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Risk-Adjusted Cancer Screening and Prevention (RiskAP):
Complementing Screening for Early Disease Detection by a Learning Screening based on Risk factors

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Executive summary

Cancer screening has been introduced in many western countries, but its effectiveness remains subject of debate, particularly now that **new possibilities to predict cancer** risk are becoming available. These are driven forward by high-throughput “multi-omics” technologies comprising, among others, genomics, transcriptomics and proteomics, which have led to the discovery of new molecular risk factors that seem to interact with each other and with non-genetic risk factors in a multiplicative manner. Personalized risk

prediction by genome-based knowledge and technology opens up new opportunities for increasingly individual-oriented risk-adjusted cancer prevention. Consumer-oriented information systems such as health-related apps and algorithms are already profoundly changing healthcare services. The convergence of such innovative information and biotechnology systems enables the dissemination of risk prediction models that will reinvent the way in which health care providers interact with individuals at risk for certain diseases.

Heritability of cancer overall has been estimated at around 33%, significantly so for skin melanoma, prostate, ovary, breast and several other cancers (1-3). For breast cancer, approximately half of the familial risk has been deciphered, and for this reason it has been the leading use case of this insight in the field of cancer prevention. Based on its genetic make-up, breast cancer can be considered as multiple rare diseases, which are influenced by different lifestyle and environmental factors. Genetic and interacting non-genetic risk factors[1] can also be used to predict future risks in healthy relatives of women affected by breast cancer. This use case will be therefore serving in this paper to illustrate and exemplify the state of the art and the current challenges in cancer prediction.

A variety of **genetic tests for predicting the risk of breast cancer** are already available on the health market, sometimes fueling an expectation to determine the specific risk for developing cancer in any given person solely on these grounds. These genetic tests are used as part of complex algorithms to determine a potentially increased risk of disease, and patients and doctors are increasingly using such tests. However, the ability to categorize risk in this way has advanced more rapidly than the development of evidence regarding the clinical utility for preventive measures. The development of comprehensive genetic and risk literacy of doctors and affected persons has been lagging behind, contributing to an often-uninformed assessment of benefits and harms associated with preventive measures. This, in turn, can lead to ill-informed management choices, potentially causing harm through unnecessary medical interventions and generating unnecessary expenses. For this reason, in a general population screening, specific clinical measures based on the sole risk prediction through genetic testing is **not justified**, as has been outlined by public health groups (4-6). On the other hand, ignoring the potential for genetic testing to improve the benefit/harm ratio for patients and populations, may impede the creation of effective strategies to improve current approaches to screening and prevention.

Introducing predictive genetic testing and risk assessment into breast cancer population screening programs in order to improve clinical care and impact on prevention will disrupt current practice and require a continuous **balancing of rigorous outcome evaluation and timely adaptation** of the health care system. Therefore, we propose a **multi-step translational concept**, which allows health care systems to meet the current demand for genetic testing while capturing evidence about its clinical utility at the same time. Specifically, the offer of risk-predictive testing should be integrated into an **evidence- or knowledge-**

[1] The distinguishment between risk factors and indicators, e.g. according to the Bradford-Hill criteria, becomes increasingly blurred the more complex the risk determination for a disease becomes. This holds true for both non-genetic and genetic risk factors. Therefore, in this paper, both factors and indicators will be simply denoted as “factors”.

generating care concept, allowing for safe and quality-controlled use of genetic testing in a clinical setting coupled with consistent recording of costs and interventions over time, impact on overall and cancer-free survival and including patient-reported outcomes around quality of life. This extended framework of data collection, eased by the newly available digital solutions for data collection, may facilitate the move towards a learning health system that allows the use of state-of-the-art technology in clinical care and at the same time complements evidence-based medicine. Also, clinical guidelines can be continuously monitored for concordance with intended patient outcome, and adapted if deemed necessary.

Key components for delivery will be translational, comprehensive care centers that are highly specialized in genomic and risk prediction medicine. They should build networks with cancer centers and primary care practitioners. Jointly, they will **deliver digitized risk estimations and risk-adjusted preventive measures** based on risk factor-driven, quality-assured, and adaptable risk prediction models. They will also define **common entry points** for administering such risk-assessment, e.g. on the occasion of existing health screening programs for the general population. Such a cross-sectoral care concept will enable the implementation of accepted outcome measures and their connection to data collected in existing and additionally established cancer registries, to ensure long-term follow-up of uptakers of screening with respect to hard endpoints such as mortality, morbidity, and quality of life. This, in turn, will allow for adjustment of the care concept within an iterative knowledge-generating cycle of care. This concept, developed specifically for breast cancer, may serve as a template for other applications of genome-driven medicine such as other hereditary tumor syndromes, in personalized as well as in targeted therapeutic strategies.

I. Introduction

Cancer screening programs have been in place in many countries. So far, existing screening programs focus on the **early diagnosis** of specific diseases, e.g. by way of mammography, or the highly specific search for disease-causing factors, like HPV infection according to well established screening criteria (7). Despite an ever-increasing catalogue of known risk factors for the development of cancers, the selection of the target population for existing screening programs is largely based on age and gender. However, a simple strategy for defining a target population, while administratively pragmatic, is not necessarily the optimal solution for best value, also from a health economic or a health improvement perspective. There are **disadvantages** of population-based screening in which many individuals are invited into a screening program despite being at low personal risk. These include stress and anxiety from the screening intervention itself, waiting for results, and from confirmatory investigation of false positive or inconclusive results requiring unnecessary additional medical interventions. Another problem of age-based population-screening is that it fails to include younger individuals already at risk levels exceeding those defined to enter the screening program, e.g. women with a *BRCA1* or *BRCA2* mutation who can develop breast cancer **much earlier** than the defined age of the screening program (8). Finally, the screening

interval and methodology that is effective for an age-based population may be inappropriate for a population at particularly high risk. E.g., even mammograms starting at age 40 would fail to detect around half the cases of breast cancer in *BRCA1*-gene carriers: These have a median age at onset of 42 years – thus almost half the cases which occur under this age would not be detected.

New knowledge about genetic and non-genetic risk factors, genetic testing and the "omics" revolution are leading to a constantly evolving understanding of **risk profiles**. It therefore seems reasonable to put to use the already existing wealth of knowledge about the multitude of other risk factors besides age and gender and offer risk-adjusted screenings using multi-factor **risk-prediction models** (6, 9-12). Conceptual frameworks have been developed to address the key issues and challenges of **risk-adjusted screening** (13-16). A streamlined intervention program could consider individual risks, including both genetic and non-genetic ones, e.g. family history, lifestyle, and many more, and should be complemented by a well-designed approach to **monitoring outcomes**. These would not only include survival but also patient-reported outcomes and health care costs allowing future analyses and iterative redesign of the program to improve the benefits and minimize the risks.

With increasing awareness and the marketing approach by a multitude of biotech companies, there is a growing **implementation gap** between what is technologically possible and what is available – or refundable by insurances or health care schemes - in practice (17). Therefore, people are increasingly accessing private options for genetic testing known as "direct to consumer tests" (DTC), whose availability is accelerated by laboratories having an incentive to introduce and offer new genetic tests at an astounding rate (18). These private options are not always well regulated and do not collect outcome data – posing a challenge for safeguarding scientific quality and not documenting or even taking into account clinical utility (19).This leads to a "data drain" from the clinical-scientific towards the commercial sector at a time when data sharing and data mining should enable reliable, evaluated and high-quality clinical data which is ever more vital for improving health care in a responsible way. The investigation of causal factors and model calibration in less common sub-types of disease, as, i.e., knowledge about the genetic factors of sub-types becomes more and more differentiated, in turn requires data collections of a size hitherto unavailable.

Because of its potential to **revolutionize or disrupt conventional medicine**, genome-based health information and technologies (GBHIT) have attracted the attention of health policy-makers throughout Europe. In the recently launched innovative Partnership for Action Against Cancer (iPAAC) Joint Action (JA), whose main objective is to implement innovative approaches to cancer control, one of the top priorities is to integrate genomics in the health care system (www.ipaac.eu). The current initiative takes up on the groundwork of the Public Health Genomics European Network (PHGEN) under the EU health program, which has provided a best practice guideline for quality assurance, provision and use of GBHIT following the public health *trias*, i.e. assessment, policy development and assurance (http://www.phgen.eu)/, in their "Declaration of Rome" from 2012 (5). Priority setting of the PHGEN comprises, among others, the improvement of genetic literacy and knowledge transfer by the provision of education programs and the involvement of electronic and mass media, the investment in dedicated

infrastructures and databases and the stimulation of research to produce evidence for clinical utility as well as cost-effectiveness. Moreover, it seems desirable that public health assessment should also take into account *personal utility* given the uniqueness of each individual genome, and beyond inter-individual *clinical utility* (5, 20). While demonstration of clinical utility is considered a prerequisite for clinical translation, the challenge is how to deal with the trade-off between the available evidence and timing the introduction of GBHIT since the evaluation of **clinical utility** is often lagging behind the market launch of genetic tests.

For adopting new health care options, including any new screening program, prospective randomized studies are considered gold standard in the hierarchy of evidence. In this respect, a risk-adjusted surveillance strategy could be compared to current standard population screening in a cluster randomized trial. However, such a trial would need to involve a very large population base, potentially be multi-national and may raise insurmountable ethical and practical barriers to a successful conclusion.

To **close this gap**, it should be possible to collect data that demonstrates clinical utility whilst already integrating genome-based selection tests for entry to clinical screening and care (21). This could be done by way of a multi-step evaluation of clinical utility, thus creating evidence and benefit at the same time, by complementing traditional evidence-based evaluation with evidence-generating clinical care. One option within this context is the "coverage with evidence development" (CED) approach which provides provisional access to novel medical interventions while the evidence needed to assess the value of an intervention, and consequently to make coverage unconditional, is generated (cf., elaborating chances and disadvantages of this approach with specific respect to the German regulatory situation: (22)). CED – in some way or form – has already been implemented in many countries throughout the world, usually as part of an established policy framework. In consequence, it is also known under various terms such as 'interim funding', 'only in research (OIR)', 'still in clinical research', and 'conditionally funded field evaluation (CFFE)'. Following such an approach would generally accommodate the rising demand of patients and doctors to use the array of available GBHIT applications, and ensure that the testing is quality-assured and the outcomes are carefully collected and collated. At the same time, clinical outcomes can be assessed confirming whether a) specific genetic alterations are associated with increased disease risk, b) genetic variants are indicative of the presence of specific clinical criteria and a predictable disease course, and c) the application of this approach to cancer screening leads to clinical interventions with improved outcome, i.e. reduction of morbidity and mortality and/or increase in quality of life.

This proposed approach would allow for **potentially more effective screening** than currently offered. Adjusting screening to fit individual risk profiles should minimize harmful effects and maximize the benefits of screening. At the same time, the generation of new medical knowledge about risk factors and their influence on disease development and prognosis could be captured for ongoing research into clinical applications of the new genomic data.

If knowledge-based conventional screening can be complemented by knowledge-generating risk-adjusted screening, it can ensure that consumers have structured and equal access to such genetically driven risk

predictions as well as clinical programs based on them (23, 24) Nevertheless, this concept requires the formation of cross-sectoral networks between highly specialized units and health care providers to guarantee **high quality genetic testing and clinical interpretation**. It also needs to be accompanied by **communication and teaching programs** in order to facilitate knowledge transfer from specialized centers to primary providers and to improve genetic and risk literacy of consumers (25-28). Finally, the generation of **high-quality clinical evidence** about genetic tests must still be pursued by the best available standards – e.g. by large-scale double-blind controlled clinical trials. By putting the new knowledge to work in the meantime, however, evidence can also be generated within their clinical use and fed back into the chain of knowledge generation. Prospective controlled cohort studies including control groups in combination with registries as prerequisites for outcomes research are considered the optimal setting for these highly translational care concepts thus enabling a dynamic and iterative bench-to-bedside and bedside-to-bench translational continuum (29-31).

In the following, the concept is outlined in more detail.

II. Risk Model Development through a Multi-Step Learning Screening for Breast Cancer: The Concept

While established screening programs aim at the identification of early disease stages, and use screening to grasp the widest-possible part of the population, any screening can these days become increasingly individualized, based on genetic and other factors known to indicate a specifically high (or low) risk.

Current scientific findings on breast cancer suggest that risk-adjusted prevention based on comprehensive risk-assessment considering genetic and non-genetic risk factors may be more effective with respect to clinical outcome and participation rates than existing breast screening programs that offer mammography screening to the general population based on a certain age range.

In general, screening programs attempt to identify occult but already manifest cancers in an early state, allowing for curative treatment and thus better prognosis. Their utility is based on the identification of early stages of disease, ideally before they become noticeable to the individual. Beyond that, **risk-adjusted screening** seeks to identify and detect, in addition to mere age, *individual* risks before, and notwithstanding, the detection of early disease stages. Risk-adjusted screening thus comprises both individual risk-assessment and early detection based on the outcome of that assessment. By exploiting all known and available risk factor information of an individual, as opposed to a single criterion like age, a personalized entry into the screening program becomes possible. Women who reach the risk threshold at earlier ages than the current entry-age can, for example, largely benefit from screening, whereas for women who do not reach that threshold, side-effects and costs can be diminished with a low risk of missing any cancer events. Early detection of breast cancer therefore becomes merely a part of an integrative screening program adapted to individual risk profiles, in which the focus lies not on early

detection but on risk management from the onset, *incorporating* methods of risk detection as needed, but not being limited to them. Specifically, a cascade system of diagnostic measures should be streamlined (a) with the available knowledge on genetic and other risk factors, and (b) with the individual risk of the person at stake.

In a ***multi-step risk-adjusted learning screening program***, risk factors are individually tested first, and with regard to the general population. For breast cancer, validated genetic risk factors exist with respect to mutation prevalence rates in the *BRCA1/2* genes (32-34). Persons positive for certain risk factors (including, as the case lies with current programs, age and gender, but also a variety of other known risk factors such as family history, mutations in risk genes and breast density) are then subjected to the second screening phase which would include a more scrutinized risk assessment, e.g. by the calculation of a comprehensive risk score including, beyond the other risk factors, genetic testing for high, moderate and low risks and their assessment by algorithms, identifying particular high risks by low-invasive means. As a third step, measures for early detection, e.g. intensified early diagnosis and monitoring, are offered in accordance with the individual risk identified in the first two steps. For example, when a person is found to have an average risk, the current screening offers would remain unchanged. Persons with a low risk could be offered less intensive, and persons with an increased risk more comprehensive early detection screening.

In order to identify persons or groups with particularly high or low risk to be offered a **cascading risk assessment, diagnosis and risk-based screening**, existing health screening programs can be **complemented** by a multi-step risk-adjusted learning screening system that includes genetic information and other risk factors. Naturally, the **appropriate time and entrance point** as well as the combination with existing health checkup or cancer screening programs should be made according to the penetrance of the respective disease. As a starting point, women in existing breast cancer mammography screenings could be additionally offered genetic analysis and pertinent non-genetic risk-factor anamnesis according to current knowledge on their impact on disease risk and offered participation in risk-adjusted structured screening programs. However, importantly, there needs to be a **minimum standard of evidence** supporting the declaration of a risk-associated factor that is sufficiently well-substantiated to justify its incorporation into the model. For instance, while sufficient evidence on clinical validity with respect to mutation prevalences and disease penetrances has been established in **specified risk groups**, it is, in most instances, still lacking for the general population, prompting for further research in order to eventually widen risk-assessment as an offer to the general population. At this given time, therefore, risk-adjusted screenings are only feasible for well-studied risk groups, such as high-risk families according to validated anamnestic criteria (35).

Finally, **end-points** can then be collected by amalgamation with, e.g., existing national registries, and other studies. Routinely collecting outcome data could also allow the development of digital systems which continuously generate more evidence on the clinical utility of risk-assessment using these tools, increasing accuracy with increasing amounts of data drawn from rolling this learning screening system out

to the general population, and paving the way to integrating evidence-based risk factor assessments into routine clinical practice in a public screening program.

III. Prerequisites for Justified Screening

The term "screening" seems to have become the subject of a relatively wide, and, accordingly, diverging use in the field.[2] For the purposes of the points made in this article, we define "screening" as a systematic offer of medical diagnostic procedures at group or population level to persons who are not known to the provider to have specific medical symptoms or complaints, targeted to find/exclude latent disease or risk factors for the development of disease, in the interest of the person involved.

The introduction of such a screening program requires **balancing the interests** of stakeholders, and assessing the potential use as well as possible harms and costs of the program. This process is commonly referred to as the justification of a particular screening program, and there has been ongoing discussion in the literature regarding the prerequisites, which need to be fulfilled to consider a program justified (7).

Important points to take into account include the relevance of screening (incidence, prevalence, burden of disease), its clinical benefit (numbers needed to screen; screening failures; interval cancers; positive and negative predictive value influence on morbidity and mortality;), medical risks and harms associated with the screening (over-diagnosis, side-effects, psychological burdens etc.), and matters of equity (access to risk counselling and preventive health care, cut-off levels, ethical aspects of the "healthy ill/sick", reimbursement and communication of risks) (7). These reflect **general trends** in Western countries and medicine, i.e. a shift from paternalism towards informed decision making, the emphasis on managed care models and quality assurance and the importance of serious genetic conditions even if they are rare. These trends also contribute to an increased role of personal utility for individual at stake rather than overall population clinical utility (4, 5). The criteria are in detail:

- The screening program should respond to a recognized need,
- the objectives of screening should be defined from the outset,
- there should be a defined target population,
- there should be scientific evidence of screening program effectiveness,
- the program should integrate education, testing, clinical services and program management,
- there should be quality assurance, with mechanisms to minimize potential risks of screening,
- the program should ensure informed choice, confidentiality and respect for autonomy,
- the program should promote equity and access to screening for the entire target population,

[2] For example, it seems that various practical experiences with the implementation of screening measures in the past have led to many political and societal discussions. Rising awareness and knowledge about risks and risk prediction have done their part to modify the traditional ideas of screening. Many initiatives to personalize risk have become known as "screening" programs, although they extend the original understanding of the term used in the context of an intervention aimed at detecting disease in a target population for the benefit of that population but regardless of the advantage or benefit to each individual.

- program evaluation should be planned from the outset,
- the overall benefits of screening should outweigh the harm.

For most of the mentioned criteria, risk-adjusted screening shows a number of **distinctions** in comparison to established screenings, which focus on a very limited risk assessment (basically, age) to open the gates for early detection. The **additional value** of risk-adjusted screening to determine risk profiles *before* putting a large number of possibly low-risk persons through early detection methods including associated psychological burdens and uncertainties associated with the detection method is an important factor for its ethical justification – since established screening programs fail to take into account the wealth of constantly evolving knowledge and its impacts on cancer risk prediction models.

Andermann (13) adds further considerations to the original criteria for genetic screening policy decisions. The additions reflect the iterative nature of decision-making and the necessary balancing of different perspectives (including individual vs. population viewpoints), comparing alternatives, considering whether implementation in a given context will allow the benefits of screening program to be realized, and emphasizing that adequate governance and regulatory frameworks are required (see below IV.5).

These criteria widely correspond to the "ACCE" model, which has been developed by the Centers of Disease Control and Prevention as early as 2004 to evaluate genetic testing through a series of 44 questions. They emphasize that Analytic validity, Clinical validity, Clinical utility, as well as the compliance with other Ethical, legal & social issues (thus the acronym ACCE, cf. CDC 2004)(36) should be a prerequisite for justified screening, and have also been adopted by the EuroGentest for the development of clinical utility gene cards (37).

Considering the current state of evidence and care situation, sufficient **analytical and clinical validity** should be a **prerequisite** for risk factors to be offered to be analyzed. This means specifically that analytical and clinical validity of risk factors must have been assured, while clinical utility of preventive measures taken on the basis of them can then be gathered by prospective follow-ups and outcome measures and comparison with cancer registries. Importantly, **clinical validity** comprises knowledge about mutation prevalence in the respective screening group as well as age-specific disease penetrances of risk-factor positive subgroups. In turn, only criteria can be included that have been **validated** at least in prospective cohort studies. Other factors which have not been identified or which have not yet shown to be statistically relevant will continue to be assessed by classic methods of clinical trials and research and can, once proven to be of significance, be introduced into risk-assessment of the risk-adjusted screening.

In structured and reimbursed clinical care programs, therefore, only such factors should be analyzed and their results communicated.

The clinical utility of an investigation of risk factors further includes evidence that, in the event of a positive test result, efficient clinical measures are available to reduce the risk of disease or improve prognosis, and that there is, overall, proof that the investigation of a risk factor brings about a positive effect in the endpoint of clinical care.

This pertains to one of the major prerequisites for a screening as defined by Wilson and Jungner above: It is the demand for scientific evidence of **screening program effectiveness**. As outlined, evidence about risk factors' influence on disease development as such, is readily available for many of them, and, naturally, only these factors should be incorporated into a model for risk-adjusted screening. However, the evidence regarding the **overall utility** of risk-adjusted screening has not been comprehensively addressed. In practice, this is mostly **hindered** both by an ever-increasing and constantly changing knowledge about risk factors and their interdependencies, but also by an increasing amount of stratification and ever-smaller subgroups of individual sets of risk factors.

Nevertheless, it remains highly doubtful that newly available and ever-increasing knowledge about further, especially genetic, risk factors, should be held back from the population while waiting for evidence regarding clinical utility of a risk factor model which will only be outdated by the end of the studies. It seems also unlikely that factors which are known to be of analytical and clinical validity and thereby suited to assessing persons' risk to develop a disease should turn out to be of no effect for improving to target the correct persons at risk for screening within a risk-adjusted screening program – which can and should, from the outset, **complement** existing screenings.

Rather, if no comprehensive risk assessment is offered by established clinical care paths, especially the use of privately offered **Direct-to-Consumer** genetic tests will likely increase due to a rising public awareness of genetic risk factors for cancer. However, in many of these tests for genetic risk factors, genetic analyses are performed without reliable knowledge of their disease association. These tests should therefore be rejected in clinical care as they may lead to uncertainty and the risk of unnecessary follow-up tests. Apart from the challenge to **safeguard** their quality and the correct interpretation to consumers, this would also hinder the generation evidence, as results from these tests' use will mostly be scattered among different providers and held in private databases, precluding an integrated evaluation of the used risk factors overall.

For these reasons, we propose that instead of providing screening measures only on the basis of already established evidence about the large-scale outcomes of the specific risk model as a prerequisite, a clear concept for the generation of scientific evidence for a risk-adjusted screening model **over its lifetime and strict ongoing evaluation** should be required for such a risk-adjusted screening, which constantly generates evidence about the model as such, the included risk factors, and multifactorial interdependencies, and which integrates new knowledge over time as it becomes available and proven. In the end, by not withholding newly available knowledge from its integration into care on the grounds of year-long evaluation of the long-term utility of different risk factors, and establishing comprehensive measures for scientific evidence and quality assurance during their use, scientific standards can be safeguarded much more quickly, effectively, and permanently. After all, since the aim of a screening program is to benefit a population of people at risk of developing a severe disease, a multi-step and self-learning screening process of risk-identification alongside safeguarding scientific standards, and the continuous update of reliable evidence for risk factors, should as such be an ethical requirement.

IV. Specific Challenges and Chances of Risk-Adjusted Screening

1. Risk Assessment

One of the major challenges lies in the **determination of individual risks**. As outlined before, the current genetic landscape of breast cancer is complex, with over 300 confidently assigned rare and common risk genes and genetic variants that are associated with high, moderate or small increases in relative risk compared to the population average. These genes and alleles act in a multiplicative manner with each other and non-genetic risk factors. It has become clear that simple Mendelian monogenic traits, in which a limited number of discrete phenotypic outcomes are due to a single gene variant, are an exception rather than the rule.

A number of genetic models to calculate absolute breast cancer risks based on gene test results are available and are continuously being updated with new information. One of the most comprehensive ones is the Breast and Ovarian Analysis of Disease Incidence and Carrier Estimation Algorithm (BOADICEA) (38), an online, CE-marked tool in which information on risk factors can be uploaded to calculate an integrated single risk score for breast and ovarian cancer. Presently, this information includes genetic data (test results of BRCA1, BRCA2, ATM, CHEK2, PALB2, and a SNP-profile), family history, hormonal risk factors, and breast density, among others. The model specifies, in a quantitative way, how these various risk factors interact. It has been validated in a number of prospective breast cancer cohorts, and shows superior calibration relative to other existing models. Since its discriminative power has been established in detail, it can be used to inform risk-adjusted screening approaches in the general population. In order to point out the particularities of genetic and non-genetic factors and their role in the manifestation of disease, breast cancer serves as an example for the general thoughts and arguments on risk-adjusted screening as it has most thoroughly been examined for the classical screening criteria as well as genetic background.

a) Genetic risk factors

After the discovery of the high-risk genes *BRCA1* and *BRCA2,* many countries have introduced gene carrier detection and prevention programs with the aim of reducing disease burden by risk-reducing surgery and improving disease survival by early detection. Published results indicate that these measures are effective with regard to reduced disease penetrance and the detection of early stage tumors although data on hard endpoints are still largely missing due to limited follow-up or study time (39-43). The spectrum and the frequency of gene mutations in particular populations are different, and the strategy for genetic testing should take into consideration the presence of frequent founder mutations. Cost-effectiveness may also be a factor in choosing testing strategies in specific populations.

Recent advances in nucleotide sequencing techniques allow the analysis of unprecedented high numbers of cases and controls, leading to the discovery of additional risk genes and alleles and underlining the genetically heterogeneous nature of breast cancer. Over the next decade, this trend is expected to make whole genome data on large numbers of population-based subjects accessible for genetic research, that will eventually **completely explain** the missing heritability and familial relative risk. Presently, many commercial companies are offering gene panel testing for the prediction of breast cancer risk, comprising all genes for which there is some evidence of association with breast cancer (44). However, according to the proposed ACCE model, only *analytical* validity, i.e., the accuracy with which a test detects the presence of a mutation, has been sufficiently evaluated for these tests. Data on *clinical* validity, i.e., age-specific associations of mutations with disease risks, and clinical utility, i.e., the outcome of preventive measures based on the genetic test results, are largely missing.

Moreover, the breast cancer risks associated with typical rare genetic defects such as those in BRCA1 and BRCA2, can be further modulated by common genetic variation (45) as well as non-genetic risk factors (46). Validation in large population-specific prospective cohorts is largely pending. The combined effect can be calculated as a polygenic risk score (PRS) by risk prediction models, such as BOADICEA, a tool that is constantly extended and improved by ongoing studies such as the HORIOZON2020 funded BRIDGES (PI Peter Devilee) and B-CAST (PI Marjanka Schmidt) studies, and the Genome-Canada funded PERSPECTIVE study (PI Jacque Simard) for the identification and validation of risk genes for breast cancer.

Table 1 summarizes currently known genetic risk factors for which a significantly increased risk for breast cancer has been demonstrated. They are therefore considered to require clinical interventions although their clinical validity with respect to age-specific disease risks and their clinical utility with respect to morbidity and mortality reduction based on the uptake of preventive measures is not sufficiently proven yet.

b) Non-genetic risk factors

For sporadic breast cancer, various **non-genetic risk factors** have been identified with varying levels of evidence, including lifestyle, hormonal and biological factors. Table 2 summarizes the major non-genetic risk factors with strong evidence from prospective cohort studies as the Million Women Study and meta-analyses. Mammographic density and hormone replacement therapy confer relative risks of greater than two whereas the other risk factors remain below a relative risk of 1.5. The factors listed in Table 2 have recently been incorporated in the comprehensive risk prediction model BOADICEA (38).

c) Determination of genetic and non-genetic risk factors and their interaction

As outlined above, a small number of women are genetically predisposed to high risks of disease, but all women will have a certain distribution of the common low risk variants which might modify their risk in either direction away from the population average. It has been estimated that the lifetime risk of overall breast cancer for women in the top 1 percentile of PRS alone (i.e., in the absence of high- or moderate risk alleles) is 32.6% (74). In addition, recent studies indicate that **lifestyle** may also contribute to the disease penetrance. In medicine, lifestyle is defined by specific behaviors of an individual, thus constituting non-genetic risk factors. They can be **influenced by or interact with** genetic factors. Even metabolism of external hormones, food or alcohol depends on the genetic composition of an individual thereby underlining the complex nature of carcinogenesis.[3]

d) Conclusion

In conclusion, one of the biggest challenges for individual risk profiling is to determine which risk factors are to be included into the risk assessment under circumstances that either preclude or hamper collecting clinical evidence. However, this task is not impossible - validating the risk prediction algorithm and defining cut-off points for the offer of either screening or irreversible and life-altering preventive measures such as mastectomies, are essential pre-requisites. A clear and pragmatic procedure for collecting **robust outcome measures** will also be necessary. While more and more risk factors become known, and multi-gene panel testing will continue to include more genes, a **strategy** must be developed in how far and in what way this new knowledge and newly available testing can be integrated into a learning risk-adjusted screening program.

Since there is a lack of prospective evidence for the predictive values from genetic testing, genotype-specific penetrance, spectrum of phenotypes and efficacy of interventions in populations (90), gaining reliable prospective evidence for risk assessment and preventive measures in genetically defined subtypes is of **prior importance**. Calibrating risk prediction models requires sufficient data in a training set and then independent testing in a validation. However, for small sub-groups of cancer types, a much larger overall cancer group would be required as well as sufficient data about the cancer type to sub-group the patients. Patient choice (especially around risk reducing surgery) will impact some outcome measures but provided

[3] Gene-environment association studies are therefore important and will eventually clarify the degree of genetic determination for each of these factors. Recently the BOADICEA tool has therefore incorporated major non-genetic risk factors by an interaction model that allows including these factors into risk stratification. Importantly, this model needs prospective validation, calibration and customization in different countries and populations 38. Lee A, Mavaddat N, Wilcox AN, Cunningham AP, Carver T, Hartley S, et al. BOADICEA: a comprehensive breast cancer risk prediction model incorporating genetic and nongenetic risk factors. Genet Med. 2019.. This can be achieved by large-scale prospective cohort studies preferably undertaken within international collaborations. The breast cancer association consortium (BCAC) and the consortium of investigators of modifiers of BRCA1/2 (CIMBA) represent excellent demonstrators that and how this can be achieved. Integrating such prospective cohorts into clinical care by the proposed cross-sectoral networks with outcome measures enabled by companion registries will allow genomic medicine to be integrated and evaluated in a non-disruptive manner in conventional medicine and will provide everyone with a structured, equitable and transparent access.

all interventions are reliably captured, these would feed into economic modelling and overall survival data to offer the most robust primary end-point. As prospective randomized clinical trials are in general not practical under these circumstances, systematic longitudinal investigations in large populations with full genetic information available, allow estimates of penetrance and clinical disease course (cf. the UK Biobank Study, PMID: 30305743; (91)). Patient-related documentation of large prospective cohort studies offers the ability to evaluate patient outcomes and is a powerful tool to generate evidence. Importantly, interpreting patient data requires checks of internal validity and sometimes the use of external data sources to validate key assumptions. As a prerequisite, entrance criteria need to be based on valid and reliable risk assessments.

2. Risk Communication and Perception

One of the most important aspects of any screening program is that those who are being offered screening should be **fully informed** about the risks and benefits so that they can give a fully informed consent. Accordingly, the communication of risk levels and the understanding by the affected person are of vital importance to meet the goal of screening programs. In particular, medical decisions depend both, on the benefits and risks of interventions as well as on individual preferences and values of persons affected. In the end, a decision is up to the affected person, not the physician: Any person is free to decide whether to undergo any medical intervention and even whether he or she wants to know about their individual risk levels. While recent studies suggest (92) that a majority of 78 % of potentially affected persons wanted to know their risk, 13 % were uncertain and 9 % declined to find out. This may be a fraction of the overall population at risk but a major aspect of personal freedom to be respected.

In order to freely decide to undergo an intervention, the person needs to be provided with true, understandable, and comprehensive information about it. This requires that both affected persons and health professionals understand the risks and benefits of available medical options (such as screening), which, in turn, requires comprehensive risk communication adapted to the individual risk and health literacy level of the affected person.

The risk estimates which need to be communicated can be worked out in a straightforward manner by combining with population incidence rates and pointing out the complexity of risk predictions in light of the immense and growing variety of risk factors.

Raising overall **health and risk literacy levels** in affected persons (and physicians) calls for a societal process. Risk communication can already be much improved by representing the information more effectively so that a person with low health literacy can also understand it. There is a vast amount of literature identifying methods of effective communication (93, 94). The most important recommendations are to use absolute rather than relative risks, to clearly specify the reference class (i.e., the denominator) and the time frame, to use natural frequencies rather than conditional probabilities, and to communicate mortality rather than survival rates. Fact boxes are an example of a successful representation that utilizes all of these principles. They are simple tabular representations of the benefits and harms of particular

treatments and have been developed and tested with laypeople e.g. by Schwartz, Woloshin, and Welch (95). Visual formats such as icon arrays are also a promising way to represent clinical evidence effectively. Most people prefer visual formats over numerical information (96), and particularly people with difficulties to understand numerical information (i.e., low numeracy) may benefit from them (97). More specifically, visual formats help to reduce judgment bias such as the ratio bias (98, 99), framing effects (100), and the undue influence of anecdotes (101). There is some indication that visual formats may be particularly helpful to convey the essential aspects of the information, whereas numerical representations are better to convey more precise aspects (102). Of course, risk communication should not be limited to risk information but should also consider psychosocial and emotional elements (103, 104).

3. Perspective of Persons at Risk

Although great advances in medicine are turning cancer more and more from a deadly into a curable or chronic illness, cancer is still among the most feared diseases. Thus, early detection and preventive measures to lower the risk of cancer development are of very **high interest**. However, risk adjusted cancer screening is a very complex issue as its prerequisites and outcomes concern various aspects of an affected person's life and may also affect the life of related family members.

Before discussing screening details, one important aspect that matters in the discussion about risk adjusted cancer screening concerns the affected person's **fear**. Screened persons may not necessarily be informed about cancer, especially about current preventive and therapeutic chances, their limitations and survival rates. The screening for and determination of risk factors may pose psychological burden of unknown threat to affected persons. People may learn about an elevated cancer risk they never connected to themselves. Therefore, it is of utmost importance to provide information and counseling **adapted** to the people's needs and level of knowledge at every step during the screening process.

Risk communication should be performed in a responsible and comprehensible way and information material presented in plain language and, if feasible, with visualizations. It should explain:

- magnitude and quality of risk assessment
- disease penetrance regarding manageable time frames
- scope of consequences of the particular risk, including effectiveness and side-effects, contributing and competing risks
- implications for care-takers, close others and family
- consequences regarding insurances or future financial plans.

In case risk assessment is performed by genetic testing, a thorough counseling concerning predictive genetic testing by an approved physician and time for consideration are important (cf. infra IV.4). The **right not to know** must be clearly communicated and applied if desired. As knowledge about a genetic predisposition to cancer may lead to insecurities and anxiety, patients should, as part of the information process, have access to psycho-oncologists and be informed about specific self-help groups.

Measures for early detection must be **stratified** according to the risk factors. Patients must be monitored close enough to prevent interval events, but loose enough so that checkups are not present in the patient's life for most of the time. The monitoring process must be as convenient as possible, psychological burdens from it must be addressed, e.g. by patient reported outcome measures (PROM).

In this respect, patients may consider surrogate factors as equally important outcomes, such as availability of less intensive treatment options in case of early diagnosis.

In summary, since risk adjusted cancer screening is addressed to persons at risk but nevertheless healthy individuals, the medical ethos *primum non nocere, secundum cavere, tertium sanare* should be met at every step.

4. Ethical and Legal Requirements

The implementation of screening measures also requires meeting legal, ethical, and social prerequisites. Firstly, the **legal framework** must allow for the implementation of a certain screening. These aspects range from specific regulations regarding informational autonomy, consent into information processing, rules on whether individuals may be contacted in order to participate in a screening, on how they can be motivated to participate, under what circumstances they can refuse to participate, as well as aspects of reimbursement for the measures by statutory health insurances and so forth. Secondly, an important **social aspect** is, that the population needs to be able to accept a screening to be introduced as "sensible". Persons at risk must be willing to participate on the grounds of an advantage to them: It seems natural that the higher the acceptability of a screening measure is and can be communicated to the population the higher the probability of participation and successful screening. Vice versa, it is of vital importance to make the public aware of the advantages of such a screening by streamlined information rather than to concentrate on the mere legal obligation or motivation. Thirdly, **ethical requirements** must be met.

In particular, one of the most important ethical issues is the **autonomy** of the person to be screened. Informed consent of an individual to participation in screening is universally, both legally and ethically, required (Article 3 of the European Charter of Fundamental Rights and specific national rules in the respective member states' jurisdictions (cf. also (105)). This means in turn that the individual must be able to choose for oneself whether to undergo risk-adjusted screening and potential subsequent treatment. Firstly, to guarantee the autonomy of the person and ensure informed consent requires that people to be screened understand why and how their risk is elevated. That is, that they understand based on which factors it is assumed that their risk is elevated (e.g., family history, age, risk-elevating behaviors), how strongly each of these factors alters their risk and to which absolute level, and how certain the knowledge about the various risk factors is. In this regard, people must be informed about what an elevated risk means exactly, which also should be provided in absolute numbers and in comparison to the general population. Secondly, they need to understand potential consequences and their impact. Potential consequences include the need for further testing, which informs whether there is an elevation in the first place and how high it is. Importantly, people also need to know that testing (particularly genetic testing)

can have implications for their relatives. Finally, people need to know about the benefits and harms of preventive measures that would be available if it turns out that their risk is elevated, and how these benefits and harms differ depending on the risk elevation. Importantly, they need to know about the whole chain of potential consequences before even making the first decision, as, for instance, deciding about whether to get genetic tests has to be considered in light of the options that are available given different test results. Personalized **risk communication** to ensure patient autonomy and informed consent is therefore challenging, yet a recent Cochrane review suggests that receiving personalized risk information yields better understanding and more informed choices than receiving general risk information (106).

If prediction is based on genetic research or analysis, **genetic counselling** must generally also be provided by a qualified person, discussing the possible medical, psychological and social questions in connection with the performance or non- performance of the genetic examination and its existing or possible examination results. While national laws differ within Europe, EU treatise (107) provides a common frame of reference, also with regard to the admissibility of genetic screening programs for health purposes in general. From a practical viewpoint, as genetic testing becomes more and more available, and can also increasingly take its role in health care, strategies will foreseeably be necessary to address the growing need of comprehensive and high-quality counseling for the persons considering to undergo genetic testing. Discussions have already ensued regarding the intensity of counseling necessary for undergoing polygenic risk score assessment versus testing for high penetrance genes. There may also be adjustments in the regulatory setting, e.g. on how to deal with incidental findings of other disease risks, and on possible **obligations** for affected persons to share findings of genetic testing with insurance companies and employers including adverse consequences deriving form testing in the long run.

Consent must also be gained regarding the **collection of data**, including the possibility of re-contact, and the particular use of the data, also in case it is to be used for scientific purposes. Local jurisdiction may impose a duty to share certain information, if itis of especially high value for the population as a whole, but regulation varies from country to country (cf., for the European framework, the General Data Protection Regulation (GDPR) and, in particular, Art. 49 para. 1 lit. g and recital 157 (108)). In addition, it needs to be considered how to deal with incidental or secondary findings. Reciprocally to the right to opt out of a screening program, different health care systems can also offer possibilities to increase motivation of individuals to take part in screening programs. Accordingly, both legally and ethically, the implications for the use of collected genetic data by screening must be taken into account: Especially, when samples are stored for future use and could be interposed with additional data to be gathered later, the ownership of samples, data and results is of the essence. Moreover, a secondary use of the resulting risk profiles could result in discrimination by third parties, e.g. insurance companies or employers.

In addition, statutory health care regimes should be updated to allow addressing certain disease risks rather than manifest disease only. This phenomenon has become known as the problem of the "**healthy sick**" – denoting persons currently without symptoms but with a high risk of developing a severe disease over time which could be avoided by early diagnosis and therapy. As many social systems have high

burdens for including new health care measures into their schemes of health care provision (109), it is of essence to identify what treatments and diagnostic measures can be particularly helpful for avoiding manifest disease in the "healthy sick". These can also contribute to cost-effectiveness, as high treatment costs for manifest disease can be avoided by much lower costs for earlier measures whenever a specific risk justifies early diagnosis. The more elaborate the knowledge about specific risks of disease will become due to advancing insights into genetic and other risk factors even before a disease manifests itself, the more important it will be to address the issue of **prevention as a part of an integrative** rather than merely curative health care scheme, and to define specific measures which are covered within its scope (110).

Finally, the prerequisites for implementation of a certain screening program in a given country must allow for the particular **design of the screening**. Legal, but also socio-cultural and ethical rules can be quite different in various jurisdictions (cf., for cervical cancer, an overview of current legal frameworks in (111)). Regarding consent and data protection, the GDPR provides harmonized protection within the jurisdictions of and across the EU. However, prerequisites for an internationally accepted risk-adjusted screening program, which is also financially accounted for in different health care systems, and the offer of a standardized high level of risk-assessment, early detection and treatment across national boards of program and strategy assessment will remain a goal for further international harmonization.

V. Call for Action

The constant gain of knowledge about genetic and non-genetic risk factors must be considered and incorporated into clinical practice rather than ignoring newly gained knowledge. While best quality evidence must continue to be sought, alternatives to RCTs will take short-term advantage of modern technologies whilst continuing to embrace the wider principles set for a public screening program. Ultimately, existing screening programs should be assessed to evaluate whether they can be adapted to accommodate an institutionalized ***multi-step risk-adjusted learning screening system***, which transcends existing approach to screening largely using age and family history to stratify risk (cf., regarding effectiveness of risk-based versus age-based screening, (112)). Persons developing the disease screened for should be offered genetic and pertinent non-genetic assessment, and collected data should be fed into a learning screening system.

Entry-points for screening should be defined according to the state of current knowledge of risk factors and models, stratified by risk groups. Relatives of affected individuals may be the first to be offered the risk adapted screening program. This system should be constantly evaluated regarding forthcoming insight into new genetic and other risk factors, allowing the application of stratified screening strategies, and continuously updating genetic risk-assessment tools within a clinical setting. Eventually, this learning screening system can be rolled out to younger women who may be carriers of genetic mutations as well as, ultimately, more general parts of the population, once evidence on its clinical utility has been established in practice.

On the grounds of the findings laid out above, we believe that the **following steps** should be taken to better target breast cancer and comparable health risks, and to ease the necessary transition from a retrospective approach of early detection screening towards a wider, earlier and more streamlined approach of risk-adjusted prediction, prevention and disease management.

a. Fostering Prospective Outcome Evaluation: Tumor registries complemented by genetic and preventive information

   Prospective cohort studies on the effectiveness of preventive measures based on validated risk factors and documented within registries will allow medical outcome measures as a prerequisite for the transition from age- to risk-adjusted screening. Several nation-wide registries already exist that can be harmonized and merged. Activities supported by the EU such as the **ERN Genturis project** (113) are already ongoing in order to establish a reference network and define a meta-registry for a pan-European development in order to harmonize patient registries and health care pathways. For example, an important outcome parameter to monitor during the implementation of risk-adjusted screening is whether the proportion of detected invasive disease remains the same, while that of over-diagnosis declines. Outcome measures should also be assessed as to whether they are not only medically determined but also patient relevant. An accompanying data protection concept addressing relevant ELSI issues that has already been compiled can serve as a paradigm for different familial tumor syndromes.

b. Research

   In order to justify making risk-adapted screening decisions on the grounds of specific risk factors, these factors need to be sufficiently substantiated by a minimum standard of evidence regarding their clinical validity. For instance, mutation prevalences and disease penetrances have been well established for specified risk groups, proving their relation to the risk of disease development. However, in most instances, such evidence is still lacking for the general population, prompting for **further research** on risk factors for other groups than identified high-risk groups.

   Also, the sensitivity of specific screening modalities depends on histology and genetic make-up. For instance, for a group of high-risk women with dense breast tissue the sensitivity of a mammogram is not sufficient. Therefore, additional imaging procedures such as tomosynthesis and MRI need to be **further explored** in those subgroups.

   Beyond medical utility and evidence, **further investigation** is required regarding the public health outcomes of implementing risk-adjusted screening in health care systems: While we assume that preventing disease instead of treating it will save costs rather than increase them, and, even so, while preemptively avoiding disease development in a person should also have a value of its own, the economic impact of risk-adjusted versus age-based screening should be **modelled and evaluated** as risk-adjusted screening becomes available from the onset, in order to gain health economic

knowledge for policy decisions which will be difficult to gather at a later point in time. Generally, these and other pressing research needs should be addressed by a **dedicated research strategy** for funding and coordinated on a high level, such as national, European, and international research programs and institutions.

c. Strengthening knowledge/evidence-generating networks

Inter- and trans-disciplinary networks need to be strengthened and widened in order to address the specific needs to implement new knowledge into routine clinical work, allowing access to screening services and risk assessment and make a **low-threshold offer** to a wide public. These services need to be fostered by educational programs constantly disseminating the generated evidence and increasing knowledge on genomic medicine with health care professionals and the general public, mainstreaming and keeping up to date the state of knowledge in clinical care. Hospitals and Health Care providers should come up with a concept how to incentivize and implement this approach, e.g. by special contracts and reimbursement with statutory sickness funds. The **German consortium** is currently providing such an approach and could already build up a trans-sectorial network capable of providing nationwide support.

d. Further development of check lists for the identification of target groups

Easy-to-use **checklists** and **guidelines** proved their worth for the identification of target groups, i.e. groups of persons at potentially higher risk, which can be identified more easily by the use of such checklists. They can be adapted to different situations according to the addressee, e.g. for healthcare professionals in practice, for patients and relatives as self-assessment and so forth. The use of an evidence-based, up-to date and comprehensive version of a checklist should be a compulsory requirement in certified cancer centers. As an example, the **German Cancer Society** stipulates the use of a **validated checklist** for the identification of persons at risk for breast cancer in certified breast cancer centers (3, 32, 114).

e. Improving risk and genetic literacy of counselors and counselees

A prerequisite for appropriate risk assessment and communication is the **competence** of health professionals in this field who will, in practice, serve as risk counsellors for the affected persons. However, the steep acceleration of knowledge gain in genomic medicine and risk calculation along with its hasty introduction into clinical diagnostics makes it nearly impossible for health care providers to either effectively deliver or prevent the development. Therefore, additional competencies need to be acquired preferentially within structured and evidence-based educational programs to guide clinicians (27, 91). The improvement of **risk and genetic literacy** both for counselors and counselees is a prerequisite for autonomous decision-making of the persons at stake,

as well as the uptake of risk-adjusted preventive measures. Specific training should be offered as well as specified and up-to date patient decision aids based on the currently best available evidence.

With the introduction of gene panel testing classification of genetic variants has become a major challenge. **Conjoint international activities** such as the ENIGMA consortium and the BRCA challenge aim to build up knowledge bases in order to continuously improve clinical interpretation and decision-making. The incorporation of genetic specialists into interdisciplinary clinical tumor boards would further promote genetic competence of clinical practitioners.

Also, decision coaching by specialized nurses could further support genetic counseling. Moreover, innovative web-based resources such as the **Public Health Genomics Knowledge Base (PHGKB) of the CDC** may support a continuous learning process and connect population-based research with public health applications on clinical genomics (115).

f. Validated risk prediction models
Reliable risk prediction is crucial and risk determination programs such as BOADICEA need to be further developed, as is the case within the EU Horizon 2020 funded BRIDGES project. According to the new medical product law, risk models need to be certified and validated (notwithstanding clinical validation as called for by the ACCE requirement, cf. above), which is best achieved within knowledge-generating networks of care. Networks of expert research centers, cancer centers and primary care practitioners should also jointly deliver **digitized risk estimations** and **risk-adjusted preventive measures** based on risk factor-driven, quality-assured, and adaptable risk prediction models, and define **common entry points** for administering such risk-assessment, e.g. on the occasion of existing health screening programs for the general population, on the basis of disease prevalence (e.g., cf. (12)). The existing knowledge and new findings about risk factors regarding different risk groups should be made available for policy makers and health professionals in **prediction and screening guidelines**.

g. Data safety and ownership
In addition to the considerations above (cf. IV.5), collected data and test results, especially when interpolated with other existing data, should be ensured to remain with the public domain in the long run. They should not be shared with or passed on to commercial interests for **economic purposes** or reasons other than disease control and public health for which the data were collected.

Given these prerequisites, we believe that cancer screening should finally be moving forward from an age-based primary early disease detection towards an **integrated, multi-step and evidence-based risk-adapted approach** in which individual risk assessment would allow a much more precise way of preventing disease for persons at high risk while at the same time saving both cost and adverse outcomes for low-risk persons. Instead of one-size-fits-all early disease detection programs leading to therapy only

when a disease is already manifest, science, medicine and politics should work together to offer **high-quality and evidence-based individualized prevention programs**, or people will resort to privately offered alternatives which can be of varying quality, profit-driven, not centrally evaluated and with uncertain outcomes. While medicine continues towards becoming increasingly individualized both in diagnosis and therapy, screening and disease prevention should, while assuring representation, justification and evaluation, follow and make good use of the new possibilities medical knowledge has to offer.

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