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Challenges with Point-Of-Care Tests (POCT) for Celiac Disease

Huan Wu, Michael Wallach and Olga Shimoni

Abstract

Current screening test for celiac disease involves blood test in centralized pathology laboratories, typically performing enzyme-linked immune-sorbent assays (ELISA) to detect specific celiac disease antibodies. Most of the current available celiac disease antibody tests detect anti-gliadin (AGA), anti-endomysial (EMA), anti-transglutaminase (tTG), or deamidated gluten peptide (DGP) antibodies from serum or whole blood samples. It requires blood collection from untreated celiac patients, which is often invasive and inconvenient. There is a rapid growth in demand for noninvasive celiac tests for the early and fast diagnosis of celiac disease to help potential celiac patients obtain results and take corresponding actions. Over the last decade, several point-of-care tests (POCT) have been introduced to the market, but these tests have not been widely accepted by clinicians. Moreover, the 2009 NICE guideline CG 86 recommended that self-tests and/or POCT for celiac disease should not be used as a substitute for laboratory-based tests. Here, we provide a background on the evolution of POCT for celiac disease. We discuss general principle of operation for the known commercial kits as well as the use of various antigens and antibodies in different tests developed over the years. Finally, we discuss challenges for future research directions in celiac disease POCTs.

Keywords: celiac disease, point-of-care tests, lateral flow test, immunoassays

1. Introduction

Celiac disease is defined as a lifelong condition as a result of ingestion of gluten among genetically susceptible people that can be relieved by the introduction of gluten-free diet; the condition relapses with gluten intake [1]. Recent studies show that it is prevalent around the world, covering from the western world, such as Europe and America, to Oceania, Africa, and Asia. The number of celiac sufferers increases, doubling its number every two decades [2]. The symptoms vary at a wide range, from flatulence, constipation, anorexia, irregular bowel habits, and irritability to numbness in limbs, foggy mind, diarrhea, and depression [3]. Therefore, it is hard to recognize the condition and deliver the diagnosis. In fact, almost 90% of celiac patients remain undiagnosed, due to the nonspecific or absent symptoms over a long period [4]. Thereby, it is of paramount significance to achieve the early-stage diagnosis of celiac disease that can lead to improving the patients' quality of life.

The current gold standard of celiac disease diagnosis, which has been also developed in a much earlier period, is to observe the small intestine atrophy obtained through biopsy [1]. This process is highly invasive, time-consuming, and inconvenient to both patients and clinicians.

Over the last several decades, researchers have found that the concentration of some certain antibodies circulating in celiac patients' body increased, and the detection of celiac disease can be achieved with the detection of these antibodies. In fact, the surface of mucosa represents the major targeted sites when foreign antigens attack the body [5]. Plausibly, 80% of all cells producing immunoglobulin (IgG) in the human body are in small bowel mucosa, which also produces the dimers of IgA [6]. Therefore, the antibodies of celiac disease among untreated patients are located in the mucosal surface [7], as extracellular deposit, some present in jejunal juice [8], and most in the intestine [9, 10]. For untreated celiac patients, the additional generation of antibodies leads to an increase of antibodies specific to celiac disease (IgA– class), most of which can be found in the circulating blood and some other bodily fluids. Among all the celiac-specific antibodies, anti-reticulín (ARA), anti-jejunal (JEA), endomysial (EMA), and tissue transglutaminase antibodies (tTG) are among the patients' own endogenous biomolecules that form as a result of immune response to antigen in the intestine, whereas anti-gliadin antibody (AGA) and deamidated gliadin peptide antibody (DGP-Ab) are formed directly against dietary gliadin [11].

Over the years, the detection of the celiac-related antibodies has shown promising results, and whole blood- or serum-based pathology tests are regularly used for screening for celiac disease. Typically, screening for celiac disease includes tests for identification of titers for AGA and/or anti-tTG antibodies, and most of these tests are based on enzyme-linked immunoassays (ELISA). Even though the method of ELISA can reach a high sensitivity and specificity, these tests cannot be used on their own in the process of celiac disease diagnosis. Furthermore, pathology tests are typically confined to centralized laboratories, where expert personnel is required, leading to slow- and high-cost detections. Thereby, it is not suitable for the use outside hospitals, such as clinical offices or home settings, leaving a high number of undiagnosed celiac cases, especially when their symptoms are not obvious or do not affect their normal life. Thus, simple and rapid detection methods are in high demand to be developed.

Fast, accurate, and noninvasive early diagnosis methods and/or devices are needed to achieve the detection of celiac disease with high sensitivity and specificity, especially facing the rapid increasing number of celiac patients. Over the last decade, several point-of-care blood tests have been developed and applied for celiac diseases screening. The most prominent tests are Simtomax[®] Blood Drop system (Augurix SA, Switzerland) and Biocard[™] celiac test (AniBiotech[®], Finland), lateral flow immunoassays that detect anti-tTG and/or anti-deamidated gliadin peptide antibodies.

Lateral flow test, also called lateral flow immunoassay or test strip, has been widely and commercially used in the rapid detection of many diseases and conditions, such as HIV, illicit drugs, and early pregnancy [12]. In the following sections, we will discuss and compare several commercial kits available as POCT devices for celiac disease. The principle of lateral flow test is outlined in the next section.

2. Lateral flow immunoassays

Lateral flow immunoassay is a simple immunochromatography technology that has successfully applied for rapid diagnostic testing [12, 13]. It typically made of nitrocellulose or paper-based porous membrane that makes it ideal to fabricate low-cost devices with little maintenance requirements. Porous membrane enables the separation, capture, and recognition of the target analytes. In addition, porous nature of the material facilitates movement of fluids, such as a whole blood, serum, or urine, by means of capillary action with no external force required.

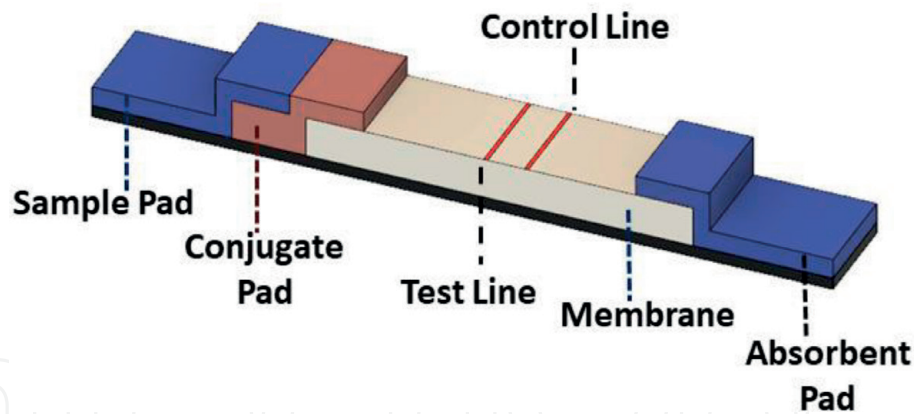


Figure 1. Schematic representation of lateral flow immunoassay in a capture format. Various important parts of the test are identified as sample, conjugate, and absorbent pads, nitrocellulose membrane with test and control lines.

There are several types of lateral flow assays available, but the most popular is the capture format. There are two types of capture: “sandwich” and competitive capture [13].

Overall, lateral flow immunoassay consists of four parts: sample pad, conjugate pad, nitrocellulose membrane (test line and control line labeled on it), and absorbent pad (also called wicking; **Figure 1**). Typically, fluid sample (blood, serum, urine, saliva) is added onto sample pad. Through the capillary action, the liquid moves to the conjugate pad, where preloaded recognition element (conjugated nanoparticles or colored reagent) is imbedded. The sample and the recognition reagent react commonly through antigen-antibody interaction. The sample together with the recognition element continues flowing within nitrocellulose membrane toward test and control lines. Depending on the type of a capture, sandwich or competitive, the test line would show a colorful line or disappear, respectively. Control line always shows colorful signal to indicate the correct functionality of the test. Absorbent pad function is to collect all the unreacted reagents as well as excess of liquids.

Lateral flow immunoassay for celiac disease is typically used to detect antibodies, such as anti-tTG, anti-DGP, and AGA antibodies from the whole blood or serum in a sandwich type of detection [14–18]. Preloaded reagent can be gold nanoparticles or dye conjugated to antigens, such as transglutaminase, deamidated gliadin peptides, and gliadin protein fragments. The detection of celiac disease-related antibodies will present as color test line that can be usually seen by the naked eye.

Lateral flow test or strip test is often used as a point-of-care test (POCT) due to its high specificity, visual color confirmation, and, especially, because of no additional instrumentation is required. In fact, most of the current commercial POCTs for celiac disease are based on lateral flow assay to detect antibodies. In the following section, we will discuss and make a comparison among commercial kits available together with the outlining principles of POCT device for celiac disease.

3. Point-of-care tests for celiac disease

3.1 Current commercial point-of-care tests

One of the most widely used commercial kits for celiac disease detection is the new generation of Biocard™ celiac test (AniBiotech®, Vantaa, Finland). In this commercial kit, lateral flow method was utilized to detect human anti-tTG IgA antibodies from a whole blood. Gold-labeled anti-human IgA antibodies are

prefixed on the conjugate pad, protein that binds to tTG antigen on the test line and anti-mouse IgG antibody on the control line [19].

The procedure is as follows: first, a drop of whole blood is taken from a finger prick, and then, the assumption is if the blood sample contains anti-tTG antibody, it will complex with liberated self-tTG found on hemolyzed red blood cells. Then the complex will flow to the conjugated pad due to the capillary force, forming a larger complex with anti-human IgA labeled on gold colloids. The larger aggregate is then recognized and captured by the tTG binding protein on the test line, and the red color will appear. The excess gold-labeled anti-IgA antibodies migrate further to control line, combining with anti-mouse IgG antibodies, which is prefixed on the control line, producing another red line (Figure 2). Both red lines represent positive result; only one red line in the control line means negative. If neither of the lines turns red, it means the subject is IgA deficient, or the test did not function properly. Usually the result can be viewed within 5–10 min; positive result can even appear after 2 min.

Since the Biocard™ celiac test has been made available on the market, a considerable number of papers have evaluated its sensitivity and specificity. Though the reported sensitivity and specificity vary in a wide range, most of them are around 90%, where some can reach as high as 93 and 94% for sensitivity and specificity, respectively [19–24]. However, this result is slightly lower than laboratory-based celiac disease test (more than 95%); therefore, this commercial kit can be only used for screening for celiac disease, but not for diagnosis. Nevertheless, this test can be also used to detect patients who have IgA antibody deficiency.

Another widely available POCT is Simtomax® Blood Drop system (Augurix SA, Switzerland). It is also a lateral flow assay device but slightly more sophisticated as it presents with two test line, A and B, in addition to a control line [25]. Test line A is used to detect both anti-DGP IgA and IgG antibodies, while test line B is for the detection of the whole IgA antibodies. Control line detects the presence of antibodies by capturing with anti-mouse antibodies. On the test line A, synthetic DGP is embedded to capture and detect anti-DGP IgA and IgG. For the test line B, mouse anti-human IgA detects total IgA. For the conjugate pad, it is secondary antibodies combined with gold colloid. If anti-DGP present in the patient's serum, anti-DGP will be captured by the secondary antibodies in the conjugate pad, and then the complex will flow further to the test line A and B, captured by A and B, and line A and B will become red. For the control line, goat anti-mouse antibodies are pre-attached;

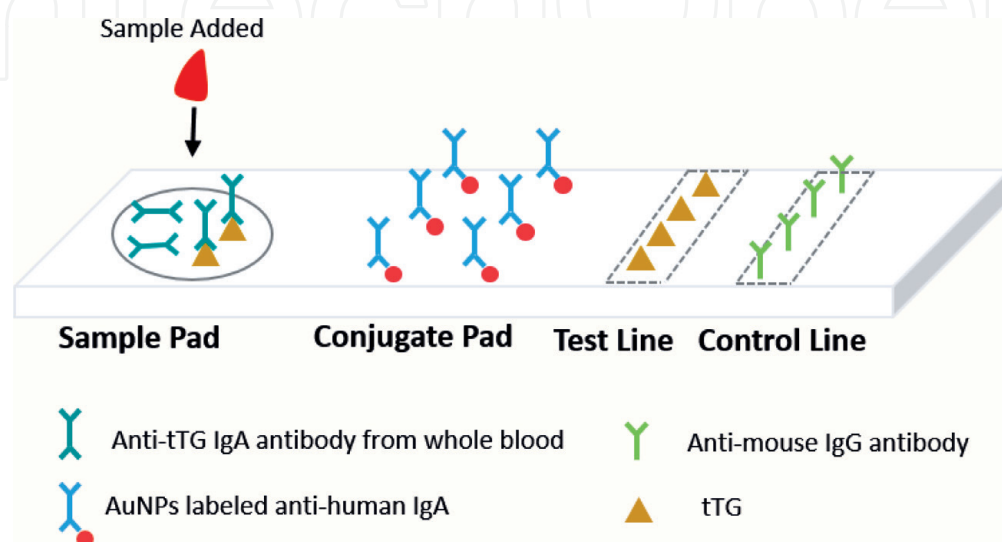


Figure 2.
Scheme of Biocard™ celiac test.

the excess conjugate of gold colloid with secondary antibodies can interact with it forming red line. All these three lines can be formed after 10 minutes, but not later than 15 min. Three red lines mean that the patient is celiac disease positive and has no IgA deficiency. If only two lines become red, in test line A and control line, then it represents that the subject is positive for celiac disease and IgA deficient, while two red lines, line B and control line, indicate that the subject is healthy, negative for celiac disease, and has IgA deficiency. Only one red line on the control means that the subject is negative for celiac disease but positive for IgA deficiency. If all of these three lines do not turn red demonstrating a non-valid result, meaning the patient needs a further test with a new device.

Various assessments have been done for this commercial kit, and it has been proved to have high sensitivity (95–100%) and specificity (93.1–95.7%) [26–28]. However, specificity of this test drastically reduced when used for patients on a gluten-free diet [26, 29]. This is not surprising as the amount of celiac-related antibodies will decrease with a strict following of gluten-free diet but still can be present due to unaware consumption of gluten.

Except the above two simple and popular POCT kits, additional lateral flow test has made commercially available, Stick CD 1 and 2 [30]. Stick CD 1 can detect IgA, IgG, and IgM antibodies against human tTG, while Stick CD 2 also detects AGA antibodies. It was demonstrated that the sensitivity of Stick CD 1 was 97% and as to CD 2, 95% for anti-tTG antibodies and 63% for AGA antibodies. The specificity of CD1 has been shown to reach 99%; as for CD 2, it was 99% for anti-tTG antibodies [30].

There are multiple ELISA-based tests that are widely available to identify celiac disease, such as Celikey[®] or QUANTA[®]. Typically, these kits use ELISA assay to detect IgA anti-tTG and/or anti-DGP antibodies. The reported sensitivity and specificity have been reported to be higher than 90% [31–33]. QUANTA[®] products have a various series of commercial kits and can detect different biomarkers with high sensitivity and specificity for celiac disease detection [34] (**Table 1**), including IgA anti-DGP, IgG anti-DGP, IgA human anti-tTG, IgA, and anti-tTG/DGP screening. It can be seen from **Table 1** that the performance of traditional ELISA-based test is still slightly higher than that of any lateral flow tests. This is one of the reasons that most of the gastroenterologists have not accepted the use of POCT as an alternative to the lab-based tests.

3.2 Research development for point-of-care tests

Although there are some commercial products for the assay of celiac disease in the market, the effort has not been stopped to devise a low-cost kit with high accuracy. In 2005, Korponay-Szabó et al. developed a POCT that could rapidly detect the autoantibodies of tTG from blood sample [35]. The test is based on a

Test	Sensitivity (95% CI) (%)	Specificity (95% CI) (%)
IgA DGP	98.4 (91.4–99.7)	92.7 (85.5–97.1)
IgG DGP	95.2 (86.7–99.0)	100.0 (96.2–100.0)
IgA human tTG	95.2 (86.7–99.0)	97.9 (92.8–99.7)
IgA and IgG DGP screen	96.8 (89.0–99.5)	99.0 (94.4–99.8)
tTG/DGP screen	100.0 (94.3–100.0)	92.8 (85.8–97.1)

Table 1.
 Performance of QUANTA lite celiac disease tests in a high-risk population.

Nunc-Immunistick (Denmark) principle with a four-wing stick. The two wings of the stick are pre-covered with gelatine to recognize and capture self-tTG/anti-tTG antibody complexes from the hemolyzed patient blood sample. The third wing is fixed with anti-human IgA antibodies, to combine with plasma IgA, which is used as a positive control. The fourth wing has no coating leading to the absence of antibody capture, and it serves as a negative control. In the test process, one drop of blood is inserted into the hemolyzing solution and incubated with the stick for 15 min. Then, the stick is washed with water and immersed for another 15 min in the solution of peroxidase-labeled anti-human IgA. To obtain a visible signal, the stick is washed again and then inserted into tetramethyl benzidine solution, which is used as a color reagent, to observe the color change. If these three wings become blue within 5 min, it means that the result is positive for celiac disease. Negative result can be confirmed when only the IgA-sensitive part turns blue. If no blue color appears, it indicates that the sample was IgA deficient, and the test is invalid. It was demonstrated that the sensitivity and specificity were 97.0 and 96.9%, respectively, after testing 164 human blood samples of untreated celiac patients [35].

In recent years, another design for POCT device to detect celiac disease has been based on electrochemical biosensor. The desirable features of POCT, such as low cost and ease of operation, match well with the utilization of electrochemical biosensor [36]. It makes biosensors suitable for the commercial applications. Moreover, commercial device to detect blood glucose has been widely used in clinics and households, boosting motivation of researchers to devise electrochemical sensors for the rapid test of celiac disease.

In 2012, Adornetto et al. developed a novel fast immunosensor to achieve anti-tTG antibody detection based on magneto-electrochemistry from serum samples [37]. In this system, tTG antigen-coated magnetic beads are used to capture and detect antibodies against tTG from positive serum samples. Alkaline phosphatase-labeled anti-human IgA antibodies are used as a control. Magnetized screen-printed electrodes coupled with a portable instrument serving to read out electrochemical signal, which is produced after the addition of α -naphthyl phosphate that is enzymatically converted into the electrochemically active α -naphthol product. The device was used to analyze 107 blood serum samples (46 positive vs. 61 negative samples), and it was able to identify with a clinical sensitivity of 100% and a specificity of 98.36%, while the cutoff was 1.0 AU/ml. This is comparable to spectrophotometric ELISA kits (98.57%, 100%, and 7.00 AU/ml, respectively).

Interestingly, in 2015, Adornetto et al. have engineered another electrochemical immunoassay system to detect the IgA anti-tTG antibodies [38]. The authors described a similar system, but the biggest change was that this device is used for the detection of celiac disease in saliva sample with high sensitivity. This is the first report that overcomes the problem associated with saliva samples, such as low levels of IgA anti-tTG antibodies and high liquid viscosity. In this device, magnetic beads were covered with the tTG antigen to react with antibodies against IgA anti-tTG, which would typically be present in saliva samples of positive celiac disease patients. The marker in this case was the conjugate of anti-human IgA and alkaline phosphate enzyme. The electrochemical transducer was created with a strip of eight magnetized screen-printed electrodes. This device showed the clinical sensitivity of 95% and specificity of 96% when analyzed in 66 saliva samples. The results show the suitability for this POCT as noninvasive screening for celiac disease.

In another study, a modular electrochemical peptide-based sensor was developed to detect anti-DGP antibody [39]. In this approach, firstly a short helical support peptide (SP) was immobilized on the surface of a gold electrode, followed by functionalization of SP with DGP and methylene blue (MB), which are used as the antigen and electrochemical tag, respectively. When the added anti-DGP IgG

monoclonal antibody was recognized and then bound with the DGP, the transfer electrons efficiency between DGP and gold surface was reduced, leading to a signal decrease in a potentiometer. This unique modular style could guarantee the background of high currents when DGP antibody is absent, even at low surface densities of DGP. This means that this system could achieve a low-limit detection of anti-DGP. Although this system presents a great potential, it was not properly assessed on a real human serum or saliva sample from celiac patients. Nevertheless, it represents an alternative direction for the future development of POCT device.

A creative electrochemiluminescence immunosensor for the test of tTG was designed based on the detection platform of a membrane-templated gold nano-electrode ensemble [40, 41]. In this platform, tTG antigen was first immobilized on the surface of polycarbonate to capture the target anti-tTG antibody present in the sample. Then it could react with the biotinylated secondary antibody, which was labeled with ruthenium-based electrochemiluminescence reagent modified with streptavidin. The application of an oxidizing potential could induce the generation of intense and sharp electrochemiluminescence signal, which was used to analyze different concentrations of anti-tTG. The result showed that its linear range was between 1.5 ng/mL and 10 µg/mL, with a detection limit of 0.5 ng/mL. This system was applied to detect human sera samples from five celiac patients and two healthy controls as a proof of concept for screening test of celiac disease with great outcomes. Nevertheless, this test still requires more human samples and more vigorous validation for the potential in POCT application.

Recently, our group has developed a novel one-step test for screening celiac disease [41]. The test is based on a precipitation principle of gliadin peptide-coated gold nanoparticles. In this test, diluted serum is added to the prepared peptide-coated gold colloids in a small tube. If AGA antibodies are present in serum, it causes agglutination of gold colloids and essentially leads to a colloid precipitation. The test was used on 30 human serum samples (26 positive celiac samples and 4 controls) in a blinded assessment. The test demonstrated an overall sensitivity and specificity of over 85%, indicating that this assay has potential to be adopted as screening tool for celiac disease. Furthermore, this test could be a part of an exclusion-based diagnostic strategy in testing high risk of celiac disease populations.

4. Outlook for the future POCT development

Over the last decade, several POCTs have been introduced to the market, but these tests have not been widely accepted by clinicians [42]. Moreover, the 2009 National Institute for Clinical Excellence (NICE) guideline CG 86 recommended that self-tests and/or POCT for celiac disease should not be used as a substitute for laboratory-based tests [43]. Therefore, even though the current POCT devices can be used to detect celiac disease with a relatively high sensitivity, their specificity somewhat lags behind lab-based tests. However, one of the biggest drawbacks of the current available POCTs is their lack of usability by a non-trained person.

Most of the lab-based tests for celiac disease are performed by trained clinical technicians, but POCTs are generally aimed to be performed by a non-trained person. Multiple steps and components, such as blood drawn from a finger prick, accurate amount of blood requirement, addition of diluents or other solutions and visual interpretation, would typically introduce user errors leading to a decrease in accuracy of the tests. The usability of POCTs has been assessed on the example of HIV self-testing kits [44]. In this particular study, authors found that almost 50% of the untrained participants performing POCT HIV test had made multiple errors during testing. It is clear that for a successful adaptation of POCTs across the globe,

ideal self-test kits must include easy-to-understand instructions, preferably one-step operation and easy-to-interpret results.

As discussed above, most of the POCT systems utilize whole blood or serum samples for celiac disease detection. Drawing blood from vein or from finger prick can be viewed by some people as invasive and painful leading to a withdrawal from voluntary testing. In addition, all the mentioned laboratory or POCTs target autoantibodies, such as antibody against tTG, DGP, or even EMA. It means that celiac disease can only be detected after antibodies are circulated in the human body. However, antibody-based tests generally fail at the latent or silent cases of celiac disease or people on voluntary gluten-free diet. Can we achieve celiac disease detection when there is a low amount or no antibodies found? Maybe it is another challenge that researchers have to face when devising the future screening methods and tools for celiac disease.

In other fields of analyte detection, including the detection of blood glucose, on-site alcohol and illicit drug tests, and confirmation of pregnancy, there are already various well-developed and commercialized products from different brands. These examples comprise of the use of nanotechnology, microfluidics, or the combination of these two methods together that provide some inspiration for future methods of POCT for celiac disease. In particular, highly accurate and sensitive fast test of HIV [45, 46], tuberculosis [47–49], and malaria [50–52] combine the utilization of lateral flow microfluidics with visual colorimetric observation detection. Indeed, these POCT diagnostic devices can probably provide the most effective and useful tool for mass diagnosis. Additionally, these tests have been proven to be cost-effective, simple, and portable, as well as with capacity for multiplexing.

5. Conclusion

In conclusion, this chapter has reviewed the current commercially and laboratory-based developed POCT devices and the challenges to be faced with for a rapid and simple test of celiac disease. It is expected that more efforts of multidisciplinary research involved in immunology, lateral flow technology, microfluidics, nanotechnology, and genetics could provide a great opportunity for the fast, accurate, and early diagnosis of celiac disease, dramatically improving the quality of human life.

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Conflict of interest

Authors declare no conflict of interest.

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