

## Update Swiss guideline for counselling and testing for predisposition to breast, ovarian, pancreatic and prostate cancer

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### Summary

This paper presents the Swiss guideline for genetic counselling 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 counselling to identify valuable candidates for testing and serves as a basis for reimbursement claims to Swiss insurance companies.

### Introduction

Since the last publication of the "Swiss guidelines for counselling 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 recognised 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 tumour tissue (tumour mutation).

In Switzerland, testing for genetic predisposition to hereditary cancer syndromes is available in a clinical setting.

Cancer risk assessment and genetic counselling are mandatory before and after genetic testing (i.e., pre- and post-test counselling) [1, 2]. DNA analysis is covered by health insurance companies only after formal genetic counselling 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 tumour mutation in a high-risk cancer predisposition gene should be referred for counselling 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 counselled regarding increased risk for the tumours 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. Inhibitors of polyadenosine diphosphate-ribose polymerase (PARP) have been shown to be very effective and well tolerated in a growing number of tumours. They are currently approved in Switzerland for patients with a *BRCA1/2* germline or tumour 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].

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*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 cumulative risk for a breast cancer of 72% and 69%, respectively, and a cumulative risk for an ovarian cancer until the age of 80 years of 44% and 17%, respectively [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 analyse 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 [1, 18].

Oncology providers should communicate the potential for incidental and secondary germline information to patients before conducting somatic 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 [1, 2], such as

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

## Methods

This guideline is based on the National Comprehensive Cancer Network (NCCN) guidelines [1] and National Institute for Health and Clinical Excellence (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 Counselling (CPTC) during a semi-annual meeting. The consensus recommendations then were summarised and sent to all members of the Network for review. The authors used a systematic re-

view of the literature and clinical experience. The literature review encompassed articles appearing in PubMed between 2017 (first publication of the Swiss guideline) to May 2021. Phase II and phase III randomised controlled trials were selected if they reported testing indications and management recommendations for carriers with germline mutations in high-risk cancer predisposition genes.

## Comments

- Meeting one or more of these criteria warrants further personalised genetic risk assessment and genetic counselling. The following issues should be the subject of discussion: explanation of inheritance pattern, available testing options, potential findings (pathogenic/likely pathogenic variants, variants of unknown significance), disease management, targeted treatment, surveillance and prevention options.
- Consider referral of cases with a limited or uninformative family history or in the case of adoption. A limited family history means:  $\leq 2$  female close relatives having lived beyond age 45 in either lineage [22].
- Borderline ovarian tumour 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 three founder variants is recommended. If no pathogenic variant can be identified a complete analysis of the *BRCA1* and *BRCA2* gene should be completed, 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 tumour tissue is widely used and influences 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 updated yearly 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

Counselling and testing of persons with a hereditary predisposition to cancer is a complex clinical and psychosocial issue requiring close interdisciplinary exchange and

Table 1:

Swiss guideline for referral, risk assessment, genetic counselling and testing of individuals with a suggested cancer predisposition syndrome.

<b>I Carrier testing</b>	Testing of an individual from a family with a known pathogenic variant in <i>BRCA1</i> , <i>BRCA2</i> or in another gene conferring high or moderate risk for breast and/or ovarian cancer	
<b>II Women with a personal history of breast cancer or ductal carcinoma in situ and one of the following</b>	Age at diagnosis $\leq 40$ y (any case) or $\leq 45$ y (at oncogeneticist's discretion)	
	Triple negative (ER, PR <sup>1</sup> and HER2 negative) BC <sup>2</sup> $\leq 60$ y	
	Bilateral BC or second separate primary	if the first cancer was diagnosed $\leq 50$ y with $\geq 1$ close relative <sup>3</sup> with BC (if only one relative affected, then age at diagnosis $\leq 50$ y)
	Age at diagnosis $\leq 50$ y with	1 close relative with BC $\leq 50$ y unknown or limited family history <sup>4</sup>
	Diagnosed at any age with	$\geq 2$ close relatives with BC a close male relative with BC $\geq 1$ close relative with ovarian or pancreatic or metastatic/intraductal/ciribiform prostate cancer at any age
<b>III Women with a personal history of ovarian cancer</b> <sup>5</sup>	Non-mucinous epithelial subtypes at any age <sup>6</sup>	
<b>IV. Men with a personal history of breast cancer</b>		
<b>V. Ashkenazi Jewish heritage</b>	Search for the 3 founder <i>BRCA1</i> and <i>BRCA2</i> pathogenic variants <sup>7</sup> regardless of personal or family history	
<b>VI. Family history only</b>	Testing of an unaffected individual when an appropriate affected family member is unavailable for testing with $\geq 1$ close relative with breast or ovarian cancer fulfilling one of the above criteria (points II-IV)	
<b>VII. Somatic pathogenic variant</b>	Germline confirmation of a pathogenic variant in a gene conferring high or moderate risk for breast and/or ovarian cancer detected by tumour profiling on any tumour type	
<b>VIII. Pancreatic cancer</b>	Exocrine pancreatic cancer at any age (first step: tumour profiling)	
	Unaffected individuals with	familial pancreatic cancer (2 first-degree relatives with pancreatic cancer) $\geq 3$ individuals with pancreatic cancer (same side of the family) <sup>8</sup>
<b>IX. Prostate cancer</b>	Metastatic, intraductal or cribriform prostate cancer at any age (first step: tumour profiling)	
	High-grade (Gleason Score $\geq 7$ ) prostate cancer and	Ashkenazi Jewish ancestry 1 close relative with breast cancer (age $\leq 50$ y) or ovarian or pancreatic cancer or metastatic/intraductal/ciribiform prostate cancer $\geq 2$ close relatives with breast or prostate cancer at any age <sup>8</sup>

<sup>1</sup> BC: breast cancer; ER: Oestrogen receptor; PR: Progesterone receptor<sup>2</sup> 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<sup>4</sup> Limited family history:  $\leq 2$  female close relatives having lived beyond age 45 y in either lineage<sup>5</sup> Ovarian cancer also includes primary peritoneal cancer and fallopian tube cancer<sup>6</sup> All epithelial ovarian cancers qualify for testing but high grade serous histology is particularly suspect<sup>7</sup> *BRCA1*: c.68\_69delAG, c.5266dupC; *BRCA2*: c.5946delT<sup>8</sup> In families with only pancreatic cancer or only prostate cancer testing should include other genes associated with hereditary risk for these tumours

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 affect the risk.

Management and/or treatment of the tested person and/or their close relatives [1]. Healthcare 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 utilisation of healthcare resources.

This guideline is not intended to substitute for independent professional judgement of the treating physician.

*This guideline represents the updated version of the guideline previously published in the Schweizerische Aerztezeitung (SAEZ) in 2017 and has been approved by the Swiss Group for Clinical Cancer Research (SAKK) Network for Cancer Predisposition Testing and Counselling. The document reflects clinical and scientific advances as of the date of publication, is subject to change and will be updated continuously.*

*A list of the members of the Swiss Group for Clinical Cancer Research (SAKK) Network for Cancer Predisposition Testing and Counselling and centres throughout Switzer-*

*land counselling individuals at risk for a hereditary cancer syndrome is available on the SAKK website.*

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#### Conflict of interest statement

Benno R othlisberger is employee of Genetica AG, Z urich, an institution offering genetic counseling and testing for predisposition to breast cancer. The other authors do not declare any conflict of interest.

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