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Genomic insights in gynecologic cancer

Erika Roddy, BA[a], Jocelyn Chapman, MD[b,*]

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ABSTRACT

Recent technological advances in DNA sequencing have enabled a remarkably detailed understanding of the molecular changes that define gynecologic and other cancers. Several groups have carried out large-scale genomic analyses of ovarian, uterine, and most recently, cervical cancer. These analyses have led to new insights into the molecular changes characterizing these cancers, which provide insight into clinical outcomes. These molecular characterizations have similarly led to new genomic-based classification schemas, which may better stratify clinical outcomes, help prognosticate and guide treatments. Discovery of characteristic mutations may also provide potential new targets for molecularly targeted chemotherapies, as has been already described with poly-ADP ribose polymerase inhibitors and ovarian cancer. The purpose of this article is to provide an overview of the defining molecular abnormalities and markers in gynecologic cancer, to discuss the clinical implications, and to provide a comprehensive view of the current state of genomic knowledge in gynecologic cancer.

[a] *School of Medicine, University of California San Francisco, San Francisco, CA*
[b] *Division of Gynecologic Oncology, Department of Obstetrics, Gynecology & Reproductive Sciences, University of California San Francisco, San Francisco, CA*
**Correspondence to: Jocelyn Chapman, MD, Division of Gynecologic Oncology, Department of Obstetrics, Gynecology & Reproductive Sciences, University of California San Francisco, 550 16th St, 7th Floor, Box 0132, San Francisco, CA 94158.*
E-mail address: jocelyn.chapman@ucsf.edu (J. Chapman).

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Introduction

Large-scale molecular profiling has revolutionized cancer research.[1] Cancer is fundamentally a disease driven by genomic changes, and understanding the molecular machinery in tumorigenesis is essential to detect cancer early in carcinogenesis, develop targeted and less toxic therapies, and understand resistance to treatment. Until recently, genetic research in cancer was limited to individual candidate gene studies, which were biased by requiring the identification of putative candidate genes in advance. Success depended on the correct choice of genes to study. However, in the past decade, techniques such as massively parallel next-generation sequencing (NGS)[2,3] have enabled the creation of a simultaneously global yet microscopic view of the genomic, transcriptomic, and epigenomic changes associated with individual cancers, including a variety of gynecologic cancers.[4-8] Importantly, such approaches are unbiased by preselection of genes. Using these techniques, specific types of malignancies as well as individual tumors themselves have been characterized in detail.[9-14] Understanding the aberrant signaling pathways in tumorigenesis and discovery of actionable or "druggable" mutations in sequenced tumors have provided the opportunity for rationally designed, targeted therapies that promise improved efficacy and decreased toxicity compared with standard cytotoxic chemotherapy and radiation treatments.[15-17]

Traditionally, cancer nomenclature and classification has been based primarily on organ location, and subsequently subclassified by cell type, histologic grade, and histopathologically identifiable molecular markers such as hormonal receptor status in breast cancer and microsatellite instability (MSI) in endometrial or colorectal cancer.[18] New data regarding molecular changes in multiple cancer types have subsequently led to further refinement of cancer subtypes, as well as new and exciting insights into the tumorigenesis and genetic diversity of cancer. Recent pancancer investigations have searched for common molecular dysregulation across cancer types.[19,20] Novel insights generated from these and other studies hold promise in improving prognostic accuracy, identifying clinically actionable genes and targets for drug development, influencing clinical trial design, and using individual tumor mutation data to create targeted therapies or identify resistance to certain therapies, in cancer in general and in gynecologic cancers in particular.

Techniques in computational genomics

Next-generation sequencing

A major goal of cancer research is to identify common mutations and anomalies within cancer types. Multiple projects have used large-scale NGS analyses of tumor samples to achieve this goal. The Cancer Genome Atlas (TCGA) is perhaps the largest, and most well known of these projects. Before the development of TCGA, genomic science was performed by individual institutions using single genomic platforms. However in 2006, TCGA was formed as a consortium for genomic research, with the goal of collecting approximately 500 samples per tumor type at numerous academic centers across the United States. Ovarian serous carcinoma, glioblastoma, and squamous cell lung cancer were included in the pilot project that has since been expanded to include a total of 31 tumor types fully sequenced and with data made publically available with an additional 12 tumor types in the analysis pipeline. In gynecologic cancer, full exome sequencing of ovarian serous, endometrioid uterine, uterine carcinosarcoma, and cervical carcinoma is complete.

Increasingly, NGS is used to help clinicians make clinical treatment decisions. For example, in breast cancer, the 70-gene panel MammaPrint was created using results from genomic analysis of breast cancer and is often used to supplement traditional pathology assessment and guide treatment.[21-23] Oncotype Dx is similarly used to determine the benefit of adjuvant chemotherapy in patients with breast cancer, thereby minimizing unnecessary treatment for women who are unlikely to benefit from chemotherapy.[24] In 2012, 19% of women with a diagnosis of