A Guide To Genetic Consenting

Module 6:
Knowledge of genetics required by healthcare professionals prior to mainstream consenting

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Learning objectives

The primary purpose of this learning module is to inform and educate non-genetics HCPs on genetic consenting.

This module will enable HCPs to:

- Distinguish between germline and somatic variants
- Be aware of the classification of gene variants, based on pathogenicity, for patients with cancer
- Understand the differences between predictive and therapeutic genetic counselling

HCP=healthcare professional

Classification of gene variants

- A genetic mutation is a permanent alteration in the DNA sequence that makes up a gene[1]
- The term “mutation” has been used to imply both “change” and “disease-causing change” within a DNA sequence[2]
- To avoid confusion or assumptions of pathogenicity, the American College of Medical Genetics and Genomics recommends using the more neutral term “gene variant” to describe altered genes[2]

Gene variants can be classified into 5 categories:[2,3]

- Pathogenic variant (class 5)
- Likely pathogenic variant (class 4)
- Variant of uncertain significance (VUS, class 3)
- Likely benign variant (class 2)
- Benign variant (class 1)

VUS=variant of uncertain significance

1. NIH What is a gene variant and how do variants occur? Availble at https://medlineplus.gov/genetics/understanding/mutationsanddisorders/genemutation/ (Last accessed July 2022); 2. Richards S, et al. *Genet Med.* 2015;17(5):405-424; 3. Houge G, et al. *Eur J Hum Genet*. 2022;30(2):150-159.

Hereditary and acquired gene variants

- Gene variants can be classified as hereditary (germline) or acquired (somatic)

Hereditary

They are called **germline** gene variants because they are inherited from parent cells via sperm or ovum cells which are known as germ cells

Germline variants can be passed from either parent to child. They are present in all cells and can be detected in blood and saliva, not just in tumour cells

Acquired

These are also known as **somatic** gene variants and can occur as a result of environmental factors or when an error is made as DNA copies itself during cell division

Somatic gene variants are clonal and present in the next set of generated cells following mitosis, for example tumour cells. They are not in all cells and cannot be passed from parent to child

NIH Genetics Home Reference. What is a gene variant and how do variants occur? Available at: https://medlineplus.gov/genetics/understanding/mutationsanddisorders/genemutation/ (last accessed July 2022)

Pathogenic variants and disease

There are a number of different pathogenic variants that have been linked to cancer susceptibility[1]

Different pathogenic variants can have large or small effects on the likelihood of developing a particular disease[2]

Some gene variants have little to no impact[3]

For example, certain variants in *BRCA1* and *BRCA2* genes greatly increase a person's risk of developing breast and ovarian cancers[4,5]

Cancer[5]	BRCA1 – Lifetime risk to age 80 years (95% CI)	BRCA2 – Lifetime risk to age 80 years (95% CI)
Breast cancer	72% (65%-79%)	69% (61%-77%)
Ovarian cancer	44% (36%-53%)	17% (11%-25%)

CI=confidence interval

1. Reza M.N, et al. *Sci Rep*. 2021;11:19264; 2. Mount Sinai bio bank study press release. Available at https://www.mountsinai.org/about/newsroom/2022/most-pathogenic-genetic-variants-have-a-low-risk-of-causing-disease. (Last accessed July 2022); 3. NIH Genetics. Do all gene variants affect health and development? Available at https://medlineplus.gov/genetics/understanding/mutationsanddisorders/neutralmutations. (Last accessed July 2022); 4. Cancer Australia. Genetic testing for breast/ovarian cancer risk. Available at: https://www.canceraustralia.gov.au/clinical-best-practice/gynaecological-cancers/familial-risk-assessment-fra-boc/genetic-testing (last accessed July 2022); 5. Kuchenbaeker K, et al. *JAMA*. 2017;317:2402-2416.

There are two main categories of genetic testing for variants

Pathogenic variant detection (diagnostic)[1]

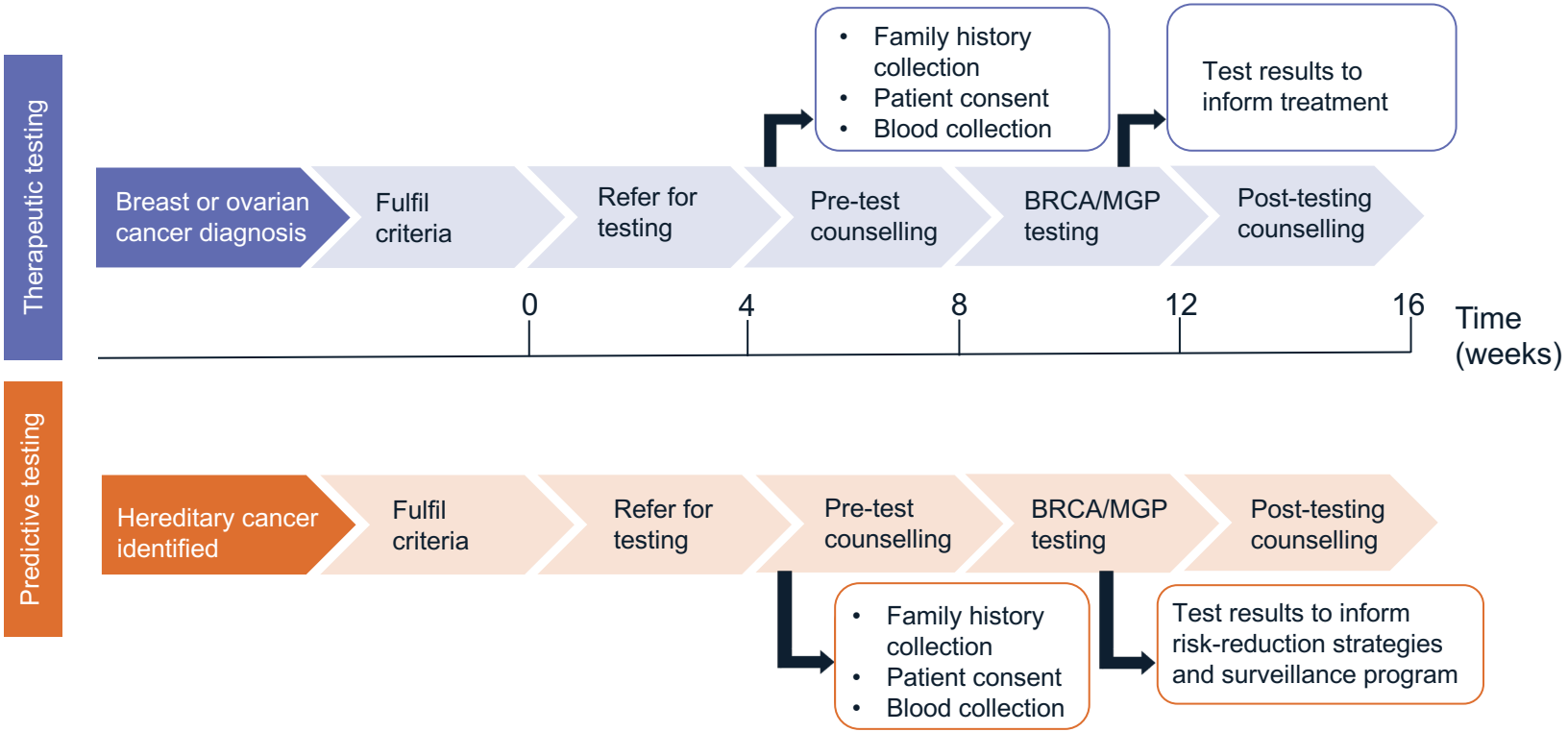
- Genetic testing looks for any pathogenic variant in specific genes (e.g. *BRCA1* and *BRCA2*) that may explain the cancer found in a patient
- A full genetic screen of *BRCA1* and *BRCA2* is performed in patients with ovarian and breast cancer
- This is usually the first time testing is done within a family
- This is a type of genetic test that can be done via the mainstream genetic testing process

Predictive testing[2]

- This is performed when a pathogenic or likely pathogenic *BRCA1* and/or *BRCA2* variant of interest has been identified in another family member

1. NIH Genetics Home Reference. What are the uses of genetic testing? Available at: https://medlineplus.gov/genetics/understanding/testing/uses/ (last accessed July 2022) 2. NHS Predictive genetic tests for cancer risk genes. Available at: https://www.nhs.uk/conditions/predictive-genetic-tests-cancer/. (Last accessed July 2022).

Current BRCAm testing pathway

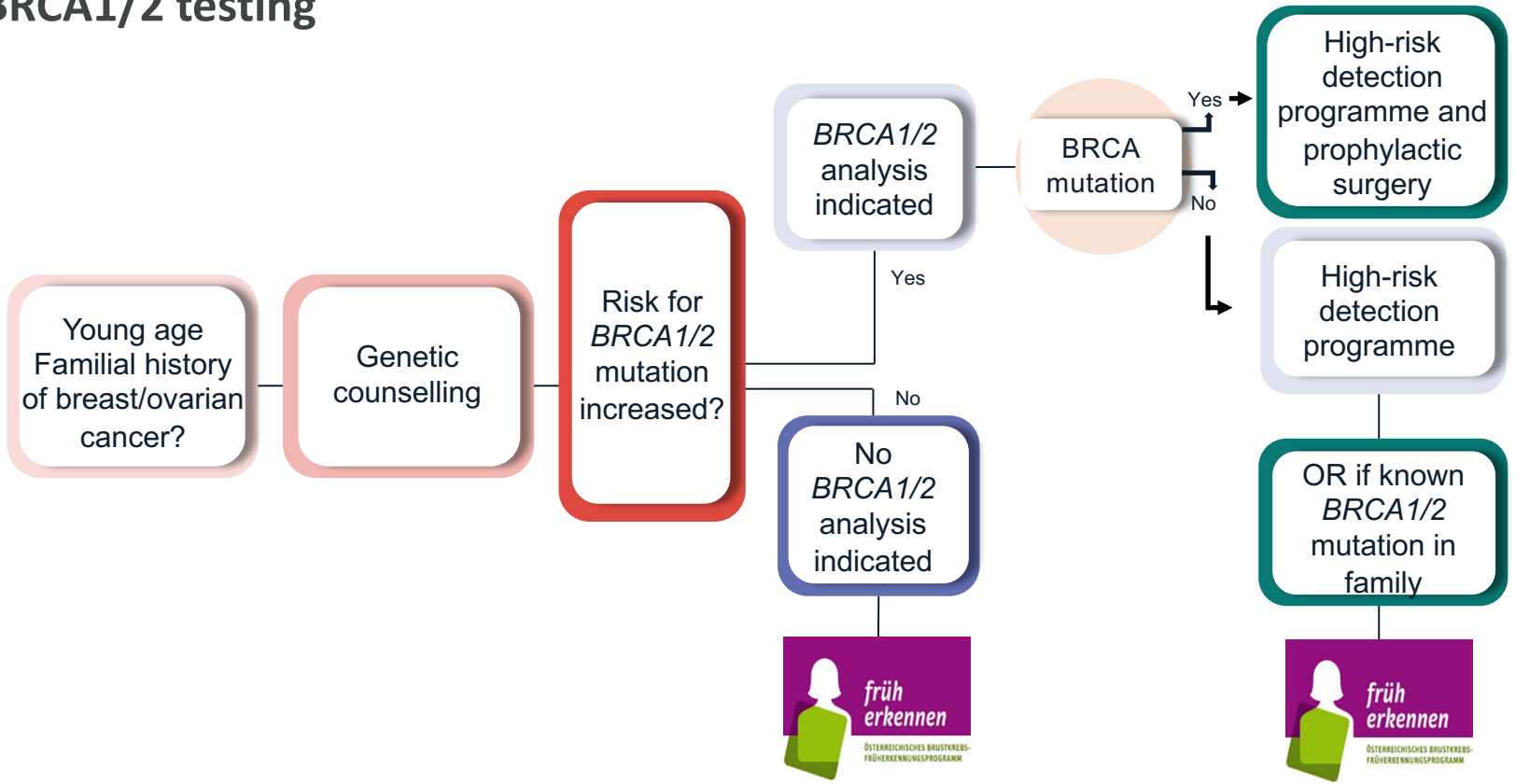


Personal slide from Yen Tan

Predictive counselling and analysis

- **Predictive testing** is aimed at identifying BRCA mutations in high-risk families
  - Only initiated after genetic counselling **if high-risk criteria** are met
- **Genetic counselling** is performed by geneticist or oncologist / surgeon / gynaecologist (regulated by Austrian genetic law)
- Predictive testing is usually offered to affected individuals first
- **High-risk screening programme** and prophylactic surgery offered to affected women

Genetic counselling: An example patient flow for predictive counselling during BRCA1/2 testing



Personal slide from Christian Singer

Therapeutic counselling and analysis in breast cancer[1,2]

- **Therapeutic testing** is aimed at personalised treatment (surgery)
- In women at risk for harbouring mutation:
  - Triple-negative breast cancer
  - Young women with breast cancer
  - Metastatic HER2-negative breast cancer
  - **NEW: expanded criteria**
- Familial aggregation of cancer cases is **not necessary**, MDT-initiated
- It is usually performed by treating **oncologist / surgeon** (regulated by Austrian genetic law)

HER2=human epidermal growth factor receptor 2; MDT=multidisciplinary team

1. Speaker communication from Christian Singer. 2. Singer CF, et al. *Clin Genet* 2014;85:72–75

Section summary

- A genetic mutation is a permanent alteration in the DNA sequence that makes up a gene[1]
- Gene variants may be classified as hereditary (germline) or acquired (somatic)[1]

- There are a number of different pathogenic variants that have been linked to cancer susceptibility[2]
- For example, certain variants in *BRCA1* and *BRCA2* genes greatly increase a person's risk of developing breast and ovarian cancers[3,4]

- Predictive testing is aimed at identifying BRCA mutations in high-risk families[5]
- Therapeutic testing is aimed at determining personalised treatment[5]

1. NIH What is a gene variant and how do variants occur? Availble at https://medlineplus.gov/genetics/understanding/mutationsanddisorders/genemutation/ (Last accessed July 2022); 2. Reza M.N, et al. *Sci Rep*. 2021;11:19264; 3. Kuchenbaeker K, et al. *JAMA*. 2017;317:2402-2416 4. Cancer Australia. Genetic testing for breast/ovarian cancer risk. Available at: https://www.canceraustralia.gov.au/clinical-best-practice/gynaecological-cancers/familial-risk-assessment-fra-boc/genetic-testing (last accessed July 2022); 5. Singer C, et al. *Clin Genet* 2014;85:72–75.