Welcome by AOECS and EUROMED officials

C. Scerri, P. Rossi, L. Marras.

Result of the Retrospective Study

F. Tucci, L. Greco; Italy

1. Prof. Greco introduced the meeting thought the last published paper “The burden of celiac disease in the Mediterranean area” where we estimated the burden of undiagnosed celiac disease (CD) in the Mediterranean area in terms of morbidity, mortality and health cost. The projected number of CD diagnoses in 2020 is more than 5 million cases (1 million of children), with a relative increase of 11% compared to 2010. A delay in diagnosis is expected to increase mortality: about 600,000 celiac patients will die in next 10 years, with an excess of 44.4% versus age- and sex-matched controls. In the near future, the burden of CD will increase tremendously. Few Mediterranean countries are able to face this expanding epidemic alone. That is why we, as an EUROMED network, have to raise the awareness of CD in the Mediterranean Area and increase and facilitate the diagnosis. We also have to consider it for the newcomers.

2. Prof Greco introduced us to the draft of the new paper about the Retrospective study explaining the debate of the ESPGHAN Committees about the new diagnostic criteria:
actually, to diagnose CD we require serology, endoscopy and accurate histologic facilities; recently the new ESPGHAN Committee explored the possibility to simplify the diagnostic procedures, avoiding the small bowel biopsy in selected conditions. If in the affluent world a simplified diagnostic procedure is considered feasible, due to the increased prevalence of the disease, this is badly needed in all the other part of the world. The vast majority of cases will come from Africa, Asia and South America: not everywhere there will be enough facilities and resources to face this burden. Hence a simplified diagnostic protocol will find in these part of the world his major justification, not where resources and know-how are largely available. The MEDICEL network includes all the countries of the Mediterranean area and aims at expanding the awareness of the incoming epidemics of CD all through this area.

3. Dr. Tucci showed the result of the retrospective study to which 15 research groups collaborated. Each country contributed with about 50 cases for a total of 798 CD cases. Aims: To get an objective picture of the facilities to diagnose CD available in each of these countries in the reference centres. To assess where the new diagnostic criteria could be applicable and on what percentage of patients. Next step will be to explore the field out of the referral centres

Expected Results:
- To estimate the percentage of patients who bear the markers required by the new approach
- To produce an original picture of the CD diagnosis in the area
- To verify the validation of the SAGE grading score, algorithm to diagnose CD obtained by the sum of symptoms (S), antibody results (A), HLA-genotype and endoscopy/histology results (E). A SAGE score 4 or higher is suggestive of CD. The SAGE score was computed either considering the endoscopy/histology results as well as excluding it in order to assess when the new criteria can be satisfied.

Methods: A simplified web data sheet is available in English and French to collect anonymous data from existing clinical files.

Results:
- N= 798 CD cases
- Female to male ratio =1.65 (497 females; 301 males)
- Age range: 6 months to 22 yy
- Mean age 5.97 yy; SD 4.35; Mode 1; Median 5
- Earlier diagnosis:
  - Spain: Mean age 3.9 years (S.D. 3.1)
  - Algeria: Mean age 8.3 years (S.D. 3.9)
  - Means are statistically different (t-test):
    - p value < 0.001; mean difference 4.32
- The majority of cases have significant clinical complaints. Asymptomatic CD cases are not very common in this unselected case list from the referral centres: in Albania, Bosnia Herzegovina, Morocco, Tunisia and Egypt there is not a single asymptomatic case.
- Biopsy results: 70% show from severe to total atrophy of the intestinal mucosa.
- Correlation between TGase levels and biopsy results: for each increment of TGase of 10.2 Units there is a progression of one Marsh Stage in the Biopsy.
- SAGE score: In a cohort of 744 CD patients, 661 (88.8%) have a SAGE score 4 or higher, namely indicative of CD diagnosis, but, when we excluded from the total score the endoscopy/histology results, the percentage of patients with SAGE score > 4 greatly decreases from 661 to 370 (49.7%) with a statistically significant difference ($\chi^2$ 14.52 p<0.001). This suggests that in several countries the omission of the biopsy might produce an high rate of under-diagnosis. Out of the 83 patients with a SAGE score 3 or lower, 76 (91.5%) did not have the HLA-genotype, that is crucial for the final SAGE score. In fact if we assume that all these cases have a typed HLA suggestive for CD (HLA SAGE score G = 1), other 59/76 (77.6%) patients can reach a score higher than 3.
So it could be possible that, in presence of this parameter, many cases could be validated by the SAGE score as well as diagnosed by the new ESPGHAN protocol.

Limitations:
- Selection bias
- Missing Values: Since the aim is to assess the applicability of the new ESPGHAN protocol in the field, it is mandatory to underline the presence of missing values in our data namely about serology, biopsy and histology and HLA typing for each centre. It may be noted that:
  - **Anti Human Tissue Transglutaminase** assay is not regularly available in Algeria (not performed in 29/50 CD cases; 58%) while the results are not reported quantitatively in Bosnia Herzegovina (100%), France (100%) and Morocco (97.1%) and partially in Egypt (68.8%) and Croatia (28%) for a total of 23.4% qualitative serological results. The remaining countries (Italy, Turkey, Greece, Albania, Slovenia, Tunisia, Spain) provided all quantitative results (66.9% of all the cases).
  - **Biopsy** results are missing for 45/798 (5.6%) of the cases namely in Albania (27/43; 62.8%), Bosnia Herzegovina (8/42; 19%) and Egypt (4/36; 12.5%).
  - Similarly, **HLA genotyping** was provided for all cases from Greece, Slovenia and Spain. HLA was not typed in all cases in Italy (Campania 11/100, 11%; Sicily 16/50, 22%), Turkey (34/50; 68%), Bosnia Herzegovina (14/42; 33.3%) and Croatia (2/50; 4%). HLA results are missing for 445/676 (65.8%) of the CD cases, especially in the majority of African countries (Algeria, Morocco, Tunisia and Egypt), Albania and Montenegro.
- Lack of standardization for the biopsy and TGase levels.

Discussion:
- Dr. Hartman underlines that half of her patients are asymptomatic and that when Israeli patients receive CD diagnosis, they are considered healthy because they need only a GF diet. HLA is not routinely done in Israel because it is very expensive so CD patients necessarily need the biopsy.
- Dr. Ben Hariz from Tunisia shows that for our retrospective study there are a lot of missing data because his unselected CD cases come from old case records. So, in new CD cases data would be more complete especially concerning TGase antibodies.
- Dr. Micetic Turk informed us that in Slovenia a preliminary study shows that there are few CD cases with > 10x levels TGase. Therefore biopsy would be impossible to omit.
- Dr. Velmishi underlined the problem of CD under diagnosis in Albania due to the excessive cost to perform serology, biopsy and HLA genotyping.
- Dr. Viala from France suggested to evaluate the specificity of the SAGE score in non CD patients.
- Dr. Koltai suggested that the SAGE score should be tested only in the new diagnosed CD patients.

Prof. Greco informed us that by the end of October we will be ready to submit our paper of the retrospective study.

He underlined that the HLA costs are crushing down because of the PCR technologies: CD-Medics could contribute to implement HLA technologies. CD diagnostic tests are not standardized: Mediterranean reality is a widespread range. A possible solution to standardize biopsy results could be to send images of the samples to the referral centre.

He also underlined that endoscopy is the limit because only in the referral centers can be done. Nevertheless, among missing data, biopsy missing values are clearly less comparing to those of serology and HLA. About the SAGE score, he remarked that it could be useful to avoid biopsy only when non invasive diagnostic test (antibodies and HLA) will be widespread available.
News from CD-Medics

C. Scerri, Malta – E. Bravi, Italy

Dr. Bravi updated about the progress of CD-Medics project. CD-Medics objectives were to develop a disposable microchip for diagnosis of CD in a portable/hand-held device carrying out multi-analyte tests with the simultaneous detection of coeliac disease associated autoantibodies (DPG and TGase, total IgA) and HLA-DQ2 and DQ8 genes. Results could be shared among health workers due to the possibility to insert results in an online database. Moreover it is possible to perform only HLA genotype or only serology, in order to reduce costs and use the instrument also for patients follow-up. The end of the project is scheduled for June 2012 and the industrial production for the beginning of 2013. The cost of the instrument should be around 5000 euro.

Dr Scerri showed the role of AOECS within CD-Medics about:
- Dissemination: namely increasing awareness amongst Health Care Professionals and general public
- Training throughout workshops and road shows
- Attendance to conferences and exhibits in order to promote the CD cause.

He described the CD-Medics website that was built during the previous 2 years and where over 3000 hits in a year were done from 71 countries with over 9000 pages visited.

He showed that CD-Medics contributes in publication with 2 issues of the Internal Newsletter: these are translated in many languages but the following are missing: Portuguese, Albanian, Serbian, Turkish, Hebrew, Norwegian, Danish, Swedish and Finnish.

Planning for the Prospective Study

a. Family recruitment

D. Micetic-Turk, Slovenia

Dr. Micetic Turk described a possible design for the MEDICEL prospective study. She showed that the prevalence of CD among family members of CD patients is ~ 10% so that the primary aim of our study could be to evaluate characteristics and severity of symptoms in first degree relatives, to determine which of the available antibody tests (rapid tTG test, TG2, EMA, DGP) are most suitable for initial diagnosis, to determine whether the determination of HLA typing adds diagnostic value in cases with the positive specific antibodies and to estimate CD risk by HLA-SNPs determination in first degree relatives.

Conditions for participation:
- To recruit at least 50-100 families/centre
- Ethical approval by the local ethical committee

Benefits of the study:
- For family members:
  - Diagnosis
- For MEDICEL partners:
  - New knowledge on local level
- For MEDICEL projects:
  - New knowledge about epidemiology of CD in Mediterranean countries, a clear clinical picture and about genetics (non-HLA genes).
b. Data management  
J.R. Bilbao, Spain

Dr. Bilbao showed how the web database has been modified in order to make it suitable for family data. Since it will be a prospective study, the website has to be considered to be modified over time. The interface would be very similar to what we used for the retrospective study, so this will be ready by the end of the month.

He is also preparing a data form that will be what participating centres would fill up (and keep), before they introduce the relevant and codified data into the web application.

The main information to collect and to record for the database are the following coded for privacy protection:
1. Health
2. Anthropometric info - to monitor growth
3. Genetics
4. Serology
5. Family
6. Dietary habits
7. Disease status
8. Environmental factors
9. Follow-up

c. BioBanking  
T. Attard, Malta

Dr. Attard described the importance of a biobank that through integration of molecular data with the clinical information represents a single, organized, common resource that can be utilized to perform multiple hypothesis-driven studies, interface with industry and monitor the evolution of CD in our societies.

Any biological material can form part of a biobank and the most common include:
- Fixed tissue samples
- DNA/RNA banks
- Body Fluids
- Cell culture banks

A collection of samples without the required clinical, demographical and other information on the donor has limited if any use. Not only these data are required to be collected but also organised in coherent and standard way. Availability of good and organised data is the key towards full usability of the samples in research projects.

Requirements for a Successful Biobank:

• Information Technology
  – Adequate database containing the fullest data possible
  – Adequate security measures in place to safeguard data protection
  – Easy protocols to share data between researchers
  – Adequate measures to identify ownership as well as recognition

• Laboratory facilities
  – Medium level – sample preparation
  – High Level – for advanced analysis

Dr. Attard also described the BBMRI (Biobanking and Biomolecular Resources Research Infrastructure), a 53-member consortium with over 280 associated organisations (largely biobanks) from over 30 countries, that will form interface between specimens and data and top-level biological and medical research.

He underlined all the implications of a biobank such as ethical considerations, data protection and types of consent. An “open” general consent form should be considered.
d. Research Topics

J. Viala, France

Dr. Viala showed how epigenetics could be important for a better focus on a complex disease as CD because it is less stable than DNA variations but it is stable enough to explain chronic diseases. It may add to or reverse the effect of DNA variations explaining uncompleted penetrances and it may explain altered sex ratio in complex diseases or incomplete concordance in monozygotic twins. He also described a possible Study design:

• 500 CD and 500 controls
• Data collection:
  – Clinical data
  – Environmental factors
• Biobanking
  – Blood (stored at 20°C)
  – Intestinal biopsies (stored at -20°C).

Main deliverables/perspectives would be:

• A set of epigenetic biomarkers associated with the disease to be tested in prospective studies.
• A comprehensive model of gene/environment integration at the epigenetic level.

e. Research Topics

J.R. Bilbao, Spain

In terms of the research project, Dr. Bilbao showed that the best approach should involve analyzing combination of the genetic/environmental factors in the different populations to come up with local combinations that can be used for risk assessment and reclassification in relatives. We could aim to recruit a fair enough number of patients and families from the different population groups in MEDICEL and try to evaluate the risk since we have access to high throughput genotyping facilities and the cost of genotyping would not be very high.

Outcome of the PREVENT-CD Study

Z. Misak, Croatia

Dr. Misak showed the preliminary results of the multicenter European project “PREVENT CD” study. The hypothesis of the study was that the introduction of small amounts of gluten at the 4th to 6th months of age while still breast feeding would reduce the number of CD by 50%.

1319 infants belonging to families with a first degree relative with CD were recruited. 905 of them, who were HLA DQ2 and/or DQ8 positive, were prospectively followed-up for the development of CD. Biopsies to confirm the diagnosis were performed if symptoms appeared and/or if two or three consecutive samples were positive for TGase or anti-gliadin (a-gli) antibodies, respectively. Preliminary results showed that 787, 450, and 207 infants were older than 12, 24 and 36 months respectively. Forty-eight biopsies were performed in 47 children and 31 diagnosis of CD diagnosis had made (CD group). In the CD group (median age 22.5 months), symptoms were present in 20 children, exclusively elevated TGase in 6 cases and elevated of both antibodies (TGase and a-gli titres) in 25 cases. In the non-CD group, 17 in total, symptoms were present in 13, elevated TGase and a-gli titers were found in 2 (potential CD) and 4 cases. Of the 207 children who reached the age of 36 mo, 14 were diagnosed with CD between the 2nd and 3rd year (prevalence = 6.76%). Of the 243 children aged 12-24 mo 15 new cases occurred (6.17%). Two more infants were diagnosed before the age of 12 mo.

These preliminary observations suggest:

1. An high incidence of CD in at-risk infants, at quite an early age
2. Two-thirds of them had symptoms
3. All had major damage (villous atrophy) involving the intestinal mucosa
4. TGase antibodies showed a high predictive value
Development of a Pilot Study

a. Study Design and Methods
   
   Luca Astarita, Italy

Dr. Astarita described how to plan a pilot study for the point of care test (POCT):

- Several study shows that POCT have almost the same sensitivity and specificity of standard serology tests
- POCT could be very useful in peripheral villages or town far from hospital and/or laboratories where EMA and TGA are available
- First ideas to develop a study design:
  - Identify villages with:
    - At least 5,000 inhabitants
    - Collaborative Health Centre/GP/Nurse
    - Possibility to store serum (hand centrifuge)
    - Possibility to communicate with a referral centre
  - Send serum to a referral centre: confirmation of diagnosis (EMA, TGase)

The aim of the study is the evaluation and feasibility of POCT for the diagnosis of CD in low-income countries. The cost for 1,000 POCTs will be around 2,250 €.

b. Working for Rural Areas
   
   M. Abu-Zekry, Egypt

Dr. Abu Zekry showed the picture of CD in Egypt. Until the year 2000 Celiac Disease was almost unknown in Egypt. Although symptoms and signs of CD are very common in the Egyptian population, children as well as adults, it is very rarely put in the differential diagnosis. A previous pilot study done by her group in 2008 showed that out of the total 1,500 children studied, 21 cases were found to be positive for CD (P: 1.4%). Above seventy percent of the population live in the rural areas out of 85 million, around sixty million.

She identified one rural area that could be useful for the POCT pilot study. The proposal is to recruit 5,000 mother and children and detect the symptomatic patients suffering from classical symptoms of CD and perform POCT. For diagnosis confirmation it will be possible to take serum from these cases and do all the serological tests needed (positive cases: intestinal biopsy will be offered). Another group with no symptoms (normal school children) will be taken as controls.

The next step would be to provide educational and social support through an International CD Foundation and the production of suitable gluten free nutrition.

c. Dissemination to Health Workers in the field
   
   A. Naima, Morocoo

Dr. Naima showed the CD situation in Morocco. There are no epidemiological studies neither of prevalence nor incidence.

Problems of care in Morocco:

- There is a lack of diagnostic tools:
  - Serology: Unavailability of TGase in hospitals
    Only some private laboratories in big cities do the test (cost around 30 €)
  - Biopsy: It is performed only in university hospitals or in private clinics (very expensive!)
• Diet:
  o High price of gluten-free products compared to the very low rural income
  o Grains (bread, meal, etc.) is the staple food in the country especially in poor areas
  o Parents have a low belief in the need of the diet (high level of illiteracy)

• Prospects:
  o Increase the awareness of CD by dissemination of information among pediatricians and general physicians through scientific meetings
  o Contribute to the spread of serological tests on the finger in front of symptoms reminiscent of CD
  o Group the seropositive patients in remote areas for a local endoscopy
  o Create an association to support patients and their parents
  o Consider a policy to encourage manufacturers to make gluten-free products locally adapted

HELPING CELIACS: progress in the development of National Celiac Societies
T. Koltai

Dr. Koltai underlined that the under diagnosis of Coeliac disease is worldwide a reality and a future public health problem. It is estimated that 1-2% of the total population is affected by CD but in the best of cases only 1 in 8 cases are diagnosed and in majority of cases this ratio drops to 1 in 15. While the diverse and sometimes mild symptoms are partly the reason for this low rate of awareness, the lack of awareness amongst the general public and medical professionals plays a major role. Once over the hurdle of diagnosis, the newly diagnosed celiac and his family faces another major hurdle, that of coping with the fact that CD is a lifelong disorder, and the only treatment is strict and lifelong gluten-free diet. While proper information and ease of supply of gluten free food is readily available in developed countries, the picture is very different in developing countries. Coeliacs in developing countries have difficulty in finding readily available GF food and when this is available the prices are usually relatively too high to be affordable. Globalization is changing local eating habits and traditions and introducing new foods that are increasingly based on gluten containing cereals.

She showed that another major problem faced by this population, is the lack of proper diagnostic and treating facilities within the national health service of these developing. In this regard the Mediterranean shows a sharp contrast with certain countries having a well organized health care system, freely available well controlled GF food and organized patient groups while in other countries this is still very embryonic if existing at all: MEDICEL, with the full cooperation of AOECS, would be an ideal platform to assist the formation and strengthening of celiac societies within these areas, help in the formulation of awareness campaigns as well as in the dissemination of information in the local language. Such a network should also act as a catalyst in the organisation of workshops, conferences and meetings including scientific conferences and training sessions directed towards tackling the problems of CD in these countries.

Patient First
a. First report on cultural attitudes to the gluten-free diet
L. Astarita, Italy, A. Kansu, Turkey

Dr. Astarita explained details of “MEDIGLU project”:
1. The idea of MEDIGLU is to develop video, podcast and web material about ‘Happy living far from gluten in the Mediterranean Area.
2. The goal of MEDIGLU is to educate (both MD and patients) that a “natural” gluten-free diet is possible.
3. Technologies (app for smart phones, internet, video) should be the way to reach our goal.
With this aim, in the month of August two young reporters did a trip around the Mediterranean Area to gather a fresh picture about traditional gluten free foods in each country, meet the local celiac society and experts, report about the ways of advising about the gluten free diet.

He showed pictures of typical GF food from Slovenia, Croatia, Bosnia, Montenegro, Albania, Greece, Turkey and Israel.

Dr. Kansu showed the dietary habits and gave some information about CD in Turkey. The estimated childhood CD is 100,000-200,000. The awareness about CD among doctors and among people and availability of testing is increasing. CD patients receive ~ 25€/month as support for the diet (cost of the flour: 10€/kg).

Turkish cuisine is extremely diverse and includes a complex mixture of spices, and recipes from northern, southern, eastern and western communities.

In Turkey, nutrition is largely wheat-based. Wheat accounts for 60% of the daily caloric intake of a typical Turkish.

They have various types of vegetable meals: soups, main dish (vegetable meal with chopped meat), cold dish (vegetable meal with olive oil), musakka, fried vegetables. Meat and fish are not eaten very much frequently. Turkey is one of the richest countries in the world in terms of fruit production.

Problems about gluten free diet in Turkey:
- Turkish cuisine is wheat based.
- Wheat is very commonly used in many soups and dishes.
- Gluten free products are mainly imported products, and they are expensive.
- Only gluten-free flour is produced in Turkey, other products are not produced.
- There are problems about food labeling.
- There are no restaurants or cafes serving for Celiac patients.
- No arrangements at school for lunch.
- Social life of Celiac patients is a big problem in Turkey.
- Celiac societies are working hard but they have limited financial sources.

b. Gluten free diet in the Arabic countries:

- M. Ben Hariz, Tunisia

Dr. Ben Hariz described problems with GFD in Tunisia.

The main problems are:
1. Availability: GF-products are available in major big cities but insufficient in small towns and villages. Distance or internet purchasing and shipping of goods by mail are not yet well developed. It is non-existent for GF-products.
2. High cost: imported products have the same price as in Europe. Local products (of lower quality) are sold at about half the price of imported products. The average annually salary in Tunisia is about 2500 euro (48500 in Swiss, 28000 in France, 13500 in Malta, 1600 in Bulgaria).
3. Support: There is no systematic support of all patients by the social security organization of Tunisia.

The state has made available to the Tunisian Association of celiac disease an annual budget (around 100,000 euro) for helping poorest families.

He also described the new Tunisian Association of CD: the association organizes in several regions of Tunisia practical training workshops. In these workshops theoretical training is provided by experts in nutrition and recipe applications are made using local and cheapest products. Its aim is to inform patients, their parents and the public to a better understanding of the problems with celiac disease and gluten-free diet and to promote disease detection.
Dr. Hartman reported that the purchase of GF-products in Israel became effortless mainly due to internet development. In Israel celiacs can now order GFP using phone, fax mail or online orders and get their products delivered to the door in a couple of days. The largest gluten-free website distributor in Israel, www.glutenfree.co.il, have also gluten-free shops where the products can be examined directly. The large food chains have also healthy and gluten-free sections, but only for pre-packed products. Small gluten-free distributors have also gluten free representatives and offer freshly backed products that can be purchased on site or ordered.

She says that the Israeli celiac association, founded in 1996, has extensive information on gluten free distributors, places to eat and tips for local and foreign travellers. The site also has information and updates on celiac disease, gluten-free recipes, gluten-free drugs and cosmetics, personal stories and links to relevant sites. GFP are labelled so and the products that contain gluten must be declared on the label, however there is no legal obligation to write anything about cross contamination. In addition there is no official gluten-free logo, so you cannot rely on such a logo.

There are no “local” GFP but during the Passover week, a lot of the Passover kosher products (cakes, waffles, chocolate and other sweets) are gluten-free and at affordable prices. Since GFP are not subsidised in Israel, the prices of, even basic products like bread, roles or pasta, are at least 2-3 times the prices of regular products. The only subsidised GFP in Israel is the “gluten-free flour”.

- M. Basir, Palestine:

Dr. Basir showed the CD situations in Palestine:

**Epidemiology:**

High frequencies of CD is due to the wide consumption of wheat and barley.

Few cases are recognized, because of the low awareness and know – how to deal with the problem and a mass screening for the disease should be done in high risk population.

**Main clinical manifestations:** Short stature, chronic diarrhoea, malabsorption, abdominal discomfort.

**Health care system:**

She reported a good improvement in their health care system during the presence of Palestinian authority and Ministry of Health in a continuous effort to get better health care.

But the opportunity and the facilities to improve their health care need a lot of economical.

**Diet:**

NO food stores with GFD (Poor labelling of GF products) are available therefore Palestinian CD patient get their food from Israel when they can get there.

**Prospects:**

She really appreciate that Palestine was involved in MEDICEL project in order to continue to work together for a better study diagnosis and treatment and to improve the health care of CD in Palestinian children.

The near future, applications and activities

G. Magazzù and L. Greco

Prof. Magazzù discussed about some limitations about the retrospective study and the applicability of the SAGE score.

He underlined that in our study there are 102 cases with a histology T0-T2, which have potential celiac disease.

These, in fact, would be diagnosed celiacs despite not having any degree of villous atrophy. Then he underlined that out of 370 of 661 CD patients with a sage score ≥4 without considering biopsy there are 40 cases with mild Marsh stage (T0-T2) where the CD diagnosis should be queried.

In addition, 83 with a score lower than 4 - but 59 of which will be achieved if certain HLA - could have a histological grade T2 would realize would be awarded 1 point and another point if it was determined the HLA. These could be diagnosed celiac symptoms by adding only 2 points. In
practice we would diagnose celiac disease by assigning 2 points to symptoms of malabsorption + 1 + 1 for HLA M2 for a degree (or T2) of Marsh, even though the serology was negative or not determined. This is particularly relevant in a setting where the infection may play an important role.

Then he considered the meaning of “10xN” of TGase level. According to our study, there are 40 patients with a M0-M” histology that have a 10xN TGase level. Also in these patients the diagnosis of CD should be questioned. Considering all the patients, with a cut off of 10xN TGase level the Sensitivity is 58%, Specificity 55% LR (Likelihood Ratio) + 1.28 and LR- 0.77.

He revised the literature and showed us that in several studies the cut off for TGase level is 100 AU, not 10xN. Considering 100 AU as cut off, in our study there is not a single patient who have a M0-M2 histology with a TGase level more than 100 AU!

In conclusion he underlined that:

- We need to validate SAGE score before applying it in different settings, assigning a different weight to the four items
- Serology needs revision and standardization
- The positive predictive value of serology and HLA-typing combination should be defined
- Potential celiac disease is not negligible and should be taken into account revising the celiac disease diagnostic protocol.