

Digital Therapeutics: Emerging New Therapy for Nonalcoholic Fatty Liver Disease

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The increased prevalence of nonalcoholic fatty liver disease (NAFLD) worldwide is particularly worrisome, as no medication has been approved to treat the disease. Lifestyle modifications aimed at promoting weight loss and weight maintenance remain the current first-line treatment for NAFLD. However, due to the lack of standard and scientific guidance and out-of-hospital supervision, long-term outcomes of lifestyle interventions for patients with NAFLD are often unsatisfactory. In addition, the COVID-19 pandemic aggravated this dilemma. At the same time, digital therapeutics (DTx) are expected to be a new method for the convenient management and treatment of patients with NAFLD and are attracting a great deal of attention. DTx, which provide evidence-based medicine through software programs for remote intervention in preventing, treating, or managing diseases, overcome the drawbacks of traditional treatment. The efficacy of the approach has already been demonstrated for some chronic diseases, but DTx have not been fully developed for NAFLD. This study reviews the concepts, clinical value, and practical applications related to DTx, with an emphasis on recommendations based on unmet needs for NAFLD. A better understanding of the current state will help clinicians and researchers develop high-quality, standardized, and efficient DTx products, with the aim of optimizing the prognosis of patients with NAFLD.



NAFLD Patients

— Digital Therapeutics — Emerging New Therapy for NAFLD patients

Management Contents Clinical application value

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|----------------------------------|---|
| • Personalized dietary guidance | • Not limited by time and space |
| • Personalized exercise guidance | • Reducing the cost of treatment |
| • Psychological Support | • Increasing the fun of treatment |
| • Medication Reminder | • Improving patient adherence |
| • Sleep Management | • Reducing patient complications |
| • Management of complications | • Reducing workload of medical staff |
| • All necessary data tracking | • Universal access to medical resources |
| • ... | • ... |

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INTRODUCTION

Nonalcoholic fatty liver disease (NAFLD) is a metabolic disorder that is characterized by fat accumulation in more than 5% of hepatocytes (1). As the obesity and metabolic syndrome epidemic continues worldwide, it has led to an increasing public health burden of NAFLD with an estimated prevalence of 25%–30% (2). NAFLD is an early-stage disease with the potential to progress from simple steatosis to nonalcoholic steatohepatitis, cirrhosis, and eventually hepatocellular carcinoma (3). Besides, NAFLD is associated with increased cardiovascular risk, kidney involvement, a high incidence of tumors, and high mortality (4). Consequently, the clinical and public health significance of this burgeoning NAFLD population cannot be understated. Currently, there are no US Food and Drug Administration–approved pharmacologic therapies for NAFLD, and lifestyle modifications aimed at weight loss remain the most established treatments (5,6). Although lifestyle interventions have been shown to result in positive outcomes among patients with NAFLD, the success rate of the interventions and the sustainability of a healthy lifestyle for patients are issues that need to be addressed (7). Furthermore, in the wake of the COVID-19 outbreak, regular treatment activities have been substantially disrupted, and the need to explore new treatment modalities for NAFLD has arguably never been greater (8,9). With the spread of the internet and the rapid development of artificial intelligence, a combination of digital medicine and remote management (digital therapeutics [DTx]) has emerged (10). DTx overcome the shortcomings of traditional treatment by remotely providing patients with personalized lifestyle guidance and management, offering an emerging treatment for the growing number of patients with NAFLD. (11). In this review, we focus on DTx as an emerging new therapy for NAFLD under the challenges faced by traditional interventions. Based on the current application status and research progress of DTx, we further discuss the existing barriers and present some suggestions to provide a reference for DTx to fully exploit their tremendous value in the field of NAFLD in the future.

CHALLENGES OF TRADITIONAL LIFESTYLE TREATMENTS FOR NAFLD

Paired liver biopsy studies have demonstrated that weight losses of $\geq 5\%$, $\geq 7\%$, and $\geq 10\%$ in patients with NAFLD are associated with a significantly lower risk of liver steatosis, liver inflammation, and risk of liver fibrosis, respectively (12). The traditional lifestyle approach with the target of weight loss consists mainly of a structured modification of diet and exercise (13). For dietary management, the most recommended model is a combination of a low-calorie diet (a 500–1,000 kcal reduction per day) and a Mediterranean diet, which focuses on vegetables, fish, grains, and olive oil and minimizes the intake of sweets, refined grains, and processed meats (14). Exercise is another cornerstone in weight management (6). Aerobic exercise reduces free fatty acids in the liver by increasing the oxidative energy supply within the liver of patients with NAFLD, whereas anaerobic exercise reduces the influx of fatty acids by increasing muscle mass and reducing total body fat and total cholesterol content, thereby improving insulin sensitivity (15). In short, physicians should

provide personalized aerobic and anaerobic exercise counseling for patients according to personal preference and degree of illness. Ideally, 150–200 minutes of moderate-intensity exercise, 3–5 times per week, with consistency, is recommended for patients with NAFLD (6).

Despite our long-standing understanding that diet- and exercise-based traditional lifestyle interventions are effective, moderate weight loss and sustainable lifestyle changes are daunting challenges for both clinicians and patients. Patients with NAFLD demonstrate a low success rate in long-term weight loss, a high abandonment rate, and poor compliance (16–18). According to previous studies, the reasons for failure are attributed to the following points. First, weight loss treatment for patients with poor self-management skills often ends in failure due to the boredom of long-term weight loss coupled with the inability of health care professionals to provide real-time out-of-hospital supervision and psychological support (19,20). Besides, because traditional treatment methods rely on face-to-face visits, there are problematic factors such as inappropriate consultation times, high transportation costs offline, and complicated offline medical procedures, which is a clear demotivation to treatment adherence (21). Apart from those, the sudden outbreak and massive spread of COVID-19 have posed greater challenges to traditional lifestyle interventions. Because of home isolation and restricted mobility, previously compliant patients also face travel restrictions and an inability to seek regular medical care during this particular period, aggravating the progression of the disease (22).

THE CONCEPT AND CLINICAL VALUE OF DTx

DTx are defined by the DTx Alliance as “an evidence-based intervention driven *via* high-quality software programs designed to prevent, manage or treat a medical disorder” (23). DTx are indicated for chronic diseases that are closely related to lifestyle, such as obesity, type 2 diabetes, and hypertension (24). DTx can be used independently or in combination with clinical treatment. By integrating medical advice and a series of subsequent operations into the DTx medical service process, patients receive not only drug prescriptions but also a series of comprehensive medical interventions, such as remote monitoring, supervision, psychological intervention, and health education (25). Health care services become more efficient and effective for patients through the use of smart digital technologies and devices such as 5 G, smart apps, medical robots, and wearable watches (26).

DTx, as an emerging therapeutic approach, present a new direction of exploration for NAFLD, and their value to patients, medical staff, the global health care services industry, and the pharmaceutical market is substantial and far-reaching. For patients, DTx provide the personalized, refined, and fun weight loss management strategies regardless of time and space (27). DTx allow for real-time disease monitoring and management to reduce the incidence of complications, reduce unnecessary medical expenditures, and improve patients’ quality of life (28). Especially for patients living in places where medical resources are scarce, DTx can bridge this inequality of medical resources (29). With

Table 1. Examples of digital-based interventions for nonalcoholic fatty liver disease

Author	Type	Professionals	Country	Time		Intervention details			Outcomes				
				Intervention	Follow-up	Main aspects	Methods	Digital platforms	Weight	Laboratory test	Behavior	Follow-up	Complications
Daniel Pfirrmann et al [2019] (34)	Prospective single-arm study	Sports therapist	Germany	8 wk	12 mo	Exercise prevention; psychology	Questionnaire; exercise instruction; peer support; lung function exercise.	Web-based approach	↓↓	↑↑	↑↑	/	/
Monica A. Tincopa et al [2021] (36)	Prospective study	Project investigator	America	6 mo	/	Diet and exercise interventions	Telephone questionnaire; recording system; mail and phone.	Fitbit software and tracker	↓↓	↑↑	↑↑	/	↓
Arianna Mazzotti et al [2018] (37)	RCT	Physicians; dietitians; psychologists	Italy	6, 12, or 24 mo	24 mo	Diet; exercise; psychology	Game; questionnaire; lectures; email	Cloud/SaaS e-learning platform	↓	↑↑	↑↑	↓	/
Su Lin Lim et al [2020] (39)	RCT	A trained nurse; a dietitian	Singapore	3 or 6 mo	6 mo	Diet and exercise interventions	Health education videos; diet and exercise recording system; peer support chat channel.	nBuddy app	↓↓	↑↑	↑↑	/	↓
Jing Li et al [2018] (40)	RCT	Nurses	China	12 mo	12 mo	Health education	Health education	WeChat	↓↓	↑↑	↑↑	/	/
Xuejiao Wang et al [2017] (41)	RCT	Medical staff	China	12 mo	12 mo	Health education	Health education; problem consultation	Weibo, QQ, and WeChat	↓↓	↑↑	↑↑	/	/

RCT, randomized controlled trial; ↑, improved; ↑↑, significantly improved; ↓, decreased; ↓↓, significantly decreased; /, no mention.

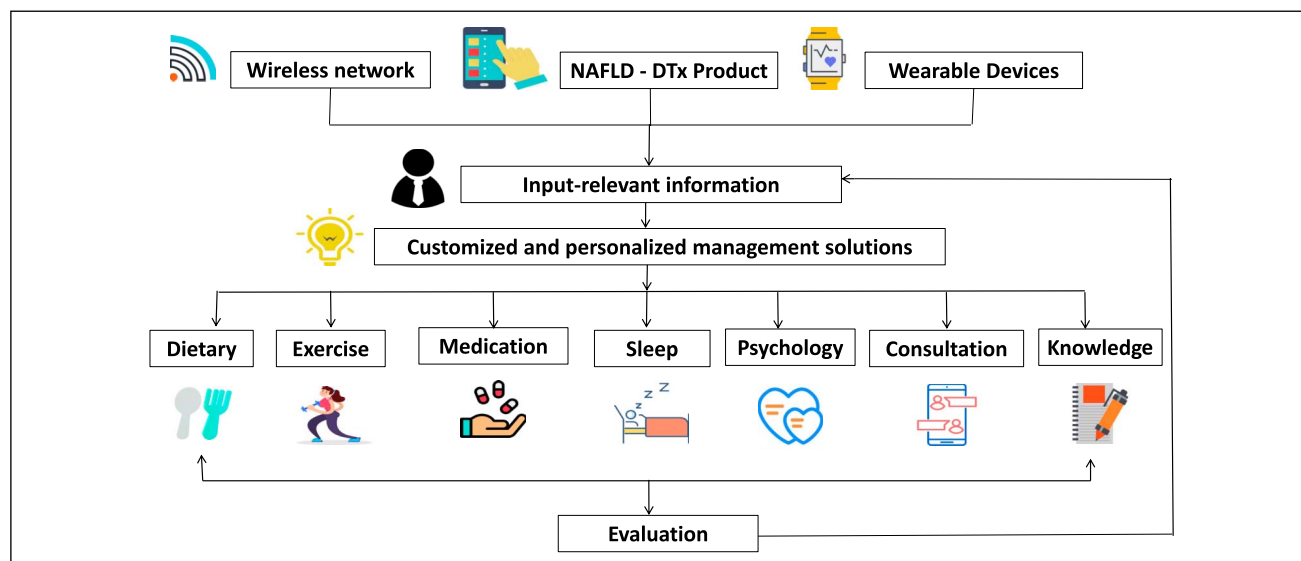


Figure 1. Flowchart of DTx for patients with NAFLD. DTx, digital therapeutics; NAFLD, nonalcoholic fatty liver disease.

regard to health care professionals, DTx essentially create a new type of workforce and relieve their heavy clinical workload (30). DTx are based on intelligent software to remotely monitor patients, provide medication reminders, guide rehabilitation, assess treatment outcomes, predict disease risks, and personalize management and treatment, which can greatly improve clinical work efficiency (31). Regarding market efficiency, the explosion of COVID-19 combined with the development of mobile technology in daily life has expanded the use of DTx in health care (32). According to the latest forecasts, the DTx market will be worth \$56 billion by 2025 (33).

THE APPLICATION OF DTx FOR NAFLD

At present, there are few studies directly reporting DTx for NAFLD, and the application of DTx in the treatment of NAFLD is still in the exploratory stage. Some scholars have conducted remote lifestyle interventions, including diet, exercise, and health education, based on web platforms, which can be regarded as a preliminary practical exploration of DTx for patients with NAFLD. We summarize these studies in Table 1.

DTx improve outcomes of exercise interventions

A German prospective exercise intervention study showed the effect of online exercise management on patients with NAFLD. All participants underwent an 8-week online training and completed a follow-up survey after 12 weeks (34). Patients joined the personalized training support platform of the network after receiving training by exercise therapists. Based on individual patient feedback, the platform systematically adjusted the weekly exercise program to ensure patient compliance with strength and endurance training and to optimize progressive exercise loading. In addition, the researchers created a communication module; on the one hand, the module facilitated communication with physicians so that patients could receive professional guidance, and on the other hand, it provided chat rooms for patients to communicate with one another and have increased access to peer support. Moreover, the study was based on the traffic-light principle to rationalize patients' daily exercise with the goal of

avoiding exercise overload and ensuring patient safety. The results showed an increase in peak oxygen uptake of 2.4 mL/kg/min from baseline to the end of the study, along with a 1.0-kg reduction in body weight. Remote exercise therapy not only helped patients with their physical condition but also improved their motivation for treatment. Another study yielded similar results, although the development of physical activity sometimes showed only moderate improvements, flexible communication and tailored support were easily integrated into patients' daily routines (35).

DTx enhance the effectiveness of integrated diet and exercise management

A US study of a 6-month structured mobile technology intervention trial of diet and exercise among patients with NAFLD was conducted (36). In terms of diet, the investigators customized a weekly diet plan for patients with reference to the principles of the Mediterranean diet or carbohydrate diet control. Telephone follow-up was performed at 3 months, and guidance was given according to dietary status and disease symptoms. In terms of exercise, treatment of NAFLD required the wearing of a Fitbit tracker, and through app-based wireless monitoring of patients' exercise data, the investigators provided personalized instructions, adjusted exercise regimens in a timely manner, and encouraged adherence to remote therapy *via* email or phone. After 6 months of combined intervention, approximately 50% of patients had a reduction in weight, triglycerides, and FibroScan liver stiffness, and 75% had improvement in controlled attenuation parameters and physical function. Several studies have shown similar results that pilot lifestyle interventions based on mobile technology are feasible and acceptable for patients with NAFLD, and this treatment modality has the potential to be scaled up to large-scale applications (37–39).

DTx promote patient self-management behaviors through health education

One study from China administered health education to patients based on the WeChat platform for 12 months. Patients joined the

Little Liver Station platform to transmit knowledge in the form of words, videos, and pictures to facilitate learning at different levels and were followed up every 3 months for reexamination. Studies have shown that the Plan-Do-Check-Action health education management model based on the WeChat platform can significantly improve the cure rate of patients with NAFLD (40). Another study provided professional management and guidance to patients using network platforms such as Weibo, QQ, and WeChat. After 1 year, liver ultrasound results of 51.67% of patients in the Internet + health management group were better than those before the intervention, whereas only 21.67% of patients in the control group had improved liver outcomes. In addition, body mass index, total cholesterol, and triglycerides improved more significantly in the internet group (41). It is important to integrate disease knowledge and psychological guidance into medical services so that patients can maintain a positive attitude and improve their compliance (42).

FUTURE PROSPECTS AND RECOMMENDATIONS

The potential benefits of DTx as an emerging therapeutic approach in the treatment and management of patients with NAFLD are tremendous and profound. However, the utility value of DTx for patients with NAFLD is also limited by product design, personalization of guidance, professionalism of the intervention content, applicability of service targets, patient compliance, accuracy of data recording, and cost issues. Based on the current status of the field, we would like to make the following recommendations for future clinical applications of DTx for NAFLD.

Improving the intelligent design of DTx for NAFLD

A number of DTx products have been developed for behavior change issues, such as MyFitnessPal, Runtastic, and Simi Move (43–45). Of note, the functions of these products are limited and the targeted service population is not specific. A critical and challenging aspect of DTx design is the development of comprehensive medical services tailored to the multifactorial health status of individuals with NAFLD (6).

Regarding the complex disease of NAFLD, we suggest designing DTx with multiple modules that integrate psychology and physiology, including diet guidance, exercise management, medication reminder, sleep management, psychological guidance, counseling services, knowledge science, and real-time assessment, as shown in Figure 1. Required data (e.g., weight, waist circumference, skeletal muscle weight, percentage of body mass, diet, and exercise) collected through wearable devices, smart apps, and measurement tools are recorded directly into DTx. According to the combination of machine learning, deep learning algorithms and the advice of remote professionals, a visual analysis of patients' clinical characteristics and personalized treatment plans can be presented to ensure a comprehensive understanding of physical health conditions and the treatment program offered. In the future, through intrahospital and extra-hospital data linkage, patients with NAFLD can enjoy one-stop health management services after registering personal information and establishing electronic medical files, all of which tend to save patients time and medical costs.

Enhancing the personalization of DTx for NAFLD

NAFLD is strongly associated with lifestyle, living conditions, and work stress, which is highly heterogeneous among different patients (46,47). Therefore, DTx should provide individualized

intervention guidance according to living habits and conditions. In terms of diet, in addition to encouraging patients to adopt a low-calorie diet and limiting the intake of high-fat, high-salt, and high-sugar foods according to guidelines, personalized adjustments need to be made according to patients' dietary habits (48). For example, young patients often eat high-fat, high-calorie takeaway food because they are busy relative to elderly patients (49). Therefore, the diet module should be targeted to make adjustments according to the patient's dietary preferences and work characteristics, thereby helping patients adhere to a sustainable healthy eating style. In terms of exercise, patients are advised to perform both aerobic (e.g., jogging, brisk walking, and cycling) and anaerobic exercise (e.g., sprinting, lifting weights, and push-ups) according to the guidelines (48). Because patients with NAFLD often abandon exercise due to various limitations, such as knee injury, heart disease, uterine prolapse, and stress urinary incontinence, individualization should be considered during the early design of DTx, and appropriate exercise protocols should be tailored to the patient's personal preferences, past history, and physical tolerance (50). During initial training with DTx products, patients should be informed about the importance of accurately providing relevant information as they enter personal preferences and information; this helps to ensure that the health care services provided by DTx products are individualized.

Emphasizing multidisciplinary NAFLD teams in DTx

NAFLD is a metabolic disease that is often combined with diabetes, hypertension, and polycystic ovary syndrome, which may involve multiple different specialties and have different treatment priorities (51–53). Therefore, the formation of multidisciplinary teams, including experts in hepatology, endocrinology, obstetrics and gynecology, nutrition, kinematics, and psychology, is crucial. During the implementation of DTx, a multidisciplinary team consisting of experts from multiple different disciplines constructs a standardized management process based on evidence while providing multiple individual treatment plans based on the patient's specific condition. Integrated multidisciplinary team therapy strengthens interdisciplinary connections, plays a complementary role, and solves individual patient problems in a relatively comprehensive and targeted manner, which is more conducive than otherwise to achieving the desired results (54). Thus, the involvement of a multidisciplinary team is required during the development and design of DTx products to ensure that the design scheme takes into account the different comorbidities of the patient.

Expanding the applicability of DTx to NAFLD populations

Mobile device-based remote internet management models need to address the applicability of digital services to special user groups. First, due to poor metabolism, intestinal microecology disorder, diabetes, and hyperlipidemia, the number of elderly patients with NAFLD is increasing (55). It is worth noting that elderly people tend to have poor learning ability and acceptance when they are exposed to network-related information devices compared with young people (56). Similarly, the large population of pediatric patients with comorbid NAFLD cannot be ignored (57). These patients can have the inability to use electronic devices freely, which requires that the role of family members be fully considered when developing DTx (58). Second, there is mounting evidence of a gender gap in internet preferences and usage patterns, which translates into a similar gap in the health care

provided by DTx (59,60). In general, men are online more than women for gaming and entertainment, whereas women use social networking sites more (61). Thus, it is essential to consider gender characteristics in the proper design and development of DTx programs and devices. Third, access to the internet may be limited for patients living in low-income areas, and internet remote management hardware is also less readily available, so simpler and more convenient programs or devices may be more accessible in these situations (62).

Enhancing adherence among patients with NAFLD

Despite the proven positive effects of lifestyle interventions that target weight loss on overall and liver-specific health among patients with NAFLD, their long-term success rate is low (63,64). Only 30% of patients with NAFLD lost $\geq 5\%$ of their body weight under the supervision of a professional team (16). Besides, although almost all participants with NAFLD considered physical activity important and wanted to be more active, only 25% of patients achieved ≥ 150 min/wk of physical activity (65). These findings suggest that the core factor affecting patients' success is their adherence to lifestyle modifications. Therefore, to achieve a healthy lifestyle through behavioral interventions, high levels of motivation are a prerequisite for high adherence (66).

Based on this, first, we suggest that DTx include a virtual health manager that can provide daily health guidance and simple human-computer dialog anytime and anywhere. Simultaneously, the DTx system is embedded with real medical providers, such as NAFLD specialists, nutritionists, and exercise managers, which can make the entire life-cycle therapy process more interactive and credible. In addition, the temporal strategy of intervention frequency is an important factor influencing DTx (67). Therefore, DTx can increase the frequency of interventions to stimulate motivation according to the patient's treatment schedule. More importantly, lifestyle management is a long and difficult process, and DTx can provide various forms of encouragement, such as voice reminders, role model incentives, awareness enhancement, gift rewards, financial rewards, and gamification when patients with NAFLD achieve milestones (68–70).

Tracking real-time data in DTx

Based on real-time and comprehensive data monitoring, tailored feedback and timely adjustment of interventions can improve the effectiveness and safety of DTx. The mainstay treatments for patients with NAFLD include physical activity and dietary remodeling, and the accuracy of real-time data recording is essential for both. The possibility of tracking physical activity by technology has been well-accepted in previous studies (71,72). Much more difficult is tracking dietary parameters (73). How to make the process of food quantification more accurate and interesting is worth further consideration by researchers.

To date, several diet quantification methods are widely used, such as weighed food records, hospital-ordered food delivery, the recall method, food frequency questionnaires, and vision-based measurement systems (74–77). Out of these methods, vision-based measurement systems show a promising future for study, as they need only a mobile camera to capture food images (78). Food calorie estimation starts with estimating the volume of food by 3-dimensional reconstructions through depth camera or planar image sequences and then calculating weight and calories or considering the food as a whole through deep learning techniques to first identify a food category in the database and then predict its

calories (79,80). Surprisingly, the development of mobile technology has given rise to some apps for food quantification based on image analysis, such as Asken and Calomeal, whose clinical applications have been proven to be accurate and convenient (81). In the subsequent upgrading of DTx, we suggest expanding food databases based on the dietary preferences of patients with NAFLD and combining biomarkers to accurately record calories for food ingredients such as fat and salt that cannot be visually evaluated.

Addressing the cost of DTx development and usage

Remarkably, DTx require the involvement of a large number of technical and medical personnel from development to implementation, which will inevitably incur financial costs and time expenditures. Currently, DTx are still in their infancy as a new nonpharmaceutical treatment, and the coordination of payments among patients, investors (e.g., software development sponsors and pharmaceutical companies), insurers, and the government needs to be explored in depth (82). In addition, differences in health care regulatory policies and reimbursement rates in countries around the world also pose challenges for DTx development (83,84). Therefore, it is necessary to conduct sufficient market research on patients with NAFLD during the development phase of DTx to clarify patients' demand for DTx and acceptance of payment programs. In the future, different levels of medical services can be provided according to the severity of the disease, the level of payment, and different national medical policies to achieve a double win for both the patients and the providers of DTx.

CONCLUSIONS

DTx overcome the drawbacks of traditional lifestyle treatments and provide patients with telecare medical services across time and space. Simultaneously, the implementation of DTx changes the self-management motivation of patients from passive to active, greatly improving the treatment adherence and therapeutic effect among patients with NAFLD. Despite the promising future of DTx in NAFLD management, a feasible, operational, and evidence-based management protocol generated with the participation of all stakeholders remains mandatory.

CONFLICTS OF INTEREST

Guarantor of the article: Junping Shi, MD, PhD.

Specific author contributions: J.S. and J.L. conceived the idea for this work. R.Z. and Y.G. drafted the manuscript. B.Z., T.K., and W.Z. conducted the literature searches and created graphs. R.Z., Y.G., and J.L. made revisions to the manuscript. J.S. provided review, interpretation, and funding support.

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