Germline pathogenic variants associated with ovarian cancer: A historical overview

Emma Lund Johansen\textsuperscript{a,b,c,*,}†, Christine Fribert Thusgaard\textsuperscript{a,b}, Mads Thomassen\textsuperscript{a,d}, Susanne Eriksen Boonen\textsuperscript{d}, Kirsten Marie Jochumsen\textsuperscript{a,b}

\textsuperscript{a} Department of Clinical Research, University of Southern Denmark, Odense, Denmark
\textsuperscript{b} Department of Gynecology and Obstetrics, Odense University Hospital, Denmark
\textsuperscript{c} Department of Clinical Genetics, Odense University Hospital, Denmark
\textsuperscript{d} Department of Gynecology and Obstetrics, Odense University Hospital, Denmark

\textbf{A B S T R A C T}

The risk of ovarian, tubal, and peritoneal cancer is related to germline pathogenic variants, and over time, the number of known disease-associated genes has increased significantly. This study reviews the literature regarding the topic from a historical perspective. The aim is to present a timeline of the knowledge gained from the early 1900s until today. The findings are put into perspective by looking at the current gene panel used for screening for suspected hereditary ovarian cancer in Denmark compared to what is known internationally. In 1929, the first familial ovarian cancer incidents were registered, and in 1950, the involvement of a genetic component was suggested for the first time. During the 1970s, several studies reported an accumulation of ovarian cancer in certain families, and during this time, it was discovered that ovarian cancer was linked to both breast cancer and colorectal cancer. The inheritance of cancer disposition has been thoroughly investigated, leading to the discovery of the \textit{BRCA} genes in the 1990s. Furthermore, new studies based on new genetic technologies have revealed several genes with germline pathogenic variants that increase the risk of ovarian cancer. The identification of these pathogenic variants has led to preventive measures and specific treatment of women with genetic disposition to ovarian cancer. In Denmark, consensus is to include at least ten genes in the screening panel for hereditary ovarian cancer, and in the future additional genes will probably be added.

\section{1. Introduction}

Ovarian cancer, including cancer in the ovaries, fallopian tube and primary peritoneal cancer, is the fourth most common cause of cancer death in women in Denmark and the most lethal of the gynecological malignancies. Every year, around 500 Danish women are diagnosed with ovarian cancer at a median age of 63 years, and women in the general population have a lifetime risk of developing ovarian cancer of a little less than 2\%. The standardized incidence rate of ovarian cancer in Denmark is 15 per 100,000 women, which is the second highest incidence rate of ovarian cancer in the world (Dansk Gynekologisk Cancer Database, 2017). Worldwide nearly 300,000 cases of ovarian cancer were diagnosed in 2018 (Khazaei et al., 2021).

Besides general risk factors such as low parity and endometriosis, more than 20\% of all ovarian cancer incidents are related to inheritance of pathogenic gene variants. Inheritance of genes like \textit{BRCA1} and \textit{BRCA2} increases the risk of developing ovarian cancer, and the mean age at diagnosis is lower in mutation carriers than in the general population (Walsh et al., 2011). In women carrying a \textit{BRCA1} mutation the cumulative ovarian cancer risk to age 80 is 49\%, and mean age at diagnosis is 51 years. For comparison, the cumulative ovarian cancer risk to age 80 is 21\%, and the mean age at diagnosis of women with a pathogenic \textit{BRCA2} variant is 61 years (Kotsopoulos et al., 2018).

The discovery of genes related to ovarian cancer has been ongoing for several decades. It began when a number of studies showed an accumulation of breast and ovarian cancer in certain families indicating a correlation between these two types of cancer (Lynch et al., 1974). Later on a relation between colorectal cancer and gynecological cancers was observed (Lynch and Lynch, 1979). The knowledge gained on the specific genes related to ovarian cancer has increased drastically within the last thirty years, starting with the discovery of the well-known \textit{BRCA} genes in the 1990s (Hall et al., 1990; Wooster et al., 1994). Since then, at
least 18 other genes have been identified to be associated with increased risk of ovarian cancer (MLH1 (Lindblom et al., 1993), MSH2 (Peltomäki et al., 1993); PMS2 (Nicolaides et al., 1994), MSH6 (Drummond et al., 1995), EPCAM (Herlyn et al., 1979), TP53 (Lane and Crawford, 1979), CDH1 (Mansouri et al., 1988), MRE11 (Petriti et al., 1995), ATM (Savitsky et al., 1995), RAD50 (Dolganov et al., 1996), BARD1 (Wu et al., 1996), PTEN (Li et al., 1997), RAD51C (Dosanjh et al., 1998), RAD51D (Pittman et al., 1998), BNN (Matsuura et al., 1998), CHEK2 (Bell et al., 1999), BRIP1 (Cantor et al., 2001) and PALB2 (Xia et al., 2006). How strongly these genes are associated with ovarian cancer risk is still discussed. In Denmark, the test panel used in screening for hereditary ovarian cancer risk includes ten genes based on national consensus via The Danish National Oncogenetic Committee in the Danish Society of Medical Genetics (BRC1A1, BRC2A2, BRIP1, EPCAM, MLH1, MSH2, MSH6, PMS2, RAD51C and RAD51D) (Dansk Selskab, 2019).

The aggressive nature of ovarian cancer and its high mortality rate means that it is vital to prevent this type of cancer, if possible. Recognition of genetic alterations that increase the risk of ovarian cancer has led to the implementation of preventive measures such as risk reducing salpingo-oophorectomy and family counseling to high-risk families.

This study reviews the current medical literature concerning germ-line pathogenic gene variants in ovarian cancer, creating a historical timeline of the knowledge. This is put into perspective by describing how it has influenced the panel of genes currently used in the screening for hereditary ovarian cancer risk in Denmark.

2. Historical overview

The epidemiology of ovarian cancer is complex and has been studied for decades. Today, it is well established that inheritance of pathogenic gene variants is a risk factor and is involved in the development of ovarian cancer. However, the idea of a hereditary component in ovarian cancer is not new. In 1929, the first familial ovarian cancer incidents were registered in American medical literature as monozygotic twins were reported to have ovarian cancer. Both twins experienced the first symptoms of ovarian cancer by the age of 39 years (Kimbrough, 1929). Approximately 20 years later; Amour Liber reported a high incidence of ovarian cancer in one family throughout five generations, and he hypothesized the possibility of a genetic link between these incidents. He even suggested that preventive gynecological surgery should be considered (Liber, 1950). During the 1960s; the epidemiology of ovarian cancer was studied further. The focus was on other factors than familial inheritance, such as religion, ethnicity, menopausal status, and parity. Despite not being able to detect it in their study, Wynder et al. mentioned the possibility of a familial association of ovarian cancer and encouraged future studies to investigate this further (Wynder et al., 1969).

During the 1970s, a growing number of familial incidents of ovarian cancer were reported. To investigate and explain the drastic increase in familial ovarian cancer incidents, the first Familial Ovarian Cancer Registry was founded in 1981 in USA. Their focus of interest was to establish whether the increase in familial ovarian cancer incidents was a result of improved data collection, a genetic component in the disease, or new environmental factors (Piver et al., 1984). Throughout the 1980s, several studies investigated the trends of inheritance of ovarian cancer, and Hartge et al. confirmed the familial association of ovarian cancer with an elevated rate ratio of 3.3 in a group of women with ovarian cancer compared to a control group of women without ovarian cancer (Hartge et al., 1989).

Along with the increasing number of reports concerning hereditary ovarian cancer, the knowledge on other hereditary cancer syndromes accelerated as well. Ovarian cancer was included in the Hereditary Breast and Ovarian Cancer syndrome and the Lynch syndrome (Lynch et al., 1974; Lynch and Lynch, 1979).

Based on the previous research regarding the transmission of genes predisposing to different cancers and the development of genetic technologies, the 1990s turned out to be a remarkable decade. During this decade, several susceptibility genes of breast, colorectal and ovarian cancer were identified. The ovarian cancer susceptibility genes described in this review are shown in Fig. 1.

2.1. The BRCA genes

In 1990, a genetic marker linked to chromosome 17q was discovered by Mary-Claire King’s group at the University of California, Berkeley by studying patients with early onset breast cancer and their family history (Hall et al., 1990). Shortly after other researchers linked the chromosome 17q marker to ovarian cancer as they studied five large families with ovarian cancer and early onset breast cancer (Narod et al., 1991). Later; in 1994 this gene was cloned by researchers at Myriad Genetics along with scientists at the University of Utah and McGill University and is today known as BRCA1 (Miki et al., 1994); and the same year Mary-Claire King published a paper confirming that BRCA1 is linked to ovarian cancer in families prone to breast and ovarian cancer (Friedman et al., 1994). The identification of BRCA1 was followed by the discovery of BRCA2. This gene was localized to chromosome 13q in 1994 by an international research group with members from several countries led by Michael R. Stratton at The Institute of Cancer Research in London (Wooster et al., 1994). In 1995; it was sequenced and identified as a new breast cancer susceptibility gene (Wooster et al., 1995). By assessing families with history of both breast and ovarian cancer an association between BRCA2 and ovarian cancer was identified in 1996 (Couch et al., 1996; Tavtigian et al., 1996). Myriad Genetics was part of the exact localization of the BRCA genes; and therefore obtained several patents in terms of research; diagnosis, and detection of the genes. These patents were invalidated in 2013 by the Supreme Court of the United States, declaring that the genes were products of nature ineligible for patenting (States SCotU, 2013).

The BRCA genes are involved in repair of double-stranded DNA breaks and are the genes involved in the Hereditary Breast and Ovarian Cancer syndrome, and pathogenic variants in these genes are found in 55–65 % of inherited ovarian cancer incidents depending on personal and family history of breast or ovarian cancer (Carter et al., 2018) (Fig. 2). Carrying a pathogenic variant in BRCA1 or BRCA2 is associated with a lifetime risk of developing ovarian cancer of 43–76 % and 8–34 %, respectively (Mavaddat et al., 2013). Since around year 2000, patients in Denmark with a relevant family history of breast and ovarian cancer has been offered to be tested for germline pathogenic variants in BRCA1 and BRCA2.

2.2. The mismatch repair genes

The four DNA mismatch repair genes MLH1 (Lindblom et al., 1993); MSH2 (Peltomäki et al., 1993); PMS2 (Nicolaides et al., 1994) and MSH6 (Drummond et al., 1995) causes the Lynch syndrome, which primarily is characterized by increased risk of colorectal cancer and cancer of the endometrium, but also to a lesser extent increased risk of ovarian cancer (Idos et al., 1995). The genes were identified between 1993 and 1995 by several groups of investigators including Paul Modrich (Orummond et al., 1995) and Bert Vogelstein (Peltomäki et al., 1993; Nicolaides et al., 1994). A fifth gene, EPCAM, also causes Lynch syndrome and thereby increases the risk of ovarian cancer. It is not a DNA mismatch repair gene but certain germline deletions in this gene cause silencing of the neighboring MSH2 by promoter hypermethylation (Idos et al., 1993). EPCAM was discovered in 1979 by Meinhard Herlyn and colleagues (Herlyn et al., 1979). The Lynch syndrome is suggested to be involved in 10–20 % of the inherited ovarian cancer incidents (Fig. 2), and women with inherited pathogenic variants Lynch syndrome genes have a 6–12 % lifetime risk of developing ovarian cancer (Malander et al., 2006; Watson et al., 2008; Aarnio et al., 1999). In Denmark, we
began to test patients with a relevant family history of ovarian cancer for the genes linked to the Lynch syndrome in 2017.

2.3. Other susceptibility genes of ovarian cancer

Several other genes predisposing to ovarian cancer have been identified, including: TP53 (Lane and Crawford, 1979) and CDH1 (Mansouri et al., 1988) in 1979 and 1988, respectively, and MRE11 (Petrini et al., 1995); ATM (Savitsky et al., 1995); RAD50 (Dolganov et al., 1996); BARD1 (Wu et al., 1996); PTEN (Li et al., 1997); RAD51C (Dosanjh et al., 1998); RAD51D (Pittman et al., 1998); NBN (Matsuura et al., 1998); CHEK2 (Bell et al., 1999); BRIP1 (Cantor et al., 2001) and PALB2 (Xia et al., 2006) from 1995 until 2006 (Fig. 1). These susceptibility genes are the most well described in the literature with the highest risk of ovarian cancer. They were not all considered as susceptibility genes of ovarian cancer at first. However, the development and implementation of next-generation sequencing technology has made it possible and easier to analyze multiple genes simultaneously at a higher speed and at lower costs. Multigene panel testing of selected hereditary predisposition tumor genes optimize the molecular diagnosis. Therefore, studies have identified germline pathogenic variants in at least 20 different genes in ovarian cancer patients including the above-mentioned genes (Walsh et al., 2011; Desmond et al., 2015; Lu et al., 2019; Suszynska et al., 2019). The clinical impact of germline variants in the different genes among all inherited ovarian cancer cases is still discussed, and currently CHEK2 and CDH1 are not recognized as specific risk factors of ovarian cancer, even though previous studies have found a significant association between these genes and some types of ovarian cancer.

The Danish National Oncogenetic Committee in the Danish Society of Medical Genetics has in 2019 published a guideline for assessment of hereditary ovarian cancer. If a specific pathogenic gene variant is already known in the family, the test will only include this. When a specific gene variant has not been identified in a family which seems to have an increased risk of ovarian cancer, national consensus is to use a panel of at least ten genes listed in Table 1 (Dansk Selskab, 2019). Besides the ten genes mentioned in Table 1, the six clinical genetic departments in Denmark may add varying different genes in their panel. Furthermore, if indicated based on family history or a specific subtype of ovarian cancer, tests for additional genes may be added.

3. Discussion

The inheritance of ovarian cancer has been thoroughly investigated during the last century leading to the discovery of several susceptibility genes of ovarian cancer during the last 30 years. Today, at least 20 different genes have been suggested as susceptibility genes of ovarian cancer, and in Denmark the screening for hereditary ovarian cancer includes ten genes.

The discovery of the genes has contributed to both preventive measures for women who have inherited a germline pathogenic gene variant...
associated to ovarian cancer (Aarnio et al., 1999) and new treatment regimens for patients with ovarian cancer. Surgery in the form of risk-reducing bilateral salpingo-oophorectomy has shown to reduce ovarian cancer risk with 72% and ovarian cancer specific mortality with 79% in women with germline pathogenic variants in the BRCA genes (Domchek et al., 2010). When genes are used to guide treatment, both germline and somatic pathogenic variants become relevant. Germline mutations are heritable, as they occur in sperm, eggs and their progenitor cells, whereas somatic mutations occur in other cell types such as cancer cells and are not heritable (Steyerson et al., 2020). In 2018, the SOLO1-study showed that poly ADP-ribose polymerase inhibitors (PARP-inhibitors) decreased the risk of disease progression and death with 70% compared to placebo, when it was given as first-line maintenance therapy after the end of adjuvant chemotherapy in women with advanced ovarian cancer and germline or somatic pathogenic variants in the BRCA genes (Moore et al., 2018). Based on this, the treatment has been implemented for the use in this group of patients (Medicinrådet, 2019). Therapeutically, it is therefore considered advantageous for the patient to have ovarian cancer caused by a pathogenic BRCA gene variant.

However, recent studies have shown that a high Homologous Recombination Deficiency score (HRD score) is related to clinical benefit of PARP-inhibitors and better overall survival independent of BRCA status. There are different types of methods testing for HRD. In Denmark, the Myriad test is used when assessing HRD score, and the test is based on an unweighted sum of loss of heterozygosity, telomeric allelic imbalance, and large-scale transitions which are all DNA-based measures of genomic instability. HRD score will possibly become an important factor in terms of individualizing and optimizing the treatment of ovarian cancer in the future (How et al., 2021).

Many years of research has made it clear that there is a strong association between histology and genetics. Epithelial ovarian cancer is commonly divided into five main subtypes based on histology. These are high-grade serous, endometrioid, clear cell, low-grade serous and mucinous. Each histotype seems to be significantly different at the genetic level. High-grade serous carcinoma is strongly associated with BRCA1 and BRCA2, whereas endometrioid and clear cell carcinoma are associated with inherited defects in the MMR-genes. The histologic subtype therefore implicates clinical aspects such as choice of treatment and prognosis (Hollis and Gourley, 2016).

The simultaneous expanding knowledge in the genetic field and improvement of testing technologies such as whole genome sequencing, whole exome sequencing and multigene panel testing has contributed to the risk assessment regarding ovarian cancer. The cognition of more susceptibility genes helps to identify a broader number of patients who will benefit from preventive strategies to decrease the risk of ovarian cancer or targeted treatment strategies when diagnosed with the disease (Zelli et al., 2020). Additionally, multigene panel testing has given us the opportunity to sequence several genes at the same time which ensures a higher sensitivity in terms of identifying relevant mutations. This has also been particularly useful in relation to the introduction of personalized medicine which uses mutations in specific genes to guide treatment and, in some cases, also preventive measures to reduce the risk of specific disease. It is widely discussed whether multigene panel testing is cost-effective, when the outcome of the test is compared to the resources spent (costs and time) and the actual use of the results in the clinical management of the patients. When investigating the cost-effectiveness of multigene panel testing of 10 genes (including BRCA 1 and 2), Foote et al. found this to be more cost-effective in women with a family history of breast or ovarian cancer than in women with no relevant family history. They suggested, however, that using this specific testing strategy should be considered on an individual basis (Foote et al., 2017). According to Walsh et al., multigene panel testing is more economically sustainable than assessing the risk of each individual gene, since more and more susceptibility genes of ovarian cancer are identified (Walsh et al., 2011). In addition, Zelli et al. describes multigene panel testing as a cost-effective and time reducing method for several genes (Zelli et al., 2020). The introduction of PARP-inhibitors as first line therapy for ovarian cancer after adjuvant chemotherapy means that all women in Denmark treated for ovarian cancer is offered to be tested for germline pathogenic variants linked associated to ovarian cancer. This was introduced in 2019 as part of the previously mentioned guideline for assessment of hereditary ovarian cancer.

Data concerning the proportion of Danish ovarian cancer cases that are related to hereditary conditions are few. In 2008 a Danish study found pathogenic BRCA variants in 5.8% of the ovarian cancer cases (Soegaard et al., 2008). Since the study only evaluated the prevalence of germline pathogenic variants in the BRCA genes; a new assessment including more susceptibility genes of ovarian cancer is highly relevant. Especially since, all patients diagnosed with ovarian cancer in Denmark has been offered genetic testing of germline pathogenic variants linked to ovarian cancer for the last three years (Danske Selskab, 2019). A new assessment would improve the understanding of hereditary ovarian cancer in Denmark.

The Danish test panel in the screening for hereditary ovarian cancer now includes ten genes, even though many studies have found germline pathogenic variants in several other genes related to ovarian cancer. Walsh et al. found a higher proportion of ovarian cancer patients with germline pathogenic variants in the CHEK2 gene than in the BRIP1, RAD51C and MSH6 genes (Walsh et al., 2011). Suszynska et al. found no pathogenic variants in the EPCAM gene and could therefore not confer a risk associated with ovarian cancer in this gene (Suszynska et al., 2019). The EPCAM gene is often analyzed as a marker for copy-number pathogenic variants in the promoter of the neighboring MSH2 gene, and therefore the consensus in Denmark is to include the EPCAM gene in the Danish screening panel. Additionally, both Desmond et al. and Suszynska et al. suggest PTEN and TP53 as genes with a high-risk of predisposition to ovarian cancer (Desmond et al., 2015; Suszynska et al., 2019) why implementing these in the Danish screening panel might be considered in the future.

Not all studies agree on the risk of developing ovarian cancer associated with the different genes. Ramus et al. performed a case-control study and were not able to detect a significantly increased risk of ovarian cancer in the PALB2, NBN or BARD1 genes (Ramus et al., 2015), whereas Suszynska et al. suggested both PALB2 and NBN as genes associated with a moderate risk of ovarian cancer (Suszynska et al., 2019). Walsh et al. found that only 0.5% of the ovarian cancer incidents were associated with the Lynch syndrome unlike other studies (Walsh et al., 2011). Lu et al. did not find a significantly increased ovarian cancer risk in the BRIP1, NBN, MRE11, RAD50 or RAD51D genes (Lu et al., 2019). Another challenge with genetic testing is how to handle variants that are not clearly benign or associated to an unknown risk of cancer. These variants are called variants of uncertain significance (VUS). The risk of detection of VUS increases with the number of genes included in the test. The interpretation of these variants is a demanding task, especially when communicated to the patients, and misinterpretation may lead to unnecessary interventions and concern. However, most VUS are reclassified as benign rather than pathogenic (Foote et al., 2017).

Despite the varying risk estimations, germline pathogenic variants have been found in at least 20 different genes, some associated with a higher risk of developing ovarian cancer than others. Still, the current multigene panel testing has not managed to detect a sufficient number of genetic variants to explain all inherited ovarian cancer incidents, suggesting that additional genetic variants remain to be identified (Jervis et al., 2014). It is a challenge to decide whether a gene is a susceptibility gene of ovarian cancer or not. Since the studies vary in number of patients included, populations described, and in number and types of genes, it is not possible to compare the risk estimations completely. This should be taken into consideration when selecting the specific genes for a national screening panel.

The data concerning distribution of pathogenic variants in the
susceptibility genes of ovarian cancer are derived from a limited number of articles. Some studies have suggested other pathogenic variants, however, with minimal evidence, and therefore these variants were not discussed. In addition, studies have found ovarian cancer risk modifying variants, which individually only gives a small to modest increase in risk, but if more than one of these variants are identified in the same patient, their combined effect may be associated with a much larger risk of ovarian cancer. This is calculated as a polygenic risk score. In the future, the calculation of polygenic risk scores can contribute to improved cancer risk prediction for carriers of germline pathogenic variants associated to ovarian cancer. It can help determine the optimal timing of preventive measures such as risk-reducing salpingo-oophorectomy in each woman with an increased risk of ovarian cancer. Thereby it will facilitate a better and more personalized management of mutation carriers (Kuchenbaecker et al., 2017).

In conclusion, a remarkable amount of knowledge about the inheritance of ovarian cancer has been gained during the last century. The amount of knowledge has especially accelerated after the first discovery of ovarian cancer associated genes 30 years ago. This has been particularly important in the screening panel for increased risk of ovarian cancer, guidance about risk-reducing surgery and oncological treatment, and consequently reducing ovarian cancer mortality in genetically disposed women. The knowledge in the field is still expanding, and more germline pathogenic variants will most likely be discovered and possibly added to the screening panel for hereditary ovarian cancer.

Declaration of Competing Interest
The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

References
Aarnio, M., Sankila, R., Pukkala, E., et al., 1999. Cancer risk in mutation carriers of DNA mismatch-repair genes. Int. J. Cancer 81 (2), 214–218.
Bell, D.W., Varley, J.M., Szydlo, T.E., et al., 1999. Heterozygous germ line hCHK2 mutations in Li-Fraumeni syndrome. Science 286 (5449), 2528–2531.
Cantor, S., Bell, D., Ganesan, S., et al., 2001. BACH1, a Novel Helicase-like Protein, Interacts Directly with BRCA1 and Contributes to Its DNA Repair Function. Cell 105 (3), 149–160.
Carter, N.J., Marshall, M.L., Suswain, L.R., et al., 2018. Germline pathogenic variants identified in women with ovarian cancers. Gynecol. Oncol. 151 (3), 481–488.
Couch, F.J., Farid, L.M., DeShano, M.L., et al., 1996. BRCA2 germline mutations in male patients with breast cancer. J. Natl. Cancer Inst. 88 (21), 160.
Dansk Gynækologisk Cancer Database. National Medicinrådet, 2019. Medicinrådets protokol for en fælles regional behandlingsvejledning vednødrende legemidler til BRCA-muterede kraft i æggestokken, æggede eller primær kraft i bugenheden 2019, August 28 [Available from: https://medicinraadet.dk/media/1/red2mm/medicinraadets-protokol-for-en-fælles-regional-behandlings- vejledning-til-kraft-i-%C3%A6ggestokken-vers-1-0-adligacy.pdf].
Hall, J.M., Lee, M.K., Newman, B., et al., 1990. Linkage of early-onset familial breast cancer to chromosome 17q21. Science 250 (4988), 1684–1689.
Savitsky, K., Bar-Shira, A., Gilad, S., et al., 1995. A single ataxia telangiectasia gene with a product similar to PI-3 kinase. Science 268 (5218), 1749–1753.

Soegaard, M., Kjaer, S.K., Cox, M., et al., 2008. BRCA1 and BRCA2 mutation prevalence and clinical characteristics of a population-based series of ovarian cancer cases from Denmark. Clin. Cancer Res.: Off. J. Am. Assoc. Cancer Res. 14 (12), 3761–3767.

States SCotU. Association for Molecular Pathology v. Myriad Genetics (US) 2013 [Available from: https://www.supremecourt.gov/opinions/12pdf/12-398_1b7d.pdf.

Suszynska, M., Klonowska, K., Jasinska, A.J., et al., 2019. Large-scale meta-analysis of mutations identified in panels of breast/ovarian cancer-related genes - Providing evidence of cancer predisposition genes. Gynecol. Oncol. 153 (2), 452–462.

Tavtigian, S.V., Simard, J., Rommens, J., et al., 1996. The complete BRCA2 gene and mutations in chromosome 13q-linked kindreds. Nat. Genet. 12 (3), 333–337.

Walsh, T., Casadei, S., Lee, M.K., et al., 2011. Mutations in 12 genes for inherited ovarian, fallopian tube, and peritoneal carcinoma identified by massively parallel sequencing. Proc. Natl. Acad. Sci. USA 108(44), 18032–18037.

Watson, P., Vasen, H.F.A., Mecklin, J.P., et al., 2008. The risk of extra-colonic, extra-endometrial cancer in the Lynch syndrome. Int. J. Cancer 123 (2), 444–449.

Wooster, R., Neuhausen, S.L., Margion, J., et al., 1994. Localization of a breast cancer susceptibility gene, BRCA2, to chromosome 13q12-13. Science 265 (5181), 2088–2090.

Wooster, R., Bignell, G., Lancaster, J., et al., 1995. Identification of the breast cancer susceptibility gene BRCA2. Nature 378 (6559), 789–792.

Xia, B., Sheng, Q., Nakanishi, K., et al., 2006. Control of BRCA2 cellular and clinical functions by a nuclear partner, PALB2. Mol. Cell 22 (6), 719–729.

Zelli, V., Compagnoni, C., Cannita, K., et al., 2020. Applications of Next Generation Sequencing to the Analysis of Familial Breast/Ovarian Cancer. High-throughput. 9 (1).