PLASMINOGEN DEFICIENCY FOUNDATION

# Newly Diagnosed Toolkit

Updated September 2022

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Plasminogen Deficiency Foundation
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## Overview

Congenital plasminogen deficiency, or PLGD-1, is an ultra-rare disorder in which a patient does not produce enough of the clotting factor plasminogen. “Ultra-rare” means that there are fewer than 1 in 50,000 patients known to have this disorder, but you are not alone! The Plasminogen Deficiency Foundation is a community of patients, families, and care providers, ready to support you in the next steps on your journey. Through ongoing research, and with the help of patients like you, we are learning more every day about how to best live with this disorder. Rest assured, you CAN have a full, happy, and meaningful life with PLGD-1. This guide is intended to help you navigate day-to-day life with PLGD-1.

# Goals

1. To assist patients and families who have been recently diagnosed with PLGD-1 to understand how to approach and manage their care moving forward
2. To assist patients in becoming advocates for themselves in living with PLGD-1

# Newly Diagnosed with PLGD-1? Start Here:

## I. Confirm the diagnosis

Do you or your doctor suspect that you may have PLGD-1, but have not yet confirmed the diagnosis? Use the **Diagnostic Checklist** (Appendix A) to help. Ultimately, the diagnosis rests on checking both **a plasminogen activity and a plasminogen antigen level**. If these levels are below what is considered the normal level for the lab where they are performed, it confirms the diagnosis of PLGD.

***PLGD-1 and PLGD-2 can be differentiated by the activity and antigen levels; see the Diagnostic Checklist for more information.

## II. Test family members

**All family members - siblings, and parents if possible - should be tested** with a plasminogen activity and antigen level as well. Family members may not yet have any symptoms but may also qualify as having PLGD-1 based on their activity and antigen levels.

## III. Establish care with a medical home

The most important step after confirming a diagnosis of PLGD-1 is to establish a "medical home" where all your care can be coordinated. Ideally **your medical home is a Hemophilia Treatment Center, or HTC,** where your care will be led by a hematologist, which is a doctor who specializes in many different disorders of the blood and blood clotting. Your HTC hematologist will have a team of nurses, pharmacists, social workers, insurance specialists, and other staff who will all work together to address your needs. If an HTC is not accessible to you, find an adult or pediatric hematologist who is comfortable managing your care and can work collaboratively with an HTC. For more information about why we recommend an HTC, see the special section below.

When you meet with your hematologist, you will have a complete history, review of systems, and physical exam to determine if symptoms are present in other areas.

**You may need referrals to other specialists,** such as Ophthalmology, Dentists, ENT, Pulmonology, GI, Renal, Ob-Gyn, or Neurology; these visits will be coordinated by your hematologist and the team.

**You may need to obtain scans** such as chest X-ray, chest CT, or abdominal ultrasound or CT.

Genetic testing can be discussed with a genetic counselor but is not required for diagnosis or management.

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WHY SHOULD I GO TO A HEMOPHILIA TREATMENT CENTER FOR MY CARE?

A Hemophilia Treatment Center, or HTC, is a clinic where a team of doctors, nurses, pharmacists, and many other staff members work together to provide the best care for rare clotting disorders. Your team will be led by a hematologist, a doctor who specializes in treating problems with bleeding or clotting, including PLGD-1.

How to find an HTC:

HTCs are located around the country. You can find a list of HTCs here (see also Appendix B). The Robust Health App (see V. Research below) can also help you locate your closest HTC.

How an HTC can help you:

There will likely be many areas of your life that are affected by PLGD-1, and an HTC is equipped to help you in all of these areas. Your hematologist is trained to examine the whole body and will monitor your symptoms and coordinate care with different specialists. The HTC staff understand not only how to administer clotting factor replacement therapy, but also how to monitor levels, and adjust dosing over time to achieve the best outcomes. They are skilled at managing chronic diseases over a patient's lifetime, and adjusting your care as your needs change.

The pharmacy staff and nurses will help you learn to infuse this medication at home. They can train young children to do infusions, and help families to access all the supplies needed to go along with the medication.

The financial assistance specialists and insurance specialists will work with you to apply for insurance coverage of Ryplazim, and can even help you to enroll in a health insurance plan if you need one. They can work with you to help you afford the treatment you need.

The social workers and child life specialists on your team will be there to support your mental health, and any needs that might arise at work or at school as a result of PLGD-1.

An HTC puts together this team for you, so you can access all the care you need in one place.

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## IV. Learn about treatment

Ryplazim (plasminogen, human-tvmh) is a replacement plasminogen derived from human plasma that is given by IV infusion. It is the only FDA-approved treatment for PLGD-1. Your symptoms will determine if you need to start this treatment, and how often you will need to infuse it. **Talk with your care team to determine if you are a candidate for Ryplazim.**

If you need to start Ryplazim, you will be taught how to do these infusions at home. Your HTC care team will work with you until you are comfortable with the process.

If you are a candidate for Ryplazim, you will need to get insurance approval; we have put together an **Insurance Approval Toolkit** (available here) to walk you through this process.

## V. Get involved in research

Consider joining a clinical trial and using an app on your phone to help doctors learn more about PLGD-1 and better treat patients like you.

**Why join a clinical trial?** There is still much to learn about PLGD-1. For example, we do not yet know why some patients develop symptoms and other patients do not develop symptoms when they have the same plasminogen activity level. We do not understand how different changes in the gene for plasminogen might affect patients' symptoms. We do not yet know the exact optimal dosing regimen for patients. You can contribute to our knowledge about these and other questions by agreeing to be followed in a clinical trial over time. Learn more about available opportunities here.

**The Robust Health app,** created by ATHN, is available free to patients and is a way to collect data about how PLGD-1 is treated in a real life setting. After you download it, you can find and link to your nearest HTC, enter data about your symptoms, and log your medication infusions, doses, and more. This data is then made available to your doctor who can monitor your care over time.

Through these ongoing efforts of patients and families, we can learn more about how to manage PLGD-1 so patients can live their best lives.

## VI. Join the Foundation Community

Consider joining our community at the Plasminogen Deficiency Foundation! Here are three big reasons to join us:

1. **Community:** connect with other patients and families, hear other patients' stories, find links to Facebook groups and join the conversation, and join our newsletter listserv.
2. **Education:** stay up to date on the latest news and research about PLGD-1, ask your questions to the experts, and get access to other Toolkits to help you along the way.

3. **Advocate:** learn about opportunities and find resources to teach others (your family and friends, your community, your other doctors, etc) about PLGD-1. Help spread the word about the ultra-rare but treatable disorder.

## VII. Be alert for new symptoms or changing symptoms throughout your life

In PLGD-1, **symptoms can get better or worse** over time. You may have times when your lesions are very visible or causing symptoms and require more frequent treatment, and times when they seem to completely go away. PLGD-1 is a chronic condition that will be with you for your entire life, until a complete cure can be developed. Until then, Ryplazim is a very effective medication, and the dose and frequency of your infusions with it may vary over your life as your symptoms are changing.

Don't forget that **new symptoms can develop** and may initially be attributed to a more common disorder. For example, do you have a hoarse voice, but it is attributed to yelling a lot? Does someone think you have developed asthma when actually you are developing lesions in your respiratory tract? Does someone think your child has recurrent ear infections when actually they are developing lesions in the inner ear? Do you have painful menses each month, but this is dismissed as "normal"? All of these symptoms can be signs of new lesion development, and it is important to report them to your HTC hematologist so they can be properly evaluated in the setting of your diagnosis of PLGD-1.

In general, you should avoid going to specialists without that specialist interacting with your HTC Hematologist, so that any diagnoses or treatment recommendations can be discussed with your entire care team and so that you can avoid any invasive procedures or treatments that are unnecessary, ineffective, or may worsen your symptoms.

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The Plasminogen Deficiency Foundation gratefully acknowledges the Indiana Hemophilia and Thrombosis Center for their assistance in the development of this Toolkit.

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# DIAGNOSTIC CHECKLIST

| | Assessment | Findings Suggestive of Plasminogen Deficiency Type 1 (PLGD-1) | Comments |
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| ☐ | Patient History / Clinical Evaluation | · Recurrent ear infections; hearing loss<br>· Gum growths/lesions<br>· History of eyelid growths (pseudomembranous lesions)1; history of frequent eye infections;<br>· Asthma; hoarseness of voice; recurrent coughing; trouble breathing; recurrent pneumonia<br>· GI symptoms: recurrent stomach ulcers, IBD<br>· Poor wound healing; juvenile colloid milia<br>· Symptoms of hydrocephalus (neonates only) or diagnosis of Dandy-Walker malformation<br>· Female dysmenorrhea or infertility of unknown cause | · PLGD-1 is the most common cause of ligneous conjunctivitis (LC)[1]<br>· LC is the most common symptoms in PLGD-1, followed by ligneous gingivitis[1]<br>· Other symptom locations include the ears, nose, respiratory tract, gastrointestinal tract, urinary tract, and female reproductive tract[1]<br>· A history of, or current findings of, the symptoms listed at left should suggest evaluation for the diagnosis of PLGD-1 |
| ☐ | Family medical history | Confirmed diagnosis of PLGD-1 in a first degree relative (parents, siblings) | Evaluate all siblings regardless of symptoms<br>PLGD-1 is inherited in an autosomal recessive fashion<br>Carriers will have lower levels of plasminogen activity, but will likely be asymptomatic<br>Siblings may be asymptomatic but be affected |
| ☐ | Plasminogen activity functional assays 4<br>· Chromogenic assay<br>· Clot lysis time | Activity level less than normal for the individual lab where test was run | Activity level ≤ 45% was used as the cut off for clinical trials, however affected patients have been noted to have levels higher than this cut off value |
| ☐ | Plasminogen antigen assays | Antigen level less than normal for the individual lab where test was run | · Antigen assays together with activity assays distinguish PLGD-1 from PLGD-2:<br><br>**Activity** **Antigen**<br>**PLGD-1** Low Low<br>**PLGD-2** Low Normal<br><br>· Patients with PLGD-1 will be symptomatic, however patients with PLGD-2 do not develop lesions and will not need treatment |
| ☐ | Molecular Genetic Test*** | Mutations in PLG gene | Genetic testing **is NOT required** as part of the diagnostic evaluation for PLGD-1; there is yet no known correlation between genetic mutation and symptom development or disease severity |
| ☐ | Lesion Biopsy*** | · Eroded epithelium with fibrin-rich deposits[1]<br>· Granulation tissue[1] | Surgical interventions, including lesion biopsy, **should NOT be performed** as part of a diagnostic evaluation, as these interventions can worsen patient symptoms, cause rapid lesion recurrence after intervention, and contribute to permanent scarring or end organ damage |

*** NOT Required for Diagnosis

References: 1. Schuster V, Seregard S. Ligneous conjunctivitis. Surv Ophthalmol. 2003;48(4):369-88. 2. Martin-Fernandez L, Marco P, Corrales I, et al. The unravelling of the genetic architecture of plasminogen deficiency and its relation to thrombotic disease. Sci Rep. 2016;6:39255. doi: 10.1038/srep39255. 3. Plasminogen deficiency. Indiana Hemophilia & Thrombosis Center website. https://www.ihtc.org/plasminogen-deficiency. Accessed January 30, 2022. 4.Plasminogen (PLG). DiaPharma website. https://diapharma.com/plasminogen-plg. Accessed January 30, 2022. 5.Schuster V, Hügle B, Tefs K. Plasminogen deficiency. J Thromb Haemost. 2007; 5(12):2315-22. 6. Tefs K, Gueorguieva M, Klammt J, et al. Molecular and clinical spectrum of type plasminogen deficiency: A series of 50 patients. Blood. 2006;108(9):3021-6. 7. Shapiro AD, Menegatti M, Palla R, et al. An international registry of patients with plasminogen deficiency (HISTORY). Haematologica. 2020;105(3):554-561.

# APPENDIX B: HTC Directory

The CDC maintains a database of all the HTCs in the country. Navigate to this website:

https://dbdgateway.cdc.gov/HTCDirSearch.aspx

and search by your state or region to find the closest HTC to you.