

4th CD SKILLS NEWSLETTER

Dear CD SKILLS partners, healthcare professionals, patients and followers,

CD SKILLS main goals were to improve and harmonize existing celiac disease management practices, to better meet social needs of all affected stakeholders in the Danube region, to detect more celiac disease patients, to treat them successfully, to increase competences, skills and knowledge of patients and healthcare professionals and to improve quality of healthcare service in the Danube region which will improve quality of life of celiac disease patients.

We just wanted to thank all of you who invested time and enthusiasm into our project. This task could never be finished without your expertise and commitment. It has been a pleasure working with you.

May your Christmas sparkle with moments of love, laughter and goodwill. And may the year ahead be full of contentment and joy. Have a Merry Christmas!



State of the art analysis of celiac disease management in the Danube region (WPT1)

Final results of WPT1 “State of the art analysis” showed some interesting results. Medical data of 676 newly diagnosed children with celiac disease were available for analysis. It was found that the mean age at diagnosis was 6 years and 5 months. **In contrast with previous FOCUS IN CD project (Interreg Central Europe) a higher proportion of patients was diagnosed without a biopsy which indicates an important change in celiac disease management practice that occurred within 5 years.** No change was found in clinical presentation with majority of patients still presenting with unspecific abdominal pain. It is also very important to note that diagnostic delay in the Danube region is short compared to many other data. Median duration from symptoms to diagnosis were found to be 6 months, which is comparable with the data from Central Europe. However, some regional differences were found with the longest delays in Moldova and shortest in Bulgaria.

As regards the knowledge of healthcare practitioners and patients we found a modest improvement in pediatric gastroenterologist, however in other groups, there was only minor change, which calls for further efforts in activities focusing on rising the awareness and improving the knowledge of all stakeholders involved in celiac disease management.

| | Danube region | | | Central Europe ¹ | | | p-value |
|----------|---------------|-------------|-------------|-----------------------------|-------------|-------------|---------|
| | TOTAL | BIOPSY | NO-BIOPSY | TOTAL | BIOPSY | NO-BIOPSY | |
| CROATIA | 61 | 25 (41%) | 36 (59%) | 58 | 54 (93.1%) | 4 (6.9%) | <0.001 |
| HUNGARY | 85 | 23 (27.1%) | 62 (72.9%) | 302 | 238 (78.8%) | 64 (21.2%) | <0.001 |
| SLOVENIA | 44 | 16 (36.4%) | 28 (63.6%) | 45 | 28 (62.2%) | 17 (37.8%) | 0.013 |
| TOTAL | 284* | 103 (36.3%) | 181 (63.7%) | 653** | 546 (83.6%) | 107 (16.3%) | <0.001 |

*Including Austria, Czech Republic, Moldova, Romania and Serbia. **Including Italy and Germany. ¹Riznik et al. *Gastroenterol Res Pract.* 2019.

Many of this interesting data was presented at several international and national events focusing on health care professionals. Despite the end of the project patient data is continued to be uploaded and many centers from outside the Danube Region are participating.

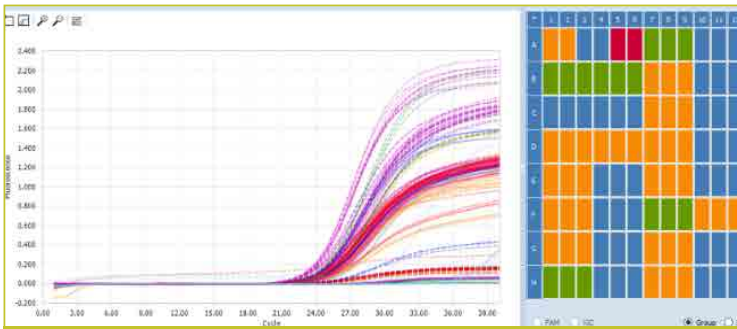


Optimization of diagnostic strategies in Celiac disease (WPT2)

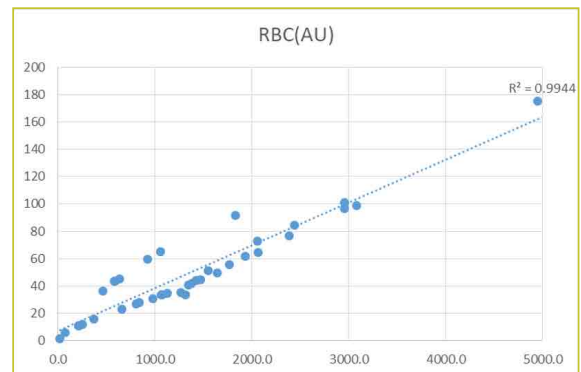
Work package „Optimization of diagnostic strategies in Celiac disease” aims to improve the diagnostics of celiac disease in the Danube region by harmonizing serum celiac antibody measurements and optimize new technical approaches. One major achievement of the project was the development of monospecific cloned calibrator antibodies which can be applied in various commercial transglutaminase antibody measurement kits for the uniform calculation of serum celiac antibody concentrations. This new approach has been tested on a panel of 320 serum samples with transglutaminase antibody results collected by the project partners. These samples had been tested with 6 different clinical assays at the partner’s hospitals earlier. These assay results were now adjusted to a harmonized value by the use of the common calibrator.

Another product of the project was the development of a near-patient quantitative celiac antibody measurement tool based on bio-layer interferometry. The project supported the purchase and use of two portable devices working with this principle and adjusted the for medical use. These devices measure celiac antibody binding to the target transglutaminase or gliadin peptide antigens by optical means without secondary labels and provide results in 5-10 minutes. The direct binding of antibodies can be quantitated in µg/ml.

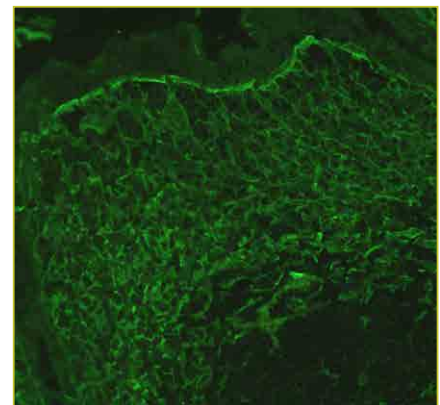
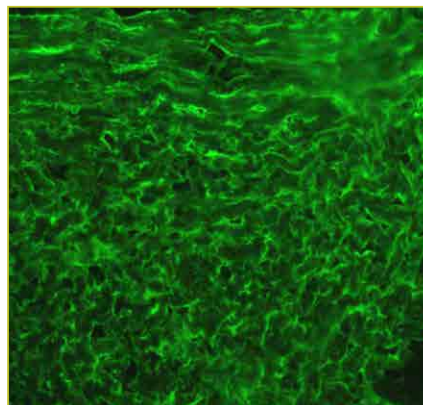
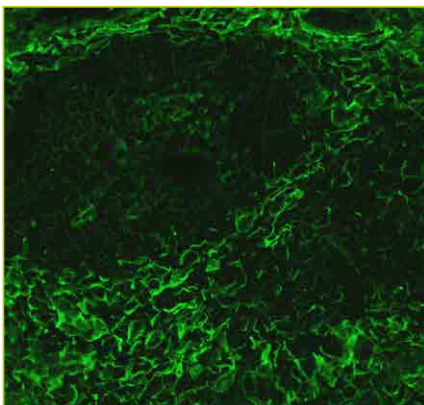
The project also worked on the development of verification tools which help finalize the definitive diagnosis of celiac disease. The immunofluorescent endomysial antibody assay (EMA test) was made easier by applying substrates which contain in addition to endomysial structures also reticulin fibres and provide results of all three classical celiac antibody assays (EMA, ARA and JEA) in one step both for IgA and IgG class antibodies using multicolour stainings. The HLA-DQ test was further developed and the project also worked on the identification of new genetic markers in cell culture using celiac and control cell lines.



HLA-DQ testing by PCR for celiac alleles DQ2 and DQ8



Measurement and comparison of serum transglutaminase antibodies by the use of the developed calibrator



EMA-ARA-JEA assay



Building knowledge capacities results (WPT3)

Work Package „Building knowledge capacities “(WPT3) had four activities and here we present results achieved during the CD SKILLS project:

1. Organisation of learning interactions

Altogether, 42 learning interactions were organized: 3 transnational, 11 regional learning interactions and 28 lectures at educational institutions: primary schools, high schools, universities (medical schools, school for nurses, faculty for pharmacy and biochemistry, faculty for agriculture and biosystemic sciences, biomedical postgraduate studies), and at university hospitals for paediatric residents and nurses.



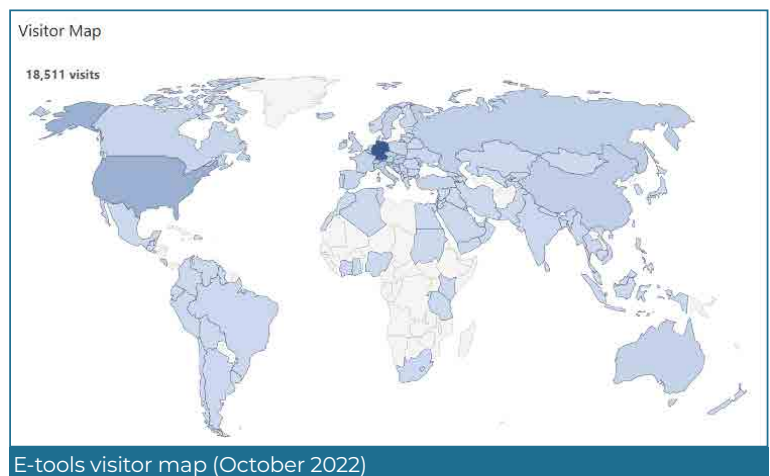
2. Implementation of innovative e-learning tools for health care professionals and patients

Within CD SKILLS project, two innovative e-learning tools has been implemented, one for health care professionals and one for patients. Implementation of these tools will contribute to reaching the objectives of CD SKILLS project, to improve and harmonize existing celiac disease management practices in the Danube region and to increase patients' self-management capacities.

The e-learning tools are being built on the existing tools developed within the CE Focus IN CD project and updated based on the new ESPGHAN (European Society of Paediatric Gastroenterology, Hepatology and Nutrition) celiac disease management guidelines published in 2020 and on the lessons learned from CE Focus IN CD project. It was shown in Focus IN CD project that the knowledge about celiac disease among HCPs and CD patients is not satisfactory and that further awareness-raising and learning activities are needed, in order to improve knowledge and to minimize the number of unrecognized patients and unnecessary diagnostic delays. In addition, patients should be informed better about their disease to reach higher compliance with the gluten-free diet. The use of tools will be promoted through the networks of medical partners, professional societies and patient support organisations and public authorities.

The e-learning tools available in English, German, Slovenian, Hungarian and Croatian language were further updated and versions in new languages of CD SKILLS partners Romanian, Czech and Romanian (MOLD) have been added.

E-tools are available at www.celiacfacts.eu



| Country | Visits |
|----------------|--------|
| Germany | 6,672 |
| United States | 2,110 |
| Croatia | 953 |
| Italy | 806 |
| Slovenia | 775 |
| Hungary | 676 |
| Russia | 566 |
| China | 521 |
| Switzerland | 364 |
| United Kingdom | 361 |

E-tools visits per country (October 2022)



As the sustainability of the project is one of project and programme priorities, we are exploring further options to keep funding the maintenance and regular updates of the E-learning (Moodle) platform.



Monitoring of the user behaviour has shown that the user base is truly worldwide. Since the implementation of the “Matomo” analytical tool in October 2021 we had 20000 visitors.

Both e-learning tools are an open on-line course that can be accessed without the need to register.

Postcards and posters were designed to promote e-tools meant to attract both health care practitioners and patients to use the webtools.

3. Establishing CD SKILLS transnational information exchange network for health care professionals

CD SKILLS transnational information exchange network - an open access web-based platform designed for health care professionals was established within the project. **The aim of the platform is to exchange knowledge and information, to discuss challenging cases and to share problems in the field of celiac disease with other members of the network.**

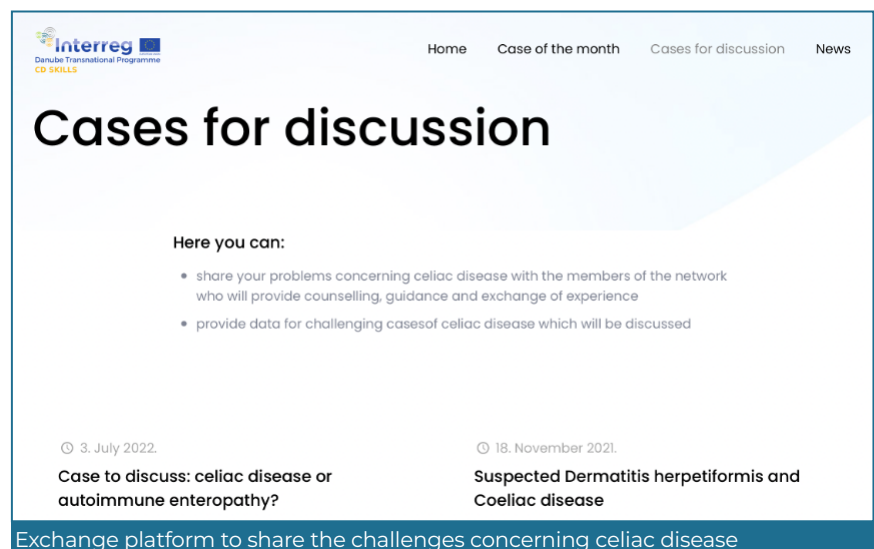
Each month an interesting and instructional clinical case is presented as a „case-of-the month“ presentation. The second part of the platform is dedicated to the „cases for discussion“ where partners and other health care professionals can present and discuss challenging celiac disease cases, ask questions and share problems.

The platform was presented at international meetings and to local health professionals at several regional and local meetings.

Please, visit the platform, which is available here: <https://cdskills.eu/>

There you can find cases like:

- Misdiagnosis because pediatrician did not follow guidelines?
- Do not exclude gluten from the diet until the final diagnosis of celiac disease
- Case to discuss: celiac disease or autoimmune enteropathy?





4. Cross-disciplinary Study visits and international professionals and patients meetings

Unfortunately, due to COVID-19 pandemics we were unable to organize cross-disciplinary study visits during the first year and a half of the project. However, during the last period five study visits were accomplished, two to Tampere, Finland, two to Maribor and one to Zagreb, Croatia.

Although because of COVID-19 pandemics, some meetings at the beginning of the project were cancelled, some postponed or held on-line, project partners managed to attend and actively participated at ten international meetings (some held online and some face-to-face meetings) such as WCPGHAN (World Congress of Pediatric Gastroenterology, Hepatology and Nutrition), ESsCD (European Society for study of Coeliac Disease), Europediatrics, UEGW (United European Gastro week), Annual Meeting of ESPGHAN (European Society of Pediatric Gastroenterology, Hepatology and Nutrition), ICDS (International Celiac Disease Symposium) where they presented progress and results of the CD SKILLS project.



Otilia Man presenting the CD SKILLS project in Tampere



CD SKILLS group at International Celiac Disease Symposium in Sorrento, Italy



CD SKILLS pilot projects implementation news (WPT4)

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The existing celiac disease management practices are insufficient in the Danube region. Project partners designed and implemented innovative pilot services aiming at early and accurate diagnosis of celiac disease, detection of complications, monitoring the patients, and improving the quality of life of celiacs.

PILOT No1: Testing for Celiac disease in general population, risk groups and elderly

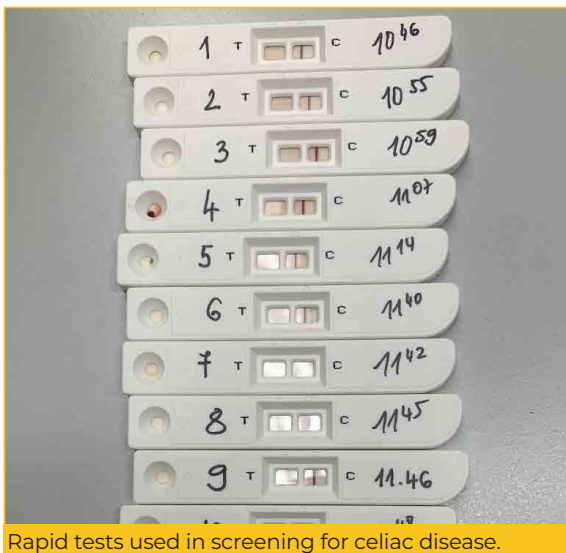
It is estimated that about 80% of people with celiac disease remain undiagnosed or are diagnosed with substantial delay. Currently, testing for Celiac disease in the Danube region of Europe is primarily done at the hands of paediatric and adult gastroenterologists on the secondary or tertiary level of medical care. There is no widespread testing for the general population and the elderly, whilst risk groups are tested (to some extent) by the specialist of their underlying condition (i. e. patients with Type 1 Diabetes by their endocrinologists) or when they develop some celiac disease - like symptoms of their own.

The use of rapid tests, which are readily accessible, cheaper, non-invasive and can be done by personnel not expert in celiac disease, is a convenient way to evaluate underprivileged target groups, screen general population and pre-select the risk groups.

These tests enable the detection of celiac disease from a fingertip blood sample within ten minutes.



Our colleagues participating to rapid testing activities at an elderly home.



Rapid tests used in screening for celiac disease.

Within the pilot, rapid tests were used for screening asymptomatic young adults and elderly. New undiagnosed celiac disease cases were detected showing the potential usefulness of rapid tests method for the on the site selection of individuals in need for further investigation for diagnostic confirmation. Rapid tests were used also for evaluating symptomatic children, allowing an early detection of celiac disease and decreasing the attendance in the second and tertiary care.

Rapid tests proved to be easily available, fast, non-invasive method that could be applied in primary care for celiac disease screening. They are not intended to be used for a final diagnosis or follow-up. It is debatable and further research is needed on assessing the rapid tests capacity of detecting celiac disease in certain target groups, such as elderly.

PILOT No2: Testing for Celiac disease related complications

People with undetected or untreated celiac disease are exposed to risk of development of serious complications. In many cases, there are delays in diagnostic, even up to 10 years, which leads to the situations that at the moment of celiac disease diagnosis, the complications are already present. Therefore, it is important, that patients are evaluated for the presence of the complications already at diagnosis. In case of patients with low adherence to the long-term strict gluten free diet, the assessment of complications is mandatory.



Within the pilot, two main groups were evaluated: newly diagnosed people and people with celiac disease on long-term (more than 2 years) gluten-free diet. Project partners defined a list of medical analyses and questionnaire for evaluation of complications, and used a questionnaire for gluten-free diet adherence assessment.

The results show that there is a correlation between symptoms presence among long-term treated patients and adherence to diet. Interestingly, there were cases, among both children and adults, with a good compliance to diet but who still presented symptoms.

The assessment also revealed differences between countries in terms of nutritional status i.e. the proportion of patients with vitamin D deficiency varies from 25% to 75%.

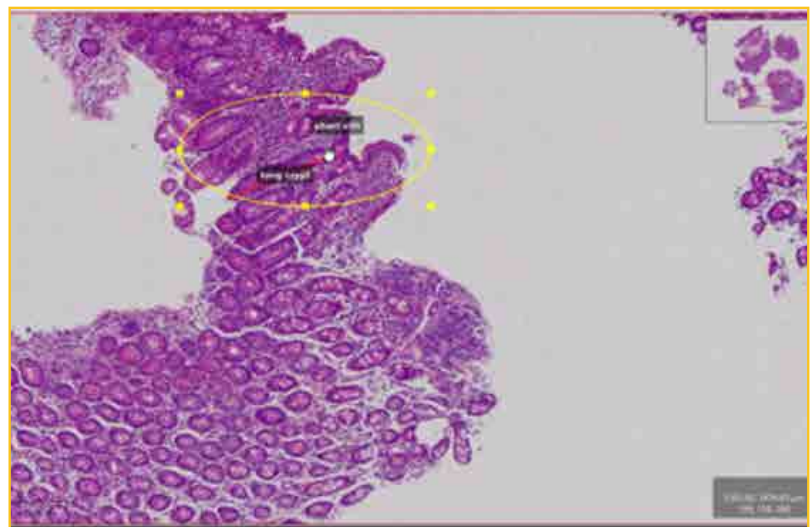
PILOT No3: ICT supported histopathology analysis of biopsy samples

Inadequate histopathology analysis of small biopsy samples and/or misinterpreted results can lead to wrong diagnoses of celiac disease. Within the pilot, partners focused on improving the knowledge and communication between clinicians and histopathologists, as well as applying and testing a technical solution developed during the project.

Pilot partners participated to a common workshop with clinicians and histopathology experts with the main objective to establish common understanding of the messages related to small intestine histology, enabling clinicians to have a deep understanding of the histopathologist statements. The workshop was organized by INSMC Bucharest and Children's Hospital Zagreb, and invited lecturer was Assoc. Prof. Davor Tomas, from the School of Medicine Zagreb and University Hospital Center Sestre Milosrdnice.

In order to further extend the knowledge and understanding of difficult non-responsive and refractory celiac disease, a second workshop was organized by LMU. Priv. Doz. Dr. med. Michael Schumann from the Division of Gastroenterology, Infectious Diseases and Rheumatology, Campus Benjamin Franklin, Charité Universitätsmedizin Berlin, Germany presented clinical cases series regarding clinical management and their specific histopathological injuries and specific methods of detecting them.

A third workshop, Histopathology analysis of biopsy samples, was organized with the objective of sharing information on how to properly analyze biopsy samples in order to establish the correct diagnosis. Dr. Alina Popp from National Institute of Mother and Child Health „Alessandrescu-Rusescu“ and University of Medicine and Pharmacy “Carol Davila”, Bucharest, gave examples of well-cut biopsy and showed how to properly recognize a good sample and how to properly measure crypts and villi on samples using an ICT method. Examples of poorly cut biopsy samples were also given and the traps of correctly reading a biopsy sample were emphasized.



Example of a difficult case where ICT histopathology provided valuable information

The ICT histopathology method used prove to provide valuable information when standard classic methods failed in the accurate assessment of the presence and severity of the lesions. Furthermore, the ICT histopathology method allows high precision measurements in a faster and trackable way. Follow-up visualization and reassessment of difficult cases by international experts is also possible with this ICT histopathology method.

The innovative ICT histopathology method was compared with standard method, with a high agreement between the methods. To our knowledge, this is the first time the ICT based histopathology morphometry measurement method was used in a multi centric study for the evaluation of the intestinal mucosa damages in children.

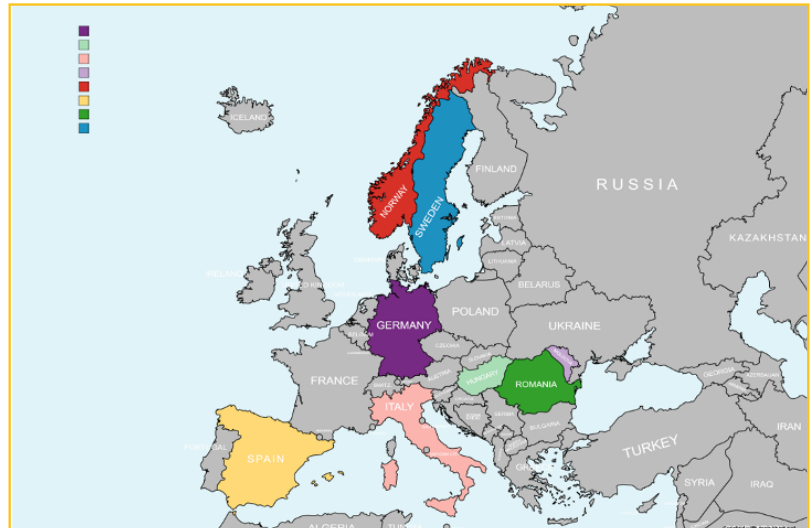


PILOT No4: Patient registry set-up

Across the Danube region, there is lack of high quality, standardized data regarding celiac disease patients.

A preliminary analysis of rules and regulations, as well as patient registries for other disease, was followed by an exploration of current practices regarding celiac disease registries outside Danube region, among members of the Celiac Disease Special Interest Group of European Society of Paediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN). Exchange of experiences revealed differences in registries set-up and ways of working, as well as a rather common challenge related to the financial support of the registries. Summary of findings were presented at 54th ESPGHAN Annual Meeting.

Pilot partners developed a common structure of a patient registry, with same type of data collected in each country, containing information about newly diagnosed patients. The approach could be used for further developments. Partners also explored solutions for establishing local registries (Moldova) or optimizing local already existing solutions (Romania).



Celiac disease patients' registries analyzed within the pilot

PILOT No5: Monitoring of celiac disease patients with telemedicine solutions



Telemedicine solutions are increasingly used in everyday practice.

COVID-19 accelerated the uptake of telemedicine solutions across various areas of healthcare system. Within the pilot, a personalized app for the follow-up of celiac disease patients was developed. The technical solution could be further used in various settings to improve the quality of regular check-ups for patients with celiac disease and minimize their exposure to the risk of infections.

Several parameters of patients with celiac disease are monitored with this app including their weight gain and general vital signs with the help of wireless devices. At the same

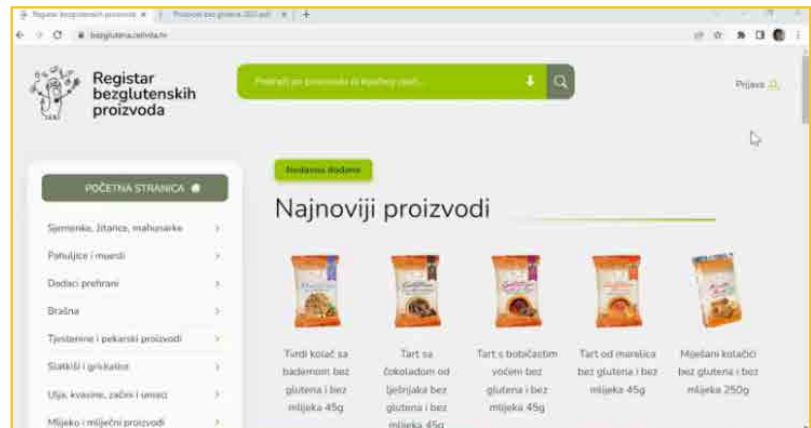
time patients are asked to fill in a questionnaire focusing on signs and symptoms as well as on their quality of life and dietary adherence. Patients can also perform POCT test and upload the image of the test. IT solution can help in detecting any abnormalities in the test. All the data is stored and doctors responsible for management of the patient can see the data and can compare it with the data collected at previous virtual visits.



PILOT No6: Development and implementation of gluten-free products registry

Quality of life and healthy ageing of people with celiac disease is affected in many ways. One of the very important challenges is the implementation of extremely strict gluten-free diet. Pilot partners developed a free, user friendly, and easy to use application aimed to provide correct and up to date information about gluten free products.

The gluten free products registry (<https://bezglutena.celivita.hr>) is used by people with celiac disease and their family members, people on a health-based gluten-free diet, institutional kitchens (schools, kindergartens, hospitals etc), players from HoReCa Sector etc. It is a very valuable tool that brings together, in one place, all safe gluten free products. Users are able to search for products, based on various criteria.



Interested stakeholders from Croatia can easily search for gluten-free products on CD Skills established gluten-free product registry (<https://bezglutena.celivita.hr>)

PILOT No7: Improved capacity of food catering providers to provide safe gluten free products



Gluten free guide for caterers is available in local languages for free on project website (<https://www.interreg-danube.eu/approved-projects/cd-skills/outputs>)

Gluten-free eating-out is a rather limited possibility across Danube region, irrespective of the context: restaurants, cafeterias, kindergartens, schools and other educational institutions, hospitals, elderly homes and other care facilities.

The evaluation of best practices revealed that around the world, there are various approaches related to the implementation of gluten free diet, based on a combination of legislative requirements and educational programs. Workshops and interviews with stakeholders

from Danube region highlighted key challenges that food-catering providers need to overcome in terms of knowledge and capacities.

Pilot partners developed free educational materials and organized a transnational event in order to improve the knowledge of caterers and all employees who are likely to be involved in the preparation of gluten-free meals for people with celiac disease, especially staff in the kitchens of kindergartens, hospitals, schools and elderly homes as well as restaurants and hotels.



A short communication activities overview (WPC)

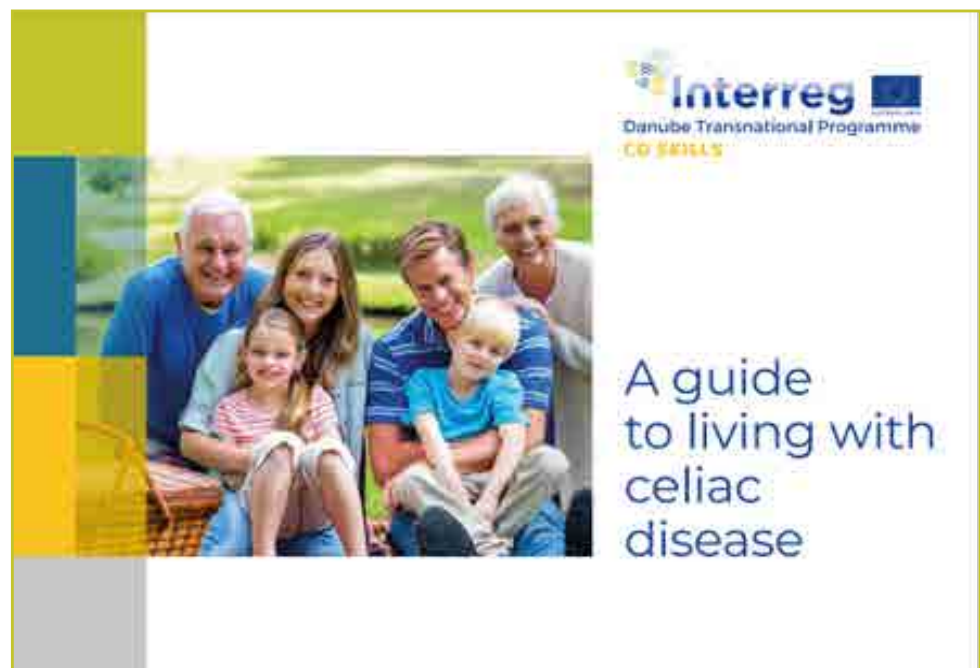
During the first project implementation months we have been active to assure a good communication and a smooth start of the project. Because of the specific COVID – 19 situation, all meetings have been organized online as well as monthly communication meetings (20 together). Project activities in 2020 started with the preparation of project roll-up and posters, the communication strategy was prepared. We set-up of FB and Twitter accounts and launched the first press release, to announce the start of the project.

In two and a half years of project implementation following publications to raise knowledge, increase competences and foster harmonization of Celiac disease (CD) management practices were published: Brochure for patients, Brochure for healthcare professionals, Brochure for caterers and Study material for students (will be available until the end of the year).

We participated at more than sixty national patient and health care professionals' events, presented the project and gave lectures about celiac disease and related challenges.

We put a lot of efforts and creative energy into our project web side, to made it interesting and to attract as many visitors as possible. We were constantly preparing additional project website content and published project news and stories, as well as educative videos. We were very active at FB and Twitter.

Two national campaigns were organized in all participating regions, the first one in May 2021 and the second one in May 2022, to mark transnational celiac disease day and to support events organized by patient organizations. A lot of regional and national media channels reported about the CD SKILLS



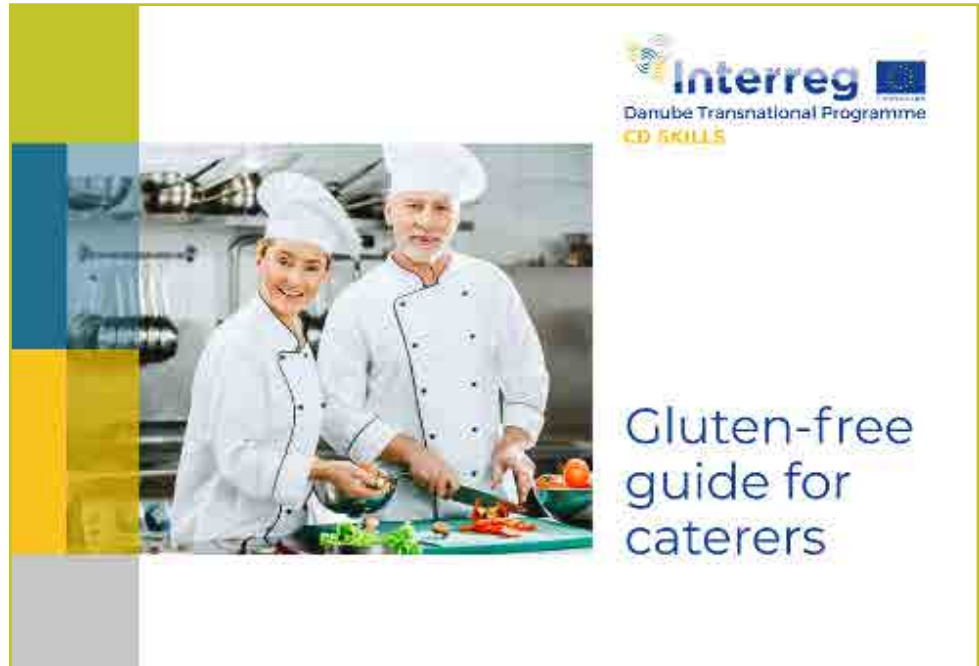


project, partners were invited to give interviews, articles were published etc. All described activities improved knowledge and raised awareness of patients, health care professionals and general public.

Project promotion material was produced and distributed to inform the target groups about the project results and to raise awareness. E-tools leaflets, postcards and posters to support the promotion of e-tools have been designed in all partner languages. Four project newsletters were launched during the project duration. We established a cooperation with DTP project D-CARE LABS.

During the fifth and last period we put a lot of efforts into effective dissemination and promotion of project results »at home and abroad«.

All publications in English and partner languages are available on the project website <https://www.interreg-danube.eu/approved-projects/cd-skills>



Visit CD SKILLS (Danube Transnational Programme) website and stay informed:
<http://www.interreg-danube.eu/approved-projects/cd-skills>

Our e-learning tools for patients and health care professionals are available at: www.celiacfacts.eu