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1 Screening for coeliac disease in the general population and in

2 high-risk groups

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22 **Running head:** Screening for coeliac disease

23 **Abbreviations:** CD, Coeliac disease; GFD, Gluten-free diet; NPV, Negative predictive value; PPV,
24 Positive predictive value; QALY, Quality-adjusted life year.

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43   **Conflict of Interest**

44   Please see statement prior to the reference section.

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ABSTRACT

46   **Background:** Coeliac disease (CD) occurs in approximately 1% of the Western population. It is a

47   lifelong disorder associated with impaired life quality and an excess risk of comorbidity and death.

48   **Objectives:** To review the literature on screening in CD in relation to the current WHO criteria for

49   mass screening.

50   **Methods:** We performed a PubMed search to identify papers on screening indexed in PubMed with

51   a publication date 1900 until 1st of June 2014. When an abstract was deemed relevant, the

52   corresponding paper was read in detail.

53   **Results:** CD fulfils several WHO criteria for mass screening (high prevalence, available treatment,

54   difficult clinical detection), but it has not yet been established that treatment of asymptomatic CD

55   reduces the excess risk of severe complications, leads to higher life quality or is cost-effective.

56   **Conclusion:** Current evidence is not sufficient to support mass screening for CD, but active case-

57   finding may be appropriate, recognizing that most patients with CD will still be missed by this

58   strategy. Although proof of benefit is still lacking, screening may be appropriate in high-risk

59   groups.

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61   **Keywords:** coeliac, Gluten-free diet, support

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Introduction

68 Coeliac disease (CD) occurs in about 1% of the Western population.[1, 2] A recent multinational study

69 in Europe found big differences in CD prevalence with the lowest prevalence (0.3%) in Germany

70 and the highest in Finland (2.4%) despite using common criteria for CD diagnosis.[3]

71 The prevalence of CD seems to be increasing.[4-7] A true increase in prevalence is probably one

72 explanation, but other factors may also have contributed. Increased awareness of the complications

73 of CD (including the mortality excess[8]), in combination with the advent of serological tests with

74 high sensitivity and specificity[9-12] mean that active case finding in CD has increased dramatically in

75 the last decades. Among groups where screening is now becoming more and more common are

76 first-degree relatives, and patients with type 1 diabetes[13, 14].

77 The main objective of this paper was to review the literature on screening for CD, in relation to the

78 established criteria for mass screening established by the World Health Organization (WHO).

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84 **Methods**

85 This project was part of a wider effort, initiated by the British Society of Gastroenterology (BSG)

86 and the Oslo group,[15] to establish recommendations for the care of coeliac patients. JFL and DSS

87 coordinated that overall effort. As part of a major review on clinical management of CD [14], we

88 briefly described the role of screening for CD. In the current paper we expand that discussion, and

89 look at the background of screening, and the pros and cons for CD screening, including the impact

90 that such detection of CD will have on dietary adherence, outcome and quality of life.

91 The working group for the present paper was made up by of seven authors from six different

92 countries (Britain: n=2; and one author each from Sweden, Finland, Italy, Argentina and the US).

93 Four authors (JFL, TC, KK and JAM) carried out the literature searches, the data collection and

94 took the main responsibility for the writing of the paper. JB, FZ and DS provided important

95 feedback, and contributed to crucial revising of the paper. All authors stand behind the paper. JFL

96 wrote the first draft.

97 The recommendations of this paper were based on a systematic literature review in PubMed for the

98 time period 1900 until June 1, 2014 (search criteria have been listed in the appendix). Initially we

99 carried out seven PubMed searches (Appendix) but given the large number of hits for three of these,

100 we limited our literature review to the remaining four terms combined with British and American

101 spelling of coeliac disease (search terms: "definition", "cultural", "diagnostic delay", and

102 "undiagnosed and (complication or comorbidity)"). The parts of this paper dealing with CD

103 prevalence, treatment (gluten-free diet, GFD) and serological sensitivity/specificity were based on

104 personal knowledge of the authors. Finally, CD screening in general was discussed within the

105 author group.

106

Results

WHO stipulates a number of criteria that need to be met to support mass screening (Table 1). While it is evident that CD readily meets many of these criteria, others have not yet been met. For example CD is more prevalent than some disorders for which there is already mass screening (e.g. phenylketonuria, PKU), but it is unclear whether early detection of CD has a positive societal impact. In contrast, detecting a child with PKU will allow prevention of devastating consequences for the development and life quality of that child.

Prevalence of CD

I) That the disease is common and well defined. In much of the western world, CD affects about 1% of the population, but the prevalence varies between countries (e.g. 0.3% in Germany,[3] 0.7% in Italy,[3] 0.7-0.8% in the US,[16, 17] and 1.8% in Sweden[2]). There are reports of even higher prevalence in certain calendar- and age-specific population-strata in Sweden[18].

The proportion of individuals with CD who have received a physician-assigned diagnosis of CD also varies (e.g. 25% in Finland and 6% in Italy)[3] probably reflecting the general awareness of CD in each country. The ratio between diagnosed and undiagnosed CD has implications for screening since with a large proportion of undiagnosed CD, the arguments for screening become stronger. Despite slightly varying prevalences of CD, it is one of the most common lifelong diseases in any Western country (especially in children). While prevalences of CD may be lower in some non-Western countries[19, 20] there are also reports of extremely high prevalences in others[21]. We conclude that this WHO condition is fulfilled.

There is currently an ongoing debate on how to define CD. Our research group recently published a paper on definitions of CD where CD was defined as "a chronic small intestinal immune-mediated

130 enteropathy precipitated by exposure to dietary gluten in genetically predisposed individuals".[15]

131 The related non-coeliac gluten sentivitity[15, 22, 23] was defined as "one or more of a variety of

132 immunological, morphological or symptomatic manifestations that are precipitated by the ingestion

133 of gluten in people in whom CD has been excluded".[15] The definition of CD has important

134 implications for CD screening since most research on complications and life-quality so far has been

135 performed in individuals with biopsy-verified CD, and data cannot automatically be extrapolated to

136 non-coeliac gluten sensitivity. The risk of complications may also vary with underlying

137 histopathology in CD[24].

138

Serology – Sensitivity and specificity

139

140 <u>II) That screening tests are simple, safe and accurate.</u> The WHO stipulates that for mass screening

141 to be an option, screening tests with high sensitivity, specificity,[25] positive predictive value (PPV)

142 and negative predictive value (NPV) must be available. For any of the available tests a most

143 important aspect is that the testing should be carried out when the patient is on a gluten-containing

144 diet. It is therefore of crucial importance that the patient remains on a normal diet throughout the

145 investigation for CD, and our discussion assumes this will be so.

146

147 So-called antigliadin antibodies used in the 1980s and 1990s have low PPV even in high-risk

148 groups; and have therefore largely been replaced by the more specific endomysium (EMA) and

149 tissue transglutaminase antibodies (TTG). The introduction of endomysium antibodies was initially

150 promising since their sensitivity and specificity seem to be at least 90-95%, but over time issues

151 regarding interobserver reliance/interpretability, and cost, have limited its use as the first-line-

152 screening tool for CD. Though TTG antibodies can also be elevated in non-CD diseases, such as

153 liver disease,[26] gastrointestinal infections[27] and certain heart diseases[28, 29], TTG like EMA offers

154 high sensitivity and specificity[30]. One further test has recently gained some popularity. This is for

155 deamidated gliadin peptide antibodies (DGP). One meta-analysis however found that TTG

156 performs better than DGP.[31]

157

158 TTG therefore is often used for screening of high-risk groups, but has also been used in large-scale

159 screening projects of the general population including that of a multi-national European study

160 encompassing more than 29,000 individuals.[3] In the European multi-centre study, 75%

161 (n=292/391) of individuals with positive TTG were positive for EMA but only 2.6% of those with

162 borderline TTG values (n=10/384).[3] In the 147 individuals with both positive EMA and

163 positive/borderline TTG, 100 had an enteropathy typical of CD, equalling 68%.[3] When Hopper *et*

164 *al* screened a population of 2000 individuals undergoing endoscopy (for various indications) the

165 PPV for CD (as defined by villous atrophy) in TTG+ individuals was 28-29%,[32] but with a much

166 higher figure reported in a general population study by Katz *et al*[33] as well as by Sugai *et al* [34].

167 Even a PPV of around 30% compares favourably with the PPV of e.g. guaiac faecal occult blood

168 (FOB) testing for colorectal cancer (a test which has already been accepted for screening in a

169 number of countries). As in the case of FOB screening however confirmatory testing is

170 recommended (in the case of CD in adults, through small intestinal biopsy[14]).

171

172 One further aspect to consider in the use of TTG is that when determining TTG (TG2 antibodies) by

173 ELISA, it is important to bear in mind that the performance of the commercial ELISA TTG assays

174 may vary depending on the quality of the TTG antigen [35]. The method of extraction, the purity of

175 TTG and the production and processing of recombinant antigen may all have an effect on test

176 results[35-37]. Furthermore, as TTG can exist in two divergent conformations (open extended or

177 closed) dependent on the activity of the enzyme,[38] this also influences the performance of the assay,

178 the open TTG being the superior antigen[39]. For the above-mentioned reasons the different

179 commercial TTG-ELISA tests can yield differing numbers of false-negative or false-positive results.

180   Sequential strategies may also be used to increase the positive predictive value[2, 40].

181   *When screening may be insufficient*

182   Under certain circumstances, a negative screening test cannot rule out CD. This will occur when the pre-test

183   probability of CD is elevated. For instance, individuals with severe gastrointestinal symptoms, especially

184   those with a family history of CD, should undergo small intestinal biopsy even in the absence of elevated

185   antibodies[41]. Similar arguments apply to children with growth failure and individuals with severe

186   gastrointestinal symptoms and at the same time another autoimmune disease such as type 1 diabetes,

187   thyroid disease or Addison's disease. Although, IgG-based serology tests have developed in recent years, a

188   combination of IgA deficiency and gastrointestinal symptoms may also constitute an indication for biopsy.

189   One way to effectively exclude CD in IgA deficient individuals is to perform an HLA-test first thereby

190   ruling out CD in those negative for DQ2 or DQ8. Differential diagnoses such as common variable

191   immunodeficiency (CVID) or and severe giardia should also be considered.

192

193   **Screening is culturally acceptable**

194   A third WHO criterion is that a <u>screening test should be culturally acceptable.</u> There are areas in the

195   world,[42] where blood testing may not be culturally but in the majority of countries (including those

196   where earlier research has shown a high prevalence of CD), blood testing is culturally accepted.

197

198   **The GFD**

199   <u>IV. That a treatment is available.</u> This condition is clearly fulfilled in CD. GFD is an effective

200   treatment for CD, and in symptomatic patients the benefits of the dietary treatment are well

201   established, as it has been shown to decrease clinical symptoms as well as reduce the excess risk of

202   complications. [43-45]

203   Nevertheless, the advantages of dietary treatment in screen-detected apparently asymptomatic

204   individuals remain doubtful, and it is by no means settled that GFD results in similar health gains.[46-

205   50 51] However, it is important to note that many screen-detected CD patients are not truly

206   asymptomatic at diagnosis, and may once on a GFD recognize that they had suffered from CD-

207   related symptoms before the diagnosis. It is suggested that many undiagnosed coeliac patients

208   accept a state of chronic vague ill health as a normal condition, but recognize this only after they

209   have been placed on a GFD[47, 52, 53 54]. A recent randomized study also showed that apparently

210   asymptomatic EMA positive subjects seem to benefit from their serological screening and

211   subsequent GFD [55], thereby supporting earlier evidence from Dickey *et al* [56]. Some authors have

212   however suggested that EMA positivity in individuals with normal mucosa constitute a separate

213   entity (potential CD), different from CD[57].

214   A strict GFD sets major limitations on daily life, it is expensive and difficult to maintain[58, 59].

215   Furthermore, removal of gluten from baked products makes them less palatable than comparable

216   products in the normal diet. Due to these unpleasant aspects, the adherence with the GFD often

217   remains inadequate[60]. Individuals found through screening programs to have CD may feel

218   themselves healthy and they do not expect to gain health on treatment similar to those detected due

219   to symptoms. Consequently, screen-detected subjects may be even less willing to adhere to a strict

220   GFD.[53, 61 62] The possible non-adherence to GFD is an essential issue when weighing the harms and

221   benefits of CD screening, as a low rate of adherence would abolish any advantages of screening. It

222   is important in this regard to recognise that good dietary adherence can be achieved in screen-

223   detected CD patients (adherence rates of 85% in symptom-detected CD patients and 79-91% in

224   screen-detected ones),[53, 63] even after long-term treatment[52, 64]. However, there is evidence to

225   suggest that dietary lapses could be more common in the initially asymptomatic screen-detected

226   patients than in the symptomatic ones[53]. Furthermore, patients suffering from type 1 diabetes

227   mellitus and found to have CD by risk-group screening, may evince lower dietary adherence rates

228   than reported in screening studies in general (40-63%)[65-67].

229 When prescribing GFD to healthy screen-detected patient, one should remember that GFD is not

230 nutritionally optimal and may have adverse consequences. GFD may potentially expose individuals

231 to high sugar and low fibre and mineral intake[68, 69], which again might cause different long-term

232 negative health consequences such as constipation[70]. In addition, there is concern that patients

233 might gain undesirable weight while on a GFD[71, 72]. Altogether, it would thus be essential to

234 evaluate the consequences of GFD treatment before any screening programs for the disease are

235 instituted.

236

237

238 **Diagnostic delay**

239 <u>V. That clinical detection is difficult</u>. Typically CD is characterized by diarrhoea, malabsorption and failure

240 to thrive in childhood although during the last two decades the age of diagnosis has shifted upward and

241 many patients have only minor symptoms.[73-75] Due to the inconsistency of the symptoms, a substantial

242 proportion of coeliac patients have a previous diagnosis of irritable bowel syndrome[76 77]. Unfortunately

243 these symptoms do not predict CD in general population studies [2, 33, 78, 79]. Furthermore, increasing numbers

244 of CD patients are diagnosed because of extraintestinal symptoms or by screening of at-risk groups[73, 74].

245 Probably due to the vague nature of presenting symptoms, the delay from first symptoms to CD diagnosis

246 has been reported to be unacceptably long, at between 5 and 10 years, for many persons[73, 80-85], and the need

247 for earlier diagnosis, even by mass screening has been advocated.

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Untreated disease leads to complications

VI. <u>That if undiagnosed and untreated the disease will lead to severe complications</u>. The WHO

stipulates that prevention of complications shall follow upon disease detection if mass screening is

implemented. This statement is conditional on two facts:

a) That undiagnosed disease confers complications; and b) that these complications can be

prevented by the "treatment", in this case the GFD. Given the importance of genetic factors in the

aetiology of CD, it may be assumed that comorbidity linked to underlying shared risk factors

cannot be modified by diagnosing CD and introducing a GFD.

It seems clear that the majority of gastrointestinal symptoms in CD are alleviated after the

introduction of a GFD, but the evidence is less clear whether most complication are influenced by

GFD. Weaknesses of previous research in this area include lack of strict evaluation of GFD, low

study power, short follow-up, and a difficulty in disentangling the effects of age at diagnosis, and

duration of gluten exposure, which will both be linked to early diagnosis.

It should be noted that duration of disease is not equal to diagnostic delay. In the recent Proconsul

study, complications in CD were associated with a short diagnostic delay[86], but it cannot be ruled

out that earlier celiac diagnosis was prompted by symptoms and signs from the celiac complication.

Morbidity and mortality in undiagnosed CD

Mortality

A number of studies have examined mortality in undiagnosed CD[6, 51, 87-90]. Two of these have

shown excess mortality[6, 90]. Of particular interest is the study by Rubio-Tapia, which is the only

study with extensive follow-up duration[6]. That study found an almost 4-fold increased risk of death

274   in young men with positive CD serology, but confidence intervals were wide (95%CI=2.0-7.5), the

275   number of participants with CD low (n=14) and the population studied was restricted (military

276   recruits) so results may not be generalizable. It is also not clear, how many of these individuals

277   would have been diagnosed applying modern aggressive case-finding for CD[91] as many individuals

278   diagnosed in screening studies have a history of CD-associated symptoms.[47] Other larger-scale

279   studies have shown no increased risk of death in undiagnosed CD (numbers of screened adults:

280   16,847;[89] 7,527;[87] and 6,987[88]).

281

282   *Autoimmunity*

283   Studies on undiagnosed CD and autoimmune disease are difficult to carry out since patients with

284   autoimmune disease are often screened for CD, and because the onset of autoimmune disease is

285   often gradual (in contrast to mortality, but also to some extent to malignancy). As far as we know,

286   none of the studies looking at undiagnosed CD and mortality have looked at development of

287   autoimmune disease.[6, 51, 87-90]

288

289   Cosnes *et al* investigated 924 patients with CD. While they concluded that the GFD had a

290   protective effect against autoimmunity, this effect was weak since it did not remain statistically

291   significant when the authors adjusted for other co-variates in their multivariate analyses (p=0.07).[92]

292   The Cosnes *et al* study also found that a *late* diagnosis of CD decreased the risk of autoimmune

293   disease.[92] Finally, two Italian studies have suggested that GFD may decrease the prevalence of

294   thyroid autoantibodies[93, 94], but whether it protects against hypo- or hyperthyroidism is still unclear.

295

296   We may however want to consider the effect of a GFD not only upon the cumulative incidence of

297   autoimmune disease in those with CD but also upon the control of disease in individuals who

298   already have an autoimmune disease (other than CD). Diagnostic delay of CD is common in type 1

299   diabetes[95] and the longterm consequences of this are unknown. Recent Swedish data however

300   indicate that long term CD is associated with excess morbidity in type 1 diabetes[96-98]. Hansen *et al*

301   screened children with type 1 diabetes, but did not see an improvement of HbA1C in diabetes

302   patients who were detected with CD and then recommended a GFD.[99] A British study of adults with

303   type 1 diabetes however found that patients with undiagnosed CD had worse HbA1C (8.2) than

304   controls (7.5)(p=0.05) at baseline, but when after 1 year the authors compared HbA1C values, there

305   was no difference between those adhering to a GFD and those with poor adherence.[100]

306

307   *Malignancy*

308   A recent meta-analysis even suggested that the overall malignancy risk in diagnosed CD was not

309   elevated compared to that of general population-based controls,[101] but individual cancers, such as

310   lymphoproliferative cancer and gastrointestinal cancers,[102, 103] may still be positively associated

311   with CD. One reason for a seemingly neutral association between diagnosed CD and risk of overall

312   cancer (or a very limited risk increase) is that high relative risks for less common cancers

313   (lymphomas) may be compensated for by lower relative risks for common cancers such as breast

314   cancer.[104, 105]

315   We know of three studies so far exploring cancer risk in undiagnosed CD, none of which found any

316   increase in overall cancer but study power was limited.[89, 106, 107] In addition to these there are at least

317   another two case control studies specifically of lymphoma, which have shown an excess risk in CD.

318   Catassi *et al*[108] found a 3.1-fold excess of Non Hodgkin Lymphoma among Italian individuals with

319   undiagnosed CD and 16.9 for gut lymphoma. The latter of these figures closely mirrors the odds

320 ratio of 15.7 for the occurrence of gut lymphoma in undetected CD from Johnston and Watson in

321 Northern Ireland[109]. As with mortality however one must consider the risk in those with diagnosed

322 disease. Since the risk of NHL remains greater in diagnosed disease at about 4 to 6 fold[24, 103, 110] (and

323 that of small bowel lymphoma (SBL) may be even higher in this group[111]) , again a substantial

324 societal benefit in the reduction of cancer occurrence or death from mass screening for celiac

325 disease seems unlikely.

326

327 Considering that the overall risk of malignancy in CD does not seem to be increased more than

328 marginally,[101] most interest with regards to the potentially protective effect of GFD focuses on

329 lymphoproliferative malignancy. That earlier research on undiagnosed CD has failed to show an

330 association with malignancy, including lymphoproliferative malignancy argues against GFD

331 playing a major role. At the same time, it should be noted that most earlier studies have been

332 underpowered to examine the relationship between GFD and lymphoproliferative malignancy

333 (number of CD patients with lymphoma or non-Hodgkin lymphoma: 9,[112] 9,[44] and 9[103]). In an effort

334 to examine the role of GFD, Olén *et al* reviewed patient charts (the researchers were blinded to CD

335 status) of 59 patients with both CD and lymphoma, as well as 137 CD patients *without* lymphoma.

336 This nested case-control study was still underpowered to confirm a suspected relationship between

337 poor dietary compliance and future lymphoma (OR=1.83; 95%CI=0.78-4.31).[113]

338 Current data implies that there is a protective effect of GFD against lymphoma, although that has

339 not yet been comprehensively proven.

340

341

342

343 *Pregnancy and fertility*

344 Adverse pregnancy outcome in maternal *undiagnosed* CD has now been confirmed by a number of

345 studies, [114-116] including two recent papers that both found increased risk estimates for preterm birth

346 in undiagnosed CD (Sweden: 1.71[117]; Denmark: 1.33[116]), but not in diagnosed CD. This association

347 strongly argues that a CD diagnosis and a GFD introduced before pregnancy influence the

348 pregnancy outcome. As both studies were of clinically diagnosed cases, they do not however

349 clearly demonstrate a benefit to screening for asymptomatic ones.

350

351 That undiagnosed CD has a negative effect on birth outcome cannot automatically be translated into

352 an effect on fertility. The largest screening study for CD in subfertile/infertile couples so far found

353 no association with CD[118], and the two largest cohort studies to this date[119, 120] have found that

354 overall fertility in CD is similar to the of general population controls, even though the Swedish

355 study found a fertility decrease in the last two years before diagnosis followed by catch up

356 fecundity after diagnosis[119]. It cannot be ruled out that the decrease in fertility just before diagnosis

357 seen in that paper is due to undiagnosed CD,[119] but it might also be due to other comorbidity which

358 lead to testing for CD, or that women postpone pregnancy when they undergo extensive medical

359 investigations.

360

361 *Advantages of undiagnosed CD?*

362 Although we do not argue that patients with symptomatic CD should remain undiagnosed, several

363 papers suggest that the prevalence of hypertension,[121] hypercholesterolemia[121, 122] and obesity[123] is

364 lower in undiagnosed CD than in the general population,[121] potentially protecting against

365 cardiovascular disease. In fact, some authors have argued that screen-detected children without

366 symptoms should not always be treated with GFD.[52] The largest study on diagnosed CD and

367 cardiovascular disease however found a small but statistically significant increased relative risk for

368 both incident ischemic heart disease and death from ischemic heart disease.[124] Such a risk increase

369 does however translate in a substantial absolute risk considering that cardiovascular disease is

370 common (in celiac individuals aged 60+ years, the excess risk was 20 myocardial infarctions per

371 1000 person-years[124]).

372

373 **Life quality aspects of screening of CD**

374 In symptomatic CD the GFD results in rapid recovery from symptoms paralleled with improvement

375 in quality of life[53] [125] [46, 126, 127] (Table 2). However, screen-detected CD patients may have considered

376 themselves healthy before the diagnosis, and now the stigma of a chronic disorder[128] and need of

377 major dietary restrictions may potentially even increase their self-perceived burden of illness and

378 impair their quality of life[129-131].

379

380 Prospective studies on quality of life in CD patients detected by screening of at-risk groups or in

381 populations in general are limited (Table 2). According to these studies quality of life in screen-

382 detected coeliac patients at or before diagnosis, especially in those who are asymptomatic, is often

383 similar to,[46, 53, 126] [50, 125] or lower [47, 52, 53] than that found in control populations. In screen-detected

384 patients, GFD treatment does not necessarily result in improvement of life-quality[46, 53, 126] but some

385 studies imply that the diet may have a positive impact in health and well-being in these patients also

386 [47, 52, 53] [125]. Still, data suggest that screen-detected patients without symptoms may experience the

387 diagnosis of CD more negatively than patients having symptoms[48, 53]. This would suggest that early

388 detection of CD by mass screening in a healthy adult population would not unequivocally result in

389 self-perceived health gain. Furthermore, data on long-term treatment in screen-detected patients is

390   scarce[52, 64]. These issues call for comprehensive studies before implementation of large-scale CD

391   screening programs.

392

Cost-benefit of screening

394   <u>VII. That testing and treatment is cost-effective.</u> As has been outlined above the likely benefit or

395   even the potential harm to undetected coeliac patients from screen detection is as yet poorly

396   defined. In addition symptomatic undiagnosed CD and diagnosed CD are both likely to confer

397   increased costs to the individual patient and to society, but these costs are shared differently in

398   different countries. Determining whether screening and detection of asymptomatic CD will lead to

399   health gains at an acceptable cost or even to economic benefits is therefore extremely difficult. A

400   number of studies have however been conducted in this area. Some of these consider only the costs

401   of detecting a new case by varying screening strategies, or apply only to specific high risk groups,

402   and there are very few which have attempted to model both costs and health benefits to determine

403   the cost of gaining a quality adjusted life year (QALY), and only three of these refer to general

404   population screening. In a UK context perhaps the most influential of these papers to date has been

405   the HTA (Health Technology Assessment) sponsored study by Dretzke *et al*[132] (the only such study

406   considered in the development of the current UK national guidelines, and one specifically looking

407   at newly diagnosed type I diabetic children). This study found that serological testing followed by

408   confirmatory biopsy and treatment with GFD provided additional QALYs at an incremental cost of

409   between £12,250 and £20,160 when performed in children with newly diagnosed type 1 diabetes.

410   To derive these estimates the authors assumed among other things that untreated asymptomatic CD

411   would cause the loss of 4 years of life, and reduce quality of life from 88% of optimal (the assumed

412   baseline for treated disease) to 82% of optimal. Another prominent analysis by Hershcovici *et al*

413   has examined the cost effectiveness of mass screening. This paper found that the cost for each

414   QALY gained through mass CD screening is about 49,000 USDs (Table 3).[133] However, it is

415   important to note that this cost, and the conclusion that mass screening in young adults is cost-

416   effective is again based on a number of assumptions. The authors of the Hershcovici *et al* paper

417   assumed that the standardized mortality ratio was 1.6 in patients with symptoms ("undiagnosed"),

418   and 1.1 in patients on a GFD ("diagnosed").[133] However, most studies on mortality in diagnosed

419   CD have found relative risks of deaths of around 1.3-1.4 [8, 104] (and in a Swedish study,[8] it was

420   estimated that 83% of patients adhered to the diet). Hence, with a smaller gap between the mortality

421   risk estimates between diagnosed and undiagnosed coeliac patients, mass screening may not be

422   cost-effective. This is well illustrated by the study by Shamir *et al* (Table 3)[134], which though

423   finding on an assumption of an SMR of 1.6 for undetected disease, screening to be cost effective,

424   showed in a sensitivity analysis that if the SMR fell to 1.3 then the cost per QALY rose to over

425     $100,000. Cost-effectiveness analyses are also dependent on degree of adherence to a GFD, and

426   where Hershcovici *et al* assumed a dietary adherence of 80% in patients with symptomatic CD, [133]

427   others have found the lowest dietary adherence in screen detected asymptomatic patients .[49] Finally,

428   cost-effectiveness is dependent on duration of symptoms before diagnosis. Hershcovici *et al*

429   reported that mass screening would be effective if diagnostic delay was 6 years of more. With

430   increased awareness of CD, diagnostic delay is likely to decrease. At present, some studies suggest

431   that the delay is ≥6 years[80, 85] but others that it is less (4.9 years[135]). Finally Park *et al*[136] recently

432   compared two different strategies to prevent bone loss and fractures in patients with undiagnosed or

433   subclinical CD. Their study found that symptomatic at-risk screening was more cost-effective than

434   universal serological screening. Though again the assumptions of their base model can be

435   challenged, they found that screening of symptomatic and high risk subjects was a dominant

436   strategy when compared to universal screening producing greater QOL gains at lower cost.

437   Furthermore this strategy remained the more cost effective option when testing the sensitivity of the

438   model to variation in their assumptions.

439   We conclude that more data on the cost-effectiveness of mass screening for CD in the general

440   population is needed.

441

442   *When and how often should we screen?*

443   It should be clear to all that for so common a disease as CD, and with so successful a therapy as

444   GFD, any patient with symptoms that might be due to CD should be tested. In this paper however

445   we are primarily concerned with the asymptomatic. For them as should be clear from the forgoing

446   we cannot point to definite benefit from the detection of CD (either in the reduction of symptoms –

447   since they have by definition none, or an increase in the quality or the quantity of life).

448   Furthermore, unlike in congenital diseases such as congenital hypothyroidism where screening once

449   is enough to rule out disease, CD can start at any age, and having a negative CD serology test does

450   not rule out future CD.

451   With regard to the second of these issues, there is at least one CD screening method with an

452   exceptionally high negative predictive value: HLA-screening. Patients with a negative HLA will

453   not develop CD and one strategy to avoid repeated CD screening is to first perform an HLA test.

454   One drawback of HLA screening is its extremely low positive predictive value (PPV)(1 in 25 DQ2-

455   DQ8 individuals will develop CD, i.e. the PPV is around 4%), while giving the patient and his/her

456   physician the impression that the patient is "positive for CD".

457   No simple work around exists however for the lack of clear evidence of the benefit of screen

458   detection. It is not unreasonable to assume however that there is a marginal benefit of such

459   detection (as has been assumed in the cost efficacy studies of screening previously discussed), and

460   any such benefit is likely to be greatest in high-risk groups where the PPV of a positive screening

461   test will be greatest. On this basis therefore it is generally assumed that the screening of high-risk

462   groups is reasonable, but direct evidence for this is lacking at present in almost all cases.

463

Special circumstances – High risk groups

First-degree relatives

466 The prevalence of CD in first-degree relatives is around 10%,[16, 137, 138] with significantly higher

467 prevalence figures in monozygotic twins, families with multiple affected or siblings who share the

468 HLA susceptibility alleles.[139]

469

Type 1 diabetes

471 Up to one in three DQ2+ individuals with type 1 diabetes expresses TTG.[140] Type 1 diabetes is also

472 one of the most common autoimmune diseases in patients with CD, [92] and the relative risk for

473 future type 1 diabetes in patients with CD has been estimated at 2.4.[141] Of note, that relative risk is

474 almost identical to the future risk of type 1 diabetes in whites who are DQ2,[142] suggesting that the

475 increased risk of type 1 diabetes may not be affected by dietary adherence.

476 Between 2% and 12% of all type 1 diabetes patients have CD.[16, 99, 143, 144]

477

Down syndrome and Turner syndrome

479 Although, most studies so far have been small, the prevalence of CD seems to be increased in both

480 Down syndrome[148-150] and Turner syndrome[151, 152]. The only direct analysis of screening cost

481 effectiveness in either of these conditions of which we are aware is the one by Swigonski *et al.*[153]

482 This study though it focuses on the prevention of lymphoma, does also address the total number of

483 QALYs resulting from a screening strategy in this group. It is notable in suggesting that screening

484   causes a reduction in QUALYs, and though this is based on the assumption that having to eat a

485   GFD represents a 1% reduction in QOL, that assumption is perhaps no more unreasonable than any

486   of those considered in the analyses of general population screening above.

487

488   *Iron-deficiency anaemia*

489   CD may cause iron-deficiency anaemia through malabsorption, but also through an ongoing

490   inflammation and potentially also through occult bleeding[145 146]. CD is also more common in

491   patients with iron-deficiency anaemia and gastrointestinal symptoms including IBS[147], and we

492   suggest that both these risk groups undergo testing.

493

494

495   *Bone mineralization disorders / Osteoporosis and osteomalacia*

496   CD is associated with an increased risk of fractures,[154-156] with relative risks of around 2 for

497   fractures after CD diagnosis. An earlier study found a similar relationship (Odds ratio around 2) for

498   fractures prior to diagnosis in patients with CD.[156]

499

Discussion and Recommendations

There is an ethical difference between aggressive case-finding among the symptomatic, and screening for disease in the general population where a diagnosis of CD in asymptomatic individuals may not confer clear benefits. Decisions on screening therefore should be carefully considered. In this paper we have tried to review the pros and cons of mass screening for CD against the established WHO criteria for mass screening, and a summary of key-points in relation to screening is given in Table 4. Though CD meets many of these criteria, the outcome of undetected asymptomatic disease, the effect upon the life expectancy and quality of life with GFD in these patients and therefore the cost efficacy of screening remains unclear. Screen-detected CD will have economic implications, leading to both higher and lower costs, for different actors, and whether mass-screening is economically sound is dependent on a number of assumptions. Though studies to date assuming that GFD improves quantity and quality of life in the asymptomatic, and is itself cost free, suggest that screening may be cost effective, to achieve certainty we need more data to reduce the number of such assumptions which must be made.

Neither the current NICE guidelines[157] on recognition and assessment of CD, nor the corresponding British Society of Gastroenterology (BSG) guidelines[14] recommend mass screening for CD in the UK. Both guidelines do however recommend that serological testing for CD should be conducted in a wide range of clinical situations ranging from, the presence of potential symptoms of the disease (diarrhoea, failure to thrive (in children), gastrointestinal symptoms, prolonged fatigue, sudden or unexpected weight loss and anaemia), through the presence of associated conditions (autoimmune thyroid disease, dermatitis herpetiformis, irritable bowel syndrome or type 1 diabetes) to the presence of CD in a first degree relative.

523   Based on our literature review we suggest that screening of high risk groups may well be cost

524   effective even if the benefit gained is small, however proof of such benefit is still lacking.

525   We recommend that future research should provide data on the outcomes of undiagnosed and of

526   treated asymptomatic CD.

527

528   In conclusion, we cannot recommend mass screening at the present stage. Though current

529   diagnostic recommendations will only lead to the discovery of a minority of patients with CD, it is

530   not yet clear that the detection of more would be of benefit to those detected.

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Conflict of Interest

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552 TC: Grant support: Coeliac UK: Crohn's and Colitis UK: Spouse is an employee of AstraZeneca.

553 DSS: has received an educational grant from Dr Schär (a gluten free food manufacturer) to
554 undertake an investigator led research study on gluten sensitivity. Also has received an educational
555 grant from both Biocard and Simtomax to undertake an investigator led research study on point of
556 care tests

557 JAM: Consultant for Alvine inc, Bayer, Flamentera, ActiogeniX, Shire, grant support from Alba
558 Therapeutics, Biocard.

559

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953 **Table 1. Summary of WHO criteria**

WHO Criteria	Valid in Coeliac disease	Comment
That the disease is common and well defined	++	There is an agreement that the disease occurs in about 1% or more of the Western population. Disease criteria have however been debated.
Screening tests are simple, safe and accurate	++	Screening tests with tissue transglutaminase have high sensitivity and specificity but the positive predictive value is well below 100%. However when combined with sequential endomysial antibody testing the positive predictive value increases.
The screening test should be culturally acceptable	+++	Only very rarely is screening not culturally accepted
Treatment is available	+++	A GFD is beneficial for both symptoms and mucosal injury, but may not protect against many future complications of CD
Clinical detection is difficult	+++	Symptoms and signs vary. Some individuals with CD are asymptomatic. Most people with CD remain undetected.
If undiagnosed and untreated the disease will lead to severe complications	+	Symptomatic patients will most often be relieved of symptoms. It is less clear if asymptomatic patients will benefit from clinical diagnosis and treatment with a GFD. It is not known if asymptomatic individuals are at risk of severe complications.
Testing and treatment is cost-effective	+	There is little research in this field, and existing research has often been based on the assumption that CD goes undiagnosed for many years. With increasing awareness of CD, diagnostic delay is likely to have decreased in recent years.

954 *CD, coeliac disease. GFD, Gluten-free diet*

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959   **Table 2. Quality of life (QoL) studies in screen-detected coeliac patients**

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Reference	*Country*	*Study design*	*No of screen-detected patients (asympto matic)*	*QoL instrument*	*Main finding*
Mustalahti 2002 [125]	Finland	Prospective	19 (14)	PGWB	At diagnosis QoL similar to that in controls; QoL improved significantly after 1-year's GFD
Johnston 2004 [46]	UK	Prospective *	14 (ND)	SF-36	At diagnosis QoL similar to that in controls; no change after 1-year's GFD
Viljamaa 2005 [64]	Finland	Cross-sectional	53 (32)	PGWB, SF-36	After long-term GFD, QoL was comparable to controls
Korponay-Szabo 2007 [47] §	Hungary	Prospective *	32 (5)	Generic child health questionnair e	Global general health, bodily pain, general health perceptions, parental emotional impact lower than in controls; QoL improved after 1-year's GFD
Whitaker 2009 [48]	UK	Cross-sectional	51 (19)	Self-made questionnair e	A quarter of the asymptomatic screen-detected patients regretted being diagnosed
Van Koppen 2009 [52] §	Netherlands	Prospective *	32 (20)	TNO-AZL# DUX 25#, CDDUX#	Social functioning, problem behavior, anxiety, positive mood, liveliness affected in cases vs. control population. Improvement on GFD

Nachman 2009 [126]	Argentina	Prospective	(8)	SF-36	At diagnosis QoL similar to that in controls; no change after 3 month's GFD
Ukkola 2011 [53]	Finland	Prospective	146 (23)	PGWB	In all group, at diagnosis QoL was lower than that in controls; QoL improved after 1-year's GFD. In asymptomatic group QoL similar to that in controls at diagnosis; no change after 1-year's GFD
Nordyke 2011 [50] §	Sweden	Cross-sectional*	148	EQ-5D	Before diagnosis QoL in screen-detected CD similar to controls
Nordyke 2013 [158] §	Sweden	Prospective	103	EQ-5D	Screen-detected cases with unrecognized CD experienced similar QoL at diagnosis. On diet boys reported less pain
Myleus 2014 [159] §	Sweden	Cross-sectional	238	Kidscreen	Comparable HRQoL as their peers
Kurppa 2014 [55]	Finland	Randomized, prospective	40	PGWB SF36, VAS	Anxiety alleviated and perception of health improved in favor of GFD, but social functioning reduced in favour of gluten consumption

961 PGWB=Psychological General Well Being , GFD=Gluten free diet, SF-36=Short For-36. ND=No
962 data.

963 # Quality of life scales. For an explanation, see the original paper by Van Koppen [52]

964 *Detected by mass-screening; other studies include patients detected by risk-group screening

965 § Study based on children and/or adolescents. All other studies were based on adults.

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968   **Table 3. Cost effectiveness of mass screening for coeliac disease.**

	Shamir et al [134]	Hershcovici et al [133]
Utility of life with untreated asymptomatic CD	100%	Irritable bowel syndrome 76% Iron deficiency anemia 73% All other presentation 100%
Utility of life on GFD	100%	98%
SMR for untreated asymptomatic CD	1.6	All assumed symptomatic. With SMR 1.6
SMR in GFD	1.1	1.1
Sensitivity of screening	85%	IgA TTG 95% IgG TTG 98.7%
Prevalence of CD	0.5%	0.9%
Specificity of screening	90% TTG 95% EMA	IgA TTG 98% IgG TTG 98.6%
Costs of screening from	2004 Medicare fees	2004 Medicare fees
Cost of GFD	Not considered	Not considered

969   *EMA, Endomysial antibodies*

970   *GFD, Gluten free diet*

971   *SMR, Standardized Mortality Ratio*

972   *TTG, Tissue transglutaminase antibodies*

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985   **Table 4. Key-points: Screening for CD**

Coeliac disease occurs in about 1-2% of the Western population
The varied presentation makes the disease difficult to diagnose, and there are screening tools available
There are still few data on complications from undiagnosed CD
We recommend active case-finding, but not mass screening

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Appendix

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1005 ***PubMed search Jan 1, 1900 until June 1, 2014. Number of hits searching for "(Coeliac or***
1006 ***coeliac)" and the below terms.***

Additional term	Hits
+ Prevalence*	3612
+ Definition	101
+Cultural	353
+Treatment *or* gluten*	141912
+Sensitivity and specificity*	1376
+Diagnostic delay	157
+undiagnosed and (complications or comorbidity)#	123

1007 *E.g. PubMed search:*

1008 ** Abstracts and/or titles not examined in detail.*

1009 *Example of search strategy: ((coeliac or coeliac) and undiagnosed and (complications or*
1010 *comorbidity)) AND ("1900/01/01"[Date - Entrez] : "2014/06/01"[Date - Entrez])*

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