ΠΑΝΕΠΙΣΤΗΜΙΟ ΘΕΣΣΑΛΙΑΣ

ΤΜΗΜΑ ΙΑΤΡΙΚΗΣ

ΠΡΟΓΡΑΜΜΑ ΜΕΤΑΠΤΥΧΙΑΚΩΝ ΣΠΟΥΔΩΝ

«Μεθοδολογία Βιοϊατρικής Έρευνας – Βιοστατιστική και Κλινική Βιοπληροφορική»

ΤΙΤΛΟΣ ΔΙΠΛΩΜΑΤΙΚΗΣ ΕΡΓΑΣΙΑΣ

«Assess the reporting quality of studies investigating the diagnostic accuracy of BRCA1 & BRCA2 in the diagnosis of breast and ovarian heredity cancer published from 2014 to 2024 using the STARD statement»

«Αξιολόγηση της ποιότητας αναφοράς μελετών διερεύνησης της διαγνωστικής ακρίβειας των BRCA1 & BRCA2 στη διάγνωση του κληρονομικού καρκίνου μαστού και ωοθηκών οι οποίες δημοσιεύθηκαν την περίοδο 2014–2024 χρησιμοποιώντας τη μέθοδο STARD»

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Abstract

Introduction: Hereditary breast and ovarian cancer is one of the most common types of cancer in recent years. Known as HBOC syndrome, these two types of cancer are primarily attributed to mutations in the BRCA1 and BRCA2 genes. For this reason, the mechanism of their mutation has been extensively studied, particularly in recent years. It has been demonstrated that early and accurate diagnosis has led to more targeted therapeutic approaches. This report evaluates studies published in the past decade regarding the diagnostic accuracy of the BRCA1 and BRCA2 genes in diagnosing hereditary breast and ovarian cancer. Widely used methods include DNA sequencing techniques such as Next Generation Sequencing (NGS).

Objectives: The primary objective of this report is to assess the quality of reporting in studies investigating the diagnostic accuracy of the BRCA1 and BRCA2 genes in diagnosing hereditary breast and ovarian cancer, as well as to evaluate their key characteristics.

Methods: A systematic review of studies was conducted using the PubMed database, assessing which studies met the inclusion criteria for the report. The selected studies were then evaluated based on the guidelines of the STARD Statement.

Results: The final score of each study was assessed according to the STARD Statement. It was found that the quality of reporting did not differ significantly between studies with low and high scores. Furthermore, no correlation was observed between the score and study characteristics such as journal impact factor and sample size.

Conclusions: To more effectively utilize studies investigating the diagnostic accuracy of BRCA1 and BRCA2, it is recommended to improve the reporting of study characteristics related to diagnostic methods, which remain an evolving field. The STARD Statement guidelines are instrumental and valuable in achieving this goal.

Keywords: BRCA1, BRCA2, breast cancer, ovarian cancer, HBOC, diagnosis, prediction, STARD.

Περίληψη

Εισαγωγή: Ο κληρονομικός καρκίνος του μαστού και των ωοθηκών αποτελεί μια από τις πιο συχνές μορφές καρκίνου τα τελευταία χρόνια. Γνωστό και ως σύνδρομο HBOC, οι δύο αυτοί τύποι καρκίνου, οφείλονται κυρίως στην μετάλλαξη των γονιδίων BRCA1 & BRCA2, και για αυτό το σκοπό έχει μελετηθεί, ειδικά τα τελευταία χρόνια, ο μηχανισμός μετάλλαξής τους. Έχει αποδειχθεί πως η έγκαιρη και έγκυρη διάγνωσή τους έχει οδηγήσει σε πιο στοχευμένες θεραπευτικές προσεγγίσεις. Η παρούσα αναφορά αξιολόγησε μελέτες που αναφέρονται στη διαγνωστική ακρίβεια των γονιδίων BRCA1 & BRCA2 στη διάγνωση του κληρονομικού καρκίνου μαστού και ωοθηκών και δημοσιεύθηκαν τα τελευταία δέκα χρόνια. Ιδιαίτερα διαδεδομένες μέθοδοι αποτελούν τεχνικές αλληλούχισης του DNA, όπως η Next Generation Sequencing (NGS).

Στόχοι: Πρωτεύον στόχος της παρούσας αναφοράς είναι η αξιολόγηση της ποιότητας αναφοράς μελετών που διερευνούν τη διαγνωστική ακρίβεια των γονιδίων BRCA1 & BRCA2 στη διάγνωση του κληρονομικού καρκίνου μαστού και ωοθηκών, καθώς και η αξιολόγηση των βασικών τους χαρακτηριστικών.

Μέθοδοι: Πραγματοποιήθηκε συστηματική ανασκόπηση μελετών μέσω της βάσης δεδομένων PubMed, εξετάσθηκε ποιες πληρούσαν τα κριτήρια ένταξης στην αναφορά και αξιολογήθηκαν με γνώμονα τις κατευθυντήριες οδηγίες του STARD Statement.

Αποτελέσματα: Αξιολογήθηκε το τελικό σκορ της κάθε μελέτης, σύμφωνα με το STARD, και αποδείχθηκε πως η ποιότητα αναφοράς των μελετών δεν διαφέρει σημαντικά ανάμεσα σε μελέτες με χαμηλό και υψηλό σκορ. Επίσης βρέθηκε πως δεν υπάρχει συσχέτιση του σκορ με χαρακτηριστικά των μελετών όπως το μέγεθος δείγματος και το impact factor του περιοδικού δημοσίευσης.

Συμπεράσματα: Προκειμένου να αξιοποιηθούν πιο αποτελεσματικά μελέτες που διερευνούν τη διαγνωστική ακρίβεια των BRCA1 & BRCA2, προτείνεται η βελτίωση των μελετών σχετικά με την αναφορά τους στα χαρακτηριστικά των μεθόδων διάγνωσης που αποτελούν πεδίο εξέλιξης. Για το σκοπό αυτό βοηθητικές και αξιοποιήσιμες είναι οι κατευθυντήριες οδηγίες του STARD Statement.

Λέξεις – κλειδιά: BRCA1, BRCA2, καρκίνος μαστού, καρκίνος ωοθηκών, διάγνωση, STARD.

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1 Introduction

1.1 Breast and Ovarian Hereditary Cancer

Cancer has emerged as one of the leading causes of death in recent years, likely second only to cardiovascular diseases. It is a significant modern challenge in clinical medicine, characterized by a set of malignant tumors that arise from uncontrolled cell proliferation in the tissue where they originate. While cancer typically affects older individuals, there are also forms that manifest in younger people, including children. Over 100 types of cancer have been identified, and this report focuses on Hereditary Breast and Ovarian Cancer, commonly referred to as HBOC Syndrome (*Torre et al., 2018*).

Hereditary Breast and Ovarian Cancer Syndrome (**HBOC**) is a genetic condition that predisposes individuals to an increased risk of developing breast, ovarian, prostate, and certain other types of cancer. HBOC results from mutations in specific genes that can be inherited across generations within families. It is also associated, to a lesser extent, with an elevated risk of pancreatic and prostate cancers in men (*Figure 1*). HBOC has become a significant focus of research aimed at developing innovative technologies for the early and accurate diagnosis of these cancers. Furthermore, it drives efforts to formulate effective preventive strategies and design targeted therapeutic approaches. Recent studies on HBOC not only identify additional cancer types associated with the syndrome but also propose personalized treatments tailored to individual patients and specific cancer types *(Yoshida, 2021)*.

Women who inherit a BRCA1 or BRCA2 gene mutation face a significantly elevated risk of developing breast cancer (60%-85%) and ovarian cancer (20%-40%), as well as an increased risk of pancreatic cancer (5%-10%). To determine if an individual belongs to a high-risk category, an evaluation begins with their personal and family medical history. This includes identifying blood relatives diagnosed with cancer, the type and age of onset, and the current age or age at death of these relatives.

Early diagnosis of HBOC is critical, as it allows patients to access appropriate treatment sooner. This is particularly important given the recent development of PARP protein inhibitors, such as olaparib, niraparib, and veliparib, which have proven to be effective therapeutic options *(Westin et al., 2021).*

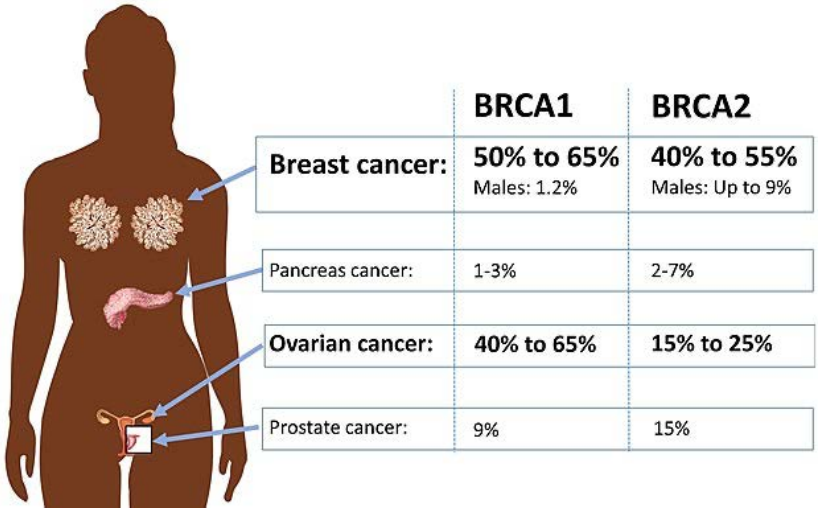


Figure 1 Types of cancer in HBOC (Adam, Feldman and Mirzaa, 1998)

1.2 BRCA1 and BRCA2

BRCA1 and BRCA2 are the most common genes associated with hereditary breast and ovarian cancer. Recent advances in molecular techniques, such as Next-Generation Sequencing (NGS), have facilitated the identification of additional genes linked to the development and predisposition to these cancers. Some of these genes include **TP53, PTEN, STK11, CDH1, PALB2, BRIP1, ATM, CHEK2, BARD1, NBN, NF1, RAD51C**, and **RAD51D** *(Angeli, Salvi and Tedaldi, 2020).* This report focuses on BRCA1 and BRCA2, emphasizing their characteristics and mechanisms in carcinogenesis.

The **BRCA1** gene is located at 17q21, near the centromere on the long arm of chromosome 17, and comprises 24 exons. The resulting protein, consisting of 1863 amino acids, includes a central N-terminal RING finger domain, a C-terminal BRCT domain, and regions encoded by exons 11–13. In contrast, the **BRCA2** gene is located on chromosome 13 (13q12-13) and contains 27 exons, encoding a protein with 3418 amino acids. The N-terminal region of BRCA2 contains the transcription activation domain (TAD), while its central region, encoded by exon 11, features eight conserved BRC repeat motifs that interact with RAD51 (*Figure 2).*

BRCA1 and BRCA2 are critical tumor suppressor genes that maintain genomic stability by mediating the repair of double-strand DNA breaks through homologous recombination. Mutations in these genes compromise their ability to repair DNA, leading to genetic alterations and genomic instability – key processes in carcinogenesis. BRCA1 is particularly involved in various cellular functions, including regulating cell cycle checkpoints and transcription. Meanwhile, BRCA2 plays a pivotal role in recruiting RAD51 to sites of DNA damage to facilitate homologous recombination repair *(Angeli, Salvi and Tedaldi, 2020).*

Loss-of-function mutations in BRCA1/2 disrupt these pathways, impairing the DNA damage response and significantly increasing susceptibility to breast and ovarian cancer. These mutations also create a heightened sensitivity to specific chemotherapeutic agents, such as platinum-based drugs and PARP inhibitors, which exploit deficient DNA repair mechanisms to target BRCA-mutated cancer cells. This mechanistic insight highlights the critical role of BRCA1/2 mutations in cancer development and informs the development of targeted therapeutic strategies.

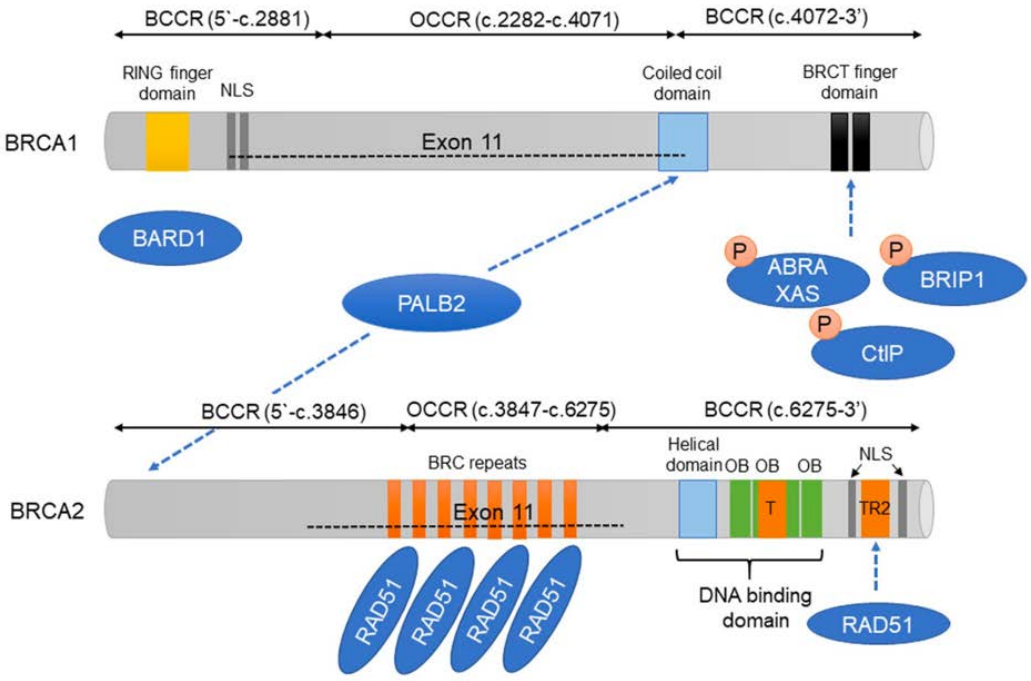


Figure 2 Site of homologous protein recombination between BRCA1 and BRCA 2 leading to their mutation resulting in breast and ovarian cancer (Yoshida, 2021)

1.3 Reporting Quality by STARD Statement

In recent years, significant qualitative advancements have been made in the evaluation of studies and the refinement of database search methodologies. The rapid increase in the volume of published studies highlights the need for heightened awareness among authors, reviewers, readers, and scientists regarding emerging data. This situation underscores the importance of continuous training in advanced search tools and the adoption of innovative methods for evaluating systematic reviews to derive accurate and reliable conclusions. Various tools and methodologies have been developed to accommodate different types of studies, enabling researchers to tailor their approaches to meet the specific requirements of the systematic reviews they conduct, such as assessing the diagnostic accuracy of studies *(Bossuyt et al., 2015).*

One such tool is **STARD 2015** (Standards for Reporting of Diagnostic Accuracy), which comprises 30 guidelines organized into sections: Title/Abstract, Abstract, Methods, Results, Discussion, and Other Information. These guidelines are designed to comprehensively cover all critical aspects of each study and assess its reporting quality (https://www.equator-network.org/reporting-guidelines/stard/).

This tool evaluates the study's structure and design, the correlation between the index test and the reference standard against which it is compared, and the sensitivity and specificity of the test. Additionally, it examines the collection and presentation of the data, the characteristics of the participants, and the interventions associated with the reported results (*Cohen et al., 2016*). The complete list of 30 guidelines, provided in the Appendix section (*Table A1*), was developed to help readers assess potential bias in studies and evaluate the applicability of the data.

1.4 Aims of the report

The aims of this report are

- to investigate diagnostic approaches for hereditary breast and ovarian cancer by examining mutations in the BRCA1 and BRCA2 genes over the last ten years (2014–2024).
- To extract data on the demographic characteristics and publication details of the studies.
- To assess the reporting quality of the studies using the guidelines outlined in the **STARD** statement.

2 Methods

2.1 Selection of studies

The initial search for studies was conducted using the **NCBI PubMed** database and the **Cochrane Library**, employing predefined search terms relevant to the report's topic.

In **PubMed**, the search was conducted using the following query:

("BRCA 1" OR "BRCA1") AND ("BRCA 2" OR "BRCA2") AND ("diagnosis" OR "identification") AND ("breast") AND ("ovarian") AND ("cancer" OR "tumor")

To refine the results and address the initial research question, the following filters were applied:

1. Studies published within the last 10 years.
2. Availability of the full text of the study.
3. Studies focusing on clinical trials and meta-analyses (excluding protocols, letters, conference documents, books, bibliographies and guidelines).
4. Studies written in English.
5. Studies concerning humans (excluding animal studies).

In **Cochrane Library** database, the search was performed using the following query:

(BRCA 1 OR BRCA1) AND (BRCA 2 OR BRCA2) AND (diagnosis OR identification) AND breast AND ovarian AND (cancer or tumor)

The following filters were applied to refine the results:

1. Studies categorized as trials (excluding protocols, reviews, editorials, or clinical answers).
2. Studies published within the last 10 years.
3. Studies written in English.

2.2 Data abstraction

Studies were selected based on their focus on the prevalence of **BRCA1** and **BRCA2** gene mutations within the populations under investigation, the association of these mutations with the development of breast and/or ovarian cancer, and the diagnostic accuracy of the Next-Generation Sequencing (NGS) method. The selected studies primarily included data from clinical observational studies, with a smaller proportion drawn from Randomized Controlled Trials (RCTs) and Cohort Studies, all featuring sample sizes exceeding 20 participants.

Additionally, main characteristics were extracted from the selected studies, which were deemed to contribute to their more comprehensive and accurate evaluation, as well as to the overall assessment of their reporting quality. These characteristics include: first author and his/her h-index, year and journal of publication, journal impact factor of the year of search, study type and type of cancer, sample size and the mean age, the population that study conducted and the diagnostic method that described.

2.3 Assessment the reporting quality of studies with STARD

To comprehensively evaluate the diagnostic accuracy of the methods described in the studies retrieved from the aforementioned databases, the **STARD** guidelines were employed, focusing specifically on the 35 guiding items

applicable to the entire text of each study. It is important to note that the guidelines were strictly adhered to. Each item under evaluation received a score based on its placement within the study: if the item was exclusively described in the section referenced by the STARD guidelines and not elsewhere, a score of **1** was assigned. Conversely, if the item was absent from the referenced section or mentioned in a different section of the text, a score of **0** was recorded.

To derive a reliable qualitative conclusion regarding the reporting quality of the studies in terms of diagnostic accuracy, the median score was used as the threshold for classification. The studies with a score below the median were categorized into the low-quality group, while those with a score above the median were categorized into the high-quality group.

2.4 Statistical methods for assessment the reporting quality with STARD

The final score from each study as well as the proportion of reporting of each STARD item was calculated with Descriptive Statistics. The verification of the results and conclusions derived from the **STARD** evaluation is performed by analyzing the correlation between each STARD item and the high – or low – quality study groups. This correlation is assessed using **Fisher's exact test** and the statistical parameter **p-value**, which indicates statistically significant associations. All statistical parameters were calculated using the **IBM SPSS Statistics.**

2.5 Correlation between STARD score and studies characteristics

Through the search and evaluation of study characteristics, the correlation of the **STARD** score with the journal's impact factor in the current year of review and the sample size was also examined for each study. The aim was to determine whether these specific characteristics influence the reporting quality of the studies. This correlation was analyzed using the **Linear Regression** method in **IBM SPSS Statistics**.

3 Results

3.1 Studies selection

The search conducted in the **PubMed** database and the **Cochrane Library** followed the steps and search terms outlined in the Methods section of the report. The search yielded a total of **770** articles, which, after the removal of duplicates (n=39), were evaluated and categorized to exclude those that, for any reason, did not align with the inclusion and exclusion criteria set at the outset of the systematic review search. The following flow diagram *(Figure 3)* illustrates the reasoning process behind the selection of studies included in the evaluation. Out of a total of **731** articles identified in the database, **14** were ultimately selected for inclusion in the report and were assessed for their diagnostic accuracy based on the STARD Statement.

The 2 of the 14 selected studies according to the search strategy, involved histological studies with data from FFPE (Formalin – Fixed Paraffin – Embedded) tissue samples, a method used for the purification and isolation of genomic DNA from formalin-fixed and paraffin-embedded biological samples (*Endris et al., 2016).* However, their data were deemed essential for inclusion in the report and were incorporated into the results.

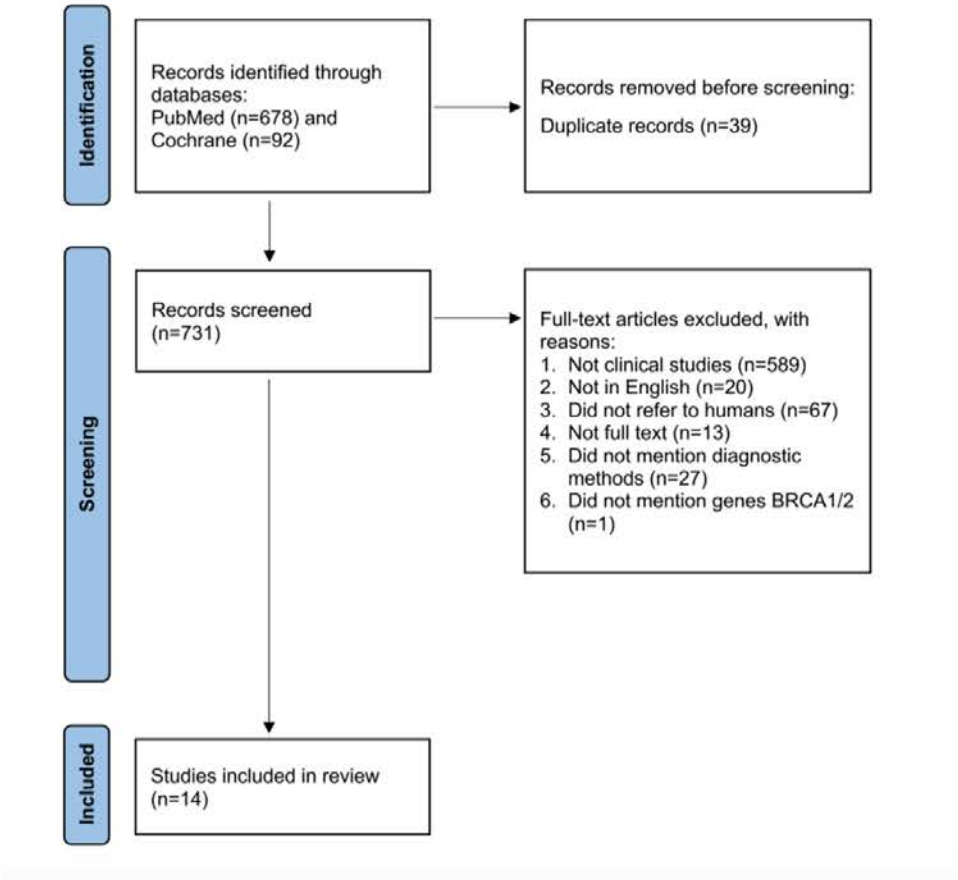


Figure 3 Flow diagram with the selected studies

A comprehensive list of selected studies retrieved from PubMed and the Cochrane Library is provided in the Appendix section (*Table A2*).

3.2 Studies characteristics

The **14 studies** included in the diagnostic accuracy evaluation were assessed based on their **main characteristics**, such as the first author, their h-index, the year of publication, the journal of publication, and journal impact factor of the year. Additionally, they were evaluated for their study design, including attributes such as study type, type of cancer, population, mean age, and study size. The majority of the studies, as shown in *Figure 4*, are observational studies (72%), with most being published in 2020 and 2021.

Additionally, 6 studies (43%) evaluated focused on hereditary breast and ovarian cancer syndrome (HBOC), while 28.5% addressed breast cancer and the remaining 28.5% focused on ovarian cancer. The country where 43% of the studies were conducted is the United States, followed by Germany, where 15% of the studies took place. *(Figure 5).*

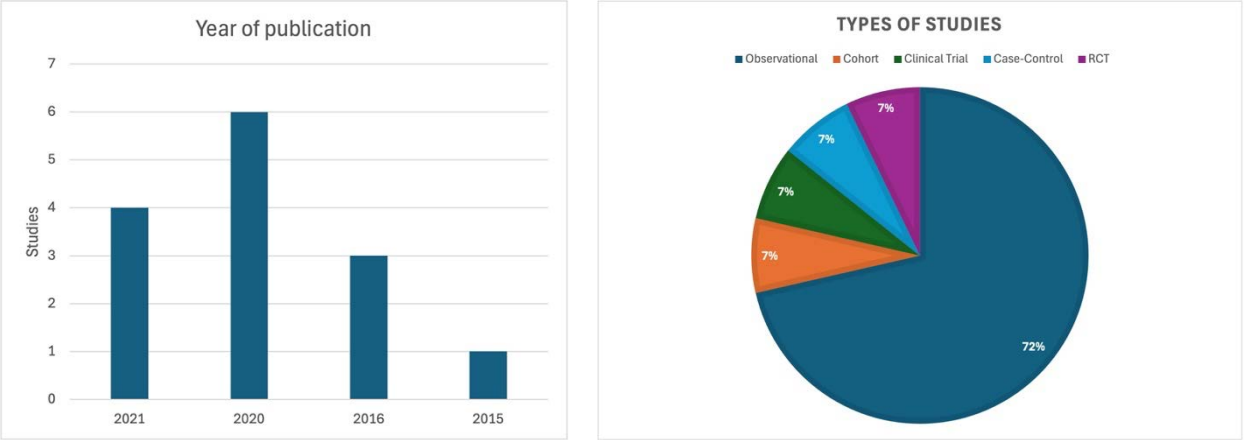
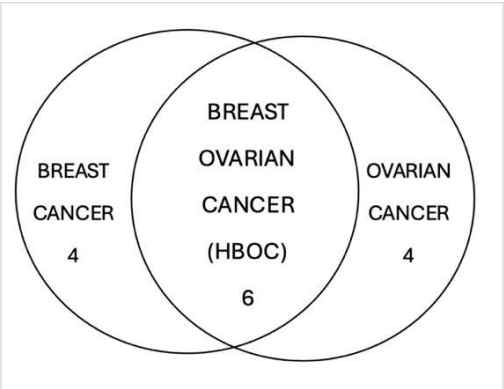


Figure 4 Year of publication and types of STARD-evaluated studies



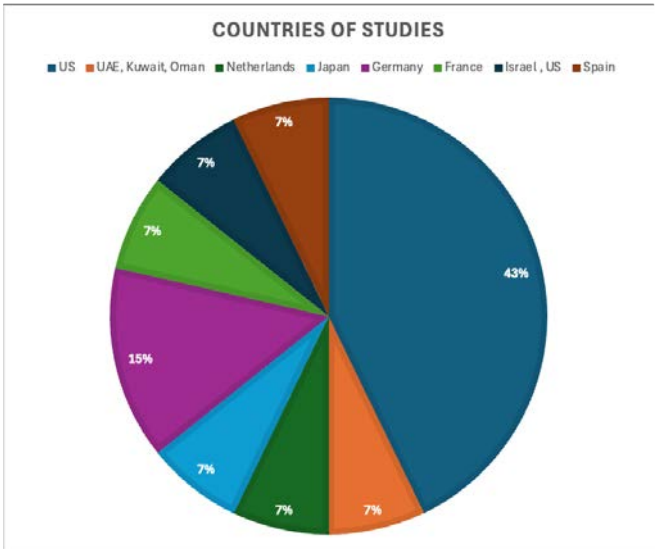


Figure 5 Types of cancer in the studies and populations in which the studies were conducted

Subsequently, the mean age of participants in each study and the sample size of each study were examined. The average of the mean age across 10 of the 14 studies was 51.7 years, with 6.50 SD (*Table 1 and Figure 6*). This data was collected from 10 out of the 14 studies, as the remaining 4 did not provide information on the mean age of participants. Specifically, in 2 of these studies, the data were derived from FFPE, as mentioned, and in the other 2 studies, there was insufficient information regarding participant age.

Descriptives Statistics						
	N Statistics	Minimum Statistic	Maximum Statistic	Mean Statistic	Mean Std. Error	Std Deviation Statistic
age	10	45.00	63.00	51.70	2.06	6.50

Table 1 Descriptives statistics of mean age of studies

Regarding the sample size of the studies, the mean is 2476.57 with 8349.38 SD (*Table 2 and Figure 6).* Notably, one study has a large-scale sample size of 31481, which skews the mean and the range of the data. Otherwise, 13 out of the 14 studies have sample size ranging from 26 to 523.

Descriptives Statistics						
	N Statistics	Minimum Statistic	Maximum Statistic	Mean Statistic	Mean Std. Error	Std Deviation Statistic
size	14	26.00	31481.00	2476.57	2231.47	8349.38

Table 2 Descriptive statistics of the size of studies

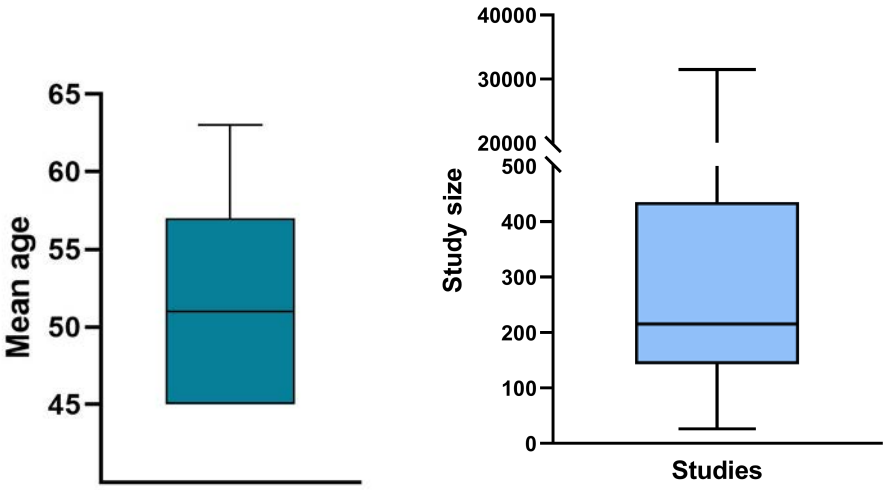


Figure 6 Boxplot of mean age and sample size of studies

The diagnostic methods mentioned and described in the evaluated studies concern:

- **DNA – sequencing** (42% of studies, *Figure 7*), such as NGS: an advanced technology designed for the sequencing of DNA and RNA as well as the identification of genetic variants and mutations, within a significantly short timeframe (*Qin, 2019*)
- **Genetic hereditary testing** (14% of studies, *Figure 7),* such as Facilitated Cascade Testing, a complete study of the inheritance and transfer of the mutation to the next generations of the organism under study
- Utilization of **medical history** (21% of studies), complete study of the inheritance and transfer of the mutation to the next generations of the proband
- **Risk Behavior Diagnosis Scale** (7% of studies), a 12-item survey, which scale specifically, comprises three questions for each of the following constructs: perceived severity, perceived susceptibility, response efficacy, and self-efficacy (*Cragun et al., 2020*)
- **DHPLC** (7% of studies), which is a method that compares two or more chromosomes by analyzing a mixture of denatured and reannealed PCR amplicons. It identifies the presence of mutations based on the differential retention of homo- and heteroduplex DNA on reversed-phase chromatography supports under conditions of partial denaturation (*Xiao and Oefner, 2001)*
- **BRCAness** method (7% of studies), that describes the underlying pathogenesis and therapeutic vulnerabilities of various cancers. It is traditionally defined as a defect in homologous recombination repair that resembles the loss of BRCA1 or BRCA2 function (*Yoshida et al., 2021*)

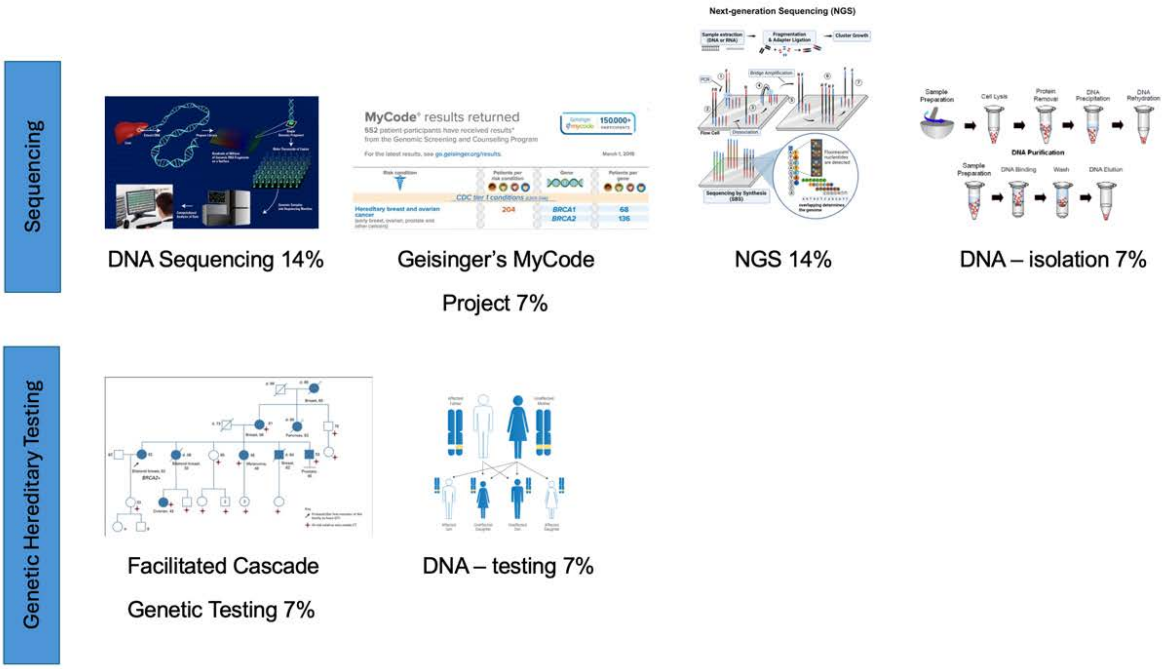


Figure 7 Diagnostic methods of DNA – sequencing and Genetic testing of hereditary cancer reported in the studies reviewed

3.3 Assessment with STARD Statement

The main analysis of the present systematic review is the assessment of all studies selected by the STARD method, with the procedure described in section «2.3 Assessment the reporting quality of studies with STARD» and the calculation of median of scores (**median=13** in total 34 items of STARD), with descriptives statistics, as the threshold for determining the groups to low/high quality. A cut-off point of **13** was established: studies scoring >13 were classified as high-quality, while those scoring <13 were categorized as low-quality. Therefore, each study was evaluated, and the final score was noted based on the STARD guidelines as shown in the scatterplot (*Figure 8*), with percentage range of score from 14% to 53% and mean 35.5%.

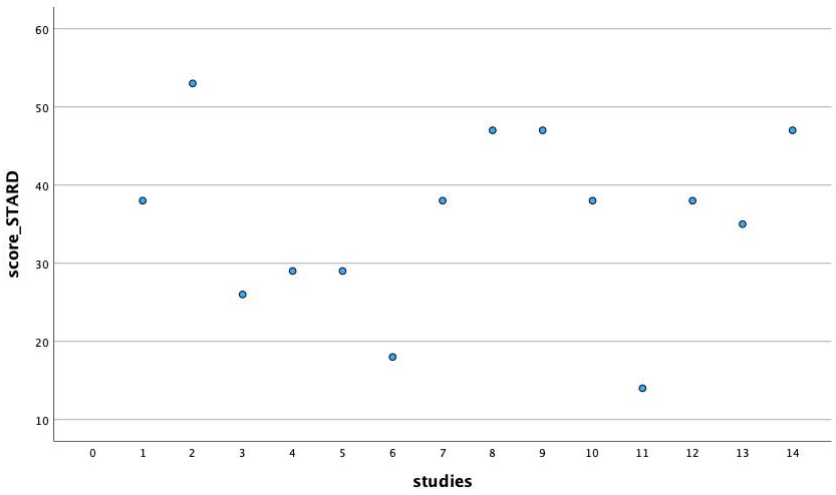


Figure 8 Scatter-dot depicting the STARD score of studies

In addition, the frequency with which each STARD item is mentioned in the studies was calculated and analyzed, in order to subsequently evaluate the diagnostic accuracy of the studies. It was observed that items **10b, 12a, 12b, 13a, 13b** (listed in the Test methods section), **15, 23,** and **25** (listed in the Test results section) were not identified in any study (*Figure 9)*.

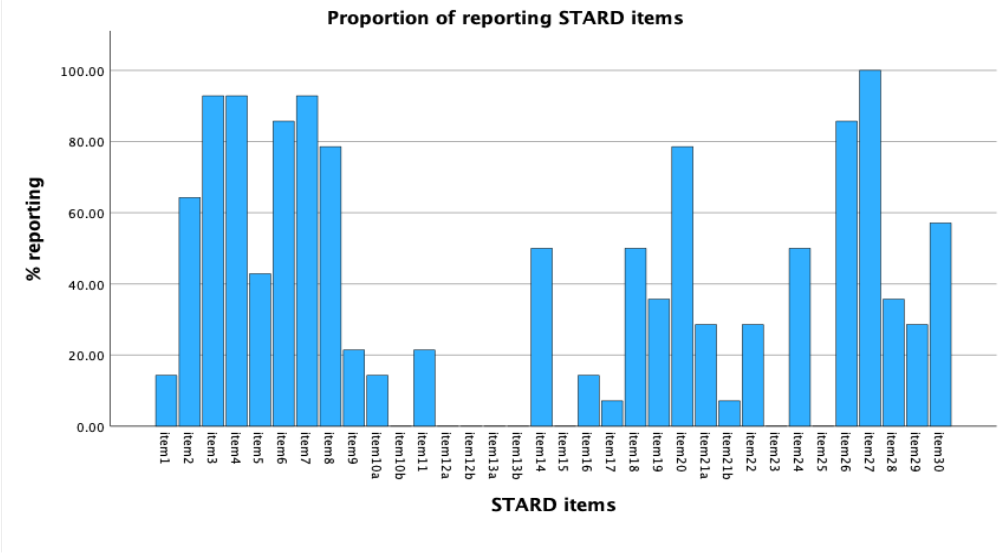


Figure 9 Proportion of items reporting in reviewed studies

Finally, the final analysis for the evaluation with STARD statement aims at the statistically significant approximation of the difference with which each STARD item appears in the two groups (low – high) of the studies. The analysis was done with **Fisher's Exact Test** in **IBM SPSS Statistics** item-by-item to

calculate the **p-value** and if indeed there is a difference between low and high studies. The analysis showed that only in one item of STARD, namely "30. Sources of funding and other support", there is a statistically significant difference between the two categories (p-value 0.031). All other items (1–29) showed no statistically significant difference between low and high quality studies (*Table 3).*

Item	overall %	% in low quality	% in high quality	p-value
1	14.29	11.11	20.00	1.000
2	64.29	55.56	80.00	0.58
3	92.86	88.89	100.00	1.000
4	92.86	88.89	100.00	1.000
5	42.86	22.22	80.00	0.091
6	85.71	77.78	100.00	0.505
7	92.86	88.89	100.00	1.000
8	78.57	77.78	80.00	1.000
9	21.43	22.22	20.00	1.000
10a	14.29	11.11	20.00	1.000
10b	0.00	0.00	0.00	-
11	21.43	11.11	40.00	0.505
12a	0.00	0.00	0.00	-
12b	0.00	0.00	0.00	-
13a	0.00	0.00	0.00	-
13b	0.00	0.00	0.00	-
14	50.00	44.44	60.00	1.000
15	0.00	0.00	0.00	-
16	14.29	11.11	20.00	1.000
17	7.14	0.00	20.00	0.357
18	50.0	33.33	80.00	0.266
19	35.71	33.33	40.00	1.000
20	78.57	66.67	100.00	0.258
21a	28.57	11.11	60.00	0.095
21b	7.14	0.00	20.00	0.357
22	28.57	33.33	20.00	1.000
23	0.00	0.00	0.00	-
24	50.00	33.33	80.00	1.000
25	0.00	0.00	0.00	-
26	85.71	77.78	100.00	0.505
27	100.00	100.00	100.00	-
28	35.71	33.33	40.00	1.000
29	28.57	33.33	20.00	1.000
30	57.14	66.67	0.00	0.031

Table 3 Proportion of reporting quality of studies with STARD

3.4 Statistical analysis of association

As mentioned in section «3.2 Studies characteristics», the information extracted from the **systematic review** of the studies includes data related to the journal of publication, specifically the impact factor. Subsequently, the potential correlation between the impact factor and the STARD evaluation score is examined using the **Regression Linear** method in IBM SPSS Statistics.

The results indicate that the linear model does not account for the variability in the data, as the **Adjusted R Square** is -0.007 (p-value 0.360), which approaches zero. Consequently, there is no linear correlation between the impact factor and the study scores following their evaluation using the STARD Statement *(Table 4).*

Linear Regression		ANOVA			
R	R Square	Adjusted R Square	Sum of Squares	F	Sig.
0.265	0.070	-0.007	117.277	0.905	0.360
Predictors (constent): impact factor					
Dependemt variable: STARD score					

Table 4 Association of journal impact factor and STARD score of the studies

Similarly, the correlation between sample size and study scores was examined to determine whether a linear relationship exists. The results of the **Linear Regression** analysis indicated no linear correlation, as the Adjusted R Square was 0.011 (p-value 0.306), approaching zero (*Table 5*).

Linear Regression		ANOVA			
R	R Square	Adjusted R Square	Sum of Squares	F	Sig.
0.295	0.087	0.011	145.632	1.145	0.306
Predictors (constent): study size					
Dependemt variable: STARD score					

Table 5 Association between sample size and STARD score of studies

4 Discussion

Hereditary breast and ovarian cancer (**HBOC**) syndrome is an increasingly frequent cause of cancer, leading to a growing demand for the development of reliable and effective diagnostic tools for cancer prognosis. According to studies, in the past decade and particularly in recent years, a valuable tool, with continuously expanding knowledge, is the understanding of the mutation mechanisms in the **BRCA1** and **BRCA2** genes and how they influence their inheritance. It serves as a foundation for the discovery of additional diagnostic methods in the coming years, with advancements in science contributing to the management of hereditary breast and ovarian cancer. Numerous cohort studies and meta-analyses have shown that the diagnosis of mutations in the BRCA1 and BRCA2 genes has led to improved overall survival in the studied population, while the same conclusion was not reached for mutations in BRCA2 alone. Therefore, their common mutation mechanism plays a crucial role in the development of cancer therapies. *(Yoshida, 2021*).

The primary objective of this report was to gather data from studies conducted over the past decade through a systematic review and to highlight the **quality of their reporting** concerning the coverage of diagnostic methods for cancer. The evaluation of the selected studies using the STARD guidelines, as well as the assessment of their various characteristics through statistical tools, contributed to the overall appraisal of the reporting quality of these studies.

It is worth noting that the threshold used in this report is considered low (median=13 out of a total of 34 STARD items), representing an area for improvement in future systematic reviews. Nevertheless, it was utilized to classify studies into **low and high quality reporting** groups to examine their statistically significant differences. This classification aimed to evaluate the overall proportion of reporting for each guideline within each group of studies. The findings indicate that the **STARD** statement guidelines can be applied to all studies, regardless of whether they fall into the low or high quality category and serve as a valuable tool for the overall assessment of the quality of studies related to diagnostic accuracy methods.

Through this comprehensive assessment, additional evaluation metrics were derived, such as:

- **the correlation** between sample size and the STARD score for each study, concluding that there is no linear regression between these two characteristics
- the correlation between the journal's impact factor the year of search and the STARD score, indicating that higher impact factor does not necessarily correspond to better reporting quality in a study

Through the search for studies and the evaluation of their main characteristics, several noteworthy findings emerged. One observational study stood out with a large-scale sample size and a high impact factor for the publishing journal compared to the other 13 studies. Although some approaches might consider it ineligible, it involved participants from the years 1937–2011, which justified its inclusion in all analyses of this report. Additionally, 4 studies lacked sufficient data regarding sample size, with 2 of them focusing on samples from preserved human tissues. These studies provided significant insights into the diagnostic value of the BRCA1 and BRCA2 genes and were therefore not excluded from the analysis.

Regarding the evaluation based on the STARD guidelines and the extent to which they were addressed in the selected studies, it was observed that guidelines related to the structure of sections such as the abstract and introduction, as well as the study design and participant selection (eligibility criteria, identification of participants), demonstrated a high reporting rate. Similarly, a high reporting rate was observed for guidelines related to results, particularly those addressing participant characteristics and the assessment of diagnostic accuracy (using 96% confidence intervals).

In contrast, low reporting rates were observed for the guidelines related to Test methods in Methods section, specifically concerning the characteristics and details of the index test and the reference standard, as well as any potential cross-referencing between them. Therefore, this represents an area for improvement in future studies on diagnostic methods that follow the STARD guidelines. Enhancing their methods with these elements would allow for their inclusion in more comprehensive systematic reviews in the future.

The **BRCA1** and **BRCA2** genes have become one of the most common and rapidly advancing approaches for uncovering the mechanisms of hereditary breast and ovarian cancer, with the goal of developing new therapeutic methods. The **STARD** guidelines can guide researchers and scientists in this direction by highlighting critical areas for improving the reporting quality of studies examining the diagnostic accuracy of BRCA1 and BRCA2.

5 References

Adam, M.P., Feldman, J. and Mirzaa, G.M. (1998) *Associated Hereditary Breast and Ovarian Cancer*.

Angeli, D., Salvi, S. and Tedaldi, G. (2020) 'Genetic predisposition to breast and ovarian cancers: How many and which genes to test?', *International Journal of Molecular Sciences*. MDPI AG. Available at: https://doi.org/10.3390/ijms21031128.

Bossuyt, P.M. *et al.* (2015) 'STARD 2015: An updated list of essential items for reporting diagnostic accuracy studies', *The BMJ*, 351. Available at: https://doi.org/10.1136/bmj.h5527.

Cohen, J.F. *et al.* (2016) 'STARD 2015 guidelines for reporting diagnostic accuracy studies: explanation and elaboration'. Available at: https://doi.org/10.1136/bmjopen-2016.

Cragun, D. *et al.* (2020) 'Cancer risk management among female BRCA1/2, PALB2, CHEK2, and ATM carriers', *Breast Cancer Research and Treatment*, 182(2), pp. 421–428. Available at: https://doi.org/10.1007/s10549-020-05699-y.

Endris, V. *et al.* (2016) 'NGS-based BRCA1/2 mutation testing of high-grade serous ovarian cancer tissue: results and conclusions of the first international round robin trial', *Virchows Archiv*, 468(6), pp. 697–705. Available at: https://doi.org/10.1007/s00428-016-1919-8.

Qin, D. (2019) 'Next-generation sequencing and its clinical application', *Cancer Biology and Medicine*, 16(1), pp. 4–10. Available at: https://doi.org/10.20892/j.issn.2095-3941.2018.0055.

Torre, L.A. *et al.* (2018) 'Ovarian cancer statistics, 2018', *CA: A Cancer Journal for Clinicians*, 68(4), pp. 284–296. Available at: https://doi.org/10.3322/caac.21456.

Westin, S.N. *et al.* (2021) 'Phase Ib Dose Expansion and Translational Analyses of Olaparib in Combination with Capivasertib in Recurrent Endometrial, Triple-Negative Breast, and Ovarian Cancer', *Clinical Cancer Research*, 27(23), pp. 6354–6365. Available at: https://doi.org/10.1158/1078-0432.CCR-21-1656.

Xiao, W. and Oefner, P.J. (2001) 'Denaturing high-performance liquid chromatography: A review', *Human Mutation*, pp. 439–474. Available at: https://doi.org/10.1002/humu.1130.

Yoshida, R. (2021) 'Hereditary breast and ovarian cancer (HBOC): review of its molecular characteristics, screening, treatment, and prognosis', *Breast Cancer*. Available at: https://doi.org/10.1007/s12282-020-01148-2.

Yoshida, R. *et al.* (2021) ‘Pathogenicity assessment of variants for breast cancer susceptibility genes based on BRCAness of tumor sample’, *Cancer Science*, 112(3), pp. 1310–1319. Available at: https://doi.org/10.1111/cas.14803.

6 Appendix

Section & Topic	No	Item
TITLE OR ABSTRACT		
	1	Identification as a study of diagnostic accuracy using at least one measure of accuracy (such as sensitivity, specificity, predictive values, or AUC)
ABSTRACT		
	2	Structured summary of study design, methods, results, and conclusions (for specific guidance, see STARD for Abstracts)
INTRODUCTION		
	3	Scientific and clinical background, including the intended use and clinical role of the index test
	4	Study objectives and hypotheses
METHODS		
Study design	**5**	Whether data collection was planned before the index test and reference standard were performed (prospective study) or after (retrospective study)
Participants	**6**	Eligibility criteria
	7	On what basis potentially eligible participants were identified (such as symptoms, results from previous tests, inclusion in registry)
	8	Where and when potentially eligible participants were identified (setting, location and dates)
	9	Whether participants formed a consecutive, random or convenience series
Test methods	**10a**	Index test, in sufficient detail to allow replication
	10b	Reference standard, in sufficient detail to allow replication
	11	Rationale for choosing the reference standard (if alternatives exist)
	12a	Definition of and rationale for test positivity cut-offs or result categories of the index test, distinguishing pre-specified from exploratory
	12b	Definition of and rationale for test positivity cut-offs or result categories of the reference standard, distinguishing pre-specified from exploratory
	13a	Whether clinical information and reference standard results were available to the performers/readers of the index test
	13b	Whether clinical information and index test results were available to the assessors of the reference standard
Analysis	**14**	Methods for estimating or comparing measures of diagnostic accuracy
	15	How indeterminate index test or reference standard results were handled
	16	How missing data on the index test and reference standard were handled
	17	Any analyses of variability in diagnostic accuracy, distinguishing pre-specified from exploratory
	18	Intended sample size and how it was determined
RESULTS		
Participants	**19**	Flow of participants, using a diagram
	20	Baseline demographic and clinical characteristics of participants
	21a	Distribution of severity of disease in those with the target condition
	21b	Distribution of alternative diagnoses in those without the target condition
	22	Time interval and any clinical interventions between index test and reference standard
Test results	**23**	Cross tabulation of the index test results (or their distribution) by the results of the reference standard
	24	Estimates of diagnostic accuracy and their precision (such as 95% confidence intervals)
	25	Any adverse events from performing the index test or the reference standard
DISCUSSION		
	26	Study limitations, including sources of potential bias, statistical uncertainty, and generalisability
	27	Implications for practice, including the intended use and clinical role of the index test
OTHER INFORMATION		
	28	Registration number and name of registry
	29	Where the full study protocol can be accessed
	30	Sources of funding and other support; role of funders

Table A1 The list of 30 items - guidelines of STARD Statement

ID	1st Author	h-index	Year	Journal	Impact Factor	Study Type	Type of cancer	Country	Study Size	Mean Age	Diagnostic Method	STARD Score (%)	DOI
1	Deborah Cragun	31	2020	Springer Science+Business Media	9.5	Observational	Breast	US	235	54	Risk Behavior Diagnosis (RBD) Scale	38	10.1007/s10549-020-05699-y
2	Fathi Azribi	6	2021	BMC Cancer	3.4	Observational	Ovarian	UAE, Kuwait, Oman	105	52	Next Generation Sequencing (NGS)	53	10.1186/s12885-021-09094-8
3	Fred H. Menko	66	2020	European Journal of Human Genetics	5.4	Observational	HBOC	Netherlands	239	50	DNA testing	26	10.1038/s41431-020-0618-8
4	Adam H. Buchanan	30	2020	Genetics in Medicine	8.2	Observational	HBOC	US	351	63	Geisinger's MyCode project	29	10.1038/s41436-020-0876-4
5	Reiko Yoshida	21	2020	Cancer Science	6.7	Cohort	Breast	Japan	413	N/A	BRCAness	29	10.1111/cas.14803.
6	Volker Endris	N/A	2016	Springer-Verlag Berlin Heidelberg	2.4	Clinical Trial	Ovarian	Germany	26	N/A	Next Generation Sequencing (NGS)	18	10.1007/s00428-016-1919-8
7	Estelle Jamard	N/A	2016	Springer Science+Business Media	9.5	Case-Control	HBOC	France	195	45	DHPLC	38	10.1007/s10689-016-9940-2.
8	Claire C. Conley	13	2020	Annals of Surgical Oncology	3.4	Observational	Breast	US	143	45	DNA sequencing	47	10.1245/s10434-019-07982-9
9	Timothy R. Rebbeck	115	2015	JAMA	63.1	Observational	HBOC	(33 countries)	31481	45	DNA sequencing	47	10.1001/jama.2014.5985
10	Tamar Safra	N/A	2021	Gynecologic Oncology	4.5	Observational	Breast	Israel, US	502	56	Medical History	38	10.1016/j.ygyno.2021.06.009
11	Roni Nitecki	N/A	2021	International Journal of Gynecological Cancer	4.8	Randomized C	HBOC	US	150	N/A	Facilitated cascade genetic testing	14	10.1136/ijgc-2020-002118
12	Sudhir K. Unni	N/A	2016	Journal of Ovarian Research	3.8	Observational	Ovarian	US	168	60	Medical History	38	10.1186/s13048-016-0227-x
13	A. J. Muñoz	15	2021	Clinical and Translational Oncology	2.8	Observational	HBOC	Spain	141	47	Venus Thromboembolism	35	10.1007/s12094-021-02678-7.
14	Jan Hauke	35	2020	Cancer Genetics	1.4	Observational	Ovarian	Germany	523	N/A	DNA isolation	47	10.1136/jmedgenet-2020-107353

Table A2 The list of 14 selected studies evaluated with STARD