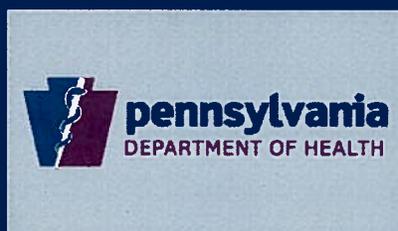


Polycythemia Vera in Northeast PA:

Research Updates

Patient and Health Professional Informational Materials

Spring 2011



To healthcare providers serving northeast Pennsylvania:

As you might know, the Pennsylvania Department of Health (PADOH) and the Agency for Toxic Substances and Disease Registry/Centers for Disease Control and Prevention (ATSDR/CDC) have identified a cluster of polycythemia vera (PV) in northeast Pennsylvania (parts of Schuylkill, Carbon and Luzerne counties).

As a healthcare provider, you are a trusted source of health information in your community. We are providing factual information about PV to assist you in answering questions from your patients. This information package includes:

- Research updates (*PINK Section*) from ATSDR, Mt. Sinai, PADEP, University of Pittsburgh, Pennsylvania Department of Health, Geisinger, Drexel University, and Geisinger/Hazleton Cancer Center.
- Patient information materials (if helpful, to copy and give to patients) (*GREEN Section*), including factsheets on JAK2 and PV, PV and myeloproliferative neoplasms (MPNs), PV in northeast PA, and resources for people with JAK2 mutation, PV or other MPNs.
- Health professional information materials (*GOLD Section*), including factsheets about the PV cluster in northeast Pennsylvania; about PV itself (risk factors pathophysiology, diagnosis, and management); public health activities and the role of health care providers; reporting PV; PV and JAK2 testing information; and the ATSDR report for the Community Health Screening for JAK2 Mutation (May 2010).
- Evaluation postcard.

For more information, please feel free to contact:

- Lora Siegmann Werner, MPH (215-814-3141, lkw9@cdc.gov)
- Elizabeth Irvin-Barnwell at CDC (jcx0@cdc.gov)
ATSDR/CDC's Principal Investigator for the PV cluster investigation
- David Marchetto at PADOH (717-346-9975, dmarchetto@state.pa.us)

You may also visit our website at: http://www.atsdr.cdc.gov/sites/polycythemia_vera/.

Thank you for your attention to this information.

Sincerely,

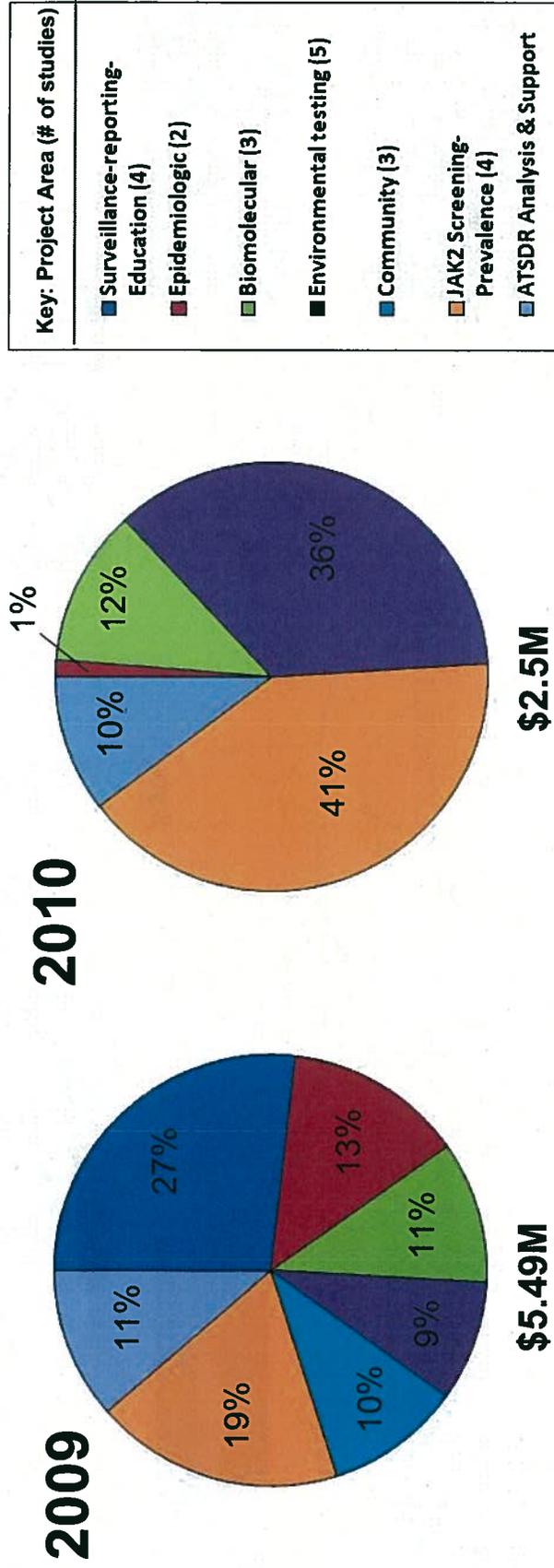


Lora Siegmann Werner, MPH
ATSDR/CDC, Region 3

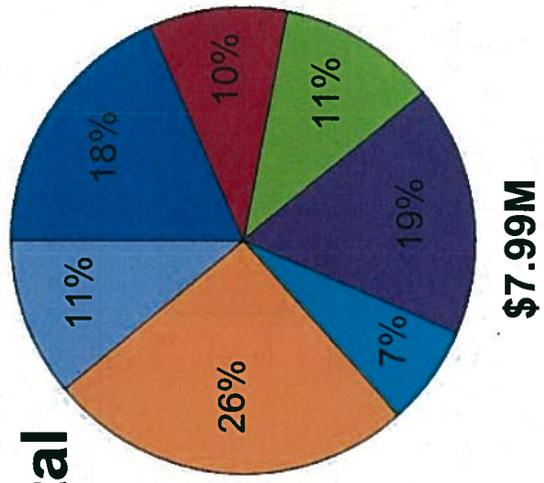




Project Area Funding for Polycythemia Vera Studies



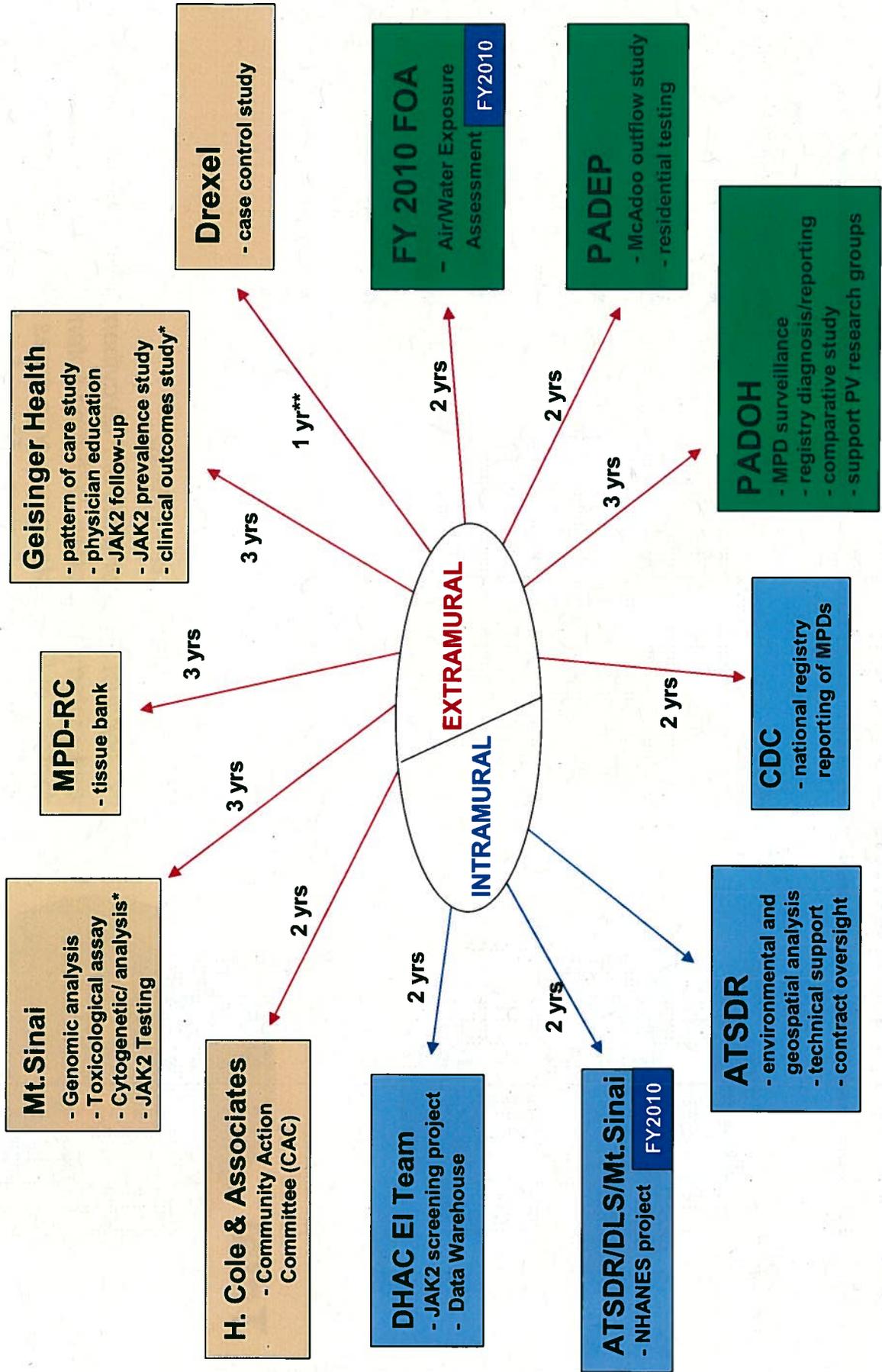
Total



PV Funding Language

"...conduct assessments of Polycythemia Vera (PV) trends and associated risk factors, including potential environmental risk factors, in PV cluster areas or in areas with potential environmental risk factors. These funds may also be used to evaluate efforts to improve reporting of PV and other hematologic cancers to cancer registries."

PV APPROPRIATIONS FUNDING – FY2009, 2010



*partially funded or conditional based on the availability of funds

**1 year no cost extension





The Prevalence of the JAK2 V617F Mutation and an Associated Haplotype in the 1999-2002 NHANES DNA Sample Set and Correlations to Demographic, Lifestyle, and Physiologic Factors

Investigators: ATSDR/NCEH, Mt. Sinai School of Medicine:

Specific Aims

- 1) Determine the prevalence of the JAK2 mutation in the general United States population
- 2) Determine the prevalence of genetic risk factors associated with the JAK2 mutation and PV.
- 3) Evaluate associations between the occurrence of the JAK2 mutation and the genetic risk factors.
- 4) Examine the relationship between the JAK2 mutation, the genetic risk factors, and hereditary, demographic, lifestyle, and physiological factors.

The NHANES 1999-2002 DNA Bank is appropriate for this purpose, as it is a complex, multistage, probability sample of the U.S. national population.

Background and Public Health Significance

The first objective of this study is to determine how common the JAK2 mutation is in individuals in the United States who do not have PV or a related blood disease. This background data is needed to evaluate and understand the results of the JAK2 screening and prevalence-testing in the PV cluster community in Pennsylvania. In addition, establishing reliable background data for the JAK2 mutation will allow its use in screening for MPN clusters in other areas. The remaining objectives are to examine associations between various potential risk factors and JAK2-status. These risk factors include hereditary, demographic, lifestyle, and physiologic attributes that have been related to JAK2-positive PV patients. The genetic risk factors associated with PV diagnosis have reported homozygous both copies of the risk factor) frequencies among European derived populations of 5% to 7% and heterozygous (one copy of the risk factor) frequencies of 38% to 41%). However, the frequencies in the U.S. are not known. It is important to establish these frequencies in order to determine the relative contribution of the risk factors to PV cases in a particular area.

PV is also associated with advanced age and occurs slightly more often in males (55%) than females (45%). A few ethnic studies of PV patients indicate that ethnic factors and ancestry may be important. There are also more Caucasians diagnosed with MPNs in the U.S.; however, this may be due to socioeconomic factors such as access to healthcare. Although no external causes have been found that lead to the JAK2 mutation or the MPNs, the discovery of the PV cluster in northeastern Pennsylvania—in an area with numerous potential environmental insults—raises the possibility that environmental factors may be involved. Recent studies have demonstrated that polycyclic aromatic hydrocarbons, documented contaminants in the cluster area, can cause genetic instability in mice. Other substances that can cause DNA damage, or act synergistically with known carcinogens, are also potential causative agents. There also may be physiologic factors, such as other medical conditions or abnormal blood chemistry that are associated with the JAK2 mutation. The data associated with the 1999-2002 NHANES DNA sample set will help identify and/or rule out potential risk factors for the JAK2 mutation, define at-risk populations, and may ultimately lead to a better understanding of MPN origins and the development of effective prevention strategies.

List of Variables Requested: Demographic, behavioral and lifestyle data and data related to MPN disease and potential risk factors – blood chemistry, blood and urine analysis of environmental agents, medical/health status, drinking water source – are requested from the NHANES 99-02 database to allow for the analysis of potential risk factors for the JAK2 mutation. We have not included a specific list of variables at this time for the following reasons: (1) the relevance of many of the variables will be established by the prevalence of the JAK2 mutation in the NHANES sample set, (2) unanticipated correlations may arise during the data analysis that will create the need for additional variables, and (3) the on-going study of the PV cluster may produce new potential associations by the time the NHANES samples have been analyzed.

We will provide a list of variables when the specimen analysis has been completed.

Period of Performance

The project period requested is 2 years. Publications should be submitted within 3 years.





Mount Sinai School of Medicine Project Updates

Submitted by: Ronald Hoffman, MD

GENE PROFILING ANALYSES

Brief Description of Project Objectives

Conduct complete genomic analyses of the PV/MPN patients from the study area and a control patient population from other geographic sites in order to detect unique genetic/hereditary features of patients in the study area.

Activities Conducted:

The analysis has been performed with blood cells isolated from 6 PV patients from the study area, 5 patients from other geographic sites and 5 normal controls. The data is now being analyzed and will likely complete in the next 3 months.

Future work:

The genome analysis will be performed with bone marrow stem cells cultured from 6 PV patients from the study area, 5 patients from other geographic sites and 5 normal controls. The data will be compared with the blood cell data. These studies are aimed to be accomplished in the next 6 months.

EVALUATION OF THE TOXIC COMPOUNDS IN THE STUDY AREA

Brief Description of Project Objectives

Develop a laboratory test to evaluate the bone marrow toxicity of toxic compounds in the study area.

Any Problems Encountered and Solutions:

The development of the assay for the evaluation of the toxic compounds has been more challenging than we originally thought. First, the concentration of each agent needs to be carefully determined since all of the selected agents are toxic compounds and high concentration will lead to cell death. However, the concentration of each agent in the study area should be very low and unlikely to have any effects in a short period of exposure. Second, the exposure time is also critical. All of the above issues have significantly slowed down our speed in the evaluation of these compounds.

Any Anticipated Problems/Issues:

The assay can be performed but it will be very difficult to determine if a specific compound was the factor to cause DNA damage and an ultimate development of PV.

Future work:

To better determine the concentration range and exposure time course. CDC will help to determine the possible estimated concentration range of each compound in the study area when the first contamination occurred.

CYTOGENETIC STUDIES - funded in September, 2010

Goal: Characterize the MPN patients by performing cytogenetic and fluorescence in situ hybridization (FISH) analysis.

FISH (fluorescence in situ hybridization) is a technique that is used to detect the presence or absence of specific DNA sequences on chromosomes. FISH is often used for finding specific features in DNA for use in genetic counseling, medicine, and species identification. This method can identify differences in the genetic make-up of individuals or groups.

Methods: Conduct FISH analysis on bone marrow cells from PV/MPN patients in the PV cluster area, PV patients from other areas, and controls (non-MPN individuals). The combined cytogenetic and gene profiling studies may help identify genetic cause of PV in the study area.

Completion date: Estimated 9 – 12 months

JAK2 MUTATIONAL TESTS

Brief Description of Project Objectives

Conduct JAK2 analysis on 1260 specimens as part of the CDC/ATSDR JAK2 mutation screening project in Pennsylvania. Conduct JAK2 confirmatory test on 30 specimens.

Activities Conducted:

- 1200 specimens were analyzed as part of the JAK2 community screening project
- Mt Sinai is now helping Geisinger with the Pennsylvania JAK2 prevalence assays
- Dr. Wenyong Zhang has left Mt Sinai and now is at Westchester Medical College. He is actively setting up his lab and establishing his assay which will be continually used for this and future studies.

Future work:

Dr. Zhang's lab and assay should be ready by the end of September and will:

- Analyze 8380 NHANES DNA specimens for the JAK2 mutation and the genetic risk factors.
- Validate the JAK2 test results for 425 DNA specimens from Geisinger Clinic.
- Screen 300 specimens and perform a validation test on 100 specimens for Drexel and/or University of Pittsburgh specimens.





Fact Sheet

Community Action Committee Public Meeting

PADEP PV Study Area Environmental Sampling

Tamaqua High School Auditorium, September 22, 2010

Phase I Sampling – March 30 2010 through May 10, 2010

PADEP contractor conducted sampling of multiple environmental media from March 30, 2010 through April 10, 2010, including the following:

- Collected surface water and sediment samples from 19 locations (one proposed location was dry at time of sampling);
- Collected private water well samples from two (2) private water supply wells;
- Collected three (3) groundwater and/or surface water samples from three (3) different power co-generation facilities including NEPCO, Wheelabrator, and Westwood power plants;
- Collected residential drinking water samples from 23 residences located in the Hazleton-McAdoo-Tamaqua region;
- Collected two (2) surface soil samples at each of five (5) of the above-mentioned residential locations, selected at random;
- Submitted all of these samples to the PADEP's Bureau of Laboratories (BOL) in Harrisburg, PA for analyses;
- Analyzed each of these samples for volatile and semi-volatile organic compounds, metals, pesticides/polychlorinated biphenyls (PCBs), herbicides, and radiological parameters;
- Received analytical data reports from the BOL and initiated the importing and Quality Control check of this data into a project-specific Microsoft-Access database in order to expedite generating data summary tables for reporting of the data;
- Performed a radon survey at 20 of these residential locations from April 5, 2010 through May 10, 2010 (three refused or were not available).

Phase II Sampling – June 14, 2010 through July 29, 2010

Conducted sampling of multiple environmental media from June 14, 2010 through July 29, 2010, including the following:

- Collected surface water and sediment samples from 18 locations (same locations as during the Phase I. Two proposed locations were dry at time of sampling);
- Collected private water well samples from the same two (2) private water supply wells;

- Collected three (3) groundwater and/or surface water samples from the same location sampled during Phase I at three (3) power co-generation facilities including NEPCO, Wheelabrator, and Westwood power plants;
- Collected residential drinking water samples from 25 additional residences (not sampled during Phase I) located in the Hazleton-McAdoo-Tamaqua region;
- Collected two (2) surface soil samples at each of five (5) of the above-mentioned residential locations, selected at random;
- Submitted all of these samples to the PADEP's Bureau of Laboratories in Harrisburg, PA for analyses;
- Analyzed each of these samples for volatile and semi-volatile organic compounds, metals, pesticides/polychlorinated biphenyls (PCBs), herbicides, and radiological parameters;
- Began receiving analytical data reports from the BOL for importing this data into a project-specific Microsoft-Access database, in order to expedite generating data summary tables for reporting of the data;
- Performed a radon survey at 20 of these residential locations (five refused or were not available);

Results

Radon analyses: have been completed for all samples collected as part of the residential radon sampling. Radon sampling is performed by placing two radon sampling canisters in each residential space to be tested. The results from each of the two canisters are averaged to determine a radon concentration for each residence tested. The Federal (EPA) action level for residential radon concentrations is 4.0 pico-curies/ liter (pCi/L). The following observations are made based on the results obtained from these two sampling events:

- The EPA action level of 4.0 pico curies/ liter (pCi/L) was exceeded in 50 percent of the residences where sampling was conducted (20 out of 40 residences);
- Relatively minor exceedances of this standard (4.0 to 10.0 pCi/L) were observed in 12 of these residences;
- Moderate exceedances (10.1 to 50.0 pCi/L) were observed in seven (7) of these residences;
- One residence exhibited a relatively high concentration of 109.0 pCi/L;

Next Steps: Results from Phase I sampling are complete. Results are undergoing a data validation process. Phase II laboratory analysis is not yet complete and once complete will have to undergo the same data validation process. Once Phase I data is validated, CDC will generate "results" letters to residents whose homes were sampled. Phase II and any future sampling results will also be provided to CDC.

Summary of indoor radon test results

Number of homes with average concentrations that exceeded the recommended action limit (≥ 4 pCi/L)
Number of homes with average concentrations lower than the recommended action limit (< 4 pCi/L)

	Phase I	Phase II
	10	10
	9	10

All homes tested

Average concentration (pCi/L)

Standard deviation

	12.1	8.2
	24.6	11.1

Of the homes with elevated concentrations (≥ 4 pCi/L)

Average concentration (pCi/L)

Standard deviation

	20.8	14.2
	32.1	13.4

Of the homes within non-elevated concentrations (< 4 pCi/L)

Average concentration (pCi/L)

Standard deviation

	2.5	2.3
	0.8	1







UNIVERSITY OF PITTSBURGH
UPDATED CASE ASCERTAINMENT STUDY FOR THE
TRI-COUNTY (Carbon, Luzerne, and Schuylkill) AREA

Community Action Committee Meeting Fact Sheet, September 22, 2010

WHAT: The **UPDATED AND EXPANDED STUDY OF POLYCYTHEMIA VERA AND OTHER MYELOPROLIFERATIVE NEOPLASMS IN THE TRI-COUNTY AREA** will build upon the last ATSDR study, conducted in 2005, by using more recent information from the Pennsylvania Cancer Registry (PCR).

The study will determine the completeness and accuracy of 2006-2008 polycythemia vera (PV) case reporting to the PCR in the Tri-county area. It will also evaluate the completeness and accuracy of other myeloproliferative neoplasms (MPNs), including essential thrombocythemia (ET), primary myelofibrosis (PMF), and chronic myelocytic leukemia (CML), in the PCR from 2001-2008.

More specifically, this study will check to see if doctors in Carbon, Luzerne, and Schuylkill Counties are reporting cases of PV, ET, PMF, and CML to the PCR. It will also check to see if these reports are accurate.

To determine if the reports are accurate, University of Pittsburgh Graduate School of Public Health (Pitt) investigators will be asking cases to agree to a review of their medical records by an expert panel of hematologists/oncologists. The investigators will offer JAK2 testing to cases not previously tested. Pitt will also ask PV, ET and PMF cases to participate in a brief interview with questions about their symptoms and ask CML cases to participate in a more detailed questionnaire with questions about their residential, medical and occupational histories.

PADOH will release updates of the study findings and a final report to the public.

WHY: PADOH has asked Pitt to update the previous work on PV by assessing changes in reporting patterns and to expand the study to assess reporting patterns of other related blood diseases.

WHO: PADOH is updating the previous ATSDR study of PV. PADOH is contracting with Pitt for this study, called the tri-county case ascertainment study.

Dr. James Logue is the Principal Investigator from PADOH for Pennsylvania's Myeloproliferative Neoplasm Program, and Mr. David Marchetto is the Program Manager.

Dr. Jeanine Buchanich, Research Assistant Professor of Biostatistics at Pitt, is the Principal Investigator for Pitt. Dr. Kristen Mertz, Assistant Professor of Epidemiology at Pitt, is the Co-Principal Investigator. Terri Washington, a Pitt staff member, will be the interviewer.

WHEN: The study recently received Institutional Review Board (IRB) approval from PADOH and Pitt. PADOH and Pitt are now finalizing the study contract. The study has an anticipated start of Oct 2010.

CONTACT INFORMATION: If you would like more information about the Pitt Tri-County Case Ascertainment Study, please contact Jeanine Buchanich or Terri Washington at 412-624-3032 or Jeanine@pitt.edu.

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PaPV Data Warehouse Project Update September 22, 2010

Purpose

ATSDR is developing an electronic PaPV Data Warehouse (database) that will contain readily accessible environmental data (such as information on contaminants in groundwater, private well water, soil, sediment, and surface water) in the tri-county area of Carbon, Luzerne, and Schuylkill counties in Pennsylvania. The purpose of the Data Warehouse is to aid researchers in their investigations of whether chemicals in the environment may be the cause of the Polycythemia Vera (PV) cancer cluster in the tri-county area.

What is the Data Warehouse?

The PaPV Data Warehouse is an electronic inventory of environmental data. The database will provide readily accessible data for the tri-county area to researchers and the public.

The PaPV Data Warehouse project is in the final stages and includes three main activities:

- gathering environmental data that is available online from the U.S. Environmental Protection Agency (EPA) and other relevant sources (such as other government agencies);
- gathering site-specific environmental data from the EPA and Pennsylvania Department of Environmental Protection (PADEP); and
- developing the PaPV Data Warehouse.

How are we gathering the data?

ATSDR reviewed appropriate online databases and found that fifteen sources have relevant environmental data for the tri-county area, along with some of the neighboring counties (Berks, Columbia, and Lehigh counties), and other counties that will be used by researchers for comparison to the tri-county area (Somerset, Bedford, Cambria, and Blair). The various online data sources will be structured into a common format and will be included in the Data Warehouse. Summaries of the information in the fifteen online data sources were prepared so ATSDR could review all the specific data that is available for each data source.

ATSDR focused on an area around the PV cancer cluster located on Ben Titus Road. This area is called the focused area. There are many sites in the focused area that could be causes of contamination, so ATSDR ranked the sites in order to identify those sites that are most important to the project. The sites within the focused area were classified into three tiers:

- Tier I sites are those known to have released contamination to the environment, such as Superfund sites and cogeneration power production plants. Data for these sites will be included in the PaPV Data Warehouse.
- Tier II sites might have released contamination to the environment. For these sites, only facility information will be included in the Data Warehouse.
- Tier III sites may not have released contamination to the environment. These sites will be listed in the Data Warehouse by name and address.

To date, ATSDR has completed five on-site file review sessions at the PADEP office in Wilkes-Barre and one at the EPA Region 3 offices. Approximately 200 Tier I sites in the focused area have been identified and readily accessible data from many of these sites have been reviewed at the PADEP offices. Documents with relevant environmental data will be included in the PaPV Data Warehouse.

Five Superfund waste sites (McAdoo Associates, EDM, Tonolli, Valmont, and C&D Recycling) are located in the focused area. For these sites, ATSDR gathered information from the EPA website and the PADEP.

What are the next steps?

- **PADEP File Review:** ATSDR will be conducting a file review session at the end of September at the PADEP offices.
- **Development of the PaPV Data Warehouse.** ATSDR is working with computer experts to develop an electronic application that can be used by researchers and the public to access the collected environmental data. Currently, ATSDR is identifying common data fields for the data; these data fields will make the Data Warehouse searchable by users.





PI Roda, Geisinger-Hazleton Cancer Center, Hazleton, PA; R Hoffman, M Xu, and W Zhang, Mount Sinai School of Medicine, New York, NY

Abstract

Background: In 2007, our consortium demonstrated that the incidence of confirmed *J. vera* in a rural area in Northeast Pennsylvania was higher than expected based on Pennsylvania and U.S. Tumor Registry data. Future plans include public health screening in this and in other communities in Pennsylvania. This project will determine if a screening program is able to detect JAK2^{V617F} mutation positive myeloproliferative neoplasms (MPNs).

Methodology: The Agency for Toxic Substances and Disease Registry offered JAK2^{V617F} mutation testing to community residents on two occasions in 2005. Participants registered in advance, and informed consent was obtained per Federal Guidelines. Samples obtained from 1,170 residents were sent to Mt. Sinai School of Medicine and tested using a quantitative JAK2^{V617F} mutation assay. Mutation positive patients were further evaluated by reviewing medical records or by a medical evaluation.

Results: Nineteen residents were JAK2^{V617F} mutation positive. One patient was known to the working group. Four patients had on MPN but were not previously known to the Pennsylvania Tumor Registry. Ten residents were medically evaluated. One resident was found to have *P. vera* and a second was found to have *E. thrombocytosis*. Two patients refused evaluation. The remaining patients have low JAK2^{V617F} mutation allele burdens without evidence of an MPN. This latter group will be monitored over the next two years to see if they convert into having a disease and whether they remain JAK2^{V617F} mutation positive.

Conclusions: Screening an "at-risk" community for the JAK2^{V617F} mutation will detect patients who carry this mutation without clinical disease as well as patients that were not reported to tumor incidence of *Polycythemia vera* (*P.V.*).

Background

Previous research identified two areas in North East Pennsylvania that had an increased incidence of *Polycythemia vera* (*P.V.*):

Use of Molecular Testing to Identify a Cluster of Patients with *Polycythemia Vera* in Eastern Pennsylvania
Seaman V, Jumanan A, Yanni E, Lewis B, Roda P et al;
Cancer Epidemiol Biomarkers Prev; Feb. 2009;18(2).

This is one of several studies to evaluate cluster that was initiated by the ATSDR / CDC Principal goal was to address community concerns by offering an opportunity for worried, asymptomatic residents to be screened.

Secondary goal was to see if further cases of JAK2^{V617F} mutation positive *P. vera* could



Figure 1. - Location of additional cases in 2007 abstract and 2009 publication

Methods and Materials

Patient selection and recruitment

- Current residents of the tri-county area were offered screening for the JAK2^{V617F} mutation
- Recruitment through local Community Action Group, flyers, and articles in the local news media
- Patients asked to schedule a visit to have blood drawn
- Informed consent obtained by ATSDR prior to participation
- Quantitative JAK2^{V617F} mutation assay was performed by Doctors Zhang and Xu at the Mount Sinai School of Medicine

Follow-up for JAK2^{V617F} mutation positive patients

- Separate (Geisinger) consent for this part of program
- Targeted evaluation performed at the Geisinger/Hazleton Cancer Center
- Records request to verify reported pre-existing "blood condition" or similar
- Focused symptom review, physical examination and lab collection
- MPN - specific QOL questionnaire
- Patients to be followed until they develop evidence of *P. vera*, *E. thrombocytosis*, or other Myeloproliferative Neoplasm

SNP 46/1 Haplotype testing

Patient genomic DNA was extracted from EDTA anti-coagulated whole blood using the Qiagen BioRobot M48 Workstation (Qiagen, Valencia, CA) according to the manufacturer's directions. Quantification of extracted DNA is performed using a NanoDrop ND-1000 spectrophotometer (NanoDrop Technologies, Wilmington, DE). Single nucleotide polymorphism (SNP) genotyping was performed on an Applied Biosystems 7500 Fast real-time PCR System (Applied Biosystems, Foster City, CA) using Taqman assay reagents for SNP rs123243867 and rs23240895 according to the manufacturer's protocol.

Results

Nineteen of 1,170 residents screened tested positive for the JAK2^{V617F} mutation.

- One patient had previously participated in a consortium sponsored study and was excluded from further analysis
- Four additional residents were under medical care for a MyeloProliferative Neoplasm
- Two patients refused participation

The remaining twelve patients underwent medical evaluation

- One diagnosed *P. vera* per 2005 WHO criteria
- One diagnosed *E. thrombocytosis*, confirmed by bone marrow exam
- Ten had no clinical evidence of disease (All ten of these patients had a positive JAK2^{V617F} mutation assay performed at least six months after the initial assay. In most cases, the titer was higher than previous.)

SNP testing for the 46/1 haplotype was performed on eleven of the above patients

- 27% homozygous
- 36% heterozygous
- 36% normal

Patient addresses were plotted by the ATSDR

There was a predominance of residency in the previously noted "Area 1" (see Table 1, below and Figure 2).

Cluster Zone**	1 st visit	2 nd visit	Total	Total # JAK2 ^{V617F}	% JAK2 ^{V617F}	JAK2 % P<0.05
C-Hazleton area	20	128	148	1	7.1	0.58
C-Silchester area	48	145	193	1	7.1	0.43
C-Terminus area	173	238	411	8	87.1	1.64
Total	240	509	749	10	71.4	1.12

Outside Cluster**	Total	# JAK2 ^{V617F}	% JAK2 ^{V617F}				
Terminus area**	16	48	64	5.5	1	7.1	1.11
Hazleton area	2	5	7	0.5	0	0.0	0.00
Frankfort area	35	110	145	12.4	0	0.0	0.00
Jim Thorpe area	23	32	55	4.7	1	7.1	1.52
Polysar area	31	85	116	10.6	2	14.3	1.38
Willsboro area	3	7	10	0.9	0	0.0	0.00
Outside	6	8	14	1.2	0	0.0	0.00
Total	116	305	421	28.0	4	29.8	0.79

Table 1. - Resident locations
** Includes area 1/1.5 miles of town/city center but outside cluster area
Order metric: Cluster Zone to Outside Cluster Zone is 1,4

Conclusions

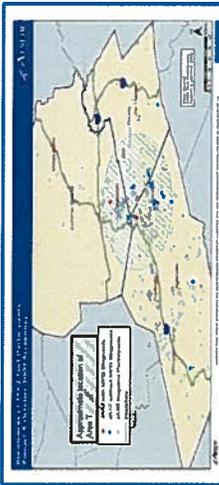
Screening for the JAK2^{V617F} mutation is a feasible public health measure and tool to assess the extent of JAK2^{V617F} mutation in a fixed population.

The additional cases detected in this project support other data indicating that there is a cluster of *P. vera* in North East Pennsylvania.

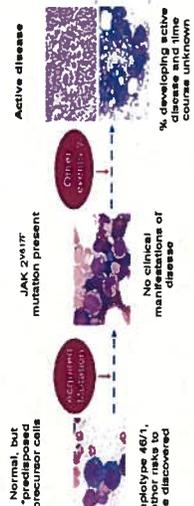
The frequency of snp haplotype 46/1 is similar to other populations tested.

- An inherited tendency to develop the JAK2^{V617F} mutation is part of the answer, but doesn't explain all of the patients.

This study has identified a preclinical cohort with the mutation but without disease. The natural history of this cohort remains to be defined.



PROPOSED PATHOGENESIS OF JAK2^{V617F} POSITIVE MPNS



Acknowledgements and Funding

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Geisinger - Hazleton Cancer Center

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Vince Seaman, Ph.D.
Ken Orloff, Ph.D, DABT
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Laura Werner, M, Ph
Elizabeth Inth-Bammwell, Ph.D
Screening performed by ATSDR
Cost recovery number A08X







Drexel University School of Public Health Case-Control Study in Northeast Pennsylvania

Fact Sheet

September 2010

What is the Drexel case-control study?

The main objective of the Drexel University study is to investigate possible risk factors for polycythemia vera (PV) and several related blood diseases – essential thrombocythemia and primary myelofibrosis – among residents of the tri-county region in Northeast Pennsylvania (Carbon, Luzerne, and Schuylkill Counties). A risk factor is anything that may have contributed to the cause of disease.

Our case-control study will compare characteristics of people who have been diagnosed with these diseases (“case” group) with a carefully selected sample of people who are not known to have these blood diseases (“control” group). Information from each group will be gathered through questionnaires and blood draws.

Study Participant Recruitment

Case information will be obtained through records from the Pennsylvania Cancer Registry. Potential cases will be mailed packets with information about the study and how to join.

A suitable control group from the tri-county population will be selected through random telephone dialing of residential phone listings. The Geisinger Survey Unit will oversee the selection of controls.

Approximately 4 controls will be selected for each case. We expect between 500 and 650 residents from the tri-county area (Carbon, Luzerne, and Schuylkill Counties) to be enrolled in the study.

Drexel Partners

Drexel has partnered with Geisinger Survey Research Unit and Geisinger Medical

Laboratories in Danville, PA to conduct all primary data collection (control recruitment, phone surveys, blood draws) in the tri-county area.

Other Collaborating Agencies

- Agency for Toxic Substances and Disease Registry (ATSDR)
- Mount Sinai School of Medicine (NY)
- Pennsylvania Department of Environmental Protection (DEP)
- Pennsylvania Department of Health (PADOH)
- University of Pittsburgh Graduate School of Public Health

Study Activities

There are two data collection phases of the study:

- 1) One-time phone questionnaire/survey (approximately an hour). Each participant will be asked for details about their current and past residences, jobs, personal and family medical histories and health behaviors, environmental and chemical exposures, and social and economic characteristics.



- 2) One-time, optional blood draw – a routine blood draw will be offered to all participants. The blood draw will test for the JAK2 mutation and for selected genetic susceptibilities to environmental toxins. The blood draw is not necessary for study participation.



Study Progress and Timeline

Drexel will begin recruiting study participants in the Fall of 2010. At that time, our collaborator Geisinger Survey Research Unit will randomly select the “controls” from the tri-county population through telephone surveying. Data collection – surveys and blood draws – will continue through 2011.

Please turn page over

To be eligible for participation in the study:

Case Inclusion Criteria (must meet all):

- 1) Diagnosis of polycythemia vera, essential thrombocythemia, or primary myelofibrosis between January 1, 2001 and December 31, 2008 *and*
- 2) Born between January 1, 1921 and December 31, 1968 *and*
- 3) Continuous residence within tri-county region (Carbon, Luzerne, or Schuylkill County) during 2000-2008.

Controls will be randomly selected from the tri-county population.

Control Inclusion Criteria (must meet all):

- 1) Born between January 1, 1921 and December 31, 1968 *and*
- 2) Continuous residence within tri-county region (Carbon, Luzerne, or Schuylkill County) during 2000-2008.

(Participants will receive a gift card after successful completion of each phase.)

Can anyone else participate?

While there is a chance you may be contacted to participate if you live in the tri-county area, our study protocol does not allow volunteers from the public to join the study – the statistically random selection process must be followed for scientific validity.

Primary Exposures of Interest

The primary exposure assessments will be drawn from residential histories, job histories, and other lifestyle characteristics provided in the phone questionnaire phase. Both environmental and non-environmental related questions will be asked of the subjects. In addition to the questionnaires, historical environmental data collected from various sites in the tri-county area will support the final data analysis.

Purposes of Blood Draw: An optional blood draw phase for cases and controls will evaluate

JAK2 mutation frequencies and certain genetic susceptibilities to environmental toxins.

Changes in genes that metabolize toxins will be studied to determine if they are related to probability of getting the diseases under study.

Realistic expectations for any community studies of cancer and the environment:

This is the first study of its kind for PV and related blood diseases in the U.S. We hope it yields important leads that will eventually be useful for preventing these diseases. It is important to remember that finding a simple and specific cause is not likely from any one study of this type. We thank the community and participants for their cooperation in taking this important step for science and public health.

Contact Information

If you would like more information about Drexel University's study in Northeast Pennsylvania, please call the Project Manager Carol Ann Gross-Davis at (215)762-6761 or email cg48@drexel.edu.

Principal Investigator:
Arthur L. Frank, MD PhD
Professor, Chair

Project Manager:
Carol Ann Gross-Davis, MS
Assistant Professor

Drexel University
School of Public Health
Department of Environmental and
Occupational Health

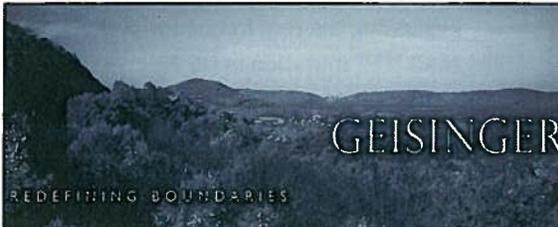
Sponsor

The Centers for Disease Control and Prevention (CDC),
Department of Health and Human Services.

CDC Research Grant Number: 1R01EH000640-01







Polycythemia vera

Ongoing research of a cluster of P. vera in North East Pennsylvania

Paul I. Roda MD., FACP
Geisinger/Hazleton Cancer Center

Issues raised by the original study

- 53% of original patient group diagnosed as "*P. vera*" actually had *P. vera*.
- Reason isn't clear
 - Coding errors
 - Pre - 2007 diagnosis not based on WHO criteria
- In spite of errors, incidence of *P. vera* in the tri-county region appears elevated
 - Pollution or other environmental issues?
 - Heredity and ancestry?
- National incidence/prevalence of *P. vera* needs to be re-assessed now that we have a molecular test to identify patients

Geisinger studies Initiated at the request of the CDC/ATSDR

- Evaluation of JAK2 mutation positive residents detected in a community screening program
 - Do they have disease ?
- Testing "MyCode," Geisinger's tissue bank
 - Evaluation of 6,000 samples for frequency of JAK2 mutation and 46/1 haplotype
- Chart review
- Physician Education

Patient selection and recruitment

- Current residents of the tri-county area offered screening for the JAK2^{V617F} mutation
 - Recruitment through local Community Action Group, flyers, and media stories
 - Multiple sites adjacent to previously identified cluster
 - Known PV cases (from the prior study) were excluded
 - A total of 1,170 residents were screened
- Quantitative JAK2^{V617F} mutation assay was performed by Mt. Sinai School of Medicine
- JAK2^{V617F} mutation pos. patients were then evaluated by either chart review or at Geisinger - Hazleton Cancer Center

Preliminary Results

- Nineteen of the (1,170) residents tested positive for the JAK2^{V617F} mutation
 - Five patients revealed they were under a physician's care for an MPN
 - Two patients refused evaluation despite mutation status
 - Leaving twelve patients not known to have an MPN
- Further evaluation offered to these twelve
 - One case each of *P. vera*, *E. thrombocytosis*
 - The remaining ten had no clinical evidence of disease
- Second round (six month) follow-up has started

JAK2+ Results Inside and Outside of the PV Cluster Area by Location

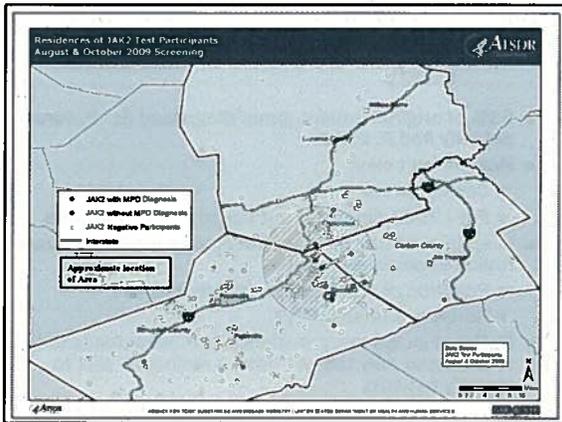
Cluster Zone*	1 st set	1 st set	Total	Total	# JAK2+	% JAK2+	JAK2 % /Patch
C-Hazleton area	20	128	148	12.8	1	7.1	0.56
C-McAdoo area	48	145	193	16.5	1	7.1	0.43
C-Tamaqua area	172	226	408	34.9	6	57.1	1.64
Totals	240	509	749	64.0	10	71.0	1.12

*Based on closest town/city center to participant address

Outside Cluster*	1 st set	1 st set	Total	Total	# JAK2+	% JAK2+	JAK2 % /Patch
Tamaqua area	16	48	64	5.5	1	7.1	1.31
Hazleton area	2	5	7	0.6	0	0.0	0.00
Franklin area	35	110	145	12.4	0	0.0	0.00
Jim Thorpe area	22	32	55	4.7	1	7.1	1.52
Pottsville area	31	95	126	10.8	2	14.3	1.33
Willow-Barre	3	7	10	0.9	0	0.0	0.00
Outside	6	6	14	1.2	0	0.0	0.00
Totals	116	305	421	36.0	4	28.6	0.79

*Includes area w/in 5 mi. of town/city center but outside cluster area;

•Odds ratio Cluster Zone to Outside Cluster is 1.4



Evaluating the real frequency of the JAK2^{V617F} mutation in NE Pa

- How common is the JAK2^{V617F} mutation ?
 - Goal is to evaluate 6,000 samples from "MyCode," including 2,500 from tri-county region
- Compare frequency of the JAK2^{V617F} mutation in the tri-county area with remainder of sample pool
- Medical records of JAK2^{V617F} mutation positive patients will be reviewed to see if they are known to have an MPN
 - Proposed future studies would evaluate JAK2^{V617F} mutation positive individuals who lack documentation of a disease
- Evaluate the role of heredity
 - By testing for the presence of a specific (46/1) haplotype
 - This is a marker on the JAK 2 gene that's common in patients who develop the myeloproliferative neoplasms

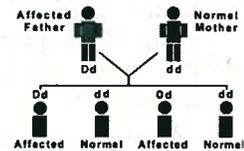
The MyCode Project

Dave Carey, Ph. D., Glenn Gerhard, M.D., Ph. D

- MyCode – a tissue bank obtained from active Geisinger patients
 - Voluntary contribution of blood samples with consent for future research testing
 - Volunteers must have Geisinger Health Plan
 - Volunteers must have been Geisinger Primary Care patients for over two years
 - Collections have initially been in North Central Pennsylvania, but have expanded to the tri-county area

Human genetic variability and MPNs

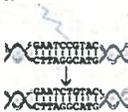
- Every human has essentially the same set of genes
 - One maternal, one paternal allele
 - But genes often differ



- Different alleles:
 - May code for different proteins
 - Blood group O vs. A vs. B
 - Genetic diseases such as Huntington's disease
 - Differences may be in control areas, silent

Single Nucleotide Polymorphisms or SNPs

- Variations of a single base between individuals:
- An SNP must occur in at least 1% of the population.
- SNPs are the most common type of variations.
 - 1/500 bases
 - 3 billion/500 = >6 million SNPs
- SNP alleles
 - Major allele (e.g., C)
 - Minor allele (e.g., G)
- An individual can be, for each polymorphic locus:
 - Homozygous for the major allele (CC).
 - Heterozygous for the major/minor allele (CG).
 - Homozygous for the minor allele (GG).
 - Multiple variants of the minor alleles probable



MyCode – Results to date

(per G. Gerhard, September 1, 2010)

- 28 JAK2^{V617F} mutation positive patients in 2,055 samples tested
 - Samples principally from other areas of NE Penn.
 - Three cases carry a chart diagnosis of an MPN – one PV, one ET., and one not otherwise specified
 - A fourth case is on hydroxyurea and has a CBC compatible with *P. vera* (but no hematologic diagnosis)
- Eighteen of 21 JAK2^{V617F} mutation pos. cases tested carry the at-risk haplotype
- Approximately 45% of the JAK2^{V617F} mutation negative population carry the SNP 46/1 haplotype

Physician Education

- Local/Regional
 - St - Luke's Miners
 - Hazleton General*
 - WB - Vet. Admin
 - Geisinger - Danville
 - Sacred Heart - Allentown
 - St. Joseph - Reading
 - St. Luke's Bethlehem*
- * Scheduled
- Statewide meetings
 - POHS meeting
 - Heme/Onc update*
- Major Centers
 - Univ. of Penn.
 - Thomas Jeff. Univ.*
 - Robert Packer - Guthrie
 - Penn State - Hershey*
 - Hahnemann Univ*
- European School of Hematology

GEISINGER

1000 North 10th Street, Danville, PA 17015 • A Division of the Geisinger Health System, Inc. • Danville, PA 17015

Physician Education

Geisinger Health System is pleased to announce the following physician education opportunities for 2011. These opportunities are available to all Geisinger Health System physicians and are subject to availability. For more information, please contact the Geisinger Health System Physician Education Department at 717.244.2222.

Local/Regional

- St. Luke's Miners
- Hazleton General*
- WB - Vet. Admin
- Geisinger - Danville
- Sacred Heart - Allentown
- St. Joseph - Reading
- St. Luke's Bethlehem*

■ * Scheduled

Statewide meetings

- POHS meeting
- Heme/Onc update*

Major Centers

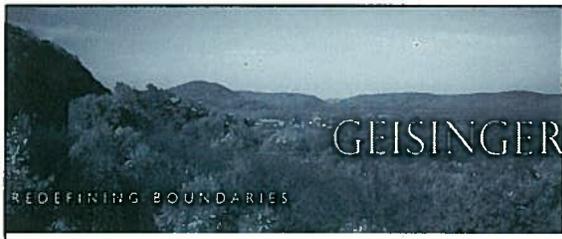
- Univ. of Penn.
- Thomas Jeff. Univ.*
- Robert Packer - Guthrie
- Penn State - Hershey*
- Hahnemann Univ*

European School of Hematology

For more information, please contact the Geisinger Health System Physician Education Department at 717.244.2222.

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Thank you for your consideration

Questions will be answered later







Air and Water Exposure Assessment Project

September 22, 2010

Purpose

ATSDR is funding a new project titled "Current and Historical Human Exposure Assessment of Drinking Water and Air Pollution Sources in the PV Cluster Area in NE Pennsylvania". The purpose of the project is to determine potential sources, pathways, and exposures via drinking water and air to the Tamaqua/cluster area community.

Objectives

There are two project objectives:

- 1) To examine hydrogeology of the project area
- 2) To estimate current and past exposures of study area residences to specific air pollutants.

How will the study help with determining exposure?

A hydrogeology determination will be conducted to assist with the evaluation of relationships between present and past PV case residences in the cluster area and the sources of potable water used in the areas. It is possible that the above hydrogeology study may necessitate field sampling, i.e. core sampling, tracer studies, and water analysis. Additionally, the work will include an evaluation of available water testing data in the cluster area, both past and present. The water testing data will determine whether potable water in the cluster area was contaminated resulting in possible exposure. Local and regional sources of air pollutants in the study area will be identified and characterized. Based on these sources, air pollutant monitoring and atmospheric dispersion models will be conducted. Present and past exposures of cluster area residents will be evaluated.

Project status

ATSDR has received applications for the project. The applications are undergoing review and the awardee will be notified by September 30, 2010. The anticipated start date of the project is October 1, 2010.





INVESTIGATIONS OF MYELOPROLIFERATIVE NEOPLASMS IN THE TRI-COUNTY AREA OF NORTHEAST PENNSYLVANIA

**2010 Northeast Epidemiology Conference
November 3-5, 2010**

David J. Marchetto, M.S., C.P.H., Program Manager

**James N. Logue, Dr.PH., M.P.H., Principal Investigator
Stephen M. Ostroff, M.D., Bureau Director**



Myeloproliferative Neoplasms (MPNs)

- **Classic BCR-ABL (fusion protein) negative MPNs**
 - **Polycythemia vera (PV)**
 - **Essential Thrombocythemia (ET)**
 - **Primary Myelofibrosis (PMF)**
- **Chronic Myelogenous Leukemia (CML)**
- **Others**



Background

- In 2004, residents in Tamaqua area of NE PA voiced concerns about high rates of cancer/ other chronic diseases
- Ostensibly related to nearby McAdoo Superfund site
- PADOH used 1996-2003 data from PA Cancer Registry (PCR) to compare rates for Carbon, Luzerne, and Schuylkill counties to overall state rates



Incidence of PV in Tamaqua Cluster compared with rest of Tri-county area and entire Tri-county region

	Area T	Rest of Tri-county	Total Tri-county
Population (% total)	86,482 (16)	447,906 (84)	528,388 (100)
Confirmed Eligible Cases	15	18	33
PV Incidence Rate	3.47	0.81	1.25
Area T rate ratio (95% confidence interval)	-	4.3 (2.2-8.5)	2.8 (1.7-4.5)
Area T Poisson Probability	-	1 in 2.2 x 10 ⁵	1 in 2.0 x 10 ³



JAK2 (617F) Mutation

- **First reports of association with PV, ET, and PMF in 2005**
- **Acquired somatic mutation**
- **Present in >95% of patients with PV**
 - **Approx. 50% in patients with ET and PMF**
- **JAK2 believed to be a driver of excess proliferation in PV, ET, and PMF**



Tri-county Area JAK2 Study - 2009

- **Offer testing of blood specimens for the residents of the Tri-county area**
- **Summer and fall of 2009**
- **Self-selected population screened**
- **Education and screening**



JAK2 Community Screening Findings

	Number	Age (range)	Age (mean)	Length of residence (mean)
All Participants	1,170	2-92	54	24
JAK2+ with Disease (1)	5	50-77	64	20
JAK2+ without Disease	14	23-88	63	28

(1) Diagnosed with or had clinical symptoms of an MPN



JAK2 Community Screening Findings

- **1.2% (14) of those screened without Hx of MPN were JAK2+**
- **Cannot determine if an increased prevalence is population based**
- **JAK2 is associated with increased risk of MPN – but not known who is at risk**
- **14 enrolled as cohort for further study**



Prevalence of JAK2 (617F) Positive Tests Results in Published Studies				
Author	Number Tested	Percent Positive (%)	Analytic Sensitivity (%)	Location
Sideon 2006	57	10 (5/57)	0.01	Belgium
Sutton 2007	57	1.8 (1/57)	0.1	OK, TN
Xu 2008	3,935	0.9 (37/3,935)	0.25	China
Rapado 2008	149	2.0 (3/149)	0.001	Spain
ATSDR/PADOH	1,165	1.2 (14/1,165)	0.05	PA



Other Studies in Cluster Area

- **MPN case update in Tri-county**
- **Case control study**
- **Toxicological study - bone marrow assay**
- **Tri-county residential environmental testing - air and water exposure assessment**

Other Studies Outside Cluster Area

Four-county PV case ascertainment study:

- **Reproduce original ATSDR investigation in a Four-county area with similar population and demographics to cluster area**



The My Code Project

Tissue Bank from active Geisinger patients:

- **Voluntary contribution of blood samples with consent for future research**
- **Must be enrolled in Geisinger Health Plan**
- **Must be primary care patient for >2 years**
- **Collections mainly in north central PA – recently expanded to the Tri-county area**



The My Code Project (con.)

- Determine prevalence of JAK2 in a select population of PA patients: 6,000 specimens from outside cluster area and 2,500 from inside
- Analyze for JAK2 and an associated risk haplotype (46/1)
- To date, 2,055 of first 6,000 DNA samples analyzed. Of these, 28 (1.4%) were JAK2 positive, 24 of which (1.2%) had no evidence of an MPN



NHANES JAK2 Mutation Prevalence Study

- ATSDR acquired DNA from 7,900 participants of CDC's National Health and Nutrition Examination Survey (NHANES)
- Analysis for JAK2 and the 46/1 risk haplotype
- Results will help establish a background prevalence of mutation and 46/1 haplotype and may identify associated demographic, behavioral, or physiologic factors



Conclusions

- **Comprehensive research portfolio will assess environmental factors, genetic predisposition and etiology of MPNs in Tri-county area**
- **JAK2 prevalence studies will determine JAK2 prevalence in general U.S. population, PV cluster area, and NE PA region**



Conclusions (con.)

- **Regardless whether specific cause of Tri-county area PV cancer cluster can be determined -- projects will benefit:**
 - **Local residents**
 - **MPN and cancer patients**
 - **Medical research community**



Questions?

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dmarchetto@state.pa.us









Summer 2010

JAK2 and Polycythemia Vera

Schuylkill, Carbon and Luzerne Counties

About ATSDR

The Agency for Toxic Substances and Disease Registry (ATSDR) is part of the U.S. Department of Health and Human Services. It is a sister agency to the Centers for Disease Control and Prevention (CDC).

ATSDR gives information to the public to help you avoid contact with harmful materials. We use the best science we can to help you protect your health.

ATSDR has partnered with the Pennsylvania Department of Health (PADOH) since 1989.

Other Mutations

The JAK2 mutation is the mutation most often tested for when a healthcare provider thinks a person might have PV. Other genetic mutations can also cause PV. Testing for these mutations is more difficult and uncommon. But your healthcare provider might order these tests if he or she strongly suspects PV even if a JAK2 test is negative.

Summary

The JAK2 mutation is a genetic change found in about 9 out of 10 people with polycythemia vera (PV). PV is a rare blood condition. In some parts of Schuylkill, Carbon and Luzerne Counties, more people than expected have PV compared with other locations.

A JAK2 blood test can help you find out if you have PV or if you *might* develop PV. A positive test does not mean you are sick or will get sick.

This fact sheet gives information about the JAK2 mutation and JAK2 blood testing.

What Is the JAK2 Mutation?

JAK2 is part of a signaling system (like a thermostat) that helps tell the bone marrow when to start and stop making blood cells. Most people with PV have acquired a mutation (change) in their JAK2. Because of this change, the bone marrow makes too many blood cells.

People with the JAK2 mutation might have or develop PV or one of the other myeloproliferative neoplasms (MPNs). On the other hand, they might never get one of these diseases.

PV and other MPNs take years to develop. You can be perfectly healthy and still have the JAK2 mutation. If you have the JAK2 mutation, you should visit your doctor regularly, even if you feel healthy. Medical care might help you avoid or delay health problems from PV or the other MPNs.

People without the JAK2 mutation likely will not develop PV—unless the mutation appears at a later time.

What Is the JAK2 Blood Test?

A JAK2 blood test can help you find out if you have PV or if you *might* develop PV. A positive test does not mean you are sick or will get sick.

To get a JAK2 blood test, visit your healthcare provider. They will draw a little blood and contact you with the results.

Should I Get the JAK2 Blood Test?

A JAK2 test is expensive (usually more than \$1,000). Your healthcare provider will probably order the test only if he or she has a reason to think you might have a blood disease—for example, if you have an unusual blood count or an enlarged spleen.

What Happens if the Test Is Positive?

Having a positive JAK2 blood test does not mean that you have or will develop PV. However, you *might* develop PV or other MPNs later in life.

If your test is positive for JAK2, talk to your healthcare provider about the test, your health and next steps. Your healthcare provider can suggest ways to:

- Check to see if you develop PV.
- Avoid or delay health problems if PV occurs.

What Does a Positive Test Mean if I'm Healthy?

Having a positive JAK2 blood test does not mean that you are sick or will get sick. However, you *might* develop PV or other MPNs later in life. Your healthcare provider might want to check your blood counts and monitor your health carefully.

How Can I Learn More?

To learn more about JAK2, PV and other MPNs, you can:

- Ask your healthcare provider.
- Visit ATSDR's Web page on PV:
http://www.atsdr.cdc.gov/sites/polycythemia_vera/index.html
- Call ATSDR's toll-free PV information line:
866-448-0242

What are MPNs and PV?

MPNs are blood disorders in which the bone marrow makes too many blood cells. PV is an MPN in which too many red blood cells cause health problems. PV and other MPNs take years to develop. People with PV might experience headaches, tiredness, shortness of breath, blood clots and heart problems.

Is the JAK2 Mutation Found With Other Diseases?

The JAK2 mutation is also found with two other MPNs:

- ***Essential thrombocythemia (ET)***
- ***Primary myelofibrosis (PMF)***

About half of people with ET or PMF have the JAK2 mutation.







Summer 2010

Polycythemia Vera and Myeloproliferative Neoplasms

Schuylkill, Carbon and Luzerne Counties

About ATSDR

ATSDR is part of the U.S. Department of Health and Human Services. It is a sister agency to the Centers for Disease Control and Prevention (CDC).

ATSDR gives information to the public to help you avoid contact with harmful materials. We use the best science we can to help you protect your health.

ATSDR has partnered with PADOH since 1989.

Bone Marrow

Bone marrow is the soft, spongy tissue inside bones. It makes blood cells.

Polycythemia literally means "many cells in the blood":

Poly = many
Cyt = cells
Hemia = blood

Summary

Polycythemia vera (PV) is a rare blood disease with no known cause. If you have PV, your bone marrow makes too many red blood cells, thickening your blood. Thick blood can lead to weakness, sweating, itching, headaches, tiredness, shortness of breath, blood clots and heart problems.

Myeloproliferative neoplasms (MPNs) are diseases where the bone marrow makes too many blood cells—red blood cells, white blood cells and/or platelets (clotting cells in blood). PV is one of the MPNs.

To diagnose PV and other MPNs, healthcare providers consider your symptoms, review your health history, do a physical exam, order blood tests and sometimes take a bone marrow sample. Right now, PV and other MPNs have no cure. But treatment can avoid or delay health problems.

In the United States, about one in 100,000 people are diagnosed with PV each year. In parts of Carbon, Luzerne and Schuylkill counties, more people than expected have PV compared with other locations. The Pennsylvania Department of Health (PADOH) and the Agency for Toxic Substances and Disease Registry (ATSDR) are working to find out why.

This fact sheet gives information about PV and other MPNs.

What Is Polycythemia Vera (PV)?

PV is a rare blood disease that develops very slowly. If you have PV, your bone marrow keeps making blood cells—red blood cells, white blood cells and platelets—even when your body does not need that many cells. Over time, having too many red blood cells thickens the blood. This is why some people call PV "thick blood."

Thick blood moves more slowly through your blood vessels, so parts of your body get less blood—and less oxygen from the blood. At first, you have no symptoms. Over time, thick blood can lead to weakness, sweating, itching, headaches, tiredness, shortness of breath and blood clots.

Blood clots are dangerous when they block the flow of blood in a blood vessel. Blocked blood flow to the heart can cause a heart attack. Blocked blood flow to the brain can cause a stroke.

Signs and Symptoms of PV (after having PV for years)

More Common	Less Common
<ul style="list-style-type: none"> • Abnormal blood cell counts • Itching, especially after bathing • Enlarged spleen • Weight loss • Weakness • Sweating 	<ul style="list-style-type: none"> • Bruising • Nosebleeds • Budd-Chiari syndrome (when blood vessels to the liver become blocked) • Mitchell's disease (when blood vessels in the feet or hands become blocked, causing pain and redness) • Gout (a painful joint condition) • Bleeding • Enlarged liver • Decreased blood flow to fingers and toes • Blood clots • Headache • Ringing, buzzing, or other noises in the ear • Dizziness • Blurred vision • Tingling sensations • Chest pain

Risk Factors

We do not know why people get PV. We do know that PV takes years to develop. The average age at diagnosis is about 60 years old. PV is more common in men than women. You are somewhat more likely to develop PV if you have a history of blood clots, other heart problems or a high platelet count.

Rarely, PV runs in families. We do not know of any specific environmental risk factors for the disease. Researchers are working to understand the reason for the PV cluster in northeast Pennsylvania. They are also working to see if there are any differences between people with PV and people without PV in the cluster area.

What Are MPNs?

MPNs are a group of diseases in which the blood-making cells in the bone marrow do not act normally. Often, the bone marrow makes too many red blood cells, white blood cells or platelets.

The three main MPNs are:

- Polycythemia vera (PV). See description of PV on previous page.
- Essential thrombocythemia (ET). In ET, the bone marrow makes too many platelets. This can cause blood clots. It can also cause serious bleeding.
- Primary myelofibrosis. In this disease, scar tissue replaces bone marrow. As bone marrow disappears, red blood cell and platelet levels drop. The liver and spleen begin to produce blood cells. This causes these organs to become larger than normal.

The three types of blood cells are:

- Red blood cells—carry oxygen to all parts of the body
- White blood cells—help fight infection
- Platelets—help blood to clot (to stop bleeding from a cut)

Myeloproliferative neoplasm
literally means "(abnormal)
new growths from fast
multiplying bone marrow":

Myelo = bone marrow
Proliferative = fast multiplying
Neo = new
Plasm = growth

Most Common Signs and Symptoms of Three Main MPNs(after having the disease for years)

Polycythemia Vera	Essential Thrombocythemia	Primary Myelofibrosis*
<ul style="list-style-type: none"> • Abnormal blood cell counts • Itching, especially after bathing • Enlarged spleen • Weight loss • Weakness • Sweating 	<ul style="list-style-type: none"> • Weakness • Bleeding • Gout (a painful joint condition) • Eye migraines • Tingling sensations 	<ul style="list-style-type: none"> • Anemia • General discomfort • Weight loss • Enlarged spleen • Loss of oxygen to the spleen • Enlarged liver • Swollen lymph nodes

* Many people with primary myelofibrosis do not have symptoms.

Risk Factors

We do not know why people get MPNs. We do know that MPNs take a long time to develop, so they are more common in middle-age and older adults. ET and primary myelofibrosis are more common in women than in men.

How are PV and Other MPNs Diagnosed?

Diagnosing PV

To find out if you have PV, your healthcare provider will:

- Consider your symptoms—to see if they match those of PV.
- Review your medical history—to see if there is a history of blood clots or heart problems.
- Do a physical exam—to see if your spleen is too large, areas of skin are reddish or purplish or if the gums are bleeding.
- Order blood tests—to check for signs of PV:
 - JAK2 mutation
 - High level of red blood cells
 - High white blood cell count
 - High platelet count
 - Abnormal levels of B12, uric acid, oxygen and erythropoietin (a hormone that helps trigger production of red blood cells)

If your healthcare provider suspects PV, he or she might take a bone marrow sample—use a needle to remove a little bone marrow from the hipbone or breastbone—to look for abnormal cells.

Diagnosing Other MPNs

To diagnose MPNs, healthcare providers once again consider symptoms, review your medical history, do a physical exam, order blood tests and sometimes take a bone marrow sample.

JAK2 Mutation

JAK2 is part of a signaling system that tells the bone marrow when to start and stop making blood cells. A mutation in JAK2 can cause the bone marrow to make too many blood cells. About 9 out of 10 people with PV have this mutation. About half of people with ET or primary myelofibrosis have the mutation.

If your healthcare provider thinks you are at risk of developing PV or another MPN, he or she might recommend a JAK2 blood test.

A positive test does not mean you definitely have or will develop PV or another MPN.

With ET, healthcare providers look for high levels of platelets, large platelets, clumps of platelets and megakaryocytes (cells that make platelets).

With primary myelofibrosis, healthcare providers look for a low red blood cell count (anemia) and young or oddly shaped red blood cells. A bone marrow sample is needed to diagnose primary myelofibrosis.

How Are PV and Other MPNs Treated?

At this time, there is no cure for PV or other MPNs. But treatment can help avoid or delay health problems from these diseases. You might not need treatment right away, or at all. Your healthcare provider will monitor your health carefully to decide if and when you need treatment.

Treatment of PV

With PV, most health problems are caused by too many red blood cells in the body—or too many platelets. If you need treatment, your healthcare provider will likely use a combination of treatments to lower your blood cell counts and control your symptoms. He or she will choose among these treatments based on your age, gender, health, nutritional status, symptoms, and blood test results. Possible treatments include:

- **Phlebotomy (blood draw).** Phlebotomy simply means drawing blood. Instead of drawing blood for tests or blood donation, you will have blood drawn to lower the number of red blood cells in your body. Sometimes this is enough. If not, you might also need to take medicine.
- **Medicine to slow production of blood cells.** The most commonly used is hydroxyurea. Other medicines include anagrelide, interferon-alpha, busulfan and chlorambucil; these drugs can increase the risk of leukemia (a type of cancer). But the need to treat PV sometimes outweighs this risk.
- **Medicine to control symptoms or bad side effects.** Antihistamines can help ease itching caused by PV. Aspirin can relieve pain and help lower the risk of blood clots.

Treatment of Other MPNs

Like PV, other MPNs require a combination of treatments. These include phlebotomy, removing platelets from the blood and blood transfusions to replace abnormal blood cells with new blood cells.

What About the Future?

Although PV has no cure, good medical care can help you avoid health problems. Many people with PV who get treatment lead normal lives.

People with PV symptoms who get appropriate treatment most often live for more than 20 years after diagnosis. People with PV symptoms who do not get appropriate treatment often die within 5 years of diagnosis.

Nutrition plays a role in health. You might want to talk about your nutritional status with your healthcare provider.

Now that we know about the JAK2 mutation, researchers are testing new medicines to treat PV and other MPNs. For example, medicines that block JAK2 are being tested in people with PV. You can learn more by talking to your healthcare provider or by visiting this website:

www.mpdfoundation.org

How Can I Learn More?

- Ask your healthcare provider about JAK2, PV and other MPNs.
- Visit ATSDR's Web page on PV:
http://www.atsdr.cdc.gov/sites/polycythemia_vera/index.html
- Call ATSDR's toll-free PV information line:
866-448-0242







Summer 2010

Polycythemia Vera in Northeast Pennsylvania

Schuylkill, Carbon and Luzerne Counties

Summary

About ATSDR

ATSDR is part of the U.S. Department of Health and Human Services. It is a sister agency to the Centers for Disease Control and Prevention (CDC).

ATSDR gives information to the public to help you avoid contact with harmful materials. We use the best science we can to help you protect your health.

ATSDR has partnered with PADOH since 1989.

In 2008, the Pennsylvania Department of Health (PADOH) and the Agency for Toxic Substances and Disease Registry (ATSDR) confirmed more cases than expected of polycythemia vera (PV) in parts of Schuylkill, Carbon and Luzerne Counties in northeast Pennsylvania.

PV is a rare blood disease with no known cause. Over time, people with PV can develop headaches, tiredness, shortness of breath, blood clots and heart problems.

ATSDR and PADOH continue to assess the patterns and possible causes of PV in northeast Pennsylvania. This fact sheet is for people who have PV or who are concerned about PV. It provides information about PV in northeast Pennsylvania.

What Is Polycythemia Vera?

PV is a rare blood disease. The bone marrow makes too many red blood cells, thickening the blood. That's why some people call PV "thick blood."

PV usually takes years to develop. Most people are diagnosed with PV later in life, most often around age 60 or older. People with PV might experience headaches, tiredness and shortness of breath. They are also at risk for getting blood clots, which can lead to heart attack and stroke.

At this time, there is no cure for PV. But treatment can control symptoms and avoid heart problems. Some people with PV do not need treatment. Even so, they should see their doctor regularly to remain as healthy as possible and catch problems early.

Myeloproliferative Neoplasms

Myeloproliferative neoplasms (MPNs) are blood disorders in which the bone marrow makes too many blood cells. PV is an MPN in which too many *red* blood cells cause health problems.

What Is JAK2?

JAK2 is part of a signaling system (like a thermostat) that helps tell the bone marrow when to start and stop making blood cells. Most people with PV have an acquired mutation (change) in their JAK2, so the bone marrow makes too many blood cells. People are not born with the JAK2 mutation. We usually find the mutation in people over the age of 40.

People with the JAK2 mutation *might* have or develop PV or other MPNs. A positive test does not mean you will definitely get PV. People without the mutation probably will not develop PV (unless the mutation appears later in life).

A JAK2 blood test can help you find out if you have or might develop PV. To get a JAK2 blood test, ask your healthcare provider. They will draw a little blood to test, then contact you with the results.

How Common Is Polycythemia Vera?

PV is rare. Each year, about one in 100,000 people are diagnosed with PV nationwide. In some parts of Schuylkill, Carbon and Luzerne counties, more people than expected have PV compared with other locations.

What Is Being Done?

To learn more about PV in northeast Pennsylvania, PADOH is tracking the patterns of PV. ATSDR and its research partners are looking for trends and risk factors for PV. And the CDC is working to improve reporting systems for PV and other diseases. These groups are also giving information about PV to doctors, nurses, pharmacists and the public.

Should I Be Concerned About My Environment?

Scientists cannot say for sure that anything in the environment causes PV. Even so, it is always a good idea to reduce your contact with harmful chemicals as much as you can, both at work and at home.

To learn more about reducing your contact with harmful chemicals in your home, visit the U.S. Department of Housing and Urban Development's Web page "Making Homes Healthier for Families" at:

<http://www.hud.gov/offices/lead/healthyhomes/index.cfm>

How Can I Learn More?

- Ask your healthcare provider about JAK2 and PV.
- Visit ATSDR's Web page on PV:
www.atsdr.cdc.gov/sites/polycythemia_vera/index.html
- Call ATSDR's toll-free PV information line:
866-448-0242

MPN Tissue Bank

ATSDR is studying tissue samples from people with PV in the cluster area. If you have PV and live in this area, we invite you to participate. Please call:

Dr. Paul Roda, MD, FACP
Geisinger/Hazleton Cancer Center
Physician Liaison for Tissue Bank
570-459-2901

Note: In the body, "tissue" is a group of cells that work together. An "organ" is a group of tissues that work together.

PV and Your Environment

ATSDR is trying to learn more about how things in your environment might alter the risk of getting PV. A few old studies suggested that PV might be caused by coming in contact with certain chemicals (benzene, embalming fluid, and petroleum products) or radiation. Other studies have not confirmed these findings.







Summer 2010

Resources for People With the JAK2 Mutation, PV or Other MPNs

Schuylkill, Carbon and Luzerne Counties

About ATSDR

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ATSDR and Your Healthcare Provider

ATSDR gives information about JAK2, PV and other MPNs to healthcare providers to keep them up to date on our research.

Summary

Polycythemia vera (PV) and other myeloproliferative neoplasms (MPNs) are a group of blood diseases. Some people with the “JAK2 mutation” have or will develop one of these diseases. Some people with the mutation might never get sick.

If you have the JAK2 mutation, PV or another MPN, help is available:

- Your healthcare provider can give you basic information.
- Local specialists can give you more information and medical care.
- Health groups can also give you information.

This fact sheet tells you where you can go to find information.

Your Healthcare Provider

Your healthcare provider can give you basic information about the JAK2 mutation, PV and other MPNs. If needed, he or she can refer you to a hematologist—a doctor who focuses on blood diseases.

Local Specialists

Here is a list of specialists who serve Schuylkill, Carbon and Luzerne Counties. ATSDR does not recommend any particular specialist. If you need a specialist, you or your healthcare provider can decide which specialist is the best fit for you.

Geisinger Hazleton Cancer Center

Paul Roda, M.D.
Harsh Gandhi, M.D.
Jose Castillo, M.D.
1740 East Broad Street
Hazleton, PA 18201
570-459-2901

Geisinger Medical Center Hematology/Oncology

Aneela Ali, M.D.
Maged Khalil, M.D.
100 North Academy Avenue
Danville, PA 17822
570-271-6045

**Geisinger Specialty Clinics—
Wilkes-Barre**

Arthur Meyer, M.D.
Charles White, M.D.
Rodrigo Erlich, M.D.
Paula Ronjon, M.D.
Albert Bernath, Jr., M.D.

The Henry Cancer Center
1000 East Mountain Boulevard
Wilkes Barre, PA 18711
570-820-6150

110 Trieble Road
Tunkhannock, PA 18657
570-996-2711

Geisinger—Pottsville
Hematology—Oncology
529 Terry Reiley Way
Pottsville, PA 17901
570-624-4444

**Lehigh Valley Physician Group
Hematology-Oncology Associates**

Lloyd Barron II M.D.
Eliot Friedman, M.D.
1240 South Cedar Crest Boulevard
Suite 103
Allentown, PA 18103
610-402-7880

**Oncology Hematology of Lehigh
Valley, PC**

Neil Belman, D.O.
Yacoub Faroun, M.D.
701 Ostrum Street
Suite 403
Bethlehem, PA 18015
610-821-2845

**Penn State Hershey Medical
Center—Hematology/Oncology**

Salah Almokadem, M.D.
David Claxton, M.D.
Leah Cream, M.D.
Joseph Drabick, M.D.
W. Christopher Ehmann, M.D.
Yixing Jiang, M.D.
Thomas Loughran, Jr., M.D.
Witold Rybka, M.D.
500 University Drive
Hershey, PA 17033
800-243-1455
717-531-5076

Pottsville Cancer Clinic

Satish Singla, M.D.
700 Schuylkill Manor Road #7
Pottsville, PA 17901
570-622-4113

Drs. Shah, Giangiulio and Ahmed

1240 South Cedar Crest Boulevard
Suite 305
Allentown, PA 18103
610-821-2700

255 Delaware Avenue
Palmerton, PA 18071
610-826-7987

800 Mahoning Street
Suite F
Lehighton, PA 18235
610-377-5737

How Can I Learn More?

- Ask your healthcare provider about JAK2, PV and other MPNs.
- Visit ATSDR's Web page on PV: http://www.atsdr.cdc.gov/sites/polycythemia_vera/index.html
- Call ATSDR's toll-free PV information line: 866-448-0242

Health Groups

You can also find information about JAK2, PV and other MPNs from these health groups.

Organization	Website	Phone Number
Northeast PA Polycythemia Vera Patient and Family Support Group	http://tricountypvcac.blogspot.com/	(no number available)
Leukemia & Lymphoma Society	www.lls.org	914-949-5213 800-955-4572
Myeloproliferative Diseases Foundation	www.mpdfoundation.org	312-683-7243
Myeloproliferative Disorders Research Consortium	www.mpd-rc.org/home.php	212-241-2296
National Institutes of Health National Heart Lung and Blood Institute	www.nhlbi.nih.gov/health/dci/Diseases/poly/poly_whatIs.html	301-592-8573
Northeast Regional Cancer Institute	www.cancernepa.org	800-424-6724







Summer 2010

Polycythemia Vera in Northeast Pennsylvania

Epidemiology for Healthcare Providers Serving Carbon, Luzerne and Schuylkill Counties

About ATSDR

The Agency for Toxic Substances and Disease Registry (ATSDR) serves the public by using the best science, taking responsive public health actions, and providing trusted health information to prevent harmful exposures and diseases related to toxic substances.

ATSDR is a sister agency to the Centers for Disease Control and Prevention (CDC) and has partnered with PADOH since 1989.

PV, MPNs and JAK2

PV is a rare, chronic myeloproliferative neoplasm (MPN) in which uncontrolled production of erythrocytes leads to hyperviscosity of the blood, resulting in signs and symptoms related to poor circulation and thrombosis. Most people develop PV later in life; the median age at diagnosis is 60 years old. The etiology of PV is unknown.

More than 90 percent of PV patients have a mutation in the gene for JAK2, a tyrosine kinase that plays a regulatory role in hematopoiesis. JAK2 testing can help determine if a patient has or might develop PV or other MPNs.

Summary

In 2004, the Pennsylvania Department of Health (PADOH) identified more cases of polycythemia vera (PV) than expected in parts of Carbon, Luzerne and Schuylkill Counties.

While state cancer data for 2001–2002 show that the incidence of PV in Pennsylvania is 1.6 in 100,000, parts of Carbon, Luzerne and Schuylkill counties have incidence values ranging from 1.7 to 5.9.

National incidence values for PV range from about 1 in 100,000 to 2.3 in 100,000.

The purpose of this fact sheet is to provide healthcare providers with information about PV epidemiology in northeast Pennsylvania.

PV Cluster in Northeast Pennsylvania

Nationally, reported incidence values for PV vary from about 1 in 100,000 to as high as 2.3 in 100,000. State cancer data from 2001 to 2002 show that the incidence of PV in Pennsylvania is 1.6 in 100,000. These same data identified three Pennsylvania counties with higher PV incidence:

- Carbon County, 1.7 per 100,000
- Luzerne County, 5.9 per 100,000
- Schuylkill County, 4.7 per 100,000

In a subsequent survey (December 2006 to July 2007), ATSDR found more confirmed cases of PV than expected in three specific areas: one area near Pottsville, another near Tamaqua and a third area in eastern Carbon County.

ATSDR's survey made use of molecular (JAK2) testing to identify patients with PV. Because the JAK2 mutation was discovered in 2005, previously PV could not be diagnosed with the same accuracy with which it can be diagnosed today. Through JAK2 testing, the ATSDR survey concluded that only 53 percent of patients who thought they had PV and could be evaluated actually had PV. Still, the PV rate in parts of the tri-county area does appear to be elevated.

Now that molecular testing for PV is available, it would be useful to reevaluate national PV incidence.

Polycythemia Vera Rates (2001–2002)
From National and State Cancer Registry Data (Adjusted for Age)

U.S. = 1.0 (5329 cases)¹



Luzerne = 5.9 (37 cases)²



Carbon = 1.7 (2 cases)²

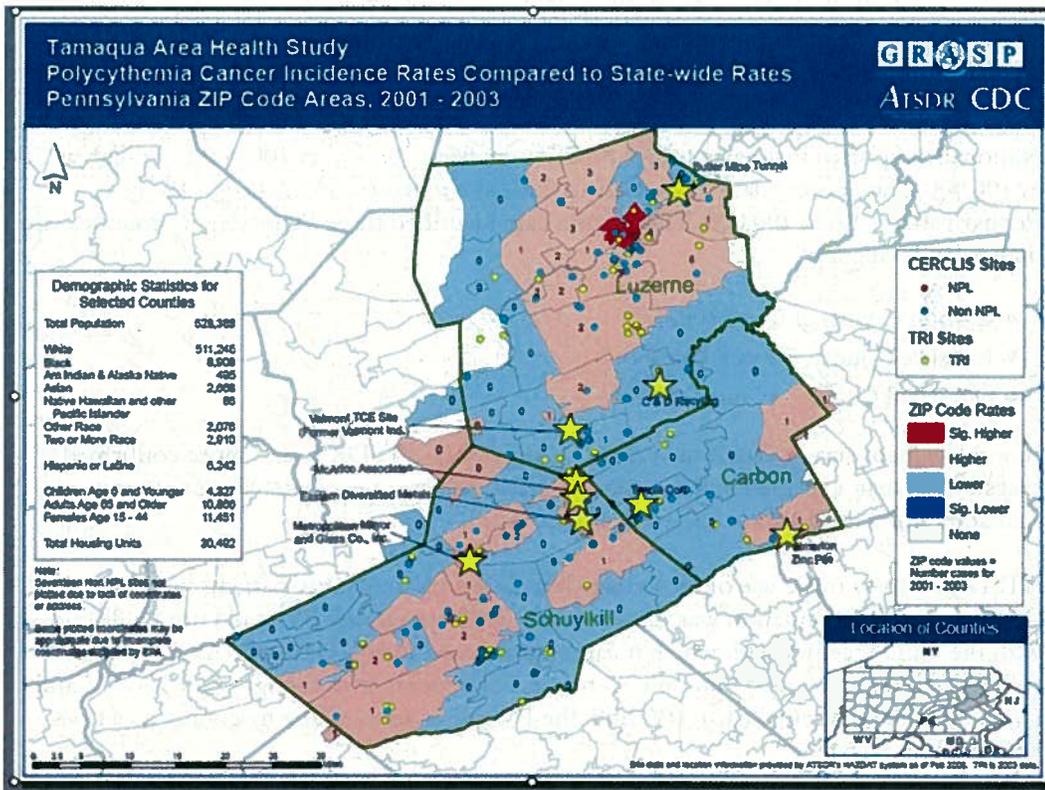
PA = 1.6 (412 cases)²



Schuylkill = 4.7 (14 cases)²

¹U.S. Cancer Statistics Working Group. United States Cancer Statistics: 1999–2004 Incidence and Mortality Web-based Report

²Pennsylvania Cancer Registry. Final 2001–2005 Report. Feb. 2008



For More Information

To obtain more information about PV, you can:

- Visit ATSDR's Web page on PV:
http://www.atsdr.cdc.gov/sites/polycythemia_vera/index.html
- Call ATSDR's toll-free PV information line:
866-448-0242

References

Ania, B.J., Suman V.J., Sobell, J.L., Codd, M.B., Silverstein, M.N., Melton, L.J. III. Trends in the incidence of polycythemia vera among Olmsted County, Minnesota residents, 1935-1989. *Am J Hematol.* 1994;46:89-93.

Pennsylvania Cancer Registry. Final 2001-2005 report. February 2008.

Silverstein, M.N., Lanier, A.P. Polycythemia vera, 1935-1969: an epidemiologic survey in Rochester, Minnesota. *Mayo Clin Proc.* 1971;46:751-753.

Tefferi A. Polycythemia vera: a comprehensive review and clinical recommendations. *Mayo Clin Proc.* 2003;78:174-94.

U.S. Cancer Statistics Working Group. United States cancer statistics: 1999-2004 incidence and mortality Web-based report.







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Polycythemia Vera

Information for Healthcare Providers Serving Carbon, Luzerne and Schuylkill Counties

About ATSDR

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Summary

Polycythemia vera (PV) is a rare, chronic myeloproliferative neoplasm (MPN) in which uncontrolled production of erythrocytes leads to hyperviscosity of the blood, resulting in signs and symptoms related to poor circulation and thrombosis. Most people develop PV later in life; the median age at diagnosis is 60 years old. The etiology of PV is unknown.

In 2008, the Pennsylvania Department of Health (PADOH) and the Agency for Toxic Substances and Disease Registry (ATSDR) identified a PV cluster in parts of Schuylkill, Carbon and Luzerne counties in northeast Pennsylvania. PADOH and ATSDR are investigating the cause of this cluster, which is currently unknown.

PV patients can be asymptomatic. As the disease progresses, patients might present with mild or vague symptoms, such as fatigue, dyspnea and headache. Eventually, patients might develop more serious complications, such as stroke and myocardial infarction.

Diagnosis is based on blood tests and sometimes bone marrow biopsy. At this time, there is no cure for PV, but treatment can control symptoms and minimize complications.

This fact sheet provides information about PV epidemiology, pathophysiology, clinical assessment, diagnosis and treatment.

Epidemiology

National Incidence and Prevalence

Reported values for national incidence of PV vary from about 1 in 100,000 to as high as 2.3 in 100,000.

National prevalence of PV is not well understood because no nationwide studies have been conducted. Based on a study of PV patients in Connecticut that reported a total prevalence of 22 per 100,000 in that state, researchers have estimated that the total number of patients living with PV in the United States in 2003 was 65,243.

Regional Incidence

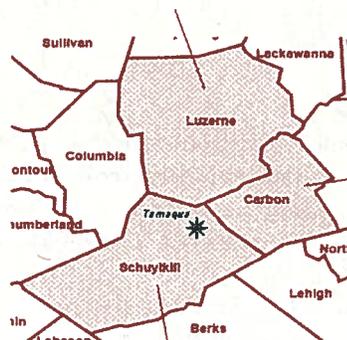
State cancer data from 2001 to 2002 show that the incidence of PV in Pennsylvania is 1.6 in 100,000. These same data identified three Pennsylvania counties with higher PV incidence:

- Carbon County, 1.7 per 100,000
- Luzerne County, 5.9 per 100,000
- Schuylkill County, 4.7 per 100,000

In a subsequent survey (December 2006 to July 2007), ATSDR found that three parts of the tri-county area had more confirmed cases of PV than expected: one area near Pottsville, another area near Tamaqua, and a third area in eastern Carbon County.

Polycythemia Vera Rates (2001–2002) for Tri-County Area (Adjusted for Age)

Luzerne = 5.9 (37 cases)²



**Carbon
= 1.7
(2 cases)²**

**Schuylkill = 4.7
(14 cases)²**

¹U.S. Cancer Statistics Working Group, *United States Cancer Statistics: 1999–2004 Incidence and Mortality Web-based Report*

²Pennsylvania Cancer Registry, *Final 2001–2005 Report, Feb. 2008*

Risk Factors

The table below summarizes risk factors for PV.

Risk Factors	
Age	Median age at diagnosis is 60 years, although anyone at any age can develop PV.
Gender	PV is slightly more common in men than in women (1.2:1).
History of thrombosis	History of thrombosis may increase risk of developing PV if other risk factors are also present.
Thrombocyte count	High thrombocyte count may increase risk of developing PV if other risk factors are also present.
Cardiovascular health	History of cardiovascular problems may increase risk of developing PV if other risk factors are also present.
Family history	PV is not considered hereditary, but there have been reported cases of family clustering.
Environment	No link has been established between environmental factors and the risk of developing PV.

Environmental Risk Factors

A few studies published more than 20 years ago reported that PV might be caused by coming in contact with certain chemicals (benzene, embalming fluid, petroleum products) or radiation. But these studies were limited by small sample size, and other studies have not confirmed these findings.

Pathophysiology

PV is one of the myeloproliferative neoplasms (MPNs), a group of blood diseases characterized by disruptions in the regulation of hematopoiesis. Major MPNs include PV, essential thrombocythemia and primary myelofibrosis.

Before 2005, the pathophysiology of PV was not well understood. Significant progress has been made since the discovery of a mutation in the gene for janus kinase 2 (JAK2), a tyrosine kinase that plays a regulatory role in hematopoiesis.

JAK2 Mutation

JAK2 is an inhibitory regulatory domain involved in Type I cytokine receptor signaling, which includes the ligands erythropoietin (EPO), thrombopoietin (TPO) and granulocyte macrophage colony stimulating factor (GM-CSF). An acquired mutation in the gene for JAK2 results in a nonfunctional inhibitory domain, resulting in overproduction of all cell lines, including thrombocytes, leukocytes and, in particular, erythrocytes. It can also lead to extramedullary erythropoiesis, increased cell turnover and eventually a spent phase, as well as sequelae related to chronic erythrocytosis.

More than 90 percent of PV patients have the JAK2 mutation. Those who do not are believed to have less common mutations that have a similar effect on the JAK2 domain. Why some people acquire the JAK2 gene mutation is unknown.

Increased Myeloid Hematopoiesis

In PV, increased myeloid hematopoiesis increases packed cell volume leading to hyperviscosity. Hyperviscosity hinders normal blood flow, potentially resulting in:

- Signs and symptoms related to poor circulation (see Clinical Assessment).
- Thrombosis and related complications (transient ischemic attacks, stroke, myocardial infarction, Budd-Chiari syndrome).

While PV is associated with a risk of thrombosis, it is also associated with a risk of hemorrhage. Vascular engorgement can lead to bleeding even in the absence of significant insult. In addition, hyperviscosity can slow the movement of platelets to injured blood vessels and hinder coagulation, which can lead to hemorrhage during injury or surgery.

Extramedullary Erythropoiesis

As hyperviscosity impedes circulation, oxygenation of tissues may become insufficient, triggering extramedullary erythropoiesis. This occurs most often in the spleen and liver, sometimes causing splenomegaly and hepatomegaly. Although less common, extramedullary hematopoiesis can also occur in the nervous system. This can lead to compression of the spinal cord, nerve root, cranial nerve, cortical brain tissue and meningeal layer.

Pathophysiology of MPNs

Myeloproliferative neoplasms involve dysregulation at the multipotent hematopoietic stem cell (CD34), with one or more of the following shared features:

- *Overproduction of one or several blood elements with dominance of a transformed clone.*
- *Hypercellular marrow or marrow fibrosis.*
- *Cytogenetic abnormalities.*
- *Thrombotic and/or hemorrhagic diatheses.*
- *Extramedullary hematopoiesis (liver/spleen).*
- *Transformation to acute leukemia.*
- *Overlapping clinical features.*

In most cases, PV begins with the JAK2 V617F mutation or one of several other rarer JAK2 mutations.

Thrombosis in PV

Although previously most experts believed that hyperviscosity was the main contributing factor to thrombosis, some newer studies show a stronger connection between thrombosis and the leukocytosis that occurs with PV.

Increased Cell Turnover

The persistent red cell hypervolemia caused by hematopoietic hyperfunction can also result in an increased rate of cell turnover. As the spleen removes larger and larger numbers of erythrocytes, the increased workload can lead to splenomegaly.

Increased cell turnover can also lead to hyperuricemia, increasing the risk of gout and urate kidney stones.

Spent Phase

Eventually, in some patients, persistent myeloid hyperfunction and hyperplasia can result in bone marrow failure, leading to myelofibrosis and anemia.

Sequelae

PV might eventually evolve into a syndrome simulating another MPN, idiopathic myelofibrosis, myelodysplastic syndrome or acute leukemia. In addition, some PV patients develop complications from chronic erythrocytosis; some of these, such as stomach ulcers or gout, may present as signs of PV (see Clinical Assessment).

Diagnosis

The World Health Organization (WHO) provides standard criteria for diagnosis of PV.

WHO Criteria for Diagnosis of Polycythemia Vera*	
Level	Specifics
Major criteria	<ol style="list-style-type: none"> Evidence of increased RBC volume, including ≥ 1 of the following: <ul style="list-style-type: none"> Hb > 18.5 g/dL in men or > 16.5 g/dL in women Hb or Hct > 99th percentile of method-specific reference range for age, sex, and altitude of residence Hb > 17 g/dL in men or 15 g/dL in women if associated with a documented and sustained increase of at least 2 g/dL from the patient's baseline value not accounted for by correction of iron deficiency Elevated RBC mass > 25% above mean normal predicted value Presence of JAK2 617VF or other functionally similar mutation (eg, JAK2 exon 12 mutation)
Minor criteria	<ol style="list-style-type: none"> Bone marrow biopsy showing hypercellularity for age with trilineage growth (panmyelosis) and prominent erythroid, granulocytic, and megakaryocytic proliferation Serum erythropoietin level below the reference range for normal Endogenous erythroid colony formation in vitro

*Diagnosis requires presence of the 2 major criteria and one minor criterion or the presence of the first major criterion plus 2 minor criteria.

¹This research was originally published in *Blood*. Adapted from Tefferi A, Thiele J, Orazi A, et al. Proposals and rationale for revision of the World Health Organization diagnostic criteria for polycythemia vera, essential thrombocythemia, and primary myelofibrosis: Recommendations from an ad hoc international expert panel. *Blood* 110:1092, 2007 ©the American Society of Hematology.

Clinical Assessment

PV patients often present as asymptomatic, especially early in the disease. As the disease progresses, PV patients might experience signs or symptoms related to increased blood cell mass and hyperviscosity. The most common symptoms are headache, fatigue, dyspnea, weakness, pruritis, vertigo and diaphoresis. Nevertheless, any of the following can be signs or symptoms of PV:

- **General:** Weakness, fatigue, diaphoresis. In more advanced cases, low-grade fever and unexplained weight loss could be caused by hypermetabolism associated with the spent phase of PV.
- **Skin:** Skin discoloration (reddish or purplish palms, ear lobes, cheeks), ischemic digits, pruritis (especially after bath or shower).
- **Cardiovascular:** Bleeding gums, bruising, epistaxis, hemorrhage, thrombotic events (e.g., arterial and venous thrombosis, cerebrovascular accident, deep venous thrombosis, myocardial infarction, peripheral arterial occlusion, pulmonary infarct).
- **Neurologic:** Headache, dizziness, paresthesias, tinnitus, erythromelalgia, vertigo, visual disturbances (e.g., diplopia, blind spots, flashes of light).
- **Abdominal:** Splenomegaly, Budd-Chiari syndrome, stomach ulcers, urate kidney stones, hepatomegaly.
- **Musculoskeletal:** Gout, bone pain (rare).

Blood Tests

A complete blood count (CBC) is essential to identify evidence of increased red blood cell mass (see WHO criteria above). The CBC must be repeated to verify persistence. Blood tests might also reveal elevated leukocyte and thrombocyte counts, microcytosis, or sideropenia (sometimes with normal hemoglobin levels).

A JAK2 test can identify the presence of the JAK2 V617F mutation (or one of several other rarer JAK2 mutations), which is present in more than 90 percent of patients with PV.

Other signs of PV include:

- Low serum EPO level.
- Presence of endogenous erythroid colony formation.

Bone Marrow Biopsy

Bone marrow histology can identify the following signs of PV:

- Hypercellularity for age, with panmyelosis.
- Increased number of megakaryocytes, including cluster formation.
- Giant megakaryocytes.
- Pleomorphism in megakaryocyte morphology.
- Mild reticulin fibrosis.
- Decreased bone marrow iron stores.

At this time, it is unknown whether all people with the JAK2 mutation will eventually develop PV or another MPN.

Differential Diagnosis

Once tests reveal polycythemia, the diagnostic question becomes whether the disease is polycythemia vera or secondary polycythemia. Differential diagnosis is accomplished via:

- Use of WHO diagnostic criteria (see above).
- Medical history (to identify other possible causes of polycythemia; see table).
- Serum EPO test (usually very low with polycythemia vera; often normal or high with secondary polycythemia).
- Bone marrow biopsy (see above).

Causes of Secondary Polycythemia	
More Common	Less Common
<ul style="list-style-type: none"> • Smoking • Chronic arterial hypoxemia • Tumors (tumor-associated erythrocytosis) 	<ul style="list-style-type: none"> • High O₂-affinity hemoglobinopathies • Erythropoietin receptor mutations • Chuvash polycythemia (in which a mutation in the <i>VHL</i> gene affects the hypoxia-sensing pathway) • Proline hydroxylase 2 and HIF-2 α mutations

Management

PV is not curable at this time, but can be managed through a combination of interventions aimed at slowing hematopoiesis, reducing the risk of thrombotic events, and controlling symptoms.

PV patients who have symptoms and do not receive medical intervention have a life expectancy of less than 5 years after diagnosis. PV patients who have symptoms and *do* receive medical intervention have a life expectancy of more than 20 years after diagnosis.

Factors to consider when choosing the appropriate management strategy(ies) include:

- Disease expression
- Rate of disease progression
- Patient's age
- Concurrent chronic diseases

Phlebotomy

For decades, periodic phlebotomy has been a primary tool to reduce hematocrit (and the risk of thrombotic events) in PV patients. Repeated phlebotomy sometimes results in iron deficiency, but otherwise presents little risk to the patient. In some cases, phlebotomy is the only intervention a patient will need.

Hematocrit and Thrombosis

Some recent studies suggest that hematocrit might not be the primary determinant of risk of thrombosis, leading some experts to question the utility of phlebotomy in reducing thrombotic episodes. Nevertheless, phlebotomy is still the widely accepted form of PV treatment.

Initially, 300 to 500 milliliters of blood are removed every other day. Less blood is removed from patients who are elderly or have cardiac or cerebrovascular disorders. Once hematocrit falls below the threshold level, it is checked monthly and phlebotomy is repeated as needed to maintain hematocrit below threshold. Common thresholds are:

- Hematocrit > 45 percent in men
- Hematocrit > 42 percent in women

Myelosuppression

Myelosuppressive agents can be used to reduce erythrocyte and thrombocyte counts. This intervention can complement phlebotomy (which can result in increased thrombocyte counts) or can be administered alone. Chronic or repeated use of some myelosuppressive agents has been associated with acute transformation of PV to leukemia.

Hydroxyurea, which inhibits the enzyme ribonucleoside diphosphate reductase, is the most commonly used myelosuppressive agent for PV. Hydroxyurea has not been shown to induce leukemic changes, but the possibility of acute leukemic transformation exists.

Patients with extremely high thrombocyte counts might benefit from other myelosuppressive agents that reduce thrombocyte counts; for example, anagrelide can be used to slow the rate of myeloid thrombopoiesis. Interferon-alpha and other chemotherapy agents may also be used in special cases to lower thrombocyte counts, but they are difficult to administer and may have serious side effects.

Aspirin

Unless contraindicated, patients undergoing phlebotomy and/or myelosuppressive therapy should take aspirin (81 to 100 milligrams po once daily) to reduce the risk of thrombotic complications.

Symptom Control

Interventions aimed at controlling symptoms include antihistamines to relieve itching and aspirin to relieve bone pain and paresthesias.

Treatment Trends

There is evidence of a trend toward increased use of phlebotomy as first-line therapy for erythrocytosis. Hydroxyurea is used more frequently than other myelosuppressive agents.

Since the discovery of the JAK2 mutation, researchers have begun developing and testing JAK2 inhibitors to treat PV and other MPNs. Drugs with the ability to inhibit JAK2 function could drastically change management of MPNs in the future.

Acute Leukemic Transformation

In PV, transformation to acute leukemia has been observed for decades. Some have questioned whether this is a natural occurrence or a result of use of myelosuppressive agents for pharmacologic cytroreduction. Research suggests that both factors contribute to the risk, with some pharmacologic agents associated with higher risk than others. The apparent lower risk of acute leukemic transformation is one reason why many physicians prefer hydroxyurea over some other agents.

Reporting PV

Pennsylvania laws and PADOH regulations require reporting of new cancer cases, including new cases of PV, to the Pennsylvania Cancer Registry (PCR).

The PCR collects information about occurrence of cancer, types of cancers diagnosed and their locations within the body, extent of cancer at the time of diagnosis, and treatment patients receive.

All malignant polycythemias and other myeloproliferative neoplasms are reportable to the PCR, including:

- PV
- Proliferative polycythemia
- Polycythemia rubra vera
- Essential thrombocytosis
- Primary myelofibrosis
- Chronic myelomonocytic leukemia

More Information

Organization	Website	Phone Number
The Myeloproliferative Diseases Foundation	www.mpdfoundation.org	312-683-7243
The National Institutes of Health National Heart Lung and Blood Institute	www.nhlbi.nih.gov/health/dci/Diseases/poly/poly_what.html	301-592-8573
Leukemia & Lymphoma Society	www.lls.org	914-949-5213 800-955-4572
Northeast Regional Cancer Institute	www.cancernepa.org	800-424-6724

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Summer 2010

Polycythemia Vera in Northeast Pennsylvania

Public Health Activities and the Role of Healthcare Providers Serving Carbon, Luzerne and Schuylkill Counties

About ATSDR

ATSDR serves the public by using the best science, taking responsive public health actions, and providing trusted health information to prevent harmful exposures and diseases related to toxic substances.

ATSDR is a sister agency to the Centers for Disease Control and Prevention (CDC) and has partnered with PADOH since 1989.

Summary

In 2004, the Pennsylvania Department of Health (PADOH) identified a cluster of polycythemia vera (PV) in northeast Pennsylvania. In 2006, the PADOH asked the Agency for Toxic Substances and Disease Registry (ATSDR) to help study patterns of PV in the area. The investigation aimed to find all residents of the three counties who were diagnosed with PV between 2001 and 2005, confirm the diagnosis of PV among these persons and collect information from people found to have PV.

From December 2006 to July 2007, ATSDR conducted a survey of possible PV cases to collect information on work and residence histories, health status and other factors that might be related to PV. After its initial investigation, ATSDR concluded:

- Thirty-three cases of PV were confirmed by testing for the janus kinase 2 (JAK2) mutation.
- There were potential environmental exposure sources common to some of the high-rate areas.
- More research is needed to understand the reasons for the high rate of PV in this area.

As a public service, in 2009 ATSDR conducted a public health screening for the JAK2 mutation in the tri-county area. The screening also allowed ATSDR to locate, confirm and characterize PV cases in the area.

As a follow-up to this investigation and screening, PADOH is tracking cases of PV in the tri-county area. ATSDR is working with research partners to look for trends and risk factors for PV. And the Centers for Disease Control and Prevention (CDC) are working to improve reporting systems for PV and other diseases. These groups are also providing information about PV to local healthcare providers and the public.

The purpose of this fact sheet is to provide information about PV-related activities conducted by PADOH and ATSDR in northeast Pennsylvania.

Past ATSDR and PADOH Activities

Initial ATSDR Investigation (2006–2008)

In 2004, four cases of PV were found in people who lived on one road in the Tamaqua area in northeast Pennsylvania. In a follow-up investigation, the PADOH found more PV cases than expected in parts of Carbon, Luzerne and Schuylkill Counties.

From December 2006 to July 2007, PADOH and ATSDR began a search for all residents in these counties who had been diagnosed with PV between 2001 and 2005. PADOH and ATSDR gathered and analyzed PV patient information, such as individual traits, ancestry and occupational experiences. ATSDR also reviewed environmental data from the Pennsylvania Department of Environmental Protection (PADEP) and the U.S. Environmental Protection Agency (EPA) to determine if any exposures were common to the high-rate areas. In 2008, ATSDR presented the final findings of this initial investigation:

1. Thirty-three cases of PV were confirmed by testing for the JAK2 mutation. The confirmed cases had no common occupations, ancestry, lifestyle choices or exposures. The Pennsylvania Cancer Registry (PCR) did not accurately reflect the true number of PV cases in the area. In some areas, PV rates were higher than those in the rest of the tri-county area; in only one of these areas was the difference statistically significant.
2. There were potential environmental exposure sources common to some of the high-rate areas. It is not known whether a relationship exists between any of these sources and the PV cases. This initial investigation was not designed to study such relationships. Further, the cause of PV is unknown. Therefore, it is difficult to link the illness to any environmental agent or any other factor.
3. More research is needed to understand the reasons for the high rate of PV in this area.

Public Health Screening (2009)

In 2009, ATSDR partnered with the Mt. Sinai School of Medicine to offer two rounds of free JAK2 screening to all residents who had lived in Schuylkill, Carbon or Luzerne counties for at least 1 year. The primary goal of this screening was to provide a public service. In addition, the screening enabled ATSDR to locate, confirm and characterize PV cases in the area.

Of the 1,170 persons tested in the 2009 screening, 19 (1.6 percent) were found to have the JAK2 mutation; 5 persons had previously been diagnosed with PV or a similar blood disease. Because other large-scale screenings have not been conducted to date, the prevalence of the JAK2 mutation in the general population is unknown.

PV and the Environment

A few studies, published more than 25 years ago, reported that PV could possibly be caused by exposure to chemicals (benzene, embalming fluid, petroleum products) or radiation. These reports were limited by small patient numbers, and their findings have not been confirmed by subsequent studies.

The 2009 public health screening in northeastern Pennsylvania was the first large-scale screening for the JAK2 genetic mutation in the United States.

Current and Future ATSDR and PADOH Activities

Current and future ATSDR and PADOH activities serve the primary goal of understanding the cause of the PV cluster in northeast Pennsylvania.

PADOH is tracking cases of PV in the tri-county area and examining the feasibility of medical records review and JAK2 testing for all newly diagnosed PV patients. To identify disease trends, PADOH is comparing PV incidence rates in the tri-county area with rates from previous years and the overall state rate.

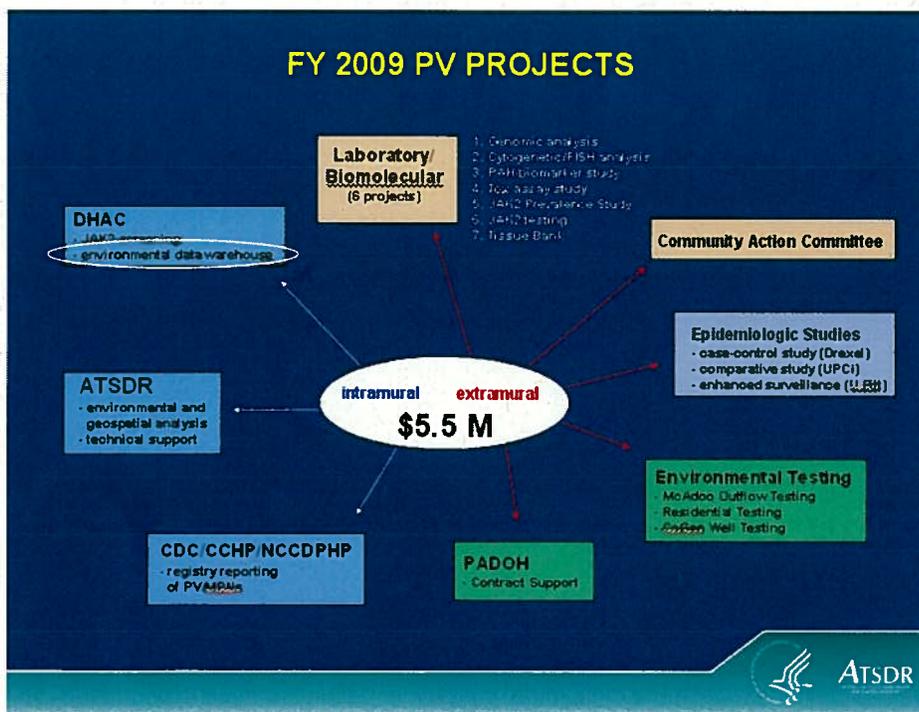
ATSDR is working with research partners to look for trends and risk factors for PV. Projects include:

- Identifying previous residence locations of PV patients in the cluster in order to determine potential environmental exposure sites and pathways.
- Identifying any differences between PV patients in the cluster and community members without the disease.
- Comparing the current cluster area with other locations having similar environmental conditions.

ATSDR will provide updates about the PV cluster in northeast Pennsylvania as more information becomes available.

The CDC is working to improve reporting systems for PV and other diseases. This will allow PADOH to track cases of PV in the tri-county area more accurately.

Finally, ATSDR/CDC and PADOH are providing information about PV to doctors, nurses, pharmacists and the public.



Role of Healthcare Providers

To assist ATSDR, PADOH and residents of the tri-county area, healthcare providers can:

- Provide medical care for patients with PV. (See the fact sheet “Polycythemia Vera,” provided in this information packet.)
- Respond to patients’ questions about the PV cluster and provide fact sheets as appropriate. (See patient information fact sheets provided in this information packet.)
- Report cases of PV to the PCR. (See the fact sheet “Reporting Polycythemia Vera,” provided in this information packet.)
- Encourage PV patients who reside in the cluster area to participate in the MPN tissue bank. For more information, contact:

Paul Roda, MD, FACP
Geisinger/Hazleton Cancer Center
Physician Liaison for Tissue Bank
570-459-2901

For More Information

For more information about PV, you can:

- Visit ATSDR’s Web page on PV:
http://www.atsdr.cdc.gov/sites/polycythemia_vera/index.html
- Call ATSDR’s toll-free PV information line:
866-448-0242







Summer 2010

Reporting Polycythemia Vera

Information for Healthcare Providers Serving Carbon, Luzerne and Schuylkill Counties

About ATSDR

ATSDR serves the public by using the best science, taking responsive public health actions, and providing trusted health information to prevent harmful exposures and diseases related to toxic substances.

ATSDR is a sister agency to the Centers for Disease Control and Prevention (CDC) and has partnered with PADOH since 1989.

Reporting Laws and Regulations

The two state laws that require reporting are:

- *Pennsylvania Cancer Control, Prevention and Research Act, 35 P.S. §5631 et seq.*
- *Disease Prevention and Control Law of 1955, 35 P.S. §521.1 et seq.*

PADOH regulations concerning Reporting of Communicable and Noncommunicable Diseases require healthcare providers to report cancer cases not referred to or previously admitted to a hospital or other healthcare facility for diagnosis or treatment of cancer.

Summary

In 2004, the Pennsylvania Department of Health (PADOH) identified more cases of polycythemia vera (PV) than expected in parts of Carbon, Luzerne and Schuylkill Counties. To further investigate the reason for this disease cluster, PADOH and the Agency for Toxic Substances and Disease Registry (ATSDR) need healthcare providers to report cases of PV to the Pennsylvania Cancer Registry (PCR). The PCR is a statewide data system with information on all new cases of cancer diagnosed or treated in Pennsylvania.

Pennsylvania laws and PADOH regulations require reporting of new cancer cases to the PCR. PADOH and ATSDR thank you in advance for your assistance.

This fact sheet provides information about procedures for reporting cases of PV.

Why Report

Two state laws require that hospitals and laboratories report all cases of cancer that are diagnosed and/or treated in these facilities. PADOH regulations require healthcare providers to report cancer cases that are *not* diagnosed or treated in these facilities.

Data reported to the PCR help public health officials:

- Answer questions about cancer incidence.
- Allocate limited cancer control resources to areas where they are most needed.
- Evaluate cancer control efforts.

PV has been on the list of diseases reportable to the PCR since 2001. In 2004, PADOH identified more PV cases than expected in parts of Carbon, Luzerne and Schuylkill Counties. Since then, PADOH and ATSDR have been investigating the reason for this disease cluster. At this time, no links have been established between PV and exposure to chemicals in the environment. But PADOH and ATSDR believe it is important to investigate further.

The initial PADOH/ATSDR investigation found that nearly half of confirmed PV cases had not been reported to the PCR. Moreover, a third of PV cases that were reported did not meet 2001 or 2008 World Health Organization (WHO) PV criteria.

PADOH and ATSDR are analyzing PCR data to learn more about the distribution of PV in northeast Pennsylvania and the characteristics (e.g., age, gender, ethnicity) of those diagnosed with PV. This analysis will enable PADOH and ATSDR to understand possible public health implications and make recommendations for follow-up or further investigation. For the results of the analysis to be meaningful, however, PCR data must be accurate and complete.

What to Report

The PCR collects information about:

- Occurrence of cancer.
- Types of cancers diagnosed and their locations within the body.
- Extent of cancer at the time of diagnosis.
- Treatment patients receive.

All malignant polycythemias are reportable to the PCR, including:

- Proliferative polycythemia.
- Polycythemia rubra vera.
- PV.

In addition, healthcare providers should report other myeloproliferative neoplasms, including:

- Essential thrombocytosis.
- Primary myelofibrosis.
- Chronic myelomonocytic leukemia.

Secondary polycythemia, such as that occurring in patients with emphysema or pneumoconiosis, is not a hematologic malignancy and should not be reported.

How to Report

Some physicians and laboratories already have a reporting mechanism established with the PCR. Those who do not have a reporting mechanism established with the PCR should contact the registry directly to discuss how to report PV cases. Please contact:

Robin Otto (Registry Manager) or other registry staff
Bureau of Health Statistics and Research
Pennsylvania Department of Health
Phone: 717-783-2548 or 800-272-1850

Most cancer cases reported to the state registry come from hospitalized patients. PV is rarely a reason for hospitalization and thus is frequently not reported through hospital registries. Therefore, it is critical that physicians' offices report PV.

Health Insurance Portability and Accountability Act (HIPAA)

Because the PCR is a public health entity, HIPAA allows the reporting of data to the PCR. Written informed consent from each cancer patient is not required.

Contacting ATSDR

In addition to the required reporting, physicians and patients are welcome to contact ATSDR informally when new cases of PV are diagnosed from Schuylkill, Carbon and Luzerne Counties:

***ATSDR PV Information Line
866-448-0242***

***Dr. Elizabeth Irvin-Barnwell
Phone: 770-488-3684
Fax: 770-488-1537
Email: jcx0@cdc.gov***







October 2009

Polycythemia Vera and JAK2 Testing Information

Schuylkill, Carbon and Luzerne Counties, Pennsylvania

Summary

In 2008, the Pennsylvania Department of Health (PADOH) and the Agency for Toxic Substances and Disease Registry (ATSDR), a federal public health agency, identified an excess of polycythemia vera (PV), a rare blood disease with no known cause, in Schuylkill, Carbon and Luzerne counties. Most people develop PV later in life. The average age at diagnosis is about 60 years old.

In 2009, ATSDR and PADOH offered public health screening for a genetic marker known as JAK2. This genetic mutation has been observed in over 90 percent of patients with PV.

Although the meaning of a positive JAK2 test for someone who is in good health is not known, it is possible that people with this mutation may develop PV later in life. For persons with this mutation, health care providers may recommend that their blood counts and health status be more closely monitored.

The purpose of this fact sheet is to provide resources for individuals who would like to learn more about PV and other related diseases.

What Is Polycythemia vera?

PV is a blood disorder in which the bone marrow makes too many red blood cells. This condition is sometimes referred to as “thick blood.” Patients with PV may have few or no symptoms. However, patients with PV are prone to develop blood clots and are at increased risk of a heart attack or stroke.

What Is The JAK2 Test?

It is a blood test that determines the presence of the JAK2 genetic marker in blood cells.

This test provides information used to help diagnose PV in patients. People who have this genetic marker may already have or may develop PV or other related blood disorders known as myeloproliferative diseases or MPDs.

About the Agency for Toxic Substances and Disease Registry

The Agency for Toxic Substances and Disease Registry serves the public by using the best science, taking responsive public health actions, and providing trusted health information to prevent harmful exposures and diseases related to toxic substances.

What Steps Should I Take?

If your health care provider thinks you are at risk of developing PV, or if you have a positive JAK2 screening result, he or she may refer you to a hematologist. A hematologist is a doctor who specializes in diseases of the blood and blood forming organs.

PV develops slowly. It may not produce signs or symptoms for years. PV is diagnosed based on signs and symptoms, medical history, a physical exam and test results. Early detection of PV, before signs or symptoms appear, could lead to medical care that prevents or delays complications of the disease.

While PV is not curable, appropriate treatment can help control the disease and its complications.

Additional Resources:

The Myeloproliferative Diseases Foundation

Web site: www.mpdfoundation.org

Phone: 312-683-7243

The National Institutes of Health National Heart Lung and Blood Institute:

Web site: www.nhlbi.nih.gov/health/dci/Diseases/poly/poly_what.html

Phone: 301-592-8573

Leukemia & Lymphoma Society

Web site: www.lls.org

Phone: 914-949-5213800 OR 800-955-4572

Northeast Regional Cancer Institute

Web site: www.cancernepa.org

Phone: 570-970-6543 OR 800-424-6724

Important!

Having a positive JAK2 test does not mean that you have or will develop PV. However, the JAK2 genetic mutation has been observed in over 90 percent of patients with PV. If you have a positive JAK2 test, talk to your healthcare provider about the test, your health, and the need for additional evaluation.

Future Investigations

Residents who test positive for the JAK2 mutation and have not been diagnosed with PV or another blood disorder will be invited to participate in a follow-up study. This study will consist of an initial examination by a local doctor who specializes in blood diseases and follow-up visits every six months. There will be no fees or charges for taking part in this study. For more information call the toll-free PV information line 866-448-0242.



Local Specialists

The following is a list of specialists serving the tri-county area. This list is not an endorsement of these providers but, rather, is a listing based on geographical proximity to the area. Individuals are encouraged to use the health care provider that best meets their specific needs.

Geisinger Hazleton Cancer Center

Paul Roda, MD
Harsh Gandhi, MD
Jose Castillo, MD
1740 East Broad Street
Hazleton, PA
570-459-2901

Drs. Shah, Giangiulio and Ahmed

1240 S Cedar Crest Blvd
Suite 305
Allentown, Pennsylvania 18103-6218
Phone: (610) 821-2700



255 Delaware Avenue
Allentown, PA 18071-1812
Phone: 610-826-7987 and

800 Mahoning Street
Suite F
Lehighton, PA 18235-1246
Phone: 610-377-5737

Lehigh Valley Physician Group Hematology-Oncology Associates

Lloyd Barron II MD
Eliot Friedman, MD
1240 S Cedar Crest Blvd
Suite 103
Allentown, Pennsylvania 18103-6218
Phone: (610) 402-7880

Oncology Hematology of LV, PC



Neil Belman, DO
Yacoub Faroun, MD
701 Ostrum Street
Suite 403
Bethlehem, Pennsylvania 18015
Phone: (610) 821-2845

Geisinger Specialty Clinics – Wilkes-Barre

Arthur Meyer, MD
Charles White, MD
Rodrigo Erlich, MD
Paula Ronjon, MD
Albert Bernath Jr, MD

The Henry Cancer Center
1000 East Mountain Blvd
Wilkes Barre, PA 18711
570-820-6150

110 Trieble Road
Tunkhannock, PA 18657
570-996-2711

Geisinger – Pottsville
Hematology – Oncology
529 Terry Reiley Way
Pottsville, PA 17901
570-624-4444

Geisinger Medical Center Hematology/Oncology

Aneela Ali, MD
Maged Khalil, MD
100 N Academy Ave
Danville, PA 17822
570-271-6045

Pottsville Cancer Clinic

Satish Singla, MD
700 Schuylkill Manor Rd #7
Pottsville, PA
570-622-4113

Penn State Hershey Medical Center - Hematology/Oncology

Salah Almokadem, M.D.
David Claxton, M.D.
Leah Cream, M.D.
Joseph Drabick, M.D.
W. Christopher Ehmann, M.D.
Yixing Jiang, M.D.
Thomas Loughran, Jr. M.D.
Witold Rybka, M.D.

500 University Drive
Hershey, PA 17033-0850
800-243-1455
or 717-531-5076

**CONTACT
INFORMATION****For information about
the screening:**

Dr. Kenneth Orloff

Agency for Toxic
Substances and Disease
Registry

770-488-0735

**For information about
other ATSDR activities in
the region:**

Lora Siegmann-Werner
lkw9@cdc.gov
(215) 814-3141

ATSDR's PV Webpage:

[www.atsdr.cdc.gov/sites/
polycythemia_vera/
index.html](http://www.atsdr.cdc.gov/sites/polycythemia_vera/index.html)







Community Health Screening Report

COMMUNITY HEALTH SCREENING FOR JAK2 (V617F) MUTATION
LUZERNE, SCHUYLKILL, and CARBON COUNTIES, PENNSYLVANIA

COST RECOVERY NUMBER: A08X

MAY 11, 2010



U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
Agency for Toxic Substances and Disease Registry
Division of Health Assessment and Consultation
Atlanta, Georgia 30333



COMMUNITY HEALTH SCREENING REPORT

**COMMUNITY HEALTH SCREENING FOR JAK2 (V617F) MUTATION
LUZERNE, SCHUYLKILL, and CARBON COUNTIES, PENNSYLVANIA**

COST RECOVERY NUMBER: A08X

Prepared By:

**Kenneth Orloff, PhD, DABT
Bruce Tierney, MD**

**U.S. Department of Health and Human Services
Agency for Toxic Substances and Disease Registry
Exposure Investigation and Site Assessment Branch
Atlanta, Georgia 30333**

Executive Summary

Polycythemia vera (PV) is a rare blood disease in which the bone marrow makes too many red blood cells. The extra red blood cells make the blood thicker than normal. As a result, blood clots can form more easily and block blood flow through arteries and veins. This can lead to heart attacks and strokes. Other symptoms of PV include headaches, dizziness, itching, and vision problems. The major goal of treatment is to prevent thrombotic events. This is accomplished by removal of blood through periodic phlebotomy and drug treatment to suppress red blood cell production by the bone marrow.

In 2009, ATSDR identified a cluster of polycythemia vera cases near the nexus of Luzerne, Schuylkill, and Carbon Counties and a second cluster in Schuylkill County, Pennsylvania. In response to these findings, ATSDR conducted community health screening. The purpose of the screening was to offer testing of blood specimens from residents of the tri-county area for the JAK2(V617F) genetic mutation. This mutation is found in approximately 95% of patients with PV, as well as in some patients with other kinds of myeloproliferative neoplasms (MPN).

ATSDR, in cooperation with the Pennsylvania Department of Health, collected blood samples from 1,170 self-selected residents, and tested them for the JAK2 mutation. About 1.2 % of participants in this screening, who had not been previously diagnosed with MPN or had symptoms of MPN, tested positive for the JAK2 genetic mutation. Available data are not adequate to conclude whether this represents an increased prevalence of the JAK2 mutation in the population tested.

A person with a positive JAK2 mutation is at increased risk of developing PV, but it is not known if everyone with this mutation eventually develops PV. It is possible that other mutations or predisposing factors are necessary for disease progression. All participants in this community health screening who had a positive test result were offered a referral for a free medical evaluation at Geisinger Health System. JAK2 positive individuals should have periodic evaluations to monitor for possible disease onset or progression.

Introduction

In 2005, the Pennsylvania Department of Health (PA DOH) released a report in which they identified a statistically significant higher incidence of polycythemia vera (PV) in Luzerne and Schuylkill Counties as compared to the rest of the state. This finding was based on reports of PV to the state cancer registry since 2001. In response to this finding, PADOH invited the Agency for Toxic Substances and Disease Registry (ATSDR) to conduct an investigation in which they attempted to (1) locate all cases of PV in Luzerne and Schuylkill Counties and in adjacent Carbon County, (2) confirm the diagnosis of PV among the registry and non-registry cases using a test for the JAK2 (V617F) genetic mutation, and (3) describe the characteristics of these individuals (Seaman et al. 2009). An analysis of these data identified clustering of PV cases near the nexus of Luzerne, Schuylkill, and Carbon Counties and in a second area of Schuylkill County (Seaman et al. 2009). The cause of the cluster of PV cases is not known.

Polycythemia vera is a myeloproliferative neoplasm characterized by increased production of red blood cells and often other blood cell lines. In the past, PV was diagnosed by clinical symptoms and traditional laboratory hematological tests. In 2005, researchers discovered a mutation in the Janus Tyrosine Kinase 2 gene (JAK2 (V617F)), which plays a pivotal role in the regulation of blood cell production (Levine et al. 2005, Kralovics et al. 2005). Approximately 95 percent of PV patients carry this acquired mutation (Baxter et al. 2005). In addition, about half of patients with the closely related blood diseases, essential thrombocythemia (ET) and primary myelofibrosis (PMF), also carry the JAK2¹ mutation (Baxter et al. 2005). In this report, these three disorders will be collectively referred to as myeloproliferative neoplasms (MPN)². Since the discovery of the JAK2 mutation, the presence of the mutation has become an important diagnostic criterion for identifying patients with PV and for reducing the potential for misdiagnosis of persons with elevated red blood cell counts.

Polycythemia vera is not considered to be a hereditary disease, although familial clustering of cases has been reported (Kralovics et al. 2003). In a recent prospective study of 1,638 patients, PV was diagnosed at a median age of 62 years, and only 4 percent of cases were below the age of 40 years (Finazzi et al. 2005). In this study, males accounted for slightly more than half (58%) of the cases. The cause (or causes) of PV is (are) not known. Risk factors, including familial predisposition, occupational history, and exposure to radiation and toxic chemicals, have been evaluated, but no clear evidence of causality has been established (Najejan et al. 1998).

¹ In this report, the "JAK2" mutation refers to the "JAK2 (V617F)" mutation, unless otherwise specified.

² Other MPNs, such as chronic eosinophilic leukemia and mastocytosis, that have not been associated with the JAK2(V617F) mutation, will not be considered in this report.

Purpose

The purpose of this community health screening was to offer JAK2 testing to residents of the tri-county area of Luzerne, Schuylkill, and Carbon Counties in northeastern Pennsylvania. ATSDR conducted this Community Health Screening in cooperation with the PA DOH.

The intent of this screening was to address individual health concerns regarding the high prevalence of PV identified in this area. As a service oriented project, this screening was not conducted in such a way as to produce information that is generalizable to the entire population within the PV cluster area. Results are only applicable to the individual participants and cannot be used to assess the prevalence of this mutation in the general population, since those electing to be tested were self-identified.

Methods

A. Criteria for participation

Any current, full-time resident of Luzerne, Schuylkill, or Carbon County who had lived in the tri-county area for 1-year or longer was eligible to participate in this screening. Because of the concerns of some community members, ATSDR also accepted a few participants who were not currently residing in the area, but who had previously been long-term residents of the area.

B. Recruiting participants

ATSDR focused its recruitment on residents who were living in the area of the previously-identified PV cluster near the confluence of the three counties. Because PV occurs primarily in people above the age of 40, recruitment was focused on this segment of the population. However, since this was a community health service, there was no minimum age requirement for eligibility.

Recruitment efforts included the following:

- (1) Representatives of ATSDR attended a public meeting on July 9, 2009 in Tamaqua. At this meeting, we described the Community Health Screening to the community and solicited participants.
- (2) We met with community leaders and asked them to encourage their friends and neighbors to participate.
- (3) We provided informational flyers to community leaders, who distributed them throughout the target area.

(4) We talked with the local news media, which ran newspaper and television stories on the community health screening being offered.

C. Sample collection

Participants in the screening were instructed to call a toll-free telephone number to make an appointment at one of the three health screening centers (Attachment A). At the screening center, the participant was required to sign an informed consent form prior to testing. Children and their parents were required to complete an applicable consent or assent form. After consent was obtained, a phlebotomist collected, by veinipuncture, a 6-ml blood sample from each participant in a heparinized tube.

ATSDR conducted the community health screening over two periods of time. The first round of screening was held on August 3-6 and August 10-14, 2009. During this time period, blood samples were obtained from 356 participants.

A second round of screening was conducted on October 19-22, October 26-29, and November 2, 2009. During these time periods, four evening sessions were held to accommodate people who could not attend a daytime session. During the second round of screening, blood samples were collected from 814 participants. Therefore, we collected a total of 1,170 blood samples during rounds 1 and 2.

To protect privacy, ATSDR labeled the tubes with a coded identification number prior to shipping them to the laboratory for analysis.

D. Sample handling and shipping

At the end of each day, ATSDR packaged the blood samples in protective Styrofoam containers and shipped them at room temperature by overnight delivery to the Mount Sinai Medical Center laboratory in New York City for analysis. Blood samples collected during the evening sessions were kept at refrigerator temperature (35-38 °F) prior to and during shipping the next day.

E. Laboratory analysis

Blood samples were analyzed at the Molecular Pathology Laboratory at the Mount Sinai School of Medicine using published methodologies (Ishii et al. 2006). The laboratory is regulated under the Clinical Laboratory Improvement Amendments (CLIA) of 1988 as qualified to perform high complexity clinical testing. Pursuant to the requirements of CLIA of 1988, the laboratory has established the test's accuracy and precision.

All blood samples were tested as follows: DNA was extracted from granulocytes and amplified by multiplex Polymerase Chain Reaction (ARMS-PCR) enabling simultaneous detection of mutant and normal alleles specific for a sequence of the JAK2 gene (V617F). PCR products were separated by agarose gel electrophoresis and detected by fluorescence. The detection limit for this assay is 0.05% of JAK2 V617F allele in a

background of wild type allele.

Blood samples that tested positive for the JAK2 (V617F) mutation were further tested by a confirmatory, quantitative real-time PCR test as follows: Total DNA was extracted, amplified in two separate real-time PCR steps using primer sets specific for either JAK2 (V617F) or wild type JAK2. Using established standard curves, absolute quantitation of JAK2 (V617F) allele and wild type allele could be made. The JAK2 (V617F) allele burden was computed as the ratio of JAK (V617F) alleles to the total alleles. The limit of detection is 0.05% JAK2 (V617F) allele in a wild-type background.

F. Notifying participants of test results

All participants received written notification of their test results and a copy of the laboratory report. Upon request, ATSDR also mailed the test results and laboratory report to a health care provider designated by the participant. ATSDR telephoned participants with positive test results to personally discuss the findings and answer any questions.

Results

A total of 1,170 blood samples from rounds 1 and 2 of the community health screening were tested for the JAK2 mutation. Of the 1,170 samples collected, 19 (1.6%) tested positive for the JAK2 mutation. Five of the participants with positive test results had previously been diagnosed with or had clinical symptoms of PV (2) or ET (3). The other 14 JAK2 mutation-positive individuals, representing 1.2% of the participants, gave no history of an MPN and reported no signs or symptoms of illness.

Figure 1 depicts the age distribution of the test participants. The mean age of all of the participants was 54 years old, and the mean age of the 19 participants with the JAK2 mutation was 63 years old. A recent study reported that the median age of patients with PV was about 62 years old (Finazzi et al. 2005). The ages of the participants in this screening with a positive test result ranged from 23 to 88 years old. Ten of the positive test results were from men, and nine were from women.

Figure 1. Number of participants vs. age of participants in JAK2 community health screening. Total number of participants = 1,170.

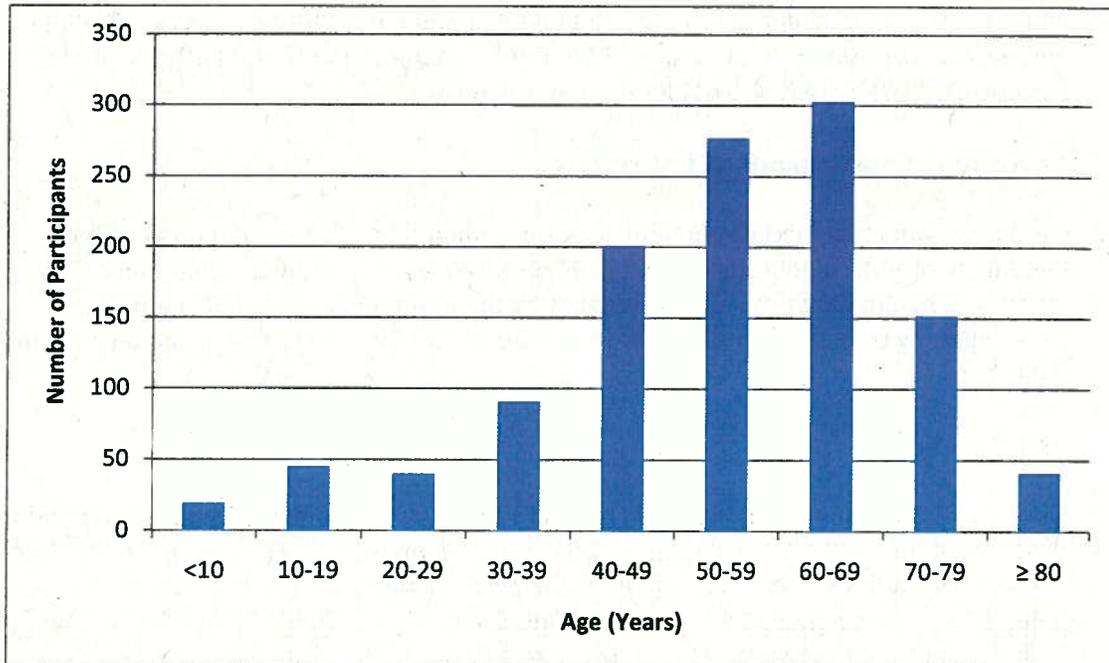


Table 1 provides summary statistics on the ages of the participants in the screening and how long they have lived at their current address.

Table 1. Ages of participants and length of residence.

	Number	Age (range)	Age (mean)	Length of residence (mean)
All participants	1,170	2-92	54	24
JAK2+ with disease ⁽¹⁾	5	50-77	64	20
JAK2+ without disease	14	23-88	63	28

(1) Diagnosed with or had clinical symptoms of an MPN

Discussion

The health significance of the presence of the JAK2 (V617F) genetic mutation is not known. About 95 percent of PV patients test positive for the JAK2 mutation, and about half of patients with ET and PMF test positive for the mutation (Baxter et al. 2005). Therefore, it is likely that a person who tests positive for the JAK2 mutation is at increased risk for one of these three myeloproliferative neoplasms.

Although the JAK2 (V617F) mutation is present in most PV patients, other JAK2 mutations have also been detected in PV patients. Researchers have identified at least five other mutations in the JAK2 gene in the small subset (5%) of PV patients who lack the JAK2 (V617F) mutation (Scott et al. 2007; Li et al. 2008).

Although about 95 percent of PV patients have the JAK2 mutation, it is not known whether everyone with the JAK2 mutation will eventually develop the disease, or the time frame between acquisition of the mutation and disease onset. It has been suggested that other mutations or predisposing factors are also involved in the development and progression of PV (Nussenzveig et al. 2007; Dupont et al. 2007).

In this screening, the JAK2 positive individuals were confirmed by a second analytical test that measured the percent of the DNA from blood granulocytes that carried the JAK2 mutation. This is referred to as the JAK2 allele burden. In a published study, patients with clinically diagnosed PV had JAK2 allele burdens ranging from 1 to 100 percent with an average of 52 percent (Antonioli et al. 2008). Longitudinal studies of PV patients have shown that the percent of mutated JAK2 DNA increases over time (Rumi et al. 2006). Furthermore, studies have shown that clinical symptoms (splenomegaly, pruritus, thrombosis) and laboratory parameters (increased hematocrit) are more likely to occur in patients with a high JAK2 allelic burden (Vannucchi et al. 2007).

In the JAK2 positive cases from this screening, the JAK2 allele burden ranged from 0.1 % to 26.8 % (detection limit of 0.05 %). The allele burden was higher in cases with previously diagnosed MPN or symptoms (8.4 %) than in cases without previously diagnosed disease (2.1 %). In 12 of 14 cases without a MPN diagnosis, the allele burden was 1.2 % or less.

Table 2. JAK2 (V617F) allele burden in positive cases

	Number	Allele Burden % (range)	Allele Burden % (average)
JAK2+ with disease ⁽¹⁾	5	2.2 – 26.8	8.4
JAK2+ without disease	14	0.1-22.5	2.1

(1) Diagnosed with or had clinical symptoms of MPN

The meaning and prognosis of a low allele burden is unknown. One possibility is that people with low allele burdens of the JAK2 mutation have only recently acquired the mutation. Disease may not occur until clonal expansion of the mutated cell line results in a higher proportion of JAK2 mutated cells. It is possible that other mutations or predisposing host factors are necessary for progression to clinically detectable disease. Alternatively, such persons may not progress to develop illness. Regardless, these individuals should be closely monitored for signs and symptoms of MPNs.

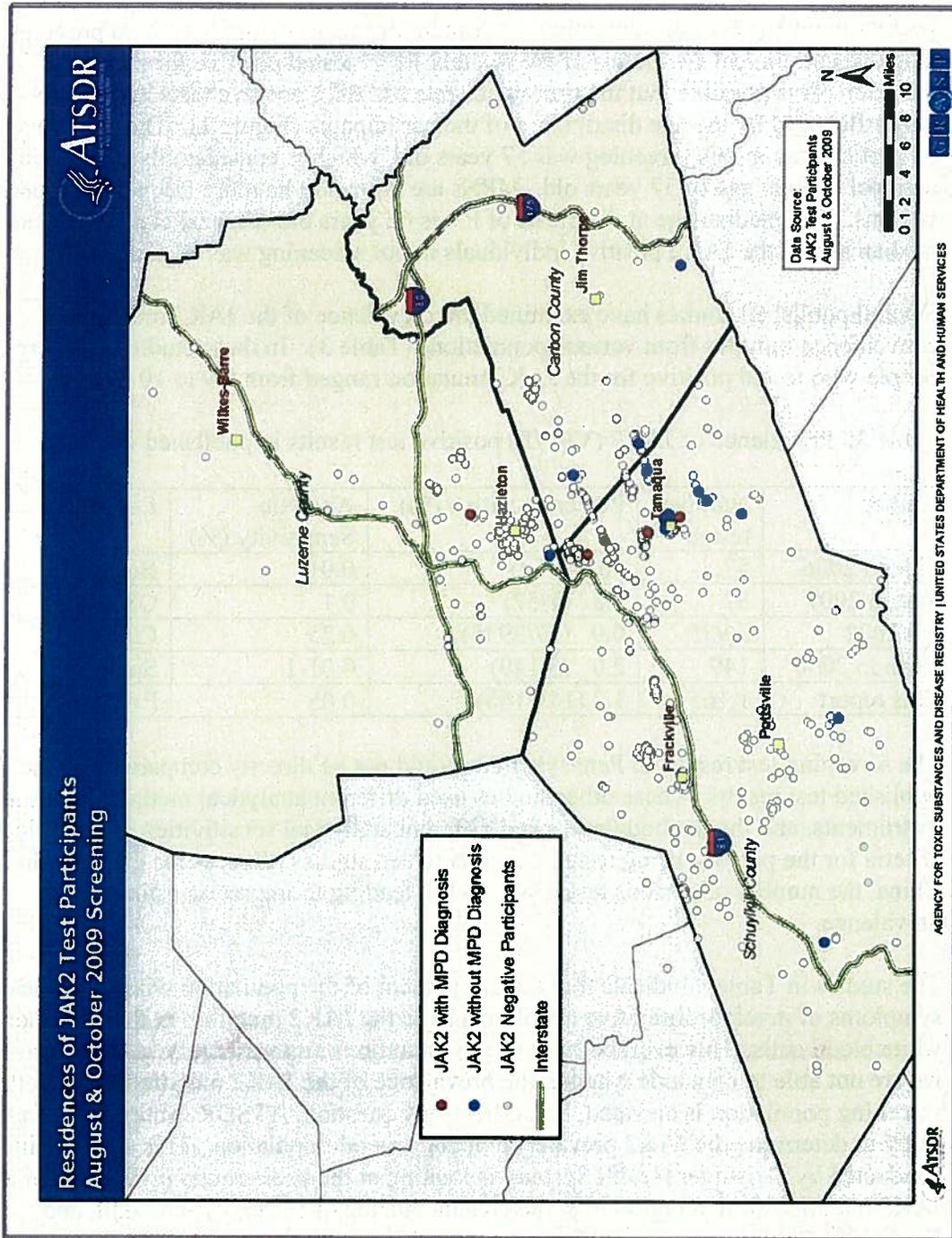
In this screening, 14 of 19 participants who tested positive for the JAK2 mutation did not self-report a diagnosis or clinical symptoms of PV or other MPN. It may be that because we used a very sensitive JAK2 screening test, we detected people who had only recently acquired the mutation. In PV patients, the initial symptoms are mild and progress as the disease develops over a period of years.

Geospatial analysis

The geographical distribution by residence of the people tested in this screening is depicted in Figure 2. Many of the participants with a positive JAK2 test lived in the previously identified PV cluster area. This area was also the focus of our recruitment efforts.

This screening was offered as a public health service, and the participants were self-selected, rather than being randomly chosen. For this reason, it is not valid to compare the prevalence rates of JAK2 positive tests across the tri-county area. Although the prevalence rate of JAK2 positive mutations appears to be higher in the cluster area, self-selection of the participants may have introduced a bias for some unknown risk factor. This is known as participation bias. As an example of this type of bias, some of the positive individuals were known to have an MPN or to have symptoms.

Figure 2. JAK2 test results



Prevalence of JAK2 positive cases in the general population

In this community health screening, 1.2 percent of the participants with no previous diagnosis or clinical symptoms of PV or other MPN tested positive for the JAK2 mutation. It is possible that the prevalence rate of JAK2 positive tests in our screening was influenced by the age distribution of the participants (Figure 1). The median age of all participants in this screening was 57 years old, which is considerably older than the national median age of 37 years old. MPNs are known to be more frequent in older persons. The median age at diagnosis of PV is 62 years old (Finazzi et al. 2005), and the median age of the JAK2 positive individuals in our screening was 68 years old.

Several published studies have examined the prevalence of the JAK2 mutation in convenience samples from various populations (Table 3). In these studies, the percent of people who tested positive for the JAK2 mutation ranged from 0.9 to 10 percent.

Table 3: Prevalence of JAK2 (V617F) positive test results in published studies.

Author	Number tested	Percent positive (%)	Analytic Sensitivity (%)	Location
Sideon 2006	57	10 (5/57)	0.01	Belgium
Sutton 2007	57	1.8 (1/57)	0.1	OK, TN
Xu 2008	3,935	0.9 (37/3935)	0.25	China
Rapado 2008	149	2.0 (3/149)	0.01-1	Spain
This report	1,165	1.2 (14/1165)	0.05	PA

The screening test results in Pennsylvania should not be directly compared to these other published test results. These other studies used different analytical methodologies and instruments, and the methodologies had different analytical sensitivities. Also, selection criteria for the persons being tested varied between studies. Except for the study in China, the number of persons tested was small, leading to imprecise estimates of prevalence.

The studies in Table 3 indicate that a small percent of the population without clinical symptoms of myeloproliferative neoplasms have the JAK2 mutation in their circulating white blood cells. However, because of the limitations and variability in these studies, we are not able to conclude whether the prevalence of the JAK2 mutation in the ATSDR screening population is elevated. To address this question, ATSDR is currently funding a study to determine the JAK2 prevalence in the general population. This study, being conducted by Geisinger Health System, is looking at the background prevalence of the JAK2 mutation from a region in Pennsylvania outside of Luzerne, Schuylkill, and Carbon Counties.

Follow-up of Positive Cases

It is prudent public health policy to consider JAK2 positive individuals to be at increased risk for developing PV or other myeloproliferative diseases. Therefore, we recommend

that JAK2 positive individuals undergo periodic medical evaluations to monitor for possible disease onset or progression. Early diagnosis and treatment of PV may improve the patient's quality of life and reduce the risk of life-threatening complications.

All participants in this EI with a positive JAK2 test were offered a referral for a follow-up medical evaluation. In addition, longitudinal evaluation of these individuals is indicated to: (1) help us to learn more about the progression of the disease and (2) help determine if everyone with the mutation goes on to develop overt disease. Therefore, ATSDR encouraged all JAK2 positive individuals to participate in an ongoing study at Geisenger medical facilities that will follow these individuals over time.

Child Health Considerations

Children are a low risk population for PV. The JAK2 mutation is an acquired mutation rather than an inherited one. Therefore, the prevalence of the JAK2 mutation is expected to increase with age, as does the prevalence of PV. The prevalence of PV in the general population for adults 65-74 years old is 99.5 cases per 100,000, whereas the prevalence of PV in patients 0-34 years old is 0.31 cases per 100,000 (Ma et al. 2008).

In the ATSDR screening, the JAK2 mutation was not detected in any children. The youngest participant who tested positive for the JAK2 mutation was 23 years old; the next youngest positive participant was 43 years old.

Conclusions

(1) ATSDR conducted community health screening for the JAK2 (V617F) mutation in self-selected residents of Luzerne, Schuylkill, and Carbon Counties. A total of 1.2 % of participants in this screening, who had not been previously diagnosed with polycythemia vera or other myeloproliferative neoplasms or had symptoms of these diseases, tested positive for the JAK2 (V617F) genetic mutation. Available studies are not adequate to conclude whether this represents an increased prevalence of the JAK2 mutation in those tested.

(2) A person with a positive JAK2 mutation may be at increased risk of developing PV or other MPN, but it is not known if everyone with this mutation will develop an MPN or the time frame for this to occur.

(3) Additional studies are needed to better define the background prevalence of the JAK2 mutation in the tri-county area, other areas in Pennsylvania, and nation-wide.

Recommendations

(1) Participants with a positive test result should have periodic medical evaluations to monitor for the development of PV and other myeloproliferative neoplasms and to assure necessary treatment if indicated.

(2) Residents who are concerned about their risk of developing PV or other myeloproliferative neoplasms should consult with their personal physician who can arrange for JAK2 genetic testing through a private laboratory.

Public Health Action Plan

ATSDR is funding studies at the Pennsylvania Department of Health, Drexel University, University of Pittsburgh, Mount Sinai Medical Center, Geisinger Health System, and ATSDR/CDC to investigate PV and other MPN in the tri-county area.

In addition, ATSDR is funding the following studies that will provide additional information on the prevalence rate of JAK2 mutations.

1. Geisinger Health Systems will screen a random sample of 2,500 people from the PV cluster area for the JAK2 mutation.
2. Geisinger Health Systems will screen 6,000 participants from outside the tri-county area to determine the "background" prevalence of the JAK2 mutation in Pennsylvania.
3. ATSDR has submitted a proposal to determine the prevalence of the JAK2 mutation in the 1999-2002 NHANES DNA sample set (7,900 samples). This will reflect the national "background" prevalence.

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Attachment A: Blood Collection Centers

Schuylkill Mall
Community Meeting Room
Route 61 and I-81
Frackville, PA 17931

Saint Jerome's Catholic Church
School Gymnasium and Alumni Room
250 West Broad Street
Tamaqua, PA 18252

Hazleton General Hospital
700 East Broad Street
O & E Building – 1st floor
Hazleton, PA 18201