Swiss guideline for counseling and testing for genetic predisposition to breast, ovarian, prostate and pancreatic cancer
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[1]Susanna Stoll, [2]Sheila Unger, [3]*Silvia Azzarello-Burri,[4]*Pierre Chappuis, [5]*Rossella Graffeo, [6]*Gabriella Pichert, [7]*Benno Röthlisberger, [8]*Francois Taban and [9]Salome Riniker on behalf of the Swiss Group for Clinical Cancer Research (SAKK) Network for Cancer Predisposition Testing and Counseling (CPTC)

[1]Stadtspital Waid und Triemli, Zürich
[2]Division of Genetic Medicine, CHUV-Lausanne University Hospital, Lausanne
[3]Institut für Medizinische Genetik der Universität Zürich, Schlieren
[4]Division of Oncology and Division of Genetic Medicine, University Hospitals of Geneva, Genève
[5]Istituto Oncologico della Svizzera Italiana, Ospedale Regionale Bellinzona e Valli, Bellinzona
[6]Onkozentrum Hirslanden, Zürich
[7]Genetica AG, Zürich
[8]Clinic Générale-Beaulieu, Genève
[9]Brustzentrum Kantonsspital St.Gallen, St.Gallen

*these authors contributed equally to this publication

Summary
This paper represents the updated version of the Swiss guideline for genetic counseling and testing of individuals with an increased probability for carrying mutations in high risk cancer predisposition genes , particularly *BRCA1* and *BRCA2*. It aims to help providers of genetic counseling to identify valuable candidates for testing and serves as a basis for reimbursement claims to Swiss insurance companies. The guideline has been approved by the Swiss Group for Clinical Cancer Research (SAKK) Network for Cancer Predisposition Testing and Counseling. The document reflects clinical and scientific advances as of the date of publication, is subject to change and will be updated continuously.

Corresponding author: Sheila Unger, MD, FRCPC
Medecin Chef, PD, MER1
Division of Genetic Medicine
Av. Pierre Decker 5
Centre Hospitalier Universitaire Vaudois
1011 Lausanne
Phone: +41 (0)21 314 32 00
Email: sheila.unger@chuv.ch

Introduction

This paper presents the Swiss guideline for genetic counseling and testing individuals with an increased probability for carrying mutations in high risk cancer predisposition genes, particularly *BRCA1* and *BRCA2*. It aims to help providers of genetic counseling to identify valuable candidates for testing and serves as a basis for reimbursement claims to Swiss insurance companies.

Since the last publication of the "Swiss guidelines for counseling and testing for genetic predisposition to breast and ovarian cancer" in 2017, much progress has been made in the rapidly evolving field of oncogenetics. This prompted us to issue an update of the guideline. The testing criteria will now take into account the expanded spectrum of cancers linked to *BRCA1* and *BRCA2* mutations. When the deleterious effects of pathogenic sequence variants of these genes were first discovered 25 years ago, they were clearly linked to hereditary breast and ovarian cancer (HBOC). However, with the knowledge gained over the last three decades, it is now internationally recognized that not only do other genes cause a hereditary predisposition to breast and ovarian cancer (hence the need for multi-gene panels) but also that mutations in *BRCA1/2* confer elevated risk for other cancers, in particular prostate and pancreatic cancers. The updated guideline also contains testing recommendations for patients with a mutation in a high risk gene detected in tumor tissue (tumor mutation).

In Switzerland testing for genetic predisposition to hereditary cancer syndromes is available in a clinical setting. Cancer risk assessment and genetic counseling are mandatory before and after genetic testing (i.e. pre- and post-test counseling) [1,2]. DNA analysis is covered by health insurance companies only after formal genetic counseling and obtention of informed consent according to the KVL/OPAS/OPre art.12d, let. f [3].

Individuals with a personal or family history suggestive of a hereditary cancer syndrome or those having a pathogenic tumor mutation in a high risk cancer predisposition gene should be referred for counseling and consideration of genetic testing.

The detection of a germline variant in a high risk gene confirms the presence of hereditary predisposition syndrome and is of considerable importance not only for the individual but also for their family members. Pre-symptomatic testing of healthy relatives enables them to be counseled regarding increased risk for the tumors known to be associated with the mutated gene. Intensified screening, prophylactic surgical interventions or chemoprevention should be discussed according to the individual risk situation [1,2,4-6].

Patients with a cancer diagnosis and an alteration in genes involved in DNA repair may benefit from targeted therapies. PARP inhibitors have been shown to be very effective and well tolerated in a growing number of tumors. They are currently admitted in Switzerland for patients with a *BRCA1/2* germline or tumor mutation and ovarian or prostate cancer or with a *BRCA1/2* germline mutation and an advanced breast or pancreatic cancer [7-12].

After identifying a germline variant carrier testing should be offered to close family members [1,2].

BRCA1 and *BRCA2* are the principal genes involved in the hereditary breast and ovarian cancer syndrome. Pathogenic variants in these genes are inherited in an autosomal dominant pattern [1]. The prevalence of germline *BRCA1* and *BRCA2* variants is about 1:400 to 1:800 among healthy women from the Western non-Jewish white population [13,14]. They confer a 72% respective 69% cumulative

risk for a breast cancer and a 44% respective 17% cumulative risk for an ovarian cancer until the age of 80 years [15].

About 3-5% of all breast cancer and 10-15% of unselected invasive ovarian cancer cases are *BRCA*-related [1,4,16]. Defects in other high to moderate risk genes may be present in patients fulfilling clinical testing criteria for *BRCA* mutations [1,17].

The introduction of multi-gene testing has altered the clinical approach to hereditary cancer testing of at-risk patients and their families. Based on next-generation sequencing (NGS) technologies, these tests simultaneously analyze a set of genes that are associated with a specific family cancer phenotype or multiple phenotypes. An individual's personal and/or family history may be explained by more than one inherited cancer syndrome [1]. Thus, a multi-gene panel test is more efficient and cost-effective and increases the detection of pathogenic/likely pathogenic variants in high risk genes over the predicted yield of targeted germline testing based on current clinical guidelines [1,17-21]. Gene panel testing has become the standard of care. However multi-gene panel testing increases the likelihood of finding variants of unknown clinical significance (VUS) [1,18].

Oncology providers should communicate the potential for incidental and secondary germline information to patients before conducting tumor mutation profiling and should review the potential benefits, limitations, and risks before testing. They should carefully ascertain patient preferences regarding the receipt of germline information and allow patients to decline it [18].

Risk-assessment is mainly based on a distinctive personal and/or family history on one or both family sides, as

- early-age of onset of cancer
- increased number of cancer cases across generations
- bilateral breast cancer
- appearance of several typical tumors in the same individual or in close relatives
- special ethnic origin as Ashkenazi Jewish ancestry

[1,2].

Methods

This Guideline is based on the NCCN Guidelines [1] and NICE Guidelines [2]. It was adapted to serve as a national reference paper for Switzerland. The authors elaborated a draft and discussed and revised it with the members of the Swiss Group for Clinical Cancer Research (SAKK) Network for Cancer Predisposition Testing and Counseling (CPTC) during a semi-annual meeting. The consensus recommendations then were summarized and sent to all members of the Network for review. The authors used a systematic review of the literature and clinical experience. The literature review encompassed articles appearing in PubMed between 2017 (first publication of the Swiss Guideline) through May 2021. Phase II and phase III randomized controlled trials were selected if they reported testing indications and management recommendations for carriers with germline mutations in high risk cancer predisposition genes.

Table 1
Swiss guideline for referral, risk assessment, genetic counseling and testing of individuals with a suggested cancer predisposition syndrome

I Carrier testing
- Testing of an individual from a family with a known pathogenic variant in *BRCA1*, *BRCA2* or in another gene conferring high or moderate risk for breast and/or ovarian cancer

II Women with a personal history of breast cancer or DCIS and one of the following
- Age at diagnosis ≤ 40 y (any case) or ≤ 45 y (at oncogeneticist's discretion)
- Triple negative (ER, PR[1] and HER2 negative) BC[2] ≤ 60 y
- Bilateral BC or second separate primary
  - if the first cancer was diagnosed ≤ 50 y
  - with ≥ 1 close relative[3] with BC (if only one relative affected, then age at diagnosis ≤ 50 y)
- Age at diagnosis ≤ 50 y with
  - 1 close relative with BC ≤ 50 y
  - unknown or limited family history[4]
- Diagnosed at any age with
  - ≥ 2 close relatives with BC
  - a close male relative with BC
  - ≥ 1 close relative with ovarian or pancreatic or metastatic/intraductal/cribriform prostate cancer at any age

III Women with a personal history of ovarian cancer[5]
- Non-mucinous epithelial subtypes at any age[6]

IV. Men with a personal history of breast cancer

V. Ashkenazi Jewish heritage
- Search for the 3 founder *BRCA1* and *BRCA2* pathogenic variants[7] regardless of personal or family history

VI. Family history only
- Testing of an unaffected individual when an appropriate affected family member is unavailable for testing with ≥ 1 close relative with breast or ovarian cancer fulfilling one of the above criteria (points II-IV)

VII. Tumor pathogenic variant
- Germline confirmation of a pathogenic variant in a gene conferring high or moderate risk for breast and/or ovarian cancer detected by tumor profiling on any tumor type

VIII. Pancreatic cancer
- Exocrine pancreatic cancer at any age (first step: tumor profiling)
- Unaffected individuals with
  - familial pancreatic cancer (2 first-degree relatives with pancreatic cancer)
  - ≥ 3 individuals with pancreatic cancer (same side of the family)[8]

IX. Prostate cancer
- Metastatic, intraductal or cribriform prostate cancer at any age (first step: tumor profiling)
- High-grade (GS ≥ 7) prostate cancer and
  - Ashkenazi Jewish ancestry
  - 1 close relative with breast cancer (age ≤ 50 y) or ovarian or pancreatic cancer or metastatic/ intraductal/cribriform prostate cancer
  - ≥ 2 close relatives with breast or prostate cancer at any age[8]

[1] ER: Estrogen receptor, PR: Progesterone receptor
[2] BC: Breast cancer
[3] Close relative: First- or second-degree relative on the same side of the family
First-degree relatives: Mother/father, sister/brother, daughter/son
Second-degree relatives: Grandparents, aunt/uncle, niece/nephew, grandchildren
[4] Limited family history: ≤ 2 female close relatives having lived beyond age 45 y in either lineage
[5] Ovarian cancer also includes primary peritoneal cancer and fallopian tube cancer
[6] All epithelial ovarian cancers qualify for testing but high grade serous histology is particularly suspect
[7] BRCA1: c.68_69delAG, c.5266dupC; BRCA2: c.5946delT
[8] In families with only pancreatic cancer or only prostate cancer testing should include other genes associated

with hereditary risk for these tumors

Comments

- Meeting one or more of these criteria warrants further personalized genetic risk assessment and genetic counseling. The following issues should be subject of the discussion: Explanation of inheritance pattern, available testing options, potential findings (pathogenic/likely pathogenic variants, variants of unknown significance (VUS)), disease management, targeted treatment, surveillance and prevention options.
- Consider referral of cases with a limited or uninformative family history or in case of adoption. A limited family history means: ≤ 2 female close relatives having lived beyond age 45 in either lineage [22].
- Borderline ovarian tumor is not considered as part of the spectrum of the hereditary breast/ovarian cancer syndrome.
- Among the Ashkenazi Jewish population, two *BRCA1* and one *BRCA2* founder pathogenic variants (*BRCA1*: c.68_69delAG, c.5266dupC; *BRCA2*: c.5946delT) account for 98-99% of all the mutations identified and are carried by about 2.6% (1/40) of this population [23,24]. Therefore primarily testing for these 3 founder variants is recommended. If no pathogenic variant can be identified a complete analysis of the *BRCA1* and *BRCA2* gene should be complemented as well as testing of further genes depending on the family history [1].
- When no appropriate affected family member is available, testing of a close relative without a cancer diagnosis should be considered [1].
- Genetic testing for adult onset diseases, such as *BRCA1*- and *BRCA2*-related disorders, is not recommended in children <18 years [1].
- Genetic testing on formalin-fixed and paraffin-embedded tumor tissue is broadly used and impacts treatment. Currently, this molecular approach does not replace the search for germline pathogenic variants based on a blood sample analysis if a hereditary cancer predisposition syndrome is suggested.

Outlook

This guideline is yearly updated and made available on the SAKK website. The composition of multi-gene panels advised for breast and/or ovarian cancer is also available on the website and those for pancreatic and prostate cancer are in development (https://www.sakk.ch/en/patients/genetic-counseling).

Conclusions

Counseling and testing of persons with a hereditary predisposition to cancer is a complex clinical and psychosocial issue requiring close interdisciplinary exchange and collaboration. The use of NGS in broad multi-gene germline panel testing confronts genetic counselors and at-risk individuals with additional challenges [18].

Testing should be considered in appropriate individuals where it is likely to impact the risk management and/or treatment of the tested person and/or their close relatives [1]. Health care professionals should be aware of the personal and/or family history patterns pointing to an increased

risk for germline pathogenic variants to allow affected families the most effective management and the most efficient utilization of health care resources.
This guideline is not intended to substitute for independent professional judgement of the treating physician.

A list of the members of the Swiss Group for Clinical Cancer Research (SAKK) Network for Cancer Predisposition Testing and Counseling and centres throughout Switzerland counseling individuals at risk for a hereditary cancer syndrome is available on the SAKK website (https://www.sakk.ch/en/patients/genetic-counseling).

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Conflict of interest
None of the authors has any conflict of interest to declare.