Epigenomics AG

Germany / Pharmaceutical/Biotechnology
Primary Exchange: Frankfurt
Bloomberg: ECX GR
ISIN: DE000A11QW50

CMS negative preliminary decision on reimbursement

RATING	**BUY**
PRICE TARGET	**€ 16.00**
Return Potential	421.2%
Risk Rating	Speculative

AMERICAN CANCER SOCIETY TAKES ISSUE WITH CMS METHODOLOGY

In its negative preliminary decision memorandum (PDM) on reimbursement coverage of Epi proColon, Centers for Medicare & Medicaid Services (CMS) write that there is no evidence that screening for colorectal cancer (CRC) with the test improves health outcomes. However, the August 2020 microsimulation study by the Cancer Intervention and Surveillance Modelling Network (CISNET) shows that the test reduces CRC cases and mortality to a greater extent than both the CMS-reimbursed FIT (fecal immunochemical test) and Cologuard. These divergent conclusions hinge upon CMS' use of one-time sensitivity and specificity values whereas the CISNET results are based on the interplay of sensitivity and specificity over a series of tests at annual intervals. The leading U.S. cancer treatment institutions as well as CMS regularly use CISNET microsimulation models to make high-stakes decisions. The American Cancer Society (ACS) is the preeminent U.S. cancer screening guideline issuing society. In its comments (published on CMS' website) on the PDM, the ACS writes: "We disagree with the CMS' proposal to set arbitrary thresholds for sensitivity and specificity as a basis for blood-based biomarker screening tests. We also disagree with the decision to not consider acceptability, i.e., adherence data, as a consideration in the evaluation of the screening test under evaluation." In our view it will be difficult for CMS to continue to disregard the CISNET study in making its final reimbursement determination (due mid-January). Over 30% of U.S. adults aged 50-75 are not up to date with CRC screening. Epi proColon's potential to raise adherence i.e. the screening rate was decisive in the FDA's 2016 approval of the test. This and the superior clinical performance vs. FIT and Cologuard identified by the CISNET microsimulation model suggest to us that the probability of CMS changing its view is >50%. We have lowered our price target to €16.00 (previously: €38.40) due to uncertainty caused by CMS' PDM. Our recommendation remains at Buy, but with the risk rating at speculative (previously: high).

FINANCIAL HISTORY & PROJECTIONS

	2018	2019	2020E	2021E	2022E	2023E
Revenue (€ m)	1.53	1.13	0.64	5.22	19.91	48.73
Y-o-y growth	-17.8%	-26.6%	-43.0%	714.4%	281.4%	144.8%
EBIT (€ m)	-12.90	-14.67	-11.43	-17.35	-11.61	4.48
EBIT margin	-841.2%	-1304.3%	-1783.7%	-332.4%	-58.3%	9.2%
Net income (€ m)	-12.69	-17.02	-11.49	-17.35	-11.61	4.48
EPS (diluted) (€)	-3.76	-3.65	-1.99	-2.41	-1.28	0.43
DPS (€)	0.00	0.00	0.00	0.00	0.00	0.00
FCF (€m)	-9.64	-13.46	-11.25	-19.14	-14.85	-2.95
Net gearing	-92.1%	-105.1%	-114.4%	-68.1%	-45.7%	-50.0%
Liquid assets (€ m)	17.14	11.04	2.96	4.40	4.63	11.76

RISKS

The main risk to our share price target is the failure of Epi proColon® to gain traction on the US market.

COMPANY PROFILE

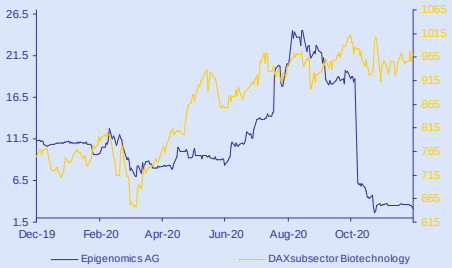
Berlin-based Epigenomics AG is a molecular diagnostics company developing and commercialising a pipeline of proprietary products for the diagnosis of cancer. Lead product, Epi proColon®, is an FDA-approved blood-based screening test for the detection of colorectal cancer. Epi proColon® is currently marketed in the US and Europe.

MARKET DATA

As of 11 Dec 2020	
Closing Price	€ 3.07
Shares outstanding	5.89m
Market Capitalisation	€ 18.09m
52-week Range	€ 2.65 / 24.56
Avg. Volume (12 Months)	21,480

Multiples	2019	2020E	2021E
P/E	n.a.	n.a.	n.a.
EV/Sales	10.8	19.0	2.3
EV/EBIT	n.a.	n.a.	n.a.
Div. Yield	0.0%	0.0%	0.0%

STOCK OVERVIEW



COMPANY DATA

As of 30 Sep 2020	
Liquid Assets	€ 6.64m
Current Assets	€ 7.36m
Intangible Assets	€ 0.19m
Total Assets	€ 8.83m
Current Liabilities	€ 2.72m
Shareholders' Equity	€ 5.54m

SHAREHOLDERS

Heidelberger Beteiligungsholding AG	15.0%
Morgan Stanley	9.9%
Bridger Healthcare Ltd.	8.3%
Gottlieb Jacob Jay	5.2%
Free float and others	61.6%

Analyst: Simon Scholes, Tel. +49 (0)30 - 80 93 96 94

INVESTMENT CASE

The ACS rejects CMS' arguments for non-coverage of Epi proColon The ACS' comments on the PDM were published on CMS' website in mid-November. Given ACS' status in the U.S. as the preeminent cancer guideline issuing society, we think these are worth quoting extensively. In the conclusion to its comments the ACS wrote: "We disagree with the CMS' proposal to set arbitrary thresholds for sensitivity and specificity as a basis for blood-based biomarker screening tests. We also disagree with the decision to not consider acceptability, i.e., adherence data, as a consideration in the evaluation of the screening test under evaluation."

We see the ACS comments as a hefty nudge to CMS to grant Epi proColon reimbursement coverage CMS wrote on page 45 of the PDM: "Observational studies measuring sensitivity and specificity, which are indicators of clinical validity, demonstrated that sensitivity of Epi proColon is no better than FIT in detection of colorectal cancer. As compared to the FIT test, the specificity for Epi proColon was lower. Therefore, compared to FIT, there is no indirect evidence that using the blood-based Epi proColon test is appropriate for prevention or early detection of colorectal cancer among Medicare beneficiaries."

ACS responded as follows: "It is not credible to state that indirect evidence only exists if a new test has the same or greater sensitivity and specificity of the comparison test. CMS should consider the following questions:

1) If the biomarker test had superior sensitivity and specificity to the lowest performing covered alternative test, but low acceptance by the target population, would it be acceptable for inclusion among the options for screening?

2) If CMS were to consider:

- the convenience and greater acceptability of a blood-based test in an unscreened population as a desirable feature, and
- if the biomarker test, with similar sensitivity to an alternative approved test, would result in an increase in the detection of occult cancer in the population that otherwise would not occur, and
- if lower specificity would result in a higher rate of follow-up testing with colonoscopy compared with the alternative test (which would not take place based on the patient's prior history of no screening), which, if normal, would likely be the last colorectal screening test a patient would ever receive given their age, and thus,
- isn't it possible that this is a desirable outcome?"

As we have already seen, the potential for Epi proColon to increase screening rates among the non-compliant population (due to what the ACS terms its "convenience and greater acceptability") was the decisive factor in the FDA's approval of the test in 2016.

Epigenomics has been successful in past appeals against FDA and CMS decisions In late 2015/early 2016 Epigenomics was successful in its appeal against the FDA's request for further data following the ADMIT trial. The FDA approved Epi proColon in April 2016. CMS made a preliminary price determination for Epi proColon of USD84 late in 2016 based on a crosswalk to test code 81287. Epigenomics' management had hoped for a price determination nearer USD160 and presented its reasoning for a crosswalk to a more highly remunerated test code to CMS in July 2017. In December 2018 CMS set a reimbursement rate of USD192 for the test.

Our recommendation is Buy but we have lowered the price target to €16.00 (previously: €38.40) As argued above, we think it will be difficult for CMS to disregard the CISNET microsimulation model in making its final reimbursement decision. The ACS states in the preface to its remarks on CMS' website, "we are not commenting on the coverage determination with respect to the Epi proColon test." However, we see the main body of its comments as a hefty nudge to CMS to grant the test reimbursement coverage. We have lowered our price target to €16.00 (previously: €38.40) due to uncertainty caused by CMS' PDM. Our recommendation remains at Buy, but with the risk rating at speculative (previously: high).

THE CISNET MICROSIMULATION MODEL AND CMS' PDM

CMS used CISNET microsimulation modelling to assess FIT and Cologuard CISNET is a consortium of National Cancer Institute-sponsored investigators who use simulation modelling to improve understanding of cancer control interventions and their effects on incidence and mortality of the disease. The ACS used a CISNET microsimulation model to arrive at their 2018 recommendation that the starting age for CRC screening should be lowered from 50 to 45. The U.S. Preventive Services Task Force (another major U.S. cancer screening guideline issuing body), the Centers for Disease Control and Prevention, as well as CMS itself, have also used CISNET microsimulation models. Indeed CISNET states on its website that CMS used its microsimulation models "for technology assessments as part of National Coverage Determinations to evaluate the cost-effectiveness of FIT, Cologuard and CT colonography in CRC screening compared to screening methods currently covered." Against this background it is surprising that CMS should write in its decision memorandum that it excluded microsimulation models from consideration of Epi proColon.

The document published by CISNET at the end of August, "Comparing the cost-effectiveness of innovative colorectal cancer screening tests" is based on MISCAN-Colon, a well-established colorectal cancer (CRC) microsimulation model. MISCAN-Colon is a stochastic microsimulation model. "Stochastic" means that the model simulates sequences of events by drawing from distributions of probabilities or durations randomly rather than using fixed values. The term "microsimulation" means that persons are moved through the model one at a time (individually) rather than as proportions of a cohort. Underlying data on clinical progression are derived from Surveillance, Epidemiology, and End Results (SEER) programme incidence rates.

Microsimulation models generate a holistic view of a test's benefits/disutilities Microsimulation models incorporate test sensitivity and specificity data and also assumptions as to test frequency and adherence to generate data on cancer incidence, death and QALYG (quality-adjusted life years gained) through screening. Cost and estimates for disutilities (for example follow-up colonoscopies) can be incorporated in the analysis to assess a screening method's cost-effectiveness.

Over 30% of U.S. adults aged 50-75 are not up to date with CRC screening According to Centers for Disease Control and Prevention (CDC), in 2018 68.8% of adults in the U.S. aged between 50 and 75 were up to date with CRC screening. The percentage of persons up to date with screening was lowest among persons aged 50–54 years (50.0%) and increased with age.

Construction of CISNET model motivated by need to raise screening rate The most widely used CRC screening methods in the US are colonoscopy and FIT. But fear and the discomfort involved in preparing for the test discourage many individuals from undergoing a colonoscopy. Meanwhile, the unpleasantness of fecal sampling acts as a disincentive with regard to FIT. The need to raise the screening rate was the prime motivation behind CISNET's construction of a microsimulation model to assess the cost effectiveness of alternatives to colonoscopy and FIT such as Cologuard, CT colonography (CTC), Epi proColon and PillCam.

CISNET microsimulation model finds that Epi proColon outperforms FIT and Cologuard The recommended screening frequencies for FIT and Cologuard are respectively once a year and once every three years. The CISNET microsimulation study found that annual screening with Epi proColon (mSEPT99) results in:

- 4% fewer CRC deaths than annual FIT
- 9% fewer CRC deaths than triennial Cologuard
- 8% fewer CRC cases than annual FIT
- 13% fewer CRC cases than triennial Cologuard
- 80% fewer CRC deaths and nearly 60% fewer CRC cases when compared to no screening

The CISNET study found the most cost effective alternatives to colonoscopy and FIT to be CTC and Epi proColon Cost effectiveness was defined as cost per quality-adjusted life year gained (QALYG). The conclusion of the CISNET study was: "This study suggests that for individuals not willing to participate in FIT or colonoscopy screening, mSEPT9 is the test of choice if the high colonoscopy referral rate is acceptable to them."

CMS' 69-page PDM included the CISNET study in its bibliography, but without explanation the authors decided to exclude microsimulation models from consideration.

Figure 1: Sensitivity and specificity of CRC screening tests

Screening test	Sensitivity	Specificity	Source
Colonoscopy	95%	100%	van Rijn et al. 2006
CTC	84%	88%	Johnson et al. 2008
PillCam	92%	83%	Rex et al. 2015
FIT	74%	96%	Imperiale et al. 2014
Cologuard	92%	90%	Imperiale et al. 2014
Epi proColon	68%	79%	Potter et al. 2014

Figure 1 shows the one-time sensitivity and specificity of CRC screening tests. Essentially CMS decided not to cover Epi proColon because its one-time sensitivity is lower than FIT and its one-time specificity is lower than Cologuard. This might be a sound approach if one-time sensitivity and specificity were the sole determinants of clinical effectiveness. But they are not. Programmatic performance (i.e. clinical effectiveness over a series of tests) is also crucial. CRC develops slowly relative to other cancers. This is why the recommended interval for colonoscopy, the highest sensitivity CRC screening test, is ten years. The FDA label for Cologuard stipulates a screening interval of three years and the standard screening interval for FIT is one year. The recommended testing interval for these tests is shorter to mitigate their lower sensitivity relative to colonoscopy.

The overall probability of cancer detection over time is given by the sensitivity of a series of tests at the recommended screening interval. Epi proColon's label does not stipulate a test-interval. The Summary of Safety and Effectiveness Data published by the FDA to accompany Epi proColon's approval in April 2016 indicates the reason for this:

"The performance of Epi proColon has been established in cross-sectional (i.e., single point in time) studies. Programmatic performance of Epi proColon (i.e., benefits and risks with repeated testing over an established period of time) has not been studied."

CISNET model establishes optimal one-year test interval for Epi ProColon The CISNET study *does* model Epi proColon's programmatic performance and arrives at an optimal testing interval of one year. But CMS' decision to ignore microsimulation tests causes it to identify three years as an appropriate screening interval for new blood-based CRC screening tests.

Epi proColon's low relative specificity is a feature not a bug The CISNET microsimulation model's finding that Epi proColon's outperforms FIT and Cologuard despite lower one time sensitivity and specificity depends on a) annual repetition of the test and b) receipt of diagnostic follow-up colonoscopy as is recommended for all non-colonoscopy-based screening strategies. Epi proColon's low specificity compared with the other tests causes a high number of the individuals simulated in the CISNET study to be referred to a diagnostic follow-up colonoscopy (51% after 3 years and 69% after 5 years). In consequence, 21% of simulated individuals with a non-advanced adenoma received a colonoscopy when screened with Epi proColon and only 7.6% of those screened with FIT. Non-advanced adenomas are generally low-risk, but they are more common than advanced adenomas and some have aggressive biology. The detection of non-advanced adenomas in these colonoscopies contributed to the higher number of CRC cases and deaths averted by Epi proColon than FIT. Similar dynamics generate Epi proColon's outperformance of Cologuard in the CISNET microsimulation test.

CISNET finds annual Epi proColon to be more cost-effective than triennial Cologuard
The CISNET study also ranked competing screening strategies on the basis of incremental cost-effectiveness relative to no screening (see figure 2 below). Strategies that were more costly and less effective than other methods were considered dominated. Remaining strategies were identified as providing good value for money i.e. were considered efficient. For the efficient strategies, the incremental cost-effectiveness ratios were calculated by dividing the additional costs by the additional quality-adjusted life years gained (QALYG) compared with the next less costly alternative strategy. Colonoscopy and FIT dominated all other methods. But given CISNET's brief to find the most cost-effective alternatives to these two strategies, CISNET also compared the alternatives among themselves. A willingness-to-pay threshold of USD100,000 per QALYG was assumed. Costs of screening included screening-related complications, payments, coinsurance, cathartic bowel preparation agents, patient- and escort time costs. Disutilities included those associated with the test itself, and those related to fear or anxiety while waiting for the test result or a follow-up colonoscopy after a positive result.

Figure 2: Outcome per 1,000 50-year-olds for different screening strategies

Screening test	Interval (years)	No. of screening tests	No. of colonoscopies	LYG	QALYG	Total costs (USD m)*	ICER (USD per QALYG)*	ICER (USD per QALYG) without FIT and colonoscopy*
No screening	-	0	108	0	0	7286	-	-
FIT	1	15,044	2,349	162	189	6,793	Cost Saving	-
CTC	5	4,292	1,824	151	177	7,479	D	1,902
Colonoscopy	10	1,995	4,735	174	209	7,751	48,155	-
epi proColon	2	5,802	3,201	151	175	8,298	D	D
epi proColon	1	7,159	3,827	165	194	8,574	D	62,253
Cologuard	3	5,583	2,279	151	175	8,887	D	-
PillCam	10	2,383	2,173	141	165	8,951	D	-
PillCam	5	3,710	2,736	166	196	9,940	D	-
Cologuard	1	10,185	3,334	173	295	10,798	D	214,974

*3% discounted; LYG = life-years gained, QALYG = quality adjusted life-years gained, ICER = incremental cost-effectiveness ratio, D = dominated

Source: Department of Public Health Erasmus University Medical Centre, Netherlands. Sponsored by NCI as part of CISNET

CISNET study identifies Epi proColon as the test of choice among alternatives to FIT and colonoscopy As figure 2 shows, FIT and colonoscopy dominate all other screening strategies, but if these strategies are excluded, only two strategies are deemed to be cost-effective and below the willingness-to-pay threshold of USD100,000 per QALYG. These are CTC and annual screening with Epi proColon. The authors of the model go on to conclude that "for people who are unwilling to be screened with FIT or colonoscopy, annual screening with Epi ProColon is the test of choice given its cost-effectiveness profile compared to CTC, PillCam and Cologuard."

ECX response to PDM published on CMS website CMS published its PDM on 16 October. During the ensuing 30-day public comment period ECX posted a vigorous rejection of the memorandum's conclusions on CMS' website. Following the end of the public comment period, CMS has 60 days to publish their final decision.

CMS included the CISNET study in the preliminary decision memorandum's bibliography but in the main body of the text did not explain its decision to disregard microsimulation studies. In its final decision we expect CMS either to accept the results of the CISNET microsimulation study or provide an explanation of why it has decided to reject them.

CMS may object that evidence from CISNET microsimulation models is of lower quality than evidence from real-world clinical trials, but then it would have to explain why it used them to make reimbursement coverage decisions for Cologuard and FIT but disregards this methodology with respect to Epi proColon.

The ACS has underlined the value of microsimulation modelling The American Cancer Society highlighted its view of the value of microsimulation modelling in 2018 when it cited "no microsimulation modelling of the newer version of the test to estimate its benefit, a benefit-harm ratio or a screening ratio for regular testing" as a reason for not including the test in its screening guidelines.

CMS proposes new accelerated pathway to reimbursement coverage CMS proposes a new accelerated pathway to reimbursement coverage known as Medicare Coverage of Innovative Technology (MCIT). It is planned that under MCIT reimbursement coverage by CMS should begin on the date of FDA market authorisation and continue for four years. MCIT is to be accompanied by a set of regulatory standards "to ensure stakeholders know the coverage criteria."

Against this background, in the PDM, CMS proposed a set of criteria for emerging blood-based biomarker screening tests. The criteria are as follows.

- FDA market authorisation with an indication for colorectal cancer screening
- proven test performance characteristics for a blood-based screening test with both sensitivity greater than or equal to 74% and specificity greater than or equal to 90% in the detection of colorectal cancer compared to the recognized standard (accepted as colonoscopy at this time), based on the pivotal studies included in the FDA labelling
- inclusion as a recommended routine colorectal cancer screening test in at least one professional society guideline or consensus statement or United States Preventive Services Task Force (USPSTF) recommendation.

CMS also proposed a three-year screening interval for emerging blood-based biomarker screening tests and stated “CMS will cover blood-based CRC screening tests at a different screening interval only if the FDA designates a different screening interval in the FDA label for a new blood-based CRC screening test.”

Epi proColon was granted FDA approval in April 2016. The figures of 74% for sensitivity and 90% for specificity are respectively the numbers for FIT and Cologuard. These numbers relate to one-time testing. As we have pointed out above, it is doubtful that one-time sensitivity and specificity numbers give a more accurate picture of clinical utility than a microsimulation model of repeated testing. The CISNET microsimulation model indicates that Epi proColon, whose sensitivity and specificity figures are both below FIT and Cologuard, generates greater clinical utility than both these tests.

Requirement for guideline inclusion runs counter to MCIT aim The declared aim of MCIT is to shorten the gap between FDA approval and reimbursement coverage, which CMS itself has referred to as the valley of death for innovators. However, the stipulation that a test be included in professional society guidelines runs counter to this aim as the professional societies only review these publications infrequently. For example the most recent ACS guidelines from 2018 were an update of a 2008 publication and the USPSTF did not update its 2008 guidelines until 2016. In addition, we note that there is no statutory requirement that reimbursement coverage be preceded by guideline inclusion. We also note that Cologuard was not included in professional society guidelines when CMS granted it reimbursement coverage.

CMS guideline inclusion requirement arbitrarily excludes non-routine screening In our view the requirement that the guideline be for routine screening arbitrarily excludes the indication for which the FDA approved Epi proColon i.e. patients who have been offered and have a history of not completing CRC screening. Epi proColon *is* included in the guidelines of the National Comprehensive Cancer Network, but only for non-routine screening.

CMS-proposed three-year screening interval would worsen performance of both FIT and Epi proColon As we have seen above, the appropriate screening interval for a test tends to decrease in line with its sensitivity. The basis for CMS’ sensitivity benchmark of 74% is FIT. FIT’s label recommends annual screening. Against this background it is strange that CMS should propose a screening interval of three years. A three year screening interval would markedly worsen the performance of both FIT and Epi proColon.

In the PDM CMS writes with regard to Epi proColon that using a test with lower specificity than other non-invasive tests (i.e. FIT and Cologuard) will lead to telling more patients “that they have cancer when they truly do not have cancer”…and “more unnecessary colonoscopies.”

We think Epi proColon’s livesaving potential outweighs modicum of distress caused by false positive result The Epi proColon patient brochure clearly states that the chances of a person receiving a positive test result actually having CRC (the positive predictive value) are 2.7%. We think this figure serves to limit the mental distress suffered by individuals receiving a false positive result. We also note that the CISNET microsimulation model took account of fear or anxiety while waiting for the test result or a follow-up colonoscopy after a positive result and still found Epi proColon to be more cost-effective than Cologuard.

As the results of the CISNET model shown in figure 2 illustrate, 1,000 50 year-olds using Epi proColon as a screening method undergo an average of 3,827 follow-up colonoscopies during their life times. This number is 63% and 68% above the numbers for annual FIT and triennial Cologuard respectively. However, Epi proColon’s higher colonoscopy burden is justified by a higher QALYG number of 194 vs. 177 for FIT and 175 for Cologuard.

Potential to raise screening rate was decisive factor in FDA approval of Epi proColon

Epi proColon's potential to raise screening rates was an important factor behind the FDA's approval of the test in 2016. The FDA did not have access to the CISNET microsimulation model data when making its decision. The premarket approval package submitted by ECX to the FDA in 2011 and 2012 comprised a clinical validation study containing the sensitivity and specificity data shown in figure 2 as well as a head-to-head comparative study which demonstrated the non-inferiority of Epi proColon to FIT. This study is to date the only head-to-head comparison of the two tests.

The FDA sent a response letter to ECX in mid-2014. The main issue addressed in the response letter was Epi proColon's capacity to increase compliance. Press coverage at the time, and the test's subsequent label indicate that a further FDA concern was that Epi proColon would become a substitute for established screening methods such as colonoscopy included in the 2008 USPSTF guidelines.

The clinical studies originally conducted by ECX were performed in patients who had agreed to a routine screening colonoscopy, and so the FDA requested ECX to demonstrate whether patients in the targeted population could be made compliant with CRC screening by Epi proColon. In order to demonstrate Epi proColon's capacity to increase participation in CRC screening, ECX undertook the ADMIT trial. ECX published results of the ADMIT study (ADherence to minimally invasive testing) in May 2015 and later submitted them to the FDA.

In its early November 2015 response letter following evaluation of the ADMIT test results, the FDA requested further data demonstrating that Epi proColon increased compliance with CRC screening. While the study showed adherence to Epi proColon of nearly 100%, the 88% participation rate in the FIT-test by far exceeded the levels seen in many studies. This suggested to the FDA that the studied population in the ADMIT trial was not fully suitable for Epi proColon and the agency requested additional data demonstrating that Epi proColon would increase compliance with CRC screening in the intended use population. In late 2015 ECX appealed against the FDA's request for additional information. In its appeal letter ECX highlighted the difficulties of measuring adherence in the intended use population under the existing regulatory framework as well as a willingness to work with the FDA to design an appropriate post-approval study. In January 2016 the FDA responded to this appeal by stating that no new data would be required for completion of the review of the Epi proColon PMA. The FDA approved Epi proColon in April 2016.

Importantly the FDA's summary of safety and effectiveness document on Epi proColon does state that the ADMIT trial demonstrated that "there is reasonable assurance that some patients who have been offered and have failed to undergo recommended CRC screening tests will be willing to take Epi proColon. "

One of ADMIT's secondary endpoints was the proportion of participants with positive results who completed colonoscopy within three months of referral. Of the 30 patients who tested positive using Epi ProColon, 17 completed a colonoscopy within three months. Three FIT-participants tested positive of which one completed a colonoscopy within three months. This result contradicts CMS' statement in the PDM that "there is unclear evidence if a patient who has refused all other tests"... "will agree to the colonoscopy since they refused screening to begin with. "

Figure 3: CISNET CRC screening test microsimulation model scenarios

Analysis	Description
Base case	**2020 NCI-sponsored MISCAN Model:** Screening from age 50 through 75 years in an average-risk population
Scenario 2	**2018 ACS Model:** Screening from age 50 through 75 years in an average-risk population
Scenario 3	**2016 USPSTF Model:** Based on lower CRC incidence inputs
Scenario 4	**Imperfect adherence MISCAN Model:** Adherence estimates in line with current CRC participation rates including colonoscopy follow-up and surveillance
Scenario 5	**Handicap Epi proColon Clinical Performance** Assume 12% of advanced adenomas and 18% of colorectal cancers are systematically missed by mSEPT9

Source: Department of Public Health Erasmus University Medical Centre, Netherlands. Sponsored by NCI as part of CISNET

Lastly we note that CISNET also ran its microsimulation model under five different scenarios (see figure 3). Under all five scenarios Epi proColon generated more QALYG than screening every three years with Cologuard or annual FIT.

Changes to forecasts reflect delayed reimbursement start The 2020 and 2021 forecasts contained in our study of 25 August were based on the assumption of a positive CMS PDM by the originally scheduled date of 28 August. On this schedule, reimbursement would have started three months later on publication of CMS' final decision memorandum in late November. But the PDM was delayed until 16 October and so the final decision memorandum will not be published until mid-January. Given that Epi proColon will not be reimbursed at any point this year, we have lowered our 2020 forecast. We have also moved our 2020 forecast for EBITDA ex-share-based payment expenses in line with the guidance given in the Q3 2020 results published in early November. This is for a figure of €-10.0m to €-11.0m (previously: €-10.5m to €-12.5m). We have reduced our 2021 forecasts to reflect both a later start to reimbursement than previously modelled and the likely impact of the SARS-CoV-2 pandemic on testing. Our forecasts for subsequent years are close to our previous forecasts (see figure 4). The lower EPS numbers reflect the impact of future share issues to finance the rollout of Epi proColon at a lower price than we previously modelled.

Figure 4: Changes to our forecasts

	FY 2020E			FY 2021E			FY 2022E			FY 2023E		
All figures in €m	**New**	**Old**	**Delta**	**New**	**Old**	**Delta**	**New**	**Old**	**Delta**	**New**	**Old**	**Delta**
Sales	0.64	0.84	-23.7%	5.22	8.45	-38.2%	19.91	19.94	-0.2%	48.73	48.94	-0.4%
EBITDA ex-share based payment expenses	-10.12	-11.39	n.a.	-15.90	-11.93	n.a.	-10.05	-10.03	n.a.	6.25	6.41	-2.4%
margin	*neg.*	*neg.*	-	*neg.*	*neg.*	-	*neg.*	*neg.*	-	*12.8%*	*13.1%*	
EBIT	-11.43	-12.71	n.a.	-17.35	-13.39	n.a.	-11.61	-11.59	n.a.	4.48	4.64	-3.3%
margin	*neg.*	*neg.*	-	*neg.*	*neg.*	-	*neg.*	*neg.*	-	*9.2%*	*9.5%*	-
Net income	-11.49	-12.77	n.a.	-17.35	-13.39	n.a.	-11.61	-11.59	n.a.	4.48	4.64	-3.3%
margin	*neg.*	*neg.*	-	*neg.*	*neg.*	-	*neg.*	*neg.*	-	*9.2%*	*9.5%*	-
EPS (in €, diluted)	-1.99	-2.16	n.a.	-2.41	-2.00	n.a.	-1.28	-1.52	n.a.	0.43	0.56	-23.7%

Source: First Berlin Equity Research estimates

Authorisation secured for €5.5m convertible bond issue at EGM on 27 November ECX's end-September balance sheet showed cash and marketable securities of €6.6m (YE 2019: €11.0m). Cash reach extends into Q1/2021. ECX held an EGM on 27 November at which it obtained authorisation until 31 March to issue up to €5.5m of zero coupon bonds convertible at €8.8 per share. The term of the bonds is a minimum of 2 years and 11 months and a maximum of 3 years and 3 months. Existing shareholders will have rights to subscribe to the bonds. Deutsche Balaton, a subsidiary of major shareholder Heidelberger Beteiligungs AG, has offered to subscribe up to €4m of the bond issue if shareholders do not exercise their subscription rights.

Our recommendation is Buy but we have lowered the price target to €16.00 (previously: €38.40) We have lowered our price target to €16.00 (previously: €38.40) due to uncertainty caused by CMS' PDM. Our recommendation remains at Buy, but with the risk rating at speculative (previously: high).

Figure 5: Pipeline valuation model

Compound	Project[1)]	Present Value	Patient Pop	Treatment Cost	Market Size	Market Share	Peak Sales	PACME[2)] Margin	Discount Factor	Time to Market
Epi proColon	CRC-US	€329M	27,712K	€167	€4,627M	10.0%	€272M	72%	15%	-
HCCBloodTest	HCC-US	€70M	3,245K	€300	€973M	20.0%	€216M	73%	15%	4 Years
PACME PV		€399M			€5,600M		€489M			
Costs PV[3)]		€280M								
NPV		€119M								
Net Cash (pro-forma)*		€46M								
Fair Value		€165M								
Share Count (pro-forma)*		10,315K								
Fair Value Per Share		€16.00								

1) A project typically refers to a specific indication or, where necessary or relevant, a combination between indication and geographic market

CRC-US - colorectal cancer in the US
HCC-US - liver cancer in the US

2) PACME (Profit After Costs and Marketing Expenses) reflects the company's profit share on future revenues.
This share may be derived in the form of royalties (outsourced marketing/manufacturing) or operating EBITDA margin (in-house model), or some mix of both (depending on the specific parameters of partnership agreements)

3) Includes company-level R&D, G&A, Financing Costs and CapEx; COGS and S&M are factored into the PACME margin for each project

* Includes PV of cash and shares associated with recently announced and expected future capital injections

Source: First Berlin Equity Research estimates

Figure 6: Changes to our pipeline valuation model

	Old	New	Delta
PACME PV	**€879.0M**	**€398.5M**	**-54.7%**
Costs PV	€631.0M	€279.5M	-55.7%
NPV	**€248.0M**	**€119.0M**	**-52.0%**
Net Cash (pro forma)	€45.0M	€46.0M	2.3%
Fair Value	**€293.0M**	**€165.0M**	-43.7%
Share Count (pro forma)	7,627K	10,315K	35.2%
Price Target	**€38.40**	**€16.00**	**-58.3%**

Source: First Berlin Equity Research estimates

INCOME STATEMENT

All figures in EUR '000	2018	2019	2020E	2021E	2022E	2023E
Total revenue	**1,533**	**1,125**	**641**	**5,220**	**19,909**	**48,732**
Cost of goods sold	**440**	**253**	**135**	**1,631**	**2,489**	**5,076**
Gross profit	**1,093**	**872**	**506**	**3,589**	**17,420**	**43,656**
S,G&A	8,703	8,935	6,942	13,940	20,584	28,772
R&D	6,418	7,340	4,012	7,500	9,000	11,000
Other operating income (expense)	1,133	730	-986	500	550	600
Operating income (EBIT)	**-12,895**	**-14,673**	**-11,434**	**-17,351**	**-11,613**	**4,484**
Net financial result	-535	107	-37	0	0	0
Pre-tax income (EBT)	**-13,430**	**-14,566**	**-11,471**	**-17,351**	**-11,613**	**4,484**
Income taxes	738	-2,454	-24	0	0	0
Net income / loss	**-12,692**	**-17,020**	**-11,495**	**-17,351**	**-11,613**	**4,484**
Diluted EPS (€)	**-3.76**	**-3.65**	**-1.99**	**-2.41**	**-1.28**	**0.43**
EBITDA before share-based payments	**-11,436**	**-14,161**	**-10,119**	**-15,896**	**-10,053**	**6,254**
Ratios						
Gross margin	71.3%	77.5%	79.0%	68.8%	87.5%	89.6%
EBIT margin	n.a.	n.a.	n.a.	n.a.	n.a.	9.2%
Net margin	n.a.	n.a.	n.a.	n.a.	n.a.	12.8%
Expenses as % of revenues						
S,G&A	567.7%	794.2%	1083.0%	267.0%	103.4%	59.0%
R&D	418.7%	652.4%	625.9%	143.7%	45.2%	22.6%
Y-Y Growth						
Total revenues	-17.8%	-26.6%	-43.0%	714.4%	281.4%	144.8%
Operating income	n.m.	n.m.	n.m.	n.m.	n.m.	n.m.
Net income/ loss	n.m.	n.m.	n.m.	n.m.	n.m.	n.m.

BALANCE SHEET

All figures in EUR '000	2018	2019	2020E	2021E	2022E	2023E
Assets						
Current Assets, Total	**18,274**	**12,123**	**3,661**	**6,749**	**13,388**	**33,199**
Cash and liquid assets	17,140	11,035	2,956	4,399	4,628	11,757
Receivables	164	89	96	783	2,986	7,310
Inventories	364	313	160	1,305	4,977	12,183
Other current assets	606	686	449	261	796	1,949
Non-Current Assets, Total	**3,553**	**1,866**	**1,497**	**1,157**	**922**	**952**
Property, plant & equipment	701	1,533	1,300	1,095	910	940
Goodwill & other intangibles	474	333	197	62	12	12
Deferred taxes	2,378	0	0	0	0	0
Total Assets	**21,827**	**13,989**	**5,158**	**7,906**	**14,310**	**34,151**
Shareholders' Equity & Debt						
Current Liabilities, Total	**3,167**	**3,619**	**2,664**	**2,097**	**5,476**	**11,538**
Accounts payable	1,411	1,430	545	783	2,986	7,310
Prepayments	23	5	83	52	199	487
Lease liabilities	0	216	240	270	300	330
Current provisions	962	600	898	783	1,195	1,949
Other current liabilities	771	1,368	897	209	796	1,462
Longterm Liabilities, Total	**47**	**741**	**645**	**702**	**899**	**1,237**
Lease liabilities	0	697	600	650	700	750
Provisions	47	44	45	52	199	487
Shareholders equity	**18,613**	**9,629**	**1,849**	**5,106**	**7,935**	**21,376**
Total consolidated equity and debt	**21,827**	**13,989**	**5,158**	**7,906**	**14,310**	**34,151**
Ratios						
Current ratio (x)	5.77	3.35	1.37	3.22	2.44	2.88
Quick ratio (x)	5.66	3.26	1.31	2.60	1.54	1.82
Net gearing	-92.1%	-105.1%	-114.4%	-68.1%	-45.7%	-50.0%
Book value per share (€)	4.13	1.77	0.31	0.62	0.80	1.92
Net cash	17,140	10,122	2,116	3,479	3,628	10,677
Return on equity (ROE)	-87.0%	-120.5%	-200.3%	-498.9%	-178.1%	30.6%

CASH FLOW STATEMENT

All figures in EUR '000	2018	2019	2020E	2021E	2022E	2023E
EBIT	**-12,895**	**-14,673**	**-11,434**	**-17,351**	**-11,613**	**4,484**
Depreciation and amortization	308	513	545	555	560	570
EBITDA	**-12,587**	**-14,160**	**-10,889**	**-16,796**	**-11,053**	**5,054**
Changes in working capital	1,090	-245	-895	-2,126	-3,473	-7,405
Stock option expenses	1,151	873	770	0	0	0
Other adjustments	-5	26	-61	0	0	0
Operating cash flow	**-10,351**	**-13,506**	**-11,074**	**-18,921**	**-14,526**	**-2,351**
Investments in tangible assets	-91	-75	-112	-150	-175	-400
Investments in intangibles	-15	-47	-64	-65	-150	-200
Proceeds from investment grants	813	0	0	0	0	0
Interest received	17	169	0	0	0	0
Cashflow from investing activities	**724**	**47**	**-176**	**-215**	**-325**	**-600**
Free cash flow	**-9,644**	**-13,459**	**-11,250**	**-19,136**	**-14,851**	**-2,951**
Lease financing	0	0	-73	80	80	80
Convertible financing, net	**-6,021**	**0**	**0**	**0**	**0**	**0**
Equity financing, net	**19,295**	**7,349**	**3,244**	**20,500**	**15,000**	**10,000**
Other changes in cash	**-252**	**-2**	**0**	**0**	**0**	**0**
Cashflow from financing activities	**13,022**	**7,347**	**3,171**	**20,580**	**15,080**	**10,080**
Net cash flow	**3,395**	**-6,112**	**-8,079**	**1,444**	**229**	**7,129**
Currency translation effects	14	7	0	0	0	0
Liquid assets, start of the year	13,731	17,140	11,035	2,956	4,399	4,628
Liquid assets, end of the year	**17,140**	**11,035**	**2,956**	**4,399**	**4,628**	**11,757**
EBITDA/share (€)	**-3.73**	**-3.04**	**-1.88**	**-2.33**	**-1.22**	**0.48**
Y-Y Growth						
Operating cash flow	n.m.	n.m.	n.m.	n.m.	n.m.	n.m.
Free cash flow	n.m.	n.m.	n.m.	n.m.	n.m.	n.m.
EBITDA/share	n.m.	n.m.	n.m.	n.m.	n.m.	n.m.

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Current market capitalisation (in €)		0 - 2 billion	> 2 billion
Strong Buy[1]	An expected favourable price trend of:	> 50%	> 30%
Buy	An expected favourable price trend of:	> 25%	> 15%
Add	An expected favourable price trend of:	0% to 25%	0% to 15%
Reduce	An expected negative price trend of:	0% to -15%	0% to -10%
Sell	An expected negative price trend of:	< -15%	< -10%

[1] The expected price trend is in combination with sizable confidence in the quality and forecast security of management.

Our recommendation system places each company into one of two market capitalisation categories. Category 1 companies have a market capitalisation of €0 – €2 billion, and Category 2 companies have a market capitalisation of > €2 billion. The expected return thresholds underlying our recommendation system are lower for Category 2 companies than for Category 1 companies. This reflects the generally lower level of risk associated with higher market capitalisation companies.

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Report No.:	Date of publication	Previous day closing price	Recommendation	Price target
Initial Report	11 June 2013	€13.50	Buy	€34.40
2...34	↓	↓	↓	↓
35	6 October 2017	€37.84	Buy	€58.40
36	19 December 2017	€28.96	Buy	€58.40
37	16 April 2018	€28.88	Buy	€56.80
38	25 August 2020	€23.76	Buy	€38.40
39	Today	€3.07	Buy	€16.00

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