Endometrial cancer (EC) is among the most common gynecological cancers affecting women worldwide. Despite the early detection and rather high overall survival rate, around 20% of the cases recur with poor prognosis. The Next Generation Sequencing (NGS) technology, also known as massively parallel sequencing, symbolizes a high-throughput, fast, sensitive and accurate way to study the molecular landscape of a cancer and this has indeed revolutionized endometrial cancer research. Understanding the potential, advantages, and limitations of NGS will be crucial for the healthcare providers and scientists in providing the genome-driven care in this era of precision medicine and pharmacogenomics. This mini review aimed to compile and critically summarize the recent findings contributed by NGS technology pertaining to EC. Importantly, we also discussed the potential of this technology for fundamental discovery research, individualized therapy, screening of at-risk individual and early diagnosis.

Keywords: next generation sequencing, endometrial cancer, molecular landscape, precision medicine, screening, early diagnosis

OVERVIEW OF ENDOMETRIAL CANCER

Endometrial cancer (EC) ranks as the sixth most frequent cancers among women worldwide with around 320,000 reported cases and 76,000 deaths (International Agency for Research on Cancer [Iarc], 2014). This cancer is normally detected early with a relatively high overall survival rate (Sgo Clinical Practice Endometrial Cancer Working Group et al., 2014). However, nearly one fifth of the cases have poor prognosis with a median survival of about 1 year (Obel et al., 2006; Salvesen et al., 2012). Unopposed estrogen therapy, estrogen producing tumors, tamoxifen, obesity, nulliparity, diabetes mellitus, and early onset of menstruation are among the risk factors associated with EC (Brinton et al., 2005).

Bokhman (1983) was the first to propose the pathogenetic dualistic model of two different types of endometrial carcinoma, named as type I and type II. Type I endometrioid endometrial cancer (EEC) is driven by estrogen and represents most of sporadic cases (Bansal et al., 2009). EEC typically occurs in premenopausal and younger postmenopausal women who often diagnosed with low-grade well-differentiated tumor thus carrying a better prognosis (Soliman et al., 2005; Garg and Soslow, 2014). On the contrary, the type II non-endometrioid endometrial carcinoma (NEEC) accounts for only 10–20% of sporadic endometrial carcinoma with no underlying estrogen exposure (Doll et al., 2008). NEEC is commonly diagnosed in older postmenopausal women, who typically present with advanced-stage disease and poor prognosis (Amant et al., 2005). It is also
associated with high mortality and reduced survival rates (Hamilton et al., 2006; Mendivil et al., 2009). This classification is imperfect as the minority of EC characteristic of both groups may overlap because of heterogeneity of this disease, especially the high grade EEC (Murali et al., 2014). Characterization of molecular landscapes will give insights into tumor classification, which may influence treatment recommendations and provides prospects for precision medicine. Therefore, there is a need to explore the molecular landscape of EC treatment using the next generation sequencing (NGS) approaches.

Lynch Syndrome (LS) is a hereditary cancer syndrome caused by germline alterations in the DNA mismatch repair (MMR) genes (Tafe et al., 2014). Those with LS will have an increased risk of colon cancer. Despite being overlooked in association with LS, individuals with this syndrome also have a 20–60% risk of developing EC (Tafe et al., 2014). The mutation frequencies of MMR genes are: 50–66% in *MSH2*, 24–40% in *MLH1*, 10–13% in *MSH6* and <5% in *PMS2* (Wang et al., 2013).

OVERVIEW OF NEXT GENERATION SEQUENCING (NGS) TECHNOLOGY

The emergence of NGS three decades after Sanger sequencing represents the potential to dramatically revolutionize biomedical research by enabling the high throughput comprehensive analysis of genomes and transcriptomes at an inexpensive scale (Shendure and Ji, 2008). Compared with Sanger sequencing, NGS technologies offer extraordinarily high throughput capacity which reduces cost per base, time and has enabled the discovery of both common and rare variants with a much deeper sequencing read coverage (Koboldt et al., 2013). NGS is also a versatile technology which enables various applications including whole genome sequencing (WGS) for model and non-model organisms (Ng and Kirkness, 2010), whole exome sequencing (Rabbani et al., 2014), targeted resequencing (Meldrum et al., 2011) as well as analysis of coding and non-coding RNA expression, alternative splicing and discovery of novel non-coding RNAs (Wang et al., 2009). In addition, while 30x coverage for WGS is considered as the standard (Rehm et al., 2013), low-pass WGS with coverage less than 10x had also been used to assess structural variation (Cancer Genome Atlas Research Network et al., 2013).

Over the past 4 years, NGS technologies were applied in EC research (Table 1). NGS has promoted and improved the detection of key types of molecular alterations such as single nucleotide substitutions, small insertions, and deletions, copy number alterations, structural variations and novel transcripts. New drug targets were identified thus providing the oncologists with various potential options in treating EC patients (Figure 1). Here, we provide an overview of the use of NGS for subtype classification, identification of potential diagnostic biomarkers and screening of therapeutic targets for personalized treatment of EC.

Whole genome sequencing provides a comprehensive view of the cancer genome including all types of somatic/germline mutations, nucleotide substitutions, small insertions and deletions, copy number variations, chromosomal rearrangements, as well as analysis of the non-coding regions (Meyerson et al., 2010). Since WGS is still expensive, laborious and produces a massive amount of data for analysis and interpretation, whole exome sequencing (WES) which concentrates only on the protein-coding exon of human genome is a preferred alternative (Rabbani et al., 2014).

However, despite being high throughput, most of the information obtained from WGS and WES are functionally unclear and the genetic alterations could be just possible passenger mutations with unknown clinical significance (Meldrum et al., 2011). Besides, WGS and WES are unsuitable for clinical application because of relatively lower read depth and this later limit the identification of low-allelic-fraction single nucleotide polymorphisms (SNPs) which is important for early diagnosis, prevention of drug resistance and residual tumor detection (Xu et al., 2014). Therefore, deep sequencing of targeted gene provides better alternative in clinical setting due to several advantages including higher coverage for increased analytical sensitivity and specificity, generate feasible and interpretable data, significant cost reduction, and shorter turnaround time (Xu et al., 2014). Targeted gene sequencing also has proven useful for a large number of applications including studying disease-relevant gene subsets, diagnostic testing for hereditary disorders and therapeutic decision-making for somatic cancers (Rehm, 2013).

Since last decade, EC transcriptomes have been predominantly investigated using hybridization-based microarray techniques (Maxwell et al., 2005; Cohn et al., 2010; Ratner et al., 2010). The advent of NGS has also revolutionized cancer transcriptomics studies. RNA and miRNA sequencing have rapidly emerged as powerful tools for genome wide expression profiling and offer several advantages over conventional microarray.

WHOLE GENOME AND WHOLE EXOME SEQUENCING

To date, there is only one publication in EC by The Cancer Genome Atlas (TCGA) group which utilized WGS to characterize the chromosomal aberration in 106 ECs (Cancer Genome Atlas Research Network et al., 2013). Recurrent translocations of genes in important cancer pathways including WNT, EGFR–RAS–MAPK, PI3K, protein kinase A, retinoblastoma and apoptosis were identified (Cancer Genome Atlas Research Network et al., 2013). The most frequent translocations were discovered in a member of the BCL family which were *BCL2, BCL7A, BCL9*, and *BCL2L11* (Cancer Genome Atlas Research Network et al., 2013). This large-scale consortium also performed WES on 248 ECs and identified novel *POLE* hotspot mutations (Pro286Arg and Val411Leu) in 13 of the 17 ultra-mutated samples (Cancer Genome Atlas Research Network et al., 2013). In addition, *PTEN, PIK3R1, PIK3CA, FBXW7*, and *KRAS* were found to be significantly mutated. This was the largest genomic characterization of EC so far and their findings propose a reclassification that might assist in personalized treatment for patients with aggressive phenotype.
So far there are four published EC studies utilizing WES (Table 1). Liang et al. (2012) was the first to perform WES in 13 ECs with matched normal DNA. In combination with functional genomics, the authors identified 12 potential driver genes including 10 tumor suppressor genes (ARID1A, INHBA, KMO, TTI1L5, GRM8, IGFBP3, AKTIP, PHKA2, TRPS1, and WNT11) and two oncogenes (ERBB3 and RPS6KC1). Concentrating on ARID1A, mutation profiles were integrated with functional proteomics in additional 222 EC samples, demonstrating the role of ARID1A as a novel regulator of PI3K pathway activity (Liang et al., 2012).

While Liang et al. (2012) characterized the exomes of ECs without stratification of grade and histological subtypes, another group (Le Gallo et al., 2012) focused on the rare but aggressive serous carcinoma subtype of EC which has high recurrence rate, poor survival and more likely to present with metastatic disease due to resistance to chemotherapy (Hamilton et al., 2006). Le Gallo et al. (2012) performed WES on 13 matched pairs of serous ECs and normal tissues. In addition to confirming the existence of alterations in TP53, PIK3CA and PPP2R1A, they also identified high frequency of somatic alterations in novel genes involved in serous ECs which were FBXW7, CHD4, MAP3K4, ABCC9, and CYP4X1 (Le Gallo et al., 2012). Chromatin remodeling and ubiquitin ligase complex pathways were found to be the most perturbed pathways which have been associated with frequent alterations in set of 11 chromatin

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**TABLE 1** | Main findings contributed by Next Generation Sequencing (NGS) in endometrial cancers (ECs).

| Method                          | Samples                                | Main findings                                                                                           | Study                          |
|--------------------------------|-----------------------------------------|---------------------------------------------------------------------------------------------------------|--------------------------------|
| Low-pass whole genome sequencing | ECs and matched DNA from normal tissues or blood (n = 106 pairs) | Recurrent translocations of genes in WNT, EGFR–RAS–MAPK, PI3K, protein kinase A, retinoblastoma and apoptosis pathway. The most frequent translocations in the member of BCL family (BCL2, BCL7A, BCL9, and BCL2L11); Significance increase of transversion mutation frequency and novel hotspot mutations in POLE in a subset of endometrioid cancers. | Cancer Genome Atlas Research Network et al., 2013 |
| Whole exome sequencing          | ECs and matched DNA from normal tissues or blood (n = 248 pairs) | Frequent mutations in PTEN, CTNNB1, PIK3CA, ARID1A, KRAS and novel mutations in ARID5B. Significant increase of transversion mutation frequency and novel hotspot mutations in POLE in a subset of endometrioid cancers. | Le Gallo et al., 2012 |
| Whole exome sequencing          | EC and matched DNA from blood (n = 13 pairs) | Mutation on ARID1A are associated with PI3K pathway activation. | Liang et al., 2012 |
| Whole exome sequencing          | Uterine serous cancer and matched normal tissues (n = 13 pairs) | Mutation on chromatin-remodeling and ubiquitin ligase complex genes. | Le Gallo et al., 2012 |
| Whole exome sequencing          | Uterine serous cancer and matched DNA from blood or tissue samples (n = 10 pairs) | Mutation on FBXW7 and amplification of CCNE1 locus (encodes cyclin E, substrate of FBXW7). | Kuhn et al., 2012 |
| Whole exome sequencing          | Uterine serous cancer (n = 52) and matched DNA from blood (n = 34) | Mutation on SPOP, CDH4, TAF1, amplification of CCNE1 and loss of MBD3. | Zhao et al., 2013 |
| Targeted gene sequencing (nine genes) | Low-grade EEC (n = 276), grade 3 EEC (n = 30), serous (n = 37) and carcinosarcoma subtype (n = 42) | Distinct mutation frequency on PTEN and TP53 on low-grade EEC and grade 3 EEC. Significantly different mutations frequency on PTEN, ARID1A, PPP2R1A, TP53, and CTNNB1 between grade 3 EEC and serous carcinoma. | McConechy et al., 2012 |
| Targeted gene sequencing (seven genes) | EEC (n = 307) and ovarian endometrioid cancer (n = 33) | Distinct mutation profile in PTEN and CTNNB1. | McConechy et al., 2014 |
| Targeted gene sequencing (578 genes) | EC (n = 10) | Frequent mutations in PTEN (50%) and genes involved in the endometrial cancer-related molecular pathway including IL-7 signaling pathway. | Chang et al., 2016 |
| RNA sequencing                  | ECs (n = 333) | Three clusters; mitotic, hormonal and immune-reactive | Cancer Genome Atlas Research Network et al., 2013 |
| Small RNA sequencing            | ECs (n = 367) | Six miRNA clusters significantly associated with MLH1 hypermethylation (miR-148a and miR-375), histology, grade (miR-21) and stage. | Cancer Genome Atlas Research Network et al., 2013 |
| RNA sequencing                  | Stage I EEC and adjacent normal tissues (n = 3 pairs) | First report on dysregulation of miRNAs (hsa-miR-196a-5p, hsa-miR-328-3p, hsa-miR-307-3p, and hsa-miR-99a-3p) in EC. | Xiong et al., 2014 |
| Small RNA sequencing            | Normal, hyperplastic, and EC biopsies (n = 10 trios) | Definition of sncRNAs signature (1229 miRNAs, 10 piRNAs and three SnoRNAs) involved in neoplastic transformation. | Ravo et al., 2015 |
| Paired end RNA sequencing        | EC with matched non-cancerous tissue (n = 9 pairs) | Significant upregulation of fusion gene TSNAX-DISC1 in EC which formed through splicing without chromosomal rearrangement. | Li et al., 2014 |

EEC, Endometrial endometrioid carcinoma; sncRNAs, Small non-coding RNAs; miRNAs, MicroRNAs; piRNAs, Piwi-interacting RNA; SnoRNAs, Small nucleolar RNAs.

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Li et al. (2012) performed WES on 13 matched pairs of serous ECs and normal tissues. In addition to confirming the existence of alterations in TP53, PIK3CA and PPP2R1A, they also identified high frequency of somatic alterations in novel genes involved in serous ECs which were FBXW7, CHD4, SPOP, MAP3K4, ABCC9, and CYP4X1 (Le Gallo et al., 2012). Chromatin remodeling and ubiquitin ligase complex pathways were found to be the most perturbed pathways which have been associated with frequent alterations in set of 11 chromatin...
remodeling genes including CHD4 gene and component of ubiquitin ligase complex (FBXW7 and SPOP gene), respectively (Le Gallo et al., 2012).

In the same year, Kuhn et al. (2012) performed WES on 10 uterine serous carcinomas with matched normal blood or tissue samples. In addition to confirming the previous discovery by Le Gallo et al. (2012), they also identified high mutation frequencies of FBXW7 and genes known to be associated with serous EC including TP53, PIK3CA, and PPP2R1A. DNA copy number analysis revealed concurrent frequent genomic amplification of the CCNE1 with FBXW7 mutations, suggesting that these genes are involved in same signaling pathway (Kuhn et al., 2012). They also proposed the role of endometrial intraepithelial carcinoma as a precursor to serous carcinoma whereby nine cases of serous carcinoma with an associated serous endometrial intraepithelial carcinoma had concordant PIK3CA, PPPR1A, and TP53 mutations (Kuhn et al., 2012). Taken together, the authors presented molecular genetic alterations involving the p53, cyclin E-FBXW7 and PI3K pathways as the major mechanisms in the uterine serous carcinoma progression.

The WES findings from both rather underpowered studies by Kuhn et al. (2012) and Le Gallo et al. (2012) were later supported by Zhao et al. (2013) using five times more samples. Fifty two uterine serous cancer patients of which 34 had matched normal tissue samples were subjected to WES (Zhao et al., 2013). In addition to earlier published studies which identified frequent alterations in TP53, PIK3CA, PPPR1A, and FBXW7, Zhao et al. (2013) also discovered high frequency mutations
of the SPOP gene which targets the protein for ubiquitination. Interestingly, this study also reported alterations in TFI1 gene, an element of the core TFIID transcriptional machinery which may result in overexpression of cyclin D and subsequently promote cell cycle progression and proliferation (Zhao et al., 2013). Frequent TP53 deletions and amplifications of chromosome segments containing PIK3CA and CCNE1 are known to be targets of FBXW7 (Kuhn et al., 2012). This study also discovered overexpression of ERBB2 which act as an upstream regulator of PIK3CA/ AKT/miTOR signaling pathway and loss of MBD3 gene function, a member of the NuRD-chromatin-modification complex (Zhao et al., 2013). To summarize, all of these studies which employed WGS and WES reported specific pathways that are frequently mutated in ECs including DNA damage, chromatin remodeling, cell cycle, and cell proliferation pathways.

TARGETED GENE SEQUENCING

Two different studies by McConney et al. (2012) took on to improve the controversial classification among pathological subtypes endometrial carcinoma (endometrioid, serous, carcinosarcoma, mixed, and clear cell) and between histological endometrioid types of EC and ovarian cancer using a panel of genes related to both cancers. The first study involved targeted enrichment sequencing on a large cohort of 393 EC samples using a nine-gene panel: ARID1A, PPP2R1A, PTEN, PIK3CA, KRAS, CTNNB1, TP53, BRAF and PPP2R5C (McConney et al., 2012). Both low-grade and grade 3 endometrioid EC demonstrated a similar pattern of high frequency of mutations in PTEN, PIK3CA, ARID1A, KRAS, and CTNNB1 (McConney et al., 2012). There is a significant increase in TP53 mutation frequency in grade 3 endometrioid EC when compared to low-grade EC (McConney et al., 2012). ARID1A mutation was significantly associated with concurrent PTEN and PIK3CA mutations in both low-grade endometrioid EC and grade 3 endometrioid ECs, suggesting a cooperative role in endometrioid carcinogenesis (McConney et al., 2012). However, this phenomenon was not observed in endometrial serous carcinomas which have frequent mutations in TP53 and PPP2R1A but lack mutations in PTEN, ARID1A, and CTNNB1. On the other hand, in carcinosarcoma, two distinct mutation profiles have been identified which were the endometrioid type (PTEN, PIK3CA, ARID1A, and KRAS mutations) and serous type (TP53 and PPP2R1A; McConney et al., 2012).

Using a panel of seven well-characterized genes in ECs (ARID1A, PTEN, PIK3CA, KRAS, CTNNB1, PPP2R1A, and TP53), McConney’s research group compared two morphologically similar cancer types, endometrial endometrioid carcinoma (n = 307) and ovarian endometrioid carcinoma (n = 33) using exon capture sequencing (McConney et al., 2014). Higher frequency of mutations was discovered in low-grade endometrial endometrioid carcinoma (67%) compared to low-grade ovarian endometrioid carcinoma (17%; McConney et al., 2014). The frequency of CTNNB1 mutation was significantly higher in ovarian endometrioid cancer (53%) when compared to endometrioid EC (28%). However, mutations frequencies in other genes were not significantly different between both cancers. They hypothesized that the different mutation spectrum in both cancers might be because of different exposures to the microenvironment during carcinogenesis, whereby the ovarian endometrioid carcinoma thrives in a highly oxidative environment that promotes tumorigenesis (Kobayashi et al., 2009). Consistent with other previously discussed studies, distinct mutation patterns in PI3K and WNT signaling pathways were identified, suggesting therapeutic opportunities for treatment of EC (McConney et al., 2014).

The most recently published endometrial research using NGS involved 10 Taiwanese EC patients (Chang et al., 2016). The exomes of 578 cancer-related genes were captured and deep-sequenced using NGS, resulting in average of 500x coverage. This study revealed 120 variants in 99 genes, with 50% of the ECs harboring mutations in the PTEN (Chang et al., 2016). Molecular aberrations in PIK3R1, AKT2 and FOXO1 that could led to putative activation of the IL-7 signaling pathway and which has not been previously linked with EC, are also reported.

Targeted NGS represents a potential to be adopted in clinical laboratory practices and have diagnostic applications for screening of individual at risk for developing EC (Tafe, 2015). To date, there are seven NGS-based assays that include LS-associated genes offered by several reference laboratories including Ambry Genetics (ColoNext; 14 genes), ARUP (Gastrointestinal Hereditary Cancer Panel; 15 genes), Baylor Miraca Genetics Laboratories (High Risk Hereditary Colorectal Cancer Panel; 12 genes), GeneDx (OncoGeneDx: Lynch/Colorectal Cancer High Risk Panel; seven genes), Mayo Medical laboratories (Hereditary Colon Cancer Multi-Gene Panel; 17 genes), Myriad (myRisk™ Hereditary Cancer Panel; 25 genes) and University of Washington (ColoSeq™; 23 genes; Tafe, 2015). However, the important challenges of NGS include interpreting incidental findings, genetic counseling, and getting informed consent from the patients. These calls for development of clinical practice guidelines for test development, validation, reporting, and reporting of incidental findings (Tafe, 2015).

RNA AND miRNA SEQUENCING

Via RNA sequencing and unsupervised k-means clustering of 333 ECs, Cancer Genome Atlas Research Network et al. (2013) identified three robust clusters which were mitotic, hormonal and immunoreactive subtypes. The mitotic subtype was characterized by TP53 alteration and mostly comprised of serous/mixed histology and endometrioid grade 3 while both of hormonal and immunoreactive subtypes were predominantly comprised of endometrioid grade 1/2 and PTEN mutated patients (Cancer Genome Atlas Research Network et al., 2013). Interestingly, the hormonal subtype exhibited upregulation of hormone related genes (ESR1, PGR and downstream targets) which could make the patients more responsive to hormonal therapy (Cancer Genome Atlas Research Network et al., 2013), implying potential for individualized treatment. In addition, the group performed
unsupervised consensus clustering of miRNA expression profiles in 367 ECs and discovered six clusters which some of them were significantly associated with MLH1 hypermethylation (miR-148a and miR-375), histology, grade (miR-21) and stage.

Xiong et al. (2014) simultaneously characterized the transcriptome of both mRNAs and miRNAs using RNA sequencing on three pairs of stage 1 endometrioid EC and adjacent non-cancerous tissue (Xiong et al., 2014). By integrating expression data of mRNAs and miRNAs, they identified a total of 438 target pairs which were inversely correlated including 320 dysregulated genes. Downstream pathway enrichment analysis revealed six differentially expressed miRNAs (hsa-let-7c-5p, hsa-miR-196a-5p, hsa-miR-328-3p, hsa-miR-337-3p, and hsa-miR-99a-3p, hsa-miR-181c-3p) targeting 11 differently expressed genes (E2F5, CDKN2A, CCNA2, TP53, BUB1B, CCNE1, CDK1, MCM4, SKP2, CDC6 and TGFβ3) in the cell cycle pathway (Xiong et al., 2014).

A genome wide characterization of small non-coding RNAs (sncRNAs) in EC carcinogenesis was performed on biopsies of normal (n = 10), hyperplastic (n = 6) and tumor Type 1 endometrial tissues (n = 10) using RNA sequencing (Ravo et al., 2015). Significant patterns in sncRNA expression between the sample groups were identified and led to the discovery of sncRNA signature (129 miRNAs, 10 piRNAs, and three snoRNAs) which is said to be involved in neoplastic transformation (Ravo et al., 2015). Integrated gene expression profiling with the aberrantly expressed sncRNAs signature revealed their involvement in multiple signaling pathway including ERK/MAPK, TGF-β and Wnt/β-catenin in both hyperplastic and neoplastic tissues (Ravo et al., 2015).

Gene fusion refers to an aberrant rearrangement between two genes which encode a new fusion protein, serving as a strong driver mutation in cancer (Mertens et al., 2015). Through pair-end RNA sequencing in nine pairs of EC and matched non-cancerous tissues, a fusion gene called chimeric translation-associated X-disrupted-in-schizophrenia (TSNAX-DISC1) in EC was discovered (Li et al., 2014). This fusion transcript was formed by intragenic splicing and its expression was further validated in 176 paired ECs and matched non-cancerous tissues. Dysregulation of TSNAX is presumed to be associated with cancer and the authors proposed the potential of TSNAX–DISC1 as an EC biomarker (Li et al., 2014).

CONCLUSION

In this mini review, we compiled and concisely review the literatures using NGS in basic EC research. NGS has indeed revolutionized EC genomics by enabling discovery of the major alterations in the genome which could serve as potential biomarkers for prognosis and drug development. The discovery of these biomarkers by NGS has the potential to accelerate application of genome-guided information into precision medicine and pharmacogenomics. Despite limited publications so far, NGS assays are already actively adopted for routine clinical testing in molecular pathology laboratories for identification of individual at risk of developing EC.

AUTHOR CONTRIBUTIONS

S-SS and N-SA drafted this manuscript. N-SA and RJ were responsible for idea conception, critical evaluation and manuscript review.

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