Patient Information Sheet: Paired tumour / germline DNA testing in patients with cancer.

1. What are genes?

Genes are sections of DNA and contain the instructions required to make proteins which are needed for the growth, development and function of cells in the body. Each person inherits two sets of genes, one from their mother and one from their father.

2. What role do genes play in the development of cancer?

Each time a cell divides, a copy of the genes is made for the new cell. Due to the millions of cells that are dividing, some cells may pass on instructions which contain mistakes. These mistakes cause mutations to occur in the new cell. While most mutations are found by our DNA and fixed naturally, some are passed on to the new cells. As people age, they accumulate an increasing number of gene mutations.

Cancer can develop when:

- Mutations occur in both copies of a gene in a cell which means there is no working copy of the protein that **protects** the cell against cancer i.e. there is a **loss of function** of the protein
- A mutation occurs in a gene which causes it to work more i.e. there is **a gain of function** of the protein which **promotes** the development of a cancer

Most cancers gain mutations in one or more genes over time. Some of these mutations make the cancer develop faster (and therefore may provide targets for treatment) whereas some mutations simply accumulate as the genetic material in the cancer cell becomes more unstable. These **acquired** (**somatic**) mutations are only present in the cancer cells within the person affected and other family members are **not** at risk of having inherited them.

In rare cases, a person can be born with a mutation in a gene which increases the risk of developing cancer. These are known as **germline** (heritable) mutations and the mutation is present in every cell of the body. These mutations may have been **inherited** from either parent or have occurred for the first time in a family member (a ***de novo*** mutation).
In both cases the child of a person with a germline mutation is at risk of inheriting the mutation.

A third possibility exists for a person to have mutated cells in some normal tissues in their body but not in others. This is called **mosaicism**. When this involves the sperm or the ova, this is called **gonadal mosaicism**. This means there is a risk that the mutation can be inherited.

3. The role of tumour and germline DNA testing in patients with cancer

3.1 Tumour (somatic) gene testing:

This may be undertaken for a number of reasons including to:

- confirm the cancer type
- provide information about the likelihood of finding a cure or how the cancer may respond to treatment
- assist with treatment decisions, including whether the patient is eligible for any government funded anti-cancer treatments
- decide if the patient is eligible for a clinical trial or the testing may be included as part of a clinical trial
- allow monitoring of the cancer's response to treatment and to detect early relapse (most commonly in haematological (blood) cancers)
- help assess the chance of the patient having an inheritable predisposition to cancer.

Somatic gene testing may only include one gene or a small number of genes. However, current technology allows a large number of genes to be tested at the same time, if required.

Somatic tumour testing may involve testing of tumour DNA or testing of paired tumour/germline DNA samples. Testing of germline DNA usually involves a blood test. In cases where the cancer involves the blood, other tissues such as hair/hair follicles, can be used.

3.2 What might be detected by germline gene testing?

Possible outcomes of germline genetic testing include:

- no mutations identified in any of the tested genes
- a change is found in one of the genes, but the significance of this change is not known (called an unclassified variant)
- a pathogenic (disease-causing) mutation is identified in a gene which will potentially change the management of the patient and/or their family (i.e. a clinically actionable result)

Patients will be asked to provide written consent for genetic testing and whether or not they wish to be advised of clinically-actionable germline genetic test results. They are able to change their mind regarding this at any time. It is their choice to undergo this testing.

Patients undergoing paired tumour/germline testing at Pathology Queensland will only be told of germline genetic test results when a pathogenic mutation is identified in a gene which will potentially change the management of the patient and/or their family.

Important factors to consider when offered germline genetic testing are:

- a negative test result does not exclude a familial predisposition to cancer
- the results may have implications for other family members including children
- unexpected results may occur. While these may ultimately provide useful information for the patient and their family, they may initially cause distress.

3.3 Referral to a cancer genetics service will be recommended if:

- a familial predisposition to cancer is suspected on the basis of family history or tumour characteristics, regardless of the genetic test result
- with the patient's consent, a clinically-actionable mutation in a cancer predisposition gene is identified after germline testing.