



# Pyruvate kinase M2 (Tumor M2-PK) as a screening tool for colorectal cancer (CRC). A review.

Ewald N, Toepler M, Akinci A, Kloer HU, Bretzel RG, Hardt PD,  
Third Medical Department and Policlinic,  
University Hospital Giessen and Marburg at Giessen Site, Germany



## Introduction:

Colonoscopy is currently supposed to be the best screening tool for colorectal cancer. However, the acceptance of this method is very poor, although it has been included in screening programs in the German health system since 2002. Therefore, evaluation of additional screening tools seems to be of great interest. Recently, testing for fecal occult blood (FOBT), genetic alterations or alterations in tumor metabolism (e.g. Tumor M2-PK) is under investigation.

## Methods:

The use of M2-PK measurement in the feces has been reported in 6 studies (original papers and abstracts) until today. The data of these studies were analysed and critically reviewed.

## Results:

The overall sensitivity of M2-PK was 77.9% concerning CRC. Specificity ranged from 74.3% (endoscopic controls) to 83.3% (general population). Overall results are given in **table 1**, study details are shown in **table 2**.

The lower specificity in endoscopic controls may be due to the fact that these patients had a clinical indication for colonoscopy and therefore diseases of the upper GI tract seemed not to be unlikely. Overall sensitivity for adenomas was 45.9%, increasing to 61.1% for adenomas larger than 1 cm. A high percentage of positive results (90.4%) was also observed in patients with chronic inflammatory bowel disease.

Table 1: Results of present studies concerning the use of M2-PK in feces for CRC screening

Author	M2PK	Endoscop . Controls	General Population	CRC	Adenomas	IBD
Hardt PD et al., 2003 [7]	Positive	-	1 (2.0%)	11 (68.8%)	4 (50.0%)	-
	Negative	-	48 (98.0%)	5 (31.2%)	4 (50.0)	-
	<b>Total</b>	-	49	16	8	-
Hardt PD et al., 2004 [8]	Positive	32 (22.2%)	-	44 (73.3%)	-	-
	Negative	112 (77.8%)	-	16 (26.7%)	-	-
	<b>Total</b>	144	-	60	-	-
Naumann M et al., 2004 [9]	Positive	26 (34.7%)	-	23 (85.2%)	11 (45.8%)	47 (90.4%)
	Negative	49 (65.3%)	-	4 (14.8%)	13 (54.2%)	5 (9.6%)
	<b>Total</b>	75	-	27	24	52
Haug U et al., 2004 [10]	Positive	-	160 (17.5%)	-	-	-
	Negative	-	756 (82.5%)	-	-	-
	<b>Total</b>	-	916	-	-	-
Vogel T et al., 2005 [11]	Positive	18 (28.1%)	-	17 (77.3%)	10 (47.6%)	?
	Negative	46 (71.9%)	-	5 (22.7%)	11 (52.4%)	-
	<b>Total</b>	64	-	22	21	-
Koss K et al., 2005 [12]	Positive	0 (0%)	-	21 (87.5%)	3 (37.5%)	-
	Negative	13 (100%)	-	3 (12.5%)	5 (62.5%)	-
	<b>Total</b>	13	-	24	8	-
<b>Total</b>	Positive	76 (25.7%)	161 (16.7%)	116 (77.9%)	28 (45.9%)	47 (90.4%)
	Negative	220 (74.3%)	804 (83.3%)	33 (22.1%)	33 (54.1%)	5 (9.6%)
	<b>Total</b>	296	965	149	61	52
<b>Specificity:</b>		74.3%	83.3%			
<b>Sensitivity:</b>				77.9%	45.9%	
					(>1 cm: 61.1%)	

M2PK: Tumor-M2-Pyruvatkinase, IBD: Inflammatory bowel disease, CRC: Colorectal carcinoma

Table 2: Study design of the currently available studies concerning the use of M2-PK in feces as a screening tool for CRC.

Author	Type of Study	Included Patients (n/N)	Mean Age	Study Population	Reason for Colonoscopy
Hardt PD et al., 2003 [7]	Unicenter, retrospective study	78 (58/29)	68.2 years	21 CRC, 8 adenomas, 47 healthy controls	Indication for colonoscopy for different reasons
Hardt PD et al., 2004 [8]	Multicenter, retrospective study	204 (not known)	Not known	144 healthy controls with screening colonoscopy, 60 CRC	Suspicion of gastrointestinal cancer
Naumann M et al., 2004 [9]	Multicenter, prospective study	232 (129/112)	Not known	232 patients with indication for colonoscopy (after endoscopy: 75 healthy subjects, 42 IBD, 30 infectious diarrhea, 27 CRC, 24 adenomas)	Unspecific abdominal symptoms, diarrhea, positive FOBT or screening colonoscopy
Haug U et al., 2004 [10]	Retrospective study	985 (not known)	50 - 70 years (mean age not given)	916 asymptomatic patients, 69 CRC	Suspicion of gastrointestinal cancer
Vogel T et al., 2005 [11]	Multicenter, prospective study	138 (61/77)	58.0 years	116 patients with indication for colonoscopy, 22 CRC	Indication for colonoscopy for different reasons
Koss K et al., 2005 [12]	Unicenter, prospective study	45 (28/17)	65.0 years	45 patients with screening colonoscopy	Screening colonoscopy

IBD: inflammatory bowel disease, FOBT: faecal occult blood test, CRC: colorectal carcinoma

## Conclusions:

According to the results of this meta-analysis the M2-PK-Test appears to be superior for CRC screening as compared to FOBT and genetic testing.

Sensitivity for FOBT is reported to be 40% for CRC [1,2] and <20% for adenomas [2]. Specificity for FOBT is reported to be 20-98% [3]. However, false-positive results are seen in up to 80% of asymptomatic patients [4]. One major reason for the limitations of FOBT is that many carcinomas do not bleed at all or bleed only intermittently [5,6].

Testing for multi-target genetic alterations seems to be promising with a reported sensitivity of 63-100% [4]. Yet, the limitations of this screening tool are its high costs and the very limited handling and shipping time of the feces.

Colonoscopy is supposed to be the gold standard of CRC screening. However, a procedure that is not accepted by the screening population can hardly be successful. Concerning handling, effectiveness and costs M2-PK seems to be a good possibility for large scale screening of colorectal carcinoma. It might even be used to detect larger adenomas. Elevated M2-PK in patients with acute and/or chronic inflammatory bowel diseases are probably due to proliferation of epithelial cells and leucocytes in the inflammatory area. Since IBD patients are subject to endoscopic surveillance anyway, they are not part of the population to be included in general CRC screening programs. Therefore, M2-PK elevation in IBD patients is not a limitation for the use of this marker in general population screening.

According to the presented data, M2-PK testing in the feces should be recommended for general population screening because of its superior performance.

## References:

- Alquist, DA, McGill DB, Schwartz S, Taylor WF, Owen RA. Fecal blood levels in health and disease. *N Engl J Med.* 1985; 312, 1422-1428.
- Towler BP, Irwig L, Glasziou P, Weller D, Kewenter J. Screening for colorectal cancer using the faecal occult blood test, Hemoccult. *Cochrane Database Syst. Rev.* 2, 1998, CD001216
- Young GP, St. John DJ. Selecting an occult blood test for use as a screening tool for large bowel cancer. *Front Gastrointest Res* 1991; 18, 135-156.
- Davies RJ, Miller R, Coleman N. Colorectal cancer screening: prospects for molecular stool analysis? *Nat Rev Cancer.* 2005; Mar 5(3):199-209.
- Macrae FA, St. John DJ. Relationship between patterns of bleeding and Haemoccult sensitivity in patients with colorectal cancers or adenomas. *Gastroenterology* 1982; 82, 891-898.
- Mandel JS. et al. Reducing mortality from colorectal cancer by screening for fecal occult blood. *Minnesota Colon Cancer Control Study.* *N Engl J Med* 1993; 328, 1365-1371.
- Hardt PD, Ngoumou BK, Rupp J, Schnell-Kretschmer H, Kloer HU. Tumor M2-pyruvate kinase: A promising tumor marker in the diagnosis of gastro-intestinal cancer. *Anticancer Res.* 2000 Nov-Dec; 20(6D):4965-8.
- Hardt PD, Mazurek S, Toepler M, Schlierbach P, Bretzel RG, Eigenbrodt E, Kloer HU. Faecal tumour M2 pyruvate kinase: a new, sensitive screening tool for colorectal cancer. *Br J Cancer.* 2004 Aug 31; 91(5):980-4.
- Naumann M, Schaum B, Oremek GM, Hanisch E, Rosch W, Mossner J, Caspary WF, Stein J. Faecal pyruvate kinase type M2-a valid screening parameter for colorectal cancer? Preliminary results from a multicenter comparative study. *Dtsch Med Wochenschr.* 2004 Aug 20; 129(34-35):1806-7.
- Haug U, Rothenbacher D, Hardt PD, Kloer HU, Stegmaier C, Brenner H. Tumor M2PK: a promising method for colorectal cancer screening. *J Cancer Res Clin Oncol* 2004; 130: S172
- Vogel T, Driemel C, Hauser A, Hansmann A, Lange S, Jonas M, Moslein G. Comparison of different stool tests for the detection of cancer of the colon. *Dtsch Med Wochenschr.* 2005 Apr 8; 130(14):872-7
- Koss K, Maxton D, Jankowski J. The potential use of fecal dimeric M2 pyruvate kinase (tumour M2PK) in screening for colorectal cancer. *Gut* 2005, April, suppl. 2, 54: 20.