Thieme

Risk, Prediction and Prevention of Hereditary Breast Cancer – Large-Scale Genomic Studies in Times of Big and Smart Data

Risiko, Vorhersage und Prävention von erblichem Brustkrebs – groß angelegte genomische Studien in Zeiten von Big und Smart Data

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ABSTRACT

Over the last two decades genetic testing for mutations in *BRCA1* and *BRCA2* has become standard of care for women and men who are at familial risk for breast or ovarian cancer. Currently, genetic testing more often also includes so-called panel genes, which are assumed to be moderate-risk genes for breast cancer. Recently, new large-scale studies provided more information about the risk estimation of those genes. The utilization of information on panel genes with regard to their association with the individual breast cancer risk might become part of future clinical practice. Furthermore, large efforts have been made to understand the influence of common genetic variants with a low impact on breast cancer risk. For this purpose, almost 450 000 individuals have been genotyped for almost 500 000 genetic variants in the OncoArray project. Based on first results it can be assumed that – together with previously identified common variants – more than 170 breast cancer risk single nucleotide polymorphisms can explain up to 18% of familial breast cancer risk. The knowledge about genetic and non-genetic risk factors and its implementation in clinical practice could especially be of use for individualized prevention. This includes an individualized risk prediction as well as the individualized selection of screening methods regarding imaging and possible lifestyle interventions. The aim of this review is to summarize the most recent developments in this area and to provide an overview on breast cancer risk genes, risk prediction models and their utilization for the individual patient.

ZUSAMMENFASSUNG

In den letzten 2 Jahrzehnten wurden genetische Testungen zur Erkennung von *BRCA1*- und *BRCA2*-Mutationen Teil der Standardversorgung für Personen mit einem erhöhten familiären Risiko, an Brust- oder Eierstockkrebs zu erkranken. Zurzeit wird bei genetischen Testungen immer öfters auch nach Mutationen in sogenannten Panel-Genen gesucht, von denen angenommen wird, dass sie mit einem mittleren Erkrankungsrisiko für Brustkrebs einhergehen. Vor Kurzem wurden die Ergebnisse neuer großangelegter Studien publiziert, die mehr Informationen über die Risikoabschätzung für diese Gene bieten. Die Nutzung dieses neuen Wissens über Panel-Gene und des damit verbundenen individuellen Erkrankungsrisikos könnte in Zukunft klinischer Alltag sein. Dazu kommt, dass auch große Anstrengungen unternommen wurden, um den Einfluss häufig vorkommender genetischer Varianten, die nur geringe Auswirkungen auf das Brustkrebsrisiko haben, zu verstehen. Zu diesem Zwecke wurde im Zuge des OncoArray-Projekts eine Genotypisierung von annähernd 500 000 genetischen Varianten bei fast 450 000 Personen vorgenommen. Basierend auf den ersten Zwischenergebnissen wird nun angenommen, dass es zusammen mit den bereits zuvor identifizierten häufig vorkommenden Varianten mehr als 170 Einzelnukleotid-Polymorphismen gibt, die ein Brustkrebsrisiko bergen und die bis zu 18 % des familiären Risikos, an Brustkrebs zu erkranken, erklären können. Die Umsetzung des Wissens von genetischen und nicht genetischen Risikofaktoren in die klinische Praxis könnte besonders für individuelle Präventionsmaßnahmen von Nutzen sein. Hierzu zählen sowohl die individuelle Risikovorhersage, die individualisierte Auswahl von bildgebenden Verfahren für Vorsorgeuntersuchungen sowie potenzielle Lebensstil-Interventionen. Ziel dieses Artikels ist es, die neuesten Entwicklungen auf diesem Gebiet zusammenzufassen sowie einen Überblick über Brustkrebsrisikogene, Risikovorhersagemodelle und deren Nutzen für individuelle Patientinnen zu geben.

Genetic Variants of High and Moderate Penetrance

With technical advances, continuously falling genotyping costs and easier access to databases for the interpretation of genotyping results, genetic testing is on the verge of a broader implementation in clinical practice. Testing for *BRCA1* and *BRCA2* is already part of clinical routine testing according to current guidelines [1, 2]. Further genes belong to a so-called panel testing [2] and seem – under trial conditions – not to be harmful with regard to clinical decisions based on the availability of those results [3]. While many of these genes have a function in the context of homologous repair *(BRCA1/2, BARD1, BRIP1, PALB2, RAD51C/D, NBN, MRE11, ATM)*, others have been described to come out of a different or to have an additional functional context *(TP53, PTEN, STK11, CDH1, CHEK2, ATM, MLH1, MSH2, MSH6, PMS2)*.

A broader application of genetic testing might be problematic with regard to several considerations. One aspect is the knowledge about risk effects and clinical implications: Most of the mutations in panel genes are rare. *CHEK2* is the most frequently mutated gene after *BRCA1/2* and has mutation frequencies in breast cancer patients of about 1.5 % and in healthy individuals of about 0.65 % [4]. All other mutations are observed less frequently. Therefore, in these mutations an interpretation with regard to breast cancer risk and clinical implications (e.g. therapy efficacy or prognosis) is more difficult than in *BRCA1/2*. The discussion concerning the prognostic relevance of *BRCA1/2*, for instance, is still ongoing [5, 6], which makes it clear that respective knowledge is specifically missing even more in rarer panel genes. Large studies in triple negative breast cancer (TNBC) also do not yield a high enough sample size to address the clinical meaning of panel genes other than *BRCA1/2* in this patient population [7]. Another aspect is that an increase of genetic testing also leads to an increase of genetic test results that have to be interpreted as variants of uncertain significance [8]. These examples illustrate that still a lot of knowledge has to be acquired before these genes can be added to routine treatment or screening recommendations.

However, the interpretation of genetic variants becomes easier with genetic information from large databases being available for approved research projects. Examples for these datasets and databases are the Exome Aggregation Consortium (ExAC) [9], the FLOSSIES dataset [10], The Cancer Genome Atlas (TCGA) [11] or the database of Genotypes and Phenotypes (dbGaP) [12]. There are several examples on how these data are used for risk calculations of rarer panel genes [4, 13, 14]. A large study with more than 65 000 breast cancer patients and healthy women provided odds ratios with reasonable confidence intervals for the majority of the currently used panel genes (▶ **Table 1**). Furthermore, information about the interpretation of test results in clinical practice is also easier to access as findings are provided in structured databases such as the database on clinical variations (ClinVar) [15] or the Genetic Testing Registry (GTR) [17], or are directly exchanged between clinicians and researchers in large international consortia like ENIGMA (Evidence-based Network for the Interpretation of Germline Mutant Alleles) [16]. With regard to unclassified variants, improved in vitro experiments might help in shortening the time frames in which their functional meaning can be assessed [18].

As poly ADP-ribose polymerase (PARP) inhibitors have been approved for the treatment of *BRCA1/2* mutated advanced breast cancer patients [19], genetic testing could be performed in this patient population. In a recent study mutation frequencies of an unselected cohort of advanced breast cancer patients have been described for *BRCA1/2* and other panel genes [20], which could help in deciding what kind of specified patient collective should be screened for genetic testing. Information about therapy efficacy of chemotherapy, PARP inhibitors or immunotherapies is still completely missing regarding the other panel genes.

▶ **Table 1** Panel genes for breast cancer.

Gene	Mutation frequency	Risk for breast cancer
BRCA1	15.9 [103]*	72% (95% CI, 65–79%) risk at age 80 [104]
BRCA2	8.3 [103]*	69% (95% CI, 61–77%) risk at age 80 [104]
TP53	1 : 5000–1 : 20 000**	50–90% lifetime risk [105]
PTEN	1 : 200 000**	50–85% lifetime risk [106]
STK11	1 : 8000–1 : 200 000**	32–54% lifetime risk [107]
CDH1	Unknown**	52% risk of lobular breast cancer at age 75 [108]
PALB2	0.80 [4]***	OR 7.46 (95% CI, 5.12–11.19; $p = 4.31 \times 10^{-38}$) lifetime risk [4]
RAD51D	0.07 [4]***	OR 3.07 (95% CI, 1.21–7.88; p = 0.01) lifetime risk [4]
ATM	0.94 [4]***	OR 2.78 (95% CI, 2.22–3.62; $p = 2.42 \times 10^{-19}$) lifetime risk [4]
CHEK2	1.46 [4]***	OR 2.26 (95% CI, 1.89–2.72; $p = 1.75 \times 10^{-20}$) lifetime risk [4]
BARD1	0.18 [4]***	OR 2.16 (95% CI, 1.31–3.63; $p = 2.26 \times 10^{-3}$) lifetime risk [4]
MSH6	0.21 [4]***	OR 1.93 (95% CI, 1.16–3.27; p = 0.01) lifetime risk [4]
BRIP1	0.25 [4]***	OR 1.63 (95% CI, 1.11–2.41; p = 0.01) lifetime risk [4]
MSH2	0.06 [4]***	OR 2.46 (95% CI, 0.81–6.93; p = 0.11) lifetime risk [4]
MLH1	0.03 [4]***	OR 1.15 (95% CI, 0.30–4.19; p > 0.99) lifetime risk [4]
NBN	0.17 [4]***	OR 1.13 (95% CI, 0.73–1.75; p = 0.59) lifetime risk [4]
MRE11A	0.07 [4]***	OR 0.86 (95% CI, 0.46–1.57; p = 0.65) lifetime risk [4]
PMS2	0.11 [4]***	OR 0.82 (95% CI, 0.44–1.47; p = 0.56) lifetime risk [4]
RAD51C	0.09 [4]***	OR 0.78 (95% CI, 0.47–1.37; p = 0.43) lifetime risk [4]

* Mutation frequency in German high risk families with breast and/or ovarian cancer according to the family criteria of the German Consortium for Hereditary Breast and Ovarian Cancer.

** Mutation frequency in the general population.

*** Mutation frequency in Northern American families with breast, ovarian, colorectal or pancreatic cancer.

Abbreviations: OR: odds ratio; CI: confidence interval.

Genetic Variants of Low Penetrance

Up to 2013 a total of 26 single nucleotide polymorphisms (SNPs; common variants) had been discovered by several independent genome wide association studies (GWAS) and one SNP in *CASP8* by a candidate gene approach [21–34]. These common variants explain up to 9% of the excess of familial breast cancer. Together with high penetrance mutations in genes like *BRCA1, BRCA2, PALB2* and further alleles in moderate-risk genes like *ATM, CHEK2* and others, another ~ 20% could be explained, so that taken together at that time up to 29% of familial breast cancer could be explained [33].

After the validation of these 27 common variants an unparalleled effort was made to join more than 55 000 breast cancer patients and 53 000 healthy women with germline DNA and clinical data available to identify and validate further common variants. For that purpose, the Collaborative Oncological Gene-environment Study (COGS; https://www.nature.com/icogs/) was formed designing an Illumina custom iSelect SNP genotyping array (iCOGS array) comprising more than 210 000 SNPs selected from previous GWAS and candidate gene nominations [35]. This project increased the number of validated common risk variants first to 77 [35–38] and by a further meta-analysis together with other GWAS to a total of 102 SNPs [39]. With these loci ~ 16% of familial breast cancer risk could be explained with common risk variants.

With about 36% (20% due to higher penetrance alleles and 16% due to common risk variants) of familial breast cancer risk explainable, further genetic risk factors have to be assumed to complete the knowledge about familial breast cancer risk. One of the most recent efforts is the OncoArray network [40] (https://epi.grants.cancer.gov/oncoarray/). In this further attempt a chip with more than 530 000 SNPs was constructed. These SNPs comprised about 230 000 SNPs serving as a GWAS backbone. Further about 330 000 SNPs were selected by several consortia (TRICL, BCAC/DRIVE/CIMBA, FOCI/OCAC, ELLIPSE/PRACTICAL and CORECT) for several reasons (e.g. fine-mapping, SNPs from existing GWAS, rare variants, candidate SNPs, SNPs from relevant tumor genes, functional SNPs, SNPs associated with survival) [40]. Of those SNPs more than 494 000 passed quality control and more than 447 000 samples were successfully genotyped from patients with breast, colon, lung, ovary and prostate cancer as well as from healthy women in the control group. With these data a genome wide association study could be performed with more than 137 000 breast cancer patients and more than 119 000 healthy women. This revealed an additional 75 common variants that could be validated as breast cancer risk loci [41,42]. We have summarized all validated risk SNPs in ▶ **Table 2**, along with the

▶ **Table 2** Validated SNPs in sporadic breast cancer.

Region; Closest Gene	SNP-Number (MAF)	OR (95% CI), Citation
1p36.22; *PEX14*	rs616488 (0.33)	0.94 (0.92–0.96) [35]
1p36.13; *KLHDC7A*	rs2992756 (0.49)	1.06 (1.04–1.08) [41]
1p34.2; *HIVEP3*	rs79724016 (0.03)	0.93 (0.88–0.97) [41]
1p34.2	rs4233486 (0.36)	0.97 (0.95–0.98) [41]
1p34.1; *PIK3R3*	rs1707302 (0.34)	0.96 (0.95–0.98) [41]
1p32.3	rs140850326 (0.49)	0.97 (0.95–0.99) [41]
1p22.3	rs17426269 (0.15)	1.05 (1.02–1.07) [41]
1p13.2; *AP4B1, DCLRE1B*	rs11552449 (0.17)	1.07 (1.04–1.10) [35]
1p12	rs7529522 (0.23)	1.06 (1.04–1.08) [41]
1p11.2; *EMBP1*	rs11249433 (0.40)	1.09 (1.07–1.11) [27, 35]
1q21.1; *NBPF10, RNF115*	rs12405132 (0.36)	0.95 (0.93–0.97) [39]
1q21.2; *OTUD7B*	rs12048493 (0.34)	1.07 (1.05–1.10) [39]
1q22; *TRIM46*	rs4971059 (0.35)	1.05 (1.03–1.07) [41]
1q32.1; *MDM4*	rs4245739 (0.26)	1.02 (1.00–1.04) [38]
1q32.1; *LGR6*	rs6678914 (0.41)	1.00 (0.98–1.02) [38]
1q32.1; *PHLDA3*	rs35383942 (0.06)	1.12 (1.08–1.17) [41]
1q41; *ESRRG*	rs11117758 (0.21)	0.95 (0.93–0.97) [41]
1q43; *EXO1*	rs72755295 (0.03)	1.15 (1.09–1.22) [39]
2p25.1; *GRHL1*	rs113577745 (0.10)	1.08 (1.05–1.11) [41]
2p24.1	rs12710696 (0.36)	1.04 (1.01–1.06) [38]
2p23.3; *ADCY3*	rs6725517 (0.41)	0.96 (0.94–0.98) [41]
2p23.3; *NCOA1*	rs200648189 (0.19)	0.94 (0.91–0.97) [42]
2q13; *BCL2L11*	rs71801447 (0.06)	1.09 (1.05–1.13) [41]
2q14.2	rs4849887 (0.10)	0.91 (0.88–0.94) [35]
2q31.1; *CDCA7*	rs1550623 (0.16)	0.94 (0.92–0.97) [35]
2q31.1; *METAP1D, DLX1, DLX2*	rs2016394 (0.48)	0.95 (0.93–0.97) [35]
2q33.1; *CASP8*	rs1045485 (0.13)	0.97 (0.94–1.00) [21, 35]
2q35; *LOC101928278, LOC105373874*	rs13387042 (0.47)	0.88 (0.86–0.90) [24, 35, 109]
2q35; *DIRC3*	rs16857609 (0.26)	1.08 (1.06–1.10) [35]
2q36.3	rs12479355 (0.21)	0.96 (0.94–0.98) [41]
3p26.2; *ITPR1, EGOT*	rs6762644 (0.40)	1.07 (1.04–1.09) [35]
3p24.1; *SLC4A7*	rs4973768 (0.47)	1.10 (1.08–1.12) [26, 35]
3p24.1; *TGFBR2*	rs12493607 (0.35)	1.06 (1.03–1.08) [35]
3p21.3	rs6796502 (0.09)	0.92 (0.89–0.95) [39]
3p13; *FOXP1*	rs6805189 (0.48)	0.97 (0.95–0.99) [41]
3p12.1; *VGLL3*	rs13066793 (0.09)	0.94 (0.91–0.97) [41]
3p12.1; *CMSS1, FILIP1L*	rs9833888 (0.22)	1.06 (1.04–1.08) [41]
3q23; *ZBTB38*	rs34207738 (0.41)	1.06 (1.04–1.08) [41]
3q26.31	rs58058861 (0.21)	1.06 (1.04–1.09) [41]
4p14	rs6815814 (0.26)	1.06 (1.04–1.08) [41]
4q21.23; *HELQ*	rs84370124 (0.47)	1.04 (1.02–1.05) [41]

▶ **Table 2** Validated SNPs in sporadic breast cancer. *(Continued)*

Region; Closest Gene	SNP-Number (MAF)	OR (95% CI), Citation
4q22.1; *LOC105 369 192*	rs10022462 (0.44)	1.04 (1.02–1.06) [41]
4q24; *TET2*	rs9790517 (0.23)	1.05 (1.03–1.08) [35]
4q28.1	rs77528541 (0.13)	0.95 (0.92–0.97) [41]
4q34.1; *ADAM29*	rs6828523 (0.13)	0.90 (0.87–0.92) [35]
5p15.33; *TERT*	rs10069690 (0.26)	1.06 (1.04–1.09) [32, 35]
5p15.33; *TERT*	rs2736108 (0.29)	0.94 (0.92–0.95) [36]
5p15.33; *AHRR*	rs116095464 (0.05)	1.06 (1.02–1.10) [41]
5p15.1; *LOC401176*	rs13162653 (0.45)	0.95 (0.93–0.97) [39]
5p13.3; *SUB1*	rs2012709 (0.46)	1.05 (1.03–1.08) [39]
5p12	rs10941679 (0.25)	1.13 (1.10–1.15) [25, 35]
5q11.1	rs35951924 (0.32)	0.95(0.93–0.97) [41]
5q11.1	rs72749841 (0.16)	0.93(0.91–0.96) [41]
5q11.2; *MAP3K1*	rs889312 (0.28)	1.12 (1.10–1.15) [22, 35]
5q11.2; *RAB3C*	rs10472076 (0.38)	1.05 (1.03–1.07) [35]
5q12.1; *PDE4D*	rs1353747 (0.10)	0.92 (0.89–0.95) [35]
5q14; *ATG10*	rs7707921 (0.23)	0.93 (0.91–0.95) [39]
5q22.1; *NREP*	rs6882649 (0.34)	0.97(0.95–0.99) [41]
5q31.1; *HSPA4*	rs6596100 (0.25)	0.94(0.92–0.96) [41]
5q33.3; *EBF1*	rs1432679 (0.43)	1.07 (1.05–1.09) [35]
5q35.1	rs4562056 (0.33)	1.05(1.03–1.07) [41]
6p25.3; *FOXQ1*	rs11242675 (0.39)	0.94 (0.92–0.96) [35]
6p23; *ANBP9*	rs204247 (0.43)	1.05 (1.03–1.07) [35]
6p22.3; *ATXN1*	rs3819405 (0.33)	0.96 (0.94–0.97) [41]
6p22.3; *CDKAL1*	rs2223621 (0.38)	1.04 (1.02–1.06) [41]
6p22.2	rs71557345 (0.07)	0.92 (0.88–0.96) [41]
6p22.1	rs9257408 (0.38)	1.05 (1.03–1.08) [39]
6q14; *LOC105377871*	rs17530068	1.12 (1.08–1.16) [34]
6q14.1	rs12207986 (0.47)	0.97 (0.95–0.98) [41]
6q14.1	rs17529111 (0.22)	1.05 (1.03–1.08) [35]
6q23.1; *L3MBTL3*	rs6569648 (0.23)	0.93 (0.90–0.95) [42]
6q25; *ESR1*	rs9383938	1.20 [34]
6q25; *ESR1*	rs2046210 (0.34)	1.08 (1.06–1.10) [28, 35]
6q25; *ESR1*	rs3757318 (0.07)	1.16 (1.12–1.21) [30, 35]
7p15.3; *DNAH11, CDCA7L*	rs7971 (0.35)	0.96 (0.94–0.98) [41]
7p15.1; *CUX1*	rs17156577 (0.11)	1.05 (1.02–1.08) [41]
7q21.3	rs17268829 (0.28)	1.05 (1.03–1.07) [41]
7q22.1; *CUX1*	rs71559437 (0.12)	0.93 (0.91–0.96) [41]
7q32.3; *FLJ43663*	rs4593472 (0.35)	0.95 (0.94–0.97) [39]
7q35; *ARHGEF5, NOBOX*	rs720475 (0.25)	0.94 (0.92–0.96) [35]
8p23.3; *RPL23AP53*	rs66823261 (0.23)	1.09 (1.06–1.12) [42]

Continued next page

▶ **Table 2** Validated SNPs in sporadic breast cancer. *(Continued)*

Region; Closest Gene	SNP-Number (MAF)	OR (95% CI), Citation
8p21.1	rs9693444 (0.32)	1.07 (1.05–1.09) [35]
8p11.23; *LOC102723593*	rs13365225 (0.17)	0.95 (0.93–0.98) [39]
8q21.11	rs6472903 (0.18)	0.91 (0.89–0.93) [35]
8q21.13; *HNF4G*	rs2943559 (0.07)	1.13 (1.09–1.17) [35]
8q22.3	rs514192 (0.32)	1.05 (1.03–1.07) [41]
8q23.1; *ZFPM3*	rs12546444 (0.10)	0.93 (0.91–0.96) [41]
8q23.3; *LINC00536*	rs13267382 (0.36)	1.05 (1.03–1.07) [39]
8q24	rs13281615 (0.41)	1.09 (1.07–1.12) [22, 35]
8q24.13; *ANXA13*	rs17350191 (0.34)	1.07 (1.04–1.09) [42]
8q24.13	rs58847541 (0.15)	1.08 (1.05–1.10) [41]
8q24.21; *MIR1208*	rs11780156 (0.16)	1.07 (1.04–1.10) [35]
9p21.3; *CDKN2A/B*	rs1011970 (0.17)	1.06 (1.03–1.08) [30, 35]
9q31; *LOC105376214*	rs865686 (0.38)	0.89 (0.88–0.91) [31, 35]
9q31.2; *TP63*	rs10759243 (0.39)	1.06 (1.03–1.08) [35]
9q33.1; *ASTN2*	rs1895062 (0.41)	0.94 (0.92–0.95) [41]
9q33.3; *LMX1B*	rs10760444 (0.43)	1.03 (1.02–1.05) [41]
9q34.2; *ABO*	rs8176636 (0.20)	1.03 (1.01–1.06) [41]
10p15.1; *ANKRD16*	rs2380205 (0.44)	0.98 (0.96–1.00) [30, 35]
10p14	rs67958007 (0.12)	1.09 (1.06–1.12) [41]
10p12.31; *DNAJC1*	rs11814448 (0.02)	1.26 (1.18–1.35) [35]
10p12.31; *DNAJC1*	rs7072776 (0.29)	1.07 (1.05–1.09) [35]
10q21.2; *ZNF365*	rs10995190 (0.16)	0.86 (0.84–0.88) [30, 35]
10q22.3; *ZMIZ1*	rs704010 (0.38)	1.08 (1.06–1.10) [30, 35]
10q23.33	rs140936696 (0.18)	1.04 (1.02–1.07) [41]
10q25.2; *TCF7L2*	rs7904519 (0.46)	1.06 (1.04–1.08) [35]
10q26.12	rs11199914 (0.32)	0.95 (0.93–0.96) [35]
10q26.13; *FGFR2*	rs2981579 (0.40)	1.27 (1.24–1.29) [30, 35]
10q26.13; *FGFR2*	rs2981582 (0.40)	1.27 (1.24–1.29) [22, 35]
11p15.5; *LSP1*	rs3817198 (0.31)	1.07 (1.05–1.09) [22, 35]
11p15; *PIDD1*	rs6597981 (0.48)	0.96 (0.94–0.97) [41]
11q13.1	rs3903072 (0.47)	0.95 (0.93–0.96) [35]
11q13.3; *CCND1*	rs554219 (0.12)	1.33 (1.28–1.37) [37]
11q13.3; *CCND1*	rs614367 (0.15)	1.21 (1.18–1.24) [30, 35]
11q13.3; *CCND1*	rs75915166 (0.06)	1.38 (1.32–1.44) [37]
11q22.3; *KDELC2*	rs11374964 (0.42)	0.94 (0.92–0.96) [42]
11q22.3; *KDELC2*	rs74911261 (0.02)	0.82 (0.75–0.89) [42]
11q24.3	rs11820646 (0.41)	0.95 (0.93–0.97) [35]
12p13.1	rs12422552 (0.26)	1.05 (1.03–1.07) [35]

▶ **Table 2** Validated SNPs in sporadic breast cancer. *(Continued)*

Region; Closest Gene	SNP-Number (MAF)	OR (95% CI), Citation
12p11.22; *PTHLH*	rs10771399 (0.12)	0.86 (0.83–0.88) [33, 35]
12p11.22; *PTHLH*	rs1975930	1.22 [34]
12q21.31	rs202049448 (0.34)	0.95 (0.93–0.97) [41]
12q22 *NTN4*	rs17356907 0.30)	0.91 (0.89–0.93) [35]
12q24; *LOC105370003*	rs1292011 (0.42)	0.92 (0.90–0.94) [33, 35]
12q24.31	rs206966 (0.16)	1.05 (1.02–1.07) [41]
13q13.1; *BRCA2*	rs11571833 (0.01)	1.26 (1.14–1.39) [35]
14q13.3; *PAX9*	rs2236007 (0.21)	0.93 (0.91–0.95) [35]
14q24.1; *RAD51B*	rs999737 (0.23)	0.92 (0.90–0.94) [27, 35]
14q24.1; *RAD51B*	rs2588809 (0.16)	1.08 (1.05–1.11) [35]
14q32.12; *RIN3*	rs11627032 (0.26)	0.94 (0.92–0.96) [39]
14q32.12; *CCDC88C*	rs941764 (0.34)	1.06 (1.04–1.09) [35]
14q32.33; *ADSSL1*	rs10623258 (0.45)	1.04 (1.02–1.06) [41]
16p13.3; *ADCY9*	rs11076805 (0.25)	0.92 (0.90–0.95) [42]
16q12.1; *TOX3*	rs3803662 (0.26)	1.24 (1.21–1.27) [22, 35]
16q12.2; *FTO*	rs11075995 (0.24)	1.04 (1.02–1.06) [38]
16q12.2; *FTO*	rs17817449 (0.40)	0.93 (0.91–0.95) [35]
16q12.2	rs28539243 (0.49)	1.05 (1.03–1.07) [41]
16q13; *AMFR*	rs2432539 (0.40)	1.03 (1.02–1.05) [41]
16q23.2; *CDYL2*	rs13329835 (0.22)	1.08 (1.05–1.10) [35]
16q24.2	rs4496150 (0.25)	0.96 (0.94–0.98) [41]
17q11.2; *ATAD5*	rs29230520 (0.20)	0.93 (0.91–0.96) [39]
17q21.2; *CNTNAP1*	rs72826962 (0.01)	1.20 (1.11–1.30) [41]
17q21.31; *KANSL1*	rs2532263 (0.19)	0.95 (0.93–0.97) [41]
17q22; *COX11*	rs6504950 (0.28)	0.94 (0.92–0.96) [26, 35]
17q25.3	rs745570 (0.50)	0.95 (0.93–0.97) [39]
18q11.2	rs527616 (0.38)	0.95 (0.93–0.97) [35]
18q11.2; *CHST9*	rs1436904 (0.40)	0.96 (0.94–0.98) [35]
18q12.1; *CDH2*	rs36194942 (0.30)	0.94 (0.91–0.96) [42]
18q12.1; *GAREM1*	rs117618124 (0.05)	0.89 (0.85–0.92) [41]
18q12.3; *SETBP1*	rs6507583 (0.07)	0.91 (0.88–0.95) [39]
19p13.31; *SMG9, KCNN4, LYPD5, ZNF283*	rs3760982 (0.46)	1.06 (1.04–1.08) [35]
19p13.13; *NFIX1*	rs78269692 (0.05)	1.09 (1.04–1.13) [41]
19p13.12	rs2594714 (0.23)	0.97 (0.95–0.99) [41]
19p13.11; *SSBP4*	rs4808801 (0.35)	0.93 (0.91–0.95) [35]
19p13.11; *GATAD2A, MIR640*	rs2965183 (0.35)	1.04 (1.02–1.06) [41]
19p13.11; *MERIT40*	rs2363956 (0.50)	1.01 (0.98–1.04) [110]
19p13.11; *MERIT40*	rs8170 (0.19)	1.04 (1.01–1.06) [29, 35]

Continued next page

▶ **Table 2** Validated SNPs in sporadic breast cancer. *(Continued)*

Region; Closest Gene	SNP-Number (MAF)	OR (95% CI), Citation
19p13.2; *TSPAN16*	rs322144 (0.47)	0.95 (0.93–0.97) [42]
19q12; *CCNE*	rs113701136 (0.32)	1.07 (1.04–1.09) [42]
19q13.22; *GIPR*	rs71338792 (0.23)	1.05 (1.03–1.07) [41]
20p12.3; *MCM8*	rs16991615 (0.06)	1.10 (1.06–1.14) [41]
20q11	rs2284378	1.08 (1.05–1.12) [34]
20q13.13	rs6122906 (0.18)	1.05 (1.03–1.07) [41]
21q21.1; *NRIP1*	rs2823093 (0.27)	0.92 (0.90–0.94) [33, 35]
22q12.2; *EMID1, RHBDD3, EWSR1*	rs132390 (0.04)	1.12 (1.07–1.18) [35]
22q13.1; *PLA2G6*	rs738321 (0.38)	0.95 (0.93–0.97) [41]
22q13.2; *MKL1*	rs6001930 (0.11)	1.12 (1.09–1.16) [35]
22q13.2; *XRCC6*	rs73161324 (0.06)	1.06 (1.02–1.09) [41]
22q13.31	rs28512361 (0.11)	1.05 (1.02–1.08) [41]

Abbreviations: SNP: single nucleotide polymorphism; MAF: minor allele frequency; OR: odds ratio; CI: confidence interval.

respective gene names or regions, the minor allele frequencies and the odds ratios. It is assumed that about 18% of the familial relative risk can be explained with these additional common variants [41].

The existing data is a plentiful resource to investigate further questions related to breast cancer with regard to therapy efficacy, prognosis, pathway analyses and gene environment interactions. The influence of common genetic variants on therapy efficacy and prognosis has previously been shown in several breast cancer studies [43–49]. Data from large international consortia additionally contribute to these questions [50–58]. The relation of common variants to well-known environmental risk factors as well as their interaction is of special interest as individuals who are at a higher risk could be identified. Data on this, however, is scarce [59–63], so that future analyses with a focus on this field of research are necessary.

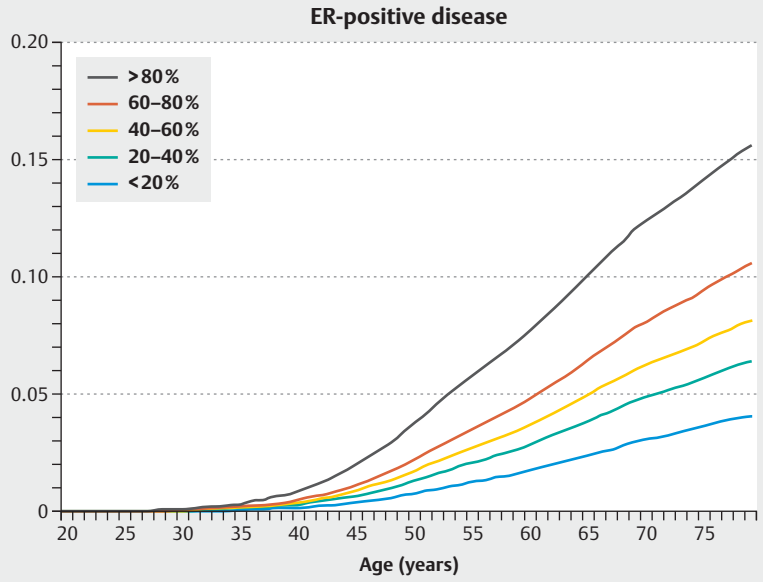
Risk Prediction Tools

With increasing knowledge about genetic and non-genetic risk factors, several risk assessment tools have been developed, validated with clinical data and continuously up-dated over the last decades. Their functionality is shown in ▶ **Table 3**. Each testing tool features different aspects of breast and/or ovarian cancer risk

▶ **Table 3** Breast cancer risk assessment tools.

Risk Factor, Reference	NCI model [111, 112]	Claus model [113]	Tyrer-Cuzick model [65, 79, 114, 115]	BRCAPRO [67, 73]	BOADICEA [66, 71, 72]	Tice [116]	Darabi [117]	Eriksson [118]
Age	+	+	+	+	+	+	+	+
Age at menarche	+		+				+	
Age at menopause			+					+
Body mass index			+				+	+
Age at first birth	+		+				+	
Mammographic density			+			+	+	+
Suspicious mammographic findings								+
History of breast biopsies	+		+			+	+	
History of premalignant lesions	+		+				+	
Hormone replacement therapy			+					+
Family history of breast cancer	+	+	+	+	+		+	+
Family history of ovarian cancer			+	+	+			
Family history of prostate cancer					+			
Family history of pancreatic cancer					+			
Contralateral breast cancer			+	+	+			
Histology of breast cancer				+	+			
BRCA1/2 mutation	+		+	+	+			
Low penetrant genetic variants			(+)				+	
Ethnicity/Ashkenazi Jewish ancestry	+		+	+	+	+	+	
Mastectomy				+				
Oophorectomy				+				

Abbreviations: NCI: National Cancer Institute; BOADICEA: Breast and Ovarian Analysis of Disease Incidence and Carrier Estimation Algorithm.



▶ **Fig. 1** Cumulative lifetime risk of developing estrogen receptor (ER)-*positive* breast cancer for women of European origin by percentiles of the polygenic risk score (PRS). Figure from [75] under the terms of the Creative Commons Attribution License.

and is more or less accurate in risk prediction depending on different risk situations [64]. To improve their performance many models have included different genetic and non-genetic risk factors such as age, body mass index (BMI), menarche and menopause status, hormone replacement therapy, mammographic density, histological characteristics, familial cancer background, ethnicity and others.

Many of these models have lately been developed forward with up-dates and more simplified versions [65 – 69]. In the light of demographic change, assessment tools have also been tested in older people such as the NCI tool for people older than 75 years [70].

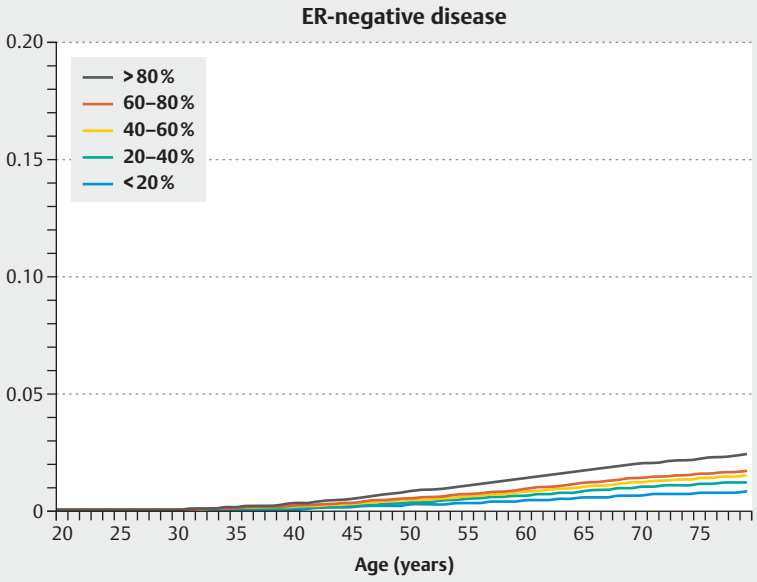
Two of the most commonly used risk models are BOADICEA [66, 71, 72] and BRCAPRO [67, 73]. Besides from predicting age-specific breast and ovarian cancer risks, both models are also capable of predicting the probability of carrying a *BRCA1/2* mutation. Both include a refinement of histopathological features as triple-negativity or estrogen receptor-negativity that increase the risk of a genetic background [66, 67]. Moreover, BRCAPRO considers mastectomy and oophorectomy and imputes age if it is not available from family history [67].

One persisting challenge is the over- and under-estimation of the individual risk by different risk tools. This leads to the issue how to find the right genetic risk tool for a patient. A recent web-based support tool, called iPrevent, can help finding the adequate risk tool for patients. Collins et al. designed a new algorithm for the selection of either BOADICEA or IBIS (= Tyrer-Cuzick model). The Tyrer-Cuzick model performs better at family constellations with fewer family members and is restricted to breast and ovarian cancer. It also includes non-genetic risk factor data like BMI, reproductive factors and personal history of high-risk breast lesions such as atypical hyperplasia and lobular carcinoma in situ. The BOADICEA model performs better at family constellations with more family members and also includes the histology of breast cancer and other cancer types such as pancreatic or prostate cancer. With that question algorithm patients are guided to the more appropriate testing tool and are divided into groups at average, intermediate and high risk [74].

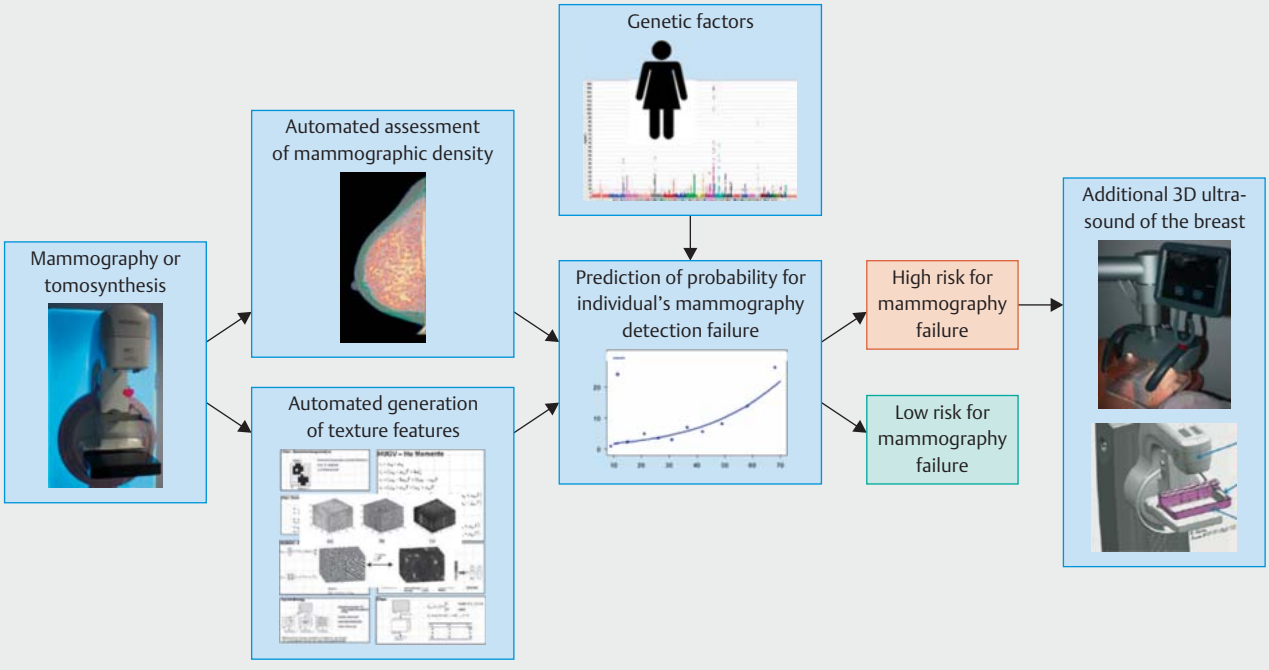
Polygenic Risk Scores

As mentioned above, although the effects on breast cancer risk are rather small, common genetic variants can explain up to 18% of the familial breast cancer risk. Therefore it is reasonable to explore in how far this information can be used for an individual risk prediction and breast cancer prevention. The developed models are usually referred to as polygenic risk scores (PRS). For breast cancer a first PRS based on a comprehensive dataset was developed after the availability of the data from the iCOGS chip and was based on 77 validated breast cancer SNPs [75].

Combining these 77 SNPs into a risk prediction model, lifetime risks and 10-year disease risks for different ages could be provided for both estrogen receptor (ER)-positive and ER-negative disease. For ER-positive disease 20% of the population with the highest risk have a lifetime risk of over 15%, and 20% of the population with the lowest risk have a lifetime risk of under 5% according to this model (▶ **Fig. 1**) [75]. Regarding ER-negative disease, the lifetime



▶ **Fig. 2** Cumulative lifetime risk of developing estrogen receptor (ER)-*negative* breast cancer for women of European origin by percentiles of the polygenic risk score (PRS). Figure from [75] under the terms of the Creative Commons Attribution License.



▶ **Fig. 3** Possible integration of automated mammography assessment and genetic risk assessment into individualized diagnostics for breast cancer.

risks are much lower with around 3% and 1%, respectively (▶ **Fig. 2**). The 10-year disease risk was highest at age 60 and was about 10% for all breast cancer types in the top 1% of the population with the highest risk based on the PRS [75].

Subsequently, several attempts have been made to combine the PRS with non-genetic risk factors and mammographic density [76–82]. The inclusion of the most comprehensive number of SNPs into a breast cancer risk model (Tyrer-Cuzick) showed that risk prediction could be improved. Nevertheless, the prediction by non-genetic risk factors and common variants was independent from each other [79]. Similar results were seen when combining the PRS with the risk factor mammographic density. Risk prediction could be improved, however, genetic factors and mammographic density also predicted risk independently from each other [78]. Mammographic density is of special interest with regard to individualized screening programs and individual accuracy of the mammography.

Screening for Different Risk Populations

It is known that screening programs are not equally effective and equally necessary for all women. Breast cancer screening might be less effective in a population with a low breast cancer risk. Recently, it has also been discussed whether screening programs can effectively reduce mortality because aggressive forms of cancer are missed [83–85]. So the question arises, whether the risk for aggressive forms of breast cancer is high enough in the screened population [86].

Women could possibly benefit from individualized screening methods as mammographic density, diagnostic accuracy and genetic risk factors interact with each other. Several studies have underlined the correlation between certain common variants and mammographic breast density [61, 87–89]. Both, mammographic density and the PRS, contribute to breast cancer risk prediction [78], and from several studies it is known that a high mammographic density reduces the sensitivity of mammography in breast cancer detection [90, 91]. Therefore an individualized algorithm might be helpful in directing individualized screening programs (▶ **Fig. 3**). With technical advances like the fusion of several imaging methods [92, 93], automated assessment of mammographic density [94] and diagnostic accuracy of mammography [95] as well as the integration of big data and machine learning into patient and tumor assessments [96, 97] such individualized screening strategies seem to be feasible and several studies are already ongoing [98–102].

Conclusion

As genetic information on breast cancer is increasing, it is important to interpret all data in a concerted way and to provide healthy women as well as breast cancer patients with sufficient information to facilitate understanding of their individual risk, decision making regarding the appropriate individual prevention strategy and choosing the right treatment option. Risk prediction programs include a growing number of parameters and are getting more precise. In addition, more data on moderate and low risk genes are available. The challenge of the next years will be to translate this knowledge into clinical routine. To provide greater numbers of breast cancer patients with relevant genetic information, it is necessary to further lower the thresholds for genetic testing and to reduce its costs. Furthermore, the integration of germline and somatic genetic data, the expression profile of the tumor as well as clinical data might provide the best treatment for the individual patient. These factors are still being investigated in research settings.

Conflict of Interest

Naiba Nabieva received honoraria from Janssen-Cilag and travel support from Novartis. Michael P. Lux received honoraria from Pfizer, Roche, MSD, Hexal, Novartis, Lilly, AstraZeneca, Celgene, Eisai, medac and Thieme for advisory boards, lectures and travel support. Peter A. Fasching received honoraria from Roche, Pfizer, Novartis and Celgene. His institution conducts research for Novartis. All other authors have declared no conflicts of interest.

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