstrated the genomic landscapes of common forms of human cancer (Fig. 2.1) [5, 6]. The valuable

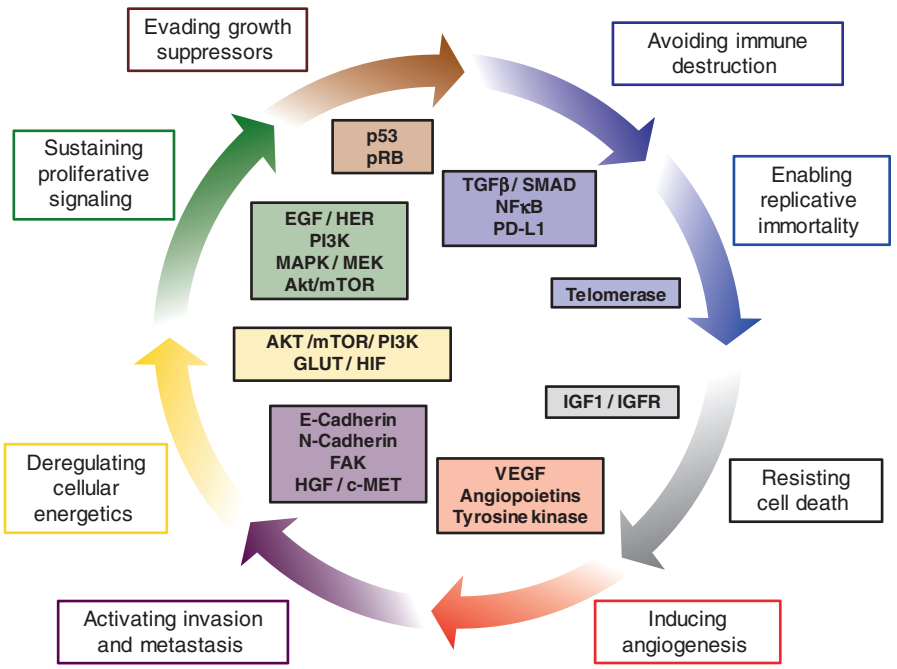

Fig. 2.1 The hallmarks of cancer. The hallmarks of cancer comprehend several capabilities acquired during the multistep development of cancers. These hallmarks constitute an organizing principle for rationalizing the complexities of cancer and also become major targets for cancer research and therapeutic strategies

information from cancer genome studies can be exploited to develop methods for prevention and early detection of cancer, which will be essential to reduce cancer morbidity and mortality [2]. Furthermore, these studies can identify the underlying molecular mechanisms that can be targeted for cancer therapy and the prediction of response to cancer therapies, affecting the clinical outcome of cancer patients [7–9].

This chapter aims to demonstrate the impact of comprehensive genomic research on gynecological cancer, including ovarian, endometrial, and cervical cancers. We review their implications for better understanding of the cancer genome, leading to improved cancer classification and development of new diagnostic methods and therapeutic approaches in gynecological malignancies. Furthermore, a vision for the future of genomic research in gynecological cancer is discussed.

2.2 The Cancer Genome Atlas Project

The latest development in the technological advances of genome-wide sequencing and bioinformatics has shed new light on the cancer genome [3, 7]. In 2005, The Cancer Genome Atlas (TCGA) was launched as the main project accelerating the comprehensive understanding of cancer genomics using innovative genomic technologies [7]. TCGA has profiled and analyzed major molecular alterations at the DNA, RNA, protein, and epigenetic levels in large cohorts of over 30 human tumors through large-scale genome-wide sequencing and integrated multidimensional analyses [8, 9]. The large amount of available data provides a crucial opportunity to develop an integrated picture of commonalities, differences, and emergent themes across tumor lineages. Evaluation of the molecular aberrations and their functional roles across tumor types will guide us in how to extend effective cancer therapies in one cancer type to others with a similar genomic profile [8].

Phase I of TCGA project aimed to test the research infrastructure based on the characterization of chosen tumors having poor prognosis: brain, lung, and ovarian cancers. Since then, phase II analyses have expanded to more than 30 different tumor types, including endometrial and cervical cancers [8]. By January 2015, TCGA announced that it had successfully collected the necessary quality and quantity of samples for all 33 selected tumor types. Table 2.1 shows a summary of the available TCGA genomic data as of May 2016. In the field of gynecological malignancies, these recent advances in innovative genome analysis technologies have resulted in an increasing understanding of molecular mechanisms with respect to the genomic features of ovarian, endometrial, and cervical cancer [10].

Table 2.1 Summary of the Cancer Genome Atlas cases with data as of May 2016

Selected cancer	No. of cases with data	Selected cancer	No. of cases with data
Breast invasive carcinoma	1097	Kidney renal papillary cell carcinoma	291
Ovarian serous cystadenocarcinoma	586	Sarcoma	261
Uterine corpus endometrial carcinoma	548	Acute myeloid leukemia	200
Kidney renal clear cell carcinoma	536	Esophageal carcinoma	185
Glioblastoma multiforme	528	Pancreatic adenocarcinoma	185
Head and neck squamous cell carcinoma	528	Pheochromocytoma and paraganglioma	179
Lung adenocarcinoma	521	Rectum adenocarcinoma	171
Brain lower grade glioma	516	Testicular germ cell tumors	150
Thyroid carcinoma	507	Thymoma	124
Lung squamous cell carcinoma	504	Mesothelioma	87
Prostate adenocarcinoma	498	Adrenocortical carcinoma	80
Skin cutaneous melanoma	470	Uveal melanoma	80
Colon adenocarcinoma	461	Kidney chromophobe	66
Stomach adenocarcinoma	443	Uterine carcinosarcoma	57
Bladder urothelial carcinoma	412	Lymphoid neoplasm diffuse large B-celll lymphoma	48
Liver hepatocellular carcinoma	377	Cholangiocarcinoma	36
Cervical squamous cell carcinoma and endocervical adenocarcinoma	307		

2.3 The Genomics of Ovarian Cancer

2.3.1 Molecular Pathogenesis of Ovarian Cancer

Epithelial ovarian cancer has the highest case fatality rate of any gynecological cancer, and it is the leading cause of death among female genital tract malignancies [11, 12]. Because most patients with ovarian cancer are diagnosed at an advanced stage, the clinical outcome for ovarian cancer is poor even after treatment with extirpative surgery and chemotherapy [13]. Despite a high response rate to initial chemotherapy, most patients will suffer relapse and the development of drug-resistant disease [14, 15].

Currently, based on histopathology, ovarian cancers are divided into five main histological types: high-grade serous carcinoma, low-grade serous carcinoma, endometrioid carcinoma, clear cell carcinoma, and mucinous carcinoma [16]. These tumors account for 98% of all ovarian cancers and can be reproducibly diagnosed by light microscopy [17]. These histological types are essentially distinct diseases, as indicated by differences in precursor lesions, patterns of spread, response to chemotherapy, and prognosis [16, 18].

Table 2.2 Dualistic model of ovarian carcinogenesis based on morphological and molecular genetic analysis

	Histological type	Precursors	Molecular genetic alterations
Type I tumors	Low-grade serous carcinoma	Serous cystadenoma/adenofibroma Atypical proliferative serous tumor Noninvasive micropapillary serous carcinoma	*BRAF* and *KRAS* mutations
	Mucinous carcinoma	Mucinous cystadenoma Atypical proliferative mucinous tumor	*KRAS* mutations
	Endometrioid carcinoma	Endometriosis Endometrioid adenofibroma Atypical proliferative endometrioid tumor	LOH or *PTEN* mutations *KRAS* mutations Microsatellite instability
	Clear cell carcinoma	Endometriosis Clear cell adenofibroma Atypical proliferative clear cell tumor	*KRAS* mutations Microsatellite instability TGF-β RII mutations
Type II tumors	High-grade serous carcinoma	Not yet identified	*p53* mutations Amplification and overexpression of *HER2/neu* gene Inactivation of *p16* gene
	Undifferentiated carcinoma	Not yet identified	Not yet identified

Recent research into molecular biology of ovarian cancers demonstrated that ovarian cancers comprise both clinically diverse and molecularly heterogeneous malignancies, encompassing subtypes with distinct gene expression patterns that are correlated with different clinical outcomes [11, 19]. In the early twenty-first century, morphologic, immunohistochemical, and molecular studies led to a new paradigm for the pathogenesis of ovarian cancer, which divided ovarian cancer into two groups designated as type I and type II (Table 2.2) [18, 20]. Type I tumors include low-grade serous carcinoma, endometrioid carcinoma, clear cell carcinoma, and mucinous carcinoma, which develop in a stepwise fashion from well-recognized precursor lesions, such as borderline tumors or endometriosis [20]. They present as large masses that are confined to the ovary; they are generally indolent and have a favorable prognosis. These tumors are genetically stable and are typically characterized by a variety of somatic sequence mutations, including *KRAS*, *BRAF*, *ERBB2*, *CTNNB1*, *PTEN*, *PIK3CA*, and *ARID1A* [16, 18, 19]. On the other hand, type II tumors comprise of high-grade serous carcinoma and undifferentiated carcinoma, which develop de novo, and are highly aggressive, and have a poor prognosis [19, 20]. These tumors are chromosomally highly unstable and harbor *TP53* mutations, and BRCA inactivation occurs in up to 40%–50% of high-grade serous carcinoma [21].

Recognition of the dualistic model of ovarian carcinogenesis provided a new opportunity for better management of ovarian cancer patients, and knowledge of molecular mechanisms and the pathogenesis of various types of ovarian cancer could lead to more targeted therapeutic interventions [14, 22].

2.3.2 Comprehensive Genomic Characterization of High-Grade Serous Ovarian Carcinoma

In 2011, TCGA project reported the results of a wide-range analysis of the genomic and epigenetic changes that occur in 489 high-grade serous ovarian carcinomas and demonstrated several potential therapeutic molecular targets [23]. TCGA scientists determined the presence of *TP53* mutation in almost all tumor specimens of high-grade serous carcinoma and a low prevalence but statistically significant frequency of somatic mutations in nine further genes, including *BRCA1*, *BRCA2*, *NF1*, *RB1*, and *CDK12*. Identification of these molecular pathways is likely to provide novel therapeutic approaches [23, 24]. Furthermore, the four molecular subtypes were validated in high-grade serous carcinoma cases using approximately 1500 intrinsically variable genes and were termed (a) immunoreactive, (b) differentiated, (c) proliferative, and (d) mesenchymal on the basis of gene expression in the clusters [23].

Understanding the molecular classification of ovarian cancer using comprehensive genomic analysis could lead to the development of prediction of response to therapies and improved prognostic indicators [22, 25]. In fact, these four molecular subtypes have been independently validated and have been shown to be of independent prognostic relevance [25, 26]. Moreover, TCGA data have helped to clarify the effect of *BRCA1/2* mutations on survival outcomes in patients with ovarian cancer [27]. These evolving subgroups in ovarian cancer have distinct biologic characteristics that can translate into different therapeutic implications, which will allow gynecologists to identify women likely to benefit from a given cancer therapy [6].

Taken together, ovarian cancer is a spectrum of diseases and not a single disease entity. Nevertheless, current clinical management fails to incorporate these facts into treatment strategies for ovarian cancer patients because of the lack of insight into distinct molecular mechanisms for these cancers. Improvements in ovarian cancer survival should be achieved by translating recent biological insights at the molecular level into personalized individual treatment strategies [2, 7].

2.4 The Genomics of Endometrial Cancer

2.4.1 Pathological and Molecular Characteristics of Endometrial Cancer

Endometrial cancer is one of the most prevalent malignant tumors of the female genital tract, and its incidence rate is increasing rapidly in developed countries [28]. The majority of patients with endometrial cancer are diagnosed at an early stage,

resulting in overall favorable prognosis with high cancer-specific survival rates [29]. However, for patients with advanced-stage disease or for those with recurrent endometrial cancer, the prognosis remains poor and the optimal adjuvant therapy is yet to be established [30].

Endometrial cancer is divided into several histologic categories based on cell type. Endometrioid carcinoma is the most common cell type, accounting for 75–80% of cases, and subdivided into grade 1 to grade 3, according to degree of differentiation [31]. In addition, other aggressive pathologic variants include serous, clear cell, mixed, and undifferentiated types [32].

In 1983, Bokhman proposed that there are two different pathogenetic types of endometrial cancer that are primarily based on light microscopic appearance, clinical behavior, and epidemiology [33, 34]. Type I tumors are mostly composed of endometrioid carcinomas and are generally correlated with endometrial hyperplasia, express estrogen, and progesterone receptors [35]. These tumors arise in a background of unopposed estrogen stimulation, occur in premenopausal and perimenopausal women, and histologically show low-grade endometrioid differentiation. In contrast, type II tumors are more aggressive and mostly include high-grade endometrioid, serous, or clear cell histological types, and generally develop from atrophic endometrial tissues unrelated to estrogen stimulation in older women [35–37].

Previous molecular studies of endometrial cancer demonstrated that type I tumors are correlated with mutations in *PTEN*, *KRAS*, *PIK3CA*, and *CTNNB1* and frequently show microsatellite instability (MSI) [38, 39] but do not usually have mutations in the *TP53* tumor suppressor gene [35]. In contrast, a majority of type II tumors have *TP53* mutations, and loss of heterozygosity (LOH) on several chromosomes, as well as molecular alterations affecting *p16*, *STK15*, *E-cadherin*, and *c-erb-B2* [35, 36].

In the past decade, it has become more obvious that endometrial cancer comprises a clinically, histologically, and genetically heterogeneous group of tumors. However, Bokhman's dualistic classification model does not entirely take into account this heterogeneity. As a consequence, traditional classifications are insufficient overall for successful treatment and are limited in predicting response to specific therapies [36].

2.4.2 New Genomic Classification of Endometrial Cancer

In 2013, TCGA Research Network reported a comprehensive genomic and transcriptomic analysis of endometrial cancers, using next-generation sequencing technologies in combination with analysis of DNA methylation, reverse phase protein array, and MSI [40]. This study focused on common histological types, including endometrioid (n = 307), serous (n = 53), and mixed endometrioid and serous (n = 13) carcinomas. On the basis of integrated analysis, endometrial cancers were classified into four distinct molecular subgroups: (a) *POLE* ultramutated, (b) MSI hypermutated, (c) copy-number low, and (d) copy-number

Table 2.3 Genomic classification of endometrial cancer

	POLE ultramutated	MSI hypermutated	Copy-number low	Copy-number high
Copy-number aberrations	Low	Low	Low	High
Mutation rate	Very high	High	Low	Low
MSI/MLH1 methylation	Mixed MSI high, low, stable	MSI high	MSI stable	MSI stable
Genes mutated (%)	*POLE* (100%) *PTEN* (94%) *PIK3CA* (71%) *PIK3R1* (65%) *FBXW7* (82%) *ARID1A* (76%) *KRAS* (53%)	*PTEN* (88%) *RPL22* (37%) *KRAS* (35%) *PIK3CA* (54%) *PIK3R1* (40%) *ARID1A* (37%)	*PTEN* (77%) *CTNNB1* (52%) *PIK3CA* (53%) *PIK3R1* (33%) *ARID1A* (42%)	*TP53* (92%) *PPP2R1A* (22%) *PIK3CA* (47%)
Histological type	Endometrioid	Endometrioid	Endometrioid	Serous, endometrioid, and mixed serous and endometrioid
Tumor histological grade	Mixed (grade 1-3)	Mixed (grade 1-3)	Grade 1 and 2	Grade 3

high (Table 2.3). The *POLE* ultramutated group was characterized by extraordinarily high mutation rates and hotspot mutations in the exonuclease domain of *POLE*, which is a catalytic subunit of DNA polymerase epsilon and is involved in nuclear DNA replication and repair. The MSI hypermutated group had tumors showing increased MSI because of *MLH1* promoter methylation. The copy-number low group was microsatellite stable and had a lower mutation frequency. In this group, most of the tumors were grade 1 and 2 endometrioid carcinomas characterized by frequent *CTNNB1* mutations. The copy-number high group had a low mutation frequency but a high rate of somatic copy number alterations, and this group contained most of the serous and mixed histology tumors with frequent *TP53* mutations [40].

Comprehension of the genomic classification of endometrial cancer has an important role in developing improved prognostic indicators. When the progression-free survival (PFS) was analyzed in TCGA study, it was demonstrated that the *POLE* ultramutated group had a significantly favorable PFS, whereas the copy-number high group had the poorest survival outcome [40].

Overall, the TCGA genomic characterization of endometrial cancers has confirmed and expanded knowledge of molecular signaling pathways and permitted reclassification of endometrial cancers, which could directly affect prognostic assessment, prediction of response to therapies, and treatment decisions [34, 36, 40]. In order to achieve the ultimate goal of developing clinical measures that will improve the outcomes of patients with endometrial cancer, further studies of genomic abnormalities in endometrial cancer are needed to identify new therapeutic molecular targets, leading to personalized individual treatment strategies.

2.5 The Genomics of Cervical Cancer

2.5.1 Molecular Mechanisms of HPV-Induced Cervical Carcinogenesis

Cervical cancer is the second most common malignancy in women worldwide after breast cancer and the leading cause of cancer-related deaths in developing countries [41]. Unlike many other solid cancers, cervical cancer is currently more prevalent in younger women. Even though early-stage and locally advanced cervical cancers may be cured with radical surgery and chemoradiotherapy, patients with metastatic cancers or recurrent disease have limited therapy options.

The major histopathologic types of cervical cancer are squamous cell carcinoma and adenocarcinoma, which constitute approximately 80% and 20% of all cases of cervical cancer, respectively [42]. Cervical squamous cell carcinoma arises in the squamocolumnar junction and is preceded by a long phase of cervical intraepithelial neoplasia [43]. Cervical adenocarcinoma originates from glandular precursor lesions of the endocervical mucosa and comprises several histological subtypes, including mucinous, endometrioid, clear cell, and serous adenocarcinomas [44].

Human papillomavirus (HPV) infection is recognized as the main cause of cervical cancer [41]. Oncogenic HPVs, mainly HPV16 and 18 genotypes, have been closely associated with the risk of developing intraepithelial lesions, squamous cell carcinoma, and adenocarcinoma of the cervix [45]. The viral oncoproteins E6 and E7 of high-risk HPVs contribute to the transformation of infected epithelial cells mainly through the inactivation of the *TP53* and *RB* tumor suppressor genes and related pathway [42]. However, recent studies have shown that alterations of additional pathways are equally important for transformation of HPV-infected cells, and these additional factors are crucial regulators of cell cycle progression, apoptosis, and chromosomal stability [42]. As a consequence, the accumulation of genetic and epigenetic alterations over time may ultimately lead to cervical cancer.

The Nobel Prize-winning identification of a causative correlation between the viral infection HPV and cervical carcinogenesis served as a driving force behind the development of HPV vaccines in an effort to prevent HPV infection. Even though, in the past, cervical cancer was the most common cause of cancer-related mortality for women, major advancements in screening and prevention during the past half-century have significantly impacted this picture.

2.5.2 Genomic Alterations in Cervical Cancer

In an effort to develop more effective cancer therapies, the focus has shifted toward improving our understanding of the genetic foundations of cervical cancer. Thus far, relatively few reports on genomic alterations in oncogenes and tumor suppressor genes have been demonstrated for cervical cancer [46, 47]. In 2014, a comprehensive genomic analysis of cervical cancers was performed by whole-exome sequencing analysis in 79 squamous cell carcinomas and 24 adenocarcinomas [48]. *PIK3CA* is

Table 2.4 Significantly mutated genes in cervical cancer

Gene	Description	Relative frequency (%)
Squamous cell carcinoma		
PIK3CA	Phosphatidylinositol-4,5-bisphosphate 3-kinase, catalytic subunit alpha	14
FBXW7	F-box and WD repeat domain containing 7	15
MAPK1	Mitogen-activated protein kinase 1	8
HLA-B	Major histocompatibility complex class 1, B	9
Ep300	E1A binding protein p300	16
STK11	Serine/threonine kinase 11	4
ERBB2	Erb-b2 receptor tyrosine kinase 2	5
EGFR	Epidermal growth factor receptor	8
PTEN	Phosphatase and tensin homolog	6
Adenocarcinoma		
PIK3CA	Phosphatidylinositol-4,5-bisphosphate 3-kinase, catalytic subunit alpha	16
KRAS	KRAS proto-oncogene	8
ELF3	E74-like factor 3	13
CBFB	Core-binding factor, beta subunit	8

one of the most commonly mutated genes associated with cervical cancer in both squamous cell carcinoma and adenocarcinoma, indicating that the PIK3CA pathway could represent a promising therapeutic strategy. Because the gene products of *TP53* and *RB1* are inactivated by E6 and E7, they are rarely mutated in cervical cancer [46]. Intriguingly, a previous study also reported that *EGFR* mutations were identified in squamous cell carcinoma only, whereas *KRAS* mutations were detected in adenocarcinoma only, demonstrating that the genetic mutation pictures differed depending on tumor histology (Table 2.4) [49]. These data suggested that molecular targeted therapies should make a promising therapeutic avenue for cervical cancer.

2.6 Evolving Genomic Comprehension of HPV in Cervical Carcinogenesis

Following the initial discovery of HPV DNA in the human genome, various studies have evaluated its genomic role in cervical cancer development [46, 48]. A crucial mechanism in cervical carcinogenesis is represented by the integration of the HPV genome into human chromosomes [50]. Adding to the complex molecular background, whole-genome sequencing and high-throughput viral integration detection have newly begun to shed light on the central role of HPV in cervical carcinogenesis [51, 52]. A recent study has reported a genome-wide analysis of HPV integration in cervical intraepithelial neoplasias and cervical cancers, and the authors of this study identified HPV integration hotspots in the human genome [51]. The most frequently affected genes are *POU5F1B*, *FHIT*, *KLF12*, *KLF5*, *LRP1B*, *HMGA2*, and *SEMA3D*, supporting their oncogenic role in cervical cancer [51]. The relationship between HPV integration and increased expression of adjacent genes may be a widespread phenomenon in cervical carcinogenesis [48].

Therefore, elucidating the mechanisms of HPV integration will yield insight into HPV-induced cervical carcinogenesis [51]. A better comprehension of the molecular pathogenesis of cervical cancer is of critical importance to identify new therapeutic targets and should lead to the development of personalized individual treatment strategies for patients with cervical cancer [41].

2.7 Future Perspectives for Integrating Genomics in Gynecological Cancer

The overarching goal of TCGA is to improve our understanding of the molecular basis of cancer and advance our ability to diagnose, treat, and prevent cancer through the discoveries and insights enabled by comprehensive mapping of various types of cancer [8, 9]. Furthermore, it is expected that translation of cancer genomics into therapeutics and diagnostics will provide a great potential to develop personalized cancer medicine [53, 54].

To date, TCGA project has provided a strong foundation for genomic studies and has stimulated a diversity of gynecological cancer research [23, 24, 40, 48, 51]. Furthermore, the development of genomic research in gynecological malignancies has led to increased enthusiasm in relation to the promises of targeted therapies and has stimulated rapid advances in genomic technologies to identify the disease biomarkers for gynecological cancer [6]. Even though there has been tremendous success in the rapid accumulation of cancer genomic studies, most of these enormous data sets have not yet been translated into meaningful clinical end points.

We hope that cancer genomic research will ultimately guide clinical decision-making in association with the discovery of novel therapeutic agents and biomarker-based clinical trials that cross boundaries between tumor types. This process will require the amalgamation of expertise and insights from cancer biology, cancer genetics, as well as clinical experiences. It is clear that there is still a long way ahead of us, but the journey to find answers to eradicate gynecological cancer is sure to be an exciting one.

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