

Fanconi Anemia and DNA Repair Disorders: Information for Ordering Providers

Several hereditary diseases are characterized by defects in DNA repair including:

Fanconi Anemia (FA)¹ is characterized by physical abnormalities (stature and skeletal limb malformations), bone marrow failure and an increased risk for malignancy. FA is associated with a number of genes, the majority of which are inherited in an autosomal recessive fashion. FA can also be inherited in an autosomal dominant or X-linked manner.

Ataxia Telangiectasia (A-T)¹ is characterized by progressive cerebellar ataxia, telangiectasias, immunodeficiency and an increased risk for malignancy. A-T is inherited in an autosomal recessive manner and is caused by pathogenic variants in *ATM*.

Bloom Syndrome¹ is characterized by severe prenatal and postnatal growth retardation, sun-sensitive facial erythema and predisposition to multiple cancers. Bloom syndrome is inherited in an autosomal recessive manner and is caused by pathogenic variants in *BLM*.

Nijmegen Breakage Syndrome (NBS)¹ is characterized by microcephaly, short stature, immunodeficiency and predisposition to cancer. NBS is inherited in an autosomal recessive manner and is caused by pathogenic variants in *NBN*.

RECQL4-related Disorders¹ include Rothmund-Thomson syndrome, Baller-Gerold syndrome and RAPADILINO syndrome. These syndromes all include radial ray defects, skeletal abnormalities, slow growth/short stature and an increased risk for malignancy. They are inherited in an autosomal recessive manner and are caused by pathogenic variants in *RECQL4*.

Indications for Testing

Patients who meet the following criteria are eligible for testing:

- For Fanconi anemia, patients with 2 or more clinical features from at least 2 of the following categories:

Physical Features	Laboratory Findings	Cancer
Short stature	Progressive bone marrow failure not related to cancer treatment	Cancer diagnosed < 5 years of age
Abnormal skin pigmentation	Aplastic anemia	Solid tumour diagnosed before age 50
Skeletal malformations	Myelodysplastic syndrome or AML	
Microcephaly	Macrocytosis	
Ophthalmic anomalies	Cytopenia	
Genitourinary tract anomalies	Increased fetal hemoglobin	
	Inordinate toxicities from chemotherapy or radiation	

- Patients with a personal history suggestive of ataxia telangiectasia, Bloom syndrome, Nijmegen breakage syndrome, or RECQL4-related disorders.



Fanconi Anemia and DNA Repair Disorders: Information for Ordering Providers

Limitations

In individuals with a hematological malignancy, genetic testing may reveal a variant that is acquired rather than inherited. Confirmatory testing on another tissue (buccal, skin or urine) may be required.

Ordering Privileges

Please refer to the APL Test Directory (<http://ahsweb.ca/lab/apl-td-lab-test-directory>) for specific ordering restrictions.

The genes included on the Fanconi Anemia NGS panel are:

<i>BRCA2</i> (<i>FANCD1</i>)	<i>BRIP1</i> (<i>FANCJ</i>)	<i>FANCA</i>	<i>FANCB</i>	<i>FANCC</i>	<i>FANCD2</i>	<i>FANCE</i>
<i>FANCF</i>	<i>FANCG</i>	<i>FANCI</i>	<i>FANCL</i>	<i>FANCM</i>	<i>PALB2</i> (<i>FANCN</i>)	<i>RAD51C</i> (<i>FANCO</i>)
<i>SLX4</i> (<i>FANCP</i>)	<i>ERCC4</i> (<i>FANCQ</i>)	<i>ATM</i>	<i>BLM</i>	<i>NBN</i>	<i>RECQL4</i>	

Associated Disorders

Hereditary Cancer: Some of the genes on this panel are associated with hereditary cancer. *BRCA2*, *BRIP1*, *ATM*, *PALB2*, and *RAD51C* are associated with an increased risk of breast and/or ovarian cancer and/or pancreatic cancer. These hereditary cancer predispositions are inherited in an autosomal dominant manner.

If a pathogenic variant is identified in one of these genes, the patient and/or their family members may be at increased risk for specific cancers. These individuals are eligible for increased cancer screening and/or risk reducing surgeries and therapeutic interventions. In addition, results may influence treatment plans for individuals with cancer. Genetic counselling is recommended for these families.

When can I expect results?

Results may take up to 4 months.

How are results reported?

Results are sent to the ordering provider and available in Netcare and Connect Care.

Requisition forms, contact information and other resources can be found at:

<http://ahsweb.ca/lab/if-lab-genetics-and-genomics>

Contact Information

Genetic Counsellors, Genetics & Genomics
Edmonton: 780-407-1015

References

1. Adam MP, Mirzaa GM, Pagon RA, et al., editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2024. Available from: <https://www.ncbi.nlm.nih.gov/books/NBK1116/>