Biomarkers currently play an important role in the detection and management of patients with several different types of gastrointestinal cancer, especially colorectal, gastric, gastro-oesophageal junction (GOJ) adenocarcinomas and gastrointestinal stromal tumors (GISTs). The aim of this article is to provide updated and evidence-based guidelines for the use of biomarkers in the different gastrointestinal malignancies. Recommended biomarkers for colorectal cancer include an immunochemical-based fecal occult blood test in screening asymptomatic subjects ≥50 years of age for neoplasia, serial CEA levels in postoperative surveillance of stage II and III patients who may be candidates for surgical resection or systemic therapy in the event of distant metastasis occurring, K-RAS mutation status for identifying patients with advanced disease likely to benefit from anti-EGFR therapeutic antibodies and microsatellite instability testing as a first-line screen for subjects with Lynch syndrome.

In advanced gastric or GOJ cancers, measurement of HER2 is recommended in selecting patients for treatment with trastuzumab. For patients with suspected GIST, determination of KIT protein should be used as a diagnostic aid, while KIT mutational analysis may be used for treatment planning in patients with diagnosed GISTs.

In recent years, biomarkers have begun to play an increasingly important role in the detection and management of patients with gastrointestinal malignancies. This applies especially for colorectal cancer (CRC), gastrointestinal stromal tumors (GISTs), gastric and gastro-oesophageal junction (GOJ) cancers. In 2003 and 2007, the European Group on Tumor Markers (EGTM) published guidelines on the use of biomarkers in the different gastrointestinal malignancies. Recommended biomarkers for colorectal cancer include an immunochemical-based fecal occult blood test in screening asymptomatic subjects ≥50 years of age for neoplasia, serial CEA levels in postoperative surveillance of stage II and III patients who may be candidates for surgical resection or systemic therapy in the event of distant metastasis occurring, K-RAS mutation status for identifying patients with advanced disease likely to benefit from anti-EGFR therapeutic antibodies and microsatellite instability testing as a first-line screen for subjects with Lynch syndrome.

The main targets of these guidelines include surgeons, physicians and nurses involved in the management of patients with gastrointestinal malignancies as well as laboratory professionals involved in the measurement of tumor biomarkers. The guidelines however, may also be useful for payers for healthcare, relevant policy makers, researchers and companies involved in the manufacture of tumor marker assays.

To prepare these guidelines, the literature relevant to the use of tumor markers in gastrointestinal cancers was reviewed. Particular attention was paid to systematic reviews, pooled or meta-analyses and to relevant guidelines issued by Expert Panels. For each guideline, we indicate the level of evidence (LOE) and strength of recommendation (SOR) for its clinical use (Table 1). In addition to reviewing clinical utility, we discuss cost-effectiveness of the recommended biomarkers and make suggestions for further research.

**Colorectal Cancer**

**Use of fecal occult blood testing in screening for early colorectal cancer**

Two types of FOBT are available, i.e., the older guaiac test (gFOBT) which detects the pseudo peroxidase activity of...
CRC,8,9 the gFOBT has many limitations as a screening test. Although extensively validated for reducing mortality form hemoglobin and the newer fecal immunochemical test (FIT) which detects the globin component of hemoglobin.6,7 Although extensively validated for reducing mortality form CRC,8,9 the gFOBT has many limitations as a screening test for CRC.10–15 These limitations include lack of specificity for human hemoglobin, (certain foodstuffs and medications may interfere with test) and relatively low clinical sensitivity and specificity for colorectal neoplasia. Furthermore, it is difficult to automate, rendering it unsuitable for large population-based screening.10

Because of these limitations, the use of gFOBT, as a screening test for CRC, is gradually being replaced by FITs.10–15 As summarized in Table 2, FITs possess many advantages over gFOBTs.10,12–15 Because of their superior performance, the EGTM panel have recommended that a FIT should be used in new centers embarking on FOBT screening. Specifically, the panel recommends use of a quantitative FIT, with an adjustable cut-off concentration.10 Recently published European Union guidelines for quality assurance in CRC screening and diagnosis also recommend use of FIT rather than gFOBT.15 All FOBTs however, lack specificity for colorectal neoplasia. Positive tests must therefore be followed-up with colonoscopy.10

An important consideration in introducing any new diagnostic procedure, especially disease screening, is cost-effectiveness. Indeed, the World Health Organization has stated that screening should only be implemented when a “good balance” exists between costs and benefits.16 In the context of CRC, several studies have concluded that when compared to no screening, all the widely investigated screening tests including FOBT offers additional years of life at a cost that is considered acceptable by most advanced countries and indeed may be cost-saving.17–25 Thus, in five cost-effectiveness analyses, the estimated mean cost per life-year gained from annual screening of subjects 50 years or older with a specific gFOBT ranged from $5,691 to $17,805.18 These costs are substantially less than the cost-effectiveness thresholds commonly used to evaluate medical interventions (e.g., ~€30,000 to €40,000 per quality life-year (QALY) gained in the EU, and $50,000–$100,000 in the USA).

The EGTM panel recommends that screening for CRC and advanced colorectal adenomas be performed with a FOBT.2,10 For new centers undertaking screening, the panel recommend use of a quantitative FIT that posses an adjustable cut-off point. Results using FITs should be expressed as micrograms of hemoglobin per gram of feces.26 Work to improve the standardization of FIT assays would be highly desirable,11 as would further research into DNA-based tests,27 including automation and cost reduction.10

CEA in determining prognosis and staging
A multiplicity of studies carried out over the last 30 years have addressed the prognostic impact of CEA levels at initial presentation in patients with CRC (reviewed in Refs. 28,29).

### Table 1. Biomarkers recommended by EGTM for use in gastrointestinal malignancies

| Marker | Cancer | Use | LOE | SOR |
|--------|--------|-----|-----|-----|
| FIT-based FOBT | CRC | Screening | I | A |
| CEA | CRC | Prognosis, especially in stage II patients | III | A |
| CEA | CRC | Postoperative surveillance | I | A |
| CEA | CRC | Monitoring therapy in advanced disease | III | A |
| K-RAS<sup>1</sup> | CRC | Predicting response/resistance to anti-EGFR antibodies | I | A |
| MSI/dMMR | CRC | Prescreen for Lynch syndrome | I | A |
| MSI/dMMR | CRC | Prognosis, especially in stage II disease | I | A |
| HER2<sup>2</sup> | Gastric/GOJ | Predicting response to trastuzumab | I | A/B |
| c-KIT | GIST | Diagnostic aid | III | A |
| c-KIT<sup>3</sup> | GIST | Therapy decision making with imatinib | III | A/B |

<sup>1</sup>Mutational status, i.e., patients with specific mutations in K-RAS are unlikely to benefit from the anti-EGFR antibodies, cetuximab or panitumumab.

<sup>2</sup>Gene amplification or overexpression, i.e., benefit from trastuzumab depends on HER2 gene amplification or overexpression.

<sup>3</sup>Mutational status, i.e., mutational status of c-KIT may be used to determine optimum dose of imatinib for patients with advanced GIST. Abbreviations: LOE, level of evidence<sup>3,4</sup>; SOR, strength of recommendation<sup>4</sup>; FIT, fecal immunochemical test; FOBT, fecal occult blood testing; dMMR, defective mismatch repair; FU, fluorouracil; GOJ, gastro-oesophageal junction; GIST, gastrointestinal stromal tumor.

### Table 2. Advantages of FITs compared to gFOBTs

- FITs have better analytical sensitivity and specificity than gFOBTs<sup>1</sup>
- FITs have greater sensitivity for advanced adenomas than gFOBTs
- Use of FITs leads to higher participation rates than use of gFOBTs
- In contrast to gFOBTs, FITs can be automated
- Use of FITs require fewer stool samples than gFOBTs
- FITs are quantitative or at least semi-quantitative
- FITs provide an adjustable cut-off point
- With FITs, no dietary or medication restriction is necessary
- FITs are more cost-effective than gFOBTs

Summarized from refs. 10–15.

<sup>1</sup>gFOBTs detect the presence of any blood, FITs are specific for human blood.
Table 3. Recent studies reporting a prognostic impact of preoperative CEA in patients with CRC cancer

| No. of patients | Tumor stages | Key findings | Ref. |
|-----------------|--------------|--------------|------|
| 9083            | I-IV         | CEA an independent prognostic marker, prognosis was worse in high CEA patients with a lower stage compared to low CEA patients with a higher stage. High CEA as strong as nodal positivity for predicting poor outcome. | (30) |
| 474             | I-III        | CEA an independent prognostic marker, CEA prognostic in stage II patients. | (31) |
| 1637            | I-III        | CEA an independent prognostic marker in total population, as well as in patients with either stages II or III disease | (32) |
| 1263            | I-III        | CEA an independent prognostic marker in total population, as well as in patients with either stages II or III disease | (33) |
| 82              | IIA          | CEA prognostic in stage IIA patients | (34) |
| 2230            | I-IV         | CEA an independent prognostic marker | (35) |
| 572             | II           | CEA prognostic in stage II patients | (36) |

1Investigated colon cancer patients only.

Although these different studies varied with respect to the specific CEA assay used, cut-off point for CEA, number of patients included, follow-up period and whether or not adjuvant chemotherapy was used, almost all concluded that elevated preoperative CEA levels were associated with adverse outcome. Indeed, several of these studies showed that CEA was an independent prognostic factor and, importantly, predicted outcome in patients with stage II disease. Key findings from the more recent and larger studies on the prognostic value of CEA in CRC are summarized in Table 3.

In agreement with other organizations, the EGTM recommends measuring preoperative CEA levels in newly diagnosed CRC patients. Preoperative levels provide prognostic information as well as a baseline value for interpreting subsequent levels. No study however, has shown that CEA can be used to select those patients with stage II CRC who would benefit from adjuvant chemotherapy.

For future research, the EGTM recommends that preoperative levels of CEA be included for risk stratification in clinical trials evaluating new adjuvant systemic treatments for patients with CRC. We also suggest that the prognostic impact of CEA be compared with other emerging prognostic markers for CRC such as microsatellite instability (MSI) and gene expression profiling (see below). In the context of biological/molecular prognostic biomarkers for CRC, measurement of CEA is likely to be considerably simpler and less expensive than determination of tissue-based biomarkers.

CEA in postoperative surveillance

At least eight published randomized controlled trials, including almost 3,000 patients in total, have addressed the impact of intensive postoperative surveillance on outcome in patients who have undergone curative surgery for colorectal cancer (for review, see Ref. 43). These randomized trials varied with respect to intensity of follow-up and diagnostic modalities used, and most were statistically underpowered to detect a significant effect of surveillance on survival. Furthermore, many were carried out prior to the use of adjuvant chemotherapy for CRC and availability of modern and more effective systemic treatment for recurrent CRC.

Nevertheless, meta-analyses of these trials showed that intensive follow-up resulted in a reduction of 20–30% in the hazard rate for all cause mortality. However, due to the different follow-up strategies used in both the intensive and nonintensive follow-up arms, it was not possible to draw conclusions about the best combination of tests or the frequency of their performance. Despite this, regular measurement of CEA, as part of an intensive follow-up regime, appears to be necessary to achieve significant improvement in survival.

Compared to other available diagnostic modalities, serial CEA determinations appear to be the most sensitive for the detection of early recurrent disease (i.e., provide the first indication), especially liver metastasis. Thus, in a recent large randomized prospective trial comparing laparoscopically-assisted colectomy with open colectomy in patients with curable colon cancer, serial CEA measurements outperformed other diagnostic modalities for patients with both early stage (stage I and IIa) and late stage disease (stage IIb and III). For the 537 patients with early stage CRC, CEA detected 29.1% of the first recurrences compared with 23.6% by CT scan, 12.7% for colonoscopy and 7.3% for chest X-ray. For the 254 patients with late stage disease, CEA detected 37.4% of the first recurrences, CT scan 26.4%, chest X-ray 12.1% and colonoscopy 8.8%.

Similar to the situation with CRC screening, intensive follow-up after curative surgery for CRC has been shown to be cost-effective. Based on data from five randomized trials, Renehan et al. calculated that the number of years gained through intensive surveillance over 5 years was between 0.73 and 0.82. The adjusted net cost for each patient was £2479 and for each life year gained was £3402. Although the most cost-effective strategy is unknown, measurement of CEA appears to be one of the least expensive tests performed as part of an intensive follow-up strategy. Thus, in an early study carried out in the US, the cost per recurrence detected was $5,696 using CEA, $10,078 with chest X-ray and $45,180 using colonoscopy. Although the absolute costs of these tests are likely to have increased since publication of this report, the relative costs are likely to be the similar.

Because of its ease of measurement, relatively low costs and sensitivity for early metastasis, most expert panels recommend regular CEA measurements during the follow-up of CRC.
of-function mutations in the mismatch repair (MMR) genes, MLH1, MSH2, PMS2 and MSH6. Loss of these genes results in defective MMR (dMMR), which in turn results in microsatellite instability (MSI).

As MSI or dMMR is present in >90% of cases, their detection is used as an initial test in the detection of LS in patients with CRC. If MSI/dMMR is present, further investigations including mutational analysis of the MSH2 and MLH1 genes should be performed. The absence of MSI or dMMR makes the presence of LS unlikely. Although MSI and MRR protein status are relative sensitive tests for LS, they are not specific, as 12–17% of all CRCs exhibit these defects, the majority of which are sporadic. In sporadic CRC however, MSI generally results from loss of MLH1 and PMS2 proteins. Loss of MLH1 expression in sporadic CRCs is due to epigenetic silencing by hypermethylation of CpG nucleotides in its gene promoter region.

Establishing a diagnosis of LS in patients with CRC is important, as these subjects are at increased risk of developing other cancers. In addition, since some family members will have inherited LS, they are also at high risk of developing CRC and possible other malignancies. Although randomized trials have not been reported, several observational studies suggest that close surveillance of Lynch syndrome subjects decreases both cancer rates and mortality. While traditionally, MSI/MMR protein measurement in CRC was limited to subjects fulfilling specific clinical characteristics such as the Amsterdam and Bethesda criteria, more recently several expert panels and some individual investigators have recommended that all patients with CRC should undergo such testing. Advantages of a universal testing approach include cost-effectiveness and increased sensitivity for detecting mutation carriers. Limited resources may however, restrict universal testing in some countries.

In agreement with other organizations, the EGTM recommends measurement of MSI or MMR proteins as prescreens for LS in patients with CRC. If MSI is present or MMR enzyme loss is detected, subjects should be offered genetic counseling and undergo germline gene testing for LS. Subjects with MSI-positive tumors that are negative for MLH1 protein may be considered for BRAF mutation and/or MLH1 promoter methylation testing, prior to further genetic testing. Future research should focus on the optimum and most cost-effective approach for LS prescreening.

Prognosis and therapy prediction. In addition to being used as a prescreen for LS, MSI/MMR status may also have use as a prognostic marker in CRC, as several studies have shown that the presence of MSI or defective MMR activity is a marker of favorable outcome. Two separate pooled analyses, as well as several large randomized trials have shown that the presence of MSI/dMMR was associated with a favorable outcome, especially in patients with Stages II and III colon cancer. All these studies when taken together provide strong evidence that MSI/MMR status is a prognostic
biomarker for Stages II and III colon cancer. Additionally, MSI status is now recommended in the WHO classification of mucinous-type CRC, with high MSI indicating good prognosis and low or absent MSI suggesting poor outcome.

Several studies including two randomized trials, a retrospective case study and a systematic review also suggest that MSI/MMR status may be a predictive biomarker for adjuvant 5-FU-based therapy, i.e., the presence of MSI/dMMR is associated with lack of benefit.

Although most studies have shown a relationship between MSI/dMMR and lack of benefit from adjuvant 5-FU, some have not confirmed these findings. Possible reasons for the conflicting data include the different protocols used for determining MSI/MMR status, especially the number of microsatellites measured when assessing MSI status, the number of patients investigated in the various studies, inadequate randomization and length of follow-up.

Because of the multiplicity of studies linking MSI/dMMR with good prognosis, the EGTM states that these parameters may be measured in patients with Stage II colon cancer who are under consideration for adjuvant 5-FU-based therapy. Patients with MSI/dMMR may not require such therapy as their prognosis is likely to be favorable. MSI-positive patients with adverse prognostic features such as pT4 stage or lymphangio-invasion however, should not be excluded from receiving chemotherapy.

Future work should compare the prognostic impact of MSI/MMR status in stage II CRC with that of CEA and the various multigene profiles currently undergoing evaluation (see below). Further research is also required to investigate whether the MSI/dMMR status is of value in predicting benefit from other chemotherapeutic drugs such as platinum salts (oxaliplatinum) and topoisomerase inhibitors (irinotecan).

**K-RAS for predicting response to anti-EGFR antibodies**

Cetuximab and panitumumab are monoclonal antibodies that bind to the extracellular domain of EGFR, thereby inhibiting downstream signaling and resulting in decreased cell proliferation and migration. Early clinical trials using these antibodies, either alone or in combination with chemotherapy, to treat unselected patients with advanced CRC gave response rates of only 10–15%. More recently, retrospective analysis of randomized controlled trials has shown that patients with specific mutations in codons 12 of the K-RAS gene almost never benefited from treatment with these antibodies. However, 15–20% of patients with wild-type K-RAS show an objective response with antibody alone and 35–40%, when administered with cetuximab or irinotecan.

While almost all of the known K-RAS mutations at codons 12 are associated with lack of benefit from cetuximab or panitumumab, a specific mutation at codon 13, i.e., G13D may be an exception. Thus, in two trials, administration of cetuximab to patients with this mutation was associated with a significantly better outcome than that seen in patients with other types of K-RAS mutations. Indeed, patients with the G13D mutation appeared to benefit to approximately the same extent as patients with K-RAS wild-type tumors from the addition of cetuximab to first-line chemotherapy. Clearly, these findings require validation in a large prospective randomized trial.

As with several of the biomarkers discussed above, an economic benefit for K-RAS testing prior to prescribing anti-EGFR antibodies for patients with metastatic CRC has been demonstrated. Using modeling data, Vijayaraghavan et al. calculated that administration of anti-EGFR antibodies only to patients with wild-type K-RAS would result in a net saving of €3,900–€9,600 in Germany and $7,500–$12,400 in the US. For these calculations, it was assumed that all patients had previously received at least one line of chemotherapy treatment.

Because of its clinical and economic benefit, EGTM recommends mutation testing of K-RAS prior to administering cetuximab or panitumumab to patients with advanced CRC. Patients with specific activating mutations especially at codon 12 should not be treated with anti-EGFR antibodies. Patients with the G13D mutation may however, benefit from combined cetuximab and chemotherapy but this remains to be confirmed. It is important that the laboratory report indicate the specific K-RAS mutation analyzed and detected as well as the methodology used. Recommendations for performing K-RAS gene mutations testing in CRC have recently been published.

Future research should aim to standardize assays for assessing the mutational status of K-RAS in CRC. Research should also focus on the identification and development of additional biomarkers in order to increase the positive predictive value for response to anti-EGFR antibodies. This should focus on validating preliminary findings suggesting a predictive or prognostic value for mutations in BRAF, PIK3CA and N-RAS, loss of PTEN and levels of EGFR ligands. Finally, as mentioned above, further work is necessary to establish which patients with which G13D mutations are likely to benefit from treatment with anti-EGFR antibodies.

Other therapeutic targets as well as emerging therapeutic targets for the treatment of CRC are listed in Table 4. Apart from the anti-EGFR antibodies discussed above, validated predictive markers are currently unavailable for the drugs inhibiting these targets.

**Gastric and Gastro-Oesophageal Junction Cancers**

**HER2 for predicting response to trastuzumab**

As with breast cancer, patients with gastric and GOJ cancers overexpress HER2 in 10–25% of cases. Consistent with this finding, HER2-positive cell lines are sensitive to trastuzumab, while patients with advanced HER2-positive gastric and GOJ tumors benefit from treatment with the anti-HER2 antibody. Based on these findings, EGTM state that for patients with advanced gastric or GOJ under consideration for systemic therapy, measurement of HER2 should be...
performed using immunohistochemistry and/or FISH. Patients with HER2-positive disease are candidates for receiving combined trastuzumab and chemotherapy. HER2 staining and scoring in gastric and GOJ cancers may be heterogeneous, multiple biopsies are necessary in order to obtain a reliable indication of the oncoprotein status.124

Gastrointestinal Stromal Tumors

KIT as a diagnostic aid

Gastrointestinal stromal tumors (GISTs) although rare are the most common mesenchymal tumor found in the gastrointestinal tract (for review, see Refs. 125,126). At a molecular level, GISTs are characterized by the presence of KIT protein and mutations in the KIT gene. Thus, the KIT protein is found in >95% of GISTs, while mutations in the KIT gene are present in ~80–85% of cases.125,126 Most of the mutations in the KIT gene are found in Exon 11 and consist of point mutations and deletions. Less frequent mutations are present in Exons 9, 13 and 17. Five to 10% of GISTs have mutations in the homologous gene, PDGFRA.125,126 Mutations in PDGFRA are mostly found in Exons 12 and 18 and appear to be mutually exclusively with mutations in KIT. Overall, 80–95% of GISTs have mutations in either the KIT or PDGFRA gene.

Because the KIT gene is almost universally expressed and/or mutated in GISTs, it has been extensively investigated as a biomarker for this disease125–127 and immunostaining for KIT protein is used as a diagnostic aid for GISTs. For the small proportion of GISTs that fail to express KIT protein (~5%), mutational analysis of the KIT and PDGFRA genes may confirm the diagnosis. However, although KIT protein is rarely detected in other abdominal tumors, it may be present in some nonabdominal tumors, including melanomas, breast cancers, and seminomas.125,128 Other markers that may aid the diagnosis of GISTs include DOG1, CD34, S100, desmin, PS100 and smooth muscle actin.125,128 Measurement of markers however, complements but does not replace histopathology in the diagnosis of GIST.

A number of expert panels including ESMO,129 a French National Consensus Group,130 and NCCN131 recommend measurement of KIT as an aid for diagnosis of GIST. Both the ESMO and NCCN Panels also state that KIT and PDGFRA mutation testing should be considered for KIT protein-negative tumors that are suspected to be GISTs.129,131

In agreement with these groups, EGTM recommend that staining for KIT protein should be used as a diagnostic aid for GIST. However, its absence does not exclude GIST. Mutational analysis of KIT or PDGFRA genes may be considered, if sample is KIT protein-negative.

KIT in predicting benefit from Imatinib

Imatinib is a tyrosine kinase inhibitor which blocks KIT and PDGFRA as well as BCR-ABL. The use of imatinib has revolutionized the treatment of patients with GISTs in recent years.125 Response to imatinib however, depends on the mutational status of the KIT gene. Thus, patients with advanced GISTs exhibiting mutations in Exon 11 of KIT had a better outcome than those with Exon 9 mutations or those without a detectable KIT mutation.132–138 Based on the above, several expert panels currently recommend KIT and PDGFRA mutational analysis prior to prescribing imatinib to patients with GISTs.

Although the use of imatinib in patients with GISTs was originally restricted to patients with advanced disease, a recent provisional clinical opinion published by a European consensus group recommended adjuvant imatinib in patients with KIT exon 11 mutations. However, adjuvant imatinib was not recommended for patients with primary GISTs containing PDGFRA D842V mutations.139

In agreement with other expert panels,129–131 EGTM state that mutational analysis of KIT and PDGFRA should be

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**Table 4. Established and emerging therapeutic targets for the treatment of colorectal cancer**

| Target | Drug | Phase of Development | Ref. |
|--------|------|----------------------|------|
| EGFR   | cetuximab, panitumumab | In clinical use | 98–101 |
| VEGF   | Bevacizumab, afiblercept | In clinical use | 109–111 |
| Multi kinases | Regorafenib | In clinical use | 112,113 |
| BRAF (mutant) | Vemurafenib, dabrafenib | In development | 114 |
| MEK    | Selutinib, pimasertib | In development | 115,116 |
| mTOR   | Everolimus | In development | 116,117 |
| PI3K   | LY294002, GDC0941 | In development | 116,118 |

1Regorafenib inhibits VEGFR1, VEGFR2, VEGFR3, PDGFRbeta, Tie-2, FGRF1, RET and BRAF.

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**Table 5. Emerging biomarkers for gastrointestinal cancers**

| Marker | Cancer | Potential use | Ref. |
|--------|--------|--------------|------|
| Multigene profiles1 | CRC | Determining prognosis | 140–142 |
| TIMP-1 | CRC | Prognosis | 143 |
| CA 19-9 | CRC | Postoperative surveillance | 144 |
| Stool DNA profiles | CRC | Screening | 145 |
| Septin 9 | CRC | Screening | 146 |
| TFAP2E | CRC | Chemoprediction | 147 |
| CA 242 | Gastric | Prognosis, monitoring therapy | 148 |
| DOG1 | GIST | Diagnostic aid | 149 |

1Amongst the best-validated multigene signatures are the ColoPrint test (Agendia) (129), 634-geneColDx (Almac) (130), and the Oncotype DX colon cancer assay (Genomic Health) (131).

Abbreviations: CRC, colorectal cancer; GIST, gastrointestinal cancer.
considered prior to administering imatinib to patients with GIST.

Emerging Markers
Table 5 lists some promising new biomarkers and multigene profiles for gastrointestinal cancer. None of the listed markers/profiles however, can currently be recommended for routine clinical utility.

Conclusion
It is clear from the above that several biomarkers are now integral to the management of patients with different types of gastrointestinal cancers (Table 1). We should point out, however, that the guidance published here and elsewhere should not replace physician judgment in specific patients. Furthermore, as new data becomes available, recommendations based on existing evidence may change. It is therefore vital that physicians using these biomarkers and the laboratories performing the assays keep up-to-date with new findings. Finally, laboratories performing the recommended assays should participate in external quality assessment schemes, be accredited by appropriate regulatory organizations and be staffed and managed by an appropriately trained work-force.

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