PAP Diagnosis and Patient Registry

Brenna Carey, MS, PhD
Assistant Professor
Translational Pulmonary Science Center
Cincinnati Children's Hospital Medical Center
PAP Foundation Secretary/Treasurer
PAP Foundation Board Member

Acknowledgments

PAP Patients and Families	
CCHMC, Cincinnati, OH, USA	
Bruce Trapnell	(Greg Grabowski)
Jennifer Stock	(Henry Greenberg)
Marissa Ruzga	(Maria Klingler)
Lauren Hill	(Cormac McCarthy)
Paritha Arumugam	(Jon Puchalski)
Matt Wessendarp	(David Roach)
Yan Ma	(Takuro Sakagami)
Christopher Towe	(Carrie Stevens)
Jeff Whitsett	(Takuji Suzuki)
Jason Woods	(Andrea Toth)
(Claudia Chalk)	(Kanji Uchida)
(Marchele Bostic)	(Robert Wood)
(Colleen Fitzpatrick)	(Susan Wert)
UCLA, Los Angeles, CA, USA	
Tisha Wang	M. Carmela Granone
Liz Tarling	Erica Godart
Elinor Lee	(Cynthia Garcia)
Jonathan Alkalai	
University of Florida, Gainesville, FL, USA	
Ali Ataya	
University of Michigan, Ann Arbor, MI, USA	
Rachel Zemans	

U. of Niigata, Japan
Koh Nakata, Ryushi Tazawa
Kinki Chest Hosp., Japan
Yoshikazu Inoue
U. Pavia, Italy
(Maruizio Luisetti), Ilaria Campo
Ruhlandklinik, Germany
Ulrich Costabel, Francesca Bonella
NIH
NHLBI - Louis Vuga, (Jerry Eu, Lora Reineck)
NCATS - Sharie Haugabook, (Holly Hamilton)
Support
Savara
Partner Therapeutics
FDA OOPD R01 FD 007604
NHLBI R01 HL085453
NHLBI R01 HL118342
Cincinnati Children's Hospital
(NCATS/TRND Program)
(NCATS UL1 TR001425-02S1)
(NCATS-NHLBI U54 HL127672)
(Genzyme - Leukine)

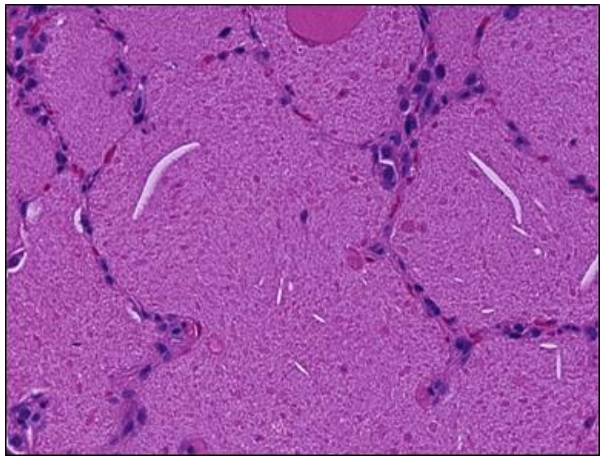
Outline

- Blood Tests to Diagnose PAP
- National PAP Registry
- Natural History and Clinical Outcome Measures for Autoimmune PAP

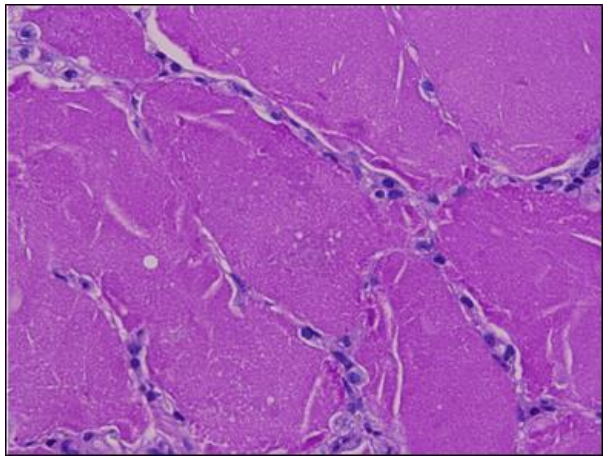
Outline

- **Blood Tests to Diagnose PAP**
- National PAP Registry
- Natural History and Clinical Outcome Measures for Autoimmune PAP

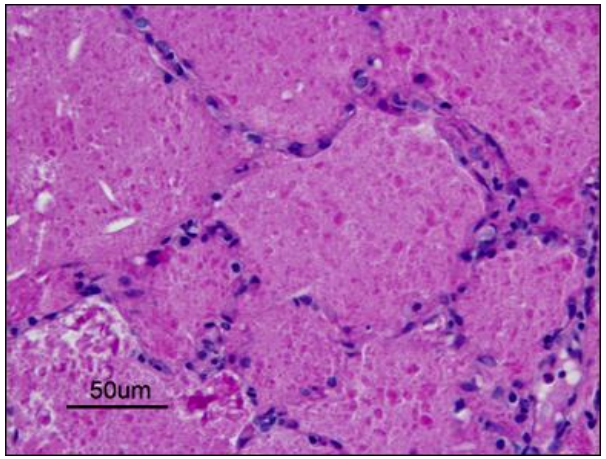
Evaluating PAP Based on Lung Biopsies



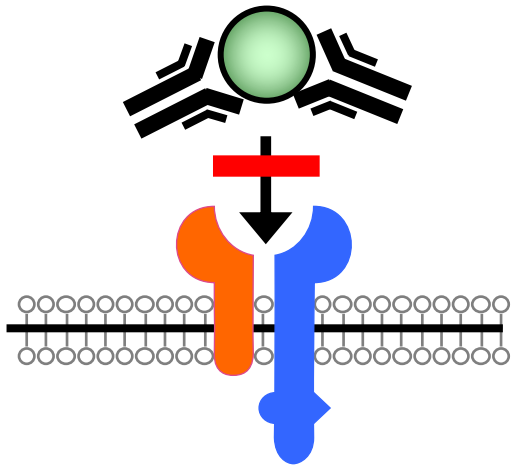
Autoimmune PAP
(GM-CSF Auto-Abs)

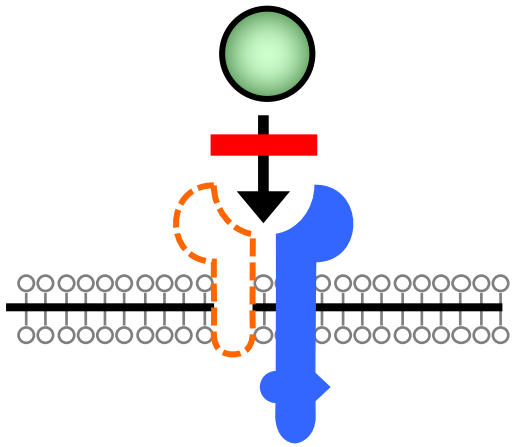


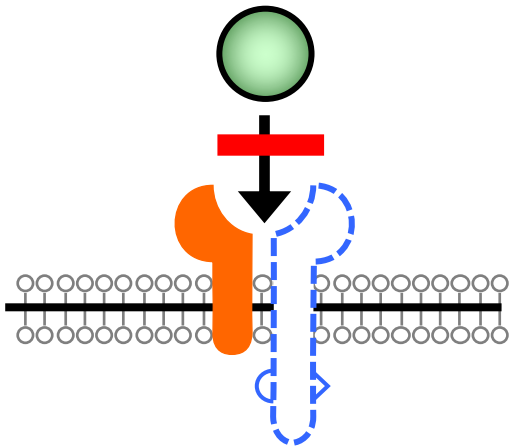
Hereditary PAP
(*CSF2RA* Mutations)



Hereditary PAP
(*CSF2RB* Mutations)







Diseases Associated with PAP Syndrome

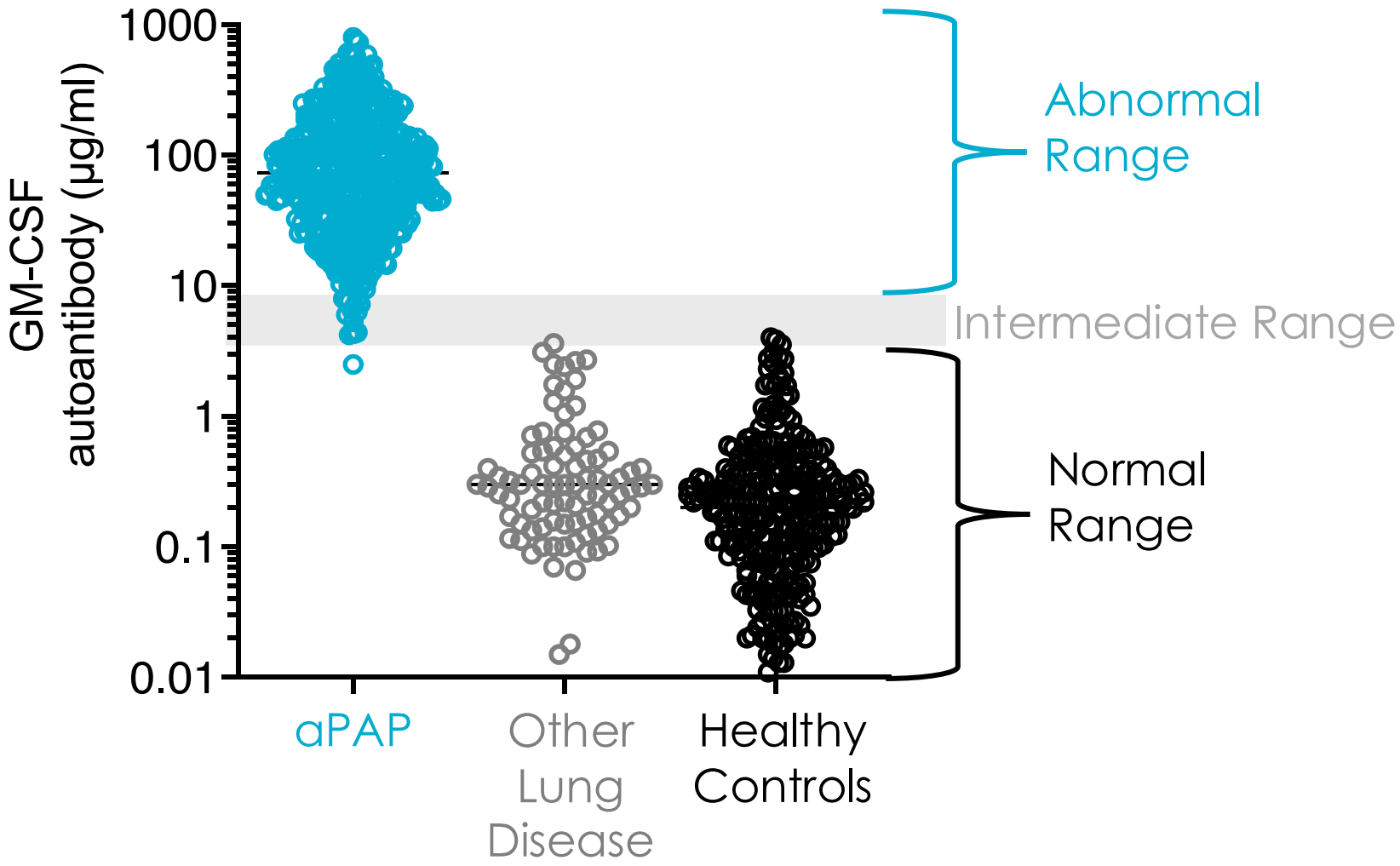
Disease	Cause	Therapeutic approaches
Autoimmune PAP (aPAP)	GM-CSF autoantibody (GMAb)	▶ WLL ▶ (GM-CSF) ▶ (Rituximab) ▶ (Plasmapheresis) ▶ (Statins)
Hereditary PAP (hPAP)	Mutations: CSF2RA or CSF2RB	▶ WLL ▶ (Bone Marrow Transplantation) ▶ (Gene Therapy) ▶ (Pulmonary Macrophage Transplantation)
Secondary PAP (sPAP)	Myelodysplasia, Inhaled particulates, others	▶ WLL (+/-) ▶ Treat underlying disease
Disorders of Surfactant Production (DSP)	Mutations: SP-B, SP-C, ABCA3, TTF1	▶ Lung Transplantation

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

Chalk/Stock/Carey

Serum GM-CSF Autoantibody Levels



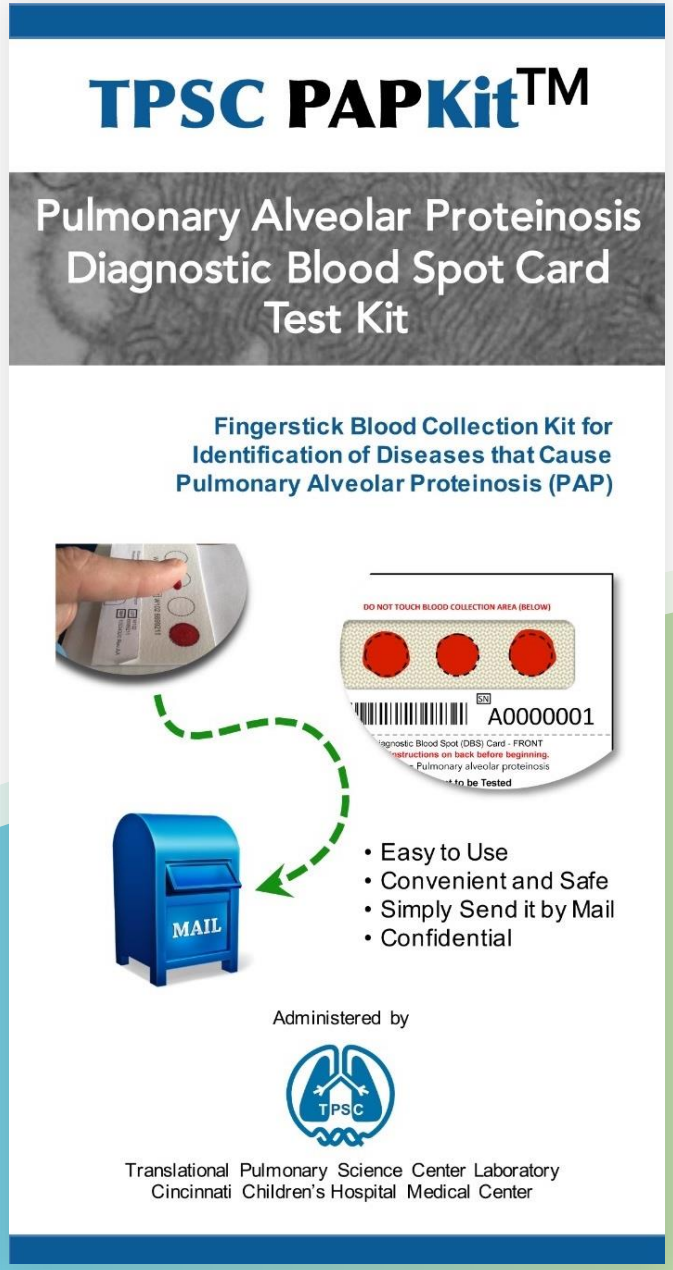
Serum GM-CSF autoantibody levels are elevated in autoimmune PAP patients.

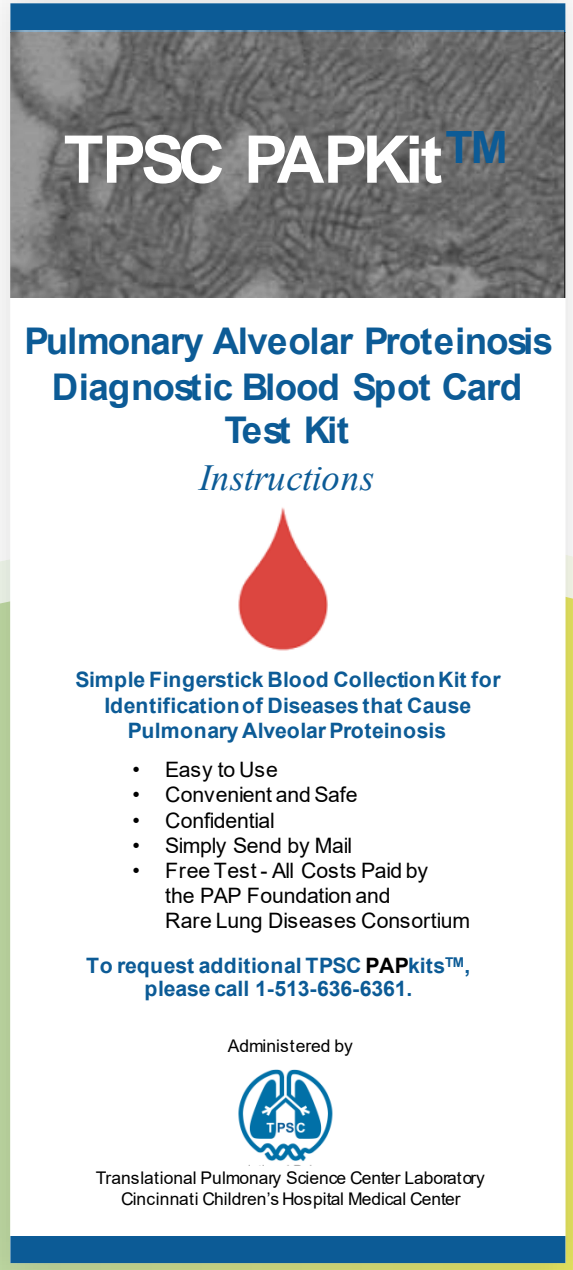
PAP Diagnosis Study

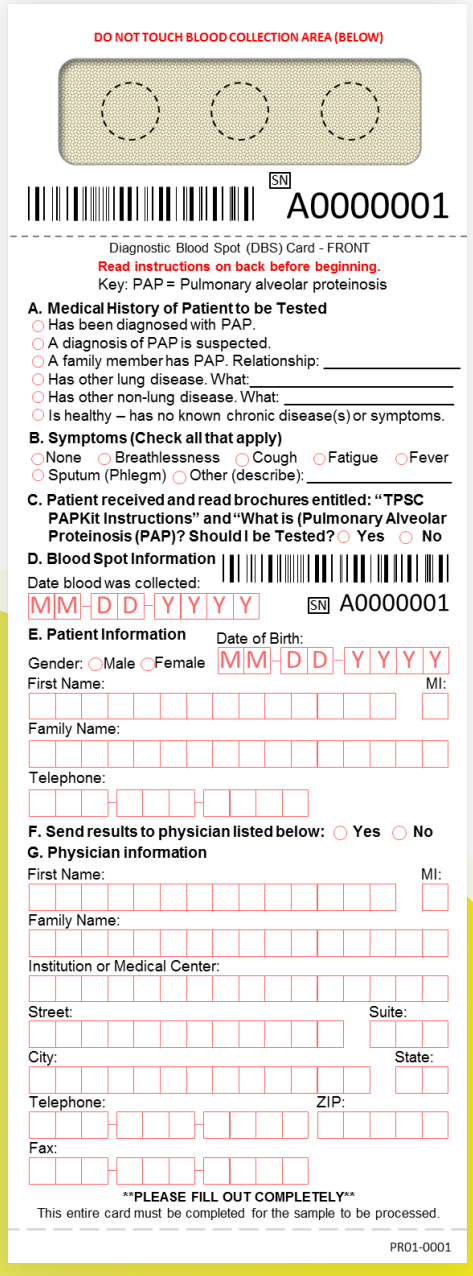
- Samples received from US, Australia, Belgium, Brazil, Canada, Chile, Croatia, Czech Republic, France, Germany, Hungary, India, Ireland, Israel, Italy, Netherlands, New Zealand, Poland, Slovenia, South Africa, Spain, Sweden, Taiwan, Turkey, United Kingdom
- To date, we have evaluated ~1300 individuals:
  - ✓ 62% – $GMAb^{pos}$, GM-CSF $signaling^{neg}$ (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

Chalk/Stock/Carey

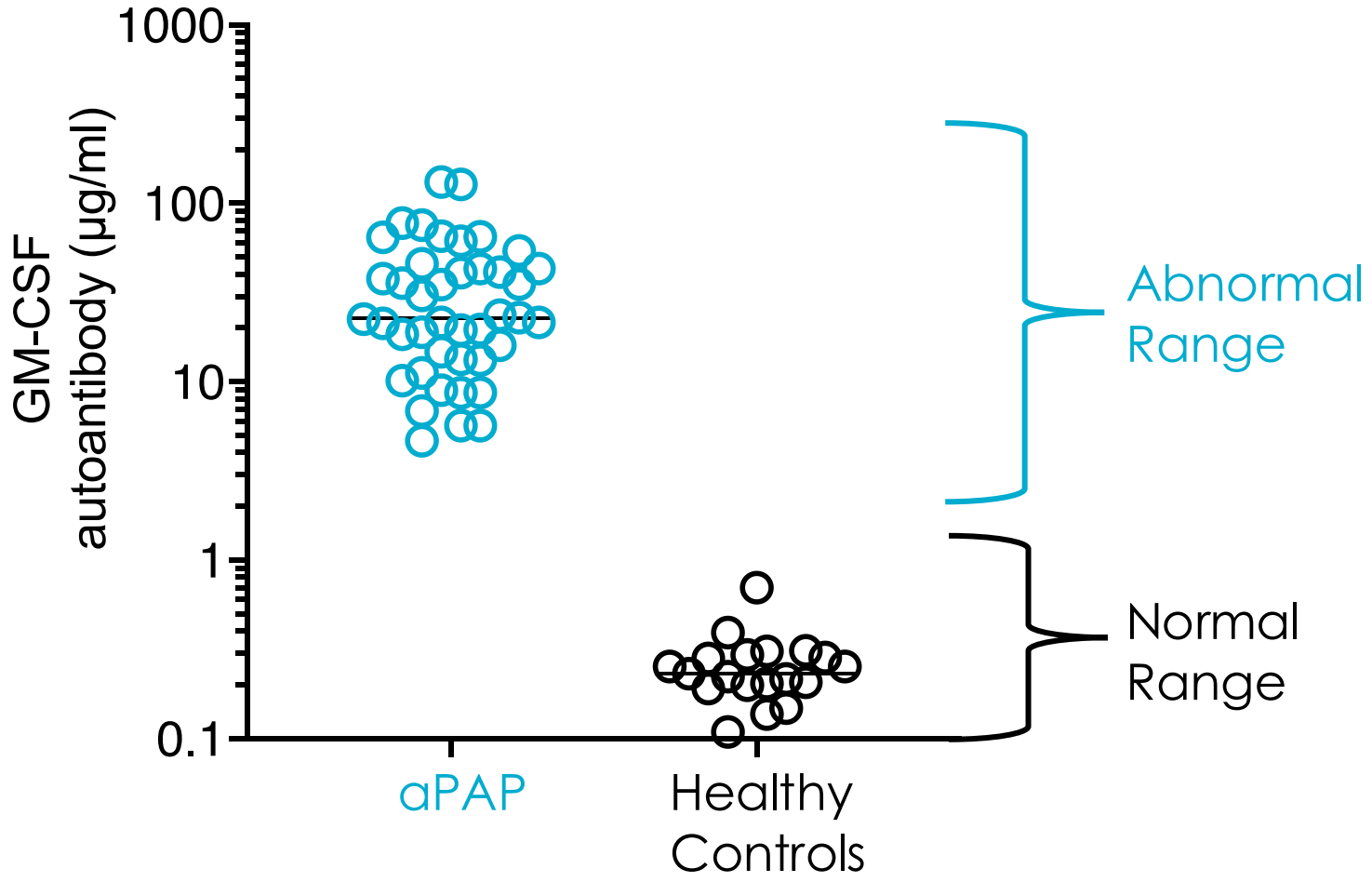
Translating PAP Testing Into the Clinic





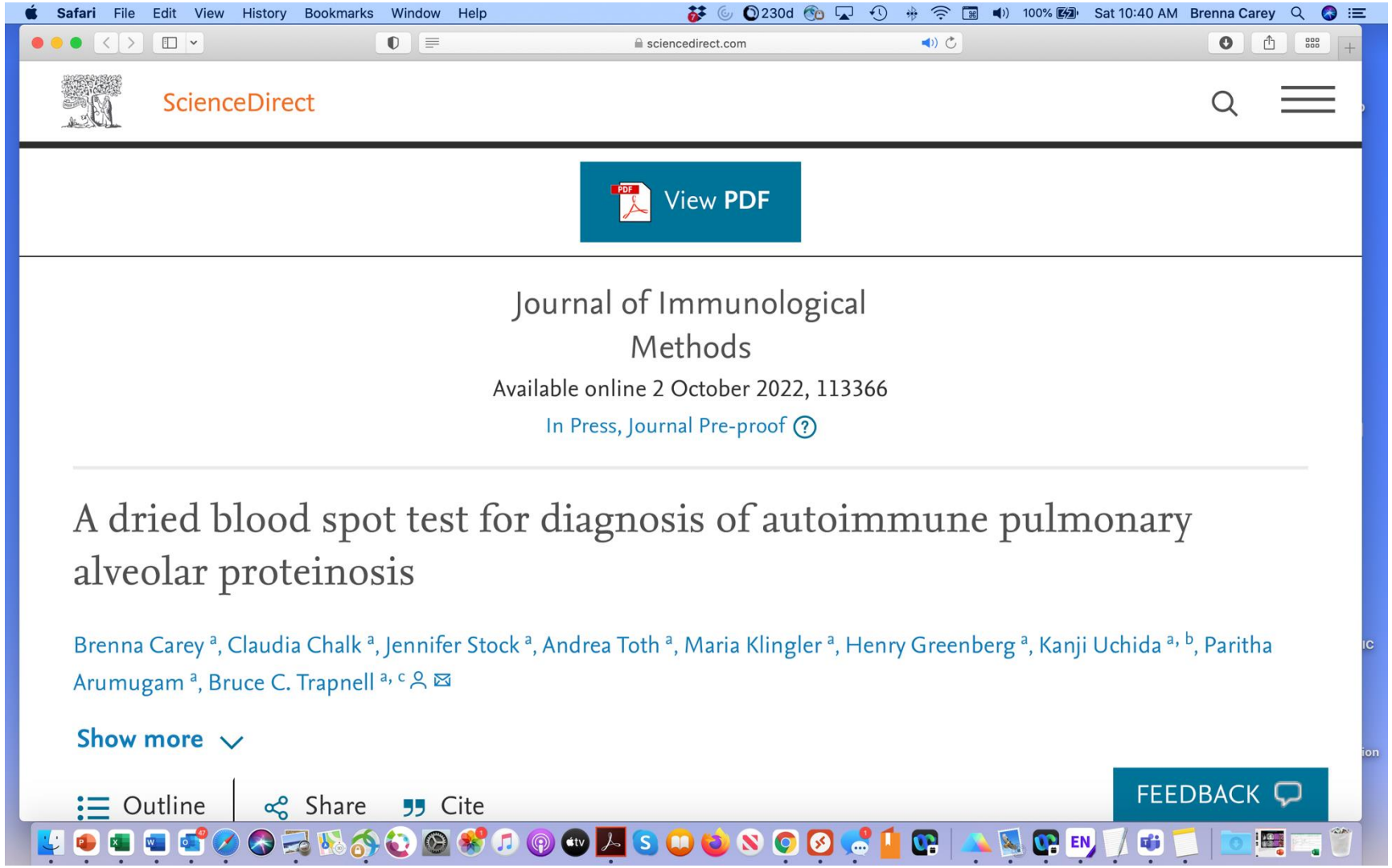


Dried Blood Spot Card GM-CSF Autoantibody



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

Development of DBSC GMAb Test



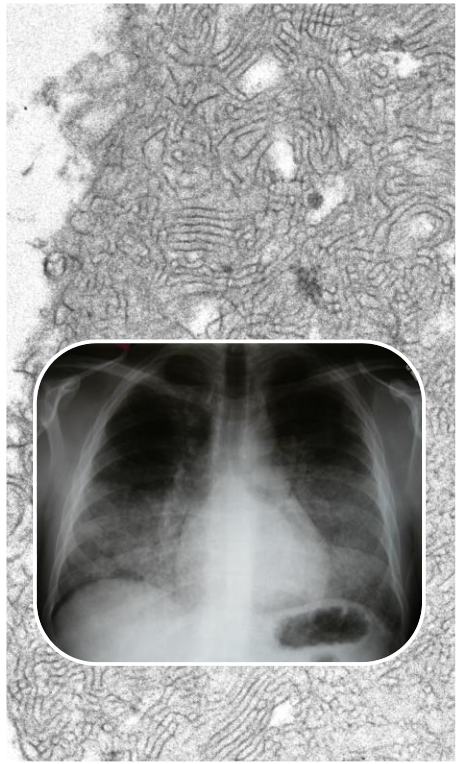
Outline

- Blood Tests to Diagnose PAP
- **National PAP Registry**
- Natural History and Clinical Outcome Measures 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.

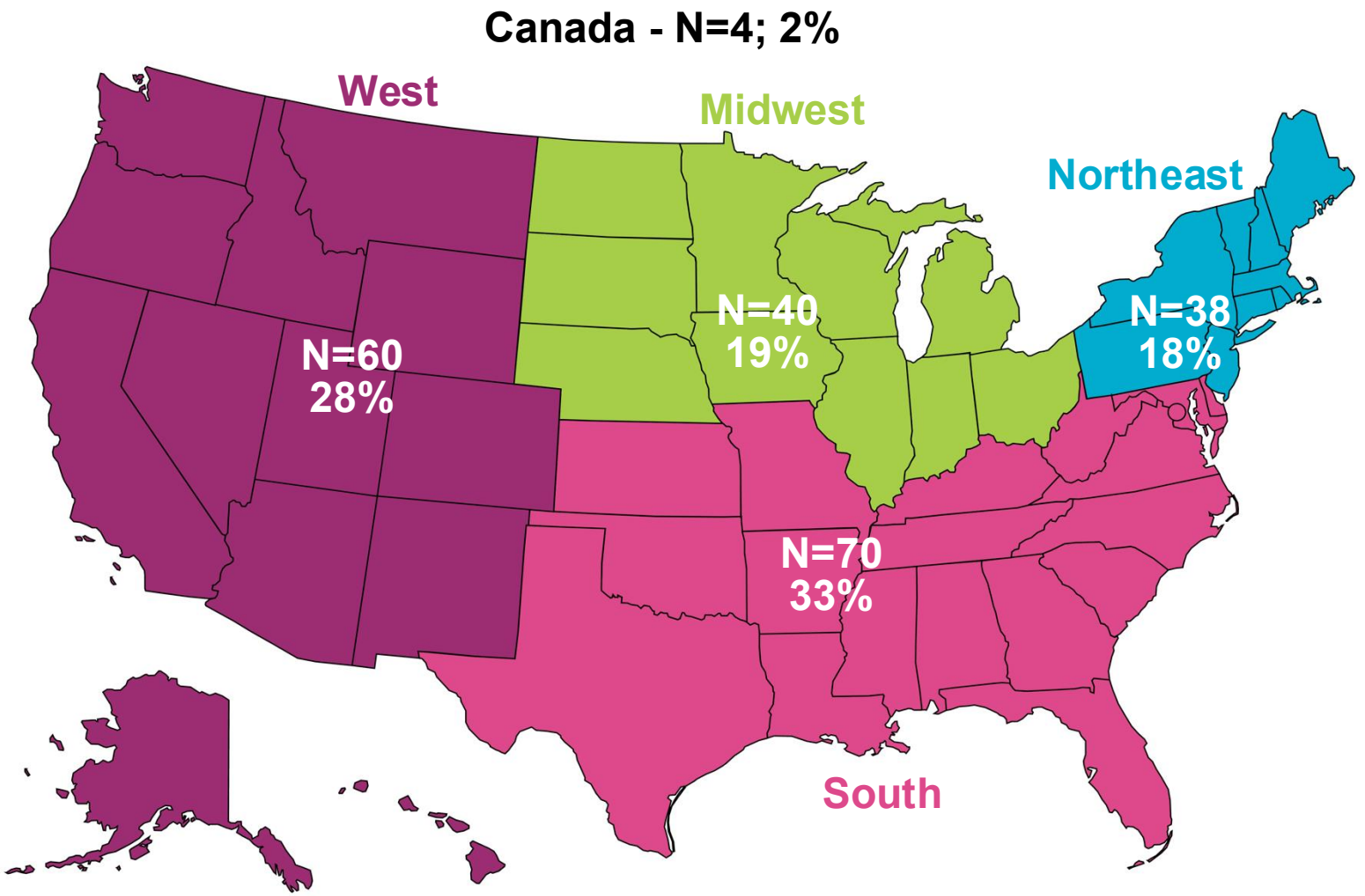
The National PAP Registry is a part of a clinical research study designed to overcome these hurdles. By gathering medical information from enough people with PAP, we can improve our understanding about this rare syndrome. This study will also facilitate the evaluation of new tests to identify PAP-causing 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 or the Rare Lung Diseases Consortium website located at 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

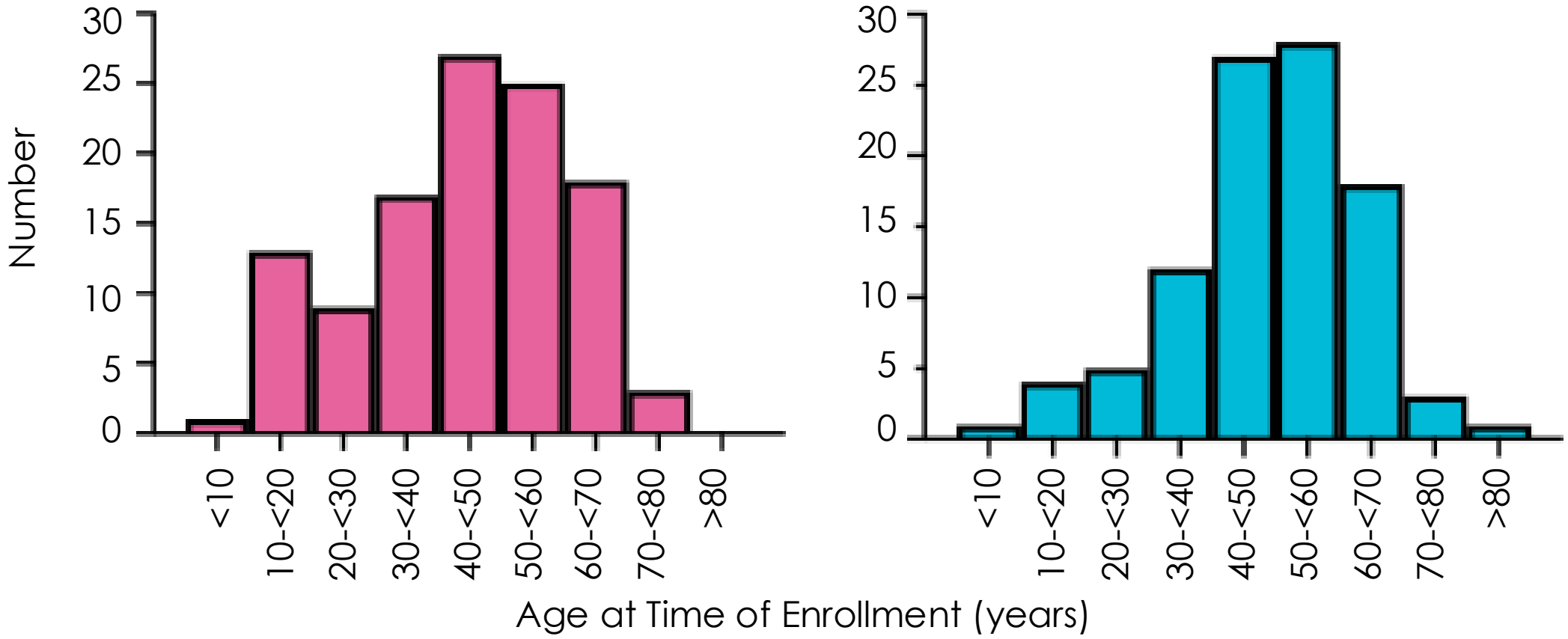


National PAP Registry participants are distributed across the United States.

National PAP Registry Participants

A. Female

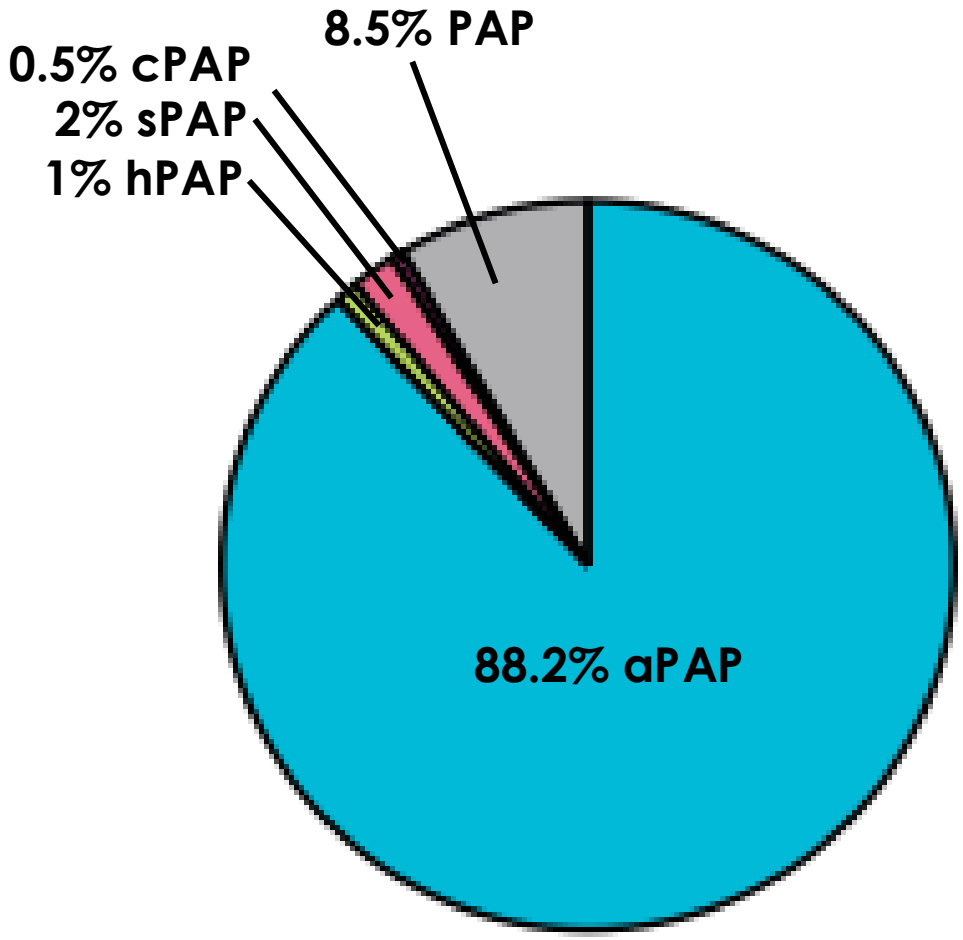
B. Male



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

N=212 PAP patients

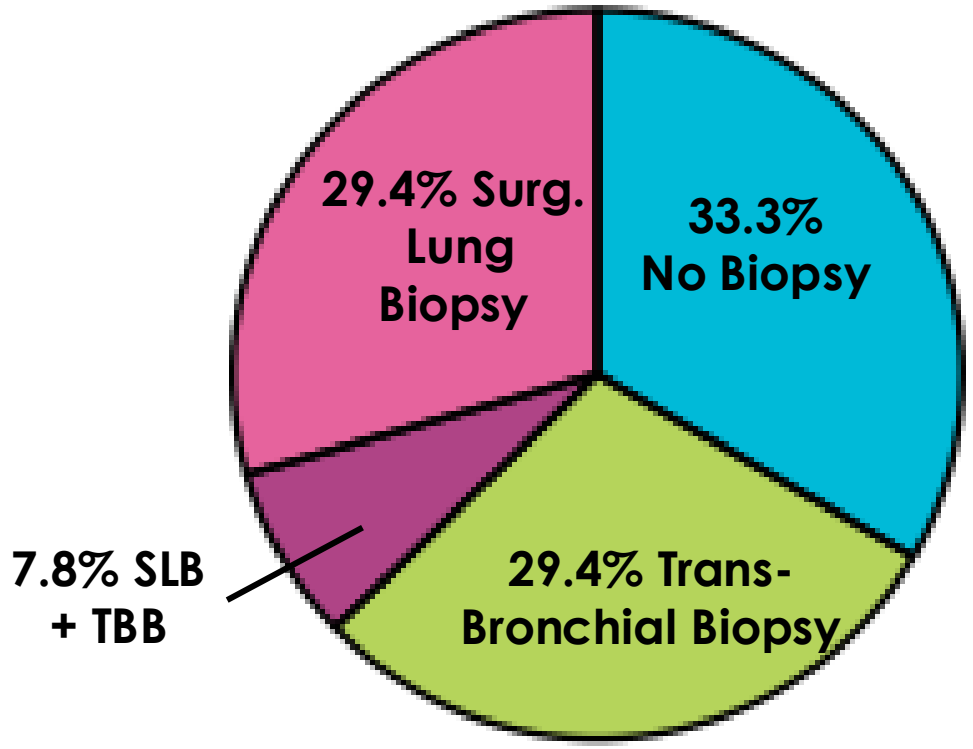
PAP Patients



The majority of patients in the National PAP Registry have autoimmune PAP.

N=212 PAP patients

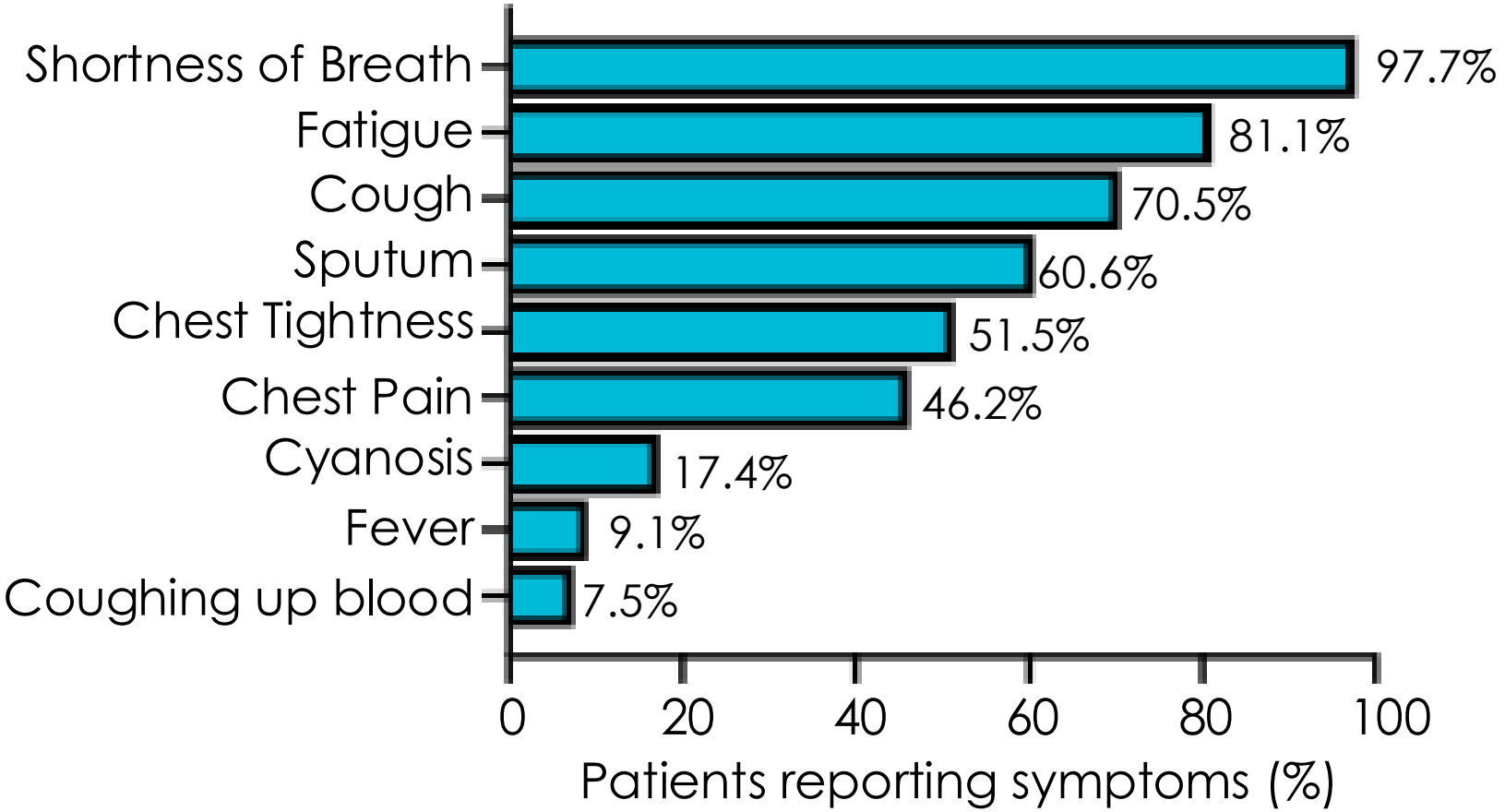
Diagnostic Lung Biopsies



Many aPAP patients undergo lung biopsies even though it is not diagnostic for any PAP-causing disease.

N=102 aPAP Patient medical records

Symptoms Reported Prior to Diagnosis

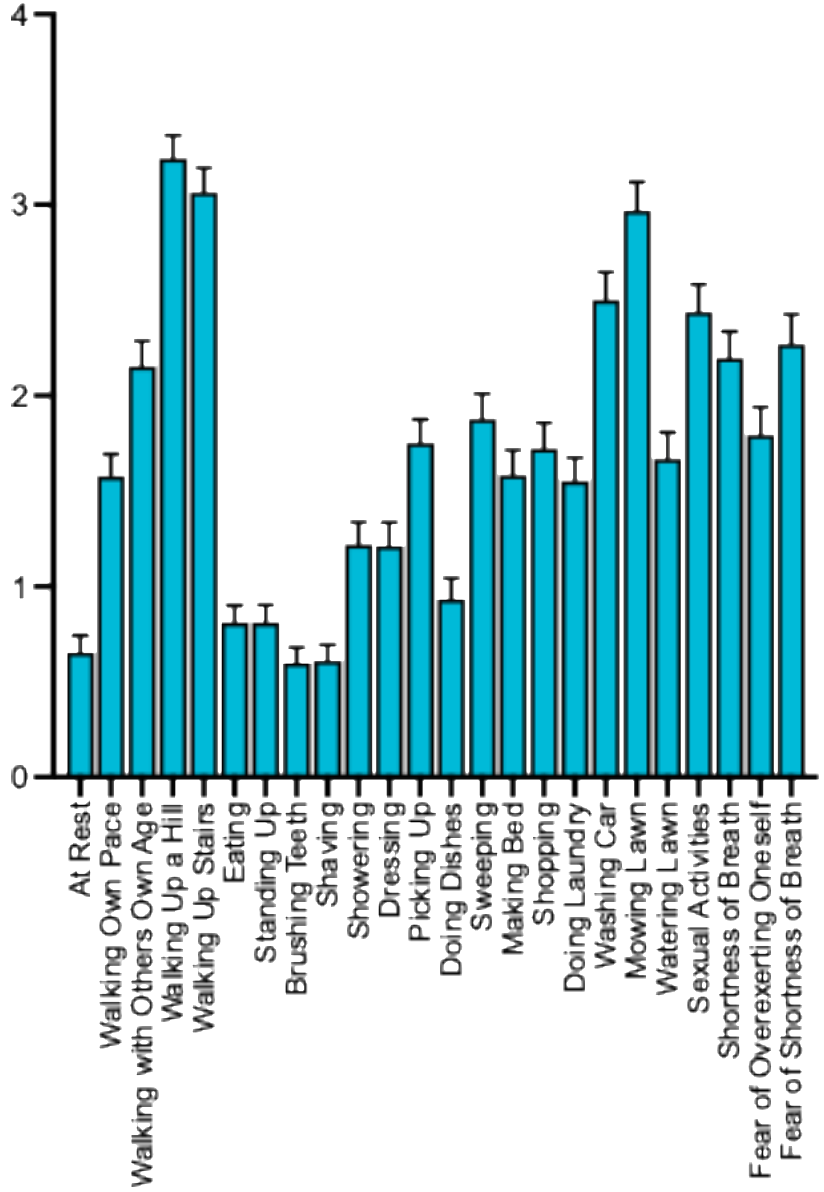


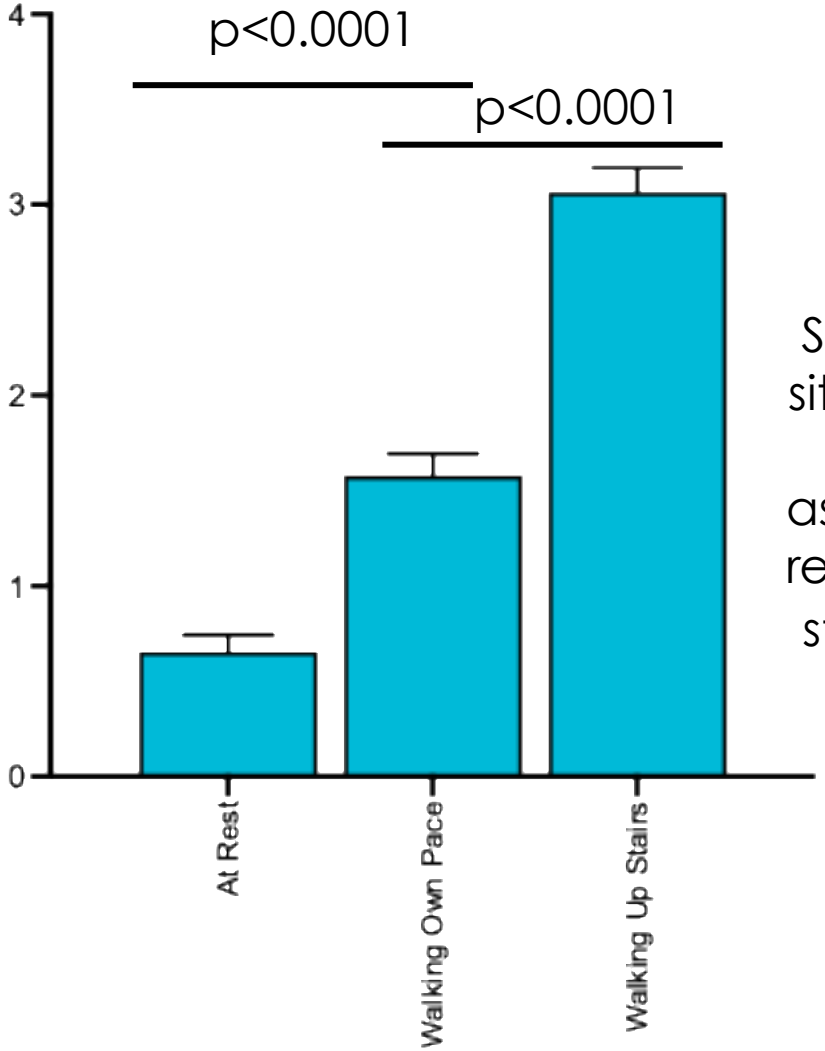
Registry participants most commonly report breathlessness, fatigue, and cough prior to diagnosis.

N=132 aPAP patient reports

Shortness of Breath Scoring

San Diego Shortness of Breath Questionnaire

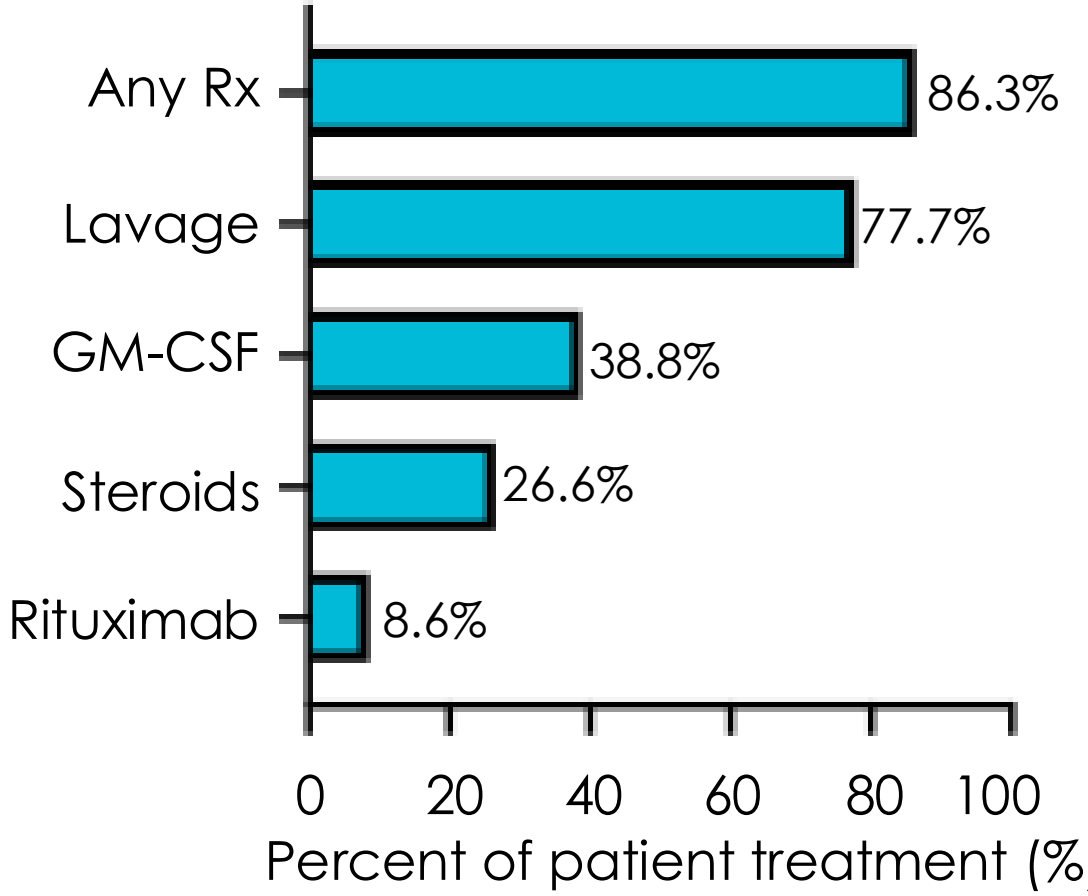




SOB associated with sitting, walking on flat ground, and ascending stairs were readily detected and statistically different.

N=137 aPAP patient reports

Utilization of Therapeutic Options for aPAP

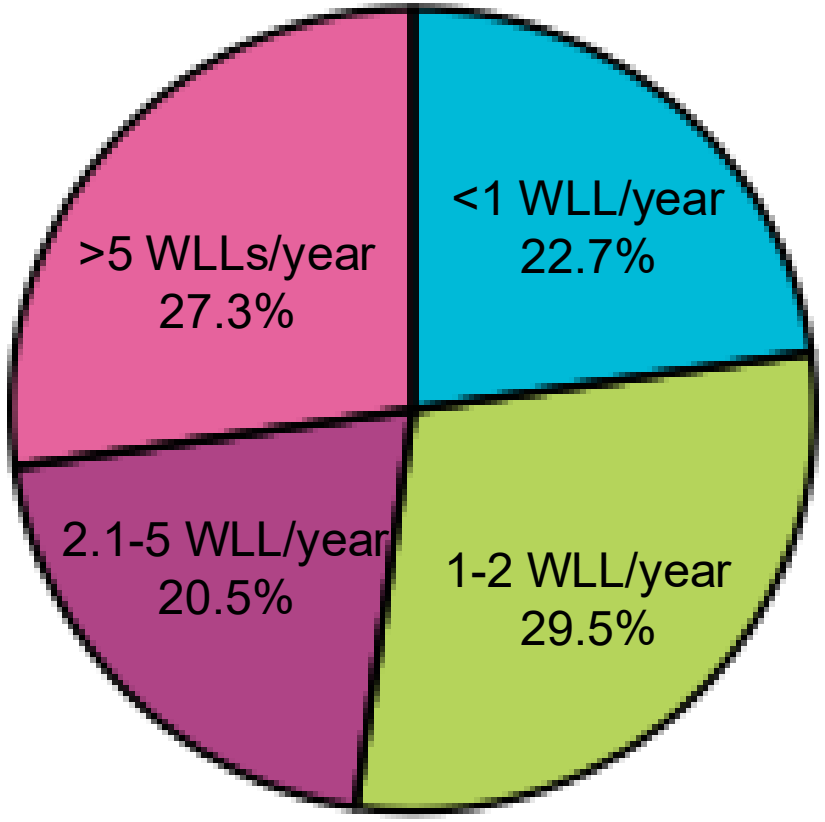


Most aPAP patient report receiving some type of treatment for PAP.

Whole lung lavage (WLL) had been performed at least once in more than 75% of patients.

N=131 aPAP patient reports

Frequency of WLL Reported by aPAP Patients



There is high variation in the frequency of WLL procedure.

N=44 evaluable patient reports

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.

Outline

- Blood Tests to Diagnose PAP
- National PAP Registry
- **Natural History and Clinical Outcome Measures for Autoimmune PAP**

Natural History and Clinical Outcome Measures for Autoimmune PAP

- We have
  - Elucidated the pathogenesis of aPAP
  - Established an accurate blood test that is the gold-standard for diagnosisa
  - Participated in trials that evaluated inhaled GM-CSF as a promising pharmacotherapy
- Despite these enormous advances in autoimmune PAP, there is
  - No longitudinal observational studies have defined the natural history of the disease,
  - No clinical or patient-reported outcome measures have been validated in aPAP patients
  - No FDA-approved therapy of aPAP is currently available in the US (to date)
- A poorly defined natural history in relation to disease progression and an absence of validated outcome measures are critical barriers to pharmacotherapeutic development

Natural History and Clinical Outcome Measures for Autoimmune PAP

- Define natural history of autoimmune PAP
- Develop and validate an aPAP-lung disease severity score
- Develop an exercise test to remotely evaluate exercise capacity

How can you participate?

- Share medical records to contribute to the database to define natural history of Autoimmune PAP
- Participate in focus groups to assess questionnaires to evaluate shortness of breath and quality of life
- At the time of regular clinic visits, complete questionnaires and share records
- Volunteer to participate in the testing of the 5-minute step test

If you are interested in participating in the research studies
Email me at Brenna.Carey@cchmc.org
Call at 513-636-8916.