

# Celiac Disease Affects 1% of Global Population: Who Will Manage All These Patients?

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**Celiac disease is a common gastrointestinal condition with an estimated global prevalence of up to 1%. Adequate long-term surveillance of patients is imperative to ensure strict adherence to treatment with a gluten-free diet and the ensuing clinical and histologic recovery. Traditionally, this has been accomplished by means of regular on-site attendance at specialist health care facilities, accompanied for most patients by follow-up endoscopic and laboratory tests. However, the rapidly increasing prevalence of celiac disease and the limited health care resources challenge the current centralized and nonindividualized follow-up strategies. The improved noninvasive surveillance tools and online health care services are further changing the landscape of celiac disease management. There is a clear need for more personalized and on-demand follow-up based on early treatment response and patient-related factors associated with long-term prognosis. Additional scientific evidence on the optimal implementation of follow-up for pediatric and adulthood celiac disease is nevertheless called for.**

*Keywords:* Celiac Disease; Follow-Up; Biopsy; Gluten-Free Diet.

The recognition of the diverse clinical presentation and improved screening tools in recent decades have shown celiac disease (CeD) to be a major public health issue. Today CeD can be detected at any age and is regarded as one of the most common chronic gastrointestinal disorders, with an increasing global prevalence of approximately 1%.<sup>1,2</sup> The clinical presentation of CeD is exceptionally diverse. Although the disease primarily affects the gastrointestinal tract, patients often experience various atypical and extraintestinal manifestations.<sup>3</sup> Such clinical

heterogeneity results in patients with CeD possibly being seen by various specialists, including, for example, gastroenterologists, pediatricians, dermatologists, rheumatologists, neurologists, hematologists, endocrinologists, and dentists. This may pose special challenges for diagnostics and follow-up. At the same time, there is an ongoing paradigm shift toward biopsy-avoiding diagnostic protocols, which may result in gastroenterologists being less involved in the management of CeD. Conversely, several nondietary therapies for nonresponsive CeD are under investigation,<sup>3</sup> which may result in a greater need for gastroenterologists to perform follow-up biopsies.

There is currently no permanent cure for CeD. The only accepted treatment is a lifelong gluten-free diet (GFD), which requires permanent elimination from the diet of food products containing natural or added gluten. For patients with CeD, a strict GFD is not a voluntary choice, but imperative to remain healthy.<sup>4</sup> The goal of treatment is to achieve intestinal healing and subsequent clinical recovery. Specifically, a strict GFD should result in the disappearance of symptoms and restoration of normal quality of life and nutritional balance in all age groups, as well as normal development and growth in children. Dietary treatment may also prevent various long-term complications associated

**Abbreviations used in this paper:** CeD, celiac disease; GFD, gluten-free diet; RCeD, refractory celiac disease.

**Most current article**

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0016-5085

<https://doi.org/10.1053/j.gastro.2023.12.026>

with untreated CeD, such as poor bone health and osteoporotic fractures, adverse cardiovascular outcomes, and possibly even increased risk of mortality.<sup>5-7</sup> A subgroup of patients may, however, lack clinical and histologic recovery, despite a strict GFD.<sup>8,9</sup> Some individuals with nonresponsive CeD may have persistent malabsorptive symptoms and so-called refractory CeD (RCeD), frequently with poor prognosis.<sup>10</sup> Owing to its crucial role in the treatment of CeD, a GFD is also an integral part of the discussion about the long-term management and quality of life of the patients.

Unfortunately, a GFD can be expensive, challenging to maintain, and socially restrictive, and thus may have a profound negative effect on everyday life. Therefore, to ensure adequate adherence and response to a GFD and timely detection of possible complications, most current guidelines recommend regular follow-up for CeD.<sup>11-13</sup> However, scientific research on the optimal implementation of follow-up and its effects on the coping and health of patients is scarce.<sup>4,14</sup> Evidence suggests that follow-up might be poorly implemented or completely lacking in most patients.<sup>14-18</sup> In fact, according to a recent study, there may be “medical inertia” regarding CeD, as up to one-third of gastroenterologists felt that the long-term management of CeD does not require physicians.<sup>19</sup> This attitude may easily be accentuated in times when health care resources are limited.

In this review, we will present the current and emerging aspects of the long-term management and monitoring of pediatric and adult CeD. In particular, we will discuss the possibilities for more cost-effective and personalized follow-up, focusing on patients with identified barriers to successful care or at-risk for poor outcomes.

## Maintenance of a Strict Gluten-Free Diet

Being well-informed about CeD and implementation of a GFD is key to successful long-term management. The main role of the physician is to provide accurate and up-to-date information in a sensitive manner, and thus facilitate acceptance of the lifelong diagnosis and necessary lifestyle changes.<sup>4</sup> During the subsequent follow-up, the physician should motivate strict dietary adherence by emphasizing the benefits of a GFD to health outcomes.<sup>5</sup> A strong physician-patient relationship is an essential contributor to the optimal long-term management of CeD. Indifferent attitude and unsatisfactory communication from health care providers are major risk factors for patients' disapproval of the diagnosis and negative perceptions toward dietary treatment.<sup>20,21</sup>

A qualified dietitian with expertise in gastrointestinal health is an equally important team member in helping patients understand the concept of a GFD and the possible presence of gluten in various—possibly unclearly labeled—food products. The dietary counseling should not only focus on gluten avoidance in everyday life and special situations, such as when traveling and dining out, but also on maintaining a healthy and nutritionally balanced diet.<sup>5</sup>

There is some variation within the current CeD guidelines, but it is usually suggested that information on a GFD and standardized dietary evaluation be provided by the dietitian, both at diagnosis and thereafter during follow-up.<sup>11-13</sup> However, in many countries there is limited availability of dietitians, in which case, education group sessions, for example, could be a better option than a dietitian with insufficient expertise in CeD or a lack of counseling altogether.<sup>22</sup>

Coping with a GFD can be challenging, the reported adherence figures range from 42% to 91%.<sup>23,24</sup> The reasons for nonadherence are diverse and often multifactorial. Unintentional lapses are common, as food products may contain untested gluten as a result of cross-contact (eg, oats) or because of inadequate labeling. Factors associated with nonadherence include younger age at diagnosis and being a teenager, low level of education, poor knowledge of CeD, low motivation to maintain a GFD, concerns about costs of the diet, and psychological stress<sup>25-49</sup> (Table 1). Interestingly, adherence does not seem to be associated with the clinical presentation or severity of symptoms at diagnosis.<sup>24,25</sup> Factors facilitating everyday coping include understanding of a GFD and food labels, membership in a patient organization, perceived benefits of strict dietary adherence, and high resilience and level of education (Table 1). Of note, hypervigilance regarding a GFD may also lead to impaired quality of life and other negative experiences among teenagers and adults with CeD.<sup>50</sup>

Patients with persistent nonadherence to a GFD are at increased risk of developing health problems and may require additional support during long-term surveillance.<sup>3</sup> Somewhat surprisingly, the significance of regular follow-up in dietary adherence or risk of complications remains unclear in both children and adults with CeD.<sup>14,16-18,24,51-53</sup> For example, recent Nordic studies reported that lack of follow-up in childhood was associated with neither adherence nor poor health outcomes,<sup>17,18</sup> and a similar finding on adherence was also observed among Finnish adults.<sup>14,25</sup> By contrast, studies from other countries have reported lower adherence among adults who do not receive CeD-focused aftercare.<sup>52-54</sup> There is likely some selection bias in these questionnaire-based studies. In fact, one of the main reasons for the lack of follow-up has been that patients do not deem it necessary or actively seek it.<sup>14,16</sup> Various patient-related and cultural factors may actually have a greater effect on a GFD adherence than regular health care surveillance (Table 1). As regards the association between follow-up and risk of complications, the data are too scant to permit reliable conclusions.

## The Role of Follow-Up Small Intestinal Biopsy in a Gluten-Free Diet

Endoscopic duodenal biopsy is currently the only reliable method to demonstrate mucosal healing on a GFD. Although widely used, there is actually no consensus on the need for routine repeat biopsy in adults with CeD.<sup>11</sup> However, full histologic healing could be considered the goal of

**Table 1.** Identifying Patients With Celiac Disease Who Could Be at Risk of Poor Treatment Outcomes Based on the Scientific Literature

Outcome	Factors related to poor outcomes	Factors related to good outcomes	References
Strict GFD adherence	Younger age at diagnosis Currently a teenager Low education level Poor knowledge of CeD Low motivation for a GFD Psychological distress Concern over cost of a GFD Cross-contamination of products Inadequate GFD labeling	Good knowledge about a GFD and food labels in general Capability to follow a GFD during stress, social events, and while traveling and dining out Confidence about health benefits of a GFD High education level Membership in celiac society	25–29
Slow histologic response	Severe histologic damage and high celiac antibody values at diagnosis Signs of malabsorption (eg, anemia, iron deficiency) at diagnosis	Mild histologic damage at diagnosis	30–32,49
Persistent histologic damage	Male sex Aged 45 y or older at diagnosis Classical presentation at diagnosis Poor clinical response Poor adherence to GFD Use of PPI, NSAID, SSRI, or ARB	Longer duration on a GFD High education level Diagnosis in the 21 <sup>st</sup> century	33–36
Persistent symptoms	Female sex Poor adherence to a GFD Long duration and severity of symptoms before diagnosis Concomitant thyroidal disease, nonceliac food intolerance or gastrointestinal disease Diagnosis at working age Low fiber intake, gut dysbiosis Use of ARB Health concerns, life restrictions	Extraintestinal clinical presentation at diagnosis	37–43
Refractory CeD	Homozygosity for HLA-DQ2 Older age, seronegativity, and classical presentation at diagnosis Long diagnostic delay History of dietary lapses Predictors of poor 5-y survival: Older age, hypoalbuminemia High proportion of aberrant IELs	Younger age at diagnosis Family history of CeD Screen-detected CeD	9,43–46
Malignancies	Older than 60 y at diagnosis Homozygosity for HLA-DQ2 <sup>a</sup>	Younger than 40 y at diagnosis, particularly diagnosis in childhood Screen-detected diagnosis <sup>b</sup>	43,47,48

ARB, angiotensin receptor blocker; IEL, intraepithelial lymphocyte; PPI, proton pump inhibitor; NSAID, nonsteroidal anti-inflammatory drug; SSRI, selective serotonin reuptake inhibitor.

<sup>a</sup>Enteropathy-associated T-cell lymphoma.

<sup>b</sup>Non-Hodgkin lymphoma.

the treatment as, for instance, in inflammatory bowel disease, as this can be expected also to result in clinical improvement and disappearance of the complication risk.<sup>13</sup> Therefore, adequate confirmation of histologic remission on a GFD would be desirable.

However, gastrointestinal endoscopy is an expensive and invasive procedure and unpleasant for the patients, hence

the substantial interest in noninvasive surrogate markers for mucosal healing. Serologic tests, particularly tissue transglutaminase antibodies, are used commonly as an indirect indicator of histologic recovery. However, although positive serology indicates nonadherence and ongoing histologic damage, seronegativity does not necessarily signify mucosal healing.<sup>55</sup> Furthermore, a subgroup of patients may

be seronegative even at diagnosis while on a gluten-containing diet.<sup>56</sup> By contrast, seronegativity is rare in children and most of them have excellent histologic recovery on a strict GFD. Moreover, they typically require general anesthesia for the endoscopy. Consequently, demonstration of clinical and serologic response has usually been considered sufficient in case of normal growth and development.<sup>57–60</sup>

Approximately one-third of adult patients with CeD are so-called “slow responders,” who show incomplete histologic healing after 1–2 years on a strict GFD, but later achieve full mucosal recovery.<sup>30,31,49</sup> The main predictor for delayed recovery is the presence of severe CeD at diagnosis in terms of histology, serology, and signs of malabsorption (Table 1). Of note, negative seroconversion of CeD autoantibodies may sometimes take several years on a strict GFD. It is currently unclear whether these patients would need, for example, vitamin supplementation before full recovery. However, slow mucosal healing does not seem to affect either the patient’s clinical recovery and quality of life or the risk of long-term complications, such as malignancies, osteoporosis, and increased mortality.<sup>30,31</sup> Taken together, the decision to proceed to repeat biopsy should preferably be more individualized and conducted after 2–5 years on a GFD, if not otherwise clinically indicated.<sup>13,31</sup>

However, if there are no signs of histologic recovery even in the long run, the risk for serious complications, such as fractures, lymphoproliferative disorders, and other malignancies, is significant.<sup>35,45,61,62</sup> The risk of excess mortality is unclear.<sup>35,63</sup> The reported prevalence of persistent nonrecovery varies from 4% to 44%, although slow responders and the fact that not all patients undergo re-biopsy may distort the figures. Poor dietary adherence is the most common cause of insufficient mucosal healing.<sup>64</sup> In recent years, testing of fecal and urinary gluten immunogenic peptides has shown promise in identifying gluten exposure in treated patients with CeD.<sup>65</sup>

Possible reasons for persistent mucosal damage despite a strict GFD include RCeD and use of proton pump inhibitors, nonsteroidal anti-inflammatory drugs, selective serotonin reuptake inhibitors, and angiotensin receptor blockers.<sup>33,36</sup> Patient-related risk factors for nonrecovery include older age and classical presentation of CeD at diagnosis, male sex, and lack of clinical response (Table 1). A recently developed score may help to identify at-risk people.<sup>35</sup> Regardless of the cause, these patients may require intensified follow-up and targeted interventions.<sup>66</sup> Of note, the causes of persistent histologic and clinical nonrecovery are somewhat different (Table 1).

### Complicated Celiac Disease

RCeD should be considered when there are persistent symptoms and signs of malabsorption and persistent or recurrent small-bowel mucosal damage despite a strict GFD for a minimum of 12 months. In addition, other possible etiologies for the mucosal lesion have to be excluded. It is essential to make a comprehensive distinction between RCeD type I and type II, as the latter is associated with high

morbidity requiring specialist care from gastroenterologists experienced in treating this condition.<sup>10,44</sup>

As mentioned, many treated patients with CeD continue to have signs of mucosal damage for extended periods of time; however, a true RCeD is rare, the reported prevalence varied from 0.3% to 7%.<sup>8,9</sup> The 2 subtypes have predictive factors in common, including older age, classical clinical presentation of CeD with diarrhea and weight loss, seronegativity at diagnosis, delayed diagnosis, and history of previous dietary lapses (Table 1). Conversely, RCeD is virtually unknown among screen-detected and asymptomatic patients.<sup>9,45</sup> Homozygosity for HLA-DQ2 also increases the risk of type II RCeD and enteropathy-associated T-cell lymphoma.<sup>43</sup> The identified risk factors are nevertheless too vague to help identify patients eventually developing RCeD. Therefore, the possibility of RCeD should be remembered and referral to a gastroenterologist or other specialist with expertise in enteropathies considered for all nonresponsive patients.

The risks of non-Hodgkin lymphoma and gastrointestinal malignancies are increased in CeD, but to a lesser extent than previously believed.<sup>61,67,68</sup> This excess risk is mostly limited to the first year of follow-up and those diagnosed after the age of 60 years. On a long-term GFD, the risk of associated malignancies declines or even disappears, although a small excessive risk of certain gastrointestinal and hematologic cancers may remain. It should also be noted that persistent small-bowel mucosal damage is associated with an increased risk of lymphoproliferative cancers.<sup>63</sup> Strict dietary adherence appears to be the most important factor in reducing the risk of developing malignant complications.<sup>48,67,68</sup>

### Persistent Symptoms on a Gluten-Free Diet

Up to 20%–50% of adults with CeD fail to achieve adequate symptomatic relief even on a long-term GFD.<sup>37,38,69</sup> This has also been reported in some pediatric patients.<sup>70</sup> The most common reason for clinical nonresponse is, again, ongoing advertent or inadvertent gluten consumption, often identified only after comprehensive dietary assessment. Another possible cause could be unrecognized comorbidity, such as irritable bowel syndrome, nonceliac food intolerance, and thyroidal disease, or, in rare cases, a true RCeD. Patient-related factors predisposing to poor clinical response include female sex, long duration and severity of symptoms before diagnosis, diagnosis in working age, low dietary fiber content, gut dysbiosis, health concerns, and certain medications (Table 1). There is some evidence that probiotics and avoidance of fermentable oligosaccharides, disaccharides, monosaccharides, and polyols could alleviate persistent symptoms on a GFD.<sup>71,72</sup>

Up to 60% of patients with CeD report extraintestinal manifestations at diagnosis.<sup>73</sup> Alleviation of these symptoms is not always evident on a GFD, possibly due to their multifactorial pathogenesis and the often limited regenerative capacity of the affected organs (eg, neurologic symptoms and dental enamel defects). Symptom-directed pharmacologic treatments may sometimes be helpful as an

adjunct to a GFD. For example, the particularly itchy rash in dermatitis herpetiformis may take months or even years on a GFD to subside. Consequently, most patients initially receive additional dapsone treatment, which usually clears up the blisters in a few days.<sup>74</sup>

## Other Issues to Consider During Follow-Up

Anemia and micronutrient deficiencies are common in untreated CeD and thus comprehensive laboratory evaluation is appropriate at diagnosis.<sup>75–77</sup> These abnormalities usually disappear on a GFD and verification of the normalization is recommended. In contrast, routine laboratory surveillance of patients with initially normal results and a strict diet appears to be unnecessary in the absence of other clinical indication.<sup>76,77</sup>

Monitoring of the appearance of comorbidities during follow-up is important. Of note, an unhealthy and nutritionally unbalanced a GFD may also be harmful, as it may lead to undesirable weight gain<sup>78</sup> and development, for example, of metabolic syndrome, metabolic dysfunction-associated steatotic liver disease,<sup>79,80</sup> and cardiovascular complications.<sup>81</sup> Therefore, the dietary counseling should aim at a diverse and healthy diet, and a physically active lifestyle should also be encouraged.

Reduced bone mineral density and increased risk of fractures are well-documented findings in untreated or poorly treated CeD.<sup>82–85</sup> The pathogenetic mechanisms are likely multifactorial. The current evidence does not support routine screening for osteoporosis in all patients.<sup>11,12</sup> Instead, measurement of bone mineral density could be considered after 1 year on a GFD in case of additional risk factors, such as older age, menopausal status, long diagnostic delay, and clinically or histologically severe CeD, and in patients with comorbidities.<sup>84–86</sup> Clinical tools, such as FRAX score, are useful for predicting fracture risk.<sup>87</sup>

CeD is often accompanied by autoimmune comorbidities, such as type 1 diabetes and thyroidal disease. Some studies suggest that the prevalence of autoimmune disorders is related to the duration of gluten exposure and that a GFD may have a protective effect,<sup>88–90</sup> but this remains debatable. However, it remains poorly defined how often and by which methods these conditions should be screened during long-term follow-up of CeD. Of note, although patients with type 1 diabetes have traditionally been screened for CeD, an opposite approach may become an attractive alternative in the dawn of novel disease-modifying pharmacotherapies for type 1 diabetes.<sup>91</sup>

Patients with CeD have an increased risk of serious infections even beyond the first year after diagnosis.<sup>92</sup> A particular risk has been associated with pneumococcal disease and severe influenza, and systematic immunizations against these infections have been recommended.<sup>93,94</sup> However, the optimal vaccination schedule and best strategies to identify patients who would benefit most from an intensified vaccination program remain obscure.

## Special Aspects in the Follow-Up of Children and Transition to Adult Care

Early diagnosis and successful treatment of CeD are particularly important in growing children, in whom the disease may progress rapidly and cause permanent health issues.<sup>95</sup> In theory, initiation of a strict GFD in childhood prevents most of the disease-associated complications and comorbidities, which could be expected to facilitate the long-term follow-up.

In 2022, the European Society for Paediatric Gastroenterology, Hepatology and Nutrition published recommendations for follow-up of children and adolescents with CeD based on a comprehensive literature review.<sup>57</sup> These guidelines advocated a follow-up after diagnosis by health care professionals with sufficient experience in treating CeD. The follow-up appointment could be with a physician or dietitian, or a combined visit. The first visit should preferably occur within 3–6 months of the diagnosis at latest and every 6–24 months thereafter.<sup>57</sup>

Besides the above-described aspects relevant in the follow-up of all patients with CeD, age-appropriate development is a particularly important treatment goal and an issue to monitor in children. Stunted growth is a common symptom of untreated CeD among children with severe clinical and histologic presentation.<sup>96</sup> Maximum catch-up growth normally occurs approximately 6 months after the diagnosis on a strict GFD,<sup>97</sup> but may continue for up to 2–3 years.

Serology normalizes after 18–24 months on a GFD in most pediatric patients with CeD.<sup>98</sup> However, a longer period is not unusual, particularly in patients with high titers at diagnosis. As in adults, decline or normalization of the serology does not predict mucosal healing reliably,<sup>57</sup> whereas persistently elevated antibody values suggest histologic nonrecovery. Clinical recovery may also sometimes be challenging to recognize in infants and toddlers. In general, however, re-biopsy during follow-up is not recommended in children with CeD.<sup>58,59</sup> Stool and urine gluten immunogenic peptides might be useful methods for monitoring dietary adherence, also in children. However, there has also been criticism, as there may be substantial inter-individual variation and inadequate correlation with the dietary assessment and mucosal damage.<sup>99–102</sup>

The entire family is the target for teaching how to cope with and follow a strict GFD. This is important because the diet affects the daily life of all family members. Given the substantial familial risk, competencies on diet and other disease-related issues may already exist. Therefore, dietary education and long-term follow-up strategies for CeD should be tailored according to the individual needs of a given family. The European Society for Paediatric Gastroenterology, Hepatology and Nutrition also recommends systematic assessment of quality of life CeD during follow-up.<sup>57</sup> Daycare and school also play important roles in the management of pediatric CeD.

Adolescents may have low motivation for a strict GFD, for example, due to peer pressure (Table 1). Children

diagnosed in infancy may not even remember their symptoms and may not understand why a strict dietary restriction is mandatory.<sup>103,104</sup> These patients could benefit from intensified follow-up and reteaching sessions.

Transition of care requires special attention to ensure appropriate dietary adherence and follow-up in adulthood. There are limited data on this issue, but retrospective studies suggest that implementation of the transition is currently inconsistent.<sup>57,105</sup> The European Society for Paediatric Gastroenterology, Hepatology and Nutrition recommends a structured transfer of care that should involve delivering relevant information to the adult health care providers, for example, about growth, comorbidities, serology, and adherence to a GFD. Use of a specific CeD “passport” may be valuable in these circumstances. There is no evidence on the optimal age of transition.<sup>57</sup> Of note, the no-biopsy criteria are widely used in children,<sup>106</sup> and it is important that the original CeD diagnosis is also accepted by the adult health care professionals without need for additional rechallenge and biopsy.

### How Should Follow-Up Be Implemented?

Optimal surveillance strategies for CeD remain contested and there is no consensus on by whom, when, and how exactly the follow-up should be implemented.<sup>4,5</sup> Providing uniform international guidelines is challenging, for example, due to varying health care systems, number of physicians per capita, income levels, and distances to health care facilities. Traditionally follow-up has been implemented in hospital outpatient clinics by multidisciplinary teams comprising gastroenterologists and pediatricians, dietitians, nurses and social workers (Table 2). In recent years, specific CeD centers have also been established in many countries. However, hospital clinics and specialized centers cannot meet the needs of the rapidly increasing CeD population.

It could be argued that routine on-site follow-up appointments and laboratory testing are of limited benefit for patients with a successful GFD.<sup>76,77</sup> Therefore, the need for such intensified surveillance should be assessed individually

and alternative approaches, such as on-demand and dietitian-led visits<sup>107-109</sup> and educational group meetings,<sup>110</sup> might be considered (Figure 1). Dietitian-led follow-up with a physician available as needed has been the most preferred policy, for example, in the United Kingdom.<sup>107-109</sup> This could also be a cost-effective solution.<sup>111</sup>

Long-term follow-up by general practitioners and other primary care providers (Table 2) has already been applied, for instance, in countries like Finland and Norway, where the prevalence of CeD is high and the patient load per site is sufficient for maintaining appropriate expertise. The widening use of novel no-biopsy diagnostic strategies may further result in gastroenterologists being less involved in the management of patients with CeD. The possible transfer of care should be carried out cautiously considering the local circumstances. The success of decentralization is dependent on the education provided on best management practices and the availability of low-threshold consultation with an experienced dietitian and other CeD specialists.<sup>112</sup>

Telemedicine is an alternative method for the follow-up of CeD.<sup>4,113,114</sup> This approach could be useful, for example, in patients who are stable but have concerns that can be addressed without the need for a face-to-face appointment. During the COVID-19 pandemic, telemedicine was widely used in the follow-up of CeD. It was considered acceptable by the patients,<sup>115</sup> particularly among younger adults more confident with digital technologies.<sup>109</sup> In addition, internet-based self-education programs could be helpful in adhering to a GFD.<sup>116</sup> eHealth tools can also be used in assessing the dietary profile and other health parameters, such as body composition and symptoms.<sup>117</sup>

### Prioritizing Patients in Long-Term Follow-Up

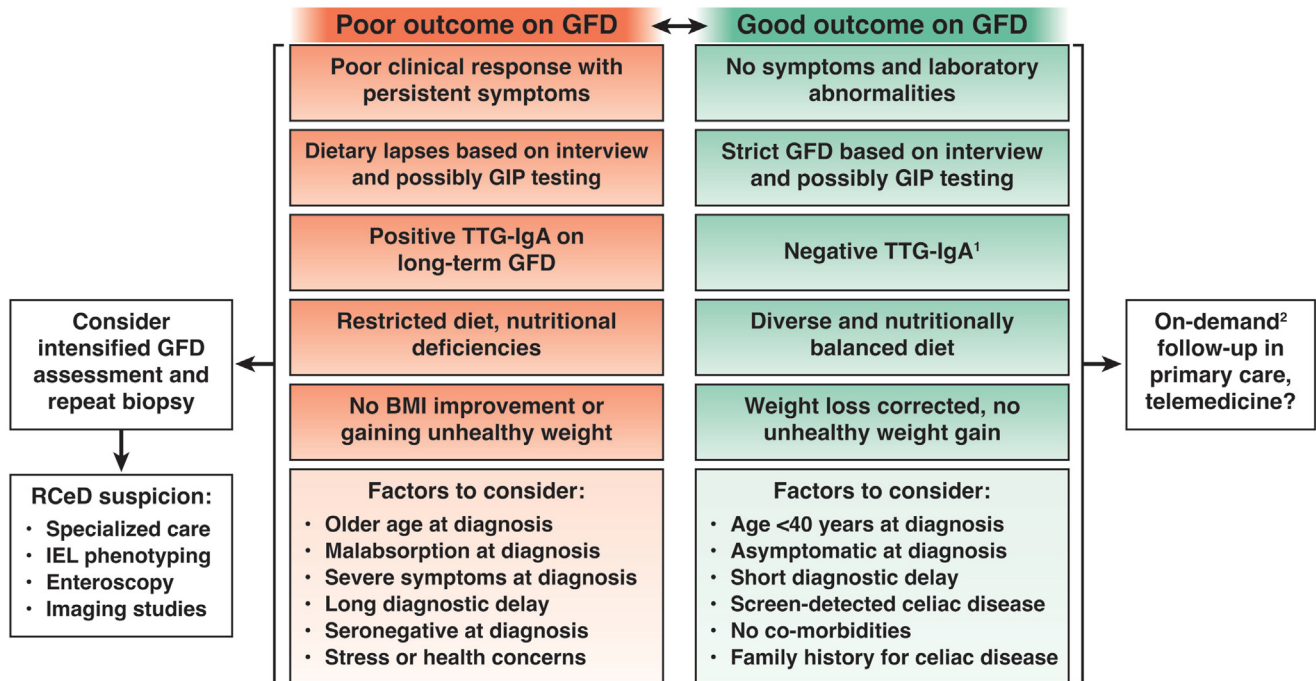
The follow-up of CeD has evidently not been implemented in clinical routine as recommended, as currently many patients are not referred to a dietitian at diagnosis and/or are not included in regular follow-up on a GFD.<sup>14-18,118,119</sup> Possible discrepancies between the use of health care services and patients’ actual needs may lead to inefficient use of resources, as well as suboptimal treatment outcomes. As the number of diagnosed patients continues to

**Table 2.** Changing Approaches to Follow-Up of Celiac Disease

Previous approaches	Current or future approaches
Hospital outpatient clinics	Mainly in primary health care
Specialized centers	Dietitians’ and general practitioners’ central role
Specialist-driven <sup>a</sup>	Online appointments and telemedicine
On-site, face-to-face visits for each patient	Educational group sessions
Routine repeat biopsies	Self-education, eHealth, and mobile applications
Routine laboratory tests and DEXA measurement	Noninvasive follow-up tools
Nonpersonalized and resource-intensive	Personalized and on-demand follow-up

DEXA, dual x-ray absorptiometry for bone mineral density.

<sup>a</sup>Including gastroenterologists, pediatric gastroenterologists, pediatricians, and dermatologists.



**Figure 1.** Suggested personalized follow-up strategies for CeD in adult patients depending on the outcome of dietary treatment. Of note, individual outcome may vary over time and the patient may consequently move between the 2 pathways. For example, a patient with initially good adherence and response to a GFD may later find coping with CeD challenging and need intensified surveillance. <sup>1</sup>Negative tissue transglutaminase IgA does not exclude all dietary lapses. <sup>2</sup>Occasional follow-up visits, for example, after major life changes could be considered even without evident difficulties with a GFD. BMI, body mass index; GIP, fecal or urine gluten immunogenic peptide; IEL, intraepithelial lymphocyte; TTG, tissue transglutaminase antibodies.

rise, it can be argued that a more personalized follow-up approach should be applied (Figure 1). This paradigm change is further accelerated by novel digital technologies and noninvasive surveillance tools. Of note, the emerging pharmacologic therapies for CeD may further change the follow-up landscape in the future.<sup>120</sup>

In general, after acceptance of the diagnosis and adaptation to a GFD, patients with CeD with a successful treatment response could have less frequent follow-up that uses, for instance, telemedicine and on-demand visits. By contrast, individuals with poor treatment outcomes would need more intensified follow-up, including on-site visits, repeat biopsies, and measurement of laboratory parameters and bone density (Figure 1). Possible complications and comorbidities should be recognized promptly, particularly RCeD, due to its often poor prognosis. Patients with any signs of complicated disease should be referred to a specialized center with a low threshold.

There are patient-related factors that could be helpful in personalizing follow-up. Predictors of poor treatment outcomes include, in particular, long diagnostic delay and older age, seronegativity, and severe clinical presentation at CeD diagnosis, and presence of stress and health concerns. By contrast, younger and screen-detected patients with no signs of complicated disease course will likely require less intense follow-up (Figure 1). Various regional and cultural differences should also be considered. At present, however, data on the optimal long-term follow-up strategies for CeD remain limited. Longitudinal studies comparing such

strategies are warranted to ensure efficient use of health care for a growing number of individuals living with CeD.

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Received November 3, 2023. Accepted December 19, 2023.

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#### Conflicts of interest

The authors disclose no conflicts.

#### Funding

This study was supported by the Competitive State Research Financing of the Expert Area of Tampere University Hospital, the Päivikki and Sakari Sohlberg Foundation, the Sigrid Jusélius Foundation, the Foundation for Pediatric Research, and the Academy of Finland.