1 Appendix C: Review Protocols & Search Strategy

A.1.1 Scoping searches

Scoping searches were undertaken on the following websites and databases (listed in alphabetical order) in October 2012 to provide information for scope development and project planning. Browsing or simple search strategies were employed.

<table>
<thead>
<tr>
<th>Guidelines/website</th>
<th>Systematic review/economic evaluations</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Audit Commission</td>
<td>• BMJ Clinical Evidence</td>
</tr>
<tr>
<td>• British Dietetic Association</td>
<td>• Cochrane Database of Systematic Reviews (CDSR)</td>
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<tr>
<td>• British Nutrition Foundation</td>
<td>• Database of Abstracts of Reviews of Effects (DARE)</td>
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<tr>
<td>• British Society of Gastroenterology</td>
<td>• DUETS</td>
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<tr>
<td>• British Society of Paediatric Gastroenterology, Hepatology and Nutrition</td>
<td>• Health Economic Evaluations Database (HEED)</td>
</tr>
<tr>
<td>• Care Quality Commission</td>
<td>• Health Technology Assessment (HTA) Database</td>
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<tr>
<td>• Coeliac UK</td>
<td>• NHS Economic Evaluation Database (NHS EED)</td>
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<tr>
<td>• COMET</td>
<td>• NIHR Health Technology Assessment</td>
</tr>
<tr>
<td>• Department of Health</td>
<td>• NIHR Health Services and Delivery Research (HS&amp;DR) Programme</td>
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<tr>
<td>• Guidelines International Network (GIN)</td>
<td>• PROSPERO</td>
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<tr>
<td>• Healthcare Improvement Scotland</td>
<td>• TRIP Database</td>
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<td>• Health Protection Agency</td>
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<tr>
<td>• King’s Fund</td>
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<td>• National Audit Office</td>
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<td>• National Patient Safety Agency</td>
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<tr>
<td>• National Institute for Health and Clinical Excellence (NICE) - published &amp; in development guidelines</td>
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<td>• National Institute for Health and Clinical Excellence (NICE) - Topic Selection</td>
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<td>• National Institute for Innovation and Improvement</td>
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<td>• National Patient Safety Agency</td>
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<td>• National Prescribing Centre</td>
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<td>• NHS Business Services Authority</td>
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<td>• NHS Evidence</td>
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<td>• NHS Information Centre</td>
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<td>• NHS Scotland</td>
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<td>• NHS Wales</td>
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<td>• New Zealand Guidelines Group</td>
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<td>• Primary Care Society for Gastroenterology</td>
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<tr>
<td>• Prodigy (formerly Clinical Knowledge Summaries)</td>
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<td>• Royal Colleges</td>
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<tr>
<td>• Royal Pharmaceutical Society of Great Britain</td>
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<tr>
<td>• Royal Society of Medicine</td>
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</table>
A.1.2 **Main searches**

Sources searched for the guideline

- Cochrane Database of Systematic Reviews – CDSR (Wiley)
- Cochrane Central Register of Controlled Trials – CENTRAL (Wiley)
- Database of Abstracts of Reviews of Effects – DARE (Wiley)
- Health Technology Assessment Database – HTA (Wiley)
- EMBASE (Ovid)
- MEDLINE (Ovid)
- MEDLINE In-Process (Ovid)

A.1.3 **Identification of evidence for clinical questions**

The searches were conducted between May 2013 and July 2014. The re-run searches took place in December 2014. The aim of the searches was to identify evidence for each of the clinical questions being asked.

The MEDLINE search strategies are presented below. These were translated for use in all of the other databases.

A.2 **Review question search strategies**

A.2.1 **Search strategy review questions 4.1, 4.2, & 4.3**

Which presenting features raise suspicion of coeliac disease?

4.1 What are the clinical signs and symptoms which raise suspicion of coeliac disease?

4.2 What populations have an increased risk of developing coeliac disease?

   i. Co-existing diseases

   ii. Other factors (ie. first-degree relatives)

4.3 What are the long-term consequences of undiagnosed or untreated coeliac disease?
### Table 1: search strategy 4.1, 4.2, & 4.3

<table>
<thead>
<tr>
<th>Search Strategy</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Medline Strategy, searched 24th July 2013 – 28th August 2014</strong></td>
<td>Database: Ovid MEDLINE(R) &lt;1946 to July Week 2 2013&gt;</td>
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<tr>
<td><strong>Search Strategy:</strong></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>(coeliac adj4 disease).tw.</td>
</tr>
<tr>
<td>2</td>
<td>(celiac adj4 disease).tw.</td>
</tr>
<tr>
<td>3</td>
<td>(coeliac adj4 sprue).tw.</td>
</tr>
<tr>
<td>4</td>
<td>(celiac adj4 sprue).tw.</td>
</tr>
<tr>
<td>5</td>
<td>((nontropical or non tropical) adj4 sprue).tw.</td>
</tr>
<tr>
<td>6</td>
<td>((celiac or coeliac) adj4 syndrome).tw.</td>
</tr>
<tr>
<td>7</td>
<td>(gluten adj4 (enteropath* or sensitiv* or hypersensitiv* or intoleran*)).tw.</td>
</tr>
<tr>
<td>8</td>
<td>((glutenin or gliadin) adj4 (sensitiv* or hypersensitiv* or intoleran*)).tw.</td>
</tr>
<tr>
<td>9</td>
<td>Celiac Disease/</td>
</tr>
<tr>
<td>10</td>
<td>or/1-9</td>
</tr>
<tr>
<td>11</td>
<td>(occurrence or prevalen* or incidence or epidemiolog*).tw.</td>
</tr>
<tr>
<td>12</td>
<td>(seroprevalence or seroepidemiol*).tw.</td>
</tr>
<tr>
<td>13</td>
<td>Prevalence/</td>
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<tr>
<td>14</td>
<td>Incidence/</td>
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<tr>
<td>15</td>
<td>Epidemiology/</td>
</tr>
<tr>
<td>16</td>
<td>or/11-15</td>
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<tr>
<td>17</td>
<td>10 and 16</td>
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<tr>
<td>18</td>
<td>(first adj4 relative*).tw.</td>
</tr>
<tr>
<td>19</td>
<td>famil*.tw.</td>
</tr>
<tr>
<td>20</td>
<td>Family/</td>
</tr>
<tr>
<td>21</td>
<td>Mothers/</td>
</tr>
<tr>
<td>22</td>
<td>Fathers/</td>
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<tr>
<td>23</td>
<td>Parents/</td>
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<tr>
<td>24</td>
<td>Nuclear Family/</td>
</tr>
<tr>
<td>25</td>
<td>Siblings/</td>
</tr>
<tr>
<td>26</td>
<td>Child/</td>
</tr>
<tr>
<td>27</td>
<td>Spouses/</td>
</tr>
<tr>
<td>28</td>
<td>(mother* or father* or brother* or sister* or parent* or child* or son* or daughter* or husband* or wive* or wife* or spouse* or aunt* or uncle* or sibling* or offspring or cousin*).tw.</td>
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<tr>
<td>29</td>
<td>genetic*.tw.</td>
</tr>
<tr>
<td>30</td>
<td>Genetic Predisposition to Disease/</td>
</tr>
<tr>
<td>31</td>
<td>Risk Factors/</td>
</tr>
<tr>
<td>32</td>
<td>risk*.tw.</td>
</tr>
<tr>
<td>33</td>
<td>or/18-28</td>
</tr>
<tr>
<td>34</td>
<td>or/29-32</td>
</tr>
<tr>
<td>35</td>
<td>10 and 33 and 34</td>
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<tr>
<td>36</td>
<td>17 or 35</td>
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<tr>
<td>37</td>
<td>undiagnosed.tw.</td>
</tr>
<tr>
<td>38</td>
<td>silent.tw.</td>
</tr>
<tr>
<td>39</td>
<td>untreated.tw.</td>
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<tr>
<td>40</td>
<td>((delay* or error*) adj4 diagnos*).tw.</td>
</tr>
<tr>
<td>41</td>
<td>(Unrecognised or unrecognized).tw.</td>
</tr>
<tr>
<td>42</td>
<td>Hidden.tw.</td>
</tr>
<tr>
<td>43</td>
<td>Missed.tw.</td>
</tr>
<tr>
<td>44</td>
<td>Misdiagnos*.tw.</td>
</tr>
<tr>
<td>45</td>
<td>Undetect*.tw.</td>
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<td>Delayed Diagnosis/</td>
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<td>Number</td>
<td>Search Term</td>
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<td>-------------------------------------------------------------------------------------------------</td>
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<tr>
<td>47</td>
<td>exp Diagnostic Error/</td>
</tr>
<tr>
<td>48</td>
<td>or/37-47</td>
</tr>
<tr>
<td>49</td>
<td>10 and 48</td>
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<tr>
<td>50</td>
<td>(severe adj4 sepsis).tw.</td>
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<td>51</td>
<td>septicemia*.tw.</td>
</tr>
<tr>
<td>52</td>
<td>(blood adj4 poisoning).tw.</td>
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<tr>
<td>53</td>
<td>Sepsis/</td>
</tr>
<tr>
<td>54</td>
<td>Rickets.tw.</td>
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<tr>
<td>55</td>
<td>Rickets/</td>
</tr>
<tr>
<td>56</td>
<td>((nonhodgkin* or non-hodgkin*) adj4 lymphoma*).tw.</td>
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<tr>
<td>57</td>
<td>Lymphoma, Non-Hodgkin/</td>
</tr>
<tr>
<td>58</td>
<td>or/51-57</td>
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<tr>
<td>59</td>
<td>10 and 58</td>
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<tr>
<td>60</td>
<td>49 or 59</td>
</tr>
<tr>
<td>61</td>
<td>exp Diabetes Mellitus, Type 1/</td>
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<tr>
<td>62</td>
<td>(diabet* or (wolfram adj4 syndrome) or (impaired adj4 glucose adj4 intolerance)).tw.</td>
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<tr>
<td>63</td>
<td>exp Thyroiditis/</td>
</tr>
<tr>
<td>64</td>
<td>thyroïdites.tw.</td>
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<tr>
<td>65</td>
<td>(thyroiditis or (hashimoto adj4 disease)).tw.</td>
</tr>
<tr>
<td>66</td>
<td>Addison Disease/</td>
</tr>
<tr>
<td>67</td>
<td>(addison* adj4 disease).tw.</td>
</tr>
<tr>
<td>68</td>
<td>((adrenal or adrenocortical) adj4 insufficiency).tw.</td>
</tr>
<tr>
<td>69</td>
<td>hypocortisolism.tw.</td>
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<tr>
<td>70</td>
<td>hypocorticism.tw.</td>
</tr>
<tr>
<td>71</td>
<td>hypoadrenalism*.tw.</td>
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<tr>
<td>72</td>
<td>exp Lupus Erythematosus, Systemic/</td>
</tr>
<tr>
<td>73</td>
<td>lupus.tw.</td>
</tr>
<tr>
<td>74</td>
<td>Hepatitis, Autoimmune/</td>
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<tr>
<td>75</td>
<td>(auto adj4 immune adj4 (liver or hepatitis)).tw.</td>
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<tr>
<td>76</td>
<td>Turner Syndrome/</td>
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<tr>
<td>77</td>
<td>(turner* adj4 syndrome*).tw.</td>
</tr>
<tr>
<td>78</td>
<td>(bonniev-ullrich adj4 syndrome*).tw.</td>
</tr>
<tr>
<td>79</td>
<td>(gonadal adj4 dysgenesis).tw.</td>
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<tr>
<td>80</td>
<td>exp Alopecia/</td>
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<tr>
<td>81</td>
<td>(alopecia or (follicular adj4 mucinosis)).tw.</td>
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<tr>
<td>82</td>
<td>baldness.tw.</td>
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<tr>
<td>83</td>
<td>IgA Deficiency/</td>
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<tr>
<td>84</td>
<td>iga deficienc*.tw.</td>
</tr>
<tr>
<td>85</td>
<td>Down Syndrome/</td>
</tr>
<tr>
<td>86</td>
<td>(down* adj4 syndrome*).tw.</td>
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<tr>
<td>87</td>
<td>(trisomy adj4 (hypocorticism or &quot;21&quot;).tw.</td>
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<tr>
<td>88</td>
<td>Williams Syndrome/</td>
</tr>
<tr>
<td>89</td>
<td>(william* adj4 syndrome*).tw.</td>
</tr>
<tr>
<td>90</td>
<td>(elfin adj4 face* adj4 syndrome*).tw.</td>
</tr>
<tr>
<td>91</td>
<td>Sjogren's Syndrome/</td>
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<tr>
<td>92</td>
<td>((Sjogren* or sjoe gren* or sicca*) adj4 Syndrome*).tw.</td>
</tr>
<tr>
<td>93</td>
<td>Comorbidity/</td>
</tr>
<tr>
<td>94</td>
<td>(co-morbid* or comorbid* or co-exist* or coexist* or co-occur* or cooccur*).tw.</td>
</tr>
<tr>
<td>95</td>
<td>or/61-94</td>
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<td>---------------------------------------------------------------</td>
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<tr>
<td>Database: Ovid MEDLINE(R) &lt;1946 to July Week 2 2013&gt;</td>
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<tr>
<td>Search Strategy:</td>
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<tr>
<td>96 10 and 95</td>
<td></td>
</tr>
<tr>
<td>97 exp Abdominal Pain/</td>
<td></td>
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<tr>
<td>98 (abdominal adj4 (distension or pain or bloat* or cramp*)).tw.</td>
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</tr>
<tr>
<td>99 (stomach adj4 (distension or pain or bloat* or cramp*)).tw.</td>
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<tr>
<td>100 exp Diarrhea/</td>
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<tr>
<td>101 (diarrhoea or diarrhea).tw.</td>
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<tr>
<td>102 Constipation/</td>
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<tr>
<td>103 constipat*.tw.</td>
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</tr>
<tr>
<td>104 (colonic adj4 inertia).tw.</td>
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<tr>
<td>105 (irritable adj4 colon).tw.</td>
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<tr>
<td>106 ((mucous or mucus) adj4 (colitis or colotides)).tw.</td>
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<tr>
<td>107 Steatorrhea/</td>
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<tr>
<td>108 (steatorrhoea or steatorrhea).tw.</td>
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<tr>
<td>109 Flatulence/</td>
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<tr>
<td>110 flatulence.tw.</td>
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<tr>
<td>111 flatus.tw.</td>
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<tr>
<td>112 meteorism.tw.</td>
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<tr>
<td>113 Irritable bowel syndrome/</td>
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<tr>
<td>114 (irritable adj4 bowel adj4 syndrome).tw.</td>
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<tr>
<td>115 ibs.tw.</td>
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<tr>
<td>116 Vomiting/</td>
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<td>117 Nausea/</td>
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<tr>
<td>118 (nausea or vomit*).tw.</td>
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<tr>
<td>119 emesis.tw.</td>
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<tr>
<td>120 Fatigue/</td>
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<td>121 Lethargy/</td>
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<td>122 (malaise or fatigue or letharg* or exhaust*).tw.</td>
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<tr>
<td>123 exp Weight loss/</td>
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<tr>
<td>124 (weight adj4 los*).tw.</td>
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<tr>
<td>125 (weight adj4 reduc*).tw.</td>
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<tr>
<td>126 malnutrition.tw.</td>
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<tr>
<td>127 emaciat*.tw.</td>
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<tr>
<td>128 Anorexia/</td>
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<tr>
<td>129 anorexia.tw.</td>
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<tr>
<td>130 Stomatitis, Aphthous/</td>
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<tr>
<td>131 (aphthous adj4 (stomatitis or stomatitides)).tw.</td>
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<tr>
<td>132 (aphthous adj4 ulcer*).tw.</td>
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<tr>
<td>133 aphthae.tw.</td>
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<tr>
<td>134 (canker adj4 sore*).tw.</td>
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<tr>
<td>135 Oral Ulcer/</td>
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<tr>
<td>136 (oral adj4 ulcer*).tw.</td>
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<td>137 (mouth adj4 ulcer*).tw.</td>
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<tr>
<td>138 Anemia, Iron-Deficiency/</td>
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<tr>
<td>139 (iron adj4 deficien*).tw.</td>
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<tr>
<td>140 (vitamin adj4 (k or d) adj4 deficien*).tw.</td>
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<tr>
<td>141 Peripheral Nervous System Diseases/</td>
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<tr>
<td>142 peripheral neuropath*.tw.</td>
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<tr>
<td>143 (peripheral adj4 nerv* adj4 disease*).tw.</td>
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<tr>
<td>144 (pns adj4 disease*).tw.</td>
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</table>
### Medline Strategy, searched 24th July 2013 – 28th August 2014

**Database:** Ovid MEDLINE(R) <1946 to July Week 2 2013>

**Search Strategy:**

| 145 | (Peripheral adj4 (oedema or edema)).tw. |
| 146 | exp Ataxia/ |
| 147 | (ataxia* or (machado adj4 joseph) or (narp adj4 syndrome) or (olivopontocerebellar adj4 atrophy) or (spinocerebellar adj4 degeneration) or (hippel adj4 lindau) or (incoordination* or inco-ordination* or dysco-ordination* or dysco-ordination* or dyssynergia or dys-synergia) or (coordination adj4 lack*) or (co-ordination adj4 lack*) or (coordination adj4 impair*) or (co-ordination adj4 impair*) or (rubral adj4 tremor*)) .tw. |
| 148 | Infertility/ |
| 149 | Infertility, Male/ |
| 150 | Infertility, Female/ |
| 151 | (infertility or subfertility or sub-fertility or sterility).tw. |
| 152 | (reduc* adj4 fertility).tw. |
| 153 | (recurrent adj4 miscarriage).tw. |
| 154 | Growth Disorders/ |
| 155 | Failure to thrive/ |
| 156 | (fail* adj4 thrive*).tw. |
| 157 | (cerebrospinal adj4 degeneration*).tw. |
| 158 | (short adj stature).tw. |
| 159 | (growth adj4 disorder*).tw. |
| 160 | Osteoporosis/ |
| 161 | (osteoporosis or osteoporoses).tw. |
| 162 | osteopenia.tw. |
| 163 | Osteomalacia/ |
| 164 | osteomalacia*.tw. |
| 165 | Puberty, Delayed/ |
| 166 | (delayed adj4 puberty).tw. |
| 167 | Headache/ |
| 168 | Headache disorders/ |
| 169 | (headache* or migraine).tw. |
| 170 | exp Epilepsy/ |
| 171 | (epilep* or seizure*).tw. |
| 172 | Depression/ |
| 173 | (depression* or depressive* or anxiet* or melanchol* or dysphoria or dysthmia or bipolar or bi-polar).tw. |
| 174 | Anxiety/ |
| 175 | Anxiety Disorders/ |
| 176 | (enamel adj4 defect*).tw. |
| 177 | (tooth adj4 discoloration).tw. |
| 178 | (tooth adj4 discoloration).tw. |
| 179 | (arthriti* or (still* adj4 disease) or (felty adj4 syndrome) or (rheumatoid adj4 nodule)).tw. |
| 180 | exp Rheumatoid Arthritis/ |
| 181 | "Signs and Symptoms"/ |
| 182 | ((sign or signs) adj6 symptom*).tw. |
| 183 | Risk Factors/ |
| 184 | factor*.tw. |
| 185 | predict*.tw. |
| 186 | or/97-185 |
| 187 | 10 and 186 |
| 188 | Liver/en [Enzymology] |
| 189 | Liver Diseases/en [Enzymology] |
### Medline Strategy, searched 24th July 2013 – 28th August 2014

**Database: Ovid MEDLINE(R) <1946 to July Week 2 2013>**

**Search Strategy:**

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<tbody>
<tr>
<td>190</td>
<td>((abnormal* or dysfunction*) adj4 liver*).tw.</td>
</tr>
<tr>
<td>191</td>
<td>((elevat* or high* or raise*) adj4 liver*).tw.</td>
</tr>
<tr>
<td>192</td>
<td>Amenorrhea/</td>
</tr>
<tr>
<td>193</td>
<td>Oligomenorrhea/</td>
</tr>
<tr>
<td>194</td>
<td>(amenorrhea* or amenorrhoea* or oligomenorrhea* or oligomenorrhoea*).tw.</td>
</tr>
<tr>
<td>195</td>
<td>Menstruation Disturbances/</td>
</tr>
<tr>
<td>196</td>
<td>((absen* or cease* or stop*) adj4 (period* or menstruat* or menses)).tw.</td>
</tr>
<tr>
<td>197</td>
<td>hyposplen*.tw.</td>
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<tr>
<td>198</td>
<td>splenic diseases/</td>
</tr>
<tr>
<td>199</td>
<td>spleen/</td>
</tr>
<tr>
<td>200</td>
<td>spleen*.tw.</td>
</tr>
<tr>
<td>201</td>
<td>(gluten adj4 (sensitiv* or neuropath*)).tw.</td>
</tr>
<tr>
<td>202</td>
<td>exp Calcinosis/ and exp brain/</td>
</tr>
<tr>
<td>203</td>
<td>((calcinos* or calcificat* or calcium*) adj4 (brain* or intracerebr* or intracran* or cerebr*)).tw.</td>
</tr>
<tr>
<td>204</td>
<td>Intussusception/</td>
</tr>
<tr>
<td>205</td>
<td>(intestin* adj4 (obstruct* or invaginat*)).tw.</td>
</tr>
<tr>
<td>206</td>
<td>(intussuscept* or intususcept*).tw.</td>
</tr>
<tr>
<td>207</td>
<td>Intestine Lymphoma/</td>
</tr>
<tr>
<td>208</td>
<td>Lymphoma/</td>
</tr>
<tr>
<td>209</td>
<td>lymphom*.tw.</td>
</tr>
<tr>
<td>210</td>
<td>207 or 208</td>
</tr>
<tr>
<td>211</td>
<td>exp Intestines/</td>
</tr>
<tr>
<td>212</td>
<td>(intestin* or bowel or gut).tw.</td>
</tr>
<tr>
<td>213</td>
<td>(gastrointestin* adj4 tract).tw.</td>
</tr>
<tr>
<td>214</td>
<td>or/210-212</td>
</tr>
<tr>
<td>215</td>
<td>209 and 213</td>
</tr>
<tr>
<td>216</td>
<td>Esophageal Neoplasms/</td>
</tr>
<tr>
<td>217</td>
<td>((oesophag* or esophag*) adj4 (neoplasm* or cancer* or carcinoma* or adenocarcinom* or tumour* or tumor* or malignant* or metastas* or lesion*)).tw.</td>
</tr>
<tr>
<td>218</td>
<td>exp Colonic Neoplasms/</td>
</tr>
<tr>
<td>219</td>
<td>((colon* or sigmoid*) adj4 (neoplasm* or cancer* or carcinoma* or adenocarcinom* or tumour* or tumor* or malignant* or metastas* or lesion*)).tw.</td>
</tr>
<tr>
<td>220</td>
<td>(Gardner* adj4 syndrome*).tw.</td>
</tr>
<tr>
<td>221</td>
<td>(polypos* adj4 (col* or intestin*)).tw.</td>
</tr>
<tr>
<td>222</td>
<td>exp anemia/</td>
</tr>
<tr>
<td>223</td>
<td>(anaemia* or anemia*).tw.</td>
</tr>
<tr>
<td>224</td>
<td>(ulcer* adj4 jejun*).tw.</td>
</tr>
<tr>
<td>225</td>
<td>exp Jejunal Diseases/</td>
</tr>
<tr>
<td>226</td>
<td>((inflam* or lesion*) adj4 jejun*).tw.</td>
</tr>
<tr>
<td>227</td>
<td>refractor*.tw.</td>
</tr>
<tr>
<td>228</td>
<td>(unrespon* or non-respon* or nonrespon* or non respon*).tw.</td>
</tr>
<tr>
<td>229</td>
<td>(fail* adj4 respon*).tw.</td>
</tr>
<tr>
<td>230</td>
<td>((ongoing or recur*) adj4 symptom*).tw.</td>
</tr>
<tr>
<td>231</td>
<td>exp Fractures, bone/</td>
</tr>
<tr>
<td>232</td>
<td>fractur*.tw.</td>
</tr>
<tr>
<td>233</td>
<td>(bone* adj4 (mineral* or densit* or soft* or decay*)).tw.</td>
</tr>
<tr>
<td>234</td>
<td>Vitamin D Deficiency/</td>
</tr>
<tr>
<td>235</td>
<td>avitaminosis D.tw.</td>
</tr>
<tr>
<td>236</td>
<td>((calciferol or cholecalciferol or colecalciferol or egocalciferol) adj4 deficien*).tw.</td>
</tr>
</tbody>
</table>
### Database: Ovid MEDLINE(R) <1946 to July Week 2 2013>

### Search Strategy:

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<thead>
<tr>
<th>Term</th>
<th>Description</th>
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</thead>
<tbody>
<tr>
<td>Vitamin B 12 Deficiency/</td>
<td></td>
</tr>
<tr>
<td>Folic Acid Deficiency/</td>
<td></td>
</tr>
<tr>
<td>((folic* or folat* or cyanocobalamin or vitamin*) adj4 defici*).tw.</td>
<td></td>
</tr>
<tr>
<td>Myocarditis/im [Immunology]</td>
<td></td>
</tr>
<tr>
<td>(autoimmune adj4 myocarditis).tw.</td>
<td></td>
</tr>
<tr>
<td>exp Bipolar Disorder/</td>
<td></td>
</tr>
<tr>
<td>(bipolar or mania*).tw.</td>
<td></td>
</tr>
<tr>
<td>((manic or depressive) adj4 (state* or episod* or psychos?s or disorder* or syndrom* or depression* or illness* or reaction*)).tw.</td>
<td></td>
</tr>
<tr>
<td>Cardiomyopathies/</td>
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<tr>
<td>Cardiomyopathy, dilated/</td>
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<tr>
<td>cardiomyopath*.tw.</td>
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</tr>
<tr>
<td>myocardopath*.tw.</td>
<td></td>
</tr>
<tr>
<td>(myocardial* adj4 disease*).tw.</td>
<td></td>
</tr>
<tr>
<td>(heart adj4 myopath*).tw.</td>
<td></td>
</tr>
<tr>
<td>(heart adj4 muscle adj4 disease*).tw.</td>
<td></td>
</tr>
<tr>
<td>(cardiac adj4 muscle adj4 disease*).tw.</td>
<td></td>
</tr>
<tr>
<td>(myocardial adj4 muscle adj4 disease*).tw.</td>
<td></td>
</tr>
<tr>
<td>(deteriorat* adj4 ((myocardium or heart or cardiac) adj4 muscle)).tw.</td>
<td></td>
</tr>
<tr>
<td>exp Purpura, Thrombocytopenic/</td>
<td></td>
</tr>
<tr>
<td>(thrombocytopen* adj4 purpura*).tw.</td>
<td></td>
</tr>
<tr>
<td>Dermatitis Herpetiformis/</td>
<td></td>
</tr>
<tr>
<td>(dermatitis adj4 herpetiformis).tw.</td>
<td></td>
</tr>
<tr>
<td>((duhring* or duehring* or duhrig* or duehrig*) adj4 (dermatit* or disease* or brocq* or brock* or morbus*)).tw.</td>
<td></td>
</tr>
<tr>
<td>exp HIV/</td>
<td></td>
</tr>
<tr>
<td>exp HIV Infections/</td>
<td></td>
</tr>
<tr>
<td>(HIV or AIDS).tw.</td>
<td></td>
</tr>
<tr>
<td>(acquired adj4 immunodeficien* adj4 syndrome*).tw.</td>
<td></td>
</tr>
<tr>
<td>(human adj4 immunodeficien* adj4 virus*).tw.</td>
<td></td>
</tr>
<tr>
<td>(lymphadenopath* adj4 assoc adj4 virus*).tw.</td>
<td></td>
</tr>
<tr>
<td>(lav-htlv-iii or lav htlv iii).tw.</td>
<td></td>
</tr>
<tr>
<td>(htlv-iii or htlv iii).tw.</td>
<td></td>
</tr>
<tr>
<td>(human* adj4 t?cell* adj4 leuk?emia*).tw.</td>
<td></td>
</tr>
<tr>
<td>(human* adj4 t?cell* adj4 lymphotrop*).tw.</td>
<td></td>
</tr>
<tr>
<td>exp Colitis, Microscopic/</td>
<td></td>
</tr>
<tr>
<td>((microscop* or collagen* or lymphoc*) adj4 colitis*).tw.</td>
<td></td>
</tr>
<tr>
<td>Liver Cirrhosis, Biliary/</td>
<td></td>
</tr>
<tr>
<td>((biliar* or liver*) adj4 cirrhos*).tw.</td>
<td></td>
</tr>
<tr>
<td>exp Sarcoidosis/</td>
<td></td>
</tr>
<tr>
<td>sarcoidos*.tw.</td>
<td></td>
</tr>
<tr>
<td>((besnier* or boeck* or schaumann* or heerfordt* or Jungling*) adj4 (syndrome* or disease* or sarcoid*)).tw.</td>
<td></td>
</tr>
<tr>
<td>(lupus adj4 pernio).tw.</td>
<td></td>
</tr>
<tr>
<td>(lymphogranuloma adj4 benignum).tw.</td>
<td></td>
</tr>
<tr>
<td>neurosarcoidosis.tw.</td>
<td></td>
</tr>
<tr>
<td>(sarcoi* adj4 granulome).tw.</td>
<td></td>
</tr>
</tbody>
</table>
**Appendix C: Review Protocols & Search Strategy**

**Medline Strategy, searched 24th July 2013 – 28th August 2014**
**Database: Ovid MEDLINE(R) <1946 to July Week 2 2013>**

**Search Strategy:**

<table>
<thead>
<tr>
<th>Step</th>
<th>Search Term</th>
</tr>
</thead>
<tbody>
<tr>
<td>284</td>
<td>(uveo adj4 parotid adj4 fever*).tw.</td>
</tr>
<tr>
<td>285</td>
<td>(uveoparotid adj4 fever*).tw.</td>
</tr>
<tr>
<td>286</td>
<td>or/188-207</td>
</tr>
<tr>
<td>287</td>
<td>or/215-285</td>
</tr>
<tr>
<td>288</td>
<td>286 or 287</td>
</tr>
<tr>
<td>289</td>
<td>10 and 288</td>
</tr>
<tr>
<td>290</td>
<td>36 or 60 or 98 or 187 or 289</td>
</tr>
<tr>
<td>291</td>
<td>animals/ not humans/</td>
</tr>
<tr>
<td>292</td>
<td>290 not 291</td>
</tr>
<tr>
<td>293</td>
<td>limit 292 to english language</td>
</tr>
</tbody>
</table>

<Insert Note here>

A.2.2 **Search strategy review question 4.4**

Should active case-finding be implemented in people with co-existing conditions/subgroups that are associated with an increased risk of coeliac disease?

**Table 2: search strategy 4.4**

**Medline Strategy, searched 28th July 2014**
**Database: Ovid MEDLINE(R) <1946 to July Week 3 2014>**

**Search Strategy:**

<table>
<thead>
<tr>
<th>Step</th>
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<tbody>
<tr>
<td>1</td>
<td>(coeliac adj4 disease).tw.</td>
</tr>
<tr>
<td>2</td>
<td>(celiac adj4 disease).tw.</td>
</tr>
<tr>
<td>3</td>
<td>(coeliac adj4 sprue).tw.</td>
</tr>
<tr>
<td>4</td>
<td>(celiac adj4 sprue).tw.</td>
</tr>
<tr>
<td>5</td>
<td>((nontropical or non tropical) adj4 sprue).tw.</td>
</tr>
<tr>
<td>6</td>
<td>((celiac or coeliac) adj4 syndrome).tw.</td>
</tr>
<tr>
<td>7</td>
<td>(gluten adj4 (enteropath$ or sensitiv$ or hypersensitiv$ or intoleran$)).tw.</td>
</tr>
<tr>
<td>8</td>
<td>((glutenin or gliadin) adj4 (sensitiv$ or hypersensitiv$ or intoleran$)).tw.</td>
</tr>
<tr>
<td>9</td>
<td>Celiac Disease/</td>
</tr>
<tr>
<td>10</td>
<td>or/1-9</td>
</tr>
<tr>
<td>11</td>
<td>Mass Screening/</td>
</tr>
<tr>
<td>12</td>
<td>exp Population Surveillance/</td>
</tr>
<tr>
<td>13</td>
<td>Case Management/</td>
</tr>
<tr>
<td>14</td>
<td>Diagnostic Tests, Routine/</td>
</tr>
<tr>
<td>15</td>
<td>(case* adj4 (find* or manage*)).tw.</td>
</tr>
<tr>
<td>16</td>
<td>(active* adj4 screen*).tw.</td>
</tr>
<tr>
<td>17</td>
<td>((routin* or target* or population*) adj4 (screen* or detect* or surveill*)).tw.</td>
</tr>
<tr>
<td>18</td>
<td>((find* or case*) adj4 (undiagnos* or undetect*)).tw.</td>
</tr>
<tr>
<td>19</td>
<td>((active* or screen* or early or proactiv*) adj4 (detect* or investigat*)).tw.</td>
</tr>
<tr>
<td>20</td>
<td>early diagnosis/</td>
</tr>
<tr>
<td>21</td>
<td>(early adj4 diagnos*).tw.</td>
</tr>
<tr>
<td>22</td>
<td>or/11-21</td>
</tr>
<tr>
<td>23</td>
<td>10 and 22</td>
</tr>
<tr>
<td>24</td>
<td>animals/ not humans/</td>
</tr>
<tr>
<td>25</td>
<td>23 not 24</td>
</tr>
<tr>
<td>26</td>
<td>limit 25 to english language</td>
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</tbody>
</table>

<Insert Note here>
A.2.3 Search strategy review questions 5.1 & 5.2

Review 5.1
a) What is the sensitivity and specificity of the serological tests for coeliac disease?
b) Are the sensitivity and specificity results different in any specified subgroups?

Review 5.2
a) Which serological test is the most appropriate to diagnose coeliac disease?
b) Depending on test results, should more than one test be used and, if so, what should be the sequence of testing?
c) Following which sequence of tests and test results is it appropriate to refer onwards for endoscopic intestinal biopsy for confirmatory diagnosis?

Table 3: search strategy 5.1 & 5.2

<table>
<thead>
<tr>
<th>Medline Strategy, searched 11th October 2013</th>
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<tbody>
<tr>
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<tr>
<td>Search Strategy:</td>
</tr>
<tr>
<td>1 (coeliac adj4 disease).tw.</td>
</tr>
<tr>
<td>2 (celiac adj4 disease).tw.</td>
</tr>
<tr>
<td>3 (coeliac adj4 sprue).tw.</td>
</tr>
<tr>
<td>4 (celiac adj4 sprue).tw.</td>
</tr>
<tr>
<td>5 ((nontropical or non tropical) adj4 sprue).tw.</td>
</tr>
<tr>
<td>6 ((celiac or coeliac) adj4 syndrome).tw.</td>
</tr>
<tr>
<td>7 (gluten adj4 (enteropath* or sensitive* or hypersensitive* or intoleran*)).tw.</td>
</tr>
<tr>
<td>8 ((glutenin or gliadin) adj4 (sensitive* or hypersensitive* or intoleran*)).tw.</td>
</tr>
<tr>
<td>9 Celiac Disease/</td>
</tr>
<tr>
<td>10 or/1-9</td>
</tr>
<tr>
<td>11 (endomyasi* adj4 antibody*).tw.</td>
</tr>
<tr>
<td>12 (immunglobulin adj4 endomyasi*).tw.</td>
</tr>
<tr>
<td>13 ((anti-endomyasi* or antiendomyasi* or anti endomyasi*) adj antibody*).tw.</td>
</tr>
<tr>
<td>14 ((iga or igg) adj4 endomyasi*).tw.</td>
</tr>
<tr>
<td>15 ((iga or igg) adj4 (anti-endomyasi* or antiendomyasi* or anti endomyasi*)).tw.</td>
</tr>
<tr>
<td>16 (immunglobulin adj4 (anti-endomyasi* or antiendomyasi* or anti endomyasi*)).tw.</td>
</tr>
<tr>
<td>17 (iga-ema or igg-ema).tw.</td>
</tr>
<tr>
<td>18 ema.tw.</td>
</tr>
<tr>
<td>19 or/11-18</td>
</tr>
<tr>
<td>20 10 and 19</td>
</tr>
<tr>
<td>21 (transglutaminase adj4 antibody*).tw.</td>
</tr>
<tr>
<td>22 (tissue adj4 transglutaminase adj4 antibody*).tw.</td>
</tr>
<tr>
<td>23 (((anti-tissue or antitissue or anti tissue) adj4 transglutaminase) and antibody*).tw.</td>
</tr>
<tr>
<td>24 (immunglobulin adj4 transglutaminase).tw.</td>
</tr>
<tr>
<td>25 ((iga or igg) adj4 transglutaminase).tw.</td>
</tr>
<tr>
<td>26 (anti-httg or anti-htg).tw.</td>
</tr>
<tr>
<td>27 ((anti-human or antihuman or anti human) adj4 transglutaminase adj4 antibody*).tw.</td>
</tr>
<tr>
<td>28 transglutaminases/</td>
</tr>
<tr>
<td>29 tTG.tw.</td>
</tr>
<tr>
<td>30 or/21-29</td>
</tr>
<tr>
<td>31 10 and 30</td>
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</table>
**A.2.4 Search strategy review question 5.3**

What are the referral indications for endoscopic intestinal biopsy for further investigation in people with coeliac disease?

**Table 4: search strategy 5.3**

<table>
<thead>
<tr>
<th>Search Strategy</th>
<th>Description</th>
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</thead>
<tbody>
<tr>
<td>1</td>
<td>(coeliac adj4 disease).tw.</td>
</tr>
<tr>
<td>2</td>
<td>(celiac adj4 disease).tw.</td>
</tr>
<tr>
<td>3</td>
<td>(coeliac adj4 sprue).tw.</td>
</tr>
<tr>
<td>4</td>
<td>(celiac adj4 sprue).tw.</td>
</tr>
<tr>
<td>5</td>
<td>((nontropical or non tropical) adj4 sprue).tw.</td>
</tr>
</tbody>
</table>
### Medline Strategy, searched 17th April 2014

**Database:** Ovid MEDLINE(R) <1946 to April Week 2 2014>

**Search Strategy:**

| 6 | ((celiac or coeliac) adj4 syndrome).tw. |
| 7 | (gluten adj4 (enteropath* or sensitiv* or hypersensitiv* or intoleran*)).tw. |
| 8 | ((glutenin or gliadin) adj4 (sensitiv* or hypersensitiv* or intoleran*)).tw. |
| 9 | Celiac Disease/ |
| 10 | or/1-9 |
| 11 | Biopsy/ |
| 12 | Biopsy Needle/ |
| 13 | exp Image-Guided Biopsy/ |
| 14 | biops*.tw. |
| 15 | or/11-14 |
| 16 | exp Intestines/ |
| 17 | intestin*.tw. |
| 18 | Duodenum/ |
| 19 | (duodenum or duodenal).tw. |
| 20 | or/16-19 |
| 21 | 10 and 15 and 20 |
| 22 | Endoscopy/ |
| 23 | (endoscop* or scope*).tw. |
| 24 | Endoscopy, Gastrointestinal/ |
| 25 | Capsule Endoscopy/ |
| 26 | Duodenoscopy/ |
| 27 | duodenoscop*.tw. |
| 28 | Gastroscopy/ |
| 29 | gastroscop*.tw. |
| 30 | Esophagoscopy/ |
| 31 | (esophagoscop* or oesophagoscop*).tw. |
| 32 | Endoscopy, Digestive System/ |
| 33 | (esophagogastroduodenscop* or oesophagogastroduodenscop*).tw. |
| 34 | or/22-33 |
| 35 | "Referral and Consultation"/ |
| 36 | (refer or referr* or consult* or second opinion* or gatekeep*).tw. |
| 37 | 35 or 36 |
| 38 | 21 and 34 |
| 39 | 21 and 37 |
| 40 | 38 or 39 |
| 41 | animals/ not humans/ |
| 42 | 40 not 41 |
| 43 | limit 42 to english language |

<Insert Note here>

### A.2.5 Search strategy review question 5.4

a) How frequently should people with coeliac disease be routinely monitored?

b) Should the frequency of routine monitoring differ for patients with at risk of developing certain complications?
c) What should routine monitoring consist of?

Table 5: Search strategy 5.4

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<th>Table 5: Search strategy 5.4</th>
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</thead>
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<tr>
<td>2  (celiac adj4 disease).tw.</td>
</tr>
<tr>
<td>3  (coeliac adj4 sprue).tw.</td>
</tr>
<tr>
<td>4  (celiac adj4 sprue).tw.</td>
</tr>
<tr>
<td>5  ((nontropical or non tropical) adj4 sprue).tw.</td>
</tr>
<tr>
<td>6  ((celiac or coeliac) adj4 syndrome).tw.</td>
</tr>
<tr>
<td>7  (gluten adj4 (enteropath* or sensitiv* or hypersensitiv* or intoleran*)).tw.</td>
</tr>
<tr>
<td>8  ((glutenin or gliadin) adj4 (sensitiv* or hypersensitiv* or intoleran*)).tw.</td>
</tr>
<tr>
<td>9  Celiac Disease/</td>
</tr>
<tr>
<td>10 or/1-9</td>
</tr>
<tr>
<td>11 Long-Term Care/</td>
</tr>
<tr>
<td>12 &quot;Continuity of Patient Care&quot;/</td>
</tr>
<tr>
<td>13 exp Patient Care Planning/</td>
</tr>
<tr>
<td>14 Disease Management/</td>
</tr>
<tr>
<td>15 Patient Compliance/</td>
</tr>
<tr>
<td>16 (patient adj4 (compliance or non-compliance or noncompliance or adherence or non-adherence or nonadherence or cooperation or co-operation)).tw. (12335)</td>
</tr>
<tr>
<td>17 lost to follow-up/</td>
</tr>
<tr>
<td>18 ((long-term or long term or longterm or life-long or life long or lifelong or active or adequa* or continu* or frequen* or repeat* or routine* or regular* or histolog* or serolog* or recommend* or length* or timing or time or number or continuity or continuum or optim* or plan or planned or planning) adj4 (followup* or follow-up* or follow up* or assess* or practice* or strateg* or review* or care or manag*)).tw.</td>
</tr>
<tr>
<td>19 monitor*.tw.</td>
</tr>
<tr>
<td>20 time factors/</td>
</tr>
<tr>
<td>21 or/11-20</td>
</tr>
<tr>
<td>22 10 and 21</td>
</tr>
<tr>
<td>23 Bone Density/</td>
</tr>
<tr>
<td>24 Osteoporosis/</td>
</tr>
<tr>
<td>25 exp &quot;Bone and Bones&quot;/</td>
</tr>
<tr>
<td>26 (bone* or osteoporos*).tw.</td>
</tr>
<tr>
<td>27 or/23-26</td>
</tr>
<tr>
<td>28 Serology/</td>
</tr>
<tr>
<td>29 exp Serologic Tests/</td>
</tr>
<tr>
<td>30 (serolog* or serodiagnos*).tw.</td>
</tr>
<tr>
<td>31 or/28-30</td>
</tr>
<tr>
<td>32 Histology/</td>
</tr>
<tr>
<td>33 histolog*.tw.</td>
</tr>
<tr>
<td>34 32 or 33</td>
</tr>
<tr>
<td>35 exp Histological Techniques/</td>
</tr>
<tr>
<td>36 Diet/</td>
</tr>
<tr>
<td>37 Diet, Gluten-Free/</td>
</tr>
<tr>
<td>38 exp Nutrition Therapy/</td>
</tr>
<tr>
<td>39 (diet* or nutrit*).tw.</td>
</tr>
<tr>
<td>40 or/35-39</td>
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</tbody>
</table>
### Search Strategy review question 6.1

a.) What are the potential causes of non-responsive coeliac disease?
b.) In patients with confirmed refractory coeliac disease what investigative procedures should be undertaken, such as:

- Clonality assessment
- Flow cytometry
- Aberrant T cell assessment
- Immunophenotyping
- Imaging

### Table 6: search strategy 6.1

<table>
<thead>
<tr>
<th>Search Strategy</th>
<th>Medline Strategy, searched 22nd April 2014</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Database: Ovid MEDLINE(R) &lt;1946 to April Week 2 2014&gt;</td>
</tr>
<tr>
<td>1</td>
<td>(coeliac adj4 disease).tw.</td>
</tr>
<tr>
<td>2</td>
<td>(celiac adj4 disease).tw.</td>
</tr>
<tr>
<td>3</td>
<td>(coeliac adj4 sprue).tw.</td>
</tr>
<tr>
<td>4</td>
<td>(celiac adj4 sprue).tw.</td>
</tr>
<tr>
<td>5</td>
<td>((nontropical or non tropical) adj4 sprue).tw.</td>
</tr>
<tr>
<td>6</td>
<td>((celiac or coeliac) adj4 syndrome).tw.</td>
</tr>
<tr>
<td>7</td>
<td>(gluten adj4 (enteropath* or sensitiv* or hypersensitiv* or intoleran*)).tw.</td>
</tr>
<tr>
<td>8</td>
<td>(glutenin or gliadin) adj4 (sensitiv* or hypersensitiv* or intoleran*)).tw.</td>
</tr>
<tr>
<td>9</td>
<td>Celiac Disease/</td>
</tr>
<tr>
<td>10</td>
<td>or/1-9</td>
</tr>
<tr>
<td>11</td>
<td>refractor*.tw.</td>
</tr>
<tr>
<td>12</td>
<td>(unrespon* or non-respon* or nonrespon* or non respon*).tw.</td>
</tr>
<tr>
<td>13</td>
<td>(fail* adj4 respon*).tw.</td>
</tr>
<tr>
<td>14</td>
<td>((ongoing or recur*) adj4 symptom*).tw.</td>
</tr>
<tr>
<td>15</td>
<td>((villous* or villus* or villi* or microvilli* or microvillus* or microvillous*) adj4 atroph*).tw.</td>
</tr>
<tr>
<td>16</td>
<td>or/11-15</td>
</tr>
<tr>
<td>17</td>
<td>Microvilli/</td>
</tr>
</tbody>
</table>
Appendix C: Review Protocols & Search Strategy

Medline Strategy, searched 22nd April 2014
Database: Ovid MEDLINE(R) <1946 to April Week 2 2014>
Search Strategy:

18 Atrophy/
19 17 and 18
20 16 or 19
21 10 and 20
22 animals/ not humans/
23 21 not 22
24 limit 23 to english language

A.2.7 Search strategy review question 6.2

What is the effectiveness of pharmacological treatments for people with refractory coeliac disease?

Table 7: search strategy 6.2

Medline Strategy, searched 14th June 2014
Database: Ovid MEDLINE(R) <1946 to June Week 1 2013>
Search Strategy:

1 Celiac Disease/
2 ((coeliac* or celiac*) adj4 disease).tw.
3 (coeliac* or celiac*) adj4 sprue).tw.
4 ((nontropical or non tropical) adj4 sprue).tw.
5 (coeliac* or celiac*) adj4 syndrome).tw.
6 (gluten adj4 (enteropath* or sensitiv* or hypersensitiv* or intoleran*)).tw.
7 (glutenor gliadin) adj4 (sensitiv* or hypersensitiv* or intoleran*)).tw.
8 or/1-7
9 Beclomethasone/ or (beclomethason* or beclametason* or beclometason*).tw.
10 Betamethasone/ or betamethason*.tw.
11 Budesonide/ or budesonid*.tw.
12 Ciclesonide/ or ciclesonid*.tw.
13 Adrenocorticotropic Hormone/
14 (adrenocorticotrop* adj4 hormone*).tw.
15 Corticotropin*.tw.
16 Cortisone/ or cortison*.tw.
17 Deflazacort*.tw.
18 Dexamethasone/ or dexamethason*.tw.
19 Fludrocortisone/ or fludrocortison*.tw.
20 flunisolid*.tw.
21 Hydrocortisone/ or hydrocortison*.tw.
22 Methylprednisolone/ or Methylprednisolon*.tw.
23 Mometasone Furoat*.tw.
24 Prednisolone/
25 prednisolon*.tw.
26 Prednisone/ or prednison*.tw.
27 Cosyntropin/ or (Tetracosactid* or cosyntropin*).tw.
Appendix C: Review Protocols & Search Strategy

Medline Strategy, searched 14th June 2014
Database: Ovid MEDLINE(R) <1946 to June Week 1 2013>

Search Strategy:

28 Triamcinolone/ or Triamcinolon*.tw.
29 Cyclosporine/ or (cyclosporin* or ciclosporin*).tw.
30 Azathioprine/ or (azathioprin* or azatioprin*).tw.
31 infliximab*.tw.
32 adalimumab*.tw.
33 etanercept*.tw.
34 golimumab*.tw.
35 certolizumab*.tw.
36 Cladribine/ or cladribin*.tw.
37 (ASA adj4 preparation*).tw.
38 Mesalamine/ or (mesalamin* or mesalazin*).tw.
39 alemtuzumab*.tw.
40 thioguanine/ or (thioguanin* or tioguanin*).tw.
41 Immunosuppressive Agents/
42 (immunosuppress* adj4 (antiproliferative* or agent* or substance* or drug*)).tw.
43 (immun* adj4 suppress*).tw.
44 Anti-Inflammatory Agents, Non-Steroidal/
45 (steroid* or non-steroid* or nonsteroid* or NSAID*).tw.
46 Antibodies, Monoclonal/
47 ((antibod* adj4 monoclonal*) or anti-tnf*).tw.
48 Antimetabolites/
49 Antimetabolites, Antineoplastic/
50 antimetabol*.tw.
51 Antineoplastic Agents/
52 ((antineoplast* or anti-cancer* or anticancer*) adj4 (drug* or agent*)).tw.
53 ((tumour* or tumor*) adj4 inhibit*).tw.
54 adrenal cortex hormones/
55 glucocorticoids/
56 glucocort*.tw.
57 (adrenal adj4 cortex* adj4 hormon*).tw.
58 (corticosteroid* or corticoid*).tw.
59 or/9-58
60 8 and 59
61 animals/ not humans/
62 60 not 61
63 limit 62 to english language

<Insert Note here>

A.2.8 Search strategy review question 6.3

What is the effectiveness of nutritional management or nutritional support for people with refractory coeliac disease?
Appendix C: Review Protocols & Search Strategy

Table 8: search strategy 6.3

Medline Strategy, searched 13th November 2013
Database: Ovid MEDLINE(R) <1946 to October Week 5 2013>

Search Strategy:

1   (coeliac adj4 disease).tw.
2   (celiac adj4 disease).tw.
3   (coeliac adj4 sprue).tw.
4   (celiac adj4 sprue).tw.
5   ((nontropical or non tropical) adj4 sprue).tw.
6   ((celiac or coeliac) adj4 syndrome).tw.
7   (gluten adj4 (enteropath* or sensitiv* or hypersensitiv* or intoleran*)).tw.
8   ((glutenin or gliadin) adj4 (sensitiv* or hypersensitiv* or intoleran*)).tw.
9   Celiac Disease/
10  or/1-9
11  Diet/
12  ((diet* or food* or nutrition*) adj4 (exclus* or exclus* or restrict* or support* or eliminat*)).tw.
13  Functional Food/
14  Food, Fortified/
15  (food* adj4 (fortif* or enrich* or additiv* or supplement*)).tw.
16  Feeding Method/
17  feed*.tw.
18  Enteral Nutrition/
19  ((enteral* or enteric* or intragastric or intestinal or intraintestinal or oral* or sip or tube or force or gastric) adj4 nutrition*).tw.
20  ((nasogastric* or gastronomy or jejuostomy) adj4 tube*).tw.
21  exp Parenteral Nutrition/
22  ((parenter* or intraven* or hyperalimentation or alimentation or fluid) adj4 nutrition*).tw.
23  exp Food Hypersensitivity/
24  ((egg* or milk or nut or nuts or peanut* or groundnut* or wheat* or soya or fish or shellfish or crustacean* or mollusc* or sesame or soybean or celery or mustard or lupin or sulphur dioxide or food* or nutrition* or diet*) adj4 (hypersensitiv* or allerg*)).tw.
25  Energy Intake/
26  ((nutrition* or food* or diet* or energy or calorie* or caloric) adj4 (intak* or ingest* or uptak* or consum* or method*)).tw.
27  (appetite adj4 regulat*).tw.
28  or/11-27
29  10 and 28
30  animals/ not humans/
31  29 not 30
32  limit 31 to english language

<Insert Note here>

A.2.9 Search strategy review question 6.4

What is the effectiveness of autologous stem cell transplant for people with refractory coeliac disease?
## Table 9: search strategy 6.4

<table>
<thead>
<tr>
<th>Search Strategy:</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Celiac Disease/</td>
</tr>
<tr>
<td>2 (coeliac* or celiac*).tw.</td>
</tr>
<tr>
<td>3 ((nontropical or non tropical) adj4 sprue).tw.</td>
</tr>
<tr>
<td>4 (gluten adj4 (enteropath* or sensitiv* or hypersensitiv* or intoleran*)).tw.</td>
</tr>
<tr>
<td>5 ((gluten or gliadin) adj4 (sensitiv* or hypersensitivi* or tolerant*)).tw.</td>
</tr>
<tr>
<td>6 Enteropathy-Associated T-Cell Lymphoma/</td>
</tr>
<tr>
<td>7 (enteropath* adj4 associat* adj4 T adj4 cell* adj4 lymphom*).tw.</td>
</tr>
<tr>
<td>8 EATL.tw.</td>
</tr>
<tr>
<td>9 or/1-8</td>
</tr>
<tr>
<td>10 Hematopoietic Stem Cell Transplantation/</td>
</tr>
<tr>
<td>11 ((hematopoiet* or hemoatopoet* or haematopoiet* or haemoatopoet* or autolog* or allogen*) adj4 (stem or cell* or transplant* or transfer* or treat*)).tw.</td>
</tr>
<tr>
<td>12 Auto-SCT.tw.</td>
</tr>
<tr>
<td>13 ((stem adj4 cell*) and (support* or transfer* or transplant* or treat*)).tw.</td>
</tr>
<tr>
<td>14 autotransplant*.tw.</td>
</tr>
<tr>
<td>15 autograft*.tw.</td>
</tr>
<tr>
<td>16 ASCT.tw.</td>
</tr>
<tr>
<td>17 HSCT.tw.</td>
</tr>
<tr>
<td>18 or/10-17</td>
</tr>
<tr>
<td>19 hematopoietic stem cells/</td>
</tr>
<tr>
<td>20 ((hematopoiet* or hematopoet* or haematopoiet* or haemoatopoet*) adj4 cell*).tw.</td>
</tr>
<tr>
<td>21 19 or 20</td>
</tr>
<tr>
<td>22 Transplantation/</td>
</tr>
<tr>
<td>23 Stem Cell Transplantation/</td>
</tr>
<tr>
<td>24 Transplants/</td>
</tr>
<tr>
<td>25 Cell Transplantation/</td>
</tr>
<tr>
<td>26 (transfer* or transplant* or graft*).tw.</td>
</tr>
<tr>
<td>27 or/22-26</td>
</tr>
<tr>
<td>28 21 and 27</td>
</tr>
<tr>
<td>29 18 or 28</td>
</tr>
<tr>
<td>30 exp drug therapy/</td>
</tr>
<tr>
<td>31 chemo*.tw.</td>
</tr>
<tr>
<td>32 30 or 31</td>
</tr>
<tr>
<td>33 29 or 32</td>
</tr>
<tr>
<td>34 9 and 33</td>
</tr>
<tr>
<td>35 animals/ not Humans/</td>
</tr>
<tr>
<td>36 34 not 35</td>
</tr>
<tr>
<td>37 limit 36 to english language</td>
</tr>
</tbody>
</table>

<Insert Note here>

### A.2.10 Search strategy review questions 7.1 & 7.2

**Review 7.1**

a) What information do people (and their family members or carers, as appropriate) need to help them decide whether to undergo initial testing for coeliac disease?
Appendix C: Review Protocols & Search Strategy

b) If people are to undergo initial testing, what dietary information do they (or their family members or carers) need before testing to ensure that test results are as accurate as possible?

Review 7.2

a) What information, education and support do people with coeliac disease (and their family members or carers, as appropriate) need to improve adherence to a gluten-free diet and self-management of their condition?

b) What is the patient perspective of self-management and how to improve adherence, including what information is required, different monitoring strategies, and with whom they are followed up?

Table 10: search strategy 7.1 & 7.2

<table>
<thead>
<tr>
<th>Medline Strategy, searched 8th May 2014</th>
<th>Database: Ovid MEDLINE(R) &lt;1946 to April Week 5 2014&gt;</th>
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</thead>
<tbody>
<tr>
<td>Search Strategy:</td>
<td></td>
</tr>
<tr>
<td>1 (coeliac adj4 disease).tw.</td>
<td></td>
</tr>
<tr>
<td>2 (celiac adj4 disease).tw.</td>
<td></td>
</tr>
<tr>
<td>3 (coeliac adj4 sprue).tw.</td>
<td></td>
</tr>
<tr>
<td>4 (celiac adj4 sprue).tw.</td>
<td></td>
</tr>
<tr>
<td>5 ((nontropical or non tropical) adj4 sprue).tw.</td>
<td></td>
</tr>
<tr>
<td>6 ((celiac or coeliac) adj4 syndrome).tw.</td>
<td></td>
</tr>
<tr>
<td>7 (gluten adj4 (enteropath* or sensitiv* or hypersensitiv* or intoleran*)).tw.</td>
<td></td>
</tr>
<tr>
<td>8 ((glutenin or gliadin) adj4 (sensitiv* or hypersensitiv* or intoleran*)).tw.</td>
<td></td>
</tr>
<tr>
<td>9 Celiac Disease/</td>
<td></td>
</tr>
<tr>
<td>10 or/1-9</td>
<td></td>
</tr>
<tr>
<td>11 Qualitative Research/</td>
<td></td>
</tr>
<tr>
<td>12 Nursing Methodology Research/</td>
<td></td>
</tr>
<tr>
<td>13 exp Interviews as topic/</td>
<td></td>
</tr>
<tr>
<td>14 Questionnaires/</td>
<td></td>
</tr>
<tr>
<td>15 Narration/</td>
<td></td>
</tr>
<tr>
<td>16 Health Care Surveys/</td>
<td></td>
</tr>
<tr>
<td>17 (qualitative* or interview* or focus group* or questionnaire* or narrative* or narration* or survey*).tw.</td>
<td></td>
</tr>
<tr>
<td>18 (ethno* or emic or etic or phenomenolog* or grounded theory or constant compar* or (thematic* adj4 analys*) or theoretical sampl* or purposive sampl*).tw.</td>
<td></td>
</tr>
<tr>
<td>19 (hermeneutic* or heidegger* or husser* or colaizzi* or van kaam* or van manen* or giorgi* or glaser* or strauss* or ricoeur* or spiegelberg* or merleau*).tw.</td>
<td></td>
</tr>
<tr>
<td>20 (metasynthes* or meta-synthes* or metasummar* or meta-summar* or metastud* or meta-stud* or metatham* or meta-them*).tw.</td>
<td></td>
</tr>
<tr>
<td>21 or/11-20</td>
<td></td>
</tr>
<tr>
<td>22 exp Patients/px</td>
<td></td>
</tr>
<tr>
<td>23 exp Family/px</td>
<td></td>
</tr>
<tr>
<td>24 Caregivers/px</td>
<td></td>
</tr>
<tr>
<td>25 ((patient* or parent* or famil* or relative* or carer* or caregiver* or care-giver* or spouses* or husband* or wife* or wife* or partner* or mother* or father* or sibling* or sister* or brother* or inpatient* or in-patient*) adj10 (experience* or belief* or stress* or emotion* or anx* or fear* or concern* or uncertain* or unsure or thought* or feeling* or felt* or view* or opinion* or perception* or perspective* or attitude* or satisfact* or know* or understand* or aware*).ti.</td>
<td></td>
</tr>
<tr>
<td>26 Stress, Psychological/</td>
<td></td>
</tr>
<tr>
<td>27 Adaptation, psychological/</td>
<td></td>
</tr>
<tr>
<td>28 Emotions/</td>
<td></td>
</tr>
<tr>
<td>29 Anxiety/</td>
<td></td>
</tr>
</tbody>
</table>
### Medline Strategy, searched 8th May 2014
Database: Ovid MEDLINE(R) <1946 to April Week 5 2014>

**Search Strategy:**

<p>| | |</p>
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</thead>
<tbody>
<tr>
<td>30</td>
<td>Fear/</td>
</tr>
<tr>
<td>31</td>
<td>exp Consumer Satisfaction/</td>
</tr>
<tr>
<td>32</td>
<td>patient* report* outcome*.tw.</td>
</tr>
<tr>
<td>33</td>
<td>or/22-32</td>
</tr>
<tr>
<td>34</td>
<td>exp Patients/</td>
</tr>
<tr>
<td>35</td>
<td>exp Family/</td>
</tr>
<tr>
<td>36</td>
<td>Caregivers/</td>
</tr>
<tr>
<td>37</td>
<td>(patient* or parent* or famil* or relative* or carer* or caregiver* or care-giver* or spous* or husband* or wife* or partner* or mother* or father* or sibling* or sister* or brother* or inpatient* or in-patient*).ti.</td>
</tr>
<tr>
<td>38</td>
<td>or/34-37</td>
</tr>
<tr>
<td>39</td>
<td>Pamphlets/</td>
</tr>
<tr>
<td>40</td>
<td>Needs Assessment/</td>
</tr>
<tr>
<td>41</td>
<td>Information Centers/</td>
</tr>
<tr>
<td>42</td>
<td>Information Services/</td>
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<td>43</td>
<td>Health Education/</td>
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<td>44</td>
<td>Information Dissemination/</td>
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<td>Counseling/</td>
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<td>Social Support/</td>
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<td>47</td>
<td>Self-Help Groups/</td>
</tr>
<tr>
<td>48</td>
<td>Self Care/</td>
</tr>
<tr>
<td>49</td>
<td>((patient* or parent* or famil* or relative* or carer* or caregiver* or care-giver* or spous* or husband* or wife* or partner*) adj6 (educat* or informat* or communica* or pamphlet* or handout* or hand-out* or hand out* or booklet* or leaflet* or support* or need* or advice* or advis*)).ti.</td>
</tr>
<tr>
<td>50</td>
<td>((patient* or parent* or famil* or relative* or carer* or caregiver* or care-giver* or spous* or husband* or wife* or partner*) adj6 (counsel* or selfhelp* or self-help* or self help* or selfcar* or self-care* or self car*)).ti.</td>
</tr>
<tr>
<td>51</td>
<td>Patient Education as Topic/</td>
</tr>
<tr>
<td>52</td>
<td>Patient Education Handout/</td>
</tr>
<tr>
<td>53</td>
<td>Consumer Health Information/</td>
</tr>
<tr>
<td>54</td>
<td>patient* diar*.tw.</td>
</tr>
<tr>
<td>55</td>
<td>or/39-54</td>
</tr>
<tr>
<td>56</td>
<td>38 and 55</td>
</tr>
<tr>
<td>57</td>
<td>21 or 33 or 56</td>
</tr>
<tr>
<td>58</td>
<td>Animals/ not Humans/</td>
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<td>57 not 58</td>
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<td>10 and 59</td>
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<tr>
<td>61</td>
<td>animals/ not humans/</td>
</tr>
<tr>
<td>62</td>
<td>60 not 61</td>
</tr>
<tr>
<td>63</td>
<td>limit 62 to english language</td>
</tr>
</tbody>
</table>

---

**A.2.11 Search strategy review question 7.3**

What dietary management strategy/advice should be given to people with coeliac disease? Should the advice include avoiding gluten-free oats as part of the exclusion diet?
Table 11: search strategy 7.3

<table>
<thead>
<tr>
<th>Search Strategy:</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. (coeliac adj4 disease).tw.</td>
</tr>
<tr>
<td>2. (celiac adj4 disease).tw.</td>
</tr>
<tr>
<td>3. (coeliac adj4 sprue).tw.</td>
</tr>
<tr>
<td>5. ((nontropical or non tropical) adj4 sprue).tw.</td>
</tr>
<tr>
<td>6. ((celiac or coeliac) adj4 syndrome).tw.</td>
</tr>
<tr>
<td>7. (gluten adj4 (enteropath* or sensitiv* or hypersensitiv* or intoleran*)).tw.</td>
</tr>
<tr>
<td>8. ((glutenin or gliadin) adj4 (sensitiv* or hypersensitiv* or intoleran*)).tw.</td>
</tr>
<tr>
<td>9. Celiac Disease/</td>
</tr>
<tr>
<td>10. or/1-9</td>
</tr>
<tr>
<td>11. Diet/</td>
</tr>
<tr>
<td>12. Dietary Supplements/</td>
</tr>
<tr>
<td>13. ((supplement* or additiv* or fortif*) adj4 (food* or diet* or nutrition*)).tw.</td>
</tr>
<tr>
<td>15. ((nutrition* or diet* or food*) adj4 (manag* or advic* or guid* or support* or strateg*)).tw.</td>
</tr>
<tr>
<td>16. Vitamins/</td>
</tr>
<tr>
<td>17. vitamin*.tw.</td>
</tr>
<tr>
<td>18. Vitamin B 12/</td>
</tr>
<tr>
<td>19. Vitamin B Complex/</td>
</tr>
<tr>
<td>20. Vitamin D/</td>
</tr>
<tr>
<td>21. Calcium/</td>
</tr>
<tr>
<td>22. calcium.tw.</td>
</tr>
<tr>
<td>23. Iron/</td>
</tr>
<tr>
<td>24. iron.tw.</td>
</tr>
<tr>
<td>25. Folic Acid/</td>
</tr>
<tr>
<td>27. (vit adj4 (m or b9 or b-9 or b 9)).tw.</td>
</tr>
<tr>
<td>28. (pteroylglutamic or folvite or folate or folacin).tw.</td>
</tr>
<tr>
<td>29. Avena Sativa/</td>
</tr>
<tr>
<td>30. (avena adj4 sativa).tw.</td>
</tr>
<tr>
<td>31. oat*.tw.</td>
</tr>
<tr>
<td>32. (cereal* or porridge* or muesli* or granola*).tw.</td>
</tr>
<tr>
<td>33. or/11-32</td>
</tr>
<tr>
<td>34. 10 and 33 (2608)</td>
</tr>
<tr>
<td>35. animals/ not humans/</td>
</tr>
<tr>
<td>36. 34 not 35</td>
</tr>
<tr>
<td>37. limit 36 to english language</td>
</tr>
</tbody>
</table>

<Insert Note here>
A.3 Health economics search strategy

A.3.1 Economic evaluations and quality of life data

Sources searched to identify economic evaluations
- NHS Economic Evaluation Database – NHS EED (Wiley)
- Health Economic Evaluations Database – HEED (Wiley)
- Embase (Ovid)
- MEDLINE (Ovid)
- MEDLINE In-Process (Ovid)
- PubMed

Search filters to retrieve economic evaluations and quality of life papers were appended to all of the search strategies above (except 5.1, 5.2, 5.3, 7.1 and 7.2) to identify relevant evidence between May 2013 and July 2014. The re-run searches took place in December 2014.

Table 12: Health economics filters

The MEDLINE economic evaluations and quality of life search filters are presented below. They were translated for use in the MEDLINE In-Process and Embase databases.

<table>
<thead>
<tr>
<th>Economic evaluations</th>
</tr>
</thead>
<tbody>
<tr>
<td>1  Economics/</td>
</tr>
<tr>
<td>2  exp &quot;Costs and Cost Analysis&quot;/</td>
</tr>
<tr>
<td>3  Economics, Dental/</td>
</tr>
<tr>
<td>4  exp Economics, Hospital/</td>
</tr>
<tr>
<td>5  exp Economics, Medical/</td>
</tr>
<tr>
<td>6  Economics, Nursing/</td>
</tr>
<tr>
<td>7  Economics, Pharmaceutical/</td>
</tr>
<tr>
<td>8  Budgets/</td>
</tr>
<tr>
<td>9  exp Models, Economic/</td>
</tr>
<tr>
<td>10 Markov Chains/</td>
</tr>
<tr>
<td>11 Monte Carlo Method/</td>
</tr>
<tr>
<td>12 Decision Trees/</td>
</tr>
<tr>
<td>13 econom$.tw.</td>
</tr>
<tr>
<td>14 cba.tw.</td>
</tr>
<tr>
<td>15 cea.tw.</td>
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<tr>
<td>16 cua.tw.</td>
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<tr>
<td>17 markov$.tw.</td>
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<tr>
<td>18 (monte adj carlo).tw.</td>
</tr>
<tr>
<td>19 (decision adj2 (tree$ or analys$)).tw.</td>
</tr>
<tr>
<td>20 (cost or costs or costing$ or costly or costed).tw.</td>
</tr>
<tr>
<td>21 (price$ or pricing$).tw.</td>
</tr>
<tr>
<td>22 budget$.tw.</td>
</tr>
<tr>
<td>23 expenditure$.tw.</td>
</tr>
<tr>
<td>24 (value adj2 (money or monetary)).tw.</td>
</tr>
<tr>
<td>25 (pharmacoeconomic$ or (pharmaco adj economic$)).tw.</td>
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<td>26 or/1-25</td>
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Quality of life

<p>| |</p>
<table>
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<tbody>
<tr>
<td>1  &quot;Value of Life&quot;/</td>
</tr>
<tr>
<td>2  Quality-Adjusted Life Years/</td>
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</table>
The MEDLINE economic evaluations and quality of life search filters are presented below. They were translated for use in the MEDLINE In-Process and Embase databases.

**Economic evaluations**

<table>
<thead>
<tr>
<th>Filter</th>
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<tbody>
<tr>
<td>3 quality adjusted life.tiw.</td>
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</tr>
<tr>
<td>4 (qaly$ or qald$ or qale$ or qtime$).tw.</td>
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</tr>
<tr>
<td>5 disability adjusted life.tiw.</td>
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<tr>
<td>6 daly$.tw.</td>
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</tr>
<tr>
<td>7 Health Status Indicators/</td>
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</tr>
<tr>
<td>8 (sf36 or sf 36 or short form 36 or shortform 36 or sf thirty six or shortform thirty six or shortform thirty six or short form thirty six or short form thirty six).tw.</td>
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<tr>
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<tr>
<td>13 (euroqol or euro qol or eq5d or eq 5d).tw.</td>
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<td>14 (hye or hyes).tw.</td>
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<tr>
<td>15 health$ year$ equivalent$.tw.</td>
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<tr>
<td>16 (health adj3 state adj3 utilit$).tw.</td>
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<td>17 (utilit$ adj3 (health$ or valu$ or weight$ or scor$ or measure$)).tw.</td>
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<tr>
<td>18 (hui or hui1 or hui2 or hui3).tw.</td>
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<tr>
<td>19 disutili$.tw.</td>
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<td>20 rosser.tw.</td>
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</tr>
<tr>
<td>21 quality of wellbeing.tw.</td>
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<tr>
<td>22 quality of well-being.tw.</td>
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<tr>
<td>23 qwb.tw.</td>
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<tr>
<td>24 willingness to pay.tw.</td>
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<td>25 standard gamble$.tw.</td>
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<tr>
<td>26 time trade off.tw.</td>
<td></td>
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<tr>
<td>27 time tradeoff.tw.</td>
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<tr>
<td>28 tto.tw.</td>
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</tr>
<tr>
<td>29 (preferen$ weight$ or health state preferen$).tw.</td>
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<td>30 or/1-30</td>
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</table>

<Insert Note here>
# Appendix C: Review Protocols & Search Strategy

## A.4 Review protocols

List of key clinical issues and review questions

<table>
<thead>
<tr>
<th>Key clinical issue</th>
<th>Areas being included</th>
<th>Question</th>
<th>Not being included</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Recognition (update)</strong></td>
<td>Presenting features that raise suspicion of coeliac disease</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Signs and symptoms</td>
<td>4.1</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Populations with increased risk of coeliac disease</td>
<td>4.1</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Long term consequences of undiagnosed coeliac disease</td>
<td>4.3</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Active case-finding</td>
<td>4.4</td>
<td></td>
</tr>
<tr>
<td><strong>Diagnosis and monitoring (update)</strong></td>
<td>Accuracy of serological tests</td>
<td>5.1</td>
<td>Self-diagnosis kits and point of care tests</td>
</tr>
<tr>
<td></td>
<td>Sequencing of serological tests</td>
<td>5.2</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Referral indications for endoscopic intestinal biopsy</td>
<td>5.3</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Frequency of routine monitoring (and if it differs by risk) and different monitoring strategies</td>
<td>5.4</td>
<td></td>
</tr>
<tr>
<td><strong>Non-responsive and refractory coeliac disease</strong></td>
<td>Diagnosis of non-responsive and refractory coeliac disease</td>
<td>6.1</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Pharmacological treatment</td>
<td>6.2</td>
<td></td>
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<tr>
<td></td>
<td>Nutritional management</td>
<td>6.3</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Autologous stem cell transplant</td>
<td>6.4</td>
<td></td>
</tr>
<tr>
<td><strong>Information, education and support</strong></td>
<td>Information provision prior to serological testing (update)</td>
<td>7.1</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Information about gluten-free diets and self-management</td>
<td>7.2</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Dietary management of people with coeliac disease</td>
<td>7.3</td>
<td></td>
</tr>
<tr>
<td>Details</td>
<td>Additional comments</td>
<td></td>
<td></td>
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<tr>
<td>---------</td>
<td>---------------------</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Review question 4.1, 4.2, 4.3</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Which presenting features raise suspicion of coeliac disease?</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4.1 What are the clinical signs and symptoms which raise suspicion of coeliac disease?</td>
<td></td>
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<td></td>
</tr>
</tbody>
</table>
| 4.2 What populations have an increased risk of developing coeliac disease?  
  i. Co-existing diseases  
  ii. Other factors (ie. first-degree relatives) | |
| 4.3 What are the long-term consequences of undiagnosed or untreated coeliac disease? | |
| **Objectives** | |
| To establish what presenting clinical features and conditions might i) raise suspicions about the presence of coeliac disease and possible need for further testing; ii) indicate subgroups who are at increased risk; iii) be associated with long-term consequences of undiagnosed coeliac disease | |
| **Type of review** | |
| Diagnostic (4.1) epidemiological (4.2), and prognostic (4.3) | |
| **Language** | |
| English only | |
| **Study design** | |
| No restriction (except qualitative studies and case reports)  
Case series are excluded for all but c. | |
| **Status** | |
| Published papers only (full text) | |
| **Population** | |
| Children, young people and adults with:  
4.1. and 4.2. undiagnosed coeliac disease, untreated coeliac disease, including at the time of diagnosis  
(for ‘other factors’: a diagnosis of coeliac disease and families of patients with coeliac disease)  
4.3. undiagnosed or untreated coeliac disease. | |
| The GDG agreed to exclude any studies which have not confirmed the diagnosis of coeliac with biopsy (including those studies which use serological tests only) because they were less confident in the ability of these tests to confirm coeliac disease.  
An exception to this was for clinical signs and symptoms (a), first degree relatives (bii), and long term consequences (c) where the GDG felt it was important to present studies which reported serological positivity only in addition to those that reported on biopsy-confirmed coeliac disease.  
The GDG felt rates confirmed on serological testing of anti-ITG and/or anti-EMA were appropriate and AGA only if it was used in conjunction with either anti-ITG or anti-EMA as it is known to result in high false positives.  
However, for examining first-degree relatives of patients with coeliac disease, they felt it was important that the index patient (or proband) had biopsy-confirmed coeliac disease.  
The GDG felt that excluding studies that did not report biopsy-confirmed coeliac disease would remove a large proportion of the relevant literature in these areas. However, they did feel it was important to present the results from biopsy-confirmed coeliac disease and serological positivity, separately. |
### Factors/Variables/Predictors

#### 4.1. Presenting clinical features:
- abnormal liver enzymes
- amenorrhoea
- chronic or intermittent diarrhoea/constipation
- dental complications (enamel deterioration)
- failure to thrive, faltering growth (in children) or delayed puberty
- functional hyposplenism
- gluten sensitive neuropathy
- intra-cerebral calcification
- intussusception (bowel telescopes within self)
- malignancy including intestinal lymphoma, oesophageal cancer, colonic cancer
- peripheral neuropathy
- persistent or unexplained gastrointestinal symptoms including nausea and vomiting
- pregnancy outcomes (sub-fertility, early miscarriage, intra-uterine growth retardation, premature babies)
- prolonged fatigue
- sudden or unexpected weight loss, height loss or fragility fractures
- ulcerative jejunitis
- unexplained iron-deficiency anaemia, or other unspecified anaemia
- recurrent abdominal pain, cramping or distension
- recurrent aphthous-ulceration
- refractory coeliac disease
- reduced bone mineral density
- vitamin D, vitamin B12, folic acid and iron deficiency

#### 4.2. Coexisting conditions:
- Addisons disease
- all autoimmune diseases (such as autoimmune thyroid disease, autoimmune myocarditis, autoimmune hepatitis)
- alopecia areata
- bipolar disorder or depression
- bone mineral disease (such as rickets or osteomalacia)
- cardiomyopathy
- chronic thrombocytopenia purpura
- dermatitis herpetiformis
- Downs syndrome
- epilepsy
- HIV
- IgA deficiency
## Appendix C: Review Protocols & Search Strategy

<table>
<thead>
<tr>
<th>Comparator</th>
<th>4.1 Confirmed diagnosis by intestinal biopsy only 4.2, 4.3 NA</th>
</tr>
</thead>
</table>
| **Outcome measures** | Specific for 4.1)  | Accuracy metrics (sensitivity, specificity, +LR, -LR, PPV, NPV, etc.)  
Predictive measures from adjusted regression model  
Specific for 4.2)  | Risk of having coeliac disease  
Risk of/event rates of complications  
Growth in children and young people  
Specific for 4.3)  | Complications of coeliac disease of  
Complications from the long-term consequences  
Growth in children and young people  
Overall:  | Mortality  
Resource use and cost  
Health related quality of life  |
| **Other criteria for inclusion / exclusion of studies** | Exclusion:  | Case reports, case series (except for c), or qualitative studies  
For long-term, consequences (c), studies with less than 50 patients  
Non coeliac disease gluten sensitivity  
Wheat allergy and sensitivity  |
| **Search strategies** | Date restriction: 2008 onwards  | To limit the amount of sifting required, the last guideline was used to identify relevant studies published prior to 2008  |
| **Review strategies** | Appropriate NICE Methodology Checklists, depending on study designs, will be used as a guide to appraise the quality of individual studies. Data on all included studies will be extracted into evidence tables.  |  |
Appendix C: Review Protocols & Search Strategy

<table>
<thead>
<tr>
<th>Identified papers</th>
<th>Sample of papers identified in NICE CG86 for a):</th>
</tr>
</thead>
</table>

| Systematic Reviews for b): |

| Sample of papers identified by NICE CG86 for b): |

| Sample of papers identified by NICE CG86 for c) |

All prioritised key outcomes from evidence will be presented in modified GRADE profiles and further summarised in evidence statements.
### Appendix C: Review Protocols & Search Strategy

<table>
<thead>
<tr>
<th>Details</th>
<th>Additional comments</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Review question 4.4</strong></td>
<td>Should active case-finding be implemented in people with co-existing conditions/subgroups that are associated with an increased risk of coeliac disease?</td>
</tr>
<tr>
<td><strong>Objectives</strong></td>
<td>To establish if patients with specific health conditions or specific subgroups with an increased risk of coeliac disease should be proactively investigated for coeliac disease?</td>
</tr>
<tr>
<td><strong>Type of review</strong></td>
<td>Intervention</td>
</tr>
<tr>
<td><strong>Language</strong></td>
<td>English only</td>
</tr>
<tr>
<td><strong>Study design</strong></td>
<td>Systematic review, Prospective cohort study, Population based screening studies</td>
</tr>
<tr>
<td><strong>Status</strong></td>
<td>Published papers only (full text)</td>
</tr>
<tr>
<td><strong>Population</strong></td>
<td>Children, young people and adults without a formal diagnosis of coeliac disease.</td>
</tr>
<tr>
<td><strong>Intervention</strong></td>
<td>Active case-finding strategies (including frequency of testing)</td>
</tr>
<tr>
<td><strong>Comparator</strong></td>
<td>No active case-finding</td>
</tr>
<tr>
<td><strong>Outcomes</strong></td>
<td>• Risk of coeliac disease • Risk of/event rates of complications • Growth in children and young people • Resource use and cost • Health-related quality of life</td>
</tr>
<tr>
<td><strong>Other criteria for inclusion / exclusion of studies</strong></td>
<td>Exclusion: • Case studies or case series • Non coeliac disease gluten sensitivity • Wheat allergy and sensitivity</td>
</tr>
<tr>
<td><strong>Search strategies</strong></td>
<td>.....</td>
</tr>
<tr>
<td><strong>Review strategies</strong></td>
<td>Appropriate NICE Methodology Checklists, depending on study designs, will be used as a guide to appraise the quality of individual studies. Data on all included studies will be extracted into evidence tables. Where statistically possible, a meta-analytic approach will be used to give an overall summary effect. All prioritised key outcomes from evidence will be presented in modified GRADE profiles and further summarised in evidence statements.</td>
</tr>
<tr>
<td>Reference</td>
<td>Details</td>
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### Appendix C: Review Protocols & Search Strategy

<table>
<thead>
<tr>
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<th>Additional comments</th>
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</thead>
<tbody>
<tr>
<td><strong>Review question 5.1</strong></td>
<td>What is the sensitivity and specificity of the serological tests for coeliac disease? Are the sensitivity and specificity results different in any specified subgroups?</td>
</tr>
<tr>
<td><strong>Objectives</strong></td>
<td>To determine the accuracy of the different serological tests for coeliac disease and any subgroups of people for whom the accuracy varies.</td>
</tr>
<tr>
<td><strong>Type of review</strong></td>
<td>Diagnostic test accuracy</td>
</tr>
<tr>
<td><strong>Language</strong></td>
<td>English only</td>
</tr>
<tr>
<td><strong>Study design</strong></td>
<td>Systematic review Test-and-treat RCT Cross-sectional study If insufficient evidence is identified, will also include: Cohort study Case-control</td>
</tr>
<tr>
<td><strong>Status</strong></td>
<td>Published papers only (full text)</td>
</tr>
<tr>
<td><strong>Population</strong></td>
<td>Children, young people and adults with suspected coeliac disease.</td>
</tr>
</tbody>
</table>
| **Index test** | Serological tests:  
- Immunoglobulin A tissue transglutaminase antibodies (IgA tTGA)  
- Immunoglobulin A endomysial antibodies (IgA EMA)  
- Immunoglobulin G tissue transglutaminase antibodies (IgG tTGA)  
- Immunoglobulin G endomysial antibodies (IgG EMA)  
- Human leukocyte antigen (HLA) DQ2/DQ8 testing  
- Deamidated gliadin peptide (DGP) antibodies |
| **Reference standard** | Intestinal biopsy  
*Head to head comparisons of different serological tests against intestinal biopsy*  
Exclude capsule biopsy |
| **Outcomes** | Clinical utility or diagnostic test accuracy (if available) including:  
- Sensitivity, specificity, positive predictive value, negative predictive value, likelihood ratios, diagnostic odds ratio, and area under the ROC analyses.  
- Test validity such as face validity, content validity, construct validity, concurrent validity, criterion validity;  
- Test reliability such as internal reliability/consistency, test-retest reliability, inter-rater reliability.  
Health-related quality of life Resource use and cost |
| **Other criteria for inclusion / exclusion of studies** | Exclusion:  
- Self-diagnosis kits  
- Point of care testing  
- Immunoglobulin G antigliadon antibody (IgG AGA)  
- Immunoglobulin A antigliadon antibody |
<table>
<thead>
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<th>(IgA AGA)</th>
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<td><strong>Search strategies</strong></td>
<td>Date restriction: 2008 onwards</td>
</tr>
<tr>
<td><strong>Review strategies</strong></td>
<td>QUADAS-2 tool will be used as a guide to appraise the quality of individual studies. Data on all included studies will be extracted into evidence tables. Where statistically possible, a meta-analytic approach will be used to give an overall summary effect. If there is sufficient data, subgroup analyses may be performed on different kids/platforms for different serological tests; subgroup analysis may also be performed for recombinant and animal tissue tTG tests. All key outcomes from evidence will be presented in modified GRADE profiles and further summarised in evidence statements. Sub-analysis will be undertaken by subgroups of patients where appropriate</td>
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### Identified papers

<table>
<thead>
<tr>
<th>Systematic Reviews:</th>
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<tbody>
<tr>
<td>Sample of papers identified in NICE CG86:</td>
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<tr>
<td>Details</td>
</tr>
<tr>
<td>---------</td>
</tr>
<tr>
<td><strong>Review question 5.2</strong></td>
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<tr>
<td><strong>Objectives</strong></td>
</tr>
<tr>
<td><strong>Type of review</strong></td>
</tr>
<tr>
<td><strong>Language</strong></td>
</tr>
<tr>
<td><strong>Study design</strong></td>
</tr>
<tr>
<td>If insufficient evidence is identified, will also include:  Cohort study  Case-control</td>
</tr>
<tr>
<td><strong>Status</strong></td>
</tr>
<tr>
<td><strong>Population</strong></td>
</tr>
<tr>
<td><strong>Index test</strong></td>
</tr>
<tr>
<td><strong>Reference standard(s)</strong></td>
</tr>
<tr>
<td><strong>Outcomes</strong></td>
</tr>
</tbody>
</table>
### Appendix C: Review Protocols & Search Strategy

<table>
<thead>
<tr>
<th>Resource use and cost</th>
<th>Other criteria for inclusion / exclusion of studies</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Exclusion:</td>
</tr>
<tr>
<td></td>
<td>• Self-diagnosis kits</td>
</tr>
<tr>
<td></td>
<td>• Point of care testing</td>
</tr>
<tr>
<td></td>
<td>• Immunoglobulin G antigliadon antibody (IgG AGA)</td>
</tr>
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<td></td>
<td>• Immunoglobulin A antigliadon antibody (IgA AGA)</td>
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<thead>
<tr>
<th>Search strategies</th>
<th>Date restriction: 2008 onwards</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>To limit the amount of sifting required, the last guideline was used to identify relevant studies published prior to 2008</td>
</tr>
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</table>

<table>
<thead>
<tr>
<th>Review strategies</th>
</tr>
</thead>
<tbody>
<tr>
<td>QUADAS-2 tool will be used as a guide to appraise the quality of individual studies. Data on all included studies will be extracted into evidence tables. Where statistically possible, a meta-analytic approach will be used to give an overall summary effect. All key outcomes from evidence will be presented in modified GRADE profiles and further summarised in evidence statements. Sub-analysis will be undertaken by subgroups of patients where appropriate</td>
</tr>
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<table>
<thead>
<tr>
<th>Identified papers</th>
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<tbody>
<tr>
<td><strong>Systematic Reviews:</strong></td>
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</table>

**Sample of papers identified in NICE CG86:**
### Appendix C: Review Protocols & Search Strategy

<table>
<thead>
<tr>
<th>Details</th>
<th>Additional comments</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Review question 5.3</strong></td>
<td>What are the referral indications for endoscopic intestinal biopsy for further investigation in people with coeliac disease?</td>
</tr>
<tr>
<td><strong>Objectives</strong></td>
<td>To establish what factors (other than the sequence of serological testing [question 4]) may indicate appropriate referral for endoscopic intestinal biopsy for people with coeliac disease.</td>
</tr>
<tr>
<td><strong>Type of review</strong></td>
<td>Prognostic</td>
</tr>
<tr>
<td><strong>Language</strong></td>
<td>English only</td>
</tr>
<tr>
<td><strong>Study design</strong></td>
<td>No restriction (except qualitative studies and case reports)</td>
</tr>
<tr>
<td><strong>Status</strong></td>
<td>Published (full text only)</td>
</tr>
<tr>
<td><strong>Population</strong></td>
<td>Children, young people and adults with diagnosed coeliac disease. This includes people with a diagnosis of coeliac disease who are being monitored and in whom an intestinal biopsy may be useful in further investigation to monitor treatment.</td>
</tr>
<tr>
<td><strong>Prognostic factor</strong></td>
<td>Indications (other than the sequence of serological testing [question 4]) may indicate appropriate referral for endoscopic intestinal biopsy.</td>
</tr>
<tr>
<td><strong>Comparator</strong></td>
<td>Not applicable</td>
</tr>
</tbody>
</table>
| **Outcomes** | • Complications of coeliac disease  
• Mortality  
• Health related quality of life  
• Resource use and cost  
Complications include, but are not limited to:  
• osteoporosis  
• ulcerative jejunitis  
• malignancy (intestinal lymphoma)  
• functional hyposplenism  
• vitamin D deficiency  
• iron deficiency  
• auto-immune diseases |
| **Other criteria for inclusion / exclusion of studies** | Exclusion:  
• Non coeliac disease gluten sensitivity  
• Studies examining clinical utility of serological testing  
• Wheat allergy and sensitivity  
• Use of intestinal biopsy for initial diagnosis  
• Aspects related to routine monitoring (this is covered in question 7) |
| **Search strategies** | ...... |
| **Review strategies** | Appropriate NICE Methodology Checklists, depending on study designs, will be used as a guide to appraise the quality of individual studies. Data on all included studies will be extracted into evidence tables. Where statistically possible, a meta-analytic approach will be used to give an overall summary effect. All key outcomes from evidence will be presented in modified GRADE profiles and further summarised in evidence statements. |
| **Identified papers** | None. |
### Review question 5.4

<table>
<thead>
<tr>
<th>Details</th>
<th>Additional comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>a) How frequently should people with coeliac disease be routinely monitored?</td>
<td></td>
</tr>
<tr>
<td>b) Should the frequency of routine monitoring differ for patients with at risk of developing certain complications?</td>
<td></td>
</tr>
<tr>
<td>c) What should routine monitoring consist of?</td>
<td></td>
</tr>
</tbody>
</table>

### Objectives

<table>
<thead>
<tr>
<th>Details</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>a) To determine how often people with coeliac disease should be followed up</td>
<td></td>
</tr>
<tr>
<td>b) To determine if any subgroups at risk of developing any particular complications should be followed up more frequently</td>
<td></td>
</tr>
<tr>
<td>c) To determine what assessments and checks should be carried out to monitor coeliac disease, particularly those at risk of developing complications.</td>
<td></td>
</tr>
</tbody>
</table>

### Type of review

**Intervention**

### Language

**English only**

### Study design

**Systematic review**  
RCTs  
If insufficient evidence is identified, will also include:  
Non-randomised controlled trials  
Prospective cohort study

### Status

**Published (full text only)**

### Population

**Children, young people and adults with coeliac disease**

### Intervention

<table>
<thead>
<tr>
<th>Details</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>a) Different follow-up frequencies</td>
<td></td>
</tr>
<tr>
<td>b) Different follow-up frequencies</td>
<td>Monitoring strategies could include bone density assessment, serology, histology, dietary assessment (adherence and quality of diet), symptomatic response</td>
</tr>
<tr>
<td>c) Monitoring strategies, tests and techniques.</td>
<td></td>
</tr>
</tbody>
</table>

### Comparator

<table>
<thead>
<tr>
<th>Details</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>a) Standard care or comparing different frequencies of follow-up</td>
<td></td>
</tr>
<tr>
<td>b) Standard care or comparing different frequencies of follow-up</td>
<td></td>
</tr>
<tr>
<td>c) Standard care (without specific monitoring strategies)</td>
<td></td>
</tr>
</tbody>
</table>

### Outcomes

- Resolution of gastrointestinal and non-gastrointestinal symptoms
- Growth in children and young people
- Complications of coeliac disease
- Dietary adherence
- Impact on carers
- Health-related quality of life

### Other criteria for inclusion / exclusion of studies

<table>
<thead>
<tr>
<th>Details</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Exclusion:</td>
<td></td>
</tr>
<tr>
<td>a) Case series and case studies</td>
<td></td>
</tr>
<tr>
<td>b) Non coeliac disease gluten sensitivity</td>
<td></td>
</tr>
<tr>
<td>c) Wheat allergy or sensitivity</td>
<td></td>
</tr>
</tbody>
</table>

### Search strategies

**……..**

### Review

Appropriate NICE Methodology Checklists,
strategies  depending on study designs, will be used as a guide to appraise the quality of individual studies. Data on all included studies will be extracted into evidence tables. Where statistically possible, a meta-analytic approach will be used to give an overall summary effect. All prioritised key outcomes from evidence will be presented in GRADE profiles and further summarised in evidence statements. Sub-analysis will be undertaken for people at risk of developing complications; adults vs. children, if appropriate.

| Identified papers | For a):  
| Studies  
| Liu, Brais, Lavergne-Slove et al (2012) Continual monitoring of intraepithelial lymphocyte immunophenotype and clonality is more important than snapshot analysis in the surveillance of refractory coeliac disease. Gut, 04 2010, vol./is. 59/4(462-60), 0017-5749;1468-3288 
| Malamut, Afchain,  
| For b):  
| Studies  
| Hutchinson, West, Robins and Howdle (2010) Long-term histological follow-up of people with coeliac disease in a UK teaching hospital. Qjm, 07 2010, vol./is. 103/7(511-7), 1460-2393:1460-2393 
| Vecsei, Graf and Vogelsang (2009) Follow-up of adult celiac patients: which non-invasive test reflects mucosal status most reliably. Endoscopy, 02 2009, vol./is. 41/2(123-8), 0013-726X:1438-8812 
### Review question 6.1

- **a) What are the potential causes of non-responsive coeliac disease?**

  This question will identify the proportion of patients with non-responsive disease who fall into each of the following categories:

  **Continued ingestion of gluten**
  - Poor compliance
  - Inadvertent (contamination)

  **Co-existing conditions:**
  - Lactose or fructose intolerance
  - Other food intolerances
  - Pancreatic insufficiency
  - Microscopic colitis
  - Bacterial overgrowth
  - Collagenous colitis or collagenous sprue
  - Irritable bowel syndrome
  - Ulcerative jejunitis
  - Enteropathy (including autoimmune enteropathy)
  - Associated T-cell lymphoma
  - Functional disorders
  - Common variable immunodeficiency

**Refractory coeliac disease**

<table>
<thead>
<tr>
<th>Details</th>
<th>Additional comments</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Objectives</strong></td>
<td>To determine the proportion of differing causes of persistent symptoms in patients with a confirmed diagnosis of coeliac disease who have been advised to exclude gluten from the diet</td>
</tr>
<tr>
<td><strong>Type of review</strong></td>
<td>Prevalence</td>
</tr>
<tr>
<td><strong>Language</strong></td>
<td>English only</td>
</tr>
</tbody>
</table>
| **Study design** | Systematic review
  Case series
  Cross-sectional study |
| **Status** | Published (full text only) |
| **Population** | All children, young people and adults with a biopsy confirmed diagnosis of coeliac disease, who have been advised by a health professional to exclude gluten from the diet and who have had persistent symptoms for more than 6 months. Under 18s and 18 and over will be assessed separately. Other age subgroups will be included if this appears to be relevant from the studies found |
| **Index test(s)** | Not relevant |
| **Reference standard(s)** | Not relevant |
| **Outcomes** | Proportion of differing causes of non-responsiveness, which should be considered as part of the differential diagnosis of non-responsive coeliac disease |
| **Other criteria for inclusion / exclusion of studies** | Exclusion:
  - Non biopsy confirmed
  - Symptoms persisting less than 6 months
  - No health care professional advice on gluten free

Depending on the studies found it may be relevant to further analyse the data after excluding the proportion of patients with continued gluten ingestion (as the latter proportion may be influenced by the level of dietary advice and support and food labelling in different countries)
# Appendix C: Review Protocols & Search Strategy

## Search strategies

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<table>
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<tr>
<td></td>
<td>diet</td>
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</table>

## Review strategies

<p>| | |</p>
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</thead>
</table>
|   | Appropriate NICE Methodology Checklists, depending on study designs, will be used as a guide to appraise the quality of individual studies.
|   | Data on all included studies will be extracted into evidence tables. Where statistically possible, a meta-analytic approach will be used to give an overall summary effect.
|   | All key outcomes from evidence will be presented in modified GRADE profiles and further summarised in evidence statements. |

## Identified papers

<p>| | |</p>
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</table>
Appendix C: Review Protocols & Search Strategy

<table>
<thead>
<tr>
<th>Details</th>
<th>Additional comments</th>
</tr>
</thead>
</table>
| **Review question 6.1** | b) In patients with confirmed refractory coeliac disease what investigative procedures should be undertaken, such as:  
  - Clonality assessment  
  - Flow cytometry  
  - Aberrant T cell assessment  
  - Immunophenotyping  
  - Imaging  
  This question will inform how to investigate patients with suspected refractory coeliac disease  
  Tests that will guide the ongoing clinical management, such as assessing the risk of lymphoma |
| **Objectives** | To determine the proportion of differing causes of persistent symptoms in patients with a confirmed diagnosis of coeliac disease who have been advised to exclude gluten from the diet |
| **Type of review** | Intervention |
| **Language** | English only |
| **Study design** | Systematic review  
  Test-and-Treat RCT  
  Cross-sectional study  
  If insufficient evidence is identified, will also include:  
  - Cohort study  
  - Case-control |
| **Status** | Published (full text only) |
| **Population** | Patients with a confirmed diagnosis of coeliac disease, *in whom persistent villous atrophy is found on biopsy*, and in whom continued exposure to gluten and co-existing conditions (causing the symptoms) have been excluded  
  Under 18s and 18 and over will be assessed separately. Other age sub-groups will be included if this appears to be relevant from the studies found |
| **Intervention** | Investigative tests:  
  - Clonality assessment  
  - Flow cytometry  
  - Aberrant T cell assessment  
  - Immunophenotyping  
  - Imaging |
| **Comparator** | Do nothing |
| **Outcomes** | Clinical utility:  
  - Change to clinical management  
  - Resource use and cost  
  - Patient outcomes at follow up  
  - Health-related quality of life |
| **Other criteria for inclusion / exclusion of studies** | Exclusion:  
  None |
| **Search strategies** | ……. |
| **Review strategies** | Appropriate NICE Methodology Checklists, depending on study designs, will be used as a guide to appraise the quality of individual studies.  
  Data on all included studies will be extracted into evidence tables. Where statistically possible, a |
A meta-analytic approach will be used to give an overall summary effect. All key outcomes from evidence will be presented in modified GRADE profiles and further summarised in evidence statements.

<table>
<thead>
<tr>
<th>Identified papers</th>
<th>Studies</th>
</tr>
</thead>
</table>
## Appendix C: Review Protocols & Search Strategy

### Review question 6.2

**What is the effectiveness of pharmacological treatments for people with refractory coeliac disease?**

### Objectives

To determine what medication can help treat coeliac disease that is not responding to dietary management and when other diagnoses have been excluded.

### Type of review

Intervention

### Language

English only

### Study design

- Systematic review
- RCTs
- Case series

Originally the GDG were interested in only considering studies with a control group but as no studies were found, they chose to include case series as well.

### Status

Published (full text only)

### Population

Children, young people and adults with refractory coeliac disease

### Intervention

Pharmacological treatments for refractory coeliac disease which include, but are not limited to:

- Anti-TNF (including infliximab [Remicade], etanercept [Enbrel], adalimumab [Humira], golimumab [Simponi], certolizumab [Cimzia])
- ASA preparation/Mesalazine/Mesalamine (Apriso, Asacol, Canasa, Lialda, pentasa, Rowasa)
- Azathioprine (Imuran)
- Prednisolone (Ak-Pred, Articulose-50, AsmalPred Plus, Delta-Cortef, Econopred, etc)
- Budesonide (Entocort, Pulmicort, Rhinocort, Symbicort)
- Cladribine (Leustatin)
- Cyclosporin (Gengraf, Neoral, Restasis, Sandimmune)
- Thioguanine (Tabloid)
- Other corticosteroids (other than prednisolone and budesonide)

### Comparator

- Standard care (including gluten-free diet)
- Placebo
- Head to head comparison

It is important to note which gluten free diet patients were on (eg gluten & wheat free). Check country and year of paper. Elemental diets have been used.

### Outcomes

- Resolution of gastrointestinal and non-gastrointestinal symptoms
- Complications of coeliac disease
- Adverse effects
- Health-related quality of life
- Impact on carers
- Serological response
- Histological response
- ...

Complications include, but are not limited to:

- osteoporosis
- ulcerative jejunitis
- malignancy (intestinal lymphoma)
- functional hyposplenism
- vitamin D deficiency
- iron deficiency
- auto-immune diseases

### Other criteria for inclusion / exclusion of studies

**Exclusion:**

- Case reports
<table>
<thead>
<tr>
<th>Search strategies</th>
<th>.......</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Review strategies</strong></td>
<td>Appropriate NICE Methodology Checklists, depending on study designs, will be used as a guide to appraise the quality of individual studies. Data on all included studies will be extracted into evidence tables. Where statistically possible, a meta-analytic approach will be used to give an overall summary effect. All prioritised key outcomes from evidence will be presented in GRADE profiles and further summarised in evidence statements.</td>
</tr>
<tr>
<td><strong>Identified papers</strong></td>
<td>Studies</td>
</tr>
</tbody>
</table>
## Review question 6.3

What is the effectiveness of nutritional management or nutritional support for people with refractory coeliac disease?

## Objectives

To determine what additional nutritional support (beyond advice on changes to the diet) can help treat coeliac disease that is not responding to dietary management and when other diagnoses have been excluded.

## Type of review

Intervention

## Language

English only

## Study design

Systematic review

RCTs

If insufficient evidence is identified, will also include:

- Non-randomised controlled trials
- Prospective cohort study

## Status

Published (full text only)

## Population

Children, young people and adults with refractory coeliac disease

## Intervention

Nutritional support for people with refractory coeliac disease which includes, but is not limited to:

- Further dietary exclusions
- Oral nutrition support (for example, fortified food)
- Enteral tube feeding (delivery of nutrition into the gut)
- Parenteral nutrition (delivery of nutrition intravenously)

Further dietary exclusions could include high allergenic foods such as soya, milk, egg, etc

## Comparator

Standard care

Placebo

Head to head comparison

## Outcomes

- Resolution of gastrointestinal and non-gastrointestinal symptoms
- Complications of coeliac disease
- Adverse events
- Health-related quality of life
- Impact on carers
- Serological response

Complications include, but are not limited to:

- osteoporosis
- ulcerative jejunitis
- malignancy (intestinal lymphoma)
- functional hyposplenism
- vitamin D deficiency
- iron deficiency
- auto-immune diseases

## Other criteria for inclusion / exclusion of studies

Exclusion:

- Retrospective cohort study, case series and case reports.

## Search strategies

......

## Review strategies

Appropriate NICE Methodology Checklists, depending on study designs, will be used as a guide to appraise the quality of individual studies. Data on all included studies will be extracted into evidence tables. Where statistically possible, a meta-analytic approach will be used to give an overall summary effect. All prioritised key outcomes from evidence will be
<table>
<thead>
<tr>
<th>Identified papers</th>
<th>Studies</th>
</tr>
</thead>
</table>
## Review question 6.4
What is the effectiveness of autologous stem cell transplant for people with refractory coeliac disease?

### Objectives
To determine how effective it is to treat refractory coeliac disease with chemotherapy followed by transplantation of stem cells from the patient’s own body.

### Type of review
Intervention

### Language
English only

### Study design
No restriction except qualitative studies and case reports.

### Status
Published (full text only)

### Population
Children, young people and adults with refractory coeliac disease

### Intervention
Chemotherapy followed by autologous stem cell transplant

### Comparator
Standard care
Placebo
Head to head comparison with pharmacological treatments

### Outcomes
- Health-related quality of life
- Impact on carers
- Resolution of gastrointestinal and non-gastrointestinal symptoms
- Complications of coeliac disease
- Complications from surgery
- Serological response
- Adverse events

### Other criteria for inclusion/exclusion of studies
Exclusion:
- Qualitative studies and case reports

### Search strategies
........

### Review strategies
Appropriate NICE Methodology Checklists, depending on study designs, will be used as a guide to appraise the quality of individual studies.

Data on all included studies will be extracted into evidence tables.

Where statistically possible, a meta-analytic approach will be used to give an overall summary effect.

All prioritised key outcomes from evidence will be presented in GRADE profiles and further summarised in evidence statements.

### Identified papers
None identified

### Additional comments
Complications include, but are not limited to:
- osteoporosis
- ulcerative jejunitis
- malignancy (intestinal lymphoma)
- functional hyposplenism
- vitamin D deficiency
- iron deficiency
- auto-immune diseases
### Appendix C: Review Protocols & Search Strategy

<table>
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<tr>
<th>Details</th>
<th>Additional comments</th>
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</thead>
<tbody>
<tr>
<td><strong>Review question 7.1</strong></td>
<td>What information do people (and their family members or carers, as appropriate) need to help them decide whether to undergo initial testing for coeliac disease? If people are to undergo initial testing, what dietary information do they (or their family members or carers) need before testing to ensure that test results are as accurate as possible?</td>
</tr>
</tbody>
</table>
| **Objectives** | To establish what information is needed by patients to:  
• help decide whether to be tested for coeliac disease  
• manage their diet before being tested |
| **Type of review** | Information and support |
| **Language** | English only |
| **Study design** | No restriction except case reports |
| **Status** | Published (full text only) |
| **Population** | Children, young people and adults being investigated for coeliac disease |
| **Intervention** | Information strategies to help people decide whether to be tested for coeliac disease  
Information to help people to manage their diet prior to the tests (to improve the accuracy of the tests). |
| **Comparator** | N/A |
| **Outcomes** | Any information identified  
Patient experience  
Resource use and cost |
| **Other criteria for inclusion / exclusion of studies** | Case reports |
| **Search strategies** | Date restriction: 2008 onwards |
| **Review strategies** | Appropriate NICE Methodology Checklists, depending on study designs, will be used as a guide to appraise the quality of individual studies.  
Data on all included studies will be extracted into evidence tables.  
Where statistically possible, a meta-analytic approach will be used to give an overall summary effect.  
All prioritised key outcomes from evidence will be presented in modified GRADE profiles and further summarised in evidence statements.  
Separate analysis will be performed where appropriate for parents and carers. |
| **Identified papers** | None. |

To limit the amount of sifting required, the last guideline was used to identify relevant studies published prior to 2008.
## Appendix C: Review Protocols & Search Strategy

### Review question 7.2

<table>
<thead>
<tr>
<th>Details</th>
<th>Additional comments</th>
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</thead>
<tbody>
<tr>
<td>a) What information, education and support do people with coeliac disease (and their family members or carers, as appropriate) need to improve adherence to a gluten-free diet and self-management of their condition?</td>
<td></td>
</tr>
<tr>
<td>b) What is the patient perspective of self-management and how to improve adherence, including what information is required, different monitoring strategies, and with whom they are followed up?</td>
<td></td>
</tr>
</tbody>
</table>

### Objectives

To establish what information, education and support is needed by people with coeliac disease to help them follow a gluten-free diet and manage their own condition.

To elicit preferences of patients to improve their self-management including information, different monitoring strategies, and with who they are followed up.

### Type of review

<table>
<thead>
<tr>
<th>Details</th>
<th>Additional comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>a) Intervention (for effectiveness of any educational or support programmes/strategies to improve adherence)</td>
<td></td>
</tr>
<tr>
<td>b) Qualitative (patient experiences about required information and monitoring strategies to improve self-management including adherence)</td>
<td></td>
</tr>
</tbody>
</table>

### Language

- English only

### Study design

<table>
<thead>
<tr>
<th>Details</th>
<th>Additional comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>a) Systematic review RCTs Prospective cohort studies</td>
<td></td>
</tr>
<tr>
<td>b) No restriction except case reports</td>
<td></td>
</tr>
</tbody>
</table>

### Status

- Published (full text only)

### Population

- Children, young people and adults with coeliac disease

### Intervention

<table>
<thead>
<tr>
<th>Details</th>
<th>Additional comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>a) Any educational or support programmes/strategies to improve adherence</td>
<td></td>
</tr>
<tr>
<td>b) Any information needs identified</td>
<td></td>
</tr>
</tbody>
</table>

### Comparator

<table>
<thead>
<tr>
<th>Details</th>
<th>Additional comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>a) Standard care</td>
<td></td>
</tr>
<tr>
<td>b) N/A</td>
<td></td>
</tr>
</tbody>
</table>

### Outcomes

- Resolution of gastrointestinal and non-gastrointestinal symptoms
- Patient experience
- Complications of coeliac disease
- Resource use and cost
- Adherence
- Health-related quality of life
- Impact on carers

### Other criteria for inclusion / exclusion of studies

**Exclusion:**
- Non coeliac disease gluten sensitivity
- Wheat allergy and sensitivity
<table>
<thead>
<tr>
<th>Search strategies</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Review strategies</strong></td>
<td>Appropriate NICE Methodology Checklists, depending on study designs, will be used as a guide to appraise the quality of individual studies. Data on all included studies will be extracted into evidence tables. Where statistically possible, a meta-analytic approach will be used to give an overall summary effect. All prioritised key outcomes from evidence will be presented in modified GRADE profiles and further summarised in evidence statements. Separate analysis will be performed where possible for parents and carers.</td>
</tr>
<tr>
<td><strong>Identified papers</strong></td>
<td>None.</td>
</tr>
</tbody>
</table>
### Review question 7.3

<table>
<thead>
<tr>
<th>Details</th>
<th>Additional comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>a) What dietary management strategy/advice should be given to people with coeliac disease?</td>
<td></td>
</tr>
<tr>
<td>b) Should the advice include avoiding gluten-free oats as part of the exclusion diet?</td>
<td></td>
</tr>
</tbody>
</table>

### Objectives
To determine what other dietary management strategy/advice should be given to people with coeliac disease.

### Type of review
Intervention

### Language
English only

### Study design
Systematic reviews  
RCTs  
If insufficient evidence is identified, will also include:  
Non-randomised controlled trials  
Prospective cohort studies

### Status
Published (full text only)

### Population
Children, young people and adults with coeliac disease

### Intervention
| a) Any dietary management/advice other than a gluten-free diet  
The use of nutritional supplements as ‘other dietary advice’ will only include: |
| calcium  |
| Vitamin D  |
| Vitamin B12  |
| Iron  |
| Folic acid  |
| b) Use of gluten-free oats as part of the exclusion diet (including thresholds for oats intake) |

### Comparator
Gluten free diet only (standard care)

### Outcomes
- Resolution of gastrointestinal and non-gastrointestinal symptoms  
- Growth in children and young people  
- Complications of coeliac disease  
- Dietary adherence  
- Impact on carers  
- Health-related quality of life  
- Serological response  
- Histological response  

### Complications include, but are not limited to:
- osteoporosis  
- ulcerative jejunitis  
- malignancy (intestinal lymphoma)  
- functional hyposplenism  
- vitamin D deficiency  
- iron deficiency  
- auto-immune diseases

### Other criteria for inclusion / exclusion of studies
Exclusion:  
- Case series and case studies  
- Non coeliac disease gluten sensitivity  
- Wheat allergy and sensitivity

### Search strategies
......

### Review strategies
Appropriate NICE Methodology Checklists, depending on study designs, will be used as a guide to appraise the quality of individual studies. Data on all included studies will be extracted into evidence tables.
Appendix C: Review Protocols & Search Strategy

Where statistically possible, a meta-analytic approach will be used to give an overall summary effect. All prioritised key outcomes from evidence will be presented in GRADE profiles and further summarised in evidence statements.

Identified papers

Systematic Reviews:


Studies


