



Membranes in action: applying learnings for a promising future



The point of care revolution: how nitrocellulose membranes have revolutionized lateral-flow test for COVID-19 and other diseases

Point-of-care (POC) testing is revolutionizing healthcare, with the development of rapid, low-cost, and convenient diagnostic devices suitable for use in both clinical and remote settings. By providing rapid results on the patient's side, POC diagnostics empower healthcare professionals to make timely clinical decisions, helping to improve patient outcomes and increase the efficiency of healthcare systems.

POC assays include immunoassays that typically use antibodies to detect the target analyte, as well as molecular assays that detect nucleic acids. Both types of POC assays are being used to detect an increasing range of clinically relevant analytes, including markers for infectious diseases, pregnancy, cancer, allergens, and more. Following the COVID-19 pandemic, the demand for POC testing has grown rapidly, and this is only set to continue. The global market size for POC diagnostics was valued at \$45.4 billion USD in 2022 and is predicted to reach \$75.5 billion by 2027 (1).

Advances in POC testing driven by the COVID-19 pandemic

The urgent need for large-scale, accessible, and rapid diagnostics to help control the COVID-19 pandemic prompted vast advancements in POC testing. Initially, PCR-based tests were the only available method to test for COVID-19 infection (2). While these tests provided a highly sensitive means of diagnosis, they required time- and labor-intensive workflows, costly instrumentation, skilled operation, and sample transportation, all of which limited the speed and scale of COVID-19 testing (2).

Just months into the pandemic, lateral flow immunoassays to detect COVID-19 antigens and antibodies were developed, quickly gaining FDA approval (3). These lateral flow tests were easy and inexpensive to manufacture at a commercial level. The available tests included rapid antigen tests that detected the SARS-CoV-2 nucleocapsid (N) protein from nasopharynx swabs, and lateral flow tests that detected antibodies, such as immunoglobulin G (IgG) and/or immunoglobulin M (IgM), from blood or plasma samples (4, 5).

Lateral flow tests to detect COVID-19 antigens provided a means of fast, remote diagnosis, whereas lateral flow tests to detect antibodies produced during COVID-19 infection were an effective tool to determine if an individual had previously contracted the virus (3).

Membranes play a central role in the design and performance of COVID-19 lateral flow immunoassays. The membranes facilitate essential assay functions including sample filtration and transport, conjugate release, protein immobilization, signal generation, and wicking. The effective choice of membranes therefore largely determines the accuracy, sensitivity, and specificity of the immunoassay test.

Various strategies to optimize the membranes used in COVID-19 lateral flow immunoassays have helped to improve test sensitivity. Moreover, these strategies have facilitated the development of several advanced types of POC tests, including lateral flow assays for nucleic acid detection, membrane-based microfluidic devices, and multiplex assays, to detect a wide range of analytes across several diagnostic fields.

To further uncover the role of membranes in POC testing, from COVID-19 and beyond, this whitepaper introduces you to the specialized membrane materials required for lateral flow assays, discussing how these have been optimized during the COVID-19 pandemic, and how they are being used in the latest POC diagnostic technologies.

An introduction to lateral flow assay membranes

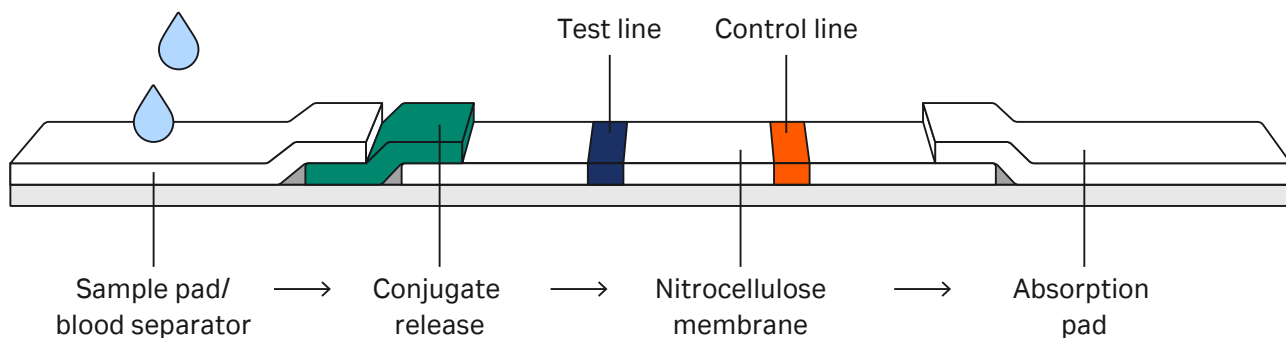


Fig 1. The various pads and membranes typically required for lateral flow assays.

Lateral flow assays require a specialized set of membranes and pads, including a sample pad or blood separator, conjugate release pad, nitrocellulose membrane, and absorption pad. Each of these components has essential assay functions (Fig 1; Table 1).

Generally, a good choice for the sample pads is low-to-medium weight cotton linter membranes, as these offer fast flow rates with high loading capacity and fine particle retention. However, glass fiber may be more suitable if a faster flow rate is required. When using blood or serum samples, a blood separator should be used to retain the red blood cells (and stop subsequent staining of the test), whilst releasing the rest of the biological material. For blood separators, a high plasma recovery material such as asymmetric polysulfone is desirable, or if motivated by a lower-priced test, a glass-fiber filter could be selected.

For the conjugate release and absorption pads, glass-fiber membranes are the most common choice, offering high absorption capacity, conjugate release rates, tensile strength, and fast rewetting. For the test membrane, nitrocellulose membranes are almost universally chosen, due to their rapid capillary flow rate and high protein binding capacity (Table 1).

Table 1. An overview of the pads/membranes used in lateral flow assays. The component, functions, and their optimal choice of membrane material is included

Component	Function	Optimal membrane material
Sample pad/blood separator	Retains unwanted particles, allowing the analyte to pass through	Cotton linter, asymmetric polysulfone, or glass fiber
Conjugate release pad	Releases the conjugate, which binds to the target analyte	Glass fiber
Nitrocellulose membrane	Contains immobilized proteins that interact with the sample to generate a signal	Nitrocellulose
Absorption pad	Acts as a sink for excess sample and buffer	Cotton linter



Visit our blog to learn more about the membrane considerations for lateral flow immunoassays

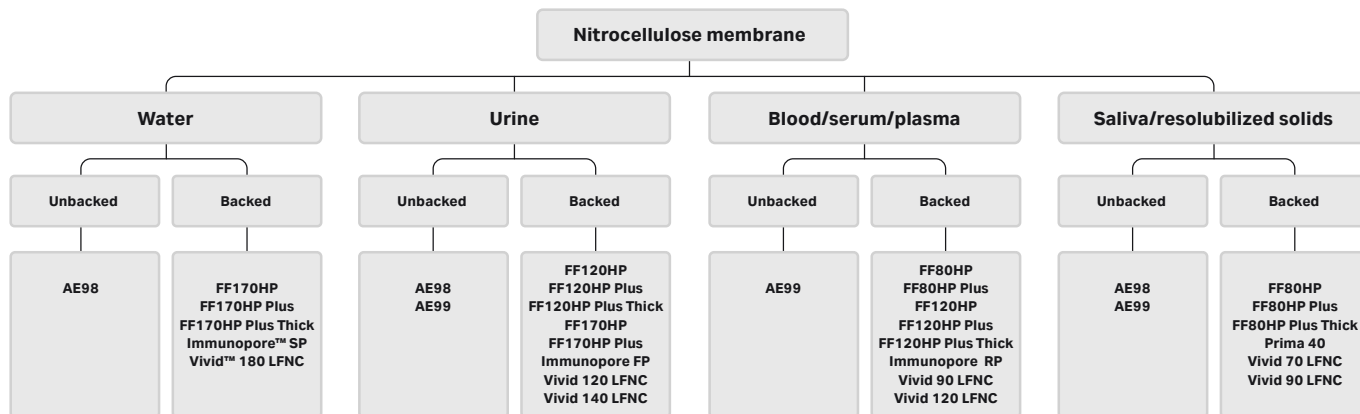



Fig 2. A schematic of commonly used sample types in lateral flow assays, with the optimal choice of nitrocellulose membranes from Cytiva.

Nitrocellulose membranes are arguably the most important membranes used in lateral flow tests, capturing the target and control molecules, and maintaining their stability and activity to produce a reliable signal. Several variants of nitrocellulose membranes are available, including those with different thicknesses, pore size, porosity, and surfactant content, influencing the membrane’s flow rate, wet strength, and binding capacity. The optimal nitrocellulose membrane used in each application will depend on several factors, including the sample viscosity and the kinetic properties of the reagents used. Below are examples of the main types of nitrocellulose membranes from Cytiva used for lateral flow immunoassays and their suitability toward different sample types and applications (Fig 2).

Nitrocellulose membranes remain the most used and are well-liked for their liquid flowing characteristics although they can provide challenges due to natural variation causing inconsistencies with flow rates, protein binding, and background. One other limitation is that they have a finite lifespan which can often be one of the shortest of all components in the test, which will limit the shelf life claim for a finished *in vitro* diagnostic (IVD) product.

 [Learn more about the different nitrocellulose membranes suitable for lateral flow immunoassays](#)

Optimizing COVID-19 lateral flow assay membranes

Initially, most COVID-19 lateral flow immunoassays contained a cellulose sample pad, glass fiber conjugate pad, nitrocellulose membrane, and cellulose absorption pad (6). Despite the careful selection of these components, the sensitivity of these tests was still largely inferior to lab-based methods.

For example, the rapid COVID-19 antigen tests were estimated to detect viral particles at levels of 100 000 to 1 000 000 viral genome copies/mL of sample, whereas lab-based methods, including real-time (RT)-PCR, were estimated to detect as little as 1 to 100 copies/mL (7). The lower sensitivity of lateral flow immunoassays increased the risk of false negative results and meant that these tests were less effective at detecting asymptomatic or early stages of the virus.

In efforts to optimize the sensitivity of COVID-19 POC testing, research groups have since optimized the membranes used in lateral flow products.

The adopted strategies include:

- Using a slower flowing sample pad.
- Adding hydrophobic structures to the nitrocellulose membrane.
- Placing additional structures between the conjugate pad and nitrocellulose membrane.
- Using a membrane with an enhanced, tighter specification range.

These strategies delay the flow of the sample and reagents through the membranes, consequently increasing the time that the capture reagent can bind to its target. However, additional strategies to increase the sensitivity of COVID-19 lateral flow immunoassays have also been proposed and are described below.

Choice of sample pads

An effective way to increase the sensitivity of COVID-19 lateral flow immunoassays is to use sample pad membranes with reduced porosity and increased binding capacity. This includes the use of a cellulose sample pad which has lower porosity, to reduce the speed at which the sample flows through the material.

Additionally, cellulose pads are rich in hydroxyl groups that interact with water molecules, forming a network of hydrogen bonds that further slow the sample flow. Changing from a glass fiber to a cellulose sample pad doubled the sensitivity of COVID-19 lateral flow immunoassays in a study detecting IgG from human serum samples (8).

Nitrocellulose membrane modifications

With nitrocellulose membranes being essential for test sensitivity, several strategies have been deployed to enhance their properties (Fig 3 and 4). This includes the use of nitrocellulose membranes with smaller pore sizes, which decreases the flow rate, and increases the binding capacity of the membrane. Together, these factors improve test sensitivity by increasing the number of immunocomplexes formed during the assay and improving the binding reaction to the membrane (9).

To increase test sensitivity further, several different hydrophobic barriers have been added to nitrocellulose membranes. Similar to other optimization tactics, this helps to modify the sample flow rate to increase the time for biorecognition. The first report of this was in 2020, with the addition of soluble wax barriers on top of the test line. To form the barriers, wax was melted across the membrane pores, creating an impermeable barrier that reduces the flow of sample at the test line (10). However, these can be problematic to incorporate into a lateral flow test system and for large-scale automated manufacturing of tests.

Since this study, several more nitrocellulose membrane modifications have been reported, using low-cost materials that are easy to manufacture at scale. This includes the addition of a hydrolyzed polyvinyl alcohol (PVA) dam on top of the nitrocellulose membrane. Placed between the conjugate pad and test lines, the PVA structure blocks the pores of the nitrocellulose membrane. This structure creates a dam that gradually dissolves as the sample passes through, slowing the diffusion of the analyte and capture reagents through the membrane. When detecting IgG from serum samples, the addition of a PVA dam increased test sensitivity by 10-fold (8).

Another technique to decrease the flow rate of nitrocellulose membranes and subsequently increase test sensitivity is the addition of a dissolvable trimethylsilyl cellulose (TMSC) barrier. Printed between the test and control lines on the nitrocellulose membrane, the addition of the TMSC barrier increased the sensitivity of IgG, IgM, and the SARS-CoV-2 N antigen by up to 5-fold (11).

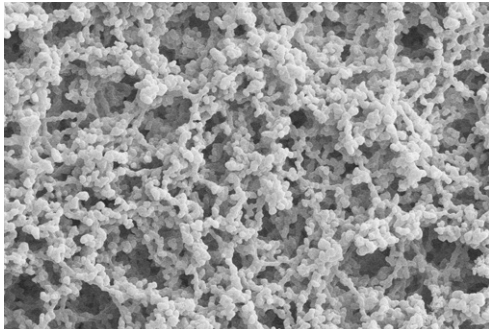


Fig 3. Scanning electron microscope (SEM) image of FF120HP nitrocellulose membrane.

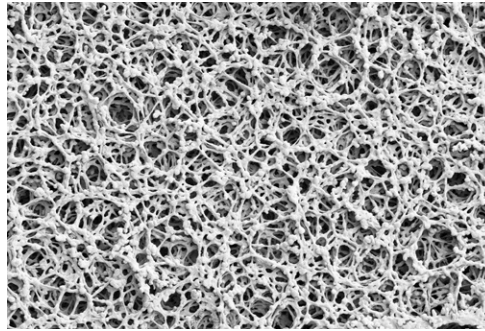


Fig 4. Scanning electron microscope (SEM) image of FF170HP Plus Thick nitrocellulose membrane.

Stacking pads between the conjugate pad and nitrocellulose membrane

Placing additional pads between the conjugate pad and the nitrocellulose membrane can delay the flow of the sample through the nitrocellulose membrane. This includes the addition of a medium-weight cotton linter membrane, which can increase the sensitivity of SARS-CoV-2 N antigen detection by 4-fold (12).

Another material suitable for use as stacking pads is cellulose nanofiber aerogels. These transform into a hydrogel-like state upon wetting, creating a small pore size of 100 nm, to reduce the sample flow rate. When used in a lateral flow immunoassay to detect mouse IgG, a limit of detection of 0.72 ng/mL was demonstrated, which could enable a 1000-fold increase in test sensitivity. However, although the addition of a cellulose nanofiber aerogel is simple and cost-effective, this material has a relatively short shelf life of 6 mo (13).

Use of signal amplification pads

Gold nanoparticles (AuNPs) are the most used reporter in lateral flow immunoassays, due to their high bioconjugation, stability, and ease of functionalization (14). An effective strategy to increase the sensitivity has been to amplify the signal intensity of the AuNPs using a glass-fiber pad overlaying the sample and conjugate pad. This membrane contains gold ions that are reduced by gold nanoparticles, increasing the size and signal intensity of AuNPs. The addition of a signal amplification pad has been shown to increase the sensitivity of SARS-CoV-2 N antigen detection from serum samples by 2-fold (15).

Using membranes with an enhanced, tighter specification

Nitrocellulose membranes come with a standard specification for capillary rise time that ranges as much as +/- 20 s of the advertised flow time, meaning that the membrane is open to a tolerance window of 40 s. Working with an enhanced membrane with a tighter specification can drastically reduce this variance by as much as 50%, improving the performance of the membrane.

Membranes in next-generation POC testing

The modification of nitrocellulose membranes has been instrumental in not only optimizing COVID-19 lateral flow assays, but also for a wide range of next-generation POC diagnostics. This includes lateral flow immunoassays, lateral flow nucleic acid tests, microfluidic POC products, and multiplex POC tests.

Lateral flow immunoassays

Since the COVID-19 pandemic, many more lateral flow immunoassays have been developed for a wide range of analytes. This includes biomarkers for cardiac failure, cancer, infectious diseases, and foodborne pathogens and toxins (16–20). Across these immunoassays, the modification of nitrocellulose membranes and the addition of signal amplification pads have successfully improved test sensitivity.

An example of this has been demonstrated in lateral flow immunoassays to detect procalcitonin, an inflammatory marker used for differentiating between bacterial and viral infections. In this test, a photosensitivity polymer was added to the sides of the nitrocellulose membrane. The addition of this polymer structure constricted the flow rate and increased the volume of sample at the test line, resulting in a 10-fold increase in test sensitivity (21).

Signal amplification pads have been used in a gold nanoparticle-based lateral flow assay to detect cortisol from saliva samples. Placing this pad between the conjugate and nitrocellulose membrane helped to increase the size of AuNPs, through the reduction of gold ions. This assay also included the use of a water-soluble polyvinyl alcohol (PVA) tape between the signal amplification pad and nitrocellulose membrane to slow the release of gold ions, resulting in a 6.9-fold increase in signal intensity (22).

Alternative membrane materials are also being used to improve the sensitivity of lateral flow immunoassays. For example, electrospun microfiber and nanofiber membranes are highly flexible, porous structures with a high surface-to-volume ratio, which enhances the membrane's binding capacity and wicking time to improve test sensitivity. When used to replace nitrocellulose membranes for the detection of the antibiotic kanamycin in food samples, a 20-fold increase in sensitivity was shown (23).



[Download 10 top tips for lateral flow assay development](#)

Molecular lateral flow assays

Molecular lateral flow assays are changing the landscape of POC testing. Detecting the nucleic acids present in a sample, these POC tests can offer increased sensitivity and specificity compared to traditional POC immunoassays. Molecular lateral flow assays are currently available to detect biomarkers for diseases such as COVID-19, Zika virus, HPV, and HIV, as well as tumor cells, STIs, and hormones (24).

Molecular lateral flow assays work similarly to lateral flow immunoassays, using capture molecules, such as antibodies, that bind with DNA or RNA. However, these tests require additional steps before the lateral flow assay can be conducted, including sample preparation, nucleic acid isolation, and amplification. Typically, the DNA is amplified using isothermal amplification techniques, such as loop-mediated isothermal amplification (LAMP) and recombinase polymerase amplification (RPA). These techniques offer easy sample loading, instrument-free readout, easy operation, and low costs (25).

Lateral flow nucleic acid tests have been the most widely used type of molecular POC assay. These tests use the same membranes and pads as lateral flow immunoassays, including a sample pad, conjugate pad, nitrocellulose membrane, and absorption pad. For these components, the selection of membranes with optimal pore size, bed volume, thickness, flow rate, and porosity are key to enhancing test performance for nucleic acid detection.

Modifications to the nitrocellulose membrane have enhanced the test sensitivity of lateral flow nucleic acid tests. For example, the addition of sugar-dissolvable barriers increased the sensitivity of assays detecting the COVID-19 ORF1ab nucleic acid by five-fold (26). Compression of nitrocellulose membranes, to delay the fluidic flow, has also been used in lateral flow nucleic acid tests. This strategy increased the sensitivity of HIV detection by 2-fold (27).

Alternative test membranes to nitrocellulose might also enhance the performance of lateral flow nucleic acid tests. This includes the use of positively charged nylon membranes, which bind to negatively charged phosphate groups of DNA probes, to increase the binding capacity. Compared to nitrocellulose membranes, nylon membranes showed much stronger signal intensity, for the detection of a DNA probe for the toxic anticancer drug doxorubicin (28).

Membrane-based microfluidic POC devices

Another type of POC test is emerging as a rapid, simple, and low-cost diagnostic. Membrane-based microfluidic devices may consist of a series of hydrophilic cellulose or nitrocellulose fibers that can transport fluid from an inlet, via porous membranes, to the test region of the device. Alternative approaches include the use of asymmetric polysulfone material which has a 100:1 difference in pore size between the top and bottom surface, which can draw fluids through microfluidic chambers. These types of tests offer high sensitivity, require low sample volumes, and can incorporate multiple, complex assay steps within the same device.

Membrane-based microfluidic devices have been developed through the miniaturization of various diagnostic technologies, including immunoassay methods such as enzyme-linked immunosorbent assays (ELISAs), mass spectrometry, and surface plasmon resonance (SPR), as well as molecular diagnostic methods, including LAMP and flow cytometry (29). Together, these devices have shown large potential across various diagnostic applications such as cancer, and chronic conditions including stroke and diabetes (30, 31).

ELISAs are the most used diagnostic assays in microfluidic POC devices. Nitrocellulose membranes are well-suited for these, due to their high protein binding capacity. However, the optimization of nitrocellulose membranes for microfluidic ELISA assays can be challenging, with the need to create complex microfluidic channels to enable several assay steps.

Microfluidic channels in nitrocellulose membranes have been created using several strategies, including their impregnation with polymers to form hydrophobic barriers. For instance, a photopolymer has been used in a microfluidic ELISA assay to detect C-reactive protein, a marker for inflammation (32). Also, polyurethane acrylate has been used in another microfluidic ELISA assay to detect the cancer markers alpha-fetoprotein and carcinoembryonic antigen (33).

Multiplexed POC testing

Multiplexed POC testing, also referred to as xPOCT, has majorly advanced healthcare diagnostics in recent years. This type of testing involves the detection of multiple analytes from a single sample. The ability to simultaneously detect multiple analytes allows for a single test to monitor multiple biomarkers, like sugar, cholesterol, iron, and vitamins. It also allows for POC tests to distinguish between different respiratory infections, such as COVID-19, respiratory syncytial virus, and influenza A and B, and distinguish between bacterial and viral infections (34–37). This has the potential to dramatically reduce the number of tests required in healthcare diagnostics, resulting in higher accuracy and efficiency in clinical decision-making.

Several types of multiplex POC tests have been developed, including lateral flow immunoassays, lateral flow nucleic acid tests, and microfluidic POC assays, to detect a wide range of analytes, including antibodies, antigens, proteins, and nucleic acids (34–37). Nitrocellulose membranes are commonly used across these tests. However, membrane optimization in multiplex POC testing can be challenging, with the need to create multiple zones for different analyte reactions, avoiding cross-reactivity and signal interference.

Various strategies have been used to modify nitrocellulose membranes, including the addition of hydrophobic barriers, and laser cutting to create distinct hydrophilic zones (33, 38). Additionally, alternative membrane materials, such as 3D electrospun polystyrene microfibers, have also been successfully used in multiplex lateral flow assays, including for the detection of Middle East respiratory syndrome (MERS) coronavirus antibodies (39).

The past, present, and future of diagnostic membranes

The COVID-19 pandemic has revolutionized POC testing, with the global-scale production of lateral flow assays achieved within months of the virus outbreak. A key learning from the development of rapid COVID-19 lateral flow assays is the importance of selecting and optimizing membranes. The modification of nitrocellulose membranes in particular proves to be an invaluable strategy for improving test sensitivity.

These learnings on membrane optimization have facilitated the development of novel POC diagnostics, including lateral flow immunoassays, molecular lateral flow assays, microfluidic POC devices, and multiplex POC tests. From controlling infectious disease outbreaks and antimicrobial resistance, to diagnosing a wide range of health conditions, advances in POC diagnostics are transforming the future of healthcare.



[View our blog: exploring the future of lateral flow assays development](#)

The power of customization

As the technologies for POC diagnostics evolve, the customization of test materials will become increasingly important. However, the selection, optimization, and validation of these can be a long and challenging process. There are many factors to consider, including membrane porosity, thickness, surfactant content, sample volume, absorption capacity, wicking rate, wet strength, and shelf life.

The use of custom diagnostic services can streamline this process. From the sample pad to the conjugate pad, reaction pad, and absorption pad, each component can be fine-tuned to ensure every POC test is precisely designed for its intended application. The use of tailored diagnostic solutions can also aid the incorporation of novel features into POC devices, such as specialized detection methods, sample types, or analytes.

Therefore, collaborating with leaders in [custom POC diagnostic development](#), such as Cytiva, can accelerate the route to the route to commercialization, helping to translate innovative diagnostic concepts into reliable and effective POC solutions.



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