**Genetic Testing and Clinical Management Practices for Variants in Non-*BRCA1/2* Breast (and/or Ovarian) Cancer Susceptibility Genes: an International Survey by the ENIGMA Clinical Working Group**

International Testing and Management Practices of Non-*BRCA1/2* Genes

S.M. Nielsen1, D.M. Eccles2, I. Romero1, F. Al-Mulla3, J. Balmaña4, M. Biancolella5, R. Blok6, M.A Caligo7, M. Calvello8, G.L. Capone9, P. Cavalli10, T.L. Chan11, K.B.M Claes12, L. Cortesi13, F.J. Couch14, M. de la Hoya15, S. De Toffol16, O. Diez4, S. M. Domchek17, R. Eeles18, A. Efremidis19, F. Fostira20, D. Goldgar21, M. Hadjisavvas22, T.v.O.Hansen23, A. Hirasawa24, C. Houdayer25, P. Kleiblova26, S. Krieger27, C. Lázaro28, M. Loizidou22, S. Manoukian29, A. R. Mensenkamp30, S. Moghadasi31, A. N. Monteiro32, L. Mori33, A. Morrow34, N. Naldi35, H.R. Nielsen36, O.I. Olopade1, N.S. Pachter37, E.I. Palmero38, I.S. Pedersen39, M. Piane40, M. Puzzo41, M. Robson42, M. Rossing23, M.C. Sini43, A. Solano44, J. Soukupova26, G. Tedaldi45, M. Teixeira46, M. Thomassen36, M.G. Tibiletti47, A. Toland48, T. Törngren49, E. Vaccari50, L. Varesco51, A. Vega52, Y. Wallis53, B. Wappenschmidt54, J. Weitzel55, A. B. Spurdle56, A. De Nicolo57, E.B. Gómez-García6

1. **US:** Center for Clinical Cancer Genetics, The University of Chicago, Department of Medicine, Chicago, IL, USA
2. **UK:** Faculty of Medicine, University of Southampton, Southampton, UK
3. **Kuwait:** Kuwait University, Faculty of Medicine, Department of Pathology, Safat, Kuwait and Genatak Center for Genomic Medicine, Kuwait
4. **Spain:** High Risk and Cancer Prevention Group (Balmaña) and Oncogenetics Group (Diez), Vall d'Hebron Institute of Oncology (VHIO); Medical Oncology Department (Balmaña) and Area of Clinical and Molecular Genetics (Diez), University Hospital of Vall d'Hebron, Barcelona, Spain
5. **Italy**: Department of Biology, University of Rome Tor Vergata, Rome, Italy
6. **Netherlands:** Department of Clinical Genetics, Maastricht University Medical Center (MUMC+), Maastricht, The Netherlands
7. **Italy:** Section of Molecular Genetics, Santa Chiara University Hospital, Pisa, Italy
8. **Italy:** Division of Cancer Prevention and Genetics, European Institute of Oncology, Milan, Italy
9. **Italy:** Department of Experimental and Clinical Biomedical Sciences, University of Florence, Florence, Italy
10. **Italy:** Servizio di Genetica, ASST Cremona, Cremona, Italy
11. **Hong Kong:** Hong Kong Sanatorium & Hospital, Hong Kong
12. **Belgium:** Centre for Medical Genetics, Ghent University Hospital, Ghent, Belgium
13. **Italy:** Department of Oncology and Hematology, University of Modena and Reggio Emilia, Modena, Italy
14. **USA:** Department of Laboratory Medicine and Pathology, Mayo Clinic, Rochester, MN, USA
15. **Spain:** Molecular Oncology Laboratory CIBERONC, Hospital Clinico San Carlos, IdISSC (Instituto de Investigación Sanitaria del Hospital Clínico San Carlos), Madrid, Spain
16. **Italy:** TOMA Advanced Biomedical Assays S.p.A, Busto Arsizio, Italy
17. **US:** Basser Center, University of Pennsylvania, Philadelphia, PA, USA
18. **UK:** The Institute of Cancer Research and Royal Marsden NHS Foundation Trust, London, UK
19. **Greece:** Medical Oncology Department,Athens Medical Center, Athens, Greece
20. **Greece**: Molecular Diagnostics Lab, National Centre for Scientific Research (NCSR) Demokritos, Athens, Greece
21. **US**: Department of Dermatology, Huntsman Cancer Institute,University of Utah School of Medicine, Salt Lake City, UT, USA
22. **Cyprus:** Department of EM/Molecular Pathology, TheCyprus Institute of Neurology and Genetics, Nicosia, Cyprus
23. **Denmark**: Center for Genomic Medicine, Copenhagen University Hospital, Rigshospitalet, Copenhagen, Denmark
24. **Japan**: Department of Obstetrics & Gynecology, Center for Medical Genetics, Keio University School of Medicine, Tokyo, Japan
25. **France:** Service de Génétique and INSERM U830 , Institut Curie, Paris, Université Paris Descartes, Sorbonne Paris Cité, Paris, France, and Unicancer Genetic Group
26. **Czech Republic:** Institute of Biochemistry and Experimental Oncology, First Faculty of Medicine, Charles University, Prague, Czech Republic
27. **France:** InsermU1245- Normandy University and Cancer Center F. Baclesse, Caen, France, and Unicancer Genetic Group
28. **Spain:** Molecular Diagnostic Unit, Hereditary Cancer Program, IDIBELL (Bellvitge Biomedical Research Institute), Catalan Institute of Oncology, Barcelona and Centro de Investigación Biomédica en Red de Cáncer (CIBERONC), Spain
29. **Italy:** Unit of Medical Genetics, Department of Medical Oncology and Hematology, Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy
30. **Netherlands:** Department of Human Genetics, Radboud University Medical Center, Nijmegen, the Netherlands
31. **Netherlands**: Department of Clinical Genetics, Leiden University Medical Centre, Leiden, the Netherlands
32. **US:** Cancer Epidemiology Program, Moffitt Cancer Center, Tampa, FL, USA
33. **Italy:** Laboratory of Molecular Medicine, Department of Clinical and Experimental Science, University of Brescia, Brescia, Italy
34. **Australia:** Prince of Wales Hospital & Community Health, Randwick NSW, Australia
35. **Italy:** Medical Oncology Unit, University Hospital of Parma, Parma, Italy
36. **Denmark:** Department of Clinical Genetics,Odense University Hospital, Odense, Denmark
37. **Australia:** Genetic Services of Western Australia, King Edward Memorial Hospital, Perth, Australia
38. **Brazil:** Molecular Oncology Research Center, Barretos Cancer Hospital, Barretos, São Paulo, Brazil
39. **Denmark:** Section of Molecular Diagnostics, Department of Clinical Biochemistry,Aalborg University Hospital, Aalborg, Denmark
40. **Italy:** Department of Clinical and Molecular Medicine, Faculty of Medicine and Psychology, Sapienza University of Rome and UO of Medical Genetics, Sant’Andrea Hospital, Rome, Italy
41. **Italy:** Azienda Ospedaliera di Cosenza, Laboratorio Analisi Cliniche Biomolecolari e Genetica, Cosenza, Italy
42. **US:** Clinical Genetics Service, Department of Medicine,Memorial Sloan-Kettering Cancer Center, New York, NY, USA
43. **Italy:** Unit of Cancer Genetics, Institute of Biomolecular Chemistry (ICB), National Research Council (CNR), Sassari, Italy
44. **Argentina:** INBIOMED, Faculty of Medicine/ CONICET and CEMIC, Department of Clinical Chemistry, Medical Direction, University of of Buenos Aires, Buenos Aires, Argentina
45. **Italy:** Biosciences Laboratory, Istituto Scientifico Romagnolo per lo Studio e la Cura dei Tumori (IRST) IRCCS, Meldola, Italy
46. **Portugal**: Instituto Português de Oncologia do Porto Francisco Gentil, E.P.E. (IPO Porto), Porto, Portugal
47. **Italy**: UO Anatomia Patologica Ospedale di Circolo ASST Settelaghi, Varese, Italy
48. **US:** Department of Cancer Biology and Genetics,The Ohio State University, Columbus, OH, USA
49. **Sweden:** Lund University, Faculty of Medicine, Department of Clinical Sciences Lund, Oncology and Pathology, Lund, Sweden
50. **US:** Dana-Farber Cancer Institute, Boston, MA, USA
51. **Italy:** Unit of Hereditary Cancer, Ospedale Policlinico San Martino IRCCS per l'oncologia, Genoa, Italy
52. **Spain:** Fundación Pública galega Medicina Xenómica-SERGAS, Grupo de Medicina Xenómica-USC, CIBERER, IDIS, Santiago de Compostela, Spain
53. **UK:** Head of Cancer Programme, West Midlands Regional Genetics Laboratory, Birmingham, Women's and Children’s NHS Foundation Trust, Birmingham, UK
54. **Germany:** Center for Hereditary Breast and Ovarian Cancer, Center for Integrated Oncology (CIO), Medical Faculty, University Hospital Cologne, Cologne, Germany; member of German Consortium of Hereditary Breast and Ovarian Cancer (GC-HBOC)
55. **US:** Divison of Cancer Genomics, City of Hope, Duarte, CA, USA
56. **Australia:** Department of Genetics and Computational Biology, QIMR Berghofer Medical Research Institute, Brisbane, Queensland, Australia
57. **Italy:** Cancer Genomics Program, Veneto Institute of Oncology IOV – IRCCS, Padua, Italy

**Correspondence address:**

Dr. E.B. Gómez García

Dept. of Clinical Genetics,Maastricht University Medical Center (MUMC+),

P. Debyelaan 25 | 6229 HX Maastricht. The Netherlands

**E** [encarna.gomezgarcia@mumc.nl](https://webmail.mumc.nl/owa/redir.aspx?C=P0Xu8yvbuEsuv9Q_ktqz4s4EaJVgP0Scpgg2v4b330FFpSwopmXVCA..&URL=mailto%3aencarna.gomezgarcia%40mumc.nl)

**T** +31(0)43-3875855

**F** [+31(0)43-3875800](https://webmail.mumc.nl/owa/redir.aspx?C=1Ya0AE_ozzuk43nnIR5-p-XGFdSlh_bGpV70Zm4wEjhFpSwopmXVCA..&URL=http%3a%2f%2fwww.mumc.nl%2f)

**Abstract**

**Aim**: To describe a snapshot of international genetic testing practices, specifically regarding the use of multigene panels, for hereditary breast cancer (BC) and breast andovarian cancer (HBOC). We conducted a survey through the Evidence-based Network for the Interpretation of Germline Mutant Alleles (ENIGMA) consortium, covering questions about 16 non-*BRCA1/2* genes.

**Methods:** Data were collected via in-person and paper/electronic surveys. ENIGMA members from around the world were invited to participate. Additional information was collected via country networks in the UK and in Italy.

**Results**: Responses from 61 cancer genetics practices across 20 countries showed that 16 genes were tested by more than 50% of the centers, but only 6, *PALB2, TP53, PTEN, CHEK2, ATM,* and *BRIP1,* were tested regularly. US-based centers tested the genes most often, while UK and Italian centers with no direct ENIGMA affiliation at the time of the survey were the least likely to regularly test them. Most centers tested the 16 genes through multigene panels; some centers tested *TP53, PTEN* and other cancer syndrome-associated genes individually. Most centers reported (likely) pathogenic variants to patients and would test family members for such variants*.* Gene-specific guidelines for BC/OC risk management were limited and differed between countries especially with regard to starting age and type of imaging and to risk-reducing surgery recommendations.

**Conclusion**: Currently, a small number of genes beyond *BRCA1/2* are routinely analyzed worldwide and management guidelines are limited and largely based on expert opinion. To attain clinical implementation of multigene panel testing through evidence-based management practices, it is paramount that clinicians (and patients) participate in international initiatives that share panel testing data, interpret sequence variants, and collect prospective data to underpin risk estimates and evaluate the outcome of risk intervention strategies.

**Key words:** gene panel, testing practices, non-*BRCA* genes,*ATM, BARD1, BRIP1, CDH1, CHEK2, MEN1, MRE11A, NBN, NF1, PALB2, PTEN, RAD50, RAD51C, RAD51D, STK11, TP53,* breast cancer, ovarian cancer, risk management, guidelines.

**Background**

Massively parallel sequencing technologies have transformed testing practices for hereditary breast cancer (BC) and breast and ovarian cancer (HBOC) predisposition. Currently, several multigene panels are available that include from <10 to >100 known or candidate cancer susceptibility genes, which are tested for diagnostic or research purposes. Some panels are targeted to diverse cancers (“pan-cancer”) while others to specific cancers only (“disease-specific”).

The ability to run multigene panels at affordable prices has expanded the eligibility criteria and increased the demand for testing.1-5 However, the rapid pace at which candidate risk genes are moving from research-based to clinical diagnostic testing has its drawbacks. Consequently, diagnostic laboratories are making inferences and clinicians are making decisions based on limited data. The rate of Variants of Uncertain Significance (VUS) has increased proportionally to the extent of the sequenced genome.5-7 Moreover, many genes currently included on multigene panels have very imprecise cancer risk estimates and there is no consensus on when to test for a given gene and how to manage a reported (likely) pathogenic variant.8,9

The aim of this study was to describe a snapshot of the landscape of international genetic testing practices and risk management approaches for BC and HBOC susceptibility genes beyond *BRCA1* and *BRCA2*. A survey was conducted amongst members of the Evidence-based Network for the Interpretation of Germline Mutant Alleles (ENIGMA), an international consortium focused on 1) determining the clinical significance of variants in *BRCA1, BRCA2* and other (ascertained or suspected) breast/ovarian cancer susceptibility genes, 2) providing expertise to global database and classification initiatives, and 3) exploring optimal avenues of communication of such information at the provider and patient level. Additional information was collected via country networks in the UK and in Italy, from centers that were not directly involved in ENIGMA research at the time of study initiation.

In total, respondents represented cancer genetics experts from 61 centers across 20 countries. To our knowledge, this is the first study to describe international testing practices and risk management guidelines for non-*BRCA1/2* genesimplicated inBC/HBOC OC susceptibility.

**Methods**

This study was submitted for approval to the ethics committees of the two coordinating sites, the University of Chicago and Maastricht University. Both concluded that review by the IRB/official committee approval was not required because the study was determined to be non-human subjects research. A survey about genetic testing practices for non-*BRCA1/2* BC/HBOC genes was developed by ENIGMA Clinical Working Group (CWG) leaders during 2016 (Supplementary Table 1). ENIGMA members were invited to complete the survey if they had clinical genetic testing or diagnostic laboratory affiliation and were involved in ordering, performing, or interpreting DNA tests for inherited susceptibility to BC/OC at their center. An ENIGMA member is currently defined as a researcher or research group (consortium) who is willing to work collaboratively towards classification of variants by contributing data from families and/or conducting statistical analysis or laboratory-based assays within a working group framework. There is no requirement for ENIGMA members to state their primary role (clinician, genetic counselor, laboratory scientist, basic researcher), but all members by definition have a research interest in the topic of gene/variant classification.

Individuals from the same center could work on the survey together or choose a designated representative to complete it, so that only one survey per center was counted.

Specific questions were asked about 16 BC/HBOC genes with published evidence of risk association that were commonly included on commercial breast cancer panels at the time of the survey: *ATM, BARD1, BRIP1, CDH1, CHEK2, MRE11A, NBN, NF1, PALB2, PTEN, RAD50, RAD51C, RAD51D, STK11, TP53,* and *MEN1–*which isconsidered a (candidate) BC susceptibility gene in the Netherlands.10

Information about testing and management approaches at individual sites, formulated as multiple-choice questions with a discrete number of options, was obtained through both in-person surveys (during conference session) and paper/electronic surveys, which included additional open-ended questions (Supplementary Table 1).

The survey process is outlined in **Figure 1**. In brief, an in-person survey of members of the CWG, consisting mainly of laboratory and clinical scientists from academic centers, was conducted during the ENIGMA consortium meeting in Limassol (Cyprus) in January 2017. A total of 30 centers from 17 countries participated.

A more detailed version of the survey was then distributed by email (paper/electronic survey) to the same 30 centers that participated in the in-person survey and to additional ENIGMA-affiliated centers worldwide. This allowed collection of information from an additional eight centers and three countries.

Both in-person and paper/electronic survey data were reviewed for consistency and completeness. Participants were sent a copy of their answers and asked to verify them or to clarify any discrepancies.

Notably, in Italy and in the UK, the paper/electronic version of the survey was also distributed, via country networks, to centers that were not actively involved in ENIGMA research. This provided the opportunity to carry out further sub-analyses (ENIGMA vs. non-ENIGMA, see Results section). In Italy, all submissions were coordinated by A. De Nicolo, as a liaison for the Network of Italian Collaborators to ENIGMA Studies and Trials (NICEST). The effort comprised both the ENIGMA-affiliated Fondazione IRCCS Istituto Nazionale dei Tumori (Milan) and the Santa Chiara University Hospital (Pisa), which were counted in the above-mentioned 38 participating ENIGMA centers, and 14 additional centers, which were not directly affiliated with ENIGMA at the time of the survey (thus, henceforth referred to as “non-ENIGMA,” Figure 1A lower panel, right). Of the 14 Italian non-ENIGMA centers, five were dedicated to diagnostic testing only and nine were dedicated to both diagnostics and research; moreover, half of them were University-affiliated and half were not. Similarly, in the UK, D.M. Eccles completed the survey for her own ENIGMA-affiliated center-i.e. one of the 38 participating ENIGMA centers-and also coordinated, with the assistance of Y. Wallis, the distribution of the survey through SurveyMonkey® via the Association for Clinical Genetic Science (ACGS) mailing list to cancer genetics leads from diagnostic laboratories providing genetic testing for the publicly funded National Health Service (NHS). The original ENIGMA survey was modified to encompass questions that were considered most relevant to NHS laboratories (see Supplementary Table 1, far right column). Nine laboratories responded (anonymously), representing about half of the active NHS laboratories in the UK (also henceforth referred to as “non-ENIGMA”, Figure 1A lower panel, left).

Comparisons were made between individual centers, US and non-US ENIGMA centers, and ENIGMA and non-ENIGMA centers.

**Results**

In total, 61 centers from 20 countries participated in the survey. The recruitment flowchart and the global distribution of participants are illustrated in **Figure 1**.

**I. Clinical utility**

In order to get a preliminary idea of the participants’ opinions about the clinical utility of the 16 genes which the survey focused on, the CWG members present at the 2017 ENIGMA meeting in Cyprus were asked to answer the following questions relating to each of them: 1) should every BC/OC patient that qualifies for (*BRCA1/2)* genetic testing (by criteria that we recognize may differ by country/center) be tested for the gene? and 2) do you agree that the cancer risk associated with (pathogenic variants in) the gene is high enough to inform clinical management? All participants (n=23 at this specific session) stated that they would test every qualifying BC patient (as defined above) for *PALB2,* and everyqualifying OC patient (as defined above) for *BRIP1, RAD51C,* and *RAD51D*. No participants stated that they would test every qualifying BC patient for *NBN, MRE11A* or *RAD50*. Results for the other nine genes were variable (Supplementary Figure 1a).

With regards to clinical management, all participants agreed that *PALB2, TP53*, *CDH1, PTEN,* and *STK11* along with *BRIP1, RAD51C,* and *RAD51D* were associated with high enough (BC or OC) risk to alter clinical management. Many participants felt that also the risk associated with *CHEK2* and *ATM* pathogenic variants could alter clinical management. *NF1, BARD1, MEN1, MRE11A, NBN,* and *RAD50* were deemed by most of the participants as genesthat currently do not impact clinical management of BC risk (Supplementary Figure 1b).

Please note that 95% confidence intervals for this figure and for all the following figures are provided in Supplementary Tables 2-10.

**II. Testing practices**

Participants were also asked (via in-person and/or paper/electronic surveys) if and how frequently they tested each gene, the method (single gene vs. gene panel) and purpose of testing (clinical vs. research), and the practices of reporting (likely) pathogenic variants and VUS to patients. The aggregate of the responses is presented below.

**II-1. *Purpose and setting***

**Figure 2** shows the absolute number and proportion of the ENIGMA centers that tested for a specified gene (for clinical or research purposes) and that tested the gene “regularly” (i.e. ordered the test for more than 50% of patients that qualified for genetic testing, by criteria that we recognize may differ by center/country). Even though each gene was tested by >50% of the centers (range 52-100%), only *PALB2, TP53, PTEN, CHEK2, ATM,* and *BRIP1* were tested regularly by >50% of centers.

Testing in a research setting in addition to the clinical setting was common for ENIGMA centers (Supplementary Figure 2). The genes that were most frequently tested (i.e. tested by at least >30% of centers) for research purposes only were: *NBN, BARD1, RAD50* and *MRE11A*. All the other genes were tested clinically by at least two- thirds of the ENIGMA centers. No center tested *TP53* solely for research purposes.

Focusing only on clinical testing, the majority of ENIGMA centers used multigene panels **(Figure 3)**. Single-gene testing was performed by a number of centers, varying from one to 21, for: *TP53, PTEN*, *CDH1, STK11, PALB2, CHEK2, NF1, ATM, MEN1,* and *NBN* (in decreasing order of frequency), often based on a specific phenotype (*PTEN* hamartoma syndrome or neurofibromatosis type 1, for example), or these genes were tested as a “reflex” only when *BRCA1/2* testing wasnon-informative. Notably, these methods were not mutually exclusive. Seven centers from four countries (Belgium, Brazil, Netherlands, and Spain) testing *CHEK2* only tested for the 1100delC variant.

Regarding the types of gene panels utilized, US respondents typically ordered broad cancer panels from commercial laboratories, though the specific panels varied depending on patient preferences, insurance considerations, and the clinical scenario. The non-US ENIGMA centers used a combination of commercial and custom “in-house” panels.

The main issues that emerged regarding barriers for panel testing, among ENIGMA and non-ENIGMA Italian centers, were: 1) lack of knowledge of cancer risk/penetrance and of management guidelines, hence, lack of “actionability”, 2) concerns about VUS , 3) validation of testing method , and 4) need for “robust, carefully curated, and constantly updated international databases” and for “global data sharing”. Separately, the nine UK NHS laboratories were asked “If you currently only report BRCA genes but might report broader panels in the future, what issues are major barriers/problems to overcome?” Responses were chosen from a menu of nine options plus “other” and the four main reasons selected (by half or more of respondents) were: 1) no request by the oncologists (of note, NHS oncologists can ask directly for *BRCA1* and *BRCA2* testing but not for multigene panels), 2) lengthy and laborious process of variant interpretation, 3) lack of standardization of reporting, and 4) lack of demand for testing.

***II-2. Reporting practices and cascade testing***

For genes analyzed through clinical testing, >90% of ENIGMA centers reported (likely) pathogenic variants to patients (for *CHEK2* and *NBN*, the percentages were slightly lower, 88% and 71%, respectively) **(Figure 4)**. Some centers reported these variants only if the patient met criteria for the associated syndrome (e.g. hereditary diffuse gastric cancer for *CDH1,* neurofibromatosis type 1 for *NF1)*. Almost all centers (67-81% for *NBN*, *RAD50,* *MRE11A,* and *BARD1* and >90% for the other genes) offered cascade testing to family members if a (likely) pathogenic variant was identified (data not shown)*.* Notably, participants from the Netherlands reported that they only tested first-degree relatives for *CHEK2* 1100delCvariant when the estimated risk based on family history was lower than the risk conferred by having the variant, so that testing for the variant had clinical utility because it would change surveillance recommendations.11

A high percentage (50-82%) of ENIGMA centers reported VUS to patients (**Figure 4)**. Most of these centers reported that they would not offer cascade testing for VUS unless it was in a research setting for co-segregation purposes to aid variant (re)classification (data not shown)**.**

**III. Variant classification systems**

All respondents reported using the IARC 5 tier classification system 12 and many also used ACMG13 classification criteria. Sources cited for (qualitative) variant classification were: literature and public databases including ClinVar,14 BIC (Breast cancer Information Core database)15, and LOVD (Leiden Open Variant Database).16 Respondents were also asked “Who takes responsibility for interpreting the clinical significance of the variants identified”- a question which was answered by 39 centers (including ENIGMA and non-ENIGMA centers) with the following answers: the clinical team, i.e. a medical geneticist or oncologist specialized in genetics (n=16 ), the laboratory team (n=11), a combination of the two (n=10), a bioinformatics pipeline (n=2).

**IV. Clinical management practices and guidelines**

Most ENIGMA centers (>80%) had risk management guidelines forthe majority of non-*BRCA1/2* genes considered reportable to patients **(Figure 5)**, exceptions being *BARD1, RAD50* and *MRE11A,* for which *<*30% of centers had guidelines.

While most ENIGMA centers reported having some type of management guidelines for all genes except *BARD1, RAD50,* and *MRE11A*, after review, only 10 out of 20 countries had national guidelines for (some of) these genes (**Table 1)**. Furthermore, in some countries (Denmark and Germany), the national guidelines were not gene-specific, i.e. they were broken down by high and moderate risk categories rather than by specific gene. Other guidelines were local (center or region-specific) or international (meaning that other countries’ national guidelines were used). Review of management guidelines disclosed both similarities and substantial differences in country-specific guidelines available for BC risk management according to gene (**Table 1**). Ten countries had national guidelines for high-risk cancer syndrome-associated genes such as *TP53, CDH1* and *PTEN* (with the exception of Belgium not having guidelines for *CDH1*). National guidelines were limited for other BC genesconsidered clinically actionable, including *PALB2*. The primary differences between countries were the starting age and type of diagnostic imaging (mammography vs. MRI vs. sonography) and the policy on risk-reducing mastectomy. For instance, there was no consensus on the age to begin mammograms/MRI for carriers of pathogenic variants in *NF1, MEN1,* *PALB2* (25 vs. 30y) or *TP53* (20 vs. 25y). The UK guidelines differed from all others in that breast MRI was not the standard imaging technique for carriers of pathogenic variants in other gene carriers (except for *TP53*). Guidelines for risk-reducing mastectomy in carriers of *PALB2* pathogenic variants ranged between: accepted (n=1), consider depending on personal/family history (n=5), and not enough evidence to recommend (n=1). For *PTEN* and *CDH1*, the guidelines that commented on preventive surgery (4 of the 7 and 5 of the 8 national guidelines, respectively) mentioned risk-reducing mastectomy as a possible option.

There were no national management guidelines for *BARD1*, *RAD50* and *MRE11A* pathogenic variant carriers, which is consistent with the indeterminate evidence for BC or OC risk associated with these genes.

For the OC susceptibility genes *BRIP1*, *RAD51C* and *RAD51D*, the US-based National Comprehensive Cancer Network(NCCN), and the Dutch guidelines recommended risk-reducing salpingo-oophorectomy (RRSO) from age 45-50 years; RRSO was recommended only for *RAD51C* and *RAD51D* by the German HBOC Consortium. Prior to RRSO, the Czech Republic guidelines also advised sonography starting from age 30.

**V. Sub-analyses: ENIGMA-US centers vs. ENIGMA-Other and vs. non-ENIGMA centers**

Responses from the 7 ENIGMA centers in the US (ENIGMA-US) were compared to those of the other 31 ENIGMA centers (ENIGMA-Other). In addition, responses from 14 non-ENIGMA centers in Italy and nine non-ENIGMA laboratories in the UK were compared to those from 38 ENIGMA centers across all countries.

Results of these comparisons are summarized in Supplementary Figures 3-4. Briefly, the ENIGMA-US centers were more likely to regularly test all genes, particularly through multigene panels, compared to ENIGMA-Other centers (Supplementary Figures 3-4). A much smaller proportion of non-ENIGMA centers from Italy and the UK tested each gene compared to ENIGMA-affiliated centers (Supplementary Figure 3).

Management guidelines were more likely to be available in the US-based ENIGMA centers compared to the other ENIGMA centers for all genes except *BARD1, RAD50, MRE11A,* and *MEN1*. Only a small proportion of the Italian and UK non-ENIGMA centers had management guidelines for the 16 genes. Non-ENIGMA UK centers reported guidelines to be available for: *TP53* (71% of centers) and *CHEK2* (14%), while the non-ENIGMA Italian centers reported available guidelines for: *PALB2* (19% of centers), *TP53* (50%), *PTEN* (19%), *CDH1* (38%), *STK11* (19%), *CHEK2* (13%) and *ATM* (6%).

**Discussion**

We surveyed a total of 61 cancer genetics centers across 20 countries asking about their genetic testing and management practices relating to 16 BC/HBOC predisposition genes. Our global survey demonstrated that: 1) only a few genes are routinely analyzed beyond *BRCA1/2*; 2) most centers clinically test them through multigene panels and 3) report (likely) pathogenic variants (and VUS, to a slightly lesser extent) to patients; 4) gene-specific guidelines for BC and OC risk management are limited and differ between countries especially in regards to starting age and type of imaging and risk-reducing surgery recommendations.

***Multigene panels (value, utility, barriers to implementation)***

With falling costs of sequencing and more genes being identified that are associated with increased BC/HBOC risk, multigene (panel) testing is becoming the norm. The results of our survey confirm this trend showing that genes that are commonly offered on commercial panels were tested by more than 50% of the surveyed centers.

Nevertheless, the value of multigene panel testing continues to be debated in the context of three main areas: 1) limited additional yield of pathogenic variants in genes other than *BRCA1/2* coupled with significantly increased interpretation workload, 2) reliability of penetrance estimates for moderate or uncertain risk genes (clinical validity) and 3) evidence for informing management recommendations to improve patient outcomes (clinical utility).9 Our international survey demonstrates that the use of panel testing varies widely between countries. US centers were early adopters of multigene testing, which is generally ordered more liberally (if insurance criteria are met) with broader gene panels. Moreover, differences were observed when comparing ENIGMA-affiliated centers with non-ENIGMA Italian and UK centers (with the latter testing non-*BRCA1/2* genes less than one-third of the time). Conceivably, because ENIGMA is a research consortium, centers that are ENIGMA members are more involved in research and might become aware of and, hence, implement novel technologies before they become mainstream. Conversely, national/universal health service providers may require a higher threshold of benefit prior to adopting new tests.

The insufficient evidence in support of clinical validity and/or utility (hence, “actionability”) of the genes included on panels was the most common concern raised by the participating centers. Easton *et al*. asserted that “a genomic test should not be offered until its clinical validity is established”8; however, the utility of a gene needs to be continuously reconsidered as more data become available and this can only be done by analyzing results from large cohorts of individuals who have been tested. Concerns about the rates of VUS were frequently expressed by the study participants, but just as variant rates have significantly decreased over the years for *BRCA1/2* due to concerted classification efforts, the same trend will likely occur for other susceptibility genes, arguably at a faster pace as (and provided that) more laboratories worldwide contribute their testing data to population and peer-reviewed databases.5,17,18 Despite the establishment of such databases, survey participants felt that “robust, constantly updated international databases” and “global data sharing” are still lacking. They also expressed the need for robust software that could help with annotation and real-time classification of each variant. This is a worthy goal, but expert judgement in variant classification methods is still required since fully automated approaches to variant classification that apply guidelines are not ready for clinical practice.6

At a basic level, some centers reported validation of the testing method as a barrier. Therefore, it is important to recognize the technological barriers in certain countries, though the transition to massively parallel sequencing is ultimately expected to increase throughput and to optimize diagnosis without significantly elevating costs.19

There were also non-medical barriers to implementing routine testing of many of these surveyed genes. Insurance can be a major barrier in the US, where, for example, Medicare (a US federal health insurance program for people who are 65 or older, and for certain younger people with disabilities) will only cover testing for individuals with a BC or OC diagnosis and many insurers will not cover multigene panel testing if the patient has already had prior genetic testing. Confounding matters, direct-to-consumer testing is becoming increasingly common in the US. In many other countries, particularly those with national (i.e. universal) health care, testing is approved on a gene-by-gene basis or as a package if research-derived evidence is considered robust enough to change clinical management.

***Cancer risks and penetrance***

In terms of risk magnitudes, *PALB2* and *TP53* are theonly BC genes, in addition to *BRCA1/2,* that consistently fall into the high risk category across studies (i.e. confer levels of risk greater than 4 times that in the general population)8; the remainder have conflicting evidence regarding the risk category into which they fit.8,9,20-22 Our survey confirmed that ENIGMA centers test *PALB2* and *TP53* relatively frequently and regardthem as clinically actionable genes. These two genes were tested much less consistently by non-ENIGMA centers thus evidencing the lack of consensus, even for genes that are generally regarded as high risk. These differences in testing approaches may be, however, more directly linked to how health care is paid (i.e. if certain genes have been approved or not for testing through the national/universal health care system).

Large-scale studies have become recently available that address the penetrance of moderate risk (i.e. 2-4 times the risk compared to the general population) BC/HBOC genes and the risk magnitudes of the genes included in multigene panels.8,9,20,21 These studies are providing us a broader perspective of risk, particularly for genes like *CHEK2* or *NBN*, for whichprevious risk estimates were based primarily on studies of founder variants only.8 Yet, most of these studies are based on predominantly white European populations and, hence, the evidence may not be generalizable.

*BRIP1, RAD51C* and *RAD51D* are ever more accepted as OC but not BC risk predisposition genes (2-5 times the risk compared to the general population).15,21 Notably, many respondents agreed that every OC patient should be tested for these three genes (in addition to *BRCA1/2*). Although there is currently no indication that OC treatment for a carrier of a pathogenic variant in one of these three genes would differ from that of a non-carrier, carriers may benefit from RRSO at menopause.

The uncertainties and inconsistencies regarding risk and testing practices are magnified when it comes to syndromic cancer genes like *PTEN, CDH1, STK11, NF1, NBN* and *MEN1,* as well as to genes conferring an uncertain risk such as *BARD1, RAD50,* and *MRE11A*. Although there is significant evidence for elevated BC risk*,* and lobular BC risk in carriers of pathogenic variants in *PTEN* and in *CDH1*, respectively, 23-25 it is likely that these BC risks (and those from the other syndromic genes) are overestimated and thus unreliable because they were derived from patients whose histories were consistent with these rare syndromes rather than from unselected patients.8

More robust and replicable penetrance estimates from large cohort and population studies are certainly needed to further define risks. In addition, better understanding of gene-gene and gene-environment interactions that affect the risk is required. However, based on both the evidence available from the literature and the results of our survey, which incorporate an international clinical perspective, the 16 genes can be grouped into five categories: 1) high BC risk: *PALB2, TP53, PTEN, CDH1*; 2) moderate BC risk: *ATM, CHEK2*; 3) BC risk of unclear magnitude (but established risk for other cancer types): *STK11, NF1, NBN, MEN1*; 4) moderate OC risk: *BRIP1, RAD51C, RAD51D*; 5) insufficient evidence for BC or OC risk: *BARD1, RAD50, MRE11A.*

***Clinical utility and cancer risk management guidelines***

The clinical utility of multigene panel testing is assessed based on the improved outcomes of those managed by evidence-based surveillance or prevention approaches. Management guidelines are largely based on expert opinion. Easton *et al.* reviewed guidelines across various countries, but they were specific to women with a family history of BC or with *BRCA1/2* mutations.8 A framework for management of moderate risk HBOC genes has been extensively reviewed by Tung *et al*., and includes a comparison of surveillance guidelines between the US, UK and Germany.9 Our survey offers a more extensive comparison of management guidelines between several countries for non-*BRCA1/2* risk genes. Results from the survey show that, many countries do not have their own guidelines yet and/or they use NCCN guidance. There are limited national guidelines available even for genes such as *PALB2, BRIP1, RAD51C* and *RAD51D*, which most participants felt should always be tested because they are clinically actionable. Most importantly, when management guidelines are available, they are largely based on expert opinion rather than being evidence-based. This explains why the guidelines often differ in important aspects such as indication for risk-reducing surgery and type of diagnostic imaging recommendations.

***Limitations of the study***

Our study was initiated to provide a snapshot of ENIGMA clinical practice for non-*BRCA1/2* genes. It included countries and centers with ENIGMA affiliation and also a small subset of centers with no direct link to the ENIGMA consortium at the time of the survey. It provides a global, yet incomplete, picture of testing practices in the world. Indeed, countrieslike Poland and Israel, with founder pathogenic variants in some of these genes, did not participate in the survey. Because panel testing is currently being implemented in large regions of the world like Asia, Africa and South America, similar surveys will need to be redistributed once more countries have established testing protocols. Even at the time of the survey, testing protocols and surveillance recommendations were in flux in some countries and broader gene panels were expected to be offered within a short time. We acknowledge that our sampling of non-ENIGMA centers was limited and we aim at surveying a more diverse collection of US, Canadian and other worldwide “regional” or “community” practices in future studies.

***Conclusions and future perspectives***

Massively parallel sequencing represents a transformational technology that we must learn to apply appropriately in health care. Although the number of genes, other than *BRCA1/2*,associated with BC/HBOC risk is growing, only a small subset of them have clinical utility, at the moment*.* Our survey reveals lack of consensus amongst most countries regarding which genes to test, how to test them, how to most efficiently interpret variants, and how to manage patients carrying pathogenic variants. The goal of this study was to highlight the differences across countries and to determine what additional information and infrastructure are still needed to move towards more uniform testing practices and management guidelines internationally.

Our collected evidence suggests that the clinical usefulness of multigene panel testing for BC/HBOC predisposition can be improved by a better definition of the cancer risks associated with genetic variation in cancer susceptibility genes and by the availability of evidence-based management guidelines. To this end, it is key that clinicians share clinical and genetic data, through ENIGMA and/or other international consortia focused on the clarification of the BC and OC risk associated with genetic variation, and that tested individuals are encouraged to participate in initiatives that collate genetic testing data and in long-term follow up studies that evaluate intervention strategies. As ENIGMA CWG, we aim at promoting the use of internationally-accepted, standard guidelines at the country level through sharing and discussion of all available management guidelines and we will continue to evaluate testing practices and risk management recommendations, periodically.

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**Figure Legends**

**Figure 1.** **Survey distribution and participating centers**

Survey distribution flow and global representation of participating centers. CWG= Clinical

Working Group, NHS= National Health Service

**Figure 2. Frequency of testing.** The y axis represents the % of ENIGMA centers that tested

each given gene. Shown above each bar: the absolutenumber of centers. In total, there were 38 participating centers, however the number of centers

that responded to the question

varied by gene (ranging from 28 to 38

).“Regularly” defined as ordered for more than 50% of eligible patients (i.e.

those that qualified for genetic testing, by

criteria that we recognize may differ by center/country).

**Figure 3.** **Clinical testing methods.** The y axis represents the % of ENIGMA centers that clinically tested a given gene through each method. Shown above each bar: absolute numbers. Only responses from those centers who stated they tested each gene were counted in the total and the number of centers that responded varied by gene (ranging from 14 to 38 ). Please note that each of the three methods is not mutually exclusive. Notably, the center in Kuwait performs whole genome sequencing for all cases, which is not represented in the figure.

**Figure 4. Reporting practices of (likely) pathogenic variants and of VUS (to patients)**. The y axis represents the % of ENIGMA centers that reported (likely) pathogenic (solid blue bar) and VUS (bar outlined in red) to patients. Shown within each bar: absolute numbers. Only responses from those centers who stated they clinically tested the given gene were counted in the total and the number of centers that responded varied by gene (ranging from 12 to 36 that responded about reporting pathogenic variants and from 4 to20 that responded about reporting VUS ).

**Figure 5. Sources of the management guidelines used by the ENIGMA centers**. The y axis represents the % of ENIGMA centers that reported existing management guidelines for each gene. Shown within each bar: the absolute numbers. A color code indicates the type of management guidelines. Only responses from centers who stated they performed clinical testing and reported (likely) pathogenic variants to patients were counted in the total and the number of centers that responded varied by gene (ranging from 10 to 31). If management guidelines were available, centers were asked to specify the source of such guidelines (local, national, or international, such as NCCN or NICE).

**Table Legend**

**Table 1. National guidelines for breast cancer management**

Y= years; CBE= Clinical Breast Exam; SBE= Self Breast Exam; Mo= month; FH= Family History; RRM= Risk Reducing Mastectomy; US= ultrasound/sonography; LR= Lifetime risk

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**Supplementary Figure Legends**

**Supplementary Figure 1.** Opinions on clinical utility of non-*BRCA1/2* BC and OC risk genes: participants who agree with the following statements:

**Supplementary Figure 1a.** Every BC (or OC) patient who meets criteria for (*BRCA1/*2) genetic testing should be tested for this gene

**Supplementary Figure 1b.** Cancer risks associated with this gene are high enough to impact clinical management

Blue bars represent BC risk genes; red bars represent OC risk genes. *MRE11A, NBN* and *RAD50* are candidate BC risk genes. Please note that these two questions were asked at a different time, during the ENIGMA meeting in Cyprus in January 2017, compared to the survey questionnaire. Thus, only 23 centers answered these questions.

**Supplementary Figure 2.** Testing setting: clinical vs. research

The y axis represents the % of ENIGMA centers testing a given gene through each method. Shown above each bar: the absolute numbers. Only responses from those centers who stated they tested the gene were counted in the total and the number of centers that responded varied by gene (ranging from 14 to 37). The centers that tested each gene through research onlywere compared to the proportion of the centers that tested the geneonly clinically and of those who tested the gene for both clinical and research purposes.

**Supplementary Figure 3.** Genes tested regularly by ENIGMA-US vs. ENIGMA-Other vs. Italian and UK non-ENIGMA centers

The y axis represents the % of centers that tested that gene regularly (defined as ordered for

more than 50% of patients eligible for genetic testing, by criteria that we recognize may

differ by center/country). Of the 7 total ENIGMA-US centers, the

number of centers that answered this question was 4-7 depending on the gene; of the 31

ENIGMA-Other centers, a range of 21-29 centers answered this question. All 14

non-ENIGMA Italian centers answered this question; all 9 non-ENIGMA

UK centersanswered this question (notably, the UK version of the survey did not give

“test regularly” as an option).

**Supplementary Figure 4.** Genes tested through panel testing by ENIGMA-US vs. ENIGMA-Other centers

The y axis represents the % of centers that tested each gene through panel testing. Only responses from those centers who stated they tested the gene were counted in the total and the number of centers that responded varied by gene (of the 7 total ENIGMA-US centers, 4-7 centers responded depending on the gene; of the remaining 31 ENIGMA-Other centers, a range of 10-30 centersresponded).

**Supplementary Table Legend**

**Supplementary Table 1.** Questions included in the surveys (by mode of distribution)

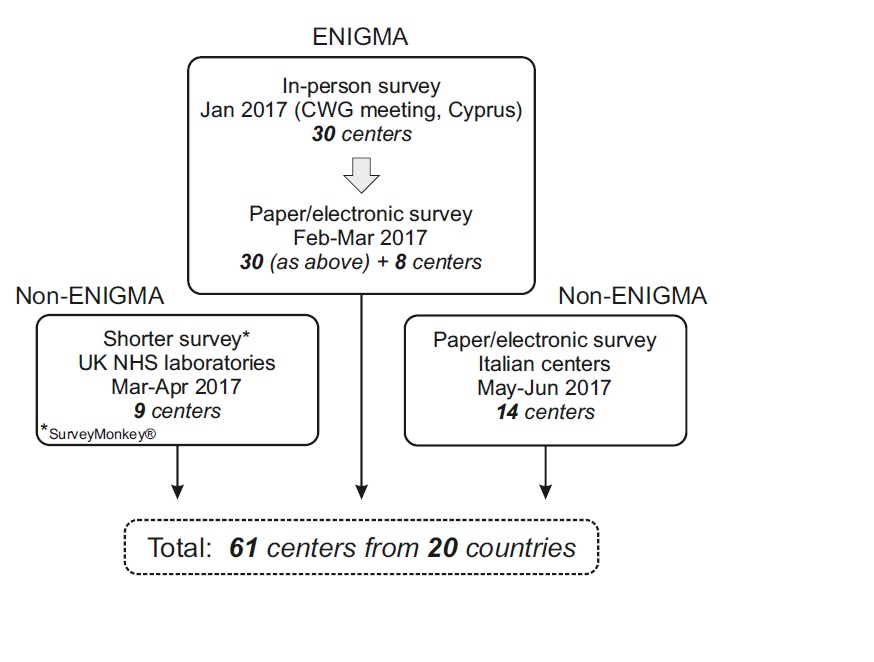
Footnote: Questions I-4 and III of the in-person survey were asked at a different time compared to the remainder of the survey, thus answers were collected only from 23 centers. Open questions were only part of the paper survey. The far right column shows the items included in the UK-specific survey conducted through SurveyMonkey®.

**Supplemental Tables 2-10**

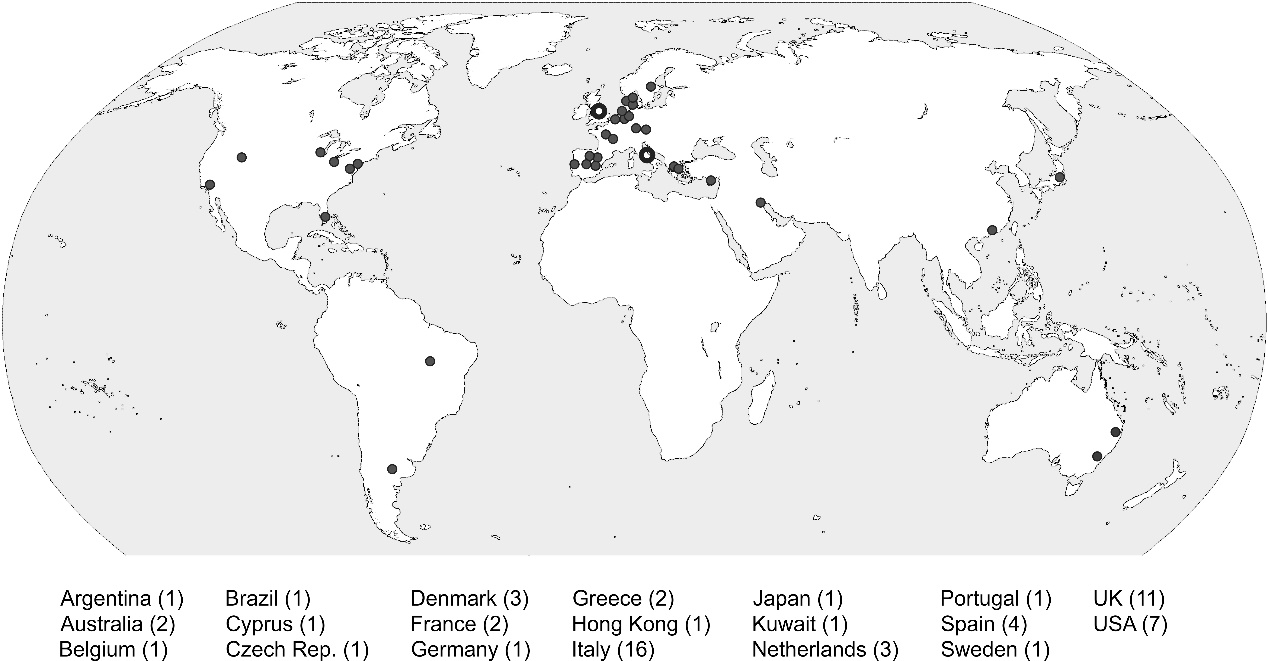
Legend: rsp= responses; CI= confidence interval; reg= regularly; pt= patient

**Figures**

**Figure 1A. Survey distribution**



**Figure 1B. Participating centers**

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**Figure 2**. **Frequency of testing**

**Figure 3.** **Clinical testing methods**

**Figure 4. Reporting practices of (likely) pathogenic variants and of VUS (to patients)**

**Figure 5. Sources of the management guidelines used by the ENIGMA centers**

**Table 1. National management guidelines for breast cancer management**

|  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **GENE/**  **MANAGEMENT** | **US (1)** | **Czech Republic (2)** | **Netherlands (3)** | **Australia (4)** | **France (5)** | **Spain (6)** | **Belgium (7)** | **UK (8)** | **Germany (9)** | **Denmark (10)** |
| ***PALB2*** |  |  |  |  |  |  |  |  |  |  |
| Surveillance | - Annual mammogram and consider breast MRI with contrast from age 30y | - SBE every mo. from age 20-25y  - Breast MRI with contrast and US, alternating every 6 mo. from age 25-29y  - Mammogram and breast MRI with contrast alternating every 6 mo. from age 30-65y  - Mammogram and US, alternating every 6 mo. from age > 65y | - 30-60y: annual breast MRI  - 30-75y: annual mammogram (\*)  - 30-75y: annual CBE by specialist  (\*) Between 60-75y and when mammogram is not easy to evaluate: alternate annual breast MRI with mammogram | - 30-50y: annual breast MRI and mammogram +/- US  - >50y: annual mammogram +/- US+ CBE  N.B.: In families with BC diagnosed <35y, individualized surveillance recommendations may apply, otherwise surveillance should start at age 30y | - 30-65y: annual MRI, mammogram and US  - >65y: mammogram and US | - Annual mammogram and MRI from age 30y |  |  | - 30\*-70y: annual  breast MRI + US  every 6 mo.  - Mammogram  <40y only in case  of conspicuous  -Mammogram  >40y at least every  2 yrs, or more often  depending on the  accessibility of  other examination  procedures, gland  tissue density and  mammographic  findings  \* or at least 5y  before earliest age  of diagnosis in  family | High-risk (≥30% LR of BC) guidelines:  - < 50y: annual mammogram from the age of 30  - 50 – 69y: Yearly clinical mammogram  - > 69y: screening mammogram every two years  General recommendations:  A breast self-exam is not recommended as a screening method  MR-scanning can be used as a part of the clinical breast examination imaging, but it is not recommended as the only screening method outside the experimental protocol |
| Surgical | Consider RRM based on FH | Consider RRM based on FH | Not enough evidence to recommend RRM. | Offer RRM followed by self-surveillance of breast area, if there is a strong FH of BC in women diagnosed <50y | RRM accepted | No statement made |  |  | RRM: individual case decision (consideration of pedigree and birth cohort) | RRM is not recommended, but the request for it is granted to women with high lifetime risk (≥ 30%) who insist on it after receiving genetic counseling |
| ***TP53*** |  |  |  |  |  |  |  |  |  |  |
| Surveillance | - 20-25y: CBE every 6-12 mo.  - 20-29y: annual breast MRI with contrast (preferred) or mammography  - 30-75y: annual mammogram and breast MRI with contrast  - >75 y: management should be considered on an individual basis | - 20 -25y: SBE every mo.  - 20-29y: annual breast MRI with contrast (preferred) or mammography  - 30-75y: annual mammogram and breast MRI with contrast.  - >75 y: management  should be considered on an individual basis | - The same as for *BRCA1/2* pathogenic variant carriers, from age 20-25y  - There is no consensus about use of mammography in combination with MRI or only MRI | - Breast awareness from the age of breast development  - From age 20y, annual breast MRI  - Other forms of imaging: mammogram +/-US only if unable to access MRI | - Annual MRI and US from age 20y | - From age 20y, annual breast MRI and add annual mammogram from age 30y | - Annual MRI recommended from age 25y  -Mammogram not recommended because of higher susceptibility to radiation  - US useful to reduce the number of false positives when MRI is difficult to interpret | - Do not offer mammogram  - 20-49y: annual MRI  - 50-60y: consider annual MRI | - 20\*-70y: annual  breast MRI + US  every 6 mo.  - Mammogram  <40y only in case  of conspicuous  -Mammogram  >40y at least every  2 yrs, or more often  depending on the  accessibility of  other examination  procedures, gland  tissue density and  mammographic  findings  \* or at least 5y  before earliest age  of diagnosis in  family | Same as *PALB2* |
| Surgical | Discuss option of RRM | Discuss option of RRM | The same as for *BRCA1/2* pathogenic variant carriers | Offer RRM especially in women <50y followed by self-surveillance of breast area | RRM accepted | RRM option should be discussed | Discuss with the patient the possibility to perform RRM | No statement made | RRM: individual case decision  (consideration of pedigree and birth cohort) | Same as *PALB2* |
| ***PTEN*** |  |  |  |  |  |  |  |  |  |  |
| Surveillance | - From age 25y or 5-10y earlier before the earliest BC in family: CBE every 6-12 mo. starting at age 25  - 30-35y or 5-10y before the earliest BC in family: annual mammogram and breast MRI with contrast  - >75 y, management should be considered on an individual basis | - From age 20y: SBE every mo.  - 30-35y or 5-10y before the earliest BC in family: annual mammogram and breast MRI with contrast  - >75y: management should be considered on an individual basis | - 25-60y: annual physical exam and breast MRI  - 30-60y:annual mammography  - From age 60y and depending on the difficulty to evaluate the mammogram, can be chosen individually between annual or biannual mammogram as part of the population surveillance programme | - In families with BC diagnosed under age 35y, individualized surveillance recommendations may apply, otherwise surveillance should start at age 30y  - 30-50y: annual MRI + mammogram (+/-US)  - >50y: annual mammogram +/-US | - Annual MRI, mammogram and US from age 30 to 65y, then mammogram and US  - Anticipated surveillance if mastopathy, with MRI and US | - Annual mammogram and breast MRI from age 30y | - Annual MRI from the age of 25 y onwards - From the age of 40 y onwards, annual MRI and annual mammography with an interval of 6 mo. between both examinations can be used -Mammogram should be used with prudence between 30 and 40y but should not be used before age 30  - US is useful to reduce the number of false positives when MRI is difficult to interpret | - 30-39y: consider annual mammogram  - 40-59y: annual mammogram  - From age 60, mammogramas part of population surveillance program | - 30\*-70y: annual  breast MRI + US  - Mammogram  <40y only in case  of conspicuous  -Mammogram  >40y at least every  2 yrs, or more often  depending on the  accessibility of  other examination  procedures, gland  tissue density and  mammographic  findings  \* or at least 5y  before earliest age  of diagnosis in  family | - Annual mammogram and breast MRI from the age of (25 to) 30y  The rest as for *PALB2* |
| Surgical | RRM: discuss option | No statement made | No statement made | Discuss RRM followed by self-surveillance of breast area (consider individual’s residual risk of BC and comorbidities) | RRM accepted and discussed at 25y if mastopathy | Discuss option of RRM | No studies have assessed efficacy of prophylactic mastectomy in Cowden Syndrome. Discuss with each patient the balance benefits/harms of RRM and counsel regarding degree of protection, extent of cancer risk and reconstruction options | No statement made | No statement made |  |
| ***CDH1*** |  |  |  |  |  |  |  |  |  |  |
| Surveillance | - Annual mammogram and consider breast MRI with contrast from age 30y | - SBE every mo. from age 18y  - CBE every 6 mo. from age 18y  - US and breast MRI with contrast alternating every 6 mo. from age 35y or 5-10y before the earliest BC in family | - From 30y: annual MRI, mammography and CBE performed by a specialist | - 30-50y: annual MRI + mammogram (+/-US)  - >50y: annual mammogram +/- annual US +CBE (consider also continuing MRI as may be superior for detection of lobular cancer) | - Annual MRI, mammogram and US from age 30 to 65y, then mammogram and US | - Annual mammography and breast MRI from the age of 35y |  | - 30-39y: consider annual mammogram  - 40-59y: annual mammogram  - From age 60, mammogram as part of population surveillance programme | -  Same as *PTEN* | Same as *PALB2* |
| Surgical | Consider RRM based on FH | No statement made | Individual case decision | RRM may be considered | RRM accepted | No statement made |  | No statement made | RRM: individual case decision  (consideration of pedigree and birth cohort) | Same as *PALB2* |
| ***STK11*** |  |  |  |  |  |  |  |  |  |  |
| Surveillance | - Mammogram and breast MRI annually beginning at ~25y | - SBE every month starting at age 20y  - Annual mammogram and breast MRI with contrast age 30-35y or 5-10 y before the earliest BC in family  - >75y: management should be considered on an individual basis | - Annual breast MRI from age 25y  - Mammogram and breast MRI from age 30y, rotating every 6 mo. | - In families with BC <35y, individualized surveillance recommendations may apply, otherwise screening should start at 30y  - 30-50y: annual MRI+  mammogram (+/-US)  - >50y: annual mammogram(+/-annual US) +CBE |  |  |  | - 30-39y: consider annual mammography  - 40-59y: annual mammogram  - From age 60: mammogram as part of population surveillance program |  | Same as *PALB2* |
| Surgical | RRM: Evidence insufficient, manage based on FH |  | No statement made | Consider RRM followed by self-surveillance of chest wall |  |  |  | No statement made |  | Same as *PALB2* |
| ***CHEK2*** |  |  |  |  |  |  |  |  |  |  |
| Surveillance | - Annual mammogram and consider breast MRI with contrast age 40y  N.B.: Risk data are based only on frameshift variants. The risks for most missense variants are unclear. |  | - Women with breast cancer heterozygous for the *CHEK2* c.1100delC pathogenic variant: Due to the increased risk of contralateral BC: Annual CBE and mammography till age 60y, or up to 10y after diagnosis of BC (if first BC occurred > 50y)  - Healthy heterozygotes: Annual CBE and mammography from 35-60y  - Healthy women not carrying the familial *CHEK2* c.11100delC pathogenic variant: advise depending on FH  - Women homozygotes for *CHEK2* c.11100delC: same advice as *BRCA1/2* carriers |  |  |  |  |  | Same as *PTEN* | Moderate risk (20-29% LR of BC) guidelines:  - < 50y: Annual mammogram from the age of 40y  - 50-69y: Screening mammogram every 2 years  > 69y: none  General recommendations:  A breast self-exam is not recommended as a screening method  MR-scanning can be used as a part of the clinical breast examination imaging, but it is not recommended as the only screening method outside the experimental protocol. |
| Surgical | RRM: evidence insufficient, manage based on family history |  | Consider for women homozygotes for the *CHEK2* c.11100delC pathogenic variant |  |  |  |  |  | RRM: individual case decision consideration of pedigree and birth cohort | RRM is not recommended. |
| ***ATM*** |  |  |  |  |  |  |  |  |  |  |
| Surveillance | - Annual mammogram and consider breast MRI with contrast starting at age 40y  N.B: Insufficient evidence to recommend against radiation therapy.  The 7271T>G mutation has higher LR of BC (up to 60%) than truncating variants |  | Draft guidelines:  *- Female ATM carriers (all pathogenic variants except for C.7271T>G):*  -40-50y: annual mammography  -50-75y: population surveillance  **-** Female carriers of c.7271T>G:  -25-60y: annual breast MRI  -30-75y: annual mammography -Exception is by heterogeneous density or high density of fibroglandular tissue (ACR 3 or 4), then advice is annual MRI alternating with mammography from 60-75y | *Guidelines for the 7271T>G pathogenic variant only:*  - 30-50y: annual MRI+ mammogram (+/-US)  - >50y: annual mammogram (+/-US) +CBE |  |  |  |  | Same as *PTEN*  - Avoid radiation of the contralateral breast | Same as *CHEK2*  Guidelines for post-operative radiation will not be modified as the result of pathogenic variants in *ATM* |
| Surgical | Consider RRM based on FH |  | No statement made | No statement made |  |  |  |  | RRM: currently not recommended | Same as *CHEK2* |
| ***NF1*** |  |  |  |  |  |  |  |  |  |  |
| Surveillance | - Annual mammogram starting at age 30y and consider breast MRI with contrast from 30-50y | - SBE exam every mo. starting at age 20y  - Annual mammogram starting at age 30y and consider breast MRI with contrast | - 35-50y: annual mammogram and physical exam by the specialist  - >50: population breast surveillance program | - All ages: Breast awareness with prompt reporting to general practitioner of persistent or unusual changes  - From age 40y: annual mammography  - From age 50y: Biannual mammogram |  |  |  | Annual breast cancer screening should be done from 40y on |  | Same as *CHEK2* |
| Surgical | RRM: Evidence insufficient, manage based on FH | No statement made | No statement made | No statement made |  |  |  |  |  | Same as *CHEK2* |
| ***NBN*** |  |  |  |  |  |  |  |  |  |  |
| Surveillance | - Annual mammogram and consider breast MRI with contrast from age 40y  N.B.: recommendations based on data from the c.657del5 Slavic truncating variant |  |  |  |  |  |  |  |  |  |
| Surgical | RRM: Evidence insufficient, manage based on FH |  |  |  |  |  |  |  |  |  |
| ***MEN1*** |  |  |  |  |  |  |  |  |  |  |
| Surveillance |  | - SBE every month starting at 20y  - Biannual mammogram starting age 40y | - 35 -50y: annual mammogram and CBO by the specialist  - >50: population breast surveillance programme |  |  |  |  |  |  |  |
| Surgical |  | No statement made | No statement made |  |  |  |  |  |  |  |

y= years; CBE= Clinical Breast Exam; SBE= Self Breast Exam; mo= month; FH= Family History; RRM= Risk Reducing Mastectomy; US= ultrasound(sonography); LR= Lifetime Risk

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**Supplementary Figure 1.** Opinions on clinical utility of non-BRCA BC and OC risk genes: participants who agree with the following statements:

**Supplementary Figure 1a.** Every BC (or OC) patient who meets criteria for (*BRCA1/2)* genetic testing should be tested for this gene

**Supplementary Figure 1b.** Cancer risks associated with this gene are high enough to impact clinical management

**Supplementary Figure 2.** Testing setting: clinical vs. research

**Supplementary Figure 3.** Genes tested regularly by ENIGMA-US vs. ENIGMA-Other vs. Italian and UK non-ENIGMA centers

**Supplementary Figure 4.** Genes tested through panel testing by ENIGMA-US vs. ENIGMA-Other centers

**Supplementary Table 1.** Questions included in the surveys (by mode of distribution)

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Questions** | **In-person survey only** | **In-person and paper survey** | **Paper survey only** | **SurveyMonkey® (UK-NHS labs only)** |
| **I-TESTING PRACTICES** |  |  |  |  |
| **I-1**  **Is DNA testing for inherited susceptibility to BC or OC carried out at your clinical practice?** |  | Yes/No |  | Yes/No |
| **I-2**  **Which of the following BC/OC susceptibility genes are tested?** |  | *ATM*  *BARD1*  *BRIP1*  *CDH1*  *CHEK2*  *MEN1*  *MRE11A*  *NBN*  *NF1*  *PALB2*  *PTEN*  *RAD50*  *RAD51C*  *RAD51D*  *STK11*  *TP53* |  | *BRCA1*  *BRCA2*  *CHEK2*  *ATM*  *CDH1*  *NBN*  *NF1*  *PALB2*  *PTEN*  *STK11*  *TP53*  Other genes (specify) |
| **I-3**  **Frequency of testing** |  | Does your center test for gene X?  Yes, regularly  Yes, occasionally  No, it does not |  | Which of the following  genes are routinely reported for all BC susceptibility requests?  (same list as above) |
| **I-4**  **Testing methods and setting** | Which genes do you agree should be tested for every BC or OC patient eligible for genetic testing? | Which method is used to test for gene X?   1. Clinical   i. Single gene  ii. Part of gene panel  iii. Reflex test (i.e. tested only if other specified genes are wild-type)   1. Research   i. Single gene  ii. Part of gene panel | Describe the gene panels currently used (if any) and if they are used in the diagnostic or research setting  If you are not currently using gene panels but may in the future, what do you think is required before starting to use them? |  |
| **II-VARIANT CLASSIFICATION** |  |  |  |  |
| **II-1**  **Classification system** |  | 1. Which scheme/criteria are used for variant classification? 2. Specify the # of tiers used for class definition |  |  |
| **II-2**  **Reporting and cascade testing of variants** |  | (Likely) pathogenic variants:   1. Are they reported to patients? 2. Is cascade testing performed? done for these (reported) variants   VUS:   1. are they reported to patients? 2. is cascade testing performed? | Do you (or your colleagues) request genetic testing directly and discuss results? | Do you routinely discuss results of uncertain significance with the referring clinician before reporting?  If you currently only report *BRCA* genes but might report broader panels in the future, what are the major  issues/problems that should be overcome? |
| **II-3**  **Variant interpretation** |  |  | Who takes responsibility for interpreting the clinical significance of the identified variants? | For cancer susceptibility genes:  Who takes responsibility for variant interpretation and reporting?   1. Clinical scientist 2. Clinical geneticist 3. Genetic counsellor 4. Oncologist (medical/surgical) 5. Other (specify)   Who takes responsibility  for discussing the clinical  significance/utility of an identified variant? (Same choices as above) |
| **III-RISK MANAGEMENT GUIDELINES** | For which genes do you agree that the cancer-associated risks are high-enough to alter clinical practice/management? | Are management guidelines available at your center for patients with (likely) pathogenic variants in these genes?   1. Yes, national guidelines 2. Yes, local guidelines or local adaptations of national guidelines 3. No, guidelines are not currently available | If clinical management guidelines are available at your center for the specified genes, please provide digital copy, reference, or website link | Are there clinical guidelines for managing patients who carry a pathogenic or likely pathogenic variant in a BC susceptibility gene? |

**Supplemental Tables 2-10. Raw data with 95% confidence intervals**

**Legend: rsp= responses; CI= confidence interval; reg= regularly; pt= patient**

**Supplemental Table 2.** Frequency of testing

|  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | Test for- Yes | # informative rsp | % | lower 95% CI | upper 95% CI | Test- Reg | # informative rsp | % | lower 95% CI | upper 95% CI |
| *PALB2* | 34 | 38 | 89 | 0.7587 | 0.9583 | 25 | 38 | 66 | 0.4989 | 0.7879 |
| *TP53* | 38 | 38 | 100 | 0.9082 | 1.0000 | 22 | 38 | 58 | 0.4219 | 0.7215 |
| *PTEN* | 38 | 38 | 100 | 0.9082 | 1.0000 | 21 | 37 | 57 | 0.4091 | 0.7133 |
| *CDH1* | 37 | 38 | 97 | 0.8651 | 0.9953 | 17 | 37 | 46 | 0.3104 | 0.6162 |
| *STK11* | 33 | 36 | 92 | 0.7817 | 0.9713 | 11 | 34 | 32 | 0.1913 | 0.4916 |
| *CHEK2* | 34 | 38 | 89 | 0.7587 | 0.9583 | 27 | 36 | 75 | 0.5893 | 0.8625 |
| *ATM* | 30 | 38 | 79 | 0.6365 | 0.8893 | 19 | 38 | 50 | 0.3485 | 0.6515 |
| *NF1* | 23 | 35 | 66 | 0.4915 | 0.7917 | 7 | 34 | 21 | 0.1035 | 0.3680 |
| *NBN* | 28 | 36 | 78 | 0.6192 | 0.8828 | 13 | 36 | 38 | 0.2246 | 0.5242 |
| *BARD1* | 25 | 32 | 78 | 0.6192 | 0.8828 | 12 | 30 | 40 | 0.2459 | 0.5768 |
| *RAD50* | 24 | 32 | 75 | 0.5789 | 0.8675 | 10 | 26 | 38 | 0.2243 | 0.5747 |
| *MRE11A* | 23 | 32 | 72 | 0.5463 | 0.8444 | 11 | 29 | 38 | 0.2269 | 0.5600 |
| *MEN1* | 15 | 29 | 52 | 0.3443 | 0.6861 | 5 | 27 | 19 | 0.0818 | 0.3670 |
| *BRIP1* | 28 | 34 | 82 | 0.6649 | 0.9165 | 15 | 30 | 50 | 0.3315 | 0.6685 |
| *RAD51C* | 30 | 33 | 91 | 0.7643 | 0.9686 | 14 | 30 | 47 | 0.3023 | 0.6386 |
| *RAD51D* | 29 | 33 | 88 | 0.7267 | 0.9518 | 14 | 31 | 4 | 0.2916 | 0.6223 |

**Supplementary Table 3.** Clinical testing methods

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | # informative rsp | Clinical- single gene | % | lower 95% CI | upper 95% CI | Clinical-panel | % | lower 95% CI | upper 95% CI | Clinical- reflex | % | lower 95% CI | upper 95% CI |
| *PALB2* | 34 | 9 | 26 | 0.1460 | 0.4312 | 29 | 85 | 0.6987 | 0.9355 | 13 | 38 | 0.2390 | 0.5496 |
| *TP53* | 38 | 21 | 55 | 0.3971 | 0.6985 | 28 | 76 | 0.5989 | 0.8664 | 15 | 41 | 0.2635 | 0.5651 |
| *PTEN* | 37 | 17 | 46 | 0.3104 | 0.6162 | 27 | 75 | 0.5893 | 0.8625 | 9 | 25 | 0.1375 | 0.4107 |
| *CDH1* | 36 | 15 | 42 | 0.2714 | 0.5780 | 27 | 77 | 0.6098 | 0.8793 | 8 | 23 | 0.1207 | 0.3902 |
| *STK11* | 33 | 11 | 33 | 0.1975 | 0.5039 | 21 | 64 | 0.4662 | 0.7782 | 7 | 21 | 0.1067 | 0.3775 |
| *CHEK2* | 32 | 5 | 16 | 0.0687 | 0.3176 | 17 | 53 | 0.3645 | 0.6913 | 3 | 9 | 0.0324 | 0.2422 |
| *ATM* | 29 | 4 | 14 | 0.0550 | 0.3056 | 20 | 69 | 0.5077 | 0.8273 | 1 | 3 | 0.0061 | 0.1718 |
| *NF1* | 23 | 5 | 22 | 0.0966 | 0.4190 | 14 | 61 | 0.4079 | 0.7784 | 2 | 9 | 0.0242 | 0.2680 |
| *NBN* | 27 | 1 | 4 | 0.0066 | 0.1828 | 15 | 56 | 0.3732 | 0.7242 | 1 | 4 | 0.0066 | 0.1828 |
| *BARD1* | 24 | 0 | 0 | 0.0000 | 0.1717 | 13 | 54 | 0.3508 | 0.7211 | 0 | 0 | 0.0000 | 0.1380 |
| *RAD50* | 24 | 0 | 0 | 0.0000 | 0.1717 | 12 | 50 | 0.3143 | 0.6857 | 0 | 0 | 0.0000 | 0.1380 |
| *MRE11A* | 23 | 0 | 0 | 0.0000 | 0.1431 | 11 | 48 | 0.2924 | 0.6704 | 0 | 0 | 0.0000 | 0.1431 |
| *MEN1* | 14 | 3 | 21 | 0.0757 | 0.4759 | 8 | 57 | 0.3259 | 0.7862 | 0 | 0 | 0.0000 | 0.2153 |
| *BRIP1* | 26 | 0 | 0 | 0.0000 | 0.1287 | 18 | 69 | 0.5001 | 0.8350 | 3 | 12 | 0.0400 | 0.2898 |
| *RAD51C* | 29 | 0 | 0 | 0.0000 | 0.1170 | 23 | 79 | 0.6161 | 0.9015 | 2 | 7 | 0.0191 | 0.2197 |
| *RAD51D* | 28 | 0 | 0 | 0.0000 | 0.1206 | 23 | 82 | 0.6441 | 0.9212 | 2 | 7 | 0.0198 | 0.2264 |

**Supplementary Table 4.** Reporting practices of (likely) pathogenic variants and of VUS to patients

|  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | # informative rsp | Report to pt (pathogenic) | % | lower 95% CI | upper 95% CI | # informative rsp | Report to pt (VUS) | % | lower 95% CI | upper95% CI |
| *PALB2* | 28 | 28 | 100 | 0.8794 | 1.0000 | 16 | 13 | 81 | 0.5699 | 0.9341 |
| *TP53* | 36 | 34 | 94 | 0.8186 | 0.9846 | 20 | 15 | 75 | 0.5313 | 0.8881 |
| *PTEN* | 35 | 34 | 97 | 0.8547 | 0.9949 | 19 | 14 | 74 | 0.5121 | 0.8819 |
| *CDH1* | 35 | 34 | 97 | 0.8547 | 0.9949 | 18 | 14 | 78 | 0.5479 | 0.9100 |
| *STK11* | 30 | 28 | 93 | 0.7868 | 0.9815 | 16 | 12 | 75 | 0.5050 | 0.8982 |
| *CHEK2* | 33 | 29 | 88 | 0.8788 | 0.7267 | 14 | 7 | 50 | 0.2680 | 0.7320 |
| *ATM* | 24 | 22 | 92 | 0.7415 | 0.9768 | 11 | 9 | 82 | 0.5230 | 0.9486 |
| *NF1* | 20 | 19 | 95 | 0.7639 | 0.9911 | 11 | 8 | 73 | 0.4344 | 0.9025 |
| *NBN* | 21 | 15 | 71 | 0.5004 | 0.8619 | 8 | 4 | 50 | 0.2152 | 0.7848 |
| *BARD1* | 16 | 15 | 94 | 0.7167 | 0.9889 | 6 | 3 | 50 | 0.1876 | 0.8124 |
| *RAD50* | 12 | 11 | 92 | 0.6461 | 0.9851 | 5 | 3 | 60 | 0.2307 | 0.8824 |
| *MRE11A* | 12 | 11 | 92 | 0.6461 | 0.9851 | 4 | 2 | 50 | 0.1500 | 0.8500 |
| *MEN1* | 12 | 11 | 92 | 0.6461 | 0.9851 | 7 | 5 | 71 | 0.3589 | 0.9178 |
| *BRIP1* | 22 | 21 | 95 | 0.8454 | 1.0000 | 11 | 8 | 73 | 0.4344 | 0.9025 |
| *RAD51C* | 25 | 25 | 100 | 0.8668 | 1.0000 | 14 | 11 | 79 | 0.5241 | 0.9243 |
| *RAD51D* | 25 | 25 | 100 | 0.8668 | 1.0000 | 14 | 10 | 71 | 0.4535 | 0.8828 |

**Supplementary Table 5.** Sources of management guidelines from the ENIGMA centers

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | # informative rsp | Yes- have guidelines | % overall | lower 95% CI | Upper 95% CI | National | % | lower 95% CI | Upper 95% CI | Local | % | lower 95% CI | Upper 95% CI | International | % | lower 95% CI | Upper 95% CI |
| *PALB2* | 25 | 23 | 92 | 0.7503 | 0.9778 | 13 | 52 | 0.335 | 0.6997 | 9 | 36 | 0.2025 | 0.5548 | 1 | 4 | 0.0071 | 0.1954 |
| *TP53* | 31 | 29 | 94 | 0.7928 | 0.9821 | 22 | 71 | 0.5341 | 0.839 | 5 | 16 | 0.0709 | 0.3263 | 2 | 6 | 0.0179 | 0.2072 |
| *PTEN* | 31 | 29 | 94 | 0.7928 | 0.9821 | 19 | 61 | 0.4382 | 0.7627 | 8 | 26 | 0.137 | 0.4 | 2 | 6 | 0.0179 | 0.2072 |
| *CDH1* | 31 | 29 | 94 | 0.7928 | 0.9821 | 19 | 61 | 0.4382 | 0.7627 | 8 | 26 | 0.137 | 0.4 | 2 | 6 | 0.0179 | 0.2072 |
| *STK11* | 26 | 23 | 88 | 0.7102 | 0.96 | 16 | 62 | 0.4253 | 0.7757 | 5 | 19 | 0.0851 | 0.3788 | 2 | 8 | 0.0214 | 0.2414 |
| *CHEK2* | 22 | 20 | 91 | 0.7219 | 0.9747 | 11 | 50 | 0.3072 | 0.6928 | 8 | 36 | 0.1973 | 0.5705 | 1 | 5 | 0.0081 | 0.218 |
| *ATM* | 20 | 18 | 90 | 0.699 | 0.9721 | 10 | 50 | 0.2993 | 0.7007 | 7 | 35 | 0.1812 | 0.5671 | 1 | 5 | 0.0089 | 0.2361 |
| *NF1* | 17 | 15 | 88 | 0.6566 | 0.9671 | 9 | 53 | 0.3096 | 0.7383 | 5 | 29 | 0.1328 | 0.5313 | 1 | 6 | 0.0105 | 0.2698 |
| *NBN* | 14 | 12 | 86 | 0.6006 | 0.9599 | 7 | 50 | 0.268 | 0.732 | 4 | 29 | 0.1172 | 0.5465 | 1 | 7 | 0.0127 | 0.3147 |
| *BARD1* | 14 | 3 | 21 | 0.0757 | 0.4759 | 0 | 0 | 0 | 0.2153 | 3 | 21 | 0.0757 | 0.4759 | 0 | 0 | 0 | 0.2153 |
| *RAD50* | 11 | 3 | 27 | 0.0975 | 0.5656 | 0 | 0 | 0 | 0.2588 | 3 | 27 | 0.0975 | 0.5656 | 0 | 0 | 0 | 0.2588 |
| *MRE11A* | 10 | 3 | 30 | 0.1078 | 0.6032 | 0 | 0 | 0 | 0.2775 | 3 | 30 | 0.1078 | 0.6032 | 0 | 0 | 0 | 0.2775 |
| *MEN1* | 10 | 8 | 80 | 0.4902 | 0.9433 | 3 | 30 | 0.1078 | 0.6032 | 4 | 40 | 0.1682 | 0.6873 | 1 | 10 | 0.0179 | 0.4042 |
| *BRIP1* | 19 | 16 | 84% | 0.6243 | 0.9448 | 8 | 42% | 0.2314 | 0.6372 | 7 | 37% | 0.1915 | 0.5896 | 1 | 5 | 0.0094 | 0.2464 |
| *RAD51C* | 24 | 21 | 88% | 0.69 | 0.9566 | 10 | 42% | 0.2447 | 0.6117 | 10 | 42% | 0.2447 | 0.6117 | 1 | 4 | 0.0074 | 0.2024 |
| *RAD51D* | 24 | 21 | 88% | 0.69 | 0.9566 | 10 | 42% | 0.2447 | 0.6117 | 10 | 42% | 0.2447 | 0.6117 | 1 | 4 | 0.0074 | 0.2024 |

**Supplementary Table 6.** Clinical utility: Every BC (or OC) patient who meets criteria for genetic testing should be tested for this gene

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
|  | # informative rsp | pt should be tested | % | lower 95% CI | upper 95% CI |
| *PALB2* | 23 | 23 | 100 | 0.8569 | 1.0000 |
| *TP53* | 23 | 9 | 39 | 0.2216 | 0.5921 |
| *PTEN* | 23 | 6 | 30 | 0.1255 | 0.4647 |
| *CDH1* | 23 | 7 | 26 | 0.1560 | 0.5087 |
| *STK11* | 23 | 4 | 17 | 0.0698 | 0.3714 |
| *CHEK2* | 23 | 15 | 65 | 0.4489 | 0.8119 |
| *ATM* | 23 | 12 | 52 | 0.3296 | 0.7076 |
| *NF1* | 23 | 1 | 4 | 0.0077 | 0.2099 |
| *BARD1* | 23 | 6 | 26 | 0.1255 | 0.4647 |
| *MEN1* | 23 | 2 | 9 | 0.0242 | 0.2680 |
| *MRE11A* | 23 | 0 | 0 | 0.0000 | 0.1431 |
| *NBN* | 23 | 0 | 0 | 0.0000 | 0.1431 |
| *RAD50* | 23 | 0 | 0 | 0.0000 | 0.1431 |
| *BRIP1* | 23 | 23 | 100 | 0.8569 | 1.0000 |
| *RAD51C* | 23 | 23 | 100 | 0.8569 | 1.0000 |
| *RAD51D* | 23 | 23 | 100 | 0.8569 | 1.0000 |

**Supplementary Table 7.** Clinical utility: cancer risks associated with this gene are high enough to impact clinical management

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
|  | # informative rsp | pt should be tested | % | lower 95% CI | upper 95% CI |
| *PALB2* | 23 | 23 | 100 | 0.8569 | 1.0000 |
| *TP53* | 23 | 23 | 100 | 0.8569 | 1.0000 |
| *PTEN* | 23 | 23 | 100 | 0.8569 | 1.0000 |
| *CDH1* | 23 | 23 | 100 | 0.8569 | 1.0000 |
| *STK11* | 23 | 23 | 100 | 0.8569 | 1.0000 |
| *CHEK2* | 23 | 20 | 87 | 0.6787 | 0.9546 |
| *ATM* | 23 | 18 | 78 | 0.5810 | 0.9034 |
| *NF1* | 23 | 8 | 35 | 0.1881 | 0.5511 |
| *BARD1* | 23 | 6 | 26 | 0.1255 | 0.4647 |
| *MEN1* | 23 | 3 | 13 | 0.0454 | 0.3213 |
| *MRE11A* | 23 | 0 | 0 | 0.0000 | 0.1431 |
| *NBN* | 23 | 0 | 0 | 0.0000 | 0.1431 |
| *RAD50* | 23 | 0 | 0 | 0.0000 | 0.1431 |
| *BRIP1* | 23 | 23 | 100 | 0.8569 | 1.0000 |
| *RAD51C* | 23 | 23 | 100 | 0.8569 | 1.0000 |
| *RAD51D* | 23 | 23 | 100 | 0.8569 | 1.0000 |

**Supplementary Table 8.** Testing setting: clinical vs. research

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | # informative rsp | Clinical testing only | % | lower 95% CI | upper 95% CI | Clinical & Research | % | lower 95% CI | upper 95% CI | Research testing only | % | lower 95% CI | upper 95% CI |
| *PALB2* | 34 | 20 | 59 | 0.4222 | 0.7363 | 11 | 32 | 0.1913 | 0.4916 | 3 | 9 | 0.0305 | 0.2296 |
| *TP53* | 37 | 23 | 62 | 0.4610 | 0.7594 | 14 | 38 | 0.2406 | 0.539 | 0 | 0 | 0.0000 | 0.0000 |
| *PTEN* | 36 | 21 | 58 | 0.4220 | 0.7286 | 14 | 39 | 0.2478 | 0.5514 | 1 | 3 | 0.0049 | 0.1417 |
| *CDH1* | 35 | 22 | 63 | 0.4634 | 0.7683 | 12 | 34 | 0.2083 | 0.5085 | 1 | 3 | 0.0051 | 0.1453 |
| *STK11* | 33 | 16 | 48 | 0.3250 | 0.6478 | 14 | 42 | 0.2724 | 0.5919 | 3 | 9 | 0.0314 | 0.2357 |
| *CHEK2* | 32 | 14 | 44 | 0.2817 | 0.6067 | 13 | 41 | 0.2552 | 0.5774 | 5 | 16 | 0.0686 | 0.3175 |
| *ATM* | 29 | 11 | 38 | 0.2269 | 0.5600 | 12 | 41 | 0.2551 | 0.5926 | 6 | 21 | 0.0985 | 0.3839 |
| *NF1* | 23 | 12 | 52 | 0.3296 | 0.7076 | 7 | 30 | 0.156 | 0.5087 | 4 | 17 | 0.0698 | 0.3714 |
| *NBN* | 27 | 6 | 22 | 0.1061 | 0.4076 | 10 | 37 | 0.2153 | 0.5577 | 11 | 41 | 0.2451 | 0.5927 |
| *BARD1* | 23 | 5 | 22 | 0.0966 | 0.4190 | 9 | 39 | 0.2216 | 0.5921 | 9 | 39 | 0.2216 | 0.5921 |
| *RAD50* | 23 | 6 | 26 | 0.1255 | 0.4647 | 7 | 30 | 0.156 | 0.5087 | 10 | 43 | 0.2563 | 0.6319 |
| *MRE11A* | 23 | 4 | 17 | 0.0698 | 0.3714 | 8 | 35 | 0.1881 | 0.5511 | 11 | 48 | 0.2924 | 0.6704 |
| *MEN1* | 14 | 5 | 36 | 0.1634 | 0.6124 | 6 | 43 | 0.2138 | 0.6741 | 3 | 21 | 0.0757 | 0.4759 |
| *BRIP1* | 27 | 10 | 37 | 0.2153 | 0.5577 | 10 | 37 | 0.2153 | 0.5577 | 7 | 26 | 0.1317 | 0.4468 |
| *RAD51C* | 29 | 12 | 41 | 0.2551 | 0.5926 | 12 | 41 | 0.2551 | 0.5926 | 5 | 17 | 0.0760 | 0.3455 |
| *RAD51D* | 28 | 12 | 43 | 0.2651 | 0.6093 | 12 | 43 | 0.2651 | 0.6093 | 4 | 14 | 0.0570 | 0.3149 |

**Supplementary Table 9.** Genes regularly tested by ENIGMA-US vs. ENIGMA-Other vs. Italian and UK non-ENIGMA centers

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | ENIGMA overall- # informative resp | Test Reg- Yes | % | Italy- informative resp | Test Reg- Yes | % | lower 95% CI | upper 95% CI | UK- informative resp | Test- Yes (reg was not an option) | % | lower 95% CI | upper 95% CI | ENIGMA-US inform resp | Test Reg-Yes | % | lower 95% CI | upper 95% CI | ENIGMA- Other- inform rsp | Test Reg-Yes | % | lower 95% CI | upper 95% CI |
| *PALB2* | 36 | 25 | 69 | 14 | 2 | 14 | 0.0401 | 0.3994 | 9 | 2 | 22 | 0.0632 | 0.5474 | 7 | 7 | 100 | 0.6457 | 1.0000 | 29 | 18 | 62 | 0.4400 | 0.7731 |
| *TP53* | 36 | 22 | 61 | 14 | 2 | 14 | 0.0401 | 0.3994 | 9 | 5 | 56 | 0.2667 | 0.8112 | 7 | 6 | 86 | 0.4869 | 0.9743 | 29 | 16 | 55 | 0.3755 | 0.7159 |
| *PTEN* | 35 | 21 | 60 | 14 | 2 | 14 | 0.0401 | 0.3994 | 9 | 3 | 33 | 0.1206 | 0.6458 | 7 | 7 | 100 | 0.6457 | 1.0000 | 28 | 14 | 50 | 0.3263 | 0.6737 |
| *CDH1* | 35 | 17 | 49 | 14 | 2 | 14 | 0.0401 | 0.3994 | 9 | 1 | 11 | 0.0199 | 0.4350 | 7 | 6 | 86 | 0.4869 | 0.9743 | 28 | 11 | 39 | 0.2357 | 0.5759 |
| *STK11* | 32 | 11 | 34 | 14 | 1 | 7 | 0.0127 | 0.3147 | 9 | 1 | 11 | 0.0199 | 0.4350 | 7 | 2 | 29 | 0.0822 | 0.6411 | 25 | 9 | 36 | 0.2025 | 0.5548 |
| *CHEK2* | 34 | 26 | 76 | 14 | 3 | 21 | 0.0757 | 0.4759 | 9 | 1 | 11 | 0.0199 | 0.4350 | 7 | 6 | 86 | 0.4869 | 0.9743 | 27 | 20 | 74 | 0.5532 | 0.8683 |
| *ATM* | 36 | 19 | 53 | 14 | 2 | 14 | 0.0401 | 0.3994 | 9 | 1 | 11 | 0.0199 | 0.4350 | 7 | 6 | 86 | 0.4869 | 0.9743 | 29 | 13 | 45 | 0.2841 | 0.6245 |
| *NF1* | 32 | 7 | 22 | 14 | 2 | 14 | 0.0401 | 0.3994 | 9 | 1 | 11 | 0.0199 | 0.4350 | 7 | 2 | 29 | 0.0822 | 0.6411 | 25 | 5 | 20 | 0.0886 | 0.3913 |
| *NBN* | 34 | 13 | 38 | 14 | 0 | 0 | 0.0000 | 0.0000 | 9 | 0 | 0 | 0.0000 | 0.0000 | 7 | 5 | 71 | 0.3589 | 0.9178 | 27 | 8 | 30 | 0.1585 | 0.4848 |
| *BARD1* | 28 | 12 | 43 | 14 | 2 | 14 | 0.0401 | 0.3994 | 9 | 0 | 0 | 0.0000 | 0.0000 | 6 | 4 | 67 | 0.3000 | 0.9032 | 22 | 8 | 36 | 0.1973 | 0.5705 |
| *RAD50* | 25 | 10 | 40 | 14 | 0 | 0 | 0.0000 | 0.0000 | 9 | 0 | 0 | 0.0000 | 0.0000 | 4 | 3 | 75 | 0.3006 | 0.9544 | 21 | 7 | 33 | 0.1719 | 0.5463 |
| *MRE11A* | 28 | 11 | 39 | 14 | 0 | 0 | 0.0000 | 0.0000 | 9 | 0 | 0 | 0.0000 | 0.0000 | 6 | 3 | 50 | 0.1876 | 0.8124 | 22 | 8 | 36 | 0.1973 | 0.5705 |
| *MEN1* | 25 | 5 | 20 | 14 | 1 | 7 | 0.0127 | 0.3147 | 9 | 0 | 0 | 0.0000 | 0.0000 | 4 | 1 | 25 | 0.0456 | 0.6994 | 21 | 4 | 19 | 0.0767 | 0.4000 |
| *BRIP1* | 29 | 15 | 52 | 14 | 1 | 7 | 0.0127 | 0.3147 | 9 | 1 | 11 | 0.0199 | 0.4350 | 7 | 5 | 71 | 0.3589 | 0.9178 | 22 | 10 | 45 | 0.2692 | 0.6534 |
| *RAD51C* | 29 | 14 | 48 | 14 | 0 | 0 | 0.0000 | 0.0000 | 9 | 3 | 33 | 0.1206 | 0.6458 | 7 | 5 | 71 | 0.3589 | 0.9178 | 22 | 9 | 41 | 0.2326 | 0.6127 |
| *RAD51D* | 29 | 14 | 48 | 14 | 0 | 0 | 0.0000 | 0.0000 | 9 | 3 | 33 | 0.1206 | 0.6458 | 7 | 5 | 71 | 0.3589 | 0.9178 | 22 | 9 | 41 | 0.2326 | 0.6127 |

**Supplementary Table 10.** Genes tested through panel testing by ENIGMA-US vs. ENIGMA-Other centers

|  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | ENIGMA-Other informative rsp | Clinical testing through panel | % | lower 95% CI | upper 95% CI | ENIGMA-US informative rsp | Clinical testing through panel | % ENIGMA US test through panel | lower 95% CI | upper 95% CI |
| *PALB2* | 27 | 22 | 81 | 0.6330 | 0.9182 | 7 | 7 | 100 | 0.6457 | 1.0000 |
| *TP53* | 30 | 21 | 70 | 0.5212 | 0.8334 | 7 | 7 | 100 | 0.6457 | 1.0000 |
| *PTEN* | 29 | 20 | 69 | 0.5077 | 0.8272 | 7 | 7 | 100 | 0.6457 | 1.0000 |
| *CDH1* | 28 | 20 | 71 | 0.5294 | 0.8475 | 7 | 7 | 100 | 0.6457 | 1.0000 |
| *STK11* | 26 | 15 | 58 | 0.3895 | 0.7446 | 7 | 6 | 86 | 0.4869 | 0.9743 |
| *CHEK2* | 25 | 11 | 44 | 0.2667 | 0.6293 | 7 | 6 | 86 | 0.4869 | 0.9743 |
| *ATM* | 22 | 13 | 59 | 0.3873 | 0.7674 | 7 | 7 | 100 | 0.6457 | 1.0000 |
| *NF1* | 16 | 8 | 50 | 0.2800 | 0.7200 | 7 | 6 | 86 | 0.4869 | 0.9743 |
| *NBN* | 21 | 9 | 43 | 0.2447 | 0.6345 | 6 | 6 | 100 | 0.6097 | 1.0000 |
| *BARD1* | 19 | 7 | 37 | 0.1915 | 0.5896 | 6 | 6 | 100 | 0.6097 | 1.0000 |
| *RAD50* | 18 | 7 | 39 | 0.2031 | 0.6138 | 6 | 5 | 83 | 0.4365 | 0.9699 |
| *MRE11A* | 17 | 6 | 35 | 0.1731 | 0.5870 | 6 | 5 | 83 | 0.4365 | 0.9699 |
| *MEN1* | 10 | 7 | 70 | 0.3968 | 0.8922 | 4 | 1 | 25 | 0.0456 | 0.6994 |
| *BRIP1* | 20 | 12 | 60 | 0.3866 | 0.7812 | 6 | 6 | 100 | 0.6097 | 1.0000 |
| *RAD51C* | 22 | 16 | 73 | 0.5185 | 0.8685 | 7 | 7 | 100 | 0.6457 | 1.0000 |
| *RAD51D* | 21 | 16 | 76 | 0.5491 | 0.8937 | 7 | 7 | 100 | 0.6457 | 1.0000 |