Colorectal Cancer: How Emerging Molecular Understanding Affects Treatment Decisions

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In this review we discuss the current treatment options in metastatic colon cancer, with a special focus on biologic agents and how molecular understanding guides treatment decisions.

Medical Treatment Options for Metastatic Colorectal Cancer

The current standard of care for metastatic colorectal cancer (mCRC) commonly combines cytotoxic chemotherapy with biologic agents. At present, there are six different classes of drugs (three classes of cytotoxic agents, three classes of biologic agents) available for the treatment of mCRC. The Table provides an overview of all agents that have been approved by the US Food and Drug Administration (FDA) for the treatment of mCRC, and gives the approved indications for the use of each. The approved conventional cytotoxic agents fall into three classes: fluoropyrimidines (fluorouracil [5-FU] and the oral fluoropyrimidine analogue capecitabine), topoisomerase I inhibitors (irinotecan), and platinum-containing compounds (oxaliplatin). Combination regimens consisting of a protracted infusion of 5-FU modulated by leucovorin and oxaliplatin (FOLFOX) or by leucovorin and irinotecan (FOLFIRI) form the backbone to which targeted agents are added in common clinical practice.[1] Capecitabine can be used as an alternate fluoropyrimidine backbone—in particular, in combination with oxaliplatin (CAPOX or XELOX).[2] However, the overlapping toxicity profiles of capecitabine and irinotecan make this combination more problematic.[3]

The targeted biologic therapies available for mCRC fall into three groups: (1) inhibitors of the vascular endothelial growth factor (VEGF) proangiogenic system (the monoclonal VEGF-A antibody bevacizumab, and afibercept, a unique fusion protein derived from extracellular receptor components of the VEGF system); (2) monoclonal antibodies against the epidermal growth factor receptor (EGFR) on the surface of tumor cells (cetuximab and panitumumab); and (3) regorafenib, an oral small-molecule inhibitor of intracellular kinases involved in various signaling cascades.

Targeting VEGF-Mediated Angiogenesis in mCRC

VEGFs are soluble growth factors that can be secreted by tumor cells. The VEGF family of growth factors is composed of seven members (VEGF-A through VEGF-E, placental growth factor [PIGF]-1 and PIGF-2), with VEGF-A being the most prominent mediator of tumor angiogenesis.[4] These ligands bind to the extracellular domains of the VEGF receptors (VEGFRs; VEGFR-1, -2, and -3) and accessory receptors, such as neuropilin-1 (NRP-1) and NRP-2. The intracellular domain of VEGFR contains catalytic tyrosine kinase domains that, when activated, initiate a signaling cascade that results in endothelial cell survival, proliferation, migration, differentiation, and increased vascular permeability. Bevacizumab is a humanized monoclonal antibody that binds to VEGF-A, preventing VEGF-A from binding to its target receptor. As a single agent, bevacizumab has little efficacy in colorectal cancer,[5] but the addition of bevacizumab to standard chemotherapy consistently leads to a significant increase in median progression-free survival (PFS) and commonly also to increases in response rate (RR) and overall survival (OS), regardless of the chemotherapy backbone used.[6] Another agent that targets the VEGF system is afibercept, which is currently approved in the United States for use in combination with FOLFIRI for the treatment of patients with mCRC that has progressed following an oxaliplatin-containing regimen.[7] It is a recombinant fusion molecule of the extracellular domain of human VEGFR-1 and VEGFR-2 fused to the fragment crystallizable (Fc) portion of human immunoglobulin G (IgG)-1. In the VELOUR trial, patients whose disease had progressed within 6 months of receiving oxaliplatin-containing chemotherapy (with or without bevacizumab) were randomly assigned to receive either FOLFIRI with afibercept or FOLFIRI with placebo.[7] Patients who received afibercept had a longer median OS and PFS regardless of prior bevacizumab exposure.
Evidence exists that prolonged inhibition of the VEGF-mediated proangiogenic system is required to maximize treatment benefit for patients receiving anti-VEGF therapy, in particular because the mechanism and onset of secondary resistance could differ between chemotherapy and bevacizumab.[8] The efficacy of prolonged VEGF inhibition with bevacizumab added to chemotherapy has been highlighted by several randomized trials. A prespecified analysis of a large phase III trial (NO16966) in which bevacizumab was added to an oxaliplatin-based first-line regimen demonstrated that improvements in PFS were much more profound in patients who received treatment until progression than in those who stopped therapy for other reasons.[9] Since the treatment-limiting toxicity of oxaliplatin-based first-line therapy is cumulative neurotoxicity, proactive strategies have to be employed to maximize treatment duration for patients who start palliative therapy with FOLFOX + bevacizumab, the most commonly used first-line regimen in the United States. Therefore, induction-maintenance approaches that include a limited number of oxaliplatin-containing treatment cycles upfront and maintenance therapy with a fluoropyrimidine-bevacizumab combination can be considered a standard of care. This concept is supported by several prospective trials, most notably by the recently presented Dutch CAIRO-3 study.[10]

Further evidence supporting the concept of prolonged VEGF inhibition as an optimized treatment approach in colorectal cancer comes from the Treatment through Multiple Lines (TMO; or ML 18147) phase III trial that documented a survival benefit when bevacizumab was continued beyond progression on first-line therapy in mCRC.[11] A smaller Italian phase II trial and a prespecified subgroup analysis of the second-line VELOUR study of aflibercept in patients with or without prior bevacizumab exposure confirmed the outcomes benefit associated with continued VEGF inhibition beyond progression.[12,13]

Potential biomarkers for anti-VEGF therapy

In recent years, a lot of our research efforts have focused on identifying potential predictive biologic markers that might provide information regarding tumor response to anti-VEGF therapy. Unfortunately, thus far, the isolation of predictive markers for anti-VEGF therapy has proven elusive. Possible marker candidates that have been investigated include plasma angiogenic molecules (VEGF, PlGF), soluble VEGFR-2, and basic fibroblast growth factor (bFGF).[14] Tests have been performed to see whether plasma levels of these proteins would change with the use of bevacizumab; unfortunately, none of these proteins have demonstrated a predictive value. Another possible candidate that has been considered is NRP-1, a coreceptor for VEGF-A, but results have not been consistent.[14,15] Most recently, circulating plasma levels of small VEGF isoforms (121, 165) have been correlated with outcomes in patients receiving bevacizumab-based therapy for noncolorectal malignancies, but validation of these findings in mCRC is pending.[15] Genetic variants of components of the VEGF system have been implicated as potential predictive markers in preliminary studies.[16]

Some studies had suggested anti-angiogenic agents have the potential to have inhibitory effects on the mobilization or proliferation of endothelial progenitor cells (EPCs) in tumor tissue, such that EPCs could then serve as predictive markers for efficacy, but more recent data have been disappointing.[17]

At this point, no predictive biomarker for anti-VEGF therapy is available that could guide clinical practice. It is established, though, that the efficacy of bevacizumab is independent of the presence of KRAS and BRAF mutations.[18]

Regorafenib: A small-molecule kinase inhibitor

In addition to targeting VEGF alone, small-molecule inhibitors are being developed that target angiogenesis in other ways. Regorafenib is an orally active small-molecule inhibitor of angiogenic, stromal, and oncogenic receptor serine-threonine and tyrosine kinase. It acts by binding to the intracellular component of VEGFR-2 and -3, as well as to Ret, Kit, platelet-derived growth factor receptor (PDGFR), and Raf kinases.[19] The CORRECT study randomly assigned patients with mCRC refractory to standard chemotherapy to receive either regorafenib and best supportive care (BSC) or placebo and BSC; the primary endpoint was OS.[20] Patients in the regorafenib-treated arm had a median OS of 6.4 months compared with 5 months in the placebo-treated arm (hazard ratio [HR] for OS, 0.77). The PFS curve demonstrates that about 50% of patients enrolled in CORRECT did not derive benefit from regorafenib. At this point in time, however, no predictive biomarker exists to identify patients who might benefit from this novel multikinase inhibitor.
Targeting EGFR in mCRC

EGFR (also known as ErB1 or HER1) is a member of the ERbB transmembrane tyrosine kinase receptor family. The binding of a ligand (epidermal growth factor [EGF], transforming growth factor [TGF]-α, amphiregulin, heparin-binding EGF, betacellulin, epiregulin) to EGFR leads to activation of the tyrosine kinase domain and of a pathway involving several intracellular signal transduction pathways, including 1) Ras/Raf/mitogen-activated protein kinase (MAPK), 2) phosphoinositide 3 kinase (PI3K)/Akt, and 3) JAK-STAT (The first two of these pathways are shown in Figure 1). Activation of these pathways will ultimately result in inhibition of apoptosis, as well as in cell differentiation and cell proliferation. Both of the monoclonal antibodies against EGFR—cetuximab, a chimeric IgG1 antibody, and panitumumab, a fully human IgG2 antibody—have single-agent efficacy in advanced colorectal cancer. An initial phase II trial confirmed the activity of cetuximab in patients who had experienced disease progression on prior irinotecan-based therapy.[21] A large international randomized phase III trial comparing cetuximab with cetuximab + irinotecan confirmed the findings with almost identical results.[22] These data served as the basis for the initial approval of cetuximab in 2004 as a treatment option for patients with mCRC who have been pretreated with irinotecan-based regimens. Single-agent panitumumab showed benefit compared with BSC in a large, international phase III trial in an extensively pretreated population, demonstrating significant improvement in PFS.[23] OS was not increased, presumably because 75% of patients crossed over from BSC to the panitumumab arm. Based on these data, panitumumab was approved as a single-agent salvage therapy option in the United States in 2006. A similar last-line trial comparing cetuximab with BSC (without crossover) yielded results almost identical to those of the panitumumab vs BSC trial in terms of RR and PFS, but also showed a survival benefit for the cetuximab arm, likely due to the absence of crossover from BSC to cetuximab.[24] A phase III head-to-head comparison of both antibodies in a salvage therapy setting in 999 patients recently confirmed the identical efficacy of both agents.[25] Both antibodies have been tested as components of first-line therapy in combination with modern chemotherapy regimens, such as FOLFOX and FOLFIRI.[26–29] In clinical practice, cetuximab and panitumumab are currently used either in combination with standard combination chemotherapy regimens, with irinotecan alone, or as single agents.

Biomarkers for EGFR antibody therapy

The search for predictive biomarkers for EGFR-targeting agents is one of the most promising and exciting areas of clinically relevant translational research in colorectal cancer at this time. Initially, protein expression levels of the drug target, EGFR, were thought to correlate with the efficacy of EGFR antibodies, similar to the findings for trastuzumab in human epidermal growth factor receptor 2 (HER2)-positive breast cancer. However, clinical trials that have attempted to correlate the level of EGFR protein expression (via immunohistochemistry [IHC]) with sensitivity to anti-EGFR antibodies have demonstrated a lack of association.[30] EGFR expression has also been evaluated with the use of molecular-based assays (ie, EGFR gene copy).[31] The current consensus is that the evaluation of EGFR gene copy as a predictor of EGFR antibody effectiveness yields inconsistent results due to inconsistent technique, uncertain level score cutoff, and lack of standardization.

The search for other potential predictive markers of response to EGFR inhibitors eventually focused on downstream targets in the EGFR signaling pathway, including KRAS, NRAS, BRAF, and PIK3CA (the gene encoding the PI3K protein). A retrospective study of 39 mCRC patients treated with cetuximab (as monotherapy or as a part of combination therapy) provided the first suggestion in a retrospective analysis of a nonrandomized study that the presence of a KRAS mutation was associated with a lack of benefit from cetuximab.[32] In 2008, the first convincing evidence from an analysis of biospecimens obtained from a large, randomized phase III trial emerged showing that KRAS mutations rendered panitumumab single-agent therapy ineffective.[33] A plethora of subsequent trials have confirmed these findings for cetuximab and panitumumab, used either as single agents or in combination with chemotherapy. KRAS is a phosphorylated signal transducer that self-inactivates via intrinsic guanosine triphosphatase (GTP)-ase activity.[34] Studies consistently demonstrate that KRAS wild-type status is necessary but not sufficient for response to EGFR inhibitors. In accordance with FDA guidelines, a test for KRAS mutational status needs to be performed before the use of EGFR monoclonal antibodies, since cetuximab and panitumumab are only indicated for mCRC tumors that are KRAS wild-type.

Seven specific mutations in exon 2 (codons 12 and 13) make up more than 90% of all KRAS
mutations, and these are the mutations currently assessed in standard tests. However, while mutations in KRAS exon 2 comprise the most commonly seen mutations, there are still subsets of KRAS and other NRAS or RAS family “mutants” that are being missed with current testing. The significance of potentially missing patients with RAS mutations and subjecting them to EGFR antibody therapy was highlighted by the results of the Dutch CAIRO-2 phase III trial. In this trial, 755 patients with chemo-naive mCRC were treated with capecitabine, oxaliplatin, and bevacizumab, and randomly assigned to additionally receive either cetuximab or only the three-drug combination. Among the patients treated with cetuximab, PFS was shorter in those with an activating KRAS mutation than in those with a KRAS wild-type tumor.[35] A similar finding was seen in the Panitumumab Randomized Trial In Combination With Chemotherapy for Metastatic Colorectal Cancer to Determine Efficacy (PRIME) study, in which patients were randomly assigned to receive either FOLFOX or FOLFOX + panitumumab as first-line therapy.[27] Patients with wild-type KRAS tumors who received panitumumab had a survival benefit compared with those who did not receive panitumumab (PFS, 10.0 months vs 8.6 months, \( P = .02 \)). Surprisingly, patients with KRAS mutations who received panitumumab in combination with FOLFOX4 had a decreased PFS compared with those who received FOLFOX4 alone (7.4 months vs 9.2 months, \( P = .02 \)). This finding suggests that the use of EGFR inhibitors is not only ineffective in patients with KRAS-mutated mCRC, but may also be potentially harmful.

Douillard and colleagues recently expanded on the mutational analysis of the PRIME study by using a prospective-retrospective study design to analyze biomarkers and treatment effect in the comparison of FOLFOX4 + panitumumab vs FOLFOX4 alone.[36] In this analysis, mutations in KRAS exon 3 (codon 61) and exon 4 (codon 117 and 146); NRAS exon 2 (codons 12 and 13), exon 3 (codon 61), and exon 4 (codon 117 and codon 146); as well as BRAF exon 15 (codon 600) were assessed. Mutations that were not prespecified were also analyzed as exploratory endpoints. Of 1,183 patients included in this randomization, 93% had been previously evaluated for a KRAS exon 2 mutation, and 40% were found to have tumors with this mutation. As part of this study, an expanded RAS mutation status was determined in 1,060 of the 1,183 patients in the study (Figure 2). Of the 1,060 patients, 48% were identified as having wild-type RAS (no KRAS or NRAS mutations in exons 2, 3, or 4). When patients were categorized by mutational status, at primary analysis, those patients without KRAS mutations in exon 2 had an increased PFS if they received panitumumab with FOLFOX4 compared with FOLFOX4 alone (9.6 months vs 8.0 months, \( P = .02 \)). When this analysis was updated with an exploratory analysis that used a later data cutoff point, patients without KRAS mutations who were treated with panitumumab + FOLFOX4 had a 4.4-month improvement in median OS (\( P = .03 \)). A similar benefit was seen when assessing PFS in patients without RAS mutations. In this subgroup, PFS was 10.1 months for panitumumab + FOLFOX4 vs 7.9 months for FOLFOX4 alone. Of the 620 patients who were originally classified as not having a mutation in KRAS (exon 2), 17% had mutations in other RAS exons. In this subgroup of patients, PFS and OS in the primary and exploratory analysis were decreased in the panitumumab + FOLFOX4 group compared with the FOLFOX4 group. Of note, previously specified mutations in KRAS and NRAS at codon 59 were identified in seven patients, and exclusion of these mutated alleles slightly improved PFS and OS. The findings in this study demonstrate that RAS mutations as well as KRAS exon 2 mutations predict a lack of response to EGFR inhibitors in patients with mCRC. This highlights the need for more effective testing of mutations beyond KRAS codon 12/13, since current testing continues to include a significant number of patients who will not benefit from therapy. In fact, the use of EGFR antibodies in the patient population with RAS mutations not identified with standard KRAS exon 2 analysis might be associated with a detrimental effect on patient outcomes.

**Head-to-Head Comparison Between EGFR Monoclonal Antibodies and Bevacizumab**

At the 2013 meeting of the American Society for Clinical Oncology, the first results of a phase III trial involving a direct comparison between cetuximab- and bevacizumab-containing first-line therapies were presented.[37] The FIRE-3 trial randomly assigned 592 patients with conventionally assessed KRAS exon 2 wild-type mCRC to receive either FOLFIRI + cetuximab or FOLFIRI + bevacizumab. The primary endpoint of the trial, investigator-assessed RR, was not reached in the intention-to-treat analysis (cetuximab, 62%; bevacizumab, 58%; \( P = .18 \)). In addition, no difference in PFS was noted between the two arms (10.0 months for cetuximab vs 10.3 months for bevacizumab); in fact, the PFS curves for the two arms were almost completely superimposable. Surprisingly, however, a statistically significant difference in OS was found—a difference in median OS of 3.7 months in favor
of FOLFIRI + cetuximab (28.7 months vs 25.0 months; HR, 0.77; P = .017). The survival curves appeared to split at 24 months—in other words, more than 12 months after the median PFS had been reached. An updated analysis that accounted for additional mutations in KRAS exons 2 and 3, as well as NRAS mutations, demonstrated an even larger difference in median OS once patients with these additional mutations beyond KRAS exon 2 had been excluded (33.1 months for FOLFIRI + cetuximab vs 25.6 months for FOLFIRI + bevacizumab; HR, 0.70; P = .011), again without a statistically significant difference in RR or PFS.[38] As outlined above, in patients with tumors harboring the additional KRAS and NRAS mutations, a detrimental effect might have been precipitated by the use of cetuximab.

Data from the larger US Intergroup study, Cancer and Leukemia Group B (CALGB)/Southwest Oncology Group (SWOG) 80405, are expected to be released in 2014. This study compared chemotherapy (FOLFOX or FOLFIRI) with cetuximab vs chemotherapy with bevacizumab as first-line therapy in KRAS exon 2 wild-type mCRC and was powered to detect an OS benefit in the chemotherapy + cetuximab arm.

**BRAF-Mutated Colorectal Cancers**

BRAF encodes a protein, guanosine triphosphate (GTP)ase, downstream of Ras. Mutations in BRAF, which can be found in about 5% to 10% of patients with advanced colorectal cancer, and KRAS mutations are mutually exclusive,[39] and BRAF mutations have consistently been found to be associated with a very poor prognosis.[28,40,41] Even in the era of modern combination therapy, the median survival of patients with BRAF-mutated cancer is only in the range of 12 to 14 months.[28]

However, more recent data suggest that an aggressive first-line treatment approach using a triplet chemotherapy combination (FOLFOXIRI) plus bevacizumab might at least partially counteract the poor prognosis of patients with BRAF-mutated colorectal cancers.[42,43] Thus, FOLFOXIRI + bevacizumab could emerge as the preferred treatment option in these patients.

The validity of BRAF mutations as a negative predictive marker for the activity of EGFR antibodies is unclear, but more recent data suggest that cetuximab and panitumumab might still have some, albeit attenuated, activity in BRAF-mutated colorectal cancers.[28]

Ideally, patients with metastatic colon cancer and BRAF mutations would be candidates for therapy with inhibitors of BRAF, which are currently being used in the treatment of melanoma. However, the clinical results with BRAF inhibitors as single agents in colorectal cancer have been disappointing. Work by Yang and colleagues in BRAF-mutant colorectal cells suggested that a BRAF mutation is necessary but not sufficient for the activity of vemurafenib.[44] Their work suggested that BRAF inhibition by vemurafenib caused rapid feedback activation of EGFR, which supported continued tumor growth despite BRAF inhibition.[44]

Ongoing randomized clinical trials looking at dual BRAF and EGFR inhibition in BRAF-mutated colorectal cancer will help shed light on whether dual pathway inhibition will allow for better survival outcomes in patients who otherwise would not benefit from BRAF inhibition.

**Other Downstream Effectors of EGFR, and Possible Modes of Resistance to Anti-EGFR Therapy**

In addition to KRAS, NRAS, and BRAF, another downstream effector of EGFR is PIK3CA, which encodes for the catalytic subunit of PI3K. In its activated mutated form, it can induce phosphorylation of Akt, which then promotes cell growth and suppresses apoptosis in colorectal cancers. Phosphatase and tensin homolog (PTEN) is a tumor suppressor that is in the PI3K pathway. Some authors suggest that the combination of KRAS mutation status and PTEN expression in colorectal cancer metastases could be a better predictive marker for patient benefit from cetuximab than KRAS mutation status alone. However, two keys points limit PTEN’s value as a predictive marker: (1) PTEN protein expression as determined by IHC can be affected by significant inter- and intra-observer method-based variability, and (2) only PTEN expression in metastases (not in primary tumors) has been associated with outcome.[45]

Beyond mutations of downstream effectors, expression levels of EGFR ligands have been correlated with the activity of EGFR antibodies.[46] In patients with KRAS wild-type tumors, sensitivity to EGFR inhibition was proportional to the levels of EGFR ligands epieregulin and amphiregulin.[47] KRAS wild-type tumors with low ligand expression were more likely to behave like KRAS-mutant tumors. There was no association between epieregulin and amphiregulin expression and sensitivity to EGFR inhibition in patients with KRAS-mutant tumors. Therefore, testing for EGFR ligands could isolate a
population that is more likely to benefit from EGFR antibody therapy.

**Practical Management Considerations**

Figure 3 outlines treatment algorithms for the practical medical management of mCRC based on clinically relevant molecular testing. The proposed approach is meant to follow existing guideline recommendations available from the National Comprehensive Cancer Network and the European Society for Medical Oncology, and highlights the importance of upfront molecular testing for RAS and BRAF mutations for treatment decisions in patients considered candidates for the combination of chemotherapy and biologic agents.

Patients with RAS-mutated mCRC should not receive EGFR antibodies. The emphasis of medical therapy in these patients should be on optimizing the duration of anti-VEGF therapy, utilizing a bevacizumab-based combination therapy upfront and continuing VEGF inhibition with either bevacizumab or aflibercept into second-line therapy.

In RAS wild-type cancers, two strategies are possible: (1) upfront use of an EGFR antibody in combination with conventional chemotherapy followed by a bevacizumab-containing second-line regimen, or (2) a focus on prolonged VEGF inhibition in first-and second-line therapy followed by use of EGFR antibodies in later lines of therapy.

For BRAF-mutated mCRC, an aggressive first-line approach with FOLFOXIRI + bevacizumab could be the most active therapy, based on subgroup analyses from existing trials. Enrollment of patients with BRAF-mutated cancers in clinical trials is strongly encouraged.

Finally, for all these molecularly defined subgroups, regorafenib can be considered as a salvage therapy option, although it should be reserved for patients with good performance status.

**Future Directions**

Even before the results of the pivotal analysis of The Cancer Genome Atlas project became available, it was obvious that colorectal cancer is not one homogenous entity, but rather is comprised of various molecularly defined subgroups with different pathways of tumorigenesis, distinct tumor characteristics, and potentially specific responsiveness to certain treatment approaches. A better understanding of the patterns and consequences of molecular alterations will allow us to pursue the next generation of clinical trials, which will move away from the empiric randomization of large, unselected cohorts of patients and toward the investigation of specific interventions in prespecified patient subgroups.

To this end, the FOCUS4 trial, a phase II trial, has been initiated in the United Kingdom with the goal of testing targeted drugs in the first-line therapy of mCRC.[48] This trial is unique in that it is one of the first to proactively determine molecular alterations and subsequently place patients into subgroups with group-specific treatment randomizations that specifically target these molecular subtypes. A similar trial is currently being developed by the US Intergroup that will help elucidate whether stratifying colorectal cancer by molecular “buckets” and selectively targeting each of those buckets will lead to better patient outcomes.

Another development that may shape the design of the next generation of clinical trials, but that will also conceivably influence clinical practice in the future, is the availability of so-called “liquid biopsies” that can be used to identify circulating mutated tumor DNA in the plasma of cancer patients before and during therapy.[49,50] Molecular markers of secondary resistance, such as the emergence of RAS-mutant tumor clones in plasma samples obtained sequentially during ongoing EGFR antibody therapy, could provide a rational basis for treatment decisions for individual patients beyond the currently used empiric approach.

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Table: FDA-Approved Agents and Indications in Metastatic Colorectal Ca...

Figure 1: EGFR-Mediated Intracellular Signaling Cascades

Figure 2: Frequency of KRAS and NRAS Mutations Beyond KRAS Exon 2 in t...

Figure 3: Treatment Algorithm for the Practical Medical Management of ...

References:


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