The role and importance of screening tests in gastrointestinal diseases

Kocna P., Vaníčková Z., Zima T.
DISEASE SCREENING
COLORECTAL CANCER
COELIAC DISEASE
ATROPHIC GASTRITIS
INFLAMMATORY BOWEL DISEASE
DISEASE SCREENING
COLORECTAL CANCER
COELIAC DISEASE
ATROPHIC GASTRITIS
INFLAMMATORY BOWEL DISEASE
### Criteria for disease screening

1. The condition screened for should be an important one

2. There should be an acceptable treatment for patients with the disease

3. The facilities for diagnosis and treatment should be available

4. There should be a recognised latent or early symptomatic stage

5. There should be a suitable test or examination which has few false positives (specificity) and few false negatives (sensitivity)

6. The test or examination should be acceptable to the population

7. The test should be cheap/cost effective

*Screening - Wilson & Jungen (WHO, 1968)*
# Recommended laboratory methods for screening in gastroenterology

<table>
<thead>
<tr>
<th>Gastrointestinal disease</th>
<th>Recommended screening test</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Worldwide used screening</strong></td>
<td></td>
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<tr>
<td>Colorectal cancer</td>
<td>quantitative immunochemical Hb in stool</td>
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<tr>
<td>Coeliac disease</td>
<td>IgA atTG and IgG DGP plasma antibodies</td>
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<tr>
<td><strong>Evaluated new screening</strong></td>
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<tr>
<td>Chronic atrophic gastritis Helicobacter pylori infection</td>
<td>plasma pepsinogen I/II ratio Helicobacter pylori antigen in stool</td>
</tr>
<tr>
<td>Inflammatory bowel disease</td>
<td>calprotectin in stool</td>
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</table>
Numbers of PubMed - Medline articles published in last 5 years with respect of reviews and screening

<table>
<thead>
<tr>
<th>Year</th>
<th>Papers (all)</th>
<th>Review</th>
<th>Screening</th>
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</table>

**Colorectal cancer**
### Numbers of PubMed - Medline articles published in last 5 years with respect of reviews and screening

#### Coeliac disease

<table>
<thead>
<tr>
<th>Year</th>
<th>Papers (all)</th>
<th>Review</th>
<th>Screening</th>
<th>Screening review</th>
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<td>2007</td>
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<td>130</td>
<td>473</td>
<td>90</td>
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<tr>
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</tr>
<tr>
<td>2011</td>
<td>156</td>
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<td>95</td>
<td>15</td>
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<tr>
<td>2010</td>
<td>159</td>
<td>20</td>
<td>107</td>
<td>6</td>
</tr>
<tr>
<td>2009</td>
<td>143</td>
<td>23</td>
<td>99</td>
<td>14</td>
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<td>2008</td>
<td>151</td>
<td>23</td>
<td>111</td>
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</tr>
<tr>
<td>2007</td>
<td>155</td>
<td>36</td>
<td>125</td>
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</tbody>
</table>

Numbers of PubMed - Medline articles published in last 5 years with respect of reviews and screening.
**Inflammatory bowel disease**

<table>
<thead>
<tr>
<th>Year</th>
<th>Papers (all)</th>
<th>Review</th>
<th>Screening</th>
<th>Screening review</th>
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</thead>
<tbody>
<tr>
<td>2011</td>
<td>2032</td>
<td>572</td>
<td>942</td>
<td>237</td>
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<td>2010</td>
<td>1794</td>
<td>458</td>
<td>842</td>
<td>168</td>
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<tr>
<td>2009</td>
<td>1565</td>
<td>484</td>
<td>720</td>
<td>183</td>
</tr>
<tr>
<td>2008</td>
<td>1449</td>
<td>421</td>
<td>666</td>
<td>165</td>
</tr>
<tr>
<td>2007</td>
<td>1349</td>
<td>401</td>
<td>632</td>
<td>157</td>
</tr>
</tbody>
</table>

**total number of papers - 54715**
Reviews on screening of these 4 GE diseases with high risk of tumour development published in last 5 years

["Colorectal cancer" OR "Coeliac disease" OR "Atrophic gastritis" OR "Inflammatory bowel disease"] AND "Screening" AND "Review" AND "Published 2007 - 2011"

<table>
<thead>
<tr>
<th>Disease</th>
<th>NLM - PubMed</th>
<th>Google Scholar</th>
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<tbody>
<tr>
<td>Colorectal cancer</td>
<td>3939</td>
<td>42110</td>
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<tr>
<td>Coeliac disease</td>
<td>485</td>
<td>6850</td>
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<tr>
<td>Atrophic gastritis</td>
<td>82</td>
<td>1853</td>
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<tr>
<td>Inflammatory bowel disease</td>
<td>910</td>
<td>16680</td>
</tr>
</tbody>
</table>

only 6000 journals all on the web 10 times more
DISEASE SCREENING

COLORECTAL CANCER
COELIAC DISEASE
ATROPHIC GASTRITIS
INFLAMMATORY BOWEL DISEASE
Colorectal cancer often has no symptoms at early (and treatable) stages.

The biggest risk factor for colorectal cancer is being age 50 or older.

Colorectal cancer is the second most frequent malignant disease in Europe and US.

If everyone age 50 or older received regular screenings, almost two-thirds (60%) of colorectal cancer deaths could be prevented.

There are different options recommended for colorectal cancer screening: choose one, and get it done.
Proteomics of colorectal cancer: overview of discovery studies and identification of commonly identified cancer-associated proteins and candidate CRC serum markers.

CRC SCREENING METHODS

- FOBT/FIT tests
- Capsule endoscopy
- Screening colonoscopy
- DNA chips
- CRC markers
- Automated analysis
- fecal Hb
- Virtual computer colonoscopy
Quantitative immunochemical - qiFOBT are 3x more reliable to guaiac FOBT

Colorectal Cancer Screening and Diagnosis Guidelines Seminar - April 2011
prof. Stephen Halloran - NHS criticized qualitative FOBTs:
No Automation - Operator Variability - Can’t adjust positivity
| Recommendations for a colorectal cancer screening programme in Ireland | 12/2008 |
| The National Cancer Screening Service Board, Ireland |
| The Board’s recommendation that the immunochemical faecal occult blood test (iFOBt) which operates on an automated testing platform. |

Immunochemical faecal occult blood tests - Evaluation report - November 2009
Centre for Evidence-based Purchasing of the NHS Purchasing and Supply Agency.
The OC-Sensor / DIANA analyser is well designed and is the most suitable system for the English bowel cancer screening programme.

A national colorectal cancer screening programme, November 17, 2009
The Health Council of the Netherlands
The Committee recommends iFOBT-based screening (OC-Sensor, one faecal sample) once every two years for men and women between fifty-five and seventy-five years old.

Faecal occult blood test-based screening programme with high compliance for colonoscopy has a strong clinical impact on colorectal cancer. British Journal of Surgery 2009 May
Parente F. on behalf of the Lecco Colorectal Cancer Screening Group
Immunochemical faecal tests (HM-Jack, Kiowa; Japan) were processed by a single central laboratory using an automated reading technique; the positivity cut-off was 100 ng/ml.

QUANTITATIVE IMMUNOCHEMICAL TESTS - qFIT IN EUROPE
A Quantitative Immunochemical Fecal Occult Blood Test for Colorectal Neoplasia
Ann Intern Med. 2007;146:244-255

<table>
<thead>
<tr>
<th>Comparison of iFOBT and g-FOBT</th>
<th>20 623 SAMPLES</th>
<th>RANDOMIZATION</th>
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</thead>
<tbody>
<tr>
<td>g-FOBT</td>
<td>i-FOBT</td>
<td></td>
</tr>
<tr>
<td>INVIAITION</td>
<td>10 301</td>
<td>10 322</td>
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<tr>
<td>PARTICIPATION</td>
<td>4 836</td>
<td>6 157</td>
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<td>POSITIVE FOB TEST</td>
<td>117</td>
<td>339</td>
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<td>EXAMINATION</td>
<td>103</td>
<td>280</td>
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<td>POLYPS AND CANCER</td>
<td>80</td>
<td>218</td>
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<tr>
<td>ADV.ADENOMAS AND CANCER</td>
<td>57</td>
<td>145</td>
</tr>
<tr>
<td>COLORECTAL CANCER</td>
<td>11</td>
<td>24</td>
</tr>
</tbody>
</table>
WHAT IS CURRENT KNOWLEDGE

✓ The quantitative immunochemical fecal occult blood test (qFIT) has shown better performance characteristics than the standard guaiac-based fecal occult blood test (GT) for detecting advanced colorectal neoplasms (ACRNs) in high-risk population.

✓ This paper confirmed with better evidence the observations of others that qFIT has a higher sensitivity for detecting ACRNs than GT, and has an acceptable specificity that significantly reduces the need for colonoscopic evaluation in the screened population.

Comparison of guaiac-based and quantitative immunochemical fecal occult blood testing in a population at average risk undergoing colorectal cancer screening -
Park DI, Ryu S, Kim YH, Lee SH, Lee CK, Eun CS, Han DS.
Am J Gastroenterol. 2010;105(9): 2017-2025
Colorectal cancer screening in the Czech Republic started 1994, national-screening with gFOBT since 2002, in January 2013 we will change to only FIT.

Colorectal cancer in the young continues to increase, with the most dramatic increase in the 40 to 44 year age group (approximately 67%), need to be re-examined age-based screening for average risk beginning at the age of 40.
Optimization of qFIT cut-off, for indication to colonoscopy:
Indicate as much as possible, all pathology - with 15% healthy subjects?
NOT indicate healthy subjects, but decrease sensitivity about 15%?

2145 subjects > 40 year with colonoscopy
76 x CRC

Higher Fecal Immunochemical Test Cutoff Levels
Terhaar sive Droste JS et al. Cancer Epidemiol Biomarkers Prev. 2011; 20(2)
OPTIMIZATION OF CUT-OFF VALUE FOR qFIT

Value defined by manufacturer (Eiken): **100 ng/ml**

Dutch study - GE specialization: **75 ng/ml**

Cutoff value determines the performance of a semi-quantitative immunochemical faecal occult blood test in a colorectal cancer screening programme.

*van Rossum LG, van Rijn AF et al. Br J Cancer. 2009;101:1274*

Pilot study in the Czech Republic: **75 ng/ml**

*Improvements in colorectal cancer screening programmes – quantitative immunochemical faecal occult blood testing.*


Dutch study - economical: **50 ng/ml**

*Cost-effectiveness analysis of a quantitative immunochemical test for colorectal cancer screening.*

*Wilschut JA, Hol L, Dekker E et al. Gastroenterology. 2011;141:1648*
Optimization of qFIT cut-off, for indication to colonoscopy:
Indicate as much as possible, all pathology - with **15% healthy subjects**?
NOT indicate healthy subjects, but **decrease sensitivity about 15%**?

2145 subjects > 40 year
with colonoscopy
76 x CRC
Faecal pyruvate kinase isoenzyme type M2 for colorectal cancer screening:
A meta-analysis - Tonus C., Sellinger M., Koss K., Neupert G.
World J Gastroenterol 2012 August 14; 18(30): 4004-4011
Septin 9 methylated DNA is a sensitive and specific blood test for colorectal cancer. Warren JD. et al. - BMC Med. 2011, 4; 133.

Sensitivity for early stage (Dukes I and II) - 86.8%
Overall sensitivity - 90% & specificity 88.3%
SCREENING OF COLORECTAL CANCER

Population screening

ONE STEP
Screening colonoscopy

Invasive, high cost
Low compliance

TWO STEPS
Stool - FOBT/FIT

positive FOBT

positive 2nd marker

negative FOBT

negative 2nd marker

When found 2nd marker
specific, sensitive &
cheaper as coloscopy

THREE STEPS
Stool - FOBT/FIT

positive FOBT

negative FOBT

2nd CRC - marker

At this time
most effective way

Colonoscopy

When found 2nd marker
specific, sensitive &
cheaper as coloscopy

Colonoscopy

Invasive, high cost
Low compliance

At this time
most effective way
WHAT COULD BE CHANGED - WHAT COULD BE DISCUSSED:

- There are different options for colorectal cancer screening: choose one, and get it done. No more valid?
- We have to change to only standardized quantitative FIT method
- We have to change any type of screenings to population-screening
- We have to optimize cut-off value according to GE - oncology - and economics
- Is it time to lower the recommended screening age?
- Could other, new, 2nd markers in stool and serum increase screening effectivity?
- May we change CRC screening from one/two step to three?
DISEASE SCREENING
COLORECTAL CANCER
COELIAC DISEASE
ATROPHIC GASTRITIS
INFLAMMATORY BOWEL DISEASE
Coeliac disease is a common disorder affecting 1% of the European population. Coeliac disease is underdiagnosed even in European countries with high knowledge of the variable clinical picture of the disease. The prevalence of coeliac disease varies markedly in different European countries.
ICEBERG HYPOTHESIS OF COELIAC INCIDENCE

CLINICAL CS

TRANSIENT CS

SILENT CS

LATENT CS

POTENTIAL CS

MUCOSAL DEFECT, ASYMPTOMATIC

NORMAL MUSOCA, + MARKERS

HLA DQw2, IEL, γ/δ IEL

INCIDENCE 1:1000

INCIDENCE 1:200

INCIDENCE 1:100

CLINICAL Dg.

ATYPICAL CS

HISTOLOGY Dg.

SEROLOGY Dg.

(NON CS)
Definitive diagnosis of CD

Gluten free diet

HLA typing, biopsy re-evaluation

negative antibodies

Low probability of coeliacs

IgA atTG / IgA EmA and total IgA

Intestinal biopsy

Provisional diagnosis of CD

Gluten free diet

Increased probability of coeliacs

Histologic features of CD

Definitive diagnosis of CD

IgG atTG, IgG EmA or IgG AGA

positive antibodies

IgA deficient

positive antibodies

High clinical suspicion

negative biopsy
New ESPGHAN guidelines for the diagnosis of Coeliac Disease in Children and Adolescents - Steffen Husby, Odense University Hospital, Denmark
Clinical practice - Coeliac disease - Eur J Pediatr. - online March 2012

C. M. Frank Kneepkens & B. Mary E. von Blomberg
INTESTINAL BIOPSY - NEW GRADING SYSTEM

Marsh-Oberhuber system

- Type 1
- Type 2
- Type 3a
- Type 3b
- Type 3c

New grading system

- Grade A
  Non-atrophic
  >25 IELs/100 enterocytes

- Grade B
  Atrophic
  Villous-crypt ratio < 3:1

- Grade B2
  Atrophic
  No detectable villi

Old and new serological tests for celiac disease screening.
### Increased Prevalence of CD in Children with Other Conditions

<table>
<thead>
<tr>
<th>Condition</th>
<th>Prevalence</th>
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<tbody>
<tr>
<td>Type 1 diabetes</td>
<td>2-12 %</td>
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<tr>
<td>Down’s syndrome</td>
<td>5-12 %</td>
</tr>
<tr>
<td>Autoimmune thyroid disease</td>
<td>to 7 %</td>
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<tr>
<td>Turner syndrome</td>
<td>2-5 %</td>
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<tr>
<td>Williams’ syndrome</td>
<td>to 9 %</td>
</tr>
<tr>
<td>IgA deficiency</td>
<td>2-8 %</td>
</tr>
<tr>
<td>Autoimmune liver disease</td>
<td>12-13 %</td>
</tr>
<tr>
<td>First degree relatives with CD</td>
<td>10-20 %</td>
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</table>

New ESPGHAN guidelines for the diagnosis of Coeliac Disease in Children and Adolescents

Steffen Husby - Odense University Hospital, Denmark
<table>
<thead>
<tr>
<th>Associated symptoms and signs</th>
<th>Associated diseases and syndromes</th>
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<tbody>
<tr>
<td>Dermatitis herpetiformis</td>
<td>Type 1 diabetes</td>
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<tr>
<td>Osteoporosis, unexplained fractures</td>
<td>Autoimmune thyroiditis</td>
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<tr>
<td>Chronic diarrhoea with abdominal distension</td>
<td>Autoimmune liver disease</td>
</tr>
<tr>
<td>Anemia</td>
<td>Systemic lupus erythematosus</td>
</tr>
<tr>
<td>Chronic fatigue syndrome</td>
<td>Primary biliary cirrhosis</td>
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<tr>
<td>Polyneuropathy</td>
<td>Primary sclerosing cholangitis</td>
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<tr>
<td>Cerebellar ataxia, epilepsy</td>
<td>Sjögren syndrome</td>
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<tr>
<td>Spont. abortion and fetal growth retardation</td>
<td>Alopecia areata</td>
</tr>
<tr>
<td>Growth retardation, pubertal delay</td>
<td>IgA nephropathy</td>
</tr>
<tr>
<td>Involuntary weight loss</td>
<td>IgA deficiency</td>
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<tr>
<td>Unexplained anaemia (iron, folic acid)</td>
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<tr>
<td>Dental enamel hypoplasia</td>
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<tr>
<td>Recurrent aphthous stomatitis</td>
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<tr>
<td>Hypertransaminasemia</td>
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TARGETED SCREENING OF COELIAC DISEASE IN CZECH REPUBLIC
Children Diagnosed with Coeliac Disease at Alberta Childrens’ Hospital

<table>
<thead>
<tr>
<th></th>
<th>Pre-screening</th>
<th>Screening</th>
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<tr>
<td>Patients</td>
<td>36</td>
<td>199</td>
</tr>
<tr>
<td>Female : male</td>
<td>1.6 : 1</td>
<td>1.6 : 1</td>
</tr>
<tr>
<td>Median age</td>
<td>2</td>
<td>9</td>
</tr>
<tr>
<td>Incidence CD</td>
<td>2.0</td>
<td>7.3</td>
</tr>
<tr>
<td>Incidence classic CD</td>
<td>0.8</td>
<td>1.6</td>
</tr>
</tbody>
</table>

- **atypical or silent coeliac**
- **classic coeliac**
- **coeliac screening started**

Celiac Disease in Children: The Calgary Clinic Data
Calgary Celiac Disease Conference, 2008 - J. Decker Butzner
CD reduces life expectancy because of a higher risk of malignancies such as:
- Small-bowel lymphoma
- Small-bowel adenocarcinoma
- Esophageal carcinoma
- Ulcerative jejunitis
- Refractory CD

SCREENING OF CD MEETS THE SIX WHO CRITERIA

- Early detection could be difficult on a clinical basis
- Available tests (atTG) are highly sensitive and specific, not expansive, with good compliance
- Treatment of the disease is available, and if not recognized, the disease could result in severe complications difficult to manage

TREATED CD ON GLUTEN-FREE DIET SIGNIFICANTLY

- Reduce risk of malignancies
- Have a beneficial effect on preservation of β-cell function in IDDM
- Change diabetes onset in IDDM children
- Will have a positive effect on autoimmune diseases
- Generally will improve subject health
DISEASE SCREENING
COLORECTAL CANCER
COELIAC DISEASE
ATROPHIC GASTRITIS
INFLAMMATORY BOWEL DISEASE
GASTRITIS - CARCINOMA SEQUENCES

1. Class cancerogen

Hp - IARC 1994

NORMAL MUCOSA

ATROPHIC GASTRITIS

INTESTINAL METAPLASIA

GASTRIC CANCER
H. pylori gastritis

No risk of a stomach disease

Increased risk of gastric or duodenal ulcer

Atrophic gastritis

Increased risk of gastric cancer

Eradicate H. pylori infection + consider gastroscopy

PGI, Pepsinogen I, ELISA
PGII, Pepsinogen II, ELISA
G-17, Gastrin 17, ELISA
HpAb, Hp antibodies IgG, ELISA

Gastropanel
serological markers of gastric mucosa status
complex solution - ELISA tests & software
Prevalence of undiagnosed advanced atrophic corpus gastritis in Finland: an observational study among 4,256 volunteers without specific complaints.

Telaranta-Keerie A, Kara R, Paloheimo L, Härkönen M, Sipponen P.
Scand J Gastroenterol. 2010 Sep;45(9):1036-41.

<table>
<thead>
<tr>
<th>Age</th>
<th>Number</th>
<th>ACG</th>
<th>H. pylori</th>
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<tr>
<td>&lt; 39</td>
<td>644</td>
<td>2 - 0.3%</td>
<td>0 - 0%</td>
</tr>
<tr>
<td>40 - 49</td>
<td>660</td>
<td>11 - 1.7%</td>
<td>5 - 45%</td>
</tr>
<tr>
<td>50 - 59</td>
<td>1091</td>
<td>27 - 2.5%</td>
<td>13 - 48%</td>
</tr>
<tr>
<td>60 - 69</td>
<td>1117</td>
<td>48 - 4.3%</td>
<td>19 - 40%</td>
</tr>
<tr>
<td>&gt; 70</td>
<td>744</td>
<td>62 - 8.3%</td>
<td>19 - 31%</td>
</tr>
<tr>
<td>total</td>
<td>4256</td>
<td>150 - 3.5%</td>
<td>56 - 37%</td>
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</table>
DISEASE SCREENING
COLORECTAL CANCER
COELIAC DISEASE
ATROPHIC GASTRITIS
INFLAMMATORY BOWEL DISEASE
Fecal calprotectin correlates more closely with the Simple Endoscopic Score for Crohn's disease (SES-CD) than CRP, blood leukocytes, and the CDAI. Schoepfer AM. Et al. - Am J Gastroenterol. 2010 Jan;105(1):162-169
PRE-ENDOSCOPIC SCREENING WITH F-CALPROTECTIN

IBD diagnostic procedure

above cut-off

Screening with F-calprotectin

below cut-off

Direct referral for endoscopy

3,639 patients
1,206 ≤ 18 years
2,433 > 18 years

Endoscopy

No-endoscopy

1,811 patients
with 50 μg/g
553 ≤ 18 years
1,275 > 18 years

2,435 patients
with 100 μg/g
351 ≤ 18 years
853 > 18 years

2,435 = 67%

Ruling out IBD: estimation of the possible economic effects of pre-endoscopic screening with F-calprotectin.

Mindemark M, Larsson A. Clin Biochem. 2012; 45(7-8): 552-555
WHAT IS ALREADY KNOWN ON THIS TOPIC

✓ Diagnosing inflammatory bowel disease requires **invasive and time consuming endoscopy**

✓ In a relatively large proportion of patients with suspected inflammatory bowel disease the results of endoscopy are negative

✓ Faecal calprotectin is a **sensitive marker of intestinal inflammation**

✓ Use of faecal calprotectin as screening test reduces the number of endoscopies with negative results in both adults and young with suspected inflammatory bowel disease

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*Faecal calprotectin for screening of patients with suspected inflammatory bowel disease: diagnostic meta-analysis.*

van Rheenen PF, Van de Vijver E, Fidler V. - BMJ. 2010 Jul 15; 341: c3369
Laboratory methods for screening in gastroenterology that meets at least five WHO criteria preventing gastrointestinal tumors

<table>
<thead>
<tr>
<th>Gastrointestinal tumor</th>
<th>Gastrointestinal disease</th>
<th>Laboratory screening test</th>
</tr>
</thead>
<tbody>
<tr>
<td>Colorectal cancers</td>
<td>Colorectal adenomas</td>
<td>Quantitative FIT</td>
</tr>
<tr>
<td>Intestinal &amp; GE cancers</td>
<td>Celiac disease</td>
<td>IgA atTG / IgG DGP</td>
</tr>
<tr>
<td>Gastric cancers</td>
<td>Atrophic gastritis</td>
<td>Pepsinogen I/II ratio</td>
</tr>
</tbody>
</table>
THANK YOU