SAMPLE REPORT

GeneMate®

Hereditary cancer risk

Report date: 2020-xx-xx
Sample received: 2020-xx-xx
Sample date (saliva): 2020-xx-xx

Customer

Elizabeth Williams
Female
YYMMDD-XXXX
Email: first.last@gmail.com

iCellate Support

iCellate Medical AB
Industrivägen 1
171 48 Solna
Email: support@icellate.se

Sample

Type: Saliva
Barcode: xxxxxxxxxx
iCellate ref.nr: ICEL000XX

A pathogenic variant was identified in *BRCA1*

According to the information you provided you have the following family cancer history:

- Mother diagnosed with breast cancer at 51 years of age.
- Maternal grandmother diagnosed with ovarian cancer at 42 years of age.

Gene	Variant (mutation)	Classification
BRCA1	c.5266dupC (p.Gln1756Profs) Alternative name: g.41209082dupG, BIC: 5382insC, 5385insC Zygosity: Heterozygot HGVS: NM_007294.3(BRCA1):c.5266dupC	Pathogenic

A note from our clinical team:

A pathogenic variant (c.5266dupC) in the *BRCA1* gene was identified in your sample by Next Generation Sequencing. The variant was confirmed by Sanger sequencing to rule out a false positive result. Pathogenic variants in *BRCA1* considerably increase the risk of breast and ovarian cancers in females and likely explain your mother's breast cancer and your grandmother's ovarian cancer. However, carrier testing is necessary to confirm that you inherited the variant from your mother's side of the family.

If have questions about your result, please book an appointment with our genetic counsellor via the link in section "What happens now?"

About your result

Testing positive for a pathogenic or likely pathogenic variant (also called a mutation) in the *BRCA1* gene considerably increases the risk of breast and ovarian cancers in women as compared to the average female population. For men, a pathogenic or likely pathogenic variant in *BRCA1* is associated with an increased risk of prostate cancer and male breast cancer. Furthermore, both men and women may also have an increased lifetime risk of pancreatic cancer. This result does not mean that you have cancer or that you definitely will develop cancer during your lifetime.

Cancer risk and screening guidelines are usually based on studies of individuals with a family history of cancer. Your individual risk may vary depending on other genetic and non-genetic factors. Measures to reduce or prevent your risk of cancer are based on national guidelines, as well as your own and your family's cancer history. Please feel free to book an appointment with our genetic counsellor. More information below.

Your result has been approved by:

Geneticist Jönsson
Clinical Laboratory Geneticist

Geneticist Jansson
Genetic Counsellor

Geneticist Jonsson, Med Dr
Clinical Geneticist

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Analysed genes

The following genes were analysed. Please see sections Test method and Limitations for further information.

APC	*ATM*	*BAP1*	*BMPR1A*	*BRCA1*
BRCA2	*BRIP1*	*CDH1*	*CDKN2A*	*CHEK2*
DICER1	*EPCAM*	*MAX*	*MEN1*	*MLH1*
MSH2	*MSH6*	*MUTYH*	*NF1*	*NF2*
PALB2	*PMS2*	*PTEN*	*RAD51C*	*RAD51D*
RB1	*RET*	*SDHA*	*SDHAF2*	*SDHB*
SDHC	*SDHD*	*SMAD4*	*SMARCB1*	*STK11*
TMEM127	*TP53*	*TSC1*	*TSC2*	*VHL*
WT1				

About the *BRCA1* gene

BRCA1 is a so-called tumour suppressor gene and acts as a template for making a protein of the same name. The protein prevents normal cells from being transformed into cancer cells by repairing damaged DNA. DNA damage occurs all the time, for example due to different environmental factors or as a result of cell division. DNA that is not repaired can lead to cancer.

A person with a pathogenic or likely pathogenic variant in *BRCA1* has an impaired ability to repair damaged DNA. However, this in and of itself does not lead to cancer. Due to the impaired ability to repair damaged DNA, the probability that other genes involved in cancer prevention also become damaged is increased. When this damage is not repaired, it spreads to more cells through cell division. As a result, more cells will have an impaired ability to repair DNA, thus increasing the risk of cancer.

How is *BRCA1* inherited?

Variants in *BRCA1* can either occur spontaneously during one's lifetime (somatic variant) or be inherited (germline variant). In some cases, however, a variant first occurs in an egg or sperm cell. After fertilization, the variant spreads to all the body's cells (*de novo* variant). GeneMate® can identify both germline and *de novo* variants in genomic DNA from saliva.

In normal inheritance a person receives two copies of a gene, one copy that is inherited from the mother and one copy that is inherited from the father. A *BRCA1* variant can be inherited either from the father or the mother. One mutated copy of *BRCA1* is sufficient to considerably increase the risk of breast and ovarian cancers and moderately increase the risk of other cancer types (see below). Siblings, children, and parents of a person with a variant in *BRCA1* have a 50 percent probability of being carriers.

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Cancer risk related to variants in *BRCA1*

Women with a pathogenic or likely pathogenic *BRCA1* variant have a considerably increased lifetime risk of developing breast and ovarian cancers as compared to the average woman (see Table 1). Breast cancer is the most common form of cancer in women – the average woman in the UK has a lifetime risk of roughly 15 percent. Women with a pathogenic or likely pathogenic variant in *BRCA1* have a lifetime risk of breast cancer of 50 to 80 percent[1]. Ovarian or fallopian tube cancer is not as common – the average woman in the UK has a lifetime risk of about 2 percent. Women with a pathogenic or likely pathogenic variant in *BRCA1* have a lifetime risk of ovarian or fallopian tube cancer of 30 to 60 percent[1]. Family cancer history can help assess where your individual risk falls on this spectrum.

Cancer type	Women in general [2]	Women with a pathogenic or likely pathogenic variant in *BRCA1*
Breast cancer	15.3%	50–80%[1]
Ovarian or fallopian tube cancer	2.0 %	30–60%[1]
Pancreatic cancer	1.8%	Increased[3,4,+]

Table 1. Lifetime risk of cancer for women, with or without a pathogenic or likely pathogenic variant in BRCA1.
+ The exact lifetime risk of cancer is not yet fully documented.

Men with a pathogenic or likely pathogenic *BRCA1* variant may have an increased lifetime risk of developing prostate cancer and male breast cancer as compared to the average man (see Table 2). Because the increase in risk is small in relation to the benefit of risk-reducing screening programs there are currently no such programs for male *BRCA1* carriers in the UK.

Cancer type	Men in general[1]	Men with a pathogenic or likely pathogenic variant in *BRCA1*
Prostate cancer	17.9%	Increased[,6,+]
Male breast cancer	0.1%	1.8%[7]
Pancreatic cancer	1.9%	Incresed[,4,+]

Table 2. Lifetime risk of cancer for men, with or without a pathogenic or likely pathogenic variant in BRCA1.
+ The exact lifetime risk of cancer is not yet fully documented.

What comes next?

Please book an appointment with one of our Genetic Counsellors to discuss the implications of your results and what your next steps are (click here).

It is important that you get in touch with a genetic services provider. More information about the NHS genetic services can be found here. Your NHS GP should be able to provide an appropriate referral based on this report. As part of the GeneMate® service, iCellate offers a complimentary consultation with a private GP. The private GP can provide a referral to private healthcare providers should you have the necessary private healthcare insurance or wish to pay yourself. Alternatively, the private GP can discuss the services that should be available to you through the NHS but cannot provide an NHS referral. Please send an email to support.uk@icellate.com if you wish to book a consultation with a private GP.

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In addition to genetic counselling, the genetic services provider will provide carrier testing for certain members of your family. The purpose of carrier testing is to determine if you have inherited the pathogenic variant from your mother or from your father or if it is a *de novo* variant. Once the origin of the variant is established, the clinic may offer carrier testing to your relatives. Carrier testing entails testing only for the specific variant found in your DNA.

Women will be informed of the measures available to decrease their cancer risk. According to The National Institute for Health and Care Excellence (NICE) guidelines[2] the following measures are suggested:

- Breast surveillance:
  - Yearly breast MRI (and sometimes mammography) from 30 years of age.
  - Yearly breast MRI and mammography from 40 years of age.
  - Yearly mammography from 50 to 70 years of age.
  - Mammography as part of the population screening programme after 70.

- Possibility of prophylactic mastectomy, in other words preventative removal of the breasts.

- Discussion regarding prophylactic salpingoophorectomy post childbearing, in other words the preventative removal of the ovaries and fallopian tubes.

UK law prohibits iCellate and the genetic services from contacting your relatives. We recommend that you inform your relatives, so that they may have the opportunity to be proactive in their cancer risk assessment. The choice to do so is your own.

Frequently asked questions

Please find more information and answers to frequently asked questions in our FAQ. Additional information about hereditary cancer can be found at:

Macmillan cancer support
Cancer Research UK
NHS

Test method

GeneMate® is a Next Generation Sequencing (NGS) service, optimized for analysing DNA associated with a predisposition for certain hereditary cancers. Genomic DNA is extracted from saliva provided by the customer and the specific regions of interest are amplified with an amplicon-based technique and then sequenced on an Illumina NextSeq550Dx platform. The sequencing reads are then mapped to the reference genome, after which different and precise bioinformatic tools are used to identify single nucleotide variants (SNV), copy number variants (CNV) and small insertions/deletions (INDELS). Identified variants are reported using the recommended HGCS-nomenclature.

The classification of genomic variants is performed in accordance with established guidelines issued by the American College of Medical Genetics and Genomics (ACMG) and are described with the recommended nomenclature for classification as one of the following: pathogenic, likely pathogenic, unknown significance, likely benign, or benign. The classifications are evaluated by our clinical team consisting of a clinical laboratory geneticist, a genetic counsellor and a clinical geneticist (medical doctor). Results will be reported as positive if a pathogenic or likely pathogenic variant is detected in conjunction with data collection. Results will be reported as negative if no variant, a benign variant or a likely benign variant is detected in conjunction with data collection. Variants of unknown significance are generally reported as negative unless otherwise recommended by the clinical team. Variants of unknown significance (VUS) are reclassified regularly as the medical literature and scientific knowledge is updated. In cases where the customer noted that they wish to be informed about future updates when ordering the test, iCellate will update customers if a variant of unknown

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significance is reclassified. Reported variants may require confirmation with an orthogonal test, including but not exclusive to Sanger sequencing (for SNVs and INDELS), and/or qPCR (for CNVs). The clinical team will also do an interpretation based on the family history of cancer if provided.

This test has been developed and its performance characteristics determined by iCellate Medical AB, an ISO 15189:2012-ackredited laboratory (Accred. no. 10473) and IVO-registered healthcare provider (Health and Social Care Inspectorate).

Limitations

iCellate Medical AB only detects and reports findings within the genes found in the panel (please see the list of genes covered by the test). There may exist clinically significant variants in the tested genes that the current technology is not designed to detect. Additional variants that are associated with hereditary cancer but not part of GeneMate® product panel and/or variants that associated with disease other than hereditary cancer will not be reported by iCellate. A follow-up consultation with a genetic counsellor is recommended to ensure complete understanding of your test result.

The GeneMate® test does not report chromosomal aneuploidies (i.e. an abnormal number of chromosomes), complex gene conversions, fusions, inversions, balanced translocations, certain repeat expansions, non-coding intronic variants deeper than 10 base pairs from exon-intron boundary and copy number variations spanning less than 6 exons/target region as defined by the panel. The sensitivity/specificity to detect specific variants may vary. This variation includes deletions and insertions in the range of 40-150 bp, deletions and insertions of certain repetitive elements, deletion-duplications or copy number variations, variants in regions with low/high GC content and within or in the vicinity of homopolymers, variants in simple sequence repeats, and in pseudogene and duplicated segments. Since we know that standard target enrichment protocols cannot reliably analyse some genomic regions, variations from those areas will not be reported. In selected genes analysis is restricted only to positions known to impact cancer risk.

Results of the current test may be inaccurate in patients receiving blood transfusion, bone marrow transplant(s), and in patients with certain haematological malignancies.

Disclaimer

While comprehensive efforts are taken by iCellate to avoid any analytical errors, iCellate is not responsible for errors in sample collection, transportation, and/or any other errors made prior to receipt of the sample at our laboratory. Laboratory and diagnostic errors may occur due to sample processing, DNA contamination, or operational procedures (including but not limited to equipment or reagent errors, or supplier errors) at any stage of the GeneMate® test. While rare, any of the above errors may limit and or affect the sensitivity, specificity, and/or accuracy of the GeneMate® test results.

All classifications are based on review, interpretation, and/or analysis of evidence available at the time of reporting, including medical literature and scientific databases, and will change as new evidence becomes available. Standard risk models may be employed to report risk assessments if pathogenic or likely pathogenic variants were not identified by guidelines following risk identification for the GeneMate® test.

The accuracy of the risk estimation for each individual based on the family history depends on the accuracy of the information provided by the tested individual. If the family history provided is incorrect or incomplete this will influence the risk estimation. Even in the case of a negative result there may be an increased risk for cancer that motivates a more detailed investigation of the family history and in some cases inclusion in screening programs.

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