

# PAP Research and Registry Overview



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# Acknowledgements



## PAP Patients and Families

### CCHMC, Cincinnati, OH, USA

Bruce Trapnell	(Marchele Bostic)
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### Support

Savara

Partner Therapeutics

NHLBI R01 HL085453

NHLBI R01 HL118342

Cincinnati Children's Hospital

(NCATS/TRND Program)

(NCATS UL1 TR001425-02S1)

(NCATS-NHLBI U54 HL127672)

(Genzyme - Leukine)



# Outline

- ▶ Blood Tests to Diagnose PAP
- ▶ Clinical Course of Autoimmune PAP
- ▶ Utilization of Therapeutic Options for Autoimmune PAP



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- ▶ **Blood Tests to Diagnose PAP**
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# Diseases Associated with PAP Syndrome



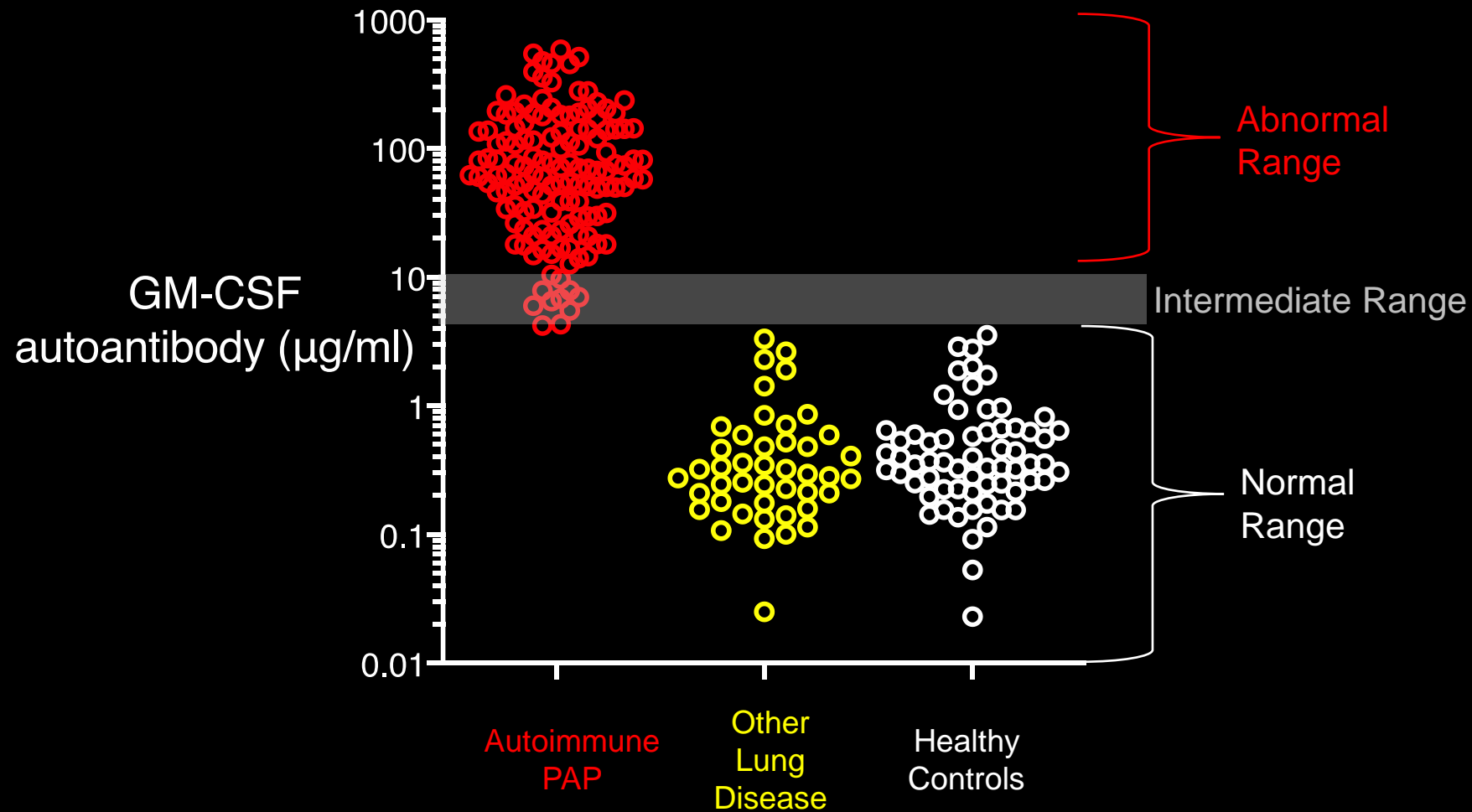
Disease	Cause	Therapeutic approaches
<b>Autoimmune PAP (aPAP)</b>	GM-CSF autoantibody (GMAb)	<ul style="list-style-type: none"> <li>▶ WLL</li> <li>▶ GM-CSF</li> <li>▶ Rituximab</li> <li>▶ Plasmapheresis</li> <li>▶ Statins</li> </ul>
<b>Hereditary PAP (hPAP)</b>	Mutations: CSF2RA or CSF2RB	<ul style="list-style-type: none"> <li>▶ WLL</li> <li>▶ Bone Marrow Transplantation</li> <li>▶ Gene therapy</li> <li>▶ Pulmonary Macrophage Transplantation</li> </ul>
<b>Secondary PAP (sPAP)</b>	Myelodysplasia, Inhaled particulates, others	<ul style="list-style-type: none"> <li>▶ WLL (+/-)</li> <li>▶ Treat underlying disease</li> </ul>
<b>Disorders of Surfactant Production (DSP)</b>	Mutations: SP-B, SP-C, ABCA3, TTF1	<ul style="list-style-type: none"> <li>▶ Lung Transplantation</li> </ul>

# PAP Diagnosis Study



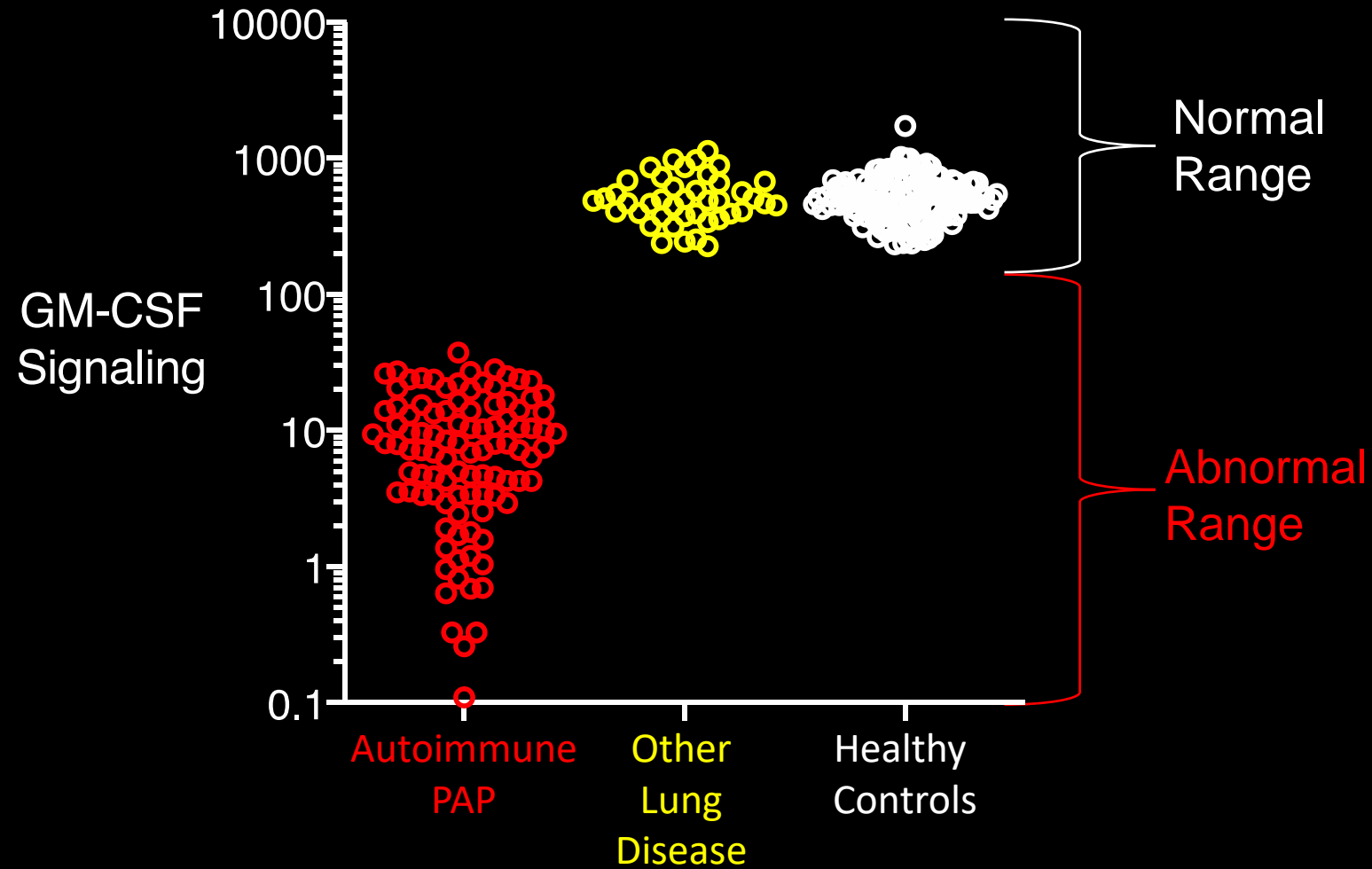
- ▶ A clinical research study has been available to help with the diagnosis of autoimmune PAP since 2004
- ▶ Consent patients, ship samples to CCHMC, and test blood for:
  - ✓ GM-CSF autoantibody
  - ✓ GM-CSF signaling

# Serum GM-CSF Autoantibody Levels



Serum GM-CSF autoantibody levels are elevated in autoimmune PAP patients.

# GM-CSF Signaling



GM-CSF signaling is impaired in autoimmune PAP patients.



# PAP Diagnosis Study



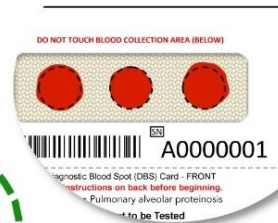
- ▶ Samples received from US and Australia, Belgium, Brazil, Canada, Chile, Croatia, Czech Republic, France, Germany, Hungary, India, Ireland, Israel, Italy, Netherlands, New Zealand, Poland, Slovenia, South Africa, Spain, Sweden, Taiwan, Turkey, United Kingdom
- ▶ To date, we have evaluated ~1000 individuals:
  - ✓ 60% – GMAbpos, GM-CSF signalingneg (autoimmune PAP)
- ▶ GM-CSF autoantibody and GM-CSF signaling assays were transferred to Diagnostic Immunology Laboratory at CCHMC to be performed under CAP/CLIA guidelines

# Translating PAP Testing Into the Clinic

## TPSC PAPKit™

### Pulmonary Alveolar Proteinosis Diagnostic Blood Spot Card Test Kit

Fingerstick Blood Collection Kit for  
Identification of Diseases that Cause  
Pulmonary Alveolar Proteinosis (PAP)



- Easy to Use
- Convenient and Safe
- Simply Send it by Mail
- Confidential

Administered by



Translational Pulmonary Science Center Laboratory  
Cincinnati Children's Hospital Medical Center



## TPSC PAPKit™

### Pulmonary Alveolar Proteinosis Diagnostic Blood Spot Card Test Kit

#### Instructions



Simple Fingerstick Blood Collection Kit for  
Identification of Diseases that Cause  
Pulmonary Alveolar Proteinosis

- Easy to Use
- Convenient and Safe
- Confidential
- Simply Send by Mail
- Free Test - All Costs Paid by the PAP Foundation and Rare Lung Diseases Consortium

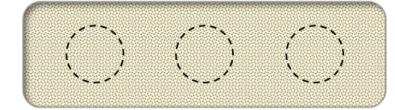
To request additional TPSC PAPkits™,  
please call 1-513-636-6361.

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Translational Pulmonary Science Center Laboratory  
Cincinnati Children's Hospital Medical Center

DO NOT TOUCH BLOOD COLLECTION AREA (BELOW)



Diagnostic Blood Spot (DBS) Card - FRONT

Read instructions on back before beginning.  
Key: PAP = Pulmonary alveolar proteinosis

#### A. Medical History of Patient to be Tested

- Has been diagnosed with PAP.
- A diagnosis of PAP is suspected.
- A family member has PAP. Relationship: \_\_\_\_\_
- Has other lung disease. What: \_\_\_\_\_
- Has other non-lung disease. What: \_\_\_\_\_
- Is healthy – has no known chronic disease(s) or symptoms.

#### B. Symptoms (Check all that apply)

- None
- Breathlessness
- Cough
- Fatigue
- Fever
- Sputum (Phlegm)
- Other (describe): \_\_\_\_\_

#### C. Patient received and read brochures entitled: "TPSC PAPKit Instructions" and "What is (Pulmonary Alveolar Proteinosis (PAP)? Should I be Tested?"

Yes  No

#### D. Blood Spot Information

Date blood was collected: \_\_\_\_\_

SN A0000001

#### E. Patient Information

Date of Birth: \_\_\_\_\_

Gender:  Male  Female

First Name: \_\_\_\_\_ MI: \_\_\_\_\_

Family Name: \_\_\_\_\_

Telephone: \_\_\_\_\_

Send results to physician listed below:  Yes  No

Physician information

First Name: \_\_\_\_\_ MI: \_\_\_\_\_

Family Name: \_\_\_\_\_

Institution or Medical Center: \_\_\_\_\_

Street: \_\_\_\_\_ Suite: \_\_\_\_\_

City: \_\_\_\_\_ State: \_\_\_\_\_

Telephone: \_\_\_\_\_ ZIP: \_\_\_\_\_

Fax: \_\_\_\_\_

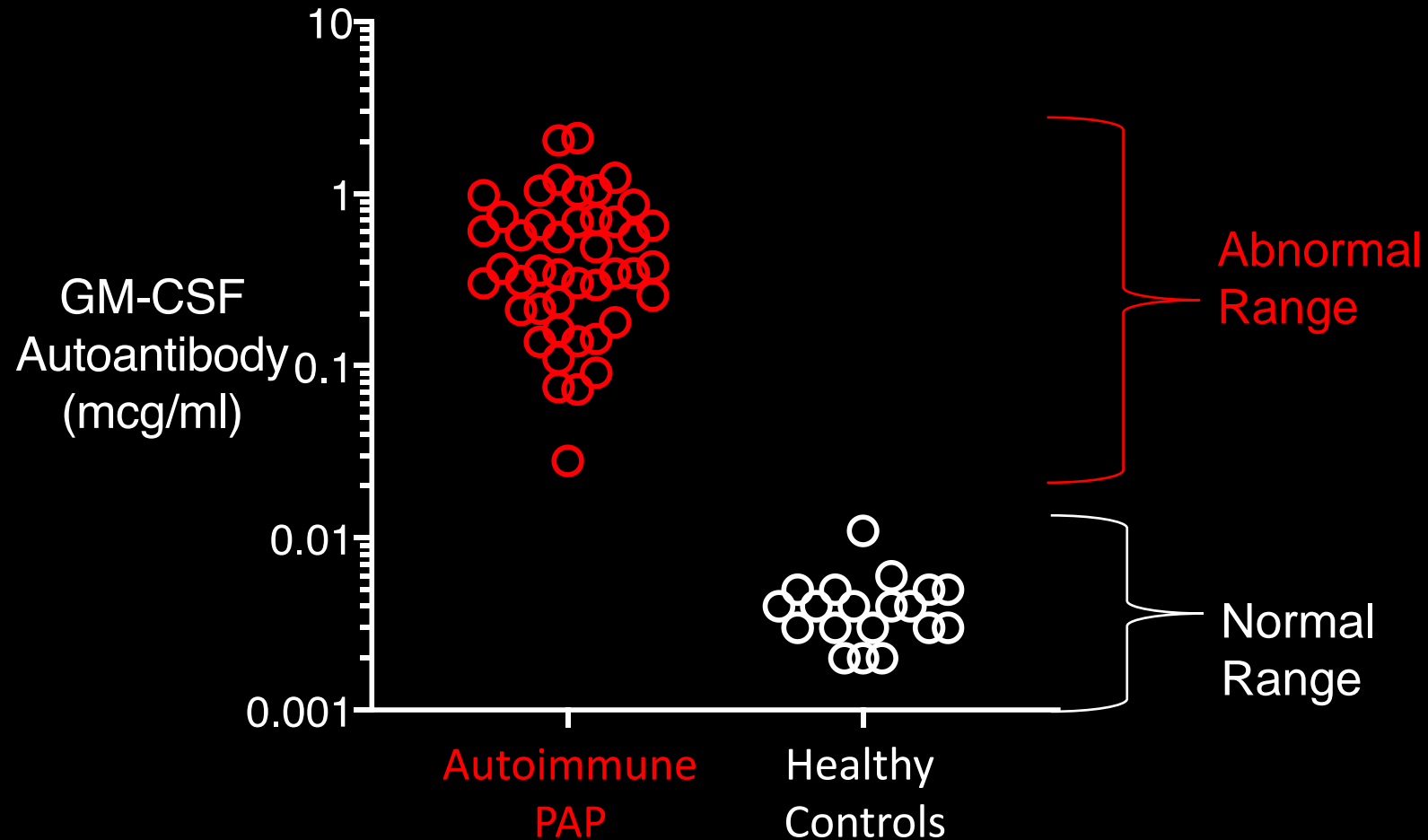
\_\_\_\_\_

\*\*PLEASE FILL OUT COMPLETELY\*\*

This entire card must be completed for the sample to be processed.

PR01-0001

# Dried Blood Spot Card GM-CSF Autoantibody Levels



GM-CSF autoantibody levels measured from dried blood spot cards are elevated in patients with autoimmune PAP.

# Outline

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- ▶ **Clinical Course of Autoimmune PAP**
- ▶ Utilization of Therapeutic Options for Autoimmune PAP

# National PAP Registry Study

What is  
Pulmonary Alveolar  
Proteinosis (PAP)?

*Should I Be  
Tested?*



National PAP Registry  
*Enrollment Questionnaire*

We invite you to join the National Registry for pulmonary alveolar proteinosis (PAP), a joint program of the PAP Foundation and the Rare Lung Diseases Consortium. The purpose of the research database is to identify a group of people who are interested in receiving information about research studies focused on PAP and possibly participating in these research studies.

One hurdle to developing effective diagnostic tests and treatments for PAP has been that PAP occurs rarely – in about 7 out of every one million people. Further, PAP is not one disease but, rather, a syndrome that occurs in multiple diseases, which are even more rare and differ in their natural history, diagnosis, prognosis, and responses to treatment. Finally, no routine clinical tests are available that doctors can use to identify the PAP-causing disease in most PAP patients.

Significant research advances have led to the development of accurate diagnostic tests and promising treatment approaches for autoimmune PAP and other PAP-causing diseases. Clinical studies of these new potential treatments are being planned. Knowing which disease is causing PAP in a person is needed to understand their clinical course, prognosis, and for choosing appropriate therapy to treat the PAP-causing disease in that person.

The National PAP Registry is a part of a clinical research study designed to overcome these hurdles. By gathering medical information from enough people with PAP, we can improve our understanding about this rare syndrome. This study will also facilitate the evaluation of new tests to identify PAP-causing diseases. Finally, it will provide information about PAP and PAP research to patients and their families and doctors. We keep all personal information about participants in strictest confidence. More information about the study and how confidentially is kept can be found in the informed consent document. You can obtain additional information from the person in charge of this study, Dr. Bruce Trapnell, using the contact information provided at the end of the Questionnaire.

We designed the Registry Questionnaire to be quick and easy by writing short answers in the space provided to the right of each question. Some numbered questions are followed by one or more unnumbered questions that refer back to the immediately preceding numbered question. Extra space is provided in some sections to permit inclusion of further information, if needed. A parent (or legal guardian) may complete the questionnaire for a Participant who is a child or minor. To maximize the value of your contribution to this study, it is important to answer all questions. All questions refer to information about the Participant, except where indicated.

**Definitions of selected key terms used in the Registry Questionnaire.** The term 'Participant' is used to indicate the person with PAP who will be enrolled in the Registry. 'You' refers to the Participant who will be enrolled in the Registry. 'Child' refers to anyone less than 18 years of age at the time the questionnaire is completed. 'Parent' will be used to refer to either a parent or legal guardian of a minor Participant. 'Symptom' refers to a Participant experience, such as cough, pain, or breathlessness – a feeling of being unable to "take a good breath" or "get enough air". Definitions of other terms and more information about the National PAP Registry can be found in brochures available from the PAP Foundation at their website located at [www.PAPFoundation.org](http://www.PAPFoundation.org) or the Rare Lung Diseases Consortium website located at [www.rarediseasesnetwork.org/rldc](http://www.rarediseasesnetwork.org/rldc).

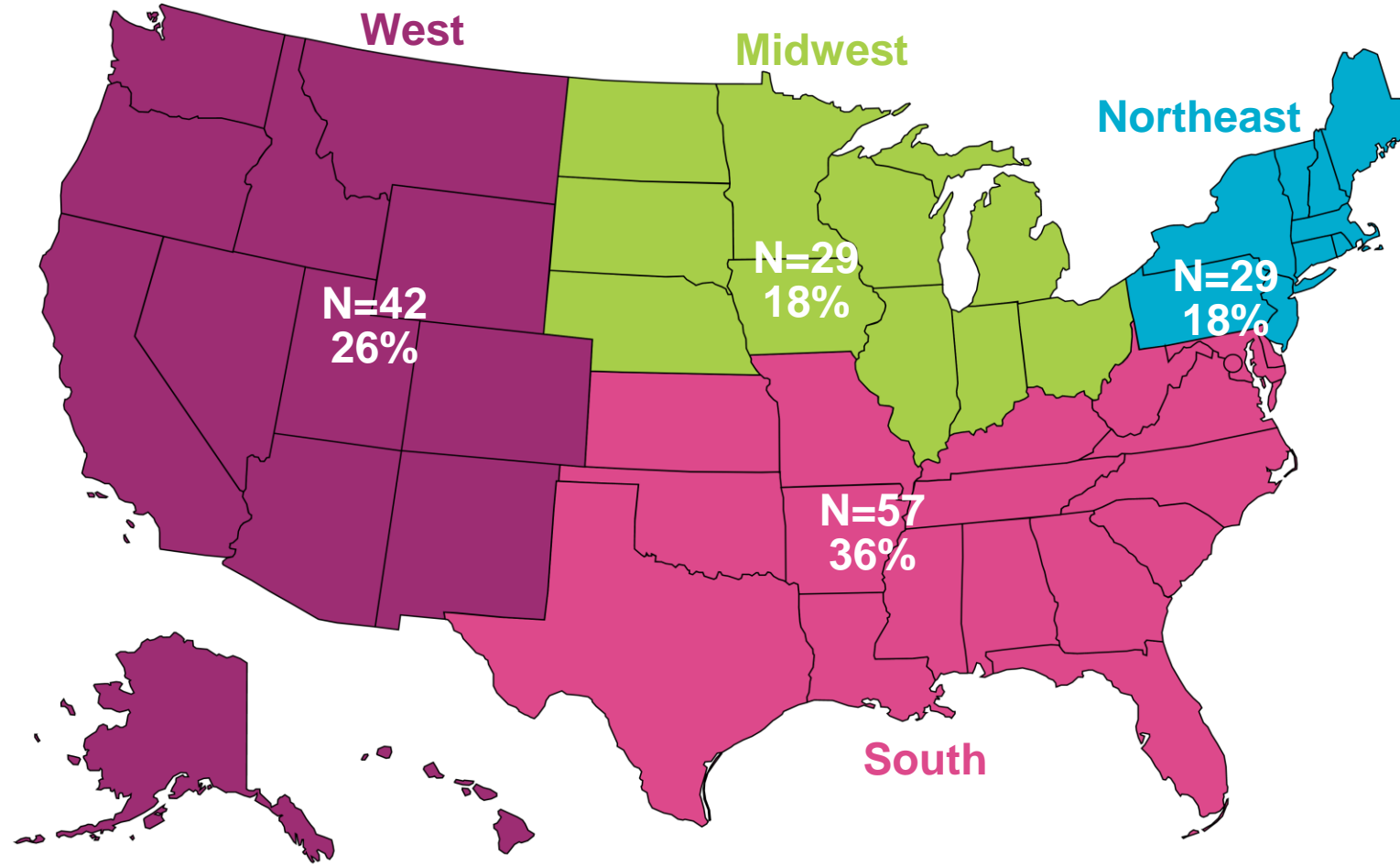
The National PAP Registry is a project developed jointly among and with support from the PAP Foundation, Rare Lung Diseases Consortium (RLDC), and Translational Pulmonary Science Center (TPSC). The RLDC is funded by the National Institutes of Health (NIH) (U54HL127672) and is a part of the National Center for Advancing Translational Science (NCATS) Rare Diseases Clinical Research Network (RDCRN). The RDCRN is an initiative of the Office of Rare Diseases Research (ORDR) and NCATS and is funded through a collaboration between NCATS and the National Heart, Lung and Blood Institute.



# Distribution of National PAP Registry Participants

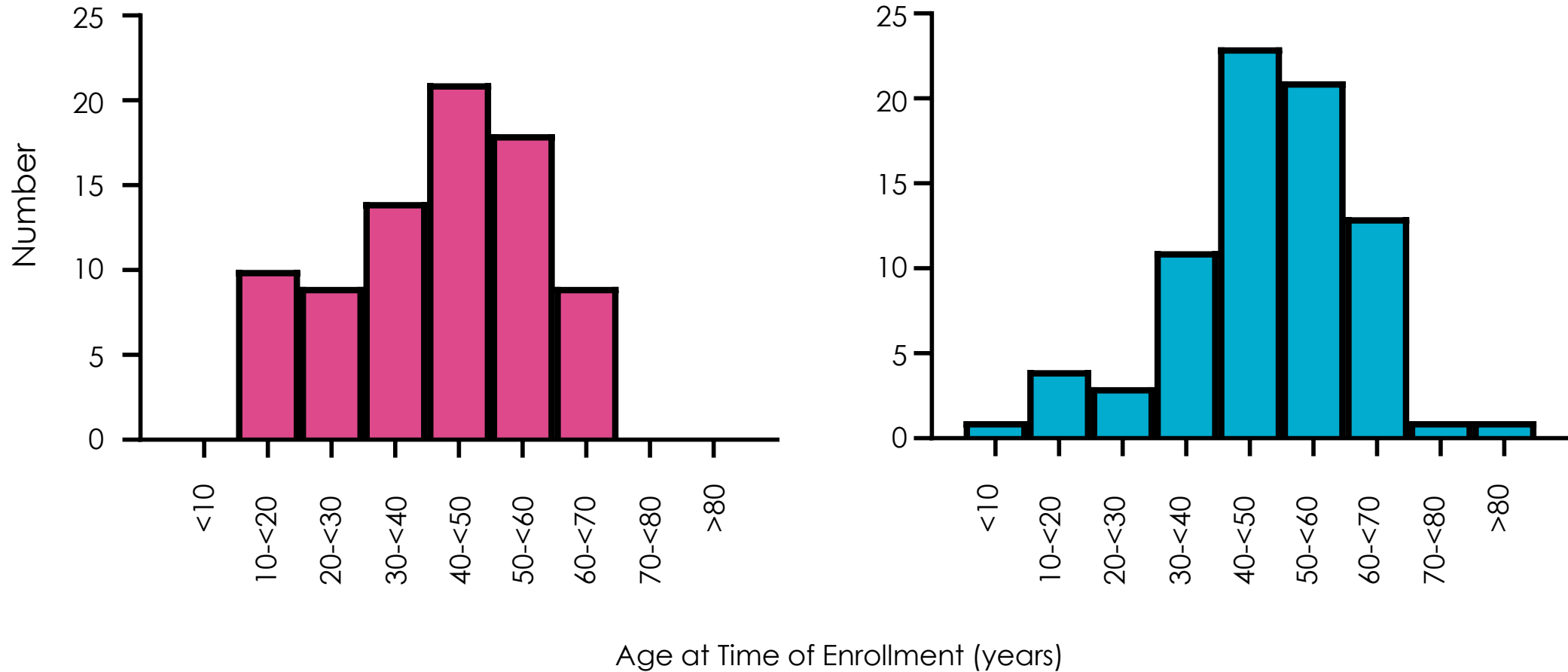


Canada - N=2; 1%



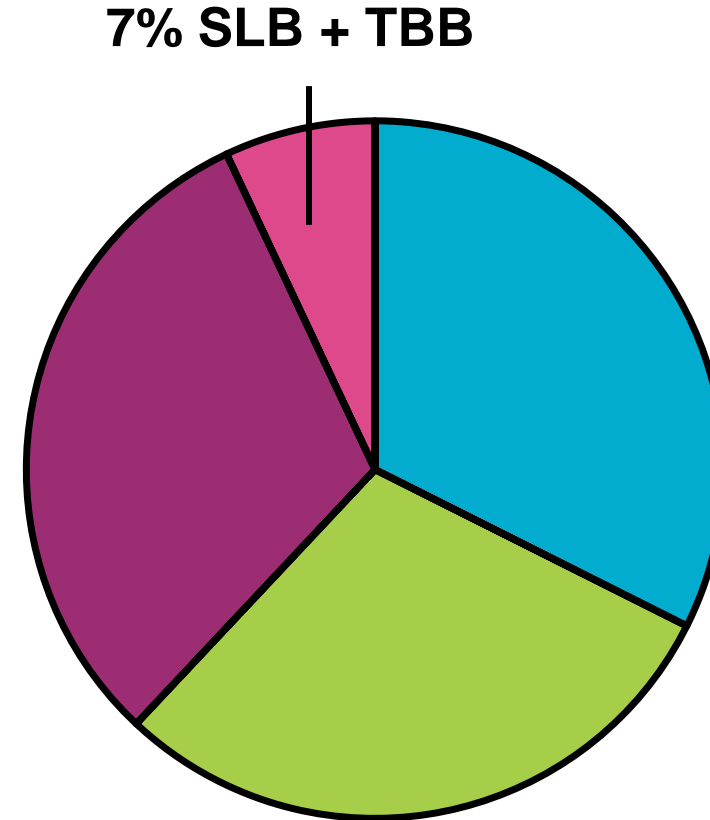
National PAP Registry participants are distributed across the United States.

# National PAP Registry Participants



National PAP Registry participants comprise both genders and multiple age groups.

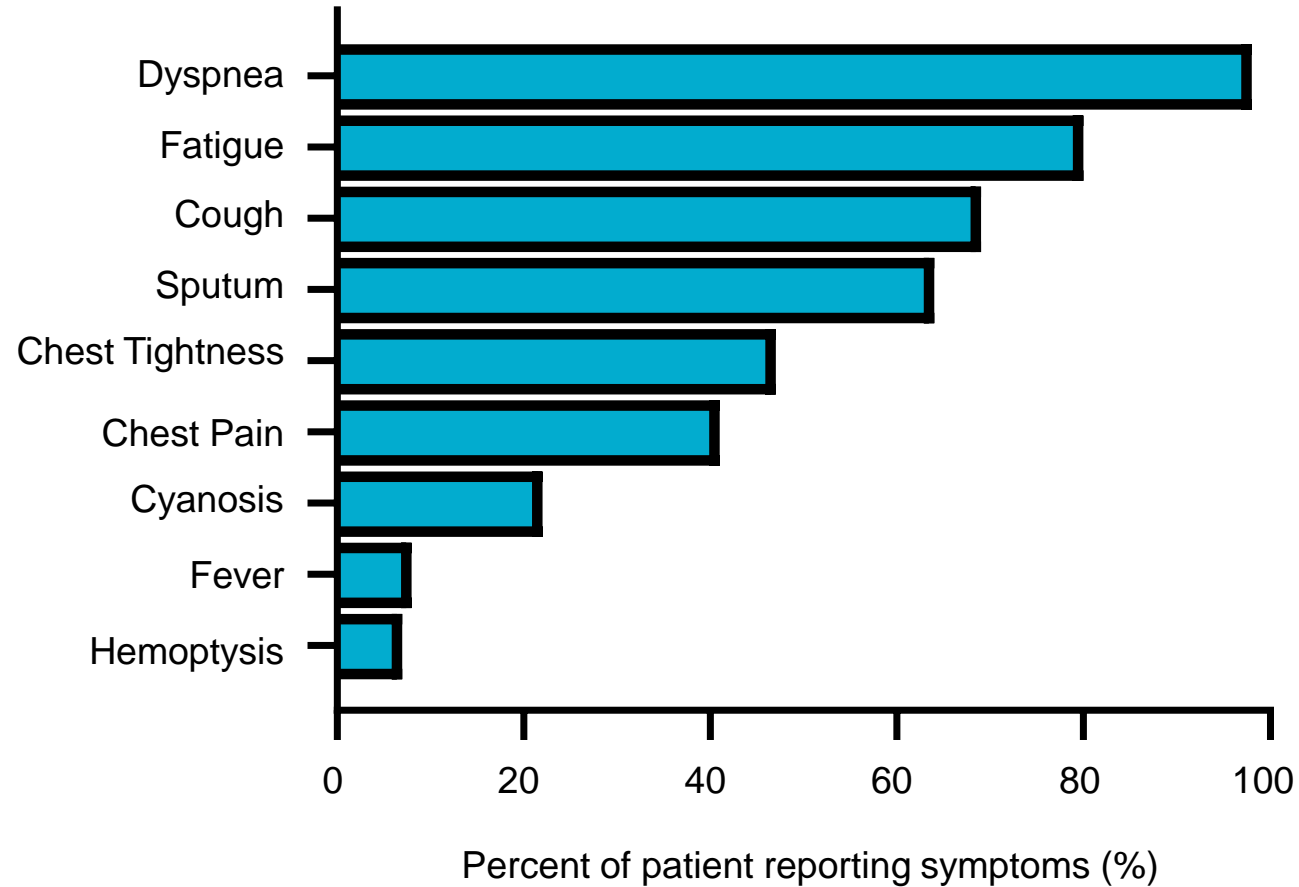
# Diagnostic Lung Biopsies



Many PAP patients undergo transbronchial biopsy, surgical lung biopsy, or both even though neither is diagnostic for any PAP-causing disease.



# Symptoms Reported Prior to Diagnosis



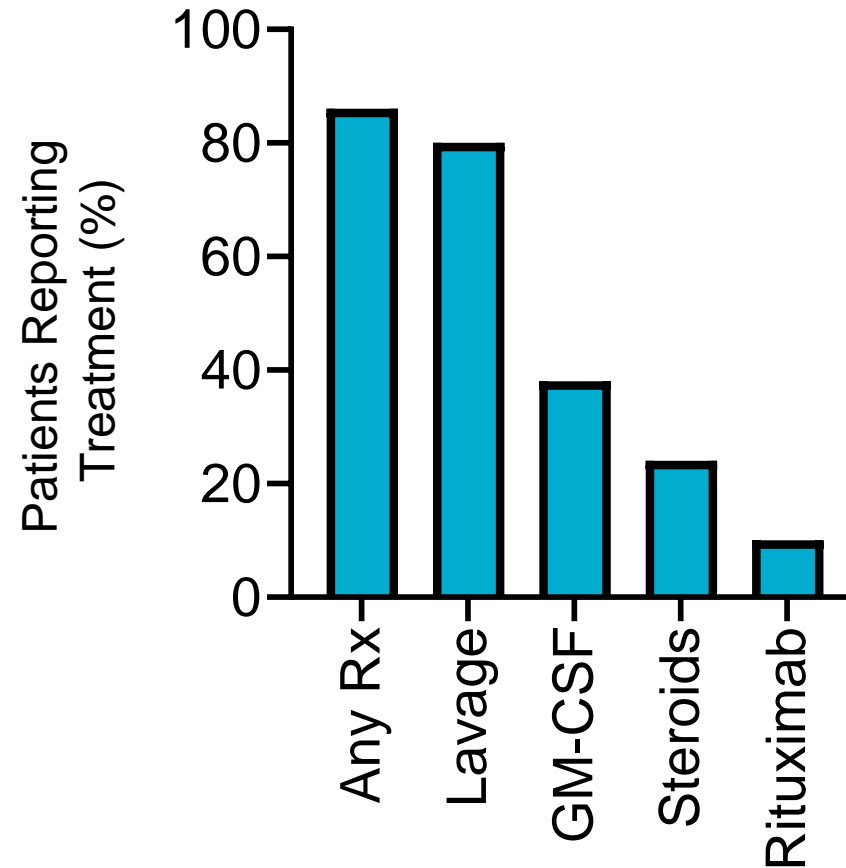
National PAP Registry participants most commonly report breathlessness, fatigue, and cough prior to diagnosis.

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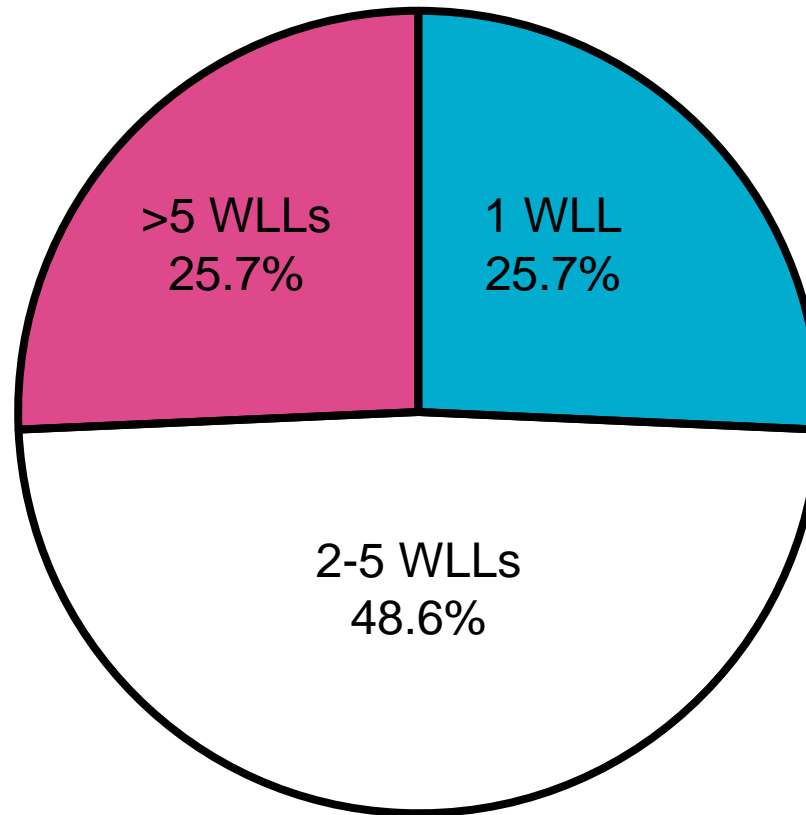


# Utilization of Therapeutic Options for Autoimmune PAP



National PAP Registry participants most commonly report breathlessness, fatigue, and cough prior to diagnosis.

# Frequency of WLL Reported by Registry Participants



National PAP Registry participants report variation in the frequency of WLLs, ranging from 1 WLL to more than 5.

# Summary



- ▶ Blood tests have been developed that are highly accurate for the diagnosis of autoimmune PAP.
- ▶ Many PAP patients undergo a lung biopsy which is not diagnostic for any PAP-causing disease. Lung biopsy should be reserved for difficult cases in which diagnosis remains unclear.
- ▶ Symptoms at presentation are non-specific and non-diagnostic. Breathlessness is the most common symptom reported by PAP patients.
- ▶ The majority of aPAP patients need therapy. The most common therapy is WLL which is required on a recurrent basis and the frequency was highly variable among individuals.



# Future Research Questions

- ▶ How reliable is the new ‘blood droplet’ test for the diagnosis of PAP?
- ▶ Are there better tests for diseases that cause PAP?
- ▶ What should be the criteria for a diagnosis of autoimmune PAP?
- ▶ What is the clinical course of autoimmune PAP over time?
- ▶ What are best indications for a whole lung lavage?
- ▶ What is the proper dose and administration frequency for GM-CSF therapy?
- ▶ How long will it take for patients to see improvement?
- ▶ The National PAP Registry is an opportunity for us to answer some of these questions.
- ▶ If you are interested in participating in the National PAP Registry, please contact me at email [Brenna.Carey@cchmc.org](mailto:Brenna.Carey@cchmc.org).