Mainstreamed Genetic Testing of Breast Cancer Patients in Two Hospitals in South Eastern Norway

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Research article

Keywords: Genetic testing, BRCA, breast cancer, mainstreaming cancer genetics

Posted Date: September 25th, 2019

DOI: https://doi.org/10.21203/rs.2.15182/v1

Version of Record: A version of this preprint was published at Familial Cancer on January 30th, 2020. See the published version at https://doi.org/10.1007/s10689-020-00160-x.

Abstract

Background: Identification of a BRCA mutation in a breast cancer patient provides critical information both for treatment decisions and for prevention of new cancers. In South Eastern Norway, genetic testing of the BRCA genes has been mainstreamed into breast cancer care. Testing is offered directly to the patients by the surgeon or oncologist if they fulfill national criteria. The purpose of this study was to investigate to what extent BC patients who fulfill these criteria are offered testing.

Methods: Three hundred and sixty one BC patients diagnosed during the first half of 2016 and 2017 at one university and one regional hospital in South Eastern Norway were included in the study. Data were collected on whether the patients fulfilled the criteria, whether they had been offered testing and if they had accepted testing.

Results: For the two hospitals combined, 75% of BC patients who fulfilled the criteria were offered testing. The numbers were 63% at the regional hospital and 90% at the university hospital. Fifty two percent of the patients who were not offered testing even though they fulfilled the criteria and were younger than 50 years at time of diagnosis. As many as 95% of the patients who were offered testing, wanted to be tested.
Conclusions: The majority of patients who fulfilled the criteria were offered testing. However, there were differences in rates of testing between the hospitals that affected all groups of patients. This indicates that diagnostic genetic testing is not equally available to all BC patients. We suggest that efforts should be made to raise awareness of and improve routines for genetic testing of BC patients in Norway.

Background

Germline mutations in *BRCA1* and *BRCA2* are associated with a high lifetime risk of breast and ovarian cancer (1–3). Identification of a mutation in one of these genes in a woman diagnosed with breast cancer (BC) provides critical information for treatment decisions for her current cancer [4–9]. In addition, future breast and ovarian cancer may be prevented through risk-reducing mastectomy and salpingo-oophorectomy in herself and her relatives who may also carry the mutation [10–12]. Genetic testing of these two genes is therefore increasingly offered to BC patients at time of diagnosis or during treatment.

In most countries, genetic testing is only offered to BC patients with an *a priori* high risk of being a mutation carrier, either because they have BC at a young age (below 50 years), triple negative BC (TNBC), or because they have a family history of breast and/or ovarian cancer. The Norwegian Breast Cancer Group (NBCG) has developed criteria for *BRCA* testing of BC patients based on such risk factors (see Table 1) [13]. Similar guidelines have been developed in other countries [14, 15]. However, several studies have demonstrated that a significant number of BC patients who fulfill these criteria are neither offered genetic testing nor referred to genetic counseling [16–20].

We have recently reported that about 39% of all BC patients in the South-Eastern Norway Regional Health Authority (hereafter called South Eastern Norway) were offered testing in 2014 and 2015 [21]. However, we do not know how many of the patients who fulfilled the criteria that were offered testing. Based on the

previous studies on rates of genetic testing, we suspect that also in Norway there may be BC patients eligible for testing according to the NBCG criteria who are not offered testing. However, we also suspect that the rate of genetic testing of BC patients may be higher in South Eastern Norway than the previous studies have shown. One explanation might be that many of the previous studies report observations from before 2010, and the awareness and availability of genetic testing has increased significantly during the last 5 years. In addition, in South Eastern Norway, genetic testing is offered directly to BC patients by the treating surgeon or oncologist as part of regular surgical and/or oncological health care, a model called “mainstreamed genetic testing” [22]. The patient is only referred to genetic counseling if a pathogenic variant or a variant of unknown clinical significance (VUS) is detected. This is different from the traditional model where genetic tests are ordered by specialists in medical genetics or genetic counselors and only after genetic counseling. It has been argued that the traditional model contributes to keeping rates of genetic testing low [23].

The role of genetic testing in treatment of BC and other cancers will increase in the coming years. This is both due to the decreasing costs associated with such testing, the increasing knowledge of different genes associated with heritable cancer risk, and the increasing opportunities for personalized treatment for hereditary tumors. Knowledge on how the health service of genetic testing is practiced is therefore needed to ensure that testing is equally available to all eligible patients across hospitals and health regions.

The aim of this study was therefore to explore to what extent genetic testing of BC patients is provided at two hospitals in South Eastern Norway, one regional and one university hospital. In both hospitals, genetic testing is offered directly to the patient by the treating surgeon or oncologist: i.e. within a “mainstreaming genetic testing” model. More specifically, we investigated how many BC patients that were offered genetic testing, and how many of them that wanted to be tested. We also explored how many of the BC patients who fulfilled the NBCG criteria were offered testing, and the characteristics of those who fulfilled the criteria that were not offered testing. Data were collected for patients diagnosed during the first half of 2016 and 2017.

Methods

Patients

The two hospitals involved in the study were Akershus University Hospital (Ahus) and Innlandet Hospital Trust (IH). Ahus serves a population of 500.000 and IH a population of 380.000.

All breast cancer patients diagnosed with invasive cancer between 1st of January and 30th of June in 2016 and 2017 were identified, 303 from Ahus and 256 from IH. All were sent an information letter and a consent form to give access to their hospital records. One hundred and ninety nine BC patients from Ahus and 162 from IH signed the consent form, giving a response rate of 65.7% and 63.3% for the two hospitals respectively. Mean age was similar for the two groups, 61.1 (range 33–92) for Ahus and 60.4

(range 28–86) for IH. The distribution of patients in different age groups was also similar for the two hospitals. See Table 2 for a description of the cohorts.

Methods

We collected data on age at diagnosis, whether the patient had bilateral BC and whether the tumor was triple negative (ER, PR and HER2 negative) from the Electronic Patient Record (EPR). In addition, information was collected on whether the patient had been asked about their family history of cancer, whether they had a family history of cancer and if yes, what type of cancers. The patients were then scored according to the NBCG criteria used at time of diagnosis (see table 1). When information in the EPR was not sufficient to score the patient according to the criteria, we registered that it was uncertain whether the patient fulfilled them. Finally, data was collected on whether or not the patient had been offered genetic testing, if yes by whom, and whether the patient had been tested. The data were registered in a web based form and stored at the Service for Sensitive Data (TSD, University of Oslo).

In the consent form the patients could tick off that they wanted to be contacted if they were eligible for genetic testing according to the criteria. Patients that ticked off the box and had not been tested before, but fulfilled the criteria in use in 2018, were contacted and offered testing. Patients who could not be scored according to the criteria in use in 2018 were contacted for evaluation of family history and offered testing if they fulfilled the criteria.

Non-responders

Ninety four BC patients at IH (36.7%) and 104 (34.3%) at Ahus did not sign the consent form. Their mean age was 64 and 60.6 years respectively. This is similar to the mean age of the patients included in the study. No other demographic information was collected on the patients that did not sign the consent form.

Statistics

We report descriptive statistics of our findings.

Ethics

The research project was evaluated by the Regional Committees for Medical and Health Research Ethics. They defined it as a quality of care study, and thereby outside of their mandate. The study has been approved by the data protection officers at Oslo University Hospital (OUH), Ahus and IH.

Results

Genetic testing of all patients

In one of the journals from IH and four from Ahus it was noted that the patient had been tested prior to their BC diagnosis. These five patients were not offered a new test during diagnosis and treatment of their BC. Excluding them from the denominator, 131 of 356 patients (36.8%) had been tested, 48/161 (29.8%) at IH and 83/195 (42.6%) at Ahus. Of the 131 who were offered testing, 125 wanted to be tested (95.4%). The test had been requested by the surgeon prior to surgery in 71/125 (56.8%) of patients, and by the oncologist in 53/125 (42.4%). See Table 3.

Fulfillment of criteria

Most of the patients who fulfilled the criteria for testing, did so due to young age at diagnosis (below 50 years): Twenty nine out of 162 (17.9%) patients at IH and 30/199 (15.1%) at Ahus. It was noted in the journal of 126/162 (77.8%) patients at IH and 189/199 (95.0%) at Ahus that they had been asked about their family history. Of these, 10/126 (7.9%) patients at IH and 5/189 (2.6%) at Ahus fulfilled the criteria due to family history of cancer only (i.e. they did not have BC<50 years/TNBC < 60 years/bilateral BC <60 years/male BC). See Table 3.

Genetic testing according to the NBCG criteria

The results regarding genetic testing according to whether or not the patient fulfilled the NBCG criteria can be found in Figure 1. Four of the patients who fulfilled the criteria had been tested previously. Excluding these, 32/51 (62.7%) and 37/41 (90.2%) of patients who fulfilled the NBCG criteria were offered genetic testing at IH and Ahus respectively. In total, 69/92 (75%) of BC patients who fulfilled the criteria were offered testing. At IH 18/31 (58.1%) had been tested by their surgeon, and 12/31 (38.7%) by their oncologist, while at Ahus, 25/35 (71.4%) were tested by their surgeon and 9/35 (25.7%) by their oncologist.

Scoring each of the 92 patients who fulfilled the NBCG criteria according to what part of the criteria they fulfilled, and according to whether or not they had been offered testing, 19 out of 29 patients (65.2%) diagnosed with BC below 50 years at IH had been offered testing and 28/30 (93.5%) at Ahus. Of the patients who were 50 years or older at time of diagnosis, and fulfilled the criteria only because they had a family history of BC and/or OC, 10/17 (58.8%) were offered testing at IH and 5/5 at Ahus. None of the two men with BC were offered testing (table 4). Twelve of the 23 patients who fulfilled the criteria but were not offered testing (52.2%) were under 50 years at time of diagnosis (table 5).

Fig. 1 Genetic testing according to the NBCG criteria

Discussion

We have investigated the current practice of genetic testing of newly diagnosed BC patients in one regional and one university hospital in South Eastern Norway where genetic testing has been mainstreamed into regular cancer care and is offered directly to the patient by the surgeon or oncologist. For the two hospitals combined, 75% of BC patients who fulfilled the NBCG criteria were offered testing. However, there were differences between the hospitals, as 63% of eligible patients were offered testing at the regional hospital (IH) and 90% at the university hospital (Ahus). Surprisingly, 52% of the patients who were not offered testing even though they fulfilled one or more of the criteria and were younger than 50 years at time of diagnosis. As many as 95% of the patients who were offered testing, wanted to be tested.

Our observations indicate that genetic testing is a health service that BC patients want. In contrast, in the DNA-BONus study, only 45.4% of BC patients who were offered testing completed the test. In this study, all breast and ovarian cancer patients diagnosed between 2012 and 2015 at hospitals in the western part of Norway were offered *BRCA* testing as part of a research project [24]. We cannot rule out that there are some selection biases in our study. Apart from this the difference might be explained by the increasing awareness of hereditary breast and ovarian cancer among cancer patients during the last years, and especially after Angelina Jolie shared her story in May 2013 [25].

Family history based criteria for testing are complex, open to interpretation, and may be difficult to use for both clinicians and patients. In addition, several studies have reported that a significant number of mutation positive BC patients have no suggestive family history of cancer [21, 26, 27]. We have previously suggested that testing should be offered to all BC patients below 60 years [21], and this is now included in the NBCG criteria [13]. An age limit for testing is not open to interpretation, and setting the threshold at 60 years would identify mutation carriers with a sensitivity similar to the family history based criteria [21]. With this in mind, it was surprising for us to see that as many as 52% of the patients who had not been offered testing even if they fulfilled the criteria, were young at time of diagnosis (below 50 years). At the regional hospital, 66% of women diagnosed with BC below 50 years were offered testing compared to 93.5% at the university hospital. Studies have shown that 5–10% of BC patients below 50 years have a *BRCA* mutation [21, 28]. Young carriers have many years ahead of them with a risk of contralateral BC and OC. They are the ones who will benefit the most from cancer prevention and hence, genetic testing. It is therefore important that routines for genetic testing ensure that these patients have access to this health service.

At Ahus and IH, 57% of all tests were requested by the surgeon at time of diagnosis, and 42% by the oncologist during chemotherapy. It is not stated in the guidelines when genetic testing should be done, but because the great majority of patients see the surgeon first, there is an understanding that it is the surgeons who bear the main responsibility. It is therefore surprising that 42% of the patients were offered testing by their oncologist. There are good arguments for discussing testing with the patient either before or after primary surgery. If a mutation is detected before surgery, the patient may choose bilateral mastectomy directly, and will be spared for one extra surgical procedure. On the other hand, at time of diagnosis, the main objective is to remove the tumor, and the patient may prefer to have more time to adjust to the new information of her mutation status and then choose to undergo prophylactic surgery.

We argue that there is a need for definitions and guidelines regarding when genetic testing should be offered, and also to ensure that patients who do not undergo chemotherapy are offered testing.

In five of the journals it was noted that the patient had been tested previously, or that their relatives had been tested. None of these patients were offered a new test. The techniques and sensitivity of the genetic tests for *BRCA* mutations have changed dramatically since the genes were discovered, from testing only for a few founder mutations in *BRCA1* to sequencing and copy number analysis of both genes. Many previously tested patients should therefore be offered a new test. Moreover, even if the patient's relatives have been tested and not found to be mutation carriers, these could be phenocopies. The patient may still carry a *BRCA* mutation, and should be offered testing.

The main objective of this study was to investigate to what extent BC patients who fulfill the NBCG criteria were offered genetic testing. We found that 75% of eligible BC patients were offered testing. Other studies have reported testing rates ranging from 15.3% to 60% [16–20]. The design of our study does not enable us to fully explain why the rates differ. However, the observed difference may at least partly reflect that some studies present data on BC patients diagnosed before 2010 when awareness of hereditary breast and ovarian cancer and availability of genetic testing was much more limited. The results may also reflect differences in organization of genetic testing of newly diagnosed BC patients, and different reimbursement schemes among countries. In Norway, all testing is covered by the national social security system, and is not dependent on insurance coverage, regional legislation or patient's co-payment. As mentioned above, genetic testing is included in regular oncological care, and offered directly by the surgeon or the oncologist without referral to pre-test genetic counseling at a genetics department in South Eastern Norway where our study is performed. In several countries, genetic testing can only be requested by a medical geneticist or genetic counselor. Because genetics departments often have long waiting lists it has been argued that restricting testing to be done only after genetic counseling creates a barrier to genetic testing that contributes to keeping the rates of testing low [23]. With the increasing demand for genetic testing in diagnosis and treatment of BC and other cancers there is a need for alternative models that ensure both high access to testing and that the patient's need for information is met [29].

As many as 90% of BC patients who were eligible for testing according to the NBCG criteria were offered testing at the university hospital (Ahus) and 63% at the regional hospital (IH). At IH, 66% of patients eligible for testing because of young age of onset and 59% of patients eligible for testing because of their family history of cancer were offered testing. The lower rates of testing therefore affected all patient groups. The numbers were 94% and 100% at Ahus for the two groups of patients. Our data do not provide systematic information on why there was a difference between the two hospitals. At the university hospital, the EPR had a standardized format with headings that included the term "heredity", whereas the EPR at the regional hospital to a lesser degree seemed to have a set structure with pre-defined headings. Having a set structure with headings will remind the clinician of asking about family history and may also remind the clinicians of genetic testing, and the number of patients who had been asked about family history was somewhat higher for the university hospital than for the regional hospital (95% vs 78%). The observed difference may also be due to differences in awareness and traditions regarding

genetic testing between the two hospitals. A clinician who more rarely discusses genetic testing with BC patients may have a higher threshold for bringing up the subject than a clinician who more regularly offers it to patients even if the patient fulfill the criteria.

We suspect that including genetic testing into routine care like it is done in South Eastern Norway contributed to the high rates of genetic testing observed in our study. However, our data indicate that even though testing has been mainstreamed into regular cancer care, it may not be equally available to all BC patients, and there may be need for efforts to raise awareness of genetic testing among clinicians across hospitals. Such efforts could include regular meetings with the regional medical genetics department. One could also establish national, standardized EPR formats that make it mandatory for the physician to include information on cancer in the patient's family, and information on whether or not the patient has been offered genetic testing. At OUH, results of genetic testing are often included on the top of journal entries together with information about TNM and hormone receptor status.

The Cancer Registry of Norway includes a national quality register for breast cancer diagnostics and treatment. The register includes several parameters relevant to evaluate the quality of the health care provision in hospitals. Currently the register does not include information on whether the patients are offered genetic testing. We will argue that including this information could increase awareness of genetic testing as an integral part of breast cancer diagnostics and treatment, and thereby increase the rates of testing. This would also enable a quantitative evaluation of the delivery of this health care service on a local, regional and national level.

There are some limitations to our study. Our data are based on information from patient records, and we cannot exclude that there may be information relevant for the study that was not recorded. Some patients may have been offered but have declined testing, without it being noted. Family history could for instance have been asked, but not registered in the EPR. The response rate was 63.3% for the regional hospital and 65.7% for the university hospital. No second reminder was sent to the patients. We have only information about those who responded. Even if the response rate was similar, we cannot exclude that the dataset may be skewed either towards those who have been offered testing and/or have accepted testing, or towards those who were not offered testing and/or did not go through with testing. However, the two cohorts were similar in terms of age distribution, and also similar to the age distribution of all BC patients in Norway [30].

Conclusions

In conclusion, at two hospitals in the South Eastern Norway where diagnostic genetic testing is offered directly to BC patients by their surgeon or oncologist, the majority of BC patients who fulfilled the criteria for diagnostic genetic testing were offered testing. However, there were important differences in rates of testing between the hospitals that affected all groups of patients. This indicates that diagnostic genetic testing of BC patients is not equally available to all patients. We have also observed that 95% of BC patients who were offered testing wanted to be tested. Based on our findings we therefore suggest that

efforts should be made to raise awareness of and improve routines for genetic testing among clinicians that in turn will contribute to make genetic testing an integral part of diagnosis and treatment of BC in Norway.

Abbreviations

Ahus: Akershus University Hospital

BC: Breast cancer

EPR: Electronic Patient Record

IH: Innlandet Hospital

NBCG: Norwegian Breast Cancer Group

OC: Ovarian cancer

OUH: Oslo University Hospital

TNBC: Triple negative breast cancer

TSD: Service for sensitive data

VUS: Variant of unknown clinical significance

Declarations

Ethical approval and consent to participate

The study was evaluated by the Regional Committees for Medical and Health Research Ethics in South Eastern Norway. They defined it as a quality of care study, and thereby outside of their mandate. The study has been approved by the data protection officers at Oslo University Hospital, Akershus University Hospital and Innlandet Hospital. Informed consent was obtained from all individual participants included in the study.

Consent for publication

Not applicable

Availability of data and materials

The dataset analysed during the current study are available from the corresponding author on reasonable request.

Acknowledgements The authors thank all the patients who have consented to inclusion in the study. The authors would also like to thank the administrative staff at the departments of surgery at Akershus University Hospital and Innlandet Hospital.

Conflict of interest

Eli Marie Grindedal has received a research grant from The Norwegian Cancer Society (grant number 194790–2017). The authors declare that they have no competing interests.

Funding

This study was funded by The Norwegian Cancer Society (grant number 194790–2017)

Authors'contributions EMG: Conception and study design. Data collection and assembling. Data analysis, interpretation, manuscript writing. Final approval. KJ: Conception and study design. Data collection and assembling. Data analysis, interpretation, manuscript writing. Final approval. PO: Conception and study design. Data interpretation. Manuscript writing. Final approval. BG: Conception and study design. Data interpretation. Manuscript writing. Final approval. HL: Conception and study design. Data interpretation. Manuscript writing. Final approval. JN: Conception and study design. Data interpretation. Manuscript writing. Final approval. ES: Conception and study design. Data interpretation. Manuscript writing. Final approval. TV: Conception and study design. Data interpretation. Manuscript writing. Final approval. TW: Conception and study design. Data interpretation. Manuscript writing. Final approval. CH: Conception and study design. Data interpretation. Manuscript writing. Final approval. LM: Conception and study design. Data interpretation. Manuscript writing. Final approval.

Acknowledgements

The authors would like to acknowledge the administrative personell at Akershus University Hospital and Innlandet Hospital who have helped out throughout the project.

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Tables

Table 1. NBCG criteria for diagnostic genetic testing of breast cancer patients in 2016

Woman with breast cancer <50 yrs[a]
Two close relatives[a] with breast cancer, mean age <55 yrs
Three close relatives[a] with breast cancer at any age
Male breast cancer
Woman with bilateral breast cancer <60 yrs
Woman with breast cancer and a close relative with ovarian cancer[b]
Woman with breast cancer and a close relative with prostate cancer < 55 yrs[b]
Woman with ovarian cancer at any age
Woman with triple negative breast cancer<60 yrs (as recommended by the National Comprehensive Cancer Network, USA)[c]

[a]In 2018, the age limit for testing was raised to 60 years

[b] Close relative is a first degree relative, or a second degree relative through a man

[c]Included in the criteria from 2017

Table 2. Description of cohorts

	Innlandet Hospital (n = 162)	Ahus (n = 199)	Combined (n = 361)
Mean age	60.4 (range 28-86)	61.1 (range 33-92)	60.8 (range 28-92)
Age cohorts			
20-29	1 (0.6%)	-	1 (0.3%)
30-39	5 (3.1%)	4 (2.0%)	9 (2.5%)
40-49	23 (14.2%)	27 (13.6%)	50 (13.9%)
50-59	48 (29.6%)	52 (26.1%)	100 (27.7%)
60-69	55 (34.0%)	77 (38.7%)	132 (36.6%)
70-	30 (18.5%)	39 (19.6%)	69 (19.1%)

Table 3. Genetic testing of all patients and evaluation of criteria

	Innlandet Hospital (n = 162)	Ahus (n = 199)	Combined (n = 361)
Genetic testing			
Offered genetic testing	n = 161[a] 48 (29.8%)	n = 195[a] 83 (42.6%)	n = 356[a] 131 (36.8%)
Tested	n = 161[a] 45 (27.8%)	n = 195[a] 80 (40.2%)	n = 356[a] 125 (34.6%)
Uptake of genetic testing	n = 48 45 (93.8%)	n = 83 80 (96.4%)	n = 131 125 (95.4%)
Test ordered by: Surgeon Oncologist Other	n = 45 23 (51.1%) 22 (48.9%)	n = 80 48 (60%) 31 (38.8%) 1 (1.3%)	n = 125 71 (56.8%) 53 (42.4%) 1 (0.8%)
Evaluation of family history			
Asked about family history of cancer	n = 162 126 (77.8%)	n = 199 189 (95.0%)	n = 361 315 (87.3%)
Reported family history of breast and/or ovarian cancer	n = 126 58 (46.0%)	n = 189 66 (34.9%)	n = 315 124 (39.4%)
Criteria fulfilled			
BC< 50 years	n = 162 29 (17.9%)	n = 199 30 (15.1%)	n = 361 59 (16.3%)
Bilateral BC <60 years	n = 162 2 (1.2%)	n = 199 1 (0.5%)	n = 361 3 (0.8%)
TNBC < 60 years	n = 162 5 (3.1%)	n = 199 6 (3.0%)	n = 361 11 (3.0%)
Male breast cancer	- -	n=199 2 (1.0%)	n=361 2 (0.5%)
Family history of BC and/or OC[b]	n = 126 10 (7.9%)	n = 189 5 (2.6%)	n = 315 15 (4.8%)

[a]Excluded patients who had been tested prior to their breast cancer diagnosis

[b]These patients were 50 years or older at time of diagnosis, and did not fulfill any of the other criteria (TNBC <60 years, bilateral B <60 years or male BC)

Table 4. Number of BC patients offered testing according to what part of the NBCG criteria they fulfill

Criteria	Innlandet Hospital	Ahus	Combined
BC< 50 years	19/29 (65.2%)	28/30 (93.5%)	47/59 (79.7%)
Bilateral BC <60 years	2/2	1/1	3/3
TNBC<60 years	1/3	3/3	4/6 (66.7%)
Family history of BC and/or OC *	10/17 (58.8%)	5/5	15/22 (68.2%)
Male breast cancer	-	0/2	0/2

*These patients were 50 years or above at time of diagnosis, and did not fulfill any of the other criteria (TNBC < 60 years, bilateral BC <60 years or male BC

Table 5. Characteristics of BC patients fulfilling criteria who were not offered testing

Criteria fulfilled	Patients (n = 23)
BC < 50	12 (52.2%)
TNBC < 60	2 (8.7%)
Family history of BC and/or OC*	7 (30.4%)
Male BC	2 (8.7%)

*These patients were 50 years or above at time of diagnosis, and did not fulfill any of the other criteria (TNBC < 60 years, bilateral BC <60 years or male BC)

Figures

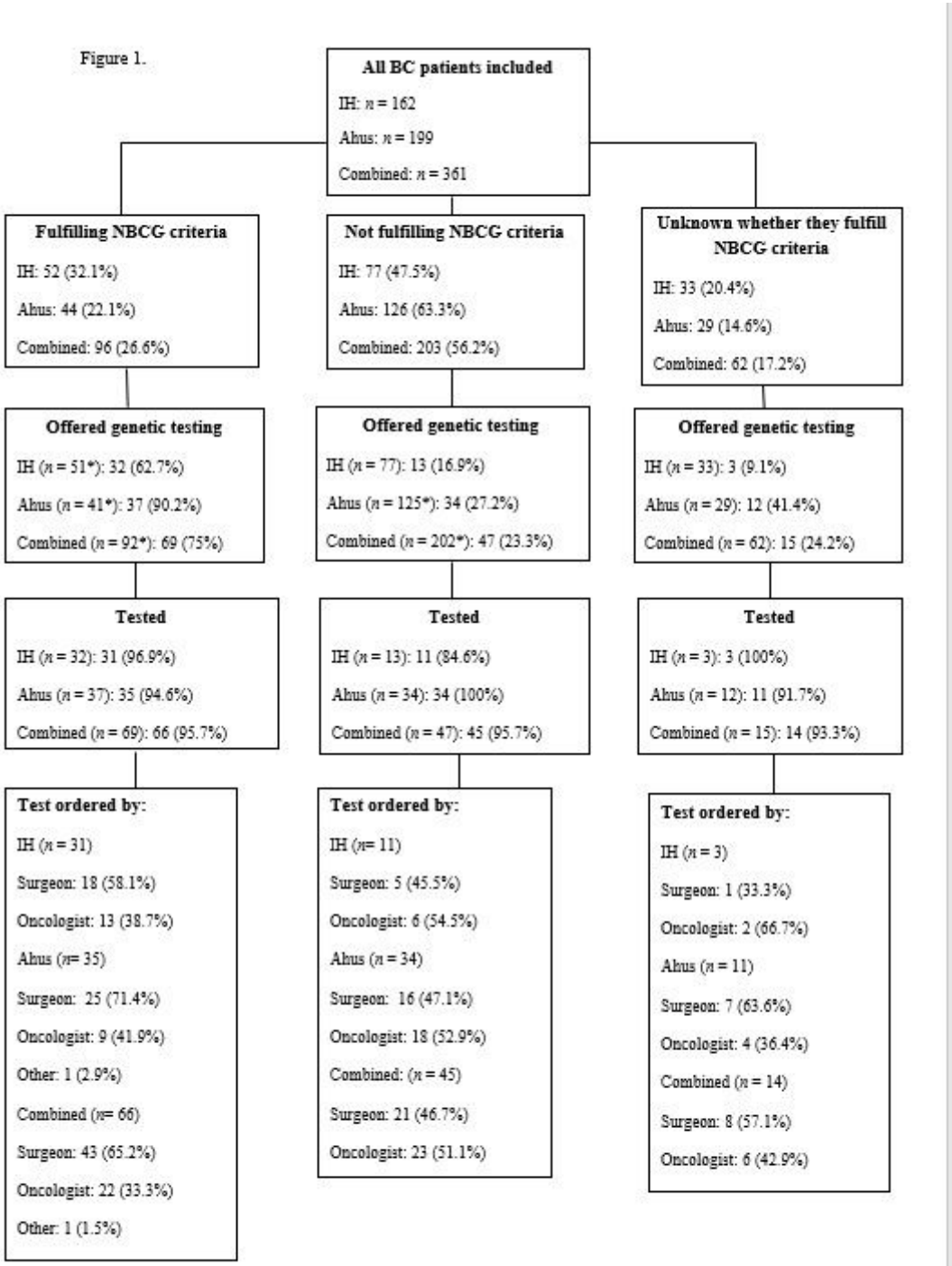

Figure 1

Genetic testing according to the NBCG criteria