The Pacific Northwest Laboratory Medicine Sentinel Monitoring Network
Final Report of the Findings of Questionnaire 17
Molecular genetic testing

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BACKGROUND

The Pacific Northwest Laboratory Medicine Sentinel Monitoring Network was created in 1995 to gather ongoing information about practices in hospital, independent and physician office laboratories (POLs) in Alaska, Idaho, Oregon, and Washington. To date, 21 questionnaires have been released to the network, exploring issues related to: testing quality; access to testing services; laboratory-related problems and errors; personnel training and changes; proficiency testing participation; point of care testing; and waived testing.

[Final reports of the findings of each questionnaire and references to journal articles based on these studies can be found on the Centers for Disease Control and Prevention (CDC) Website: http://www.phppo.cdc.gov/dls/mlp/pnlmsmn.asp]

Questionnaire 17

The intent of this questionnaire was to gather the following information:

- What molecular genetic tests are being ordered?
- Where are molecular genetic tests being performed?
- How is the laboratory that performs the genetic test chosen?

Questionnaire 17 was mailed to 330 moderate and high complexity laboratory network participants in January 2002. Two hundred four laboratories returned a completed questionnaire in time for analysis, a 62% response rate.

Demographic characteristics of the respondents are summarized in the following table. For comparison, the same characteristics of the network and of all moderate- and high-complexity laboratories in the four-state region are also included.

Table 1 - Demographic characteristics of questionnaire respondents

	Questionnaire 17 respondents N=204	**All network participants** (Moderate and high complexity laboratories) N=330	**All laboratories in the Pacific Northwest** (Moderate and high complexity laboratories) N=1539
	PERCENT OF LABORATORIES		
Alaska	9	9	6
Idaho	19	19	16
Oregon	22	22	32
Washington	50	49	46
Urban / Rural	54 / 46	56 / 44	68 / 32
Alaska	37 / 63	29 / 71	39 / 61
Idaho	11 / 89	19 / 81	39 / 61
Oregon	71 / 29	71 / 29	71 / 29
Washington	67 / 33	69 / 31	80 / 20
POL* / Hospital / Independent	59 / 31 / 9	59 / 31 / 10	73 / 17 / 10
Alaska	58 / 32 / 10	61 / 29 / 10	70 / 24 / 6
Idaho	58 / 34 / 8	55 / 39 / 6	77 / 17 / 6
Oregon	58 / 33 / 9	60 / 31 / 10	72 / 17 / 11
Washington	61 / 29 / 10	61 / 28 / 12	74 / 16 / 10
Accredited Yes	32	32	30
Alaska	32	35	46
Idaho	18	22	15
Oregon	56	49	41
Washington	26	28	25

* POL includes: Physician office laboratories (POLs), clinics, community health centers, rural health clinics, health departments/districts, and student health centers.

In the cover sheet accompanying the questionnaire, a molecular genetic test was defined as:

"An analysis performed on human DNA or RNA to detect heritable or acquired disease-related genotypes, mutations or phenotypes for clinical purposes. Such purposes include diagnostic testing, predicting risk of disease, and identifying carriers."

Prior to the first question, commonly ordered molecular genetic tests were listed, as follows:

Angelman Syndrome
BCR/ABL translocation (Philadelphia chromosome)
BRCA-1 or BRCA-2 (Hereditary Breast Cancer)
Cystic Fibrosis
Duchenne Muscular Dystrophy
Factor V Leiden Thrombophilia
Familial Adenomatous Polyposis
Fragile X Syndrome
Hemochromatosis
Huntington Disease
Hemoglobin S (Sickle Cell Anemia)
Hereditary Non-Polyposis Colon Cancer
Prader-Willi Syndrome
Y Chromosome Detection

FINDINGS

Molecular genetic test orders

Participants were asked if clinicians ordered any of the tests listed or any other molecular genetic tests in the past 3 months. Overall, 109 laboratories (53%) said they handled orders during this time frame. Table 2 shows a summary of the responses by various demographic categories of interest.

Table 2 - Molecular genetic test orders (N=204 laboratories)

Type of laboratory	**Number**	**Any molecular genetic tests ordered?** (Percent)		
		Yes	**No**	**Do not know**
All	204	53	43	3
POL	121	46	50	3
Hospital	64	66	34	0
Independent	19	58	26	16
Urban	111	56	40	4

Rural	93	51	46	3

A total of 320 tests were listed, averaging 3 tests per laboratory, and a range of 1 to 16 tests. Table 3 shows the specific molecular genetic tests ordered.

Table 3 - Molecular genetic tests ordered (109 laboratories)

Molecular genetic test	**Number of times listed**
Factor V Leiden Thrombophilia	70
Fragile X Syndrome	46
Hemochromatosis	44
Cystic Fibrosis	32
Hemoglobin S	22
BCR/ABL translocation	18
BRCA-1 or BRCA-2	13
Huntington Disease	13
Prader-Willi Syndrome	12
Y Chromosome Detection	10
Duchenne Muscular Dystrophy	8
Angelman Syndrome	5
Factor II (Prothrombin) 20210	5
Familial Adenomatous Polyposis	2
Hereditary Non-Polyposis Colon Cancer	1
JH/BCL2	1
MEN II	1
Rett Syndrome	1
Alpha-1-antitrypsin deficiency	1
B & T cell gene rearrangements	1

Charcot-Marie-Tooth	1
Fetal Rh D/Cc/Ee	1

NOTE: A brief description of these diseases can be found in Appendix A.

The following tests of bacterial or viral genetic material were listed: Whipple's disease; pertussis (PCR); and hepatitis C genotype.

Other tests listed included: Maternal serum alpha-fetoprotein; Cardiolipin (IgM, IgG, IgA); Chromosome analysis; Cytogenetics; Von Willebrand's disease; Hemoglobin S (Sickledex and electrophoresis); Lupus anticoagulant.

On-site testing

Network participants were asked if they performed any molecular genetic tests on-site. Four respondents (2%) indicated that they did. The following table describes these laboratories.

Table 4 - Network laboratories performing molecular genetic testing on-site

	Laboratory type	**State**	**Location**	**Accreditation status**
1	Hospital	Washington	Urban	Accredited
2	Independent	Washington	Urban	Accredited
3	Independent	Oregon	Urban	Accredited
4	Independent	Oregon	Urban	Accredited

A total of 27 tests were listed by these four laboratories. The following table shows a summary of responses.

Table 5 - Molecular genetic tests performed on-site (N=4 laboratories)

Molecular genetic test	**Number of times listed**
Factor V Leiden Thrombophilia	4
Factor II (Prothrombin) 20210 mutation	4
FISH* probes for leukemia, lymphoma, neoplasms	2
BCR/ABL translocation	2
Hemochromatosis	1
FISH*-constitutional microdeletion syndromes	1
MTHFR	1
Fragile X Syndrome	1
Hemoglobin S	1
Fetal Rh D/Cc/Ee	1
DiGeorge/Velo-Cardio-Facial Syndrome (FISH*)	1
Williams Syndrome-Elastin Gene (FISH*)	1
Lissencephaly/Miller-Dieker Syndrome (FISH*)	1
Prader-Willi/Angelman Syndrome	1
Smith-Magenis Syndrome	1
B & T cell gene rearrangement	1
JH/BCL2 (RT-PCR**)	1
FISH* probes for HER-2/neu	1
FISH* probes for N-MYC	1
* Fluorescent In-Situ Hybridization ** Reverse transcriptase-Polymerase chain reaction	

NOTE: A brief description of these diseases can be found in Appendix A.

Send-out testing

Network participants were asked whether they send their specimens for molecular genetic testing: to a reference laboratory, who in turn sends them to a genetic testing laboratory of their choice; directly to the laboratory where the genetic testing is actually performed; or a combination of both.

The highest percentage of respondents (62%) said they sent all their specimens for molecular genetic testing directly to their reference laboratory, who in turn decided where the test would be performed. Seven percent said they sent their specimens directly to the genetic testing laboratory and 31% said they did some combination of these.

How is the genetic testing laboratory chosen?

Network participants were asked "For the molecular genetic test orders you send directly to the genetic testing laboratory, how was the laboratory chosen?" They were given the following choices, and asked to check any that applied:

- Information was provided by our reference laboratory
- Information was provided by a medical geneticist
- Information was provided by a genetic counselor
- Mandated by an insurance contract or managed care agreement
- From an Internet resource
- Do not know
- Other, briefly describe

Ninety-five responses were given by the 76 respondents that sent some or all of their tests directly to the genetic testing laboratory.

Table 6 shows the resources used in choosing a genetic testing laboratory by these respondents.

Table 6 - How is the genetic testing laboratory chosen? (N=76 respondents)

Resources used in choosing a genetic testing laboratory	**Number of responses**
Information provided by our reference laboratory	35
Information provided by a genetic counselor	11
The patient's provider chooses the testing laboratory	11
Information provided by a medical geneticist	9
Do not know	5
Mandated by an insurance contract or managed care agreement	4
Directed by a neurologist	3
Patient comes to us with a laboratory already chosen - It is unknown how the laboratory was selected	3
Patient's provider receives information from colleagues or medical education meeting	2
From an Internet resource (www.genetests.org)	2
Tests are done at the State Laboratory	2
Recommended by an oncologist	1
Recommended by a pathologist	1
Recommended by a medical school	1
Recommended by a genetic testing laboratory sales representative	1
Recommended by a cytogenetics laboratory	1
Use of in-house esoteric test reference manual	1
Based on reputation	1
It is our selected hospital	1

Participants were asked to record the name and location of each laboratory where molecular genetic tests they handled were actually performed. Table 7 shows the genetic testing laboratories

listed by the respondents.

Table 7 - Genetic testing laboratories used

Laboratory name	Location	Number of responses
ARUP	Salt Lake City, UT	11
Athena Diagnostics	Worcester, MA	9
Barnes Hospital	St. Louis, MO	1
Baylor University	Houston, TX	4
Children's Hospital & Medical Center	Seattle, WA	7
Diagnostic Cytogenetics	Seattle, WA	1
Dynacare Laboratories	Seattle, WA	5
Dynagene	Houston, TX	1
Fred Hutchinson Cancer Center	Seattle, WA	1
Genelex	Seattle, WA	1
Genetic Lab	Salt Lake City, UT	1
Genetics Testing Lab	Seattle, WA	1
Genzyme	Framingham, MA Boston, MA Santa Fe, NM California	7
Greenwood Genetics	Greenwood, SC	1
Hematologics	Seattle, WA	1
Idaho State Laboratory	Boise, ID	2
Impath	Los Angeles, CA	1
Jefferson Neurogenetics	Philadelphia, PA	1
Kaiser	Portland, OR	1

Lab Corp (Locations were listed as: Seattle, WA; Salt Lake City, UT; Burlington, NC. All molecular genetic testing is performed at Research Triangle Park, NC)	Research Triangle Park, NC	11
Legacy Lab	Portland, OR	3
Laboratory name	**Location**	**Number of responses**
Mayo Medical Laboratories	Rochester, MN	6
Myriad	Salt Lake City, UT	2
Oregon Health Sciences University	Portland, OR	16
Oregon Medical Laboratories	Eugene, OR	4
Pathology Associates Medical Laboratories	Spokane, WA	12
Puget Sound Blood Center	Seattle, WA	3
Quest/Nichols Institute (Locations were listed as: Seattle, WA; Los Angeles, CA; Portland, OR; Pendelton, OR. All molecular genetic testing is performed at San Juan Capistrano, CA)	San Juan Capistrano, CA	26
Reproductive Immunology Associates	Van Nuys, CA	1
Sacred Heart Medical Center	Spokane, WA	16
Specialty Laboratories	Santa Monica, CA Los Angeles, CA	8
Swedish Hospital Medical Center	Seattle, WA	1
UCLA Children's Hospital	Los Angeles, CA	1
University of Pennsylvania	Philadelphia, PA	1
University of Utah	Utah	2
University of Washington	Seattle, WA	20
Utah State University	Salt Lake City, UT	1

One hundred forty-three genetic testing laboratories were listed by the 76 respondents who sent some or all of their specimens directly to the site performing the genetic testing.

We found that about half (52%) of the genetic testing laboratories used are located in the Pacific Northwest region. Of the 48% of genetic testing sites located outside the region, 15% represent sites owned by one of the large national reference laboratories (Lab Corp or Quest). These patterns differ by state and are likely influenced by the number of genetic testing sites located in each state. The respondents in Washington and Oregon kept more genetic testing in their state than the respondents from the other two states. Respondents in Alaska sent all testing to laboratories out of their state, but used a high percentage of laboratories in the region. Respondents in Idaho and Oregon used laboratories out of the region to a higher degree than Alaska and Washington. Table 8 shows these responses by state.

Table 8 - Are selected genetic testing sites local, regional, national?

	Location of questionnaire respondent				
	Alaska	**Idaho**	**Oregon**	**Washington**	**Pacific NW**
Number of genetic testing labs listed	10	22	40	71	143
Percent sent to genetic testing labs:					
In-state	0	9	43	56	41
Out-of-state, but within Pacific NW	60	32	0	4	11
Total within Pacific NW region	60	41	43	61	52
Out of region - National reference lab	20	23	10	14	15
Out of region - Other genetic lab	20	36	48	25	33
Total out of region	40	59	58	39	48

DISCUSSION

In the past few years, there has been tremendous progress in the discovery of molecular changes in genes related to human diseases. As these molecular changes are identified, diagnostic genetic tests are rapidly being developed, with a subsequent migration from the research laboratory to the clinical laboratory setting.

In an article published in the June 2001 edition of the *Laboratory Industry Report* [1], genetic tests were available for 811 hereditary diseases in 2000 (excluding tests for hereditary cancers and infectious diseases), according to Genetests.org, a not-for-profit research organization based in Seattle, Washington. That number represented a 22% increase from the 667 tests available in 1999. (By January 2002, the number had risen again, to 905).

With this questionnaire, our intent was to develop a snapshot of the types of molecular genetic tests being ordered in the Pacific Northwest in 2002 and to identify where the testing is being performed. We also wanted to find out how clinical sites choose a laboratory to perform such testing.

We found about half of the respondents (53%) handled orders for molecular testing. Hospitals and independent laboratories handled more genetic test orders than POLs. Tests for venous thrombosis, Fragile X Syndrome, hemochromatosis and cystic fibrosis were the most commonly ordered. We also saw a number of tests relating to cancer detection/prognosis.

Very few of the network respondent laboratories (2%) performed genetic testing on-site. [For comparison, 1.8% of the 716 moderate and high complexity laboratories in Washington State perform molecular genetic testing. This information is not readily available for Alaska, Idaho and Oregon.]

Most of the respondents (62%) sent their orders directly to their reference laboratory, who in turn chose where the test would be performed. Even when respondents chose their own sites for genetic testing, they frequently turned to their reference laboratory for advice in making their selection. Genetic counselors, medical geneticists, and the ordering physician also played a role in helping our respondent laboratories choose the genetic testing laboratory. Test orders were referred most commonly to laboratories in university settings and to specialized genetic testing laboratories.

In a recent satellite conference hosted by CDC [2], experts predicted a rapid migration of genetic

testing orders from specialists to hospitals to doctors' offices to patients. In turn, there will be an increased need to educate non-geneticist care providers.

Laboratorians may need to become more involved in educational efforts for health care providers to know which tests to order and how to address the additional issues and activities that surround genetic testing orders, including: pre- and post-test counseling; documentation of informed consent; and strict confidentiality.

REFERENCES

1. Dennis W. Weissman, Publisher. “Demand for Genetic Counselors Is Booming.” Laboratory Industry Report. Vol. X, No. 6/June 2001.

2. Centers for Disease Control and Prevention - National Laboratory Training Network Satellite Conference: “Genetics for the Public’s Health,” November 6, 2001.

Appendix A - Description of Genetic Diseases

Disease	**Description**
Alpha-1-antitrypsin deficiency	Lung damage, emphysema
Angelman Syndrome	Developmental delay or mental retardation
BCR/ABL translocation (Philadelphia chromosome)	Chronic myelogeneous leukemia (CML)
BRCA-1, BRCA-2	Predisposition to breast, ovarian, prostate, colon, other cancers
Charcot-Marie-Tooth	Chronic motor and sensory polyneuropathy
Cystic Fibrosis	Complex multi-system disease
DiGeorge/Velo-Cardio-Facial Syndrome	Range of findings, including: Congenital heart disease; Palate abnormalities; Learning difficulties
Duchenne Muscular Dystrophy	Muscle disease
Factor II (Prothrombin) G20210A	Risk factor for venous thromboembolic disease
Factor V Leiden Thrombophilia	Increased risk of venous thromboembolism
Familial Adenomatous Polyposis	Colon cancer predisposition syndrome
Fragile X Syndrome	Mild to moderate mental retardation
Hemoglobin S	Sickle cell disease. Prenatal diagnosis by DNA analysis
HER-2/neu	Breast cancer marker to assist in prognosis/treatment
Hereditary Hemochromatosis	High absorption and excessive storage of iron. Can lead to diabetes, congestive heart failure, arthritis.
Huntington Disease	Progressive disorder of motor, cognitive, psychiatric disturbances.
JH/BCL2	Characterize certain types of lymphoma

Lissencephaly/Miller-Dieker Syndrome	Severe brain malformations
MEN II oncogene (Multiple endocrine neoplasia)	High risk for medullary carcinoma of thyroid; pheochromocytoma; parathyroid adenoma
Disease	**Description**
MTHFR	Elevated levels of homocysteine. Risk factor for arterial and venous thrombosis.
N-MYC oncogene	Determination of prognosis of neuroblastoma
Prader-Willi Syndrome	Feeding difficulties in early infancy, excessive eating and development of morbid obesity in later infancy. Cognitive impairment.
Rett Syndrome	Progressive neurological disorder in females
Smith-Magenis Syndrome	Physical, developmental, behavioral features
Williams Syndrome-Elastin gene	Cognitive impairment
Y Chromosome Detection	Risk for gonadoblastoma;Sex reversal-XY females or XX males; Risk for X-linked recessive conditions