Cancer Association of South Africa (CANSA)

Research • Educate • Support

Fact Sheet on Polycythaemia Vera

Introduction

Polycythaemia Vera is a slow-growing type of blood cancer in which the bone marrow makes too many red blood cells – it is one of the blood disorders called myeloproliferative neoplasm.

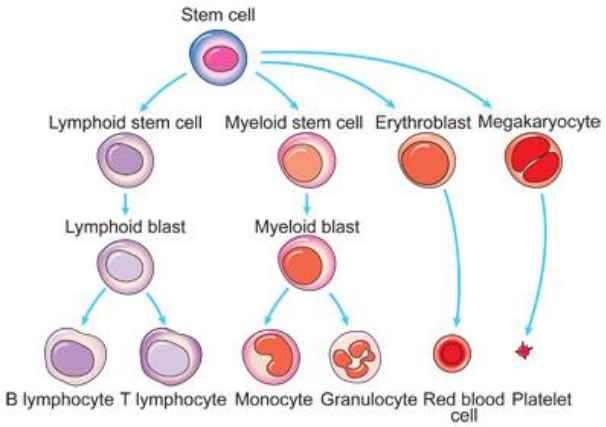


Diagram showing how blood cells are made

Polycythaemia Vera may result in production of too many of the other types of blood cells — white blood cells and platelets. These excess cells thicken one's blood and cause complications, such as a risk of blood clots or bleeding. 'Poly' means many and 'cythaemia' relates to blood cells. It is also sometimes called erythrocytosis, which means too many red blood cells. And it used to be called polycythaemia rubra vera or PCRV. PV is a type of rare blood disorder called a myeloproliferative neoplasm. These are conditions that cause an abnormal increase in the number of blood cells.

Blood cells are made in the soft inner part of the bones, the bone marrow. All blood cells start from the same type of cell called a blood stem cell. The stem cell makes immature blood cells. The immature cells go through various stages of development before they become fully developed blood cells and are released into the blood as:

- Red blood cells to carry oxygen
- White blood cells to fight infection
- Platelets to help the blood clot

The diagram above shows how the various different types of cells develop from a single blood stem cell.

In Polycythaemia Vera, the stem cells make too many red blood cells. This makes the blood become thicker. Sometimes the extra cells collect in the spleen, which may then become enlarged.

Most of the health concerns associated with Polycythaemia Vera are caused by the blood being thicker as a result of the increased red blood cells. It is more common in the elderly and may be symptomatic or asymptomatic. Common signs and symptoms include itching (pruritus), and severe burning pain in the hands or feet that is usually accompanied by a

reddish or bluish coloration of the skin. Patients with Polycythaemia Vera are more likely to have gouty arthritis.
(Wikipedia; Mayo Clinic; Cancer Research UK).

Other names for Polycythaemia Vera (PV)
Polycythaemia Vera is also known as:

- Primary polycythaemia
- Polycythaemia rubra vera
- Erythremia
- Splenomegalic polycythaemia
- Vaquez's Disease
- Osler's Disease
- Polycythaemia with chronic cyanosis
- Myelopathic polycythaemia
- Erythrocytosis megalosplenica
- Cryptogenic polycythaemia

The US spelling of polycythaemia is "polycythemia"
(MPD Voice).

Incidence of Polycythaemia Vera in South Africa (PV)
The National Cancer Registry (2012) does not provide any information on the incidence of Polycythaemia Vera in South Africa.

In providing the incidence figures of Leukaemia in South Africa, The National Cancer Registry (2012) does not make provision for the reporting of the different types of Leukaemia – it also does not differentiate between acute and chronic Leukaemia - neither does it provide for different statistics for cases of adult and childhood Leukaemia.

According to the National Cancer Registry (2012) the following number of Leukaemia cases was histologically diagnosed in South Africa during 2012:

Group - Males 2012	Actual No of Cases	Estimated Lifetime Risk	Percentage of All Cancers
All males	380	1:502	1,03%
Asian males	11	1:666	1,34%
Black males	201	1:762	1,73%
Coloured males	42	1:452	0,97%
White males	126	1:232	0,63%

Group - Females 2012	Actual No of Cases	Estimated Lifetime Risk	Percentage of All Cancers
All females	285	1:955	0,76%
Asian females	5	1:1 777	0,47%
Black females	160	1:1 409	0,97%
Coloured females	49	1:440	1,17%
White females	72	1:480	0,45%

The frequency of histologically diagnosed cases of Leukaemia in South Africa for 2012 was as follows (National Cancer Registry, 2012):

Group - Males 2012	0 – 19 Years	20 – 29 Years	30 – 39 Years	40 – 49 Years	50 – 59 Years	60 – 69 Years	70 – 79 Years	80+ Years
All males	88	29	38	42	50	54	54	20
Asian males	3	1	0	0	1	2	2	2
Black males	67	21	25	20	20	23	13	3
Coloured males	6	2	5	1	8	6	8	4
White males	12	5	6	18	18	23	30	11

Group - Females 2012	0 – 19 Years	20 – 29 Years	30 – 39 Years	40 – 49 Years	50 – 59 Years	60 – 69 Years	70 – 79 Years	80+ Years
All females	63	19	24	34	42	37	31	20
Asian females	0	1	1	2	1	0	0	0
Black females	40	18	27	16	22	11	12	6
Coloured females	10	4	3	3	5	13	5	5
White females	12	3	1	6	14	12	14	9

N.B. In the event that the totals in any of the above tables do not tally, this may be the result of uncertainties as to the age, race or sex of the individual. The totals for 'all males' and 'all females', however, always reflect the correct totals.

Signs and Symptoms of Polycythaemia Vera (PV)

For many people, Polycythaemia Vera may not cause any signs or symptoms. However, some people may experience:

[Picture Credit: Polycythaemia Vera]

Itchiness, especially following a warm bath or shower

- Headache
- Dizziness
- Weakness
- Excessive sweating
- Painful swelling of one joint, often the big toe
- Shortness of breath
- Breathing difficulty when you lie down
- Numbness, tingling, burning or weakness in your hands, feet, arms or legs
- A feeling of fullness or bloating in your left upper abdomen due to an enlarged spleen

(Mayo Clinic).

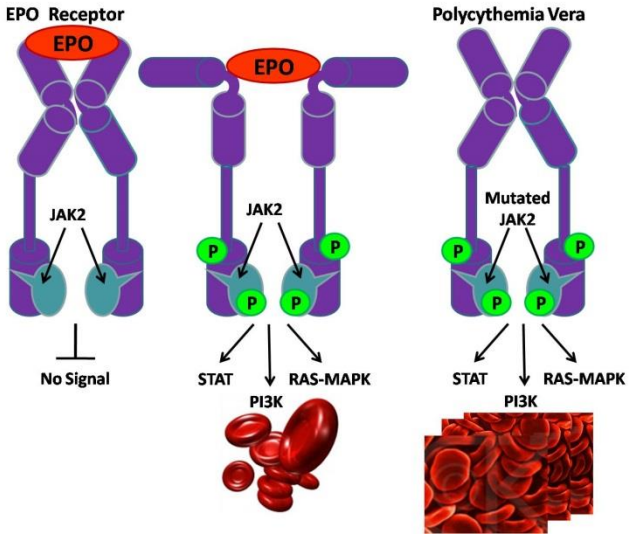
Genetics and Inheritance of Polycythaemia Vera (PV)

Mutations in the *JAK2* and *TET2* genes are associated with Polycythaemia Vera. Although it remains unclear exactly what initiates Polycythaemia Vera, researchers believe that it begins when mutations occur in the DNA of a hematopoietic stem cell. These stem cells are located in the bone marrow and have the potential to develop into red blood cells, white blood cells, and platelets. *JAK2* gene mutations seem to be particularly important for the development of Polycythaemia Vera, as nearly all affected individuals have a mutation in this gene. The *JAK2* gene provides instructions for making a protein that promotes the growth and division (proliferation) of cells. The JAK2 protein is especially important for controlling the production of blood cells from hematopoietic stem cells.

JAK2 gene mutations result in the production of a JAK2 protein that is constantly turned on (constitutively activated), which increases production of blood cells and prolongs their survival. With so many extra cells in the bloodstream, abnormal blood clots are more likely to

form. Thicker blood also flows more slowly throughout the body, which prevents organs from receiving enough oxygen. Many of the signs and symptoms of Polycythaemia Vera are related to a shortage of oxygen in body tissues.
The *JAK2* mutation test may be used, along with other tests such as erythropoietin, to help diagnose bone marrow disorders that lead to overproduction of blood cells. These conditions are known as myeloproliferative neoplasms (MPNs).

[Picture Credit: JAK2 Gene Mutation]



The MPNs most commonly associated with *JAK2* mutation are: polycythemia vera (PV), where bone marrow makes too many red blood cells; essential thrombocythemia (ET), where there are too many platelet-producing cells in the bone marrow; and primary myelofibrosis (PMF), also known as chronic idiopathic myelofibrosis or agnogenic myeloid metaplasia, where there are too many platelet-producing cells and cells that produce scar tissue in the bone marrow. The *JAK2*mutation test is typically ordered as a follow-up test if a person has a significantly increased haemoglobin and/or platelet count and the health care provider suspects that the person may have an MPN.

JAK2 V617F is named for a mutation at a specific location in the *JAK2 gene* and is the primary genetic test for *JAK2*mutations that lead to MPNs. *JAK2* mutations are acquired as opposed to inherited and result in the change of a single DNA nucleotide base pair, called a point mutation. This change results in a JAK2 protein that is constantly "on," leading to uncontrolled blood cell growth.

Mutations in other coding portions (called exons; they code for protein) of the *JAK2* gene are also associated with MPNs. There is a test also available to detect changes in *JAK2* exon 12. Two to five percent of people with PV have an exon 12 mutation.

The presence of a *JAK2* mutation helps a health care provider make a definitive diagnosis of MPN (PV, ET or PMF), but the absence of a *JAK2* mutation does not rule out MPN. In 2008, the World Health Organization (WHO) revised its diagnostic criteria for PV and ET, adding the presence of *JAK2* mutation as a criterion. However, consensus has not yet been achieved for the optimal diagnostic criteria for PV.

The finding of a *JAK2* mutation associated with uncontrolled blood cell growth in MPN also suggests a possible therapeutic approach to some MPN. As an example, one *JAK2* inhibitor has been approved for the treatment of intermediate and high risk myelofibrosis.

The function of the *TET2* gene is unknown. Although mutations in the *TET2* gene have been found in approximately 16 percent of people with Polycythaemia Vera, it is unclear what role these mutations play in the development of the condition.
Most cases of Polycythaemia Vera are not inherited. This condition is associated with genetic changes that are somatic, which means they are acquired during a person's lifetime and are present only in certain cells.

In rare instances, Polycythaemia Vera has been found to run in families. In some of these families, the risk of developing Polycythaemia Vera appears to have an autosomal dominant pattern of inheritance. Autosomal dominant inheritance means that one copy of an altered gene in each cell is sufficient to increase the risk of developing Polycythaemia Vera, although the cause of this condition in familial cases is unknown. In these families, people seem to inherit an increased risk of Polycythaemia Vera, not the disease itself.
(Genetic Home Reference; Lab Test Online).

Possible Complications of Polycythaemia Vera
Possible complications of polycythaemia vera include:

Blood clots - Polycythaemia vera causes one's blood to be thicker than normal, which can slow the rate of blood flow through the veins and arteries. Increased blood thickness and decreased blood flow, as well as abnormalities in the platelets, increase the risk of blood clots. Blood clots can cause a stroke, a heart attack, or blockage of an artery in the lungs (pulmonary embolism) or in a vein deep within a muscle (deep vein thrombosis).

Enlarged spleen (splenomegaly) - The spleen helps one's body fight infection and filters unwanted material, such as old or damaged blood cells. The increased number of blood cells caused by polycythaemia vera makes the spleen work harder than normal, which causes it to enlarge.

Skin problems **-** Polycythaemia vera may cause the skin to itch, especially after a warm bath or shower, or after sleeping in a warm bed. Individuals may experience a burning or tingling sensation in the skin, particularly on the arms, legs, hands or feet. The skin may also appear red, especially on the face.

Problems due to high levels of red blood cells - Too many red blood cells can lead to a number of other complications, including open sores on the inside lining of the stomach, upper small intestine or oesophagus (peptic ulcers) and inflammation in the joints (gout).

Other blood disorders like acute leukaemia - In rare cases, polycythaemia vera may lead to other blood diseases, including a progressive disorder in which bone marrow is replaced with scar tissue (myelofibrosis), a condition in which stem cells do not mature or function properly (myelodysplastic syndrome), or cancer of the blood and bone marrow (acute leukaemia).

Diagnosis of Polycythaemia Vera (PV)
The proposed revised World Health Organization criteria for the diagnosis of Polycythemia Vera (P. vera) requires two major criteria and one minor criterion or the first major criterion together with two minor criteria.

Major Criteria
- Haemoglobin of more than 18.5 g/dL in men, 16.5 g/dL in women, or elevated red cell mass greater than 25% above mean normal predicted value.
- Presence of *JAK2* 617V greater than F or other functionally similar mutations, such as the exon 12 mutation of *JAK2*.

Minor Criteria

- Bone marrow biopsy showing hypercellularity with prominent erythroid, granulocytic, and megakaryocytic proliferation.
- Serum erythropoietin level below normal range.
- Endogenous erythroid colony formation *in vitro*.

Other confirmatory findings no longer required for diagnosis include:

- Oxygen saturation with arterial blood gas greater than 92%.
- Splenomegaly.
- Thrombocytosis (>400,000 platelets/mm^3).
- Leukocytosis (>12,000/mm^3).
- Leukocyte alkaline phosphatase (>100 units in the absence of fever or infection).

There is no staging system for this disease.

Several tests are used to confirm the diagnosis of PV and to help the haematologist to understand the condition. The following tests may be needed:

- Full blood count (blood test) - The haematologist may repeat this test for verification if the test was previously done by a General Practitioner

- JAK2 test - The haematologist can test the blood to see if the person has a change (or mutation) called JAK2 V617F mutation. Approximately 98% who have PV have this mutation

- Chest x-ray

- Liver, kidney and urine tests

- EPO test Measurement of your erythropoietin (EPO) level

- Iron, folate and vitamin B 12

- Oxygen Measurement of oxygen levels in the blood

- Abdominal ultrasound - If someone has PV, his/her spleen may be enlarged. This is because in PV the spleen may begin to produce blood cells, and these collect inside the spleen. The ultrasound is a painless test

- Bone marrow biopsy (BMB) - A bone marrow biopsy is a test of one's bone marrow that is done in the hospital. The person will not need stay overnight in the hospital, and will generally just need local anaesthesia. The haematologist will give the patient some medication to prevent pain, and then he or she will extract some bone marrow from the patient's hip bone using a needle. The bone marrow tissue can then be examined in a laboratory so that the haematologist can see how the cells in the bone marrow are functioning

The following additional tests may be needed:

- Lung function test
- A red cell mass test

- Blood test measuring haemoglobin binding to oxygen
- An ECG (echocardiogram) to examine the heart
- Genetic testing of the erythropoietin receptor
- A sleep study

(MPD Voice; National Cancer Institute).

Approved Test to Evaluate Patients for Suspected Polycythaemia Vera (PV)

The Food and Drug Administration (FDA) has approved the ipsogen JAK2 RGQ PCR Kit (Qiagen), the first authorised test intended to help clinicians evaluate patients for suspected polycythemia vera (PV).

The presence of JAK2 mutations is one of the major criteria for clinical confirmation of PV. The ipsogen JAK2 RGQ PCR Kit is a qualitative *in vitro* diagnostic test for the detection of the JAK2 V617F/G1849T allele in genomic DNA extracted from EDTA whole blood; the V617F/G1849T mutation affecting the JAK2 gene is detected in > 94% of patients with PV. The test can be used as an adjunct to evaluation of suspected PV, in conjunction with other clinicopathological factors

The approval is based on data from a trial of 216 suspected patients with PV which compared results from the ipsogen JAK2 RGQ PCR Kit to those obtained with Sanger sequencing when each is used as a major criterion as described in World Health Organization (WHO) criteria. In the study, the ipsogen JAK2 RGQ PCR Kit test detected PV with 94.6% sensitivity and 98.1% specificity.

The ipsogen JAK2 RGQ PCR Kit does not detect less common mutations associated with PV including mutations in exon 12. It is also not intended for stand-alone diagnosis of PV. (MPR).

Treatment and Management of Polycythaemia Vera (PV)

The long-term risks of Polycythaemia Vera (PV) include leukaemic and fibrotic transformation, which occurs in fewer than 5% and 10% of patients, respectively, at 10 years. Current treatment modalities do not change these outcomes. Instead, treatment for PV is intended to decrease the risk of arterial and venous thrombotic events, which could be approximately 20%.

Patients can be risk-stratified for their risk of thrombosis according to their age and history of thrombosis. Patients older than 60 years or with a previous history of thrombosis are considered to be high risk. Patients younger than 60 years and with no prior history of thrombosis are considered low risk.

All patients with PV should undergo phlebotomy to keep their haematocrit below 45% and should take aspirin, 81 mg daily. In addition, if a patient is at high risk for thrombosis, cytoreductive therapy is added to the management plan. Hydroxyurea at a starting dose of 500 mg twice daily is the most commonly used cytoreductive agent. It can be titrated on the basis of blood counts. In patients who are refractory to or intolerant of hydroxyurea, interferon-alpha can be used as an alternative. Busulfan is also an option for patients older than 65 years.

Phlebotomy (bloodletting) has long been the mainstay of therapy for Polycythaemia Vera (PV). The object is to remove excess cellular elements, mainly red blood cells, to improve the circulation of blood by lowering the blood viscosity. Because phlebotomy is the most efficient method of lowering the haemoglobin and haematocrit levels to the reference range, all newly diagnosed patients are initially phlebotomised to decrease the risk of complications.

Patients can be phlebotomised once or twice a week to reduce the haematocrit to the range of less than 45%. A recent randomised trial demonstrated a significant difference in the rate of thrombotic events and cardiovascular deaths (2.7 % vs 9.8%) when the haematocrit goal was 45% versus 50%. Patients with severe plethora who have altered mentation or associated vascular compromise can be bled more vigorously, with daily removal of 500ml of whole blood.

Elderly patients with some cardiovascular compromise or cerebral vascular complications should have the volume replaced with saline solution after each procedure to avoid postural hypotension. The presence of elevated platelet counts, which may be exacerbated by phlebotomy, is an indication to use myelosuppressive agents to avoid thrombotic or haemorrhagic complications.

Once the patient's haemoglobin and haematocrit values are reduced to within the reference range, implement a maintenance program either by inducing iron deficiency by continuous phlebotomies (the frequency of the procedure depends on the rate of reaccumulation of the red blood cells) or by using a myelosuppressive agent. The choice depends on the risks of secondary leukaemias and the rate of thrombosis or bleeding. Patients must be cautioned to not take iron supplements.

The risks for secondary leukaemia depend on the type of therapy (e.g., phlebotomy, radioactive phosphorus-32 [^{32} P], chlorambucil) or the type of myelosuppressive agents (e.g., hydroxyurea [HU], anagrelide, interferon alfa) and duration of therapy.

The Polycythaemia Vera Study Group (PVSG) demonstrated a decreased survival rate and increased mortality rate from acute leukaemia in the first 5 years, and a total of 17% of patients had leukaemia after 15 years with chlorambucil and with ^{32} P. An increased incidence of thrombotic complications occurred in the phlebotomy arm. This indicates that phlebotomy is not ideal for patients with elevated platelet counts and previous thrombosis, as are observed in patients who are older. In this situation, using HU has decreased these complications.

Hydroxyurea has been the mainstay therapy for PV since the PVSG results indicated it is an effective agent for myelosuppression; however, concerns have been raised regarding long-term risks for leukaemic transformation. In the PVSG trial, HU therapy reduced the risk of thrombosis compared with phlebotomy alone; the PVSG recommended that HU should be the drug of choice for patients older than 40 years.

The role of HU in leukaemic transformation is not clear. Several nonrandomised studies have supported or refuted a significant rise in leukaemic conversion with the long-term use of HU in patients with essential thrombocythaemia (from 0% to 5.5%) and in patients with PV (from 2.1% to 10%).

The PVSG closed the chlorambucil arm because of increased rates of acute leukaemia after 7 years. However, in the 15-year follow-up of the HU arm compared with the phlebotomy-alone arm, the trend for leukaemic transformation was greater in the HU arm but the differences did not meet statistical significance. Follow-up for a median of 8.6 years and a

maximum of 795 weeks showed that 5.4% of patients developed leukaemia in the HU arm compared with 1.5% of patients treated with phlebotomy alone.

Other case series have reported secondary leukaemia in 3-4% of patients, which is relatively low compared with the benefits of preventing thrombotic complications.

In an open-label study by Huang and colleagues that included 136 patients with JAK2V617F mutation–positive PV, treatment with interferon alfa 2b (IFN α-2b) did not produce a superior overall haematologic response, compared with HU. However, IFN α-2b provided better 5-year progression-free survival (66.3% versus 46.7%, P< 0.01) and clinical improvement (in vasomotor symptoms, distal paraesthesias, and erythromelalgia). No severe haematological adverse events were observed in patients receiving IFN α-2b.

Alkylating agents should not be administered to younger patients (< 40 y) who need long-term treatment. Alternative non-leukaemogenic agents are needed for these patients
Low-dose aspirin suppresses thromboxane biosynthesis by platelets, which is increased in PV and essential thrombocythaemia. The European Collaboration on Low-dose Aspirin in Polycythaemia Vera (ECLAP) found that low doses of aspirin (40mg per day) were effective for preventing thrombosis and controlling microvascular painful symptoms (erythromelalgia), which result from spontaneous platelet aggregation, in patients with PV and essential thrombocythaemia, without creating a bleeding diathesis.
(Medscape).

Medical Disclaimer

Sources and References

Cancer Research UK
http://www.cancerresearchuk.org/about-cancer/cancers-in-general/cancer-questions/polycythaemia-vera

Genetic Home Reference
http://ghr.nlm.nih.gov/condition/polycythemia-vera

Jak2 Gene Mutation
http://mpnforum.com/lab-rev/

Lab Test Online
http://labtestsonline.org/understanding/analytes/jak2/tab/test/

Mayo Clinic
http://www.mayoclinic.org/diseases-conditions/polycythemia-vera/basics/symptoms/con-20031013

Medscape
http://emedicine.medscape.com/article/205114-treatment#aw2aab6b6b3

MPD Voice
http://www.mpdvoice.org.uk/about-mpds/polycythaemia-vera/

MPR
http://www.empr.com/news/pv-evaluation-kit-qiagen-ipsogen-jak2-rgq-pcr/article/649365/?DCMP=EMC-MPR_DailyDose_cp_20170407&cpn=hemonc_all&hmSubId=i7VmYKZCM_41&hmEmail=OdsiBxRYPdkldpZ00Ap-a5dX4uYlpfYu0&NID=&c_id=&dl=0&spMailingID=16964260&spUserID=MzMyODk3NTcxNTcS1&spJobID=1000604771&spReportId=MTAwMDYwNDc3MQS2

National Cancer Institute
http://www.cancer.gov/cancertopics/pdq/treatment/myeloproliferative/HealthProfessional/page3

Polycythaemia Vera
http://www.healthline.com/health/skin-redness

Wikipedia
http://en.wikipedia.org/wiki/Polycythemia_vera