# 2. THE ROLE AND IMPORTANCE OF SCREENING TESTS IN GASTROINTESTINAL DISEASES

Petr Kocna

## 2.1 INTRODUCTION

This paper 'has been prepared as proceeding for the 12th EFLM Continuous Postgraduate Course on Gastrointestinal Diseases. We summarize the general overview about screening, their benefits and rules (1-3) and main aspects for laboratory methods (Table 2.1) used as screening tests in gastrointestinal diseases, published in last years, as well as our experiences in the Czech Republic.

**Table 2.1** Recommended laboratory methods for screening in gastroenterology.

| **Gastrointestinal disease** | **Recommended screening test** |
|---|---|
| **Worldwide used screening** | |
| Colorectal cancer | quantitative immunochemical Hb in stool |
| Celiac disease | IgG, tTGA and IgG DGP plasma antibodies |
| **Evaluated new screening** | |
| Chronic atrophic gastritis<br>Helicobacter pylori infection | plasma pepsinogen I/II ratio<br>Helicobacter pylori antigen in stool |
| Inflammatory bowel disease | calprotectin in stool |

Legend: Hb - haemoglobin; IgG - imunoglobulin class G; tTGA - imunoglobulin A antibodies to tissue transglutaminase; IgG DGP - imunoglobulin G antibodies to deamidated gliadin peptide.

## 2.2 COLORECTAL CANCER

Colorectal cancer (CRCA) is the second most frequent malignant disease in Europe. Every year, 412 000 people are diagnosed with this condition, and 207 000 patients die of it (4) and estimated to cause 49 920 deaths in the U.S. in 2009 (5).

The pathogenesis of CRCA ordinarily occurs in a staged progression from normal mucosa, to adenoma, and finally carcinoma over a period of approximately 7–10 years (6). This sequenced progression over time provides an excellent opportunity for the utilization of screening tests for early detection of CRCA, with the goal of reducing cancer deaths by removal of pre-malignant adenomas and early localized cancer prior to onset of more advanced stages, and CRCA screening reduces mortality from colorectal cancer.

The introduction of national population-wide screening programs is a priority for the healthcare policy of individual states, and this is also being addressed at the highest level by European Union (EU) administrators. A screening program of one sort or another has been implemented in 19 of 27 European countries. The most frequently applied method is testing stool for occult bleeding (faecal occult blood test, FOBT). In the Czech Republic we started

CRCA screening programs in 1994 (7), and population-based, national screening with FOBT was started in 2002. The involvement of GPs has been found to improve patient compliance with bowel cancer screening (8).

The first level of FOBTs were guaiac based, gFOBT methods., which is still used in many countries as traditional methods of screening with high significance of Evidence-based-medicine, and recommended as one of many faecal screening methods by American College of Physicians (9). 20-years experiences with gFOBT were published recently in the UK (10). Guaiac methods are not specific for human haemoglobin. The gFOBT test is based on the oxidation of guaiac impregnated on the card) by hydrogen peroxide catalyzed by the peroxidase activity of haemoglobin. This oxidative reaction could as well occur with any peroxidase found in faeces (eg. plant peroxidases) or by certain chemicals (eg. vitamin C). The sensitivity of gFOBT for colorectal cancer is lower then 30% and these methods of FOBT will be changed in most of countries to immunological FIT.

The second level of FOBTs were immunochemical based, iFOBT (FIT) methods uses an antibody against human globin - the protein part of haemoglobin. The iFOBT are specific for human, haemoglobin, and are more sensitive than the gFOBT methods (11). Immunochemical-qualitative methods have very different accuracy and sensitivity in range 29-72% (12), use different sampling devices and different stability of haemoglobin extract in sampling buffer. Additional biochemical markers, haptoglobin and transferrin are used as a second detected analyte in these qualitative iFOBT tests, to increase screening accuracy (13,14).

The third level of FOBTs is now quantitative methods of faecal haemoglobin determination with automated analysers - qiFOBT. These modern methods increase accuracy to 90 - 95%, enabling setting to country-specific optimal cut-off and most important to be controlled by the External Quality Assurance Services (EQAS) programs. The European Group on Tumour Markers recommends use of a quantitative iFOBT with an adjustable cut-off point to all new centres undertaking FOBT for colorectal neoplasia (15), and organized faecal immunochemical test screening has been associated with an increase in annually detected CRC (16).

Three available analytical systems for quantitative FOBT test (Magstream HT, OC-Sensor/DIANA, FOB Gold/SENTiFOB) were compared for their accuracy, analytical sensitivity, and sample stability as well for sample mailing by tested subjects (17-20). Quantitative FOBT has found to be superior in compliance and colorectal cancer detection, compared with guaiac FOBTs as well with flexible sigmoidoscopy (21).

Diagnostic yield improves with collection of 2 samples of qiFOBT (22,23), increasing as well screening cost. Cost-effectiveness analysis of quantitative immunochemical test for colorectal cancer screening has been in high details described by Dutch working groups (24,25) publishing recently the optimal cut-off for qiFOBT to be 50 ug Hb/g. The pilot study with OC-Sensor qiFOBT recommends 50ng Hb/ml as optimal cut-off value for the screening in the Czech Republic (26).

Fecal immunochemical test results may be expressed as the haemoglobin concentration in the sampling device buffer and, sometimes, albeit rarely, as the haemoglobin concentration per mass of faeces. The current lack of consistency in units for reporting haemoglobin concentration is particularly problematic because apparently similar haemoglobin concentrations obtained with different devices can lead to very different clinical interpretations suggesting a proposal to standardize reporting units for qiFOBT (27,28).

Stool-based DNA testing for colorectal cancer is becoming a favored alternative to existing DNA screening tests. The basis for sDNA screening is the identification of genetic alterations in the initiation of a sequenced progression from adenoma to carcinoma, such as mutations in APC, K-ras, DCC, and p53 (29-32). Proteomics in combination with other techniques is rapidly being developed and there could be such a promising route for the diagnosis of early colorectal cancers (33). Hypermethylation of the plasma septin-9 gene shows promise as a nonstool-based screening tool (34,35). Blood-based biomarkers do not seem to be an alternative to FOBT-based CRC screening, but could be used in combination with iFOBT to increase colorectal screening accuracy (36-38). Tumour pyruvate kinase M2 (tumour M2-PK) is a key enzyme in the altered metabolism of tumor tissue. In cancer, it is known to be present in high concentrations in malignant tissue, plasma and other body fluids (39,40). Plasma and faecal levels of M2-PK could be used as other tumour markers better as prognostic marker, and it's not recommended for screening, its diagnostic efficiency was similar to that of gFOBT (41).

## 2.3 CELIAC DISEASE

Celiac disease (CD) is a common chronic small-bowel disorder of autoimmune origin occurring in both children and adults, and is one of the most commonly underdiagnosed diseases in general practice with incidence 1:100. This disease is genetically determined, has a strong HLA association with DQ2 (DQA1*0501/DQB1*02), and gliadin peptides derived from wheat gluten were identified as precipitating factors (42,43).

Screening strategies and diagnostic algorithms for the detection of CD, especially concerning serological markers, are included in research priorities of European Working Group on Serological Screening for Celiac Disease. The specificity and sensitivity of serological markers were reported in numerous studies for individual antibodies, ranging from 31% to 100%, and there no one marker could be neither 100% specific or 100% sensitive, and that a combination are able to detect all 100% celiac cases (44-7). The diagnostic accuracy of serology for CD has progressively increased in the last few years. IgA antibodies to tissue transglutaminase (tTGA) have been suggested as the first level test owing to their high sensitivity but accuracy could be confirmed by IgA endomysium antibodies (EmA), IgG tTGA should be performed in cases with a concomitant IgA deficiency, and IgA AGA is indicated for children under 2 year of age. A new antibody strategy designed for CD screening is therefore based on the combination of IgA tTG and IgG DGP (48). The new definition of celiac disease as well new ESPGHAN (European Society of Paediatric Gastroenterology, Hepatology and Nutrition) guidelines modifies the screening rules. TG2A levels exceeding 10 times the cut-off and confirmed in an independent blood sample by EmA testing are the first requirement for a celiac diagnosis without duodenal biopsy in symptomatic children (49,50).

Celiac disease has a prevalence of nearly 1% in the US and Europe, diagnosed cases of celiac disease only has a prevalence of about 0.27% or even less. The risk of celiac disease in various autoimmune diseases is approximately 5% - 10% (51,52). There is increased risk of complications in untreated celiac disease patients, which include malignancy and severe malabsorption. The early diagnosis of celiac disease and subsequent adherence to a gluten-free diet may prevent the development of other autoimmune diseases and decreases risk of mortality.

Mass screening for celiac disease (CD) as a public health intervention is controversial (53). The main argument against screening is adherence to the gluten-free diet, which might be low

in screen-detected patients, even in symptomatic patients (46). In contrast to the general population, screening in high-prevalence groups may prove to have a favorable cost–benefit ratio. The guidelines for targeted screening for celiac disease in the Czech Republic has been defined in the Bulletin of the Ministry of Health of Czech Republic in February 2011 indicating this high-prevalence subjects (Table 2.2). Recently new way in celiac screening started in 2011 in Italian primary schoolchildren with salivary anti-transglutaminase autoantibodies (54).

**Table 2.2** Celiac disease associated disease, syndromes and signs indicating screening.

| Associated symptoms and signs | Associated diseases and syndromes |
|---|---|
| Dermatitis herpetiformis | Type 1 diabetes |
| Osteoporosis, unexplained fractures | Autoimmune thyroiditis |
| Chronic diarrhoea with abdominal distension | Autoimmune liver disease |
| Anemia | Systemic lupus erythematosus |
| Chronic fatigue syndrome | Primary biliary cirrhosis |
| Polyneuropathy | Primary sclerosing cholangitis |
| Cerebellar ataxia, epilepsy | Sjögren syndrome |
| Spontaneous abortion and fetal growth retardation | Alopecia areata |
| Growth retardation, pubertal delay | IgA nephropathy |
| Involuntary weight loss | IgA deficiency |
| Unexplained anaemia (iron, folic acid) | |
| Dental enamel hypoplasia | |
| Recurrent aphthous stomatitis | |
| Hypertransaminasemia | |

## 2.4 CHRONIC ATROPHIC GASTRITIS

Chronic atrophic gastritis (CAG) is an inflammatory condition characterized by the loss of gastric glandular structures, which are replaced by connective tissue (non-metaplastic atrophy) or by glandular structures inappropriate for location (metaplastic atrophy). Diagnosis and screening of CAG with stomach-specific plasma biomarkers could help as well with prevention of gastric carcinoma. Invasive gastric carcinoma are preceded by a cascade of precancerous lesions, multifocal atrophic gastritis (MAG) and intestinal metaplasia. It is accepted that a multistep process initiating from Helicobacter pylori-related chronic inflammation of the gastric mucosa progresses to CAG, intestinal metaplasia, dysplasia and, finally, leads to the development of gastric cancer (55,56). The diagnosis of Helicobacter pylori infection are now simple, easy with high sensitivity and specificity 92-98%, using both UBT (Urea Breath Test) and stool antigen tests (57,58).

Parallel assays of PGI, of the PGI/II ratio, and of amidated gastrin-17 comprise an exact and validated set or panel of biomarkers that reflect the degree of mucosal inflammation, the extent and grade of atrophic gastritis in the stomach, and the capacity of the existing mucosa to secrete acid and gastrin-17 (59,60). The sensitivity and specificity of these biomarker test panel (commercial test panel (GastroPanel, Finland) were 71-83% and 95-98%, respectively (61). High prevalence, more then 3%, of advanced atrophic corpus gastritis (ACG) among Finnish adult volunteers without specific complaints was diagnosed last year (62).

## 2.5 INFLAMMATORY BOWEL DISEASE

Differentiating patients with inflammatory bowel disease (IBD) from patients without intestinal pathology, in particular those with irritable bowel syndrome (IBS), poses a diagnostic challenge. Current guidelines suggest performing invasive endoscopy with histological sampling for further diagnosis. There is, consequently, a need for a reliable, non-invasive, simple, and cheap test that could provide objective evidence of whether the underlying disease is organic or functional. Measuring calprotectin, a neutrophilic protein, in faeces has been proposed as a surrogate marker of intestinal inflammation. Calprotectin values have been shown to reliably differentiate between IBD and non-organic disease in symptomatic patients and, when elevated, warrant early endoscopic investigation to rule out IBD and other organic pathologies (63-5). On the other hand, the use of faecal calprotectin as a screening test substantially could reduce the number of invasive measurements necessary in the diagnostic work-up of patients with suspected IBD (63), in adults, using faecal calprotectin as a screening test in suspected IBD to decide upon the need for endoscopy would result in a 67% reduction of patients requiring endoscopy (66). Calprotectin, lactoferrin, M2-pyruvate kinase, and other faecal markers could help us in differential diagnostics as well in screening of large bowel disease, colorectal cancer and IBD.

**LITERATURE:**


1. Holland WW, Stewart S, Masseria C. Screening in Europe-Policy Brief. European Observatory on Health Systems and Policies, WHO European Centre for Health Policy 2006;1–72.
2. Thorner RM, Remein QR. Principles and Procedures in the Evaluation of Screening for Disease. Public Health Monograph 67, Washington, Public Health Service.1961.
3. Wilson JMG, Jungner G. Principles and Practice of Screening for Disease. Geneva, World Health Organization 1968. Available from: http://www.who.int/bulletin/volumes/86/4/07-050112bp.pdf, Accessed on 20th October 2012.
4. Zavoral M, Suchanek S, Zavada F, Dusek L, Muzik J, Seifert B et al. Colorectal cancer screening in Europe. World J Gastroenterol 2009;15(47):5907-15.
5. Miller S, Steele S. Novel Molecular Screening Approaches in Colorectal Cancer. Journal of Surgical Oncology 2012;105:459-67.
6. Wong JL, Hawkins NJ, Ward RL. Colorectal cancer: A model for epigenetic tumorigenesis. Gut 2007;56:140-8.
7. Fric P, Zavoral M, Dvorakova H, Zoubek V, Roth Z. An adapted program of colorectal cancer screening - 7 years experience and cost-benefit analysis. Hepato-gastroenterology 1994;41:413-16.
8. Damery S, Smith S, Clements A, Holder R, Nichols L, Draper H et al. Evaluating the effectiveness of GP endorsement on increasing participation in the NHS Bowel Cancer Screening Programme in England: study protocol for a randomized controlled trial. Trials 2012;13:18. Available at: http://www.trialsjournal.com/content/13/1/18, Accessed on 20th October 2012.
9. Qaseem A, Denberg TD, Hopkins RH, Humphrey LL, Levine J, Sweet DE et al. Screening for colorectal cancer: a guidance statement from the American College of Physicians. Ann Intern Med 2012;156(5):378-86.
10. Scholefield JH, Moss SM, Mangham CM, Whynes DK, Hardcastle JD. Nottingham trial of faecal occult blood testing for colorectal cancer: a 20-year follow-up. Gut 2012;61(7):1036-40.

11. Rabeneck L, Rumble RB, Thompson F, Mills M, Oleschuk C, Whibley A et al. Fecal immunochemical tests compared with guaiac fecal occult blood tests for population-based colorectal cancer screening. Can J Gastroenterol 2012;26(3):131-47.
12. Brenner H, Haug U, Hundt S. Inter-test agreement and quantitative cross-validation of immunochromatographical fecal occult blood tests. Int J Cancer 2010;127(7):1643-9.
13. Sheng JQ, Li SR, Wu ZT, Xia CH, Wu X, Chen J et al. Transferrin dipstick as a potential novel test for colon cancer screening: a comparative study with immuno fecal occult blood test. Cancer Epidemiol Biomarkers Prev 2009;18(8):2182-5.
14. Chalkias A, Nikotian G, Koutsovasilis A, Bramis J, Manouras A, Mystrioti D et al. Patients with colorectal cancer are characterized by increased concentration of fecal hb-hp complex, myeloperoxidase, and secretory IgA. Am J Clin Oncol 2011;34(6):561-6.
15. Duffy MJ, van Rossum LG, van Turenhout ST, Malminiemi O, Sturgeon C, Lamerz R et al. Use of faecal markers in screening for colorectal neoplasia: a European group on tumor markers position paper. Int J Cancer 2011;128(1):3-11.
16. Levin TR, Jamieson L, Burley DA, Reyes J, Oehrli M, Caldwell C. Organized colorectal cancer screening in integrated health care systems. Epidemiol Rev 2011;33(1):101-10.
17. Park DI, Ryu S, Kim YH, Lee SH, Lee CK, Eun CS et al. Comparison of guaiac-based and quantitative immunochemical fecal occult blood testing in a population at average risk undergoing colorectal cancer screening. Am J Gastroenterol 2010;105(9):2017-25.
18. Guittet L, Guillaume E, Levillain R, Beley P, Tichet J, Lantieri O et al. Analytical comparison of three quantitative immunochemical fecal occult blood tests for colorectal cancer screening. Cancer Epidemiol Biomarkers Prev 2011;20(7):1492-501.
19. Omata F, Shintani A, Isozaki M, Masuda K, Fujita Y, Fukui T. Diagnostic performance of quantitative fecal immunochemical test and multivariate prediction model for colorectal neoplasms in asymptomatic individuals. Eur J Gastroenterol Hepatol 2011;23(11):1036-41.
20. Park MJ, Choi KS, Lee YK, Jun JK, Lee HY. A comparison of qualitative and quantitative fecal immunochemical tests in the Korean national colorectal cancer screening program. Scand J Gastroenterol 2012;47(4):461-6.
21. Hol L, van Leerdam ME, van Ballegooijen M, van Vuuren AJ, van Dekken H, Reijerink JC at al. Screening for colorectal cancer: randomised trial comparing guaiac-based and immunochemical faecal occult blood testing and flexible sigmoidoscopy. Gut 2010;59(1):62-8.
22. van Roon AH, Wilschut JA, Hol L, van Ballegooijen M, Reijerink JC, Mannetje H et al. Diagnostic yield improves with collection of 2 samples in fecal immunochemical test screening without affecting attendance. Clin Gastroenterol Hepatol 2011;9(4):333-9.
23. Goede SL, van Roon AH, Reijerink JC, van Vuuren AJ, Lansdorp-Vogelaar I, Habbema JD et al. Cost-effectiveness of one versus two sample faecal immunochemical testing for colorectal cancer screening. Gut 2012; doi:10.1136/gutjnl-2011-301917, Available at: http://gut.bmj.com/content/early/2012/04/04/gutjnl-2011-301917.long, Accessed on 20th October 2012.
24. Wilschut JA, Hol L, Dekker E, Jansen JB, Van Leerdam ME, Lansdorp-Vogelaar I et al. Cost-effectiveness analysis of a quantitative immunochemical test for colorectal cancer screening. Gastroenterology 2011;141(5):1648-55.
25. van Rossum LG, van Rijn AF, Verbeek AL, van Oijen MG, Laheij RJ, Fockens P et al. Colorectal cancer screening comparing no screening, immunochemical and guaiac fecal occult blood tests: a cost-effectiveness analysis. Int J Cancer 2011;128(8):1908-17.
26. Kovarova JT, Zavoral M, Zima T, Zak A, Kocna P, Kohout P at al. Improvements in colorectal cancer screening programmes – quantitative immunochemical faecal occult blood testing – how to set the cut-off for a particular population. Biomed Papers 2012; 156(2):143-50.
27. Fraser CG, Allison JE, Halloran SP, Young GP. A Proposal to Standardize Reporting Units for Fecal Immunochemical Tests for Hemoglobin. J Natl Cancer Inst 2012; 104 (11):810-4.
28. Allison JE, Fraser CG, Halloran SP, Young GP. Comparing fecal immunochemical tests: improved standardization is needed. Gastroenterology 2012;142(3):422-4.

29. Zauber AG, Levin TR, Jaffe CC, Galen BA, Ransohoff DF, Brown ML. Implications of new colorectal cancer screening technologies for primary care practice. Med Care 2008;46:138–46.
30. Li BS, Wang XY, Xu AG, Ma FL, Ma QY, Li Z et al. High-Resolution Melting Assay (HRMA) is a Simple and Sensitive Stool-Based DNA Test for the Detection of Mutations in Colorectal Neoplasms. Clin Colorectal Cancer 2012; Available at: http://dx.doi.org/10.1016/j.clcc.2012.04.001, Accessed on 20th October 2012.
31. Ahlquist DA, Zou H, Domanico M, Mahoney DW, Yab TC, Taylor WR et al. Next-generation stool DNA test accurately detects colorectal cancer and large adenomas. Gastroenterology 2012;142(2):248-56.
32. Miller S, Steele S. Novel molecular screening approaches in colorectal cancer. J Surg Oncol. 2012;105(5):459-67.
33. Jin X, Lin M, Zhang H, Han Y, He Y, Zhang Q et al. Serum biomarkers of colorectal cancer with AU and NP20 chips including a diagnosis model. Hepatogastroenterology 2012;59(113):124-9.
34. Warren JD, Xiong W, Bunker AM, Vaughn CP, Furtado LV, Roberts WL et al. Septin 9 methylated DNA is a sensitive and specific blood test for colorectal cancer. BMC Med 2011;9:133.
35. Ahlquist DA, Taylor WR, Mahoney DW, Zou H, Domanico M, Thibodeau SN et al. The stool DNA test is more accurate than the plasma septin 9 test in detecting colorectal neoplasia. Clin Gastroenterol Hepatol 2012;10(3):272-77.
36. Tao S, Haug U, Kuhn K, Brenner H. Comparison and combination of blood-based inflammatory markers with faecal occult blood tests for non-invasive colorectal cancer screening. Br J Cancer 2012;106(8):1424-30.
37. Newton KF, Newman W, Hill J. Review of biomarkers in colorectal cancer. Colorectal Dis 2012;14(1):3-17.
38. Lumachi F, Marino F, Orlando R, Chiara GB, Basso SM. Simultaneous multianalyte immunoassay measurement of five serum tumor markers in the detection of colorectal cancer. Anticancer Res 2012;32(3):985-8.
39. Pox C. Colon cancer screening: which non-invasive filter tests? Dig Dis 2011;29 (Supp1):56-9.
40. Fatela-Cantillo D, Fernandez-Suarez A, Moreno MA, Gutierrez JJ, Iglesias JM. Prognostic value of plasmatic tumor M2 pyruvate kinase and carcinoembryonic antigen in the survival of colorectal cancer patients. Tumour Biol 2012;33(3):825-32.
41. Li R, Liu J, Xue H, Huang G. Diagnostic value of fecal tumor M2-pyruvate kinase for CRC screening: A systematic review and meta-analysis. Int J Cancer. 2012; 131(8):1837-45.
42. Mubarak A, Houwen RH, Wolters VM. Celiac disease: an overview from pathophysiology to treatment. Minerva Pediatr 2012;64(3):271-87.
43. Kocna P, Vaníčková Z, Perušičová J, Dvořák M. Tissue Transglutaminase-Serology Markers for Coeliac Disease. Clin Chem Lab Med 2002; 40(5):485-92.
44. Volta U, Fabbri A, Parisi C, Piscaglia M, Caio G, Tovoli F et al. Old and new serological tests for celiac disease screening. Expert Rev Gastroenterol Hepatol 2010;4(1):31-35.
45. Giersiepen K, Lelgemann M, Stuhldreher N, Ronfani L, Husby S, Koletzko S et al. ESPGHAN Working Group on Coeliac Disease Diagnosis. Accuracy of diagnostic antibody tests for coeliac disease in children: summary of an evidence report. J Pediatr Gastroenterol Nutr 2012;54(2):229-41.
46. Lewis NR, Scott BB. Meta-analysis: deamidated gliadin peptide antibody and tissue transglutaminase antibody compared as screening tests for coeliac disease. Aliment Pharmacol Ther 2010;31(1):73-81.
47. Aggarwal S, Lebwohl B, Green PH. Screening for celiac disease in average-risk and high-risk populations. Therap Adv Gastroenterol 2012;5(1):37-47.
48. Volta U, Fabbri A, Parisi C, Piscaglia M, Caio G, Tovoli F et al. Old and new serological tests for celiac disease screening. Expert Rev Gastroenterol Hepatol 2010;4(1):31-5.
49. Husby S, Koletzko S, Korponay-Szabó IR, Mearin ML, Phillips A, Shamir R at al. European Society for Pediatric Gastroenterology, Hepatology, and Nutrition guidelines for the diagnosis of coeliac disease. J Pediatr Gastroenterol Nutr 2012;54(1):136-60.

50. Kneepkens CM, von Blomberg BM. Clinical practice: Coeliac disease. Eur J Pediatr 2012; 171(7):1011–21.
51. Jiskra J, Límanová Z, Vaníčková Z, Kocna P. IgA and IgG Antigliadin, IgA Anti-tissue Transglutaminase and Antiendomysial Antibodies in Patients with Autoimmune Thyroid Diseases and Their Relationship to Thyroidal Replacement Therapy. Physiol Res 2003;52:79-88.
52. Vančíková Z, Chlumecký V, Sokol D, Horáková D, Hamšíková E, Fučíková T et al. The Serologic Screening for Celiac Disease in the General Population (Blood Donors) and in Some High-Risk Groups of Adults (Patients with Autoimmune Diseases, Osteoporosis and Infertility) in the Czech Republic. Folia Microbiol 2002;47(6):753-8.
53. Rosén A, Emmelin M, Carlsson A, Hammarroth S, Karlsson E, Ivarsson A. Mass screening for celiac disease from the perspective of newly diagnosed adolescents and their parents: a mixed-method study. BMC Public Health 2011;11:822. Available at: http://www.biomedcentral.com/1471-2458/11/822, Accessed on 20th October 2012.
54. Bonamico M, Nenna R, Montuori M, Luparia RP, Turchetti A, Mennini M at al. First salivary screening of celiac disease by detection of anti-transglutaminase autoantibody radioimmunoassay in 5000 Italian primary schoolchildren. J Pediatr Gastroenterol Nutr 2011;52(1):17-20.
55. Correa P, Piazuelo MB. The gastric precancerous cascade. J Dig Dis 2012;13(1):2-9.
56. Vannella L, Lahner E, Annibale B. Risk for gastric neoplasias in patients with chronic atrophic gastritis: A critical reappraisal. World J Gastroenterol 2012;18(12):1279-85.
57. Ricci C, Holton J, Vaira D. Diagnosis of Helicobacter pylori: invasive and non-invasive tests. Best Pract Res Clin Gastroenterol 2007;21(2): 299-313.
58. Mégraud F. The most important diagnostic modalities for Helicobacter pylori, now and in the future. Eur J Gastroenterol Hepatol 2012;9 (Suppl 1): S13-5.
59. Agréus L, Kuipers EJ, Kupcinskas L, Malfertheiner P, Di Mario F, Leja M et al. Rationale in diagnosis and screening of atrophic gastritis with stomach-specific plasma biomarkers. Scand J Gastroenterol 2012;47(2):136-47.
60. Leja M, Kupcinskas L, Funka K, Sudraba A, Jonaitis L, Ivanauskas A et al. The validity of a biomarker method for indirect detection of gastric mucosal atrophy versus standard histopathology. Dig Dis Sci 2009;54(11):2377-84.
61. Väänänen H, Vauhkonen M, Helske T, Kääriäinen I, Rasmussen M, Tunturi-Hihnala H et al. Non-endoscopic diagnosis of atrophic gastritis with a blood test. Correlation between gastric histology and serum levels of gastrin-17 and pepsinogen I: a multicentre study. Eur J Gastroenterol Hepatol 2003;15:885-91.
62. Telaranta-Keerie A, Kara R, Paloheimo L, Härkönen M, Sipponen P. Prevalence of undiagnosed advanced atrophic corpus gastritis in Finland: an observational study among 4,256 volunteers without specific complaints. Scand J Gastroenterol 2010;45(9):1036-41.
63. Mindemark M, Larsson A. Ruling out IBD: Estimation of the possible economic effects of pre-endoscopic screening with F-calprotectin. Clin Biochem 2012;45(7-8):552-5.
64. Burri E, Beglinger C. Faecal calprotectin - a useful tool in the management of inflammatory bowel disease. Swiss Med Wkly 2012;142:w13557.
65. van Rheenen PF, Van de Vijver E, Fidler V. Faecal calprotectin for screening of patients with suspected inflammatory bowel disease: diagnostic meta-analysis. BMJ 2010;341:c3369.
66. Burri E, Beglinger C. Faecal calprotectin in the diagnosis of inflammatory bowel disease. Biochem Med 2011;21(3):245-25.